### ABSTRACTS

#### How to cite the abstracts:

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Authors</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>SESSION OVERVIEW: PROGRAM COMMITTEE WORKSHOP FOR NEW INVESTIGATORS AND TRAINEES</strong>&lt;br&gt;John W. Mellors&lt;sup&gt;1&lt;/sup&gt;, Serena S. Spudich&lt;sup&gt;2&lt;/sup&gt;&lt;br&gt;&lt;sup&gt;1&lt;/sup&gt;University of Pittsburgh, Pittsburgh, PA, USA, &lt;sup&gt;2&lt;/sup&gt;Yale University, New Haven, CT, USA</td>
<td>Over the past four decades, remarkable progress has been made in understanding HIV epidemiology, pathogenesis, treatment, and prevention from the combined efforts of community members, clinicians, investigators, and funding agencies worldwide. Yet more work and new approaches are needed to achieve the ambitious goal of ending the epidemic and ensuring optimal quality of life for those living with HIV. To encourage and stimulate the next generation of investigators, the CROI Program Committee organizes an annual Workshop for New Investigators and Trainees comprised of expert and comprehensible talks to cover current knowledge and controversies in basic, clinical and public health investigation into HIV and related infections, and to highlight relevant work to be presented over the ensuing days at CROI. This year’s Workshop will begin with Dr. Wes Sundquist who will review aspects of HIV-1 replication and innate immunity, in particular recent developments in our understanding of mechanisms of virus sensing, early steps in the viral replication cycle, and virus-host arms races. Dr. Richard Koup will cover recent preclinical HIV vaccine advances, concentrating on efforts to induce either broad neutralizing antibody responses or protective CD8 T cells, and discuss the latest data on the development and use of broadly neutralizing antibodies in prevention and treatment of HIV. Dr. Hermione Lyall will review ongoing challenges in prevention of vertical HIV transmission during pregnancy and breastfeeding, short and long term challenges of getting infants on to treatment, and approaches to sustaining health and supporting ‘undetectable=untransmittable’ in youth with HIV. Dr. Susan Buchbinder will describe the current status of new infections globally, and discuss recent advances in biomedical HIV-1 prevention including treatment as prevention, pre-exposure prophylaxis, topical preventive agents, HIV vaccines, and combination approaches to HIV prevention. Finally, Dr. Nicolas Chomont will review the mechanisms that contribute to HIV persistence during ART, highlight the role of cell proliferation in that process and present recent therapeutic approaches aimed at curing HIV infection. The Workshop serves as the initial opportunity for Trainees and New Investigators to interact with Program Committee members. Such interactions will continue during new morning sessions organized to provide support and guidance for emerging investigators at this year’s CROI.</td>
<td><strong>Top Antivir Med.</strong> 2020;28(1):483.</td>
</tr>
<tr>
<td>2</td>
<td><strong>SHIFTING FROM ACUTE TO CHRONIC, AGING, LONGEVITY, AND LIVED EXPERIENCE</strong>&lt;br&gt;Jim Pickett&lt;sup&gt;1&lt;/sup&gt;, Martha Tholakan&lt;sup&gt;1&lt;/sup&gt;, Gabriel Maldonado&lt;sup&gt;1&lt;/sup&gt;, Celeste Watkins-Hayes&lt;sup&gt;1&lt;/sup&gt;&lt;br&gt;&lt;sup&gt;1&lt;/sup&gt;AIDS Foundation of Chicago, Chicago, IL, USA, &lt;sup&gt;2&lt;/sup&gt;Advocate, Harare, Zimbabwe, &lt;sup&gt;3&lt;/sup&gt;TruEvolution, Riverside, CA, USA, &lt;sup&gt;4&lt;/sup&gt;Northwestern University, Chicago, IL, USA</td>
<td>Globally, there were 5.7 million (4.7 million – 6.6 million) people living with HIV (PLHIV) 50 years of age and older (50+) in 2016. Although the proportion of PLHIV50+ was greater in high-income countries, low- and middle-income countries have higher numbers of PLHIV50+ that are expected to continue to increase by 2040. The proportion of PLHIV50+ across the world increased substantially from 8% in 2000 to 16% in 2016 and is expected to increase to 21% by 2020. In the United States, it is estimated that more than 70% of PLHIV will be 50 or older in 2020. Thirty-nine years into the epidemic, we’ve seen a remarkable shift in the trajectory of HIV. No longer is an HIV diagnosis simply a death sentence, individuals with HIV are living longer than ever before. Issues related to aging, long ignored due largely to irrelevance, are coming to the fore. What does it mean to age with HIV across the lifespan? How do co-morbidities, polypharmacy, long-term adherence to medications, mental health, neurocognitive impairment, stigma, discrimination, and fatigue factor into long-term survival? How do resilience and other mechanisms shift the narrative from surviving to thriving? What factors must be considered beyond viral suppression when assessing the quality of life? Each panelist will share their distinctive perspectives and experiences and will then open up the discussion to include audience members.</td>
<td><strong>Top Antivir Med.</strong> 2020;28(1):483.</td>
</tr>
<tr>
<td>3</td>
<td><strong>SHAPING VACCINES WITH DNA ORIGAMI</strong>&lt;br&gt;Mark Bathe, MIT, Cambridge, MA, USA</td>
<td>Viral-like structured DNA and RNA assemblies, also known as DNA and RNA origami, offer the ability to co-formulate gene-length single-stranded DNA or mRNA with CRISPR-RNPs, siRNAs, or ASOs, with the integration of active cellular targeting, stimulation, and uptake moieties including peptides, sugars, and small molecules. Biological stability and immunostimulation can additionally be programmed selectively through the use of chemical modifications. Scalable bacterial production of custom length and sequence single-stranded DNA offers a low-cost path towards clinical-scale production. Here, I will present our lab’s formulation and preclinical work in the context of the field, to produce preclinical scale, endotoxin-free structured DNA and RNA assemblies for targeted delivery of nucleic acid gene therapeutics and vaccines, including a case study of viral-like DNA assemblies applied to an HIV vaccine candidate.</td>
<td><strong>Top Antivir Med.</strong> 2020;28(1):483.</td>
</tr>
<tr>
<td>4</td>
<td><strong>CONCEPTS IN RESERVOIR MEASUREMENTS</strong>&lt;br&gt;Janet M. Siliciano, Johns Hopkins University School of Medicine, Baltimore, MD, USA</td>
<td>A stable latent reservoir for HIV-1 in resting CD4+ T cells precludes cure. Curative strategies targeting the reservoir are being tested and require accurate, scalable reservoir assays. The reservoir was originally defined with a quantitative viral outgrowth assays (QVOA) for cells releasing infectious virus following one round of T cell activation. This assay requires growing virus from individual latently infected cells and is costly and time consuming. Therefore, many studies have used DNA PCR to detect HIV-1 proviruses in infected cells or RT-PCR to detect the induction of viral RNA production from latently infected cells. However, two fundamental findings have altered how we view reservoir measurements. The first is that the vast majority of HIV-1 proviruses are defective due to the presence of large deletions and/or APOBEC-mediated hypermutation, as revealed by near-full genome viral sequencing. These defective proviruses cannot contribute to viral rebound and should not be considered part of the latent reservoir. Most PCR assays fail to distinguish intact and defective proviruses. Therefore, they dramatically overestimate reservoir size and should not be used. The second important finding is that not all intact proviruses are induced by a single round of in vitro T cells activation. Therefore, induction assays that measure viral outgrowth or viral RNA production after a single round of T cell activation will underestimate reservoir size. A conceptually novel approach to measuring the latent reservoir is to count all of the intact proviruses regardless of their transcriptional status at any particular time. This can be done with the intact proviral DNA assay (IPDA). More recently identified conceptual issues in reservoir measurement include the problem of clonal expansion. The reservoir is dominated by large clones of infected cells that wax and wane over time, and current measurements do not capture dynamic changes in reservoir composition. In addition, the relationship between the viruses that</td>
<td><strong>Top Antivir Med.</strong> 2020;28(1):483.</td>
</tr>
</tbody>
</table>
cause rebound following interruption of antiretroviral therapy and the viruses detected in various reservoir assays needs to be clarified. This talk will discuss these issues and summarize the current state of reservoir measurements.

5 CHARTING GENOME-WIDE INTEGRATION

Mary F. Kearney, National Cancer Institute, Frederick, MD, USA

The HIV replication cycle includes integration of the reverse-transcribed viral genome into the host cell DNA where the provirus is retained for the life of the cell. Cellular machinery is used for proviral genetic expression, however, by means that are not fully understood, some HIV proviruses can maintain a latent, or transcriptionally-silent, state. It is thought that cells expressing HIV are susceptible to cell killing by cytotoxic effects or immune responses. It stands to reason, therefore, that long-lived latently-infected cells may accumulate over the course of HIV infection and persist after ART is initiated. Indeed, many studies have demonstrated the persistence of latently-infected cells during ART and, it is believed that such cells carrying replication-competent proviruses, when activated, are the source of viral rebound when ART is interrupted. It was recently discovered that HIV infected T-cells can persist in vivo through cellular proliferation, which occurs both prior to and during ART. Several cases, thus far, have described highly expanded infected CD4+ T cell clones that were shown to be the source of persistent infectious viremia during ART. This talk will summarize emerging data from studies investigating HIV infected CD4+ T cell clones including their sites of HIV integration in blood and tissues both prior to and during ART, the fraction of HIV expressing cells within cell clones, including those carrying replication-competent proviruses, and explore new technologies for investigating HIV integration landscape and full-length proviral structures. Understanding the integration site landscape in cell clones that persist during ART will lead to a better understanding of the HIV reservoir, the nature of latency, and the sources of rebound viremia when ART is interrupted.

6 SINGLE-CELL EPIGENETICS: COLORING IMMUNE CELLS WITH A RICH PALETTE OF HISTONE MARKS

Alex J. Kuo, Stanford University, Stanford, CA, USA

Chromatin-based epigenetic mechanisms govern diverse cellular and organismal phenotypes without DNA base alterations. Post-translational modifications of histone proteins, often referred to as histone marks, directly modulate chromatin dynamics and genome organization, adding additional complexity and plasticity to the relatively static genetic code. The harmonious orchestration of chromatin regulators is essential for hematopoiesis and immune system development, effective immune responses against foreign substances and pathogens, and immune tolerance to prevent damage to host tissues. Previously, we have leveraged highly multiplexed single-cell mass cytometry to characterize global histone modification profiles of various immune cells in the human immune system. This powerful analytic platform, which we term “Epigenetic landscape profiling using cytometry by Time-Of-Flight (EpitoF)” facilitates the discovery of histone marks preferentially enriched in selected immune cells. We identify cell subtype- and hematopoietic lineage-specific epigenetic patterns, which predict immune cell identity. Differential analysis between younger and older adults reveals increased epigenetic variation between individuals, and elevated cell-to-cell epigenetic variability between single cells with age. Analysis of a twin cohort further shows that these aging-related epigenetic alterations are driven predominantly by non-heritable influences. Recently, we have demonstrated how EpitoF can be integrated with genomic methods to investigate chromatin dynamics (i.e. ChIP-seq, ATAC-seq), and combined with transcriptomic and functional analyses to gain a comprehensive understanding of how the immune system is regulated by chromatin-based mechanisms. Using this “systems epigenetics” approach, we have extensively characterized the biological significance of a histone mark involving histone H3 proteolytic cleavage in monocyte-to-macrophage differentiation. Our findings have marked implications for cellular fate determination, trained immunity, and human diseases with prominent monocyte and/or macrophage involvements. Together, EpitoF provides a unique opportunity to interrogate epigenetic regulation of the immune system. We propose that a systems epigenetics approach will i) reveal how acute and chronic viral infection alters the host chromatin landscape; ii) uncover chromatin-based mechanisms by which host immune cells develop an effective defense against viruses, and iii) provide insights into the variability of anti-viral response between single cells and between individuals.

7 PUTTING ANALYSIS INTO ANALYTICAL TREATMENT INTERRUPTIONS

Lu (Summer) Zheng, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Analytic treatment interruption (ATI) is an essential component for HIV clinical trials assessing efficacy of interventions aimed at achieving HIV remission or virological control in the absence of antiretroviral or other treatments. With recent experiences of evaluating a variety of novel therapeutic interventions, including latency-reversing agents, therapeutic vaccines, and broadly neutralizing antibodies utilizing ATI, the design of treatment interruption studies has evolved towards shorter durations with more frequent monitoring and time to viral rebound as primary outcome measure. This talk will review and discuss the current practices of ATI studies on analytical approaches, design features related to the mechanism of action of the agents being evaluated, including the selection of study outcomes, ART re-initiation criteria, using historical controls vs. placebo-controlled design, as well as ethical considerations.

8 ADVANCING FROM PHASE II TO PHASE III: NAVIGATING THE LAND OF EXPECTATIONS

Patrick Phillips, University of California San Francisco, San Francisco, CA, USA

Mycobacteria tuberculosis kills more people every year than any other single pathogen, yet the first-line treatment regimen used globally has remained largely unchanged for 40 years. Shorter, safer, and more effective regimens are urgently needed to halt the epidemic. Clinical trials for new drugs to treat HIV depend on changes in HIV viral load as an established marker of infection and treatment response. In contrast, while several new TB drugs are in clinical development, the absence of a reliable surrogate endpoint hampers decisions about whether and when a new TB regimen is ready for confirmatory phase III evaluation. Further challenges include the necessity of determining the optimal combination and duration of therapy during phase II development alongside the limited funding for TB drug development and the allure of accelerated approval. In this workshop, I will talk about the burden of expectations and the latest developments in designing phase II trials to identify the best regimens to advance to phase III. I will talk about platform and other adaptive treatment-selection trial designs, the novel phase IIC design, designs to identify the optimal duration of therapy and the role of an internal control. I will also touch on challenges in TB prevention trials in the absence of a true marker of infection.

9 NONINEFIRIORITY COMPLEX

Jeffrey Murray, FDA, Silver Spring, MD, USA

In general, active-controlled noninferiority (NI) trials are considered when superiority trials, to an active control or placebo, are not possible due to ethical or other considerations. NI trials share some of the same biases as historically controlled trials because they rely on information external to the clinical trial. Food and Drug Administration (FDA) guidance states that NI designs are credible and appropriate only in situations in which the active control has shown a consistent effect (generally compared to placebo) in prior superiority trials conducted in a patient population similar to the population in the clinical investigation being planned. This is called the constancy assumption and allows for assay sensitivity in an NI trial. NI is met if the new intervention is ‘not unacceptably worse’ than the active control by a specified amount, the NI margin. The NI margin should be no larger than the effect the active control had in previous trials. Unless a placebo group is also included, NI trials depend on the assumption that the active control had its expected effect in the trial. From a regulatory perspective knowing the active control had its expected effect is necessary to ensure that a trial that concludes NI has identified a treatment that is superior to placebo. HIV treatment trials have successfully used NI trials for antiretroviral (ARV) drug development for many years; however, quantifying the treatment effect of each component of an ARV regimen has been challenging as drug regimens evolve, which can have consequences when designing an NI trial. HIV prevention research also illustrates the limitations of NI trial designs. Although collective data show that emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) can be highly efficacious at preventing HIV infection when taken as prescribed in uninfected individuals, the prophylactic effect has been highly variable over time and by population. Two trials that included FTC/TDF arms in cisgender women in Africa showed a lack of pre-exposure prophylaxis (PrEP) efficacy due to poor adherence. The lack of a consistent PrEP effect across trials in all populations invalidates a constancy assumption of FTC/TDF as an active control in an NI trial for some populations. Other types of trial designs using
10 INCLUSION OF DIVERSE POPULATIONS IN TRIALS
Mark Harrington, Treatment Action Group, New York, NY, USA
The unprecedented nature of AIDS as a syndrome and a pandemic created unprecedented demands on clinical trials investigators and networks to creatively and meaningfully address the syndromic nature of AIDS, the complex etiology and pathogenesis of HIV infection, its associated opportunistic infections, coinfections, and malignant, end-organ, and neurologic sequelae, in diverse affected populations including men who have sex with men, drug users, sex workers, young people, infants, children, adolescents, pregnant women, and people grappling with multiple syndemics (opioids, viral hepatitis, sexually transmitted infections), social and structural barriers to research, prevention, treatment, access, care, and support. Traditional models of infectious disease clinical research needed to be adapted to the complex disease settings and diverse populations which made studying HIV and its complications more challenging than studies of a single drug for a single infectious agent. In this talk I will review 1) contributions made by activists, people living with HIV, and their communities to restructure and reform clinical trial designs to make them more relevant, ethical and efficient in the early days of clinical HIV research, including by expanding eligible trial populations and changing trial designs to make them more flexible, inclusive, and adapted to the real needs of people living with HIV; 2) the impact of broadened inclusion criteria and community priorities on HIV clinical research in the discovery of highly effective combination therapy (cART), pre-exposure prophylaxis (PrEP), and defining the optimal time to begin cART in all people living with HIV; and 3) current challenges and opportunities facing trial designers and networks in selected key high priority populations including those co-infected with HIV and Mycobacterium tuberculosis and those at risk for those infections in current and upcoming multi-modality prevention and treatment trials in selected diverse populations. I will close with some observations about the impact of diverse community engagement and participation in all aspects of the clinical trial process.

11 WHEN AT THIRD YOU DON'T SUCCEED
David L. Wyles, Denver Health and Hospital Authority, Denver, CO, USA
Current HCV direct acting antiviral (DAA) regimens are highly efficacious; including in populations previously recognized to have poor responses to interferon-based therapies (e.g. HIV co-infection, cirrhosis etc.). However, as DAAs are used in a greater number of patients in clinical practice, scenarios which have not been adequately addressed in clinical trials, or are impractical to study, will invariably arise. The approach to management of HCV treatment interruptions of varying durations at different times during therapy and retreatment for multiple DAA regimen failures are examples of such scenarios. In this interactive session, cases will be used to highlight clinical conundrums focusing on:
• Determination or HCV relapse versus reinfection
• Multiple DAA regimen failure retreatment
• Approach to treatment interruptions during DAA therapy

While FDA approved options for retreatment exist for initial DAAs regimen failure, robust data are lacking for patients failing multiple DAA regimens and retreatment approaches are not standardized. Inferences from studies in other HCV scenarios can provide insight into reasonable re-treatment approaches which generally rely on extension of therapy with addition of other drug classes and ribavirin when possible. In situations where no data exists—such as evidence of viral genomes and the lentiviral Vif proteins that antagonize APOBEC3 activity. Study of the functional and evolutionary relationships between APOBEC3 proteins in primates and Vif proteins that antagonize APOBEC3 activity.

12 “A” CASE TO REMEMBER: HEPATITIS A - MANAGING AN OLD VIRUS IN NEW POPULATIONS AT RISK
Darcy Wooten, University of California San Diego, San Diego, CA, USA
This session will use a case-based approach with audience response questions to review important updates in epidemiological risk factors for hepatitis A virus (HAV) infection, unusual presentations and complications that occur with HAV, and strategies for prevention.

13 Hepatocellular Carcinoma
Susanna Naggie, Duke University, Durham, NC, USA
Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death globally. Viral hepatitis, specifically hepatitis B and hepatitis C infections are a major cause of HCC. Antiviral therapies for both HBV and HCV infection can decrease the risk of HCC. This presentation will focus on the contribution of HCC to global liver-related mortality and the impact of antiviral therapies on the incidence of HCC. This presentation will discuss the emerging data on the impact of direct-acting antivirals (DAAs) on HCC incidence and recurrence and on the role of DAA therapies in patients diagnosed with HCC. In particular, the presentation will discuss in detail (1) the evidence supporting the safety of DAA therapies in patients with cirrhosis as it relates to risk of HCC development, (2) the optimal timing for initiating DAA therapy in patients who have been diagnosed with HCC and will discuss the impact, if any, of HCC diagnosis on response to DAA therapy, and (3) the impact of SVR on HCC incidence. Lastly, the presentation will discuss monitoring for HCC after SVR in patients with HCC and will highlight emerging non-invasive biomarkers that may be utilized after DAA HCV cure to improve risk stratification. When possible the presentation will discuss differences in HCC presentation and outcome in people with HIV and viral hepatitis.

14 NONALCOHOLIC STEATOHEPATITIS
Kathleen E. Corey, Massachusetts General Hospital, Boston, MA, USA
Non-alcoholic fatty liver disease (NAFLD) impacts affecting 25% of adults worldwide. NAFLD is a spectrum of pathology including steatosis and non-alcoholic steatohepatitis (NASH), the progressive form of NASH which can lead to fibrosis development, cirrhosis, end-stage liver disease, and hepatocellular carcinoma. NASH cirrhosis is the second leading indication for liver transplantation in the United States. In addition, NAFLD is strongly associated with the metabolic syndrome and obesity and is an independent risk factor for cardiovascular disease (CVD) and CVD-related death. In persons with HIV (PWH) liver disease is a significant cause of mortality. With the high prevalence of diabetes and metabolic disease in PWH, NAFLD and NASH are being increasingly diagnosed. This talk will present strategies for the risk factors for and diagnosis and management of NAFLD in PWH.

15 THE ANCIENT AND MODERN ORIGINS OF HIV
Michael Emerman, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
How did HIV-1 become a human pathogen? In this talk, I will trace the origins of HIV-1 through the cross-species transmissions and viral adaptations that preceded its emergence in humans. The immediate precursor of HIV-1 is a virus that infects chimpanzees, Simian Immunodeficiency Virus of Chimpanzees (SIVcpz). SIVcpz is itself derived from other SIV lineages that infect old world monkeys. Cross-species transmission events require mutations to the viral genome that allow adaptation to replicate in a new host. Much of this adaptation involves gaining the ability to counteract or evade a repertoire of antiviral genes, called restriction factors. The selective pressure between host restriction factors and the viral proteins that antagonize these factors sets up an “arms-race” that can be read out in the rapid evolution of the two proteins. The example of such restriction factors and viral antagonists that I will describe in the most detail is that of the primate APOBEC3 proteins that hypermutate viral genomes and the lentiviral Vif proteins that antagonize APOBEC3 activity. Study of the functional and evolutionary relationships between APOBEC3 proteins in primates and Vif proteins in primate lentiviruses allow us to make inferences about how long lentiviruses have been present in primates and about the steps that occurred for a lentivirus in monkeys to adapt to replicate first in chimpanzees, and then in humans. This talk will also highlight the role that basic science can play in ending the current HIV-1 pandemic.

16 TRANSLATING HIV SCIENCE INTO POPULATION IMPACT: A REALITY CHECK FROM THE FRONTLINE
Alex G. Coutinho, Partners in Health, Kigali, Rwanda
Over the past 20 years, tremendous strides have been achieved in the response to HIV/AIDS, especially in the incredible scale-up of life-saving ART to over 25 million people globally, most of them in Africa. This heroic achievement has resulted in an estimated 56% reduction in mortality since 2004 and as a consequence led to an increasing life expectancy and a marked drop in HIV/ AIDS orphans — all of which are significant population impacts. However, the expected reductions in new infections have only been achieved modestly with an estimated reduction of HIV incidence of 16% in the 10 years since 2010. This is in part due to the challenge of translating scientifically proven HIV prevention interventions like ART, PrMTCT, and VMMC and PrEP into an environment that
has many obstacles and challenges that include funding constraints, struggling health systems, disempowered communities and structural barriers. In particular, HIV prevention faces the challenge of promoting approaches like condoms that often face opposition from some politicians, cultural leaders, and religious leaders. Other approaches like VMMC and PrEP face both opposition and skepticism, on the grounds that there are fears that individuals using these partially effective approaches will exhibit a rebound increase in risky sexual behaviors that will lead to new HIV infections. In addition, many of the target populations that are at greatest risk for HIV infection are also the groups that are the hardest to reach because they are considered illegal, are harassed and discriminated and often live and operate underground to avoid scrutiny. However, there are several excellent examples of effective scale-up of scientifically proven interventions and population impact, as well as a few examples of large scale combination HIV treatment/prevention interventions that have reduced HIV incidence at a population level. These examples provide hope and a template to use when planning to scale up new technologies like PrEP, as well as scaling up the use of older technologies like condoms. However for this to be successful at the frontline it will require scientists and politicians and communities and frontline implementers to sit down together, listen to each other, understand the science AND the realities of people's lives and the systems that support them, and come up with scientifically sound and pragmatic approaches to scale up services, impact populations and measure progress. The history of HIV has many lessons for us as we look into the future. Science, even brilliant science, will not end the HIV epidemic without collaboration and synergy with a wide range of other actors, strategies and full involvement of infected and affected communities.

17 HIV CURE FROM BENCH TO BEDSIDE
Sharon R. Lewin, University of Melbourne, Melbourne, Australia

Despite the great success of antiviral therapy (ART), treatment is life long for the majority of people living with HIV (PLWH). Antiviral treatment is simple and relatively cheap and close to 60% of PLWH have access to treatment. However, ART is still not available or secure for many, drug resistance is common globally and there are emerging toxicities from some of the most potent antivirals. Modelling studies of the cost and impact of a cure have identified that the need for frequent follow up and viral load testing after cessation of ART, unpredictable viral rebound and lack of protection from re-infection will all reduce the impact of a cure at a population level. Therefore there is now an increasing focus in the field to achieve a true cure and not HIV remission. Understanding where and how virus persists is key to the development of novel interventions to achieve a cure. Recent work has identified the significant contribution of proliferation of infected cells to HIV persistence on ART. Understanding the drivers of proliferation and clonal expansion remains a key unanswered question. In addition, multiple factors including the site of integration can influence the transcriptional activity of a virus and a deeper state of latency may reduce the chance of viral rebound off ART. Finally, the majority of viruses that persist on ART are defective and unable to replicate. A cure may therefore occur with loss of intact virus but persistency of all defective forms. New high throughput assays can now quantify intact and defective viruses more accurately and positive emission tomography and imaging can potentially identify tissue reservoirs of virus persistence. Multiple strategies to achieve a cure are being evaluated in both animal models and human clinical trials including combination immunotherapy to reduce the viral burden and enhance immune clearance. Results from recent clinical trials of newer latency reversing agents, immune checkpoint blockade and other immune adjuvants, broadly neutralising antibodies and gene therapy will be discussed. It is likely that in the next few years long acting and implantable antiretrovirals will be available and these newer modalities may address many of the current challenges of ART. Therefore, ongoing consultation is needed with PLWH and all other stakeholders to develop an acceptable target product profile for a cure that will have the greatest personal and population impact and can be implemented at scale.

18 UNIVERSAL TEST AND TREAT (UTT): LESSONS FROM THE PAST AND FOR THE FUTURE
Kevin M. De Cock, US CDC Nairobi, Nairobi, Kenya

This presentation discusses the four recently completed community randomized trials of “Universal Test and Treat” (UTT) in East and southern Africa and their implications. Three themes developed in parallel and led to these ambitious implementation studies: recognition of the centrality of viral load for HIV pathogenesis and HIV transmission; studies showing >90% effectiveness of “treatment for prevention”; and evolution of antiretroviral treatment guidelines that since 2015 recommend immediate treatment of all persons living with HIV. Mathematical modeling in 2008 suggested UTT, with repeated and regular HIV testing, could eliminate HIV in an epidemic of South African severity (Granich et al, Lancet, 2009). Political advocacy highlighted the concept of “Ending AIDS” while scientific debate culminated in four community randomized trials aiming to assess UTT with HIV incidence as the primary outcome in Botswana (BCPP), Kenya and Uganda (SEARCH); South Africa (TASP); and South Africa and Zambia (PopART), from 2012-2018. Primary results of the four trials were published in Lancet HIV (TASP; 2018) and NEJM (2019) and additional analyses, including on cost-effectiveness, are underway. All four trials achieved >90% knowledge of HIV serostatus but TASP yielded low linkage to treatment. The other three trials met the UNAIDS 90:90:90 targets, achieving 74–88% population-level viral suppression. Treatment guidelines changed over the studies’ course, resulting in some erosion of differences between intervention and control communities. BCP and one of PopART’s two intervention arms showed 30% reduction in HIV incidence compared to control communities, while no significant differences were found in the other studies. Despite the successful achievement of 90:90:90 targets, HIV incidence in intervention communities (6-22.3/1000/year) remained well above an arbitrary definition of HIV elimination of <1/1000/year. Knowledge of HIV serostatus and early treatment are essential for individual and public health, but UTT alone will not lead to HIV elimination. Priorities include expansion in scale and scope of HIV testing to reduce the diagnostic and treatment gap in generalized epidemic settings; addressing needs of key and underserved populations (including youth and men), and scale-up of highly effective interventions such as voluntary medical male circumcision and PrEP. Greater focus on measuring HIV incidence and mortality is required to better understand epidemic trends in the face of combinations of preventive interventions.

19 MECHANISMS OF PSGL-1 AND CD43 RESTRICTION OF HIV INFECTION OF CD4 T CELLS
Yajing Fu1, Yuntao Wu2, Sijia He3, Abdul A. Waheed4, Deemah Dabbagh5, Hong Shang1, David N Levy6, Eric O. Freed7
1George Mason University, Fairfax, VA, USA, 2NIH, Frederick, MD, USA, 3‘China Medical University, Shenyang, China, 4New York University College of Dentistry, New York, NY, USA, 5National Cancer Institute, Frederick, MD, USA

Background: PSGL-1 (P-selectin glycoprotein ligand-1) and CD43 are surface glycoproteins that are expressed on blood CD4 T cells to bind to selectins for T cell tethering, rolling, and migration into inflamed tissues. PSGL-1 is primarily expressed on the surface of lymphoid and myeloid cells and is up-regulated during inflammation to mediate leukocyte tethering and rolling on the surface of the endothelium for migration into inflamed tissues. Recently, PSGL-1 has also been identified as an INF-γ-regulated anti-HIV-1 restriction factor that inactivates virion infectivity. However, the mechanisms of PSGL-1-mediated anti-HIV activity remain to be elucidated.

Methods: We studied PSGL-1 and CD43 restriction of HIV-1 virion infectivity by co-expression of PSGL-1 or CD43 DNA with HIV-1 DNA in virion producer cells, and then quantified virus infectivity in an HIV Rev-dependent GFP indicator cell. We also studied virion incorporation of PSGL-1 by gradient ultracentrifugation and western blot detection of PSGL-1 in virion particles. In addition, we examined virion proteins of PSGL-1 imprinted particles. We also performed mapping studies to identify functional domains of PSGL-1 necessary for blocking virion infectivity. Furthermore, we performed HIV-1 entry and attachment assays to study the interaction of PSGL-1 imprinted virion particles with target cells.

Results: We found that the expression of PSGL-1 in virus-producing cells inhibits virion infectivity by inhibiting virion attachment to target cells. Mapping studies show that the extracellular, N-terminal domain of PSGL-1 is necessary for its anti-HIV-1 activity, and the PSGL-1 cytoplasmic tail contributes to inhibition. In addition, we demonstrate that the PSGL-1 related monomeric E-selectin binding glycoprotein CD43 also effectively blocks HIV-1 infectivity. HIV-1 infection, or expression of either Vpu or Nef, downregulates PSGL-1 from the cell surface; expression of Vpu appears to be primarily responsible for enabling the virus to partially escape PSGL-1-mediated restriction. Finally,
we found that PSGL-1 inhibits the infectivity of other viruses such as murine leukemia virus and influenza A virus.

**Conclusion:** These findings demonstrate that PSGL-1 is a broad-spectrum antiviral host factor with a novel mechanism of action. Further elucidation of PSGL-1 and CD43 interaction with HIV-1 and other viruses may offer new therapeutic strategies for targeting viral infections.

**20 STRUCTURAL ANALYSES OF A BOUND ANTI-CD4 ADNECTIN INHIBITOR OF HIV-1**

David Wensel1, Shawn Williams2, David P. Dixon3, Paris Ward4, Patti McCormick5, Nestor Concha6, Eugene Stewart7, Xuan Hong8, Shreya Pal9, Charles Maxxucco10, Bo Ding11, Mark Krystal12

1ViiV Healthcare, Branford, CT, USA, 2GlaxoSmithKline, Collegeville, PA, USA, 3GlucoSmithKline, Collegeville, PA, USA, 4GlucoSmithKline, Uxbridge, UK

**Background:** GSK3732394 is a multi-specific biologic inhibitor of HIV entry currently under clinical evaluation. A key component of this molecule is an Adnectin that binds to CD4 and inhibits downstream actions of gp120. Studies were performed to help elucidate the binding site of the Adnectin on CD4 and understand the mechanism of inhibition.

**Methods:** Hydrogen-deuterium exchange mass spectrometry (HDX) was used to examine comparative deuteration rates of amide backbone protons of CD4, either in the absence or presence of saturating amounts of Adnectin. In addition, crystal structures of CD4 bound to both the Adnectin and a Fab subunit of ibalizumab were solved at a 3.7Å resolution. Cryo-EM studies of Adnectin bound to soluble CD4 were also generated. Finally, mutagenic analyses on CD4 were performed to confirm and extend these findings.

**Results:** Using HDX, CD4 peptides at the N-terminus of D2 and in D3 showed differential rates of deuteration (both enhanced and slowed) in the presence of the Adnectin that mapped predominantly to the D2-D3 interface. The structure of the ibalizumab Fab/CD4 D1-D4/Adnectin complex revealed an extensive interface between the Adnectin and residues on CD4 domains D2-D4 that stabilize a novel T-shaped CD4 conformation. A cryo-EM map of the gp140/CD4/combineCT complex clearly shows the bent conformation for CD4 while bound to gp140. Mutagenic analyses on CD4 confirmed that amino acid F202 forms a critical determinant of the specificity for binding to human CD4 protein over related primate CD4 molecules. Mutation of L151 to R (the residue present in cynomolgus monkey CD4) abrogated Adnectin binding to human CD4, while the reverse mutation (R151L) restored binding to cynomolgus monkey CD4.

**Conclusion:** The significant conformational change of CD4 upon Adnectin binding brings the D1 domain of CD4 in proximity to the host cell membrane surface and provides a potential explanation for the ability of the CD4-bound Adnectin to inhibit HIV-1 infection. In addition, mutations of D2-D3-interface residues, specifically F202 and L151, dramatically impacted Adnectin binding to human and primate CD4, providing a rationale for the observed species specificity of the Adnectin.

**21LB SERINC3/S PERTURB HIV MEMBRANE FUSION POST-HEMIFUSION AT FUSION-PORE DILATION STEPS**

Amanda E. Ward1, Volker Kiesling1, Judith M. White1, Owen Pornillos2, Babie K. Ganser-Pornillos1, Lukas K. Tam1

1University of Virginia, Charlottesville, VA, USA

**Background:** Serinc3 and Serinc5 are recently described host restriction factors that in the absence of Nef, can block HIV infection by incorporating into budding viral particles and decreasing their ability to infect subsequent cells. Serincs are thought to block the very earliest stages of infection, membrane fusion and cell entry, by an incompletely understood mechanism.

**Methods:** We used giant plasma membrane vesicles (blebs) as model target membranes to study ‘wildtype’ and Serinc-disrupted HIV membrane fusion at a single-particle level with cryoElectron Tomography and Total Internal Reflection Fluorescence (TIRF) microscopy.

**Results:** Using fluorescent reporters of membrane and content mixing, we observed that Serinc3 and Serinc5 do not cause a defect in mixing of the outer lipid leaflets (hemifusion), but a pronounced defect in fusion pore opening. Additionally, cryo-electron tomography of HIV pseudoviruses mixed with blebs showed rearrangements of viral and target membranes and proteins at multiple intermediates steps of HIV membrane fusion. We found that Serinc3 and Serinc5 increased the number of hemifusion and early fusion product events and that many of the fusion products are cinched between former virus and bleb.

**Conclusion:** These results suggest that Serinc3 and Serinc5 create bottlenecks in the process of membrane fusion; a first bottleneck after hemifusion and an additional bottleneck that prevents full fusion pore dilation such that the viral capsid cannot pass into the cytosol. Understanding how Serincs disrupt HIV membrane fusion will clarify the requirements for normal HIV membrane fusion and potentially identify new viral weaknesses that could become drug targets.

**22 CRISPR-INDUCED MUTAGENESIS POINTS TOWARD A ROLE OF TRN-SR2 IN HIV NUCLEAR IMPORT**

Frauke Christ1, Julie Janssens2, Flore De Wit3, Joël Blokken4, Youlai Lampi5, Irena Zurnic6, Rick Gijssbers7, Zeger Debyser8

1Katholieke University Leuven, Leuven, Belgium

**Background:** In order to infect non-dividing cells, HIV needs to cross the nuclear envelope. In 2010 we reported the identification of the importin TRN-SR2 (TNPO3) as the determining host factor for nuclear import. While the importance of TRN-SR2 for HIV nuclear import is generally accepted, the detailed mechanism and role of TRN-SR2 remains under debate. According to one model the direct interaction of TRN-SR2 with HIV integrase drives nuclear import of the pre-integration complex (PIC), alternatively TRN-SR2 may play an indirect role linked to uncoupling of the PIC and the protein CPSF6.

**Methods:** We have designed CRISPR-Cas9 guide RNAs targeting exon 2 and 8 of TNPO3 in HeLaP4 cells. After selection of clones with reduced TRN-SR2 expression on both mRNA (QPCR) and protein expression levels (western blotting), a detailed analysis of HIV replication and PIC nuclear import was performed.

**Results:** CRISPR-Cas9 induced DNA breaks in TNPO3 using guide 2 and 8 failed to generate complete knockout clones but instead allowed for selection of 2 HeLaP4 clones with a single allelic KO, resulting in 2-fold reduced TRN-SR2 levels (clone #20 and #25). Nevertheless, HIV single round and multiple round replication was severely hampered in clone #20 and #25. Interestingly genome sequencing of TNPO3 revealed that the remaining allele showed small in-frame deletions resulting in deletion of AA (V103 and 373LHAL376). We then analyzed the PIC nuclear import in the respective cell lines by QPCR and fluorescent imaging of eGFP-IN labeled PICs. Both techniques evidenced a strong defect in nuclear import. Recombinant TRN-SR2 deletion mutants demonstrated an impairment of the molecular interaction with HIV-integrase.

**Conclusion:** CRISPR-Cas9 targeting two different exons of TNPO3 failed to generate KO cell lines indicating that a full KO of TRN-SR2 might be toxic for HeLaP4. Yet, CRISPR-Cas9 unexpectedly led to mutagenesis. The resulting clones were fully viable but failed to support HIV replication. The block of replication was pinpointed to nuclear import and the corresponding recombinant mutant TRN-SR2 was impaired for interaction with HIV-IN. The presented data support the notion that TRN-SR2 is a genuine co-factor of HIV replication and interacts differently with HIV-IN than with its cellular cargoes.

**23 NUCLEAR UNCOATING OF HIV-1 OCCURS NEAR SITES OF INTEGRATION**

Ryan C. Burdick1, Chenglei Li2, Mohamed Husen Munshi3, Jonathan Rawson4, Kunio Nagashima5, Wei-Shau Hu6, Vinay K. Pathak7

1National Cancer Institute, Frederick, MD, USA, 2Leidos Biomedical Research, Inc, Frederick, MD, USA

**Background:** A critical step in HIV-1 replication is the disassembly (uncoating) of the viral core. Remarkably, the timing and intracellular location of HIV-1 uncoating remain unknown. Studies of HIV-1 uncoating have been hampered by an inability to accurately quantify capsid protein (CA) loss from the viral complexes and by an inability to identify rare infectious viral complexes (~1/50) in infected cells.

**Methods:** We developed methods to label CA with GFP (GFP-CA) in infectious viral complexes and to identify transcriptionally-active proviruses in live-cell imaging assays. We analyzed the dynamics of viral complex association with nuclear envelope and nuclear uncoating, and identified rare viral complexes that integrate to form transcriptionally active proviruses.

**Results:** Using live-cell imaging, we observed >10 GFP-CA labeled infectious viral complexes that integrated and expressed HIV-1 RNA and the gfp reporter gene. The infectious viral complexes maintained steady GFP-CA fluorescence signals for several hours after nuclear import followed by abrupt (~20 min) GFP-CA loss ~ 10.5 hours after infection, signifying nuclear uncoating. HIV-1 transcription sites appeared near the sites of nuclear uncoating, indicating
that uncoating occurs at or very close to the site of integration. Similar GFP-CA fluorescence intensities of viral nuclear virions and viral cores in vitro suggest that viral cores in the nucleus retain >90% of the CA and that nuclear uncoating is the major uncoating event. The nuclear GFP-CA-labeled viral complexes rapidly disassembled after treatment of the infected cells with capsid inhibitor PF74 indicating that the nuclear viral complexes retained CA hexamers. Time-of-addition assays with PF74, nevirapine, and raltegravir indicate that nuclear uncoating occurs ∼3 hrs after the completion of reverse transcription and ∼1 hr before integration. We probed the potential mechanism by which viral cores enter the nucleus and found that cleavage and polyadenylation specificity factor 6 (CPSF6), a host nuclear protein that binds to CA, influences the intracellular location of uncoating and facilitates the nuclear import of intact or nearly intact viral cores.

**Conclusion:** Intact or nearly intact viral cores of infectious viral complexes that retain >90% of their CA enter the nucleus and uncoat near their genomic integration sites just before integration.

### 24LB RECONSTITUTION OF HIV-1 CAPSID-DEPENDENT REPLICATION AND INTEGRATION IN VITRO

Devin E. Christensen¹, Barbie K. Ganser-Pornillos², Owen Pornillos², Wesley I. Sundquist³

¹University of Utah, Salt Lake City, UT, USA, ²University of Virginia, Charlottesville, VA, USA

**Background:** To initiate an infection, the HIV-1 genome must be reverse transcribed and integrated into the DNA of the host cell. Despite progress in characterizing and inhibiting these viral processes, detailed mechanistic and structural studies remain challenging because they are executed by individual preintegration complexes deep within cells.

**Methods:** To address these limitations, we have reconstituted the early stages of HIV-1 replication in a cell-free system. Starting with purified virions, membrane permeabilization, capsid stabilization, and dNTPs were used to release viral cores and initiate the process of reverse transcription. Cell-free extracts were used to facilitate efficient integration into a target plasmid. Quantitative PCR (qPCR) was used to monitor three different stages of reverse transcription (Strong Stop, First Strand Transfer, and Late RT). Integration was assayed using three different approaches: 1) a two-step PCR system designed to amplify HIV-1 integration sites coupled with qPCR, 2) deep sequencing of PCR-amplified integration sites, and 3) cloning and sequencing of target plasmids to test for concerted HIV-1 integration.

**Results:** HIV-1 core particles released from permeabilized virions supported highly efficient, capsid-dependent endogenous reverse transcription to produce ~0.8 double-stranded DNA genomes/core. Conected integration of the transcribed viral genome into a target plasmid then proceeded in a cell extract-dependent reaction. Controls established that, as expected, reverse transcription and integration required active RT and IN enzymes. Efficient viral replication required a stable capsid as assayed by CA mutagenesis and transcription and integration required active RT and IN enzymes. Efficient viral replication depended on viral core integrity as assessed by CA mutagenesis.

**Conclusion:** Time-of-addition assays with PF74, nevirapine, and raltegravir indicate that uncoating is the major uncoating event. The nuclear GFP-CA-labeled viral complexes rapidly disassembled after treatment of the infected cells with capsid inhibitor PF74 indicating that the nuclear viral complexes retained CA hexamers. Time-of-addition assays with PF74, nevirapine, and raltegravir indicate that nuclear uncoating occurs ∼3 hrs after the completion of reverse transcription and ∼1 hr before integration. We probed the potential mechanism by which viral cores enter the nucleus and found that cleavage and polyadenylation specificity factor 6 (CPSF6), a host nuclear protein that binds to CA, influences the intracellular location of uncoating and facilitates the nuclear import of intact or nearly intact viral cores.

**Conclusion:** Intact or nearly intact viral cores of infectious viral complexes that retain >90% of their CA enter the nucleus and uncoat near their genomic integration sites just before integration.

### 25 STRUCTURAL BASIS OF SECOND-GENERATION HIV INTEGRASE INHIBITOR ACTION AND VIRUS ESCAPE

Nicola Cook¹, Wen Li¹, Dénes Berta¹, Magd Badaoui², Allison Ballandras-Colas¹, Andrea Nans¹, Abhaya Kotecha¹, Edina Rosta¹, Alan N. Engelman³, Peter Cherepanov³

¹The Francis Crick Institute, London, UK, ²Dana–Farber Cancer Institute, Boston, MA, USA, ³King’s College Hospital, London, UK

**Background:** During integration, a multimer of integrase (IN) assembles on viral DNA ends, forming a highly stable nucleoprotein complex termed the intasome. The HIV IN strand transfer inhibitors (INSTIs) specifically target the IN active site engaged with the viral DNA end, in the context of the intasome. Previously, we adopted the intasome from the prototype foamy virus (PFV), which is amenable to X-ray crystallography, to study INSTI binding. However, scarce amino sequence identity with HIV-1 IN outside of the active site greatly limits the use of this highly tractable system in studies of drug resistance. For the same reason, the PFV structures are not ideal templates for optimization of the clinical INSTIs.

**Methods:** To derive a robust model suited to informing INSTI development, we characterized IN proteins from a wide range of simian immunodeficiency viruses (SIVs). We discovered that IN from SIVrcm, which shares a recent common ancestor and 75% amino acid IN sequence identity with HIV-1, readily forms functional nucleoprotein complexes with viral DNA in vitro. Moreover, virus rescued from the available sequence information was highly susceptible to the first and second-generation INSTIs. We used single-particle cryo-electron microscopy to visualize at near atomic resolution the advanced clinical INSTIs dolutegravir and bictegravir bound to the SIVrcm intasome.

**Results:** We showed that the expanded second-generation INSTI scaffolds span the active site, making critical stabilizing contacts with its boundary defined by the IN β4-α2 connector element. The Q148H/G140S mutations that pervade clinical INSTI failure perturb optimal magnesium ion coordination in the intasome active site. The expanded chemical scaffolds of the second-generation drugs mediate novel interactions with the protein backbone, which are critical for antagonising Q148H/G140S mutant virus.

**Conclusion:** Our results reveal that binding to magnesium ions underpins a fundamental weakness of the INSTI pharmacophore that is exploited by the virus and provide structural framework for the development of this important class of anti-HIV/AIDS therapeutics.

### 26 THE CHROMATIN LANDSCAPE AT THE HIV-1 INTEGRATION SITE DETERMINES VIRAL EXPRESSION

Gerlinde Vansant¹, Julie Janssens¹, Heng-Chang Chen¹, Eduard Zorita¹, Frauke Christ¹, Guillaume Fillion¹, Zeger Debyser¹

¹Katholieke University Leuven, Leuven, Belgium

**Background:** Since the HIV provirus persists lifelong in memory cells of the immune system but rebounds upon treatment interruption, the latent reservoir is the main target for HIV cure. One of the least studied determinants of latency is the impact of integration site selection on HIV expression. HIV integration is catalyzed by integrase that uses the host chromatin reader LEDGF/p75 to target integration to active genes. We previously showed that inhibition of the LEDGF/p75-IN interaction by LEDGInns retargets residual integration out of active genes. Moreover, these proviruses were more often in a latent state and refractory to reactivation. These results suggested a direct link between HIV-1 integration and transcription.

**Methods:** We now studied the underlying mechanism with two advanced technologies. (1) Barcoded HIV (B-HIVE) tags the HIV genome with a unique barcode that allows to determine insert-specific HIV-1 expression by simultaneously tracking the barcode in the DNA and RNA of infected cells. (2) Branchanded (bDNA) imaging was used to visualize the effect of LEDGInns at the single cell level. bDNA is a signal amplification method for Fluorescent In Situ Hybridization (FISH) that enables simultaneous detection of viral DNA and mRNA.

**Results:** B-HIVE confirmed that LEDGInn treatment retargets integration out of gene-dense regions. LEDGInns increased the distance to H3K36me3 (recognized by LEDGF/p75). Viral RNA expression per DNA barcode was reduced while the proportion of silent proviruses increased. Yet, at high concentrations of LEDGInns some rare residual proviruses with high RNA expression were detected. The silent proviruses after LEDGInn treatment were located further away from epigenetic marks associated with active transcription. Interestingly, while the distance to H3K36me3 changed after treatment, proximity to (super)enhancers stimulated transcription independently of LEDGF/p75. bDNA imaging of SupT1 cells infected with HIV-1 in the presence of LEDGInns showed a dose-dependent reduction in both DNA spots and RNA expression. The DNA spots obtained after treatment with LEDGInns were located at increased distance from the nuclear rim. Finally, LEDGInns hampered reactivation upon stimulation with TNFα 10 days post infection.

**Conclusion:** Our studies reveal how the direct link between integration site selection and transcriptional status of the provirus is mediated by the epigenetic landscape surrounding the integration site. The results support block-and-lock strategies to cure HIV infection.

### 27 SINGLE-CELL GENOMIC ANALYSIS OF BLOOD AND CSF CELLS IN HIV-1 AND HIV–ADULTS

Shelli Farhadian¹, Ofir Lindenbaum¹, Jun Zhao¹, Rolando Garcia-Milan¹, Jennifer Chiarella¹, Michelle Chiantanaphol¹, Rachela Calvi¹, Yujal Kluger¹, Serena S. Spudich¹

¹Yale University, New Haven, CT, USA
28 GREATER BURDEN OF INTRACRANIAL ARTERIAL-WALL ENHANCEMENT IN PERSONS LIVING WITH HIV

Felicia C. Chow1, Andrew Callen, Victor Arechiga, David Saloner, Jared Narvid, Priscilla Hsue

1University of California San Francisco, San Francisco, CA, USA

Background: The biology driving central nervous system T cell dysregulation in people with HIV (PWH) during antiretroviral therapy (ART) remain incompletely understood. Single cell RNAseq allows high resolution characterization of immune cells, including T cells contained in cerebrospinal fluid (CSF) and blood. We applied distinct approaches to the computational analysis of scRNAseq of T cells to identify genes distinguishing treated-HIV from the HIV-negative state.

Methods: scRNA seq was performed on CSF cells and peripheral blood mononuclear cells (PBMC) from PWH on ART (plasma HIV RNA <20 cps/mL for > 1 yr, n=5) and HIV- individuals (n=4). With each fluid, to compare T cell transcripts differentiating ART-suppressed HIV from the HIV- state we applied: 1. Standard differential expression, using the Seurat FindMarkers function, based on the Wilcoxon rank sum test; and 2. Feature selection, using logistic least absolute shrinkage (LASSO), a machine learning approach to identify genes whose variable expression is most predictive of disease state.

Results: Single cell transcriptomes were analyzed from 31,175 CSF cells and 35,694 PBMC. CSF cells comprised of T cells (93%), B cells (0.5%), Monocytes (3%), Dendritic cells (1.9%), and NK cells (1.7%); PBMC subset frequencies did not differ between PWH and HIV-.

Differential expression analysis identified 64 and 128 genes that were differentially expressed between PWH and HIV-, in CSF and blood T cells, respectively, with 33 genes that were differentially expressed in both blood and CSF T cells based on HIV infection (log fold change >0.1; FDR< 0.01). We next trained two logistic LASSO PBMC-based and CSF-based models to differentiate T cells from a HIV- or a PWH and tested them in a leave-one-out cross validation (LOOCV) approach. Expression of ~200 genes differentiated a T cell from a PWH versus a HIV- at accuracy of >0.62. 64 and 54 genes were stably selected in all LOOCV iterations for the CSF and PBMC models, respectively.

Out of the 62 genes selected in the CSF model, 41 were common to the PBMC model. Ingenuity pathway analysis revealed a significant association between HIV status and signaling downstream of the pro-inflammatory cytokine IL-15 in both blood and CSF.

Conclusion: By using a multimodal analysis including machine-learning of single cell gene expression data in T cells, we identified potential regulators of immune dysfunction during ART-suppressed HIV infection, including IL-15 pathways.

29 PET IMAGING OF SYNAPTIC DENSITY IN HIV: PRELIMINARY FINDINGS FROM A PILOT STUDY

Julian Weiss1, Rachela Calvi1, Mika Naganawa, Takuya Toyonaga, Shelli Farhadian, Michelle Chintanaphol, Jennifer Ciarella, Ming-Qiang Zheng, Jim Rophcher, Yiyun Huang, Richard Carson, Serena S. Spudich1

1Yale University, New Haven, CT, USA

Background: Synaptic injury, which is potentially reversible, is a pathological hallmark of HIV-associated neurocognitive disorder (HAND) in people living with HIV (PLWH) on antiretroviral therapy (ART), but it has only been assessed in post-mortem studies in humans. Here we report initial results from a pilot positron emission tomography (PET) study employing the novel ligand 11C-UCB-J for synaptic vesicle protein 2A (SV2A) to measure synaptic density in vireologically suppressed PLWH and healthy controls (HC).

Methods: Six male PLWH and seven age-matched HC underwent 3T magnetic resonance imaging (MRI) and high-resolution PET scanning with 11C-UCB-J combined with arterial blood sampling. Distribution volume (VT, mL/cm3) and binding potential (BPND), a measure of SV2A binding, were assessed in 28 regions of interest (ROIs) using the centrum semiovale as a reference region. Partial volume correction using Freesurfer was performed to correct for atrophy. Differences in VT and BPND between the groups were analyzed using a Student’s t-test.

Results: There were no significant differences in age (HC: mean [SD], 59 [8]; PLWH: 61 [5]; p=0.53), race, or body mass index between the groups. PLWH were well-suppressed on ART (mean [SD], CD4 T cells 703 [194] cells/mL, duration of ART 21 [8] years), and all participants had CSF and plasma HIV RNA <20 copies/mL. VT values of the reference region were similar in both groups (HC: 4.08 [0.70]; PLWH: 4.37 [1.01]; p=0.57). PLWH had significantly lower SV2A specific binding (BPND) in eight cortical ROIs compared with HC (p<0.05), illustrated by representative cases (Figure 1). Four of these ROIs, including the precuneus (HC: 6.13 [0.87]; PLWH: 4.89 [0.85]; p=0.03) and superior parietal lobe (HC: 6.04 [0.65]; PLWH: 4.71 [1.07]; p=0.03), are within the parietal lobe, which as a whole trended toward significance (HC: 6.19 [0.88]; PLWH: 5.07 [1.04]; p=0.07). There were no significant differences in VT, though lower values in PLWH were noted in the eight cortical ROIs with significantly decreased BPND.

Conclusion: This preliminary analysis of an ongoing pilot study demonstrates the potential utility of SV2A PET imaging in identifying regions of reduced synaptic density in suppressed PLWH. A larger sample is needed to draw conclusions on which ROIs are most affected, and to explore associations between synaptic density and lab and clinical parameters including antiretroviral therapy with undetectable plasma viral load. Demographics-matched persons without HIV were friends and family of PWH or recruited through flyers. Participants underwent a time-of-flight (TOF) MR angiogram (MRA) and 3D high resolution variable flip angle black blood post-contrast VW-MRI (CUBE) on a GE 3T Discovery scanner. The primary outcome was the number of visualized arterial segments with abnormal wall enhancement. Poisson models were used to compare the mean number of enhancing segments by HIV status.

Results: Of 31 participants (mean age 58 years, 97% men), 19 were PWH (median CD4 count 492 cells/mm3). There were no significant differences in age, sex, race, or CV risk factors between PWH and persons without HIV. A greater proportion of PWH were on a statin (84% versus 42%, p=0.0021). The mean number of enhancing arterial segments for PWH was 1.8 (SD 1.3) versus 0.4 (SD 0.9) for persons without HIV (p=0.003). The majority (80%) of enhancement was eccentric, which did not differ by HIV status. Over half (53%) of PWH with abnormal wall enhancement did not have associated luminal narrowing on TOF MRA. The greater mean number of enhancing arterial segments in PWH remained statistically significant after adjusting for demographics and CV risk factors. In a model adjusted for age, sex, race, and statin use, PWH had an average 4.58 times as many enhancing arterial segments as persons without HIV (95% CI 1.51-13.83; p=0.007).

Conclusion: PWH had a greater burden of primarily eccentric arterial wall enhancement compared with persons without HIV. Furthermore, luminal imaging with TOF MRA underestimated the burden of arterial disease in more than half of PWH. Future studies should investigate the association of arterial wall enhancement with indices of immune activation and radiologic markers of cerebrovascular disease.
neuropsychological performance. SV2A imaging may be a promising outcome measure for interventional trials of HAND.

HIV-INFECTED MACROPHAGES EVADE NK CELL-MEDIATED KILLING WHILE DRIVING INFLAMMATION

Kiera L. Clayton1, Heather Stuart1, Geetha H. Mylvaganam1, Alonso Villasmil Ocando1, Marcela Maus2, Bruce D. Walker1

1Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, 2Massachusetts General Hospital, Boston, MA, USA

Background: The primary targets for HIV infection are CD4+ T cells, however macrophages also become infected and persist despite antiretroviral therapy, suggesting evasion of immune responses. Our previous work shows that while HIV-infected macrophages are recognized by cytolytic CD8+ T lymphocytes (CTL), killing is inefficient due to resistance to CTL-derived granzymes. This poor killing delays CTL detachment from its target, causing hypersummation of CTL-derived cytokines that propagate inflammation, emphasizing the need for rapid killing and release of effector-target contacts to limit inflammation. Thus, we hypothesized that cells with greater cytolytic potential compared to CTL, such as NK cells, would be able to rapidly kill HIV-infected macrophages while limiting excessive inflammation.

Methods: To test this hypothesis, innate interactions between NK cells and autologous HIV-infected macrophages or CD4+ T cells were assessed via flow cytometry-based recognition and killing assays. To characterize the potential for antibody-dependent cellular cytotoxicity (ADCC), HIV envelope expression on macrophages was characterized by flow cytometry, imaging flow cytometry, and confocal microscopy using HIV-specific antibodies, and HIV-specific CAR T cells were used to confirm envelope accessibility on target cells. Finally, ADCC responses against infected CD4+ T cells and macrophages were assessed via flow cytometry.

Results: Despite similar levels of total recognition of HIV-infected CD4+ T cells and macrophages (degranulation and TNF-α production), NK responses to macrophages were significantly skewed towards non-cytolytic, cytokine production (p<0.0001), which was associated with poor elimination (p<0.0001). HIV antibody-based detection confirmed that envelope was transiently expressed on the macrophage cell surface, and recognition of infected macrophages by HIV-specific CAR T cells was comparable to that of CD4+ T cells, suggesting that HIV envelope is equally accessible on both cell types. ADCC enhanced NK cell responses to both cell types, however, total responses to macrophages were significantly lower compared to that of CD4+ T cells (p<0.001 for 3BNC117 and p<0.05 for PGT121).

Conclusion: Together, these data suggest HIV-infected macrophages employ a unique mechanism to evade cytolytic recognition by NK cells while preserving pro-inflammatory cytokine responses, emphasizing the need to develop alternative strategies to eliminate infected macrophages.

EFFECTS OF HIV AND AGING ON RESTING-STATE NETWORKS

Patrick Luckett1, Anupama Melam1, Sarah A. Cooley1, Joshua Shimony1, Beau Ances1

1Washington University in St Louis, St Louis, MO, USA

Background: Despite the use of combination antiretroviral therapy, many HIV associated conditions, such as HIV associated neurocognitive disorders and frailty still exist in people living with HIV (PLWH). A potential biomarker reflective of these conditions is resting state functional connectivity (rsFC). Changes in rsFC strength have been hypothesized to reflect a compensatory reaction due to damage caused by persistent inflammation and chronic immune activation. Within a large cohort of PLWH and HIV- controls we identified networks most affected over the life span of HIV infection using machine learning methods.

Methods: A total of 538 rsFC scans from 318 PLWH (mean age 47.2y, 77% male, 31% Caucasian, mean duration of infection 12.8y; +/−9.4, 84% viral load <200) collected from studies at Washington University School of Medicine (WUSM) and 2791 scans from 2133 HIV- controls (mean age 44.4y, 42% male, 69% Caucasian) collected from studies at WUSM and other sources were analyzed. Ages ranged from 20 to 70 years old (Figure 1b). Ten rsFC networks were evaluated, and preprocessing was performed using in house methods. Correlation matrices were generated for all participants, and an average correlation matrix was computed for each year of age for both groups. A Relief feature selection algorithm was used to identify the strongest predictive networks of HIV status. We then evaluated which networks showed significantly different trajectories reflective of these conditions is resting state functional connectivity (rsFC).

Results: The Relief algorithm identified the strongest predictors of HIV status as multiple connections between the somatomotor, cingulo-opercular, and dorsal attention networks. The strongest difference in average connectivity between PLWH and HIV- controls we identified networks most affected over the life span of HIV infection using machine learning methods.

HIV DNA DETECTED IN IMMUNE CELL SUBSETS IN CSF DURING ART

Shelli Farhadian1, Joshua C. Sykter1, Asma Naqvi2, Michael J. Corley3, Jennifer Chiarella1, Rachela Calvi1, Michelle Chintanaphol1, Geoffrey Lyon1, Diane Trotta1, John W. Mellors1, Serena S. Spudich1

1Yale University, New Haven, CT, USA, 2University of Pittsburgh, Pittsburgh, PA, USA, 3University of Hawaii, Honolulu, HI, USA

Background: HIV-infected cells persist in the central nervous system (CNS) in at least half of people with HIV (PWH) on antiretroviral therapy (ART). We previously reported on a novel population of myeloid lineage microglia-like cells in cerebrospinal fluid (CSF) from PWH on ART; however the identity of CNS cells containing proviruses remains unknown.

Methods: Fresh CSF and blood were collected from PWH (median 20yrs on ART, range 4-24yrs). Single cell CITE-seq was performed to validate CD204 as a marker for CSF microglia-like cells. CSF cells and peripheral blood mononuclear cells (PBMCs) were separated using fluorescence activated cell sorting into three subsets based on expression of: CD3+CD4+, CD3+CD8+, and CD3-CD20-CD127+. HIV DNA levels were determined in each subset using a sensitive qPCR assay targeting HIV integrase (iCAD). HIV DNA measurements were normalized for cell equivalents determined by CCR5 qPCR.

Results: Six donors had plasma HIV RNA levels <20 copies/mL; one had 748 copies/mL. Two donors had HIV RNA detected in CSF despite plasma viral suppression, with 95 and 163 copies/mL HIV RNA detected in CSF. The median number of CSF cells obtained per donors was 35,327 (range 13,000-85,000) in 25mL of CSF. HIV DNA was detected in blood CD4+ T cells from 6/7 donors, and not detected in blood CD4+ T cells in one donor. In CSF, HIV DNA was detected in CD4+ T cells in 6/7 donors (of which 5 donors also had HIV DNA detected in blood CD4+ T cells). HIV DNA copies per 1 million cell equivalents was higher (median 7.1 fold, range 0.3-132) in CSF CD4+ T cells than in blood CD4+ T cells in 5/6 donors. No donor had HIV DNA detected in CSF CD8+ T cells.

We isolated genomic DNA from CD204+ CSF cells in three participants and observed that one participant had HIV DNA detected in CD204+ CSF cells. This donor had plasma HIV RNA 748 copies/mL and CSF HIV RNA 87 copies/mL. HIV DNA levels in this participant were 4368 copies per 1 million CD204+ CSF cells, 2769 copies per 1 million in CD4+ T cells, and 401 copies per 1 million blood CD4+ T cells.

Conclusion: We detected HIV DNA in CD4+T and myeloid cells in CSF in a limited sample of PWH on ART. Normalized HIV DNA in CD4+ T cells from CSF was higher than in blood in most donors. Larger studies should assess whether the HIV DNA detected in is replication-competent proviruses, and whether other CNS immune cell types are HIV-infected.
Background: HIV adversely affects myelin and leads to white matter pallor. With a recently developed method, myelin content can be assessed by T1-weighted (T1w) and T2-weighted (T2w) MRI. The overall pattern in the myelin maps is affected by disease with increases in the T1w/T2w ratio seen in neurodegenerative conditions. We hypothesized that older (> 50 years old) persons living with HIV (PLWH) who had virological failure (VF) would have an increase in the T1w/T2w ratio compared to individuals with virological suppression (VS) or healthy controls (HC).

Methods: Structural T1w and T2w MRI scans were obtained from 424 participants including 206 HC, 140 PLWH with VS, and 78 PLWH with VF. T1w images were processed with FreeSurfer 6.0 to generate brain parcellations. Standard pipelines established for the Human Connectome Project (HCP) were used to derive myelin maps for each individual. Their myelin was estimated from each FreeSurfer parcel was computed. Omnibus ANCOVA analysis with age and gender as a covariate was used to identify the regions of interest (ROI) where myelin maps is affected by disease with increases in the T1w/T2w ratio seen in neurodegenerative conditions. We hypothesized that older (> 50 years old) persons living with HIV (PLWH) who had virological failure (VF) would have an increase in the T1w/T2w ratio compared to individuals with virological suppression (VS) or healthy controls (HC).

Results: Exemplar myelin content maps from a characteristic PLWH are presented in Figure 1A. Regions of interest (ROI) from the Desikan–Killiany cortical atlas exhibited significantly elevated T1w/T2w ratio for PLWH with VF compared to PLWH with VS and HC. Areas that were significantly different included the right posterior cingulate, right inferior temporal, left orbitofrontal, right and left rostral middle frontal. Within PLWH with VF there was no significant correlation between the T1w/T2w ratio and VL for any of the regions.

Conclusion: Our results suggest that PLWH who have VF have increases in myelin content compared to PLWH who have VS and HIV- controls. The observed increases in T1w/T2w ratio may reflect myelin damage or increases in inflammation and are similar to what has been observed in other neurodegenerative diseases. The T1w/T2w ratio does not measure virological failure.

Background: The 2-drug regimen of long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV) dosed i.m. every 4 weeks (Q4W) was noninferior to daily oral 3-drug ART in Phase 3 studies. These results and supportive CAB+RPV LA pharmacokinetics enable regimen evaluation at a longer and potentially more convenient 8-week dosing interval (Q8W).

Methods: ATLAS-2M is a multicenter, open-label, Phase 3b noninferiority (NI) study of CAB+RPV LA maintenance therapy, administered Q8W (600mg CAB + 900mg RPV) or Q4W (400mg CAB + 600mg RPV) to treatment-experienced, HIV-infected adults. Virologically suppressed individuals on CAB+RPV LA Q4W (ATLAS study rollover) or oral standard-of-care were randomized 1:1 to receive CAB+RPV LA Q8W or Q4W. The primary endpoint at Week 48 was the proportion with plasma HIV-1 RNA <50 c/mL (Snapshot, ITT-exposed [ITTe]) with an NI margin of 4%. The key secondary endpoint was the proportion with HIV-1 RNA <50 c/mL (Snapshot, ITTe) with an NI margin of -10%.

Results: 1045 participants were randomized and treated with CAB+RPV LA Q8W (n=522) or Q4W (n=523). 27% were female, 73% were white. Median age was 42 years (range 19–83); 65% were naive to CAB+RPV LA while 35% transitioned from Q4W CAB+RPV LA in ATLAS. CAB+RPV LA Q8W was noninferior to Q4W dosing in both the primary (1.7% vs 1.0%) and secondary analysis (94.3% vs 93.5%; see Table). There were 8 and 2 confirmed virologic failures (CVFs) and both Q4W CVFs. The safety profile was similar for Q4W and Q8W dosing (Table). Injection site reactions (ISRs) were mostly mild or moderate (98% overall) with a median duration of 3 days. Discontinuation for an adverse event occurred in 2% of patients (Q8W, n=12; Q4W, n=13), with 3% (1%) in each group due to ISRs. There was one death (Q8W, sepsis). Of those treated Q8W in ATLAS 2M after ≥48 weeks of Q4W dosing in ATLAS, 93% (115/124) expressed a preference for Q8W dosing.

Conclusion: Q8W dosing of CAB+RPV LA was noninferior to Q4W dosing and well tolerated. These results support the therapeutic potential of CAB+RPV LA administered every 2 months.
PROSPECTIVE ENHANCED MONITORING OF Dolutegravir-Based First Line in Malawi

Elvis Temfack1, Andreas Jahn2, Thokozani Kalua3, Joseph Bitilinyu-Bangoh4, Rose Nyirenda5, Anne-Geneviève Marcelin6, Vincent Calvez4, Diane Descamps5, Gilles Peytavin6, Sarala Nicholas1, David Maman6, Sofie Spiers1, Elisabeth Poulet1, Elisabeth Szumilin7, Birgitt Schramm8,9,

1Epicentre, Paris, France; 2Malawi Department of HIV and AIDS, Lilongwe, Malawi; 3Queen Elizabeth Central Hospital, Blantyre, Malawi; 4AP–HP, Hôpitaux Universitaires Pitié Salpêtrière, Paris, France; 5AP–HP, Hôpital Bichat-Claude Bernard, Paris, France; 6MSF, Lilongwe, Malawi; 7MSF, Paris, France

Background: In January 2019 the Ministry of Health of Malawi rolled-out tenofovir-lamivudine-dolutegravir (TLD) as national first-line antiretroviral therapy (ART). Transitioning of patients already on non-nucleoside-reverse-transcriptase-inhibitor (NNRTI) first-line ART was planned only after prior HIV-1 viral load (VL) testing. VL monitoring and drug resistance testing (DRT) are still in-scale up in Malawi. In parallel to the national ART policy change, a prospective enhanced monitoring is conducted in three health centres of the decentralized HIV-programme in rural Chiradzulu District. We present 6 months outcome.

Methods: Inclusion criteria were age >20 years (male), ≥45 years (female) and eligible for TLD by Malawian guidelines. Plasma VL is assessed at baseline, 3, 6, 12- and 18-months post-TLD start. Baseline VL was assessed retrospectively from blood collected at inclusion. Virological suppression was defined as VL<50 copies/ml. Participants with VL>50 copies/ml during follow-up receive enhanced adherence counselling and a confirmatory VL test three months later. For virological failure (VF), VL>50 copies/ml at confirmatory test, resistance genotyping (dried blood spots) is done and plasma ARV concentration is measured. Serious adverse events (SAE), including treatment discontinuation, are reported.

Results: From January–May 2019, 1928 participants were included: 49% female, 98.2% TLD-transitioners, with a median 98.2 months (IQR: 50.9 – 135.5) on ART, and 35 ART-initiators. Baseline VL-suppression of transitioners was 94.5% (95%CI: 93.3 – 95.4), 3.3% had VL>1000 copies/ml. Among TLD-initiators, 98.2% TLD-transitioners, with a median 98.2 months (IQR: 50.9 – 135.5) on ART, and 35 ART-initiators. Baseline VL-suppression of transitioners was 98.2% (95%CI: 97.5 – 98.6) at M3 (among 1361 currently assessed). Six (0.4%) of tested transitioners had M6 VF. Among three with currently available DRT, two had DTG resistance (mutation R263K or G118R) in combination with resistance to NNRTIs. Two treatment discontinuations occurred before M3, both due to severe neuropsychiatric events reported as related to dolutegravir.

Conclusion: In a cohort highly suppressed on NNRTI-first-line ART, VL-suppression was well maintained at 6-months post-transitioning to TLD, and VL-suppression was high among the few ART-initiators. Of concern are 2 cases of DRT resistance detected after 6 months on TLD, emphasizing the importance of further monitoring and resistance surveillance.

IMPACT OF ANTI-PD-1 AND ANTI-CTLA-4 ON THE HIV RESERVOIR IN VIVO: THE AMC-095 STUDY

Thomas A. Rasmussen1, Laskhmi Rajdev2, Ajantha Solomon3, Ashanti Dantanarayana4, Surekha Tennakoon1, Socheata Chea1, Rachel L. Rutishauser3, Danielle Rigau4, Shelly Lensing5, Sonia Bakkour6, Michael P. Busch6, Dirk Dittmer7, Steven G. Deeks3, Christine Durand4, Sharon R. Lewin1

1Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia; 2Albert Einstein College of Medicine, Bronx, NY, USA; 3University of California San Francisco, San Francisco, CA, USA; 4University of Arkansas for Medical Sciences, Little Rock, AR, USA; 5Vitalant Research Institute, San Francisco, CA, USA; 6University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

In the Phase 3 BRAVE 2020 study, adults with HIV who self-identified as Black or African American and were virologically suppressed on 2 NRTIs plus a 3rd agent were randomized (2:1) to switch to open-label B/F/TAF once daily or stay on their baseline regimen (SBR). Prior virologic failure was permitted with the exception of failure on an INSTI-based regimen. Prior resistance to NNRTIs, PIs or NRTIs was permitted except for K65R/F/L ≥3 thymidine analogue mutations or IF/1/9 insertions; primary INSTI-resistance was excluded. Primary efficacy endpoint was the proportion with HIV-1 RNA ≥50 c/mL at Week 24 (FDA snapshot); noninferiority was assessed through 95% confidence intervals (CI). Change from baseline in CD4 was a secondary endpoint. The HIV-Treatment Satisfaction Questionnaire (HIV-TSQ) was assessed at baseline, Week 4 and Week 24.

Results: 558 were screened, 495 randomized and treated (B/F/TAF n=338; SBR n=166); 32% cis women, 2% trans women, median age 49 years (range 18-79), median HIV treatment duration 10 years (IQR 6.7), 11% had M184V/I mutation, 62% lived in the US South. Baseline 3 agents: INSTIs 61%, NNRTIs 31% and PIs 9%. At W24, 0.6% on B/F/TAF and 1.8% on SBR had HIV-1 RNA ≥50 c/mL (difference -1.2%; 95% CI -4.8% to 0.9%) demonstrating noninferiority of B/F/TAF. The proportion with HIV-1 RNA <50 c/mL was 96% B/F/TAF and 95% SBR. No participant had treatment emergent resistance to study drugs. The mean (SD) changes in CD4 were +13 (209) and +1 (171) (p=0.56), median changes in weight 0.9 and 0.2 kg for B/F/TAF and SBR respectively. Study drug related AEs occurred in 10% on B/F/TAF, most were grade 1. Drug related AEs led to discontinuation in 5 participants on B/F/TAF vs 0 on SBR. Participants on B/F/TAF had higher HIV-TSQ scores at W4 and W24 compared to SBR (p<0.001).

Conclusion: For Black Americans, switching to B/F/TAF was noninferior to continuing their regimen with high efficacy in both arms. The single-tablet regimen B/F/TAF was safe and effective for people switching from a variety of regimen, including those with pre-existing NRTI resistance, and was associated with greater treatment satisfaction.
**Background:** Antibodies to PD-1 and CTLA-4 may perturb HIV persistence during antiretroviral therapy (ART) by reversing HIV-latency and/or boosting HIV-specific immunity. We tested this hypothesis in a prospective multi-center clinical trial of individuals on ART who had cancer and received single immune checkpoint blockade (ICB) with nivolumab (anti-PD-1) or combination therapy with nivolumab and ipilimumab (anti-CTLA-4).

**Methods:** This is a substudy of the AIDS Malignancy Consortium–095 Study. ART-suppressed HIV-infected participants with advanced malignancies were assigned to nivolumab (anti-PD-1) 240 mg every two weeks or nivolumab and ipilimumab (anti-CTLA-4).

**Results:** Forty participants were included, 36 males and 4 females. Of these, 33 received anti-PD-1 alone and 7 received anti-PD-1 plus anti-CTLA-4. At baseline, median age was 53.0 (IQR 47.0–58.5) and CD4 count was 315 (IQR 227–465). Whereas CA US HIV RNA did not change from baseline in those receiving anti-PD-1 alone, we detected a median 1.44 fold-increase (IQR 1.16–1.89) within 24 hours of the first dose in participants on combination ICB (P=0.031). This increase was also significantly higher compared to the corresponding change from baseline in those on anti-PD-1 alone (P=0.025). There were no significant changes from baseline in plasma HIV RNA. We also detected no changes during ICB in the level of HIV DNA or the frequency of cells containing replication-competent HIV (n=10).

**Conclusion:** Dual ICB with anti-PD-1 and anti-CTLA-4 induced a larger increase in CA-US HIV RNA than anti-PD-1 alone without effect on plasma HIV RNA or the latent HIV reservoir.

38 A RANDOMIZED TRIAL OF THE IMPACT OF 3BNC117 AND ROMIDEPSIN ON THE HIV-1 RESERVOIR

Henning Gruell1, Yehuda Z. Cohen1, Jesper D. Guns3, Marie H. Pahus3, Henning Gruell2, Yehuda Z. Cohen1, Jesper D. Guns3, Marie H. Pahus3, Clara Lehmann1, Katrinna Millard1, Martin Tolstrup1, Julio C. Lorenzi1, Michel Nussenzweig1, Gerd Fätkenheuer1, Florian Klein1, Marina Caskey1, Ole S. Segaard1

Cologne University Hospital, Cologne, Germany, 2 The Rockefeller University, New York, NY, USA, 3 Aarhus University Hospital, Aarhus, Denmark

**Background:** Broadly neutralizing antibodies (bNAbs) administered prior to reversal of latency may facilitate killing of HIV-1-infected CD4+ T cells and could be a component of an HIV-1 cure strategy. To clinically assess this concept in individuals on antiretroviral therapy (ART), we evaluated the impact of the bNAb 3BNC117 followed by latency reversal with romidepsin on measures of viral transcription, reservoir size, as well as time to viral rebound during analytical treatment interruption (ATI).

**Methods:** This randomized phase Ib/IIa trial enrolled 20 HIV-1-infected adults on long-term ART. Group A received 3BNC117 (30 mg/kg) 2 days prior to each romidepsin cycle, with romidepsin (5 mg/m2) administered at weeks 0, 1, and 2 (cycle 1), and weeks 8, 9, and 10 (cycle 2). Group B received cycles 1 and 2 but no 3BNC117. This was followed by an ATI at week 24 when bNAb levels were expected to be low or undetectable. The primary endpoint was time to viral rebound (≥200 copies/mL) during ATI. Secondary endpoints were safety, changes in HIV-1 reservoir measures, as well as effects on HIV-1-specific immunity.

**Results:** Nineteen of 20 enrolled participants (3 females, 17 males, median age 44 years, median of 645 CD4+ cells/mm3) completed all treatment cycles; 11 in Group A and 8 in Group B. Two participants (one in each group) opted out of the ATI. Seven participants (Group A = 4, Group B = 3) had detectable viral blips (21-144 copies/mL) after romidepsin infusions. Unspliced HIV-1 RNA increased in most individuals after the 2rd and 3rd infusions in each romidepsin cycle. Decline in total HIV-1 DNA was 90 vs 61 copies/106 CD4+ T cells for group A vs B (p=0.79). Median time from interrupting ART to plasma HIV-1 RNA ≥200 copies/mL during ATI was 2.5 weeks for Group A and 4.0 weeks for Group B. A total of 237 AEs were recorded (184 grade 1, 52 grade 2, and 1 grade 3), of which 64 (27.4%) were considered at least possibly related to study medications.

**Conclusion:** This is the first reported trial of the combination of a latency-reversing agent and potent bNAb designed to target the HIV-1 reservoir. While the combination was safe, it did not reduce the combined defective and intact proviral reservoir as measured by total HIV DNA, or delay viral rebound during ATI. These results may serve as a benchmark for further optimization of HIV-1 cure strategies under ART.

**SAFETY & PHARMACOKINETICS OF GS-9722 IN HIV-NEGATIVE PARTICIPANTS AND PEOPLE WITH HIV**

Peter Ruane1, Eric Daar2, Kimberly Workowski1, Rebecca Begley1, Rita Humeniuk1, Tarino Makadzange1, Steve K. West3, Hui Liu1, Yizhao Li1, John Ling4, Luisa M. Stamm5, Polina German6, Joseph J. Eron7, Princy N. Kumar1, Edwin DeJesus8

1 Peter J Ruane, MD, Inc, Los Angeles, CA, USA, 2Harbor-UCLA Medical Center, Torrance, CA, USA, 3Emory University, Atlanta, GA, USA, 4Gilead Sciences, Inc, Foster City, CA, USA, 5University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 6MedStar Health, Washington, DC, USA, 8Orlando Immunology Center, Orlando, FL, USA

**Background:** GS-9722 is an effector-enhanced, broadly neutralizing antibody (bNAb) targeting a V3 glycan motif of the HIV envelope protein which is being developed for use in a HIV cure regimen. GS-9722 is a derivative of the bNAb PGT121 which has demonstrated immune cell-mediated killing of HIV-infected cells in vitro and efficacy in SHIV-infected monkeys. The safety, tolerability and pharmacokinetics (PK) of GS-9722 administered intravenously (IV; 30° infusion were evaluated in a first-in-human study in HIV-negative participants (Study 1) and in virally suppressed people with HIV (VS-PWH; Study 2).

**Methods:** Two randomized, blinded, placebo-controlled, staggered dose escalation studies were conducted. In Study 1, HIV-negative participants received single dose (SD; 150, 500, or 1500 mg) or multiple doses (MD; 150, 500, or 1000 mg every other week [QOW] for three doses) of GS 9722 (n=6/cohort) or placebo (n=2/cohort). In Study 2, VS-PWH received SD or MD (QOW for five doses) GS-9722 150 or 500 mg (n=6/cohort) or placebo (n=2/cohort). Study 1 has completed; Study 2 is ongoing. Safety and PK are assessed throughout each study.

**Results:** In Studies 1 and 2, 45 of 49 and 12 of 32 participants completed treatment, respectively. In Study 1, dose-proportional increases in GS-9722 AUC and Cmax were observed (Table). GS-9722 t1/2 was ~26 days, supportive of at least QOW dosing. Preliminary SD PK data in VS-PWH are similar to HIV-negative participants (Table); PK analysis in MD VS-PWH cohorts is ongoing.

Most AEs were grade 1 or 2. In Study 1, two participants discontinued study drug due to AEs (1000 mg; MD), both of which were considered related to study drug; one participant had a grade 3 SAE of thrombocytopenia and the other had a grade 2 AE of infusion related-reaction. In Study 2, one participant had a grade 3 unrelated SAE of small intestinal obstruction (150 mg; SD). No other SAEs or AEs leading to study drug discontinuation were reported to date.

**Conclusion:** These studies demonstrate that GS-9722 is generally safe and well tolerated in HIV-negative participants and VS-PWH, with similar single dose PK in the two populations. These data support ongoing evaluation of GS-9722 as part of a combination therapy for HIV cure.
Results: Participants were randomized 2:1 to receive 10 biweekly doses of VES 4-8 mg or placebo while continuing ART, followed by carefully monitored analytical treatment interruption (ATI). Viral rebound and safety were evaluated through at least 24 weeks (w) of ATI.

Twenty-five participants were randomized to VES (n=17) or placebo (n=8). The median age was 45 years (range 27-66 yrs) and 16% were women. The median pre-ART HIV-1 RNA 3.2 log₁₀ c/mL (IQR 3, 3.3) and the median time on ART was 2.7 yrs (range 0.7-17.2 yrs). VES was well tolerated, with no drug-related discontinuations. Most common study-drug related AEs were lymphoadenopathy, chills, and headache. Pharmacodynamic activity of VES was confirmed by increases in whole blood interferon stimulated gene mRNAs and plasma cytokine levels. During the ATI, 47 (94%) of 50 patients had plasma HIV-1 RNA of 50 to ≤5,000 c/mL. Participants were randomized for a second ATI at 5 w (3.9-6) for the VES group, and 3.9 w (2.0-4.1) and 4 w (2-4.4) for placebo (p=0.036; p=0.024; see Figure). Median (95% CI) plasma viral set-point change from pre-ART value was -0.34 (-0.60, 0.06) log₁₀ c/mL for placebo (p=0.035) and -0.28 (-0.75, 0.32) log₁₀ c/mL for VES (p=0.035). Four individuals in the VES group had no virologic rebound (>50 c/mL) for ≥6 w, with one participant rebounding at 15 w (and >200 c/mL at 31 w); this participant also had a 0.94 log₁₀ c/mL decrease in viral set-point and completed the study after 48 w off ART with HIV-1 RNA 164-215 c/mL.

Conclusion: VES was well tolerated in HIV controllers at multiple doses up to 8 mg and was associated with a modest increase in time to viral rebound after ATI, potentially due to an augmented antiviral immune response. Trials evaluating the efficacy of VES in combination with other agents such as CD8-inducing vaccines and monoclonal antibodies are warranted.

INDEX FACTORS INCREASE PARTNER NOTIFICATION YIELD FOR KENYAN PEOPLE WHO INJECT DRUGS

Brandon Guthrie1, Aliza Monroe-Wise1, Loie Mbogo2, Natasha Ludwig-Barroni, John D. Scott3, Bill Sinkele4, Matthew Dunbar1, Paul Macharia1, Esther Gitau1, Betsy Sambari5, Helgar Musyuko1, Sarah Masyuko1, Joshua T. Herbeck1, Carey Farquhar1

1University of Washington, Seattle, WA, USA, 2University of Washington, Seattle, WA, USA, 3Support for Addictions Prevention and Treatment in Africa Foundation, Nairobi, Kenya, 4Kenyatta National Hospital, Nairobi, Kenya, 5National AIDS and STI Control Programme, Nairobi, Kenya

Background: Assisted partner notification services (aPNS) to find, test, and link to care partners of HIV+ individuals may aid in achieving HIV care cascade goals in key populations. Our ongoing evaluation of aPNS for people who inject drugs (PWID) in Kenya identifies characteristics of indexes associated with highest yield for this community.

Methods: Indexes were recruited from needle/syringe programs and methadone clinics in Nairobi and Kilifi County and offered enrollment if HIV+. Indexes provided contact information for injection and sexual partners (past 3 years). Community-embedded peer educators traced partners and referred them to study sites for HIV testing. aPNS efficiency was assessed by number of indexes needed to interview (NNTI) to find one additional HIV+ partner not on ART.

Results: 441 enrolled indexes named 1821 partners (70% injection partners, 18% sexual, and 11% sexual and injection). Indexes named a median of 4 partners (interquartile range [IQR] 2-4) and identified 2082 HIV+ partners. aPNS yielded 470 HIV+ partners, of whom 116 (25%) were not on ART and 50 (11%) were unaware of their HIV status. One or more HIV+ partners were identified for 262 (59%) indexes, with a single HIV+ partner identified for 34% of indexes and ≥2 HIV+ identified for 25% of indexes.

Overall, NNTI was 3.8 to identify one partner not on ART, aPNS in Nairobi was more likely than Kilifi County to yield HIV+ partners not on ART (NNTI=3.3 vs 9.1; p<0.001). NNTI to identify partners not on ART was 2.5 for female indexes versus 7.1 for males (p<0.001). Adjusted for sex of the index, aPNS was more efficient for...
43 COMMUNITY-BASED MULTIMONTH DISPENSING OF ART: A CLUSTER RANDOMISED TRIAL IN LESOTHO
Betty B. Tukei1, Geoffrey Fati2, Appolinaire Tiam3, Vincent Tukei1, Thapelo Matoe1, Ian Sanne1, Thembisile Kulu1, Nicky Mahbaha1, Francis Akpan1, Ian Membre1, Yiyola Fatuiryie1, Justine Mirembe1, Kgotsi Maile1, Makatleho Sejana1, Charles Chaselal
1Right to Care, Johannesburg, South Africa, 2Kheth'Impilo AIDS Free Living, Cape Town, South Africa, 3Elisabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA, 4Kheth'Impilo, Cape Town, South Africa, 5United States Agency for International Development, Washington, DC, USA

Background: Lesotho adopted the test and start strategy for HIV services in June 2016 with anticipated increase in patient load. Our study evaluated community-based differentiated models of multi-month dispensing (MMMD) of ART among stable HIV-infected adults in Lesotho. We report 12 month outcomes of the study.

Methods: The cluster-randomised trial was conducted in 30 selected clusters, stratified into rural and urban geo-locations. The clusters were randomised to three differentiated model of care arms: (i) 3 monthly ART supply at facilities (3MF) as control, (ii) 3 monthly ART supply through community ART groups (3MC) as intervention; (iii) 6 monthly ART supply through community ART distribution points (6MCD) as intervention. The primary outcome was retention in care with virologic suppression as secondary outcome. Outcome analysis were by intention-to-treat. We compared risk differences between arms with binomial population and used Cox’s proportional hazards regression to compare subgroups and cluster contamination was substantial. This intervention may be a useful community-based component of a comprehensive HIV response.

Results: A total of 3364 participants were enrolled, 3MF (1998), 3MC (1558) and 6MCD (1880) arms. Retention in ART care was not different across the arms and achieved the noninferiority limit (-3.25%) with 3MC vs. 3MF 6MCD vs. 3MF (control) and 6MCD vs. 3MC, adjusted RD= -0.1% (95% CI: -0.6% to 1.5%), adjusted RD= -1.3% (95% CI: -3.0% to 0.5%), and adjusted RD= -1.2% (95% CI: -2.9% to 0.5%), respectively. Retention in the intervention arms for both 3MC and 6MCD arms did not differ vs. 3MF, adjusted RD=1.1% (95% CI: -0.6% to 2.8%) and adjusted RD= -0.6% (95% CI: -2.4% to 1.1%), respectively. However, there was a slight reduction in 6MCD vs 3MC, adjusted RD= -1.9% (95% CI: -3.6% to -0.2%). Amongst 1503, 1126 and 1285 participants with available viral load results after 12 months, 1482 (98.6%), 1104 (98.1%) and 1263 (98.3%) were virally suppressed in arms 3MF, 3MC and 6MCD, respectively. There were no differences in viral suppression between 3MC, or 6MCD vs. control, risk ratio (RR)=1.00 (95% CI: 0.98-1.01) and RR=1.00 (95% CI: 0.98-1.01), respectively.

Conclusion: There is no difference in retention in care or virologic suppression for stable patients receiving 3 or 6 month dispensing of ART within community-based differentiated models of care when compared to the standard 3 month facility dispensing model.

45 IMPROVED TIME IN CARE AND VIRAL SUPPRESSION WITH STREAMLINED CARE IN THE SEARCH STUDY
Matthew D. Hickey1, James Ayioko1, Daisone Kwarisimia1, Fredrick J. Opel1, Asphas Dovareangise2, Laura B. Balzer1, Gabriel Chamie3, Vivek Jain1, James Peng1, Edwin D. Charlebois4, Craig R. Cohen5, Elizabeth A. Bukusi5, Moses R. Kamya1, Maya L. Petersen1, Diane V. Havlir1
1University of California San Francisco, San Francisco, CA, USA, 2KEMRI-USEC, Kisumu, Kenya, 3Infectious Diseases Research Collaboration, Kampala, Uganda, 4University of Massachusetts Amherst, Amherst, MA, USA, 5Makerere University, Kampala, Uganda, 6University of California Berkeley, Berkeley, CA, USA

Background: HIV differentiated service delivery (DSD) models are being scaled up in resource-limited settings for stable patients; less is known about DSD outcomes for patients newly linked or re-linked to care. We evaluated the effect of the SEARCH streamlined care intervention by comparing care engagement and viral suppression (VS) between intervention and control arms among HIV+ persons ART eligible by country guidelines at study start who were already enrolled or who linked to care after universal HIV testing in the SEARCH trial (NCT:01864603).

Methods: Our analysis included HIV+ adults (age ≥15 years) at baseline (2013) who were country guideline ART eligible (prior ART experience or CD4≤350) and had ≥1 clinic visit for HIV care between 2013-2017 in SEARCH communities randomized to intervention (N=16) or control (N=16). We assessed the effect of streamlined care (patient-centered care, increased appointment spacing, improved clinic access, reminders, and tracking) on time in care (TIC) and viral suppression (VS) at 3 years. TIC was defined as the proportion of total follow up time that patients adhered to visit schedules. Analysis was stratified by baseline care status, namely: 1) ART-experienced with baseline CD4≤350, 2) ART-experienced with baseline viiremia, or 3) ART-naive with baseline CD4≤350. Comparisons between study arms used cluster-level TMLE.
46  COLLABORATIVE DATA-TO-CARE MODEL IMPROVES HIV CARE OUTCOMES IN PLWH IN PHILADELPHIA

Sindhu Shamasunder1, Crystal Lucas1, Shedane Shaw1, Briana Gibson1, Olivia Kirby1, Melissa Miller1, Kathleen A. Brady1

1Philadelphia Department of Public Health, Philadelphia, PA, USA

Background: Among the 19,199 people living with HIV (PLWH) in Philadelphia, 6,401 (33%) were out of care (OOC) in 2017. Engagement in care is integral to decreasing HIV transmission and achieving Ending the Epidemic outcomes. This analysis aims to characterize persons OOC and assess outcomes of a collaborative health department/medical provider data-to-care randomized control trial.

Methods: OOC patients were randomized to Standard of Care (SOC) or Intervention, in which Disease Intervention Specialists assisted patients with reengagement. Criteria for inclusion were age >18, in-care at a participating clinic during a 12-month eligibility period and no care in the following 6 months. Chi-square testing was used to determine differences in demographics between study arms. Multivariable logistic regression was used to assess predictors of 3 outcomes: re-engagement (CD4/VL within 90 days), retention (2 or more CD4/VLs at least 90 days apart within 1 year) and viral suppression (VL <200 c/mL within 1 year).

Results: 449 OOC PLWH were randomized to each study arm between 8/2016-12/2017, with no significant differences in demographic characteristics between arms. The majority of patients were evenly distributed across age groups (~30% to 50% male). HIV incidence was measured via repeat testing between 13 to 15 times as likely as SOC patients to re-engage in care, become retained in care, and achieve viral suppression (VL <200 c/mL within 1 year) and viral suppression (VL <200 c/mL within 1 year).

Conclusion: Results indicate that a collaborative data-to-care intervention can improve re-engagement in care, retention in care and viral suppression among PLWH who are OOC. Next steps include expansion of this model to determine feasibility of city-wide implementation.

Results: Among 4,391 HIV+ persons (35% men, 8% youth 15-24 yrs) in care and eligible for ART by country guidelines, 2,958 (67%) were ART-experienced with baseline TIC, 368 (13%) were ART-experienced with baseline viremia, and 865 (20%) were ART-naïve with CD4≤350. Among ART-experienced patients with baseline viremia, streamlined care was associated with both higher TIC (RR 1.11, 95% CI 1.01-1.21) and VS (67% vs 47%, RR 1.41, 95% CI 1.04-1.92). Among ART-naïve persons, streamlined care was associated with higher TIC (RR 1.10, 95% CI 1.05-1.21) but VS was not significantly higher (83% vs 78%, RR 1.06, 95% CI 0.95-1.19). Among ART-experienced persons with baseline VS, effects of streamlined care were observed on TIC (RR 1.07, 95% CI 1.01-1.13), although nearly all were virally suppressed after 3 years regardless of the care delivery model (97% intervention vs 95% control, RR 1.02, 95% CI 1.00-1.03).

Conclusion: Streamlined care was associated with better engagement in care for all groups and viral suppression for ART-experienced patients with viremia in this randomized comparison of patients ART eligible at study start who linked to care after universal HIV testing.

Table 1. Effect of streamlined care on engagement and viral suppression among patients eligible for ART by WHO 2013 guidelines linked to care by baseline care status

<table>
<thead>
<tr>
<th></th>
<th>ART-experienced with baseline viremia</th>
<th>ART-naive with baseline CD4≤350</th>
<th>ART-experienced with baseline VS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in care (TIC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>61%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>51%</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td>31%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Engagement (CD4/VL within 90 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89%</td>
<td>91%</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>Retention (2 or more CD4/VLs at least 90 days apart within 1 year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72%</td>
<td>73%</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>Viral suppression (VL &lt;200 c/mL within 1 year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>92%</td>
<td>89%</td>
<td></td>
</tr>
</tbody>
</table>

47  POPULATION-LEVEL VIREMIA PREDICTS HIV INCIDENCE ACROSS UNIVERSAL TEST & TREAT STUDIES

Maya L. Petersen1, Joseph Larmarange1, Kathleen Wirth1, Timothy Skalland2, Helen Ayles1, Moses R. Kamya3, Shahn Lockman4, Collins C. Iwuji5, François Dabis6, Joseph MakHEMA7, Diane V. Havlir8, Sian Floyd9, Richard J. Hayes10, for the UT3C

1University of California Berkeley, Berkeley, CA, USA, 2Paris Descartes University, Paris, France, 3Harvard T.H. Chan School of Public Health, Boston, MA, USA, 4Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 5Zambart, Lusaka, Zambia, 6Makerere University College of Health Sciences, Kampala, Uganda, 7Africa Health Research Institute, Mtubatuba, South Africa, 8Université de Bordeaux, Bordeaux, France, 9Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 10University of California San Francisco, San Francisco, CA, USA, 11London School of Hygiene & Tropical Medicine, London, UK

Background: Improved understanding of the extent to which increased population-level viral suppression will reduce HIV incidence is needed. Using data from four large Universal Test and Treat Trials, we evaluated the relationship between viremia and incidence and its consistency across epidemic contexts.

Methods: We analyzed data from 105 communities in the PopART (21 communities in South Africa and Zambia, ~25,000 adults each), BCPP (30 communities in Botswana, ~3,600 adults each), ANRS 12249 TasP (22 communities in South Africa, ~1,300 adults each) and SEARCH (32 communities in Uganda and Kenya, ~5,000 adults each) studies. Communities ranged from rural to urban and varied in the mobility of their populations and their sex ratio (~30% to 50% male). HIV incidence was measured via repeat testing between 2012-2018. Population viremia — % of all HIV+ (HIV+ or -HIV+) with HIV viremia — was estimated at midpoint of follow-up based on HIV prevalence and non-suppression among HIV+, with adjustment for differences between the measurement cohort and underlying population. Community-level regression, adjusted for study, was used to quantify the association between HIV incidence and viremia and to evaluate cross-study heterogeneity.

Results: HIV prevalence (measured in 257,929 total persons, PopART: 37,006; BCPP: 12,570; TasP: 20,978; SEARCH: 187,375) ranged from 2% to 40% by community. Non-suppression among HIV+ (measured in 39,928 persons, PopART: 6,233; BCPP: 2,318; TasP: 6,617; SEARCH: 16,209) ranged from 3% to 70%. HIV incidence (measured over 345,844 person-years, PopART: 39,702; BCPP: 8,551; TasP: 26,832; SEARCH: 270,759) ranged from 0.03 to 3.4 per 100PY. Population-level viremia was strongly associated with HIV incidence; pooling across studies, HIV incidence decreased by 0.07/100PY (95% CI: 0.05, 0.10, p<0.001) for each 1% absolute decrease in viremia. Incidence was significantly associated with viremia in each study; however, both strength of the incidence-viremia relationship (slope) and projected incidence at 0% viremia (intercept) differed (Figure).

Conclusion: Lower population-level HIV viremia was associated with lower HIV incidence in all four Universal Test and Treat Studies, conducted in a wide range of epidemic contexts in sub-Saharan Africa. Differences in external infection
DECREASING COMMUNITY VIREMIA IS ASSOCIATED WITH DECREASING HIV INCIDENCE IN AUSTRALIA

Denton J. Callander\(^1\), Mark Stookey\(^2\), Hamish McManus\(^1\), Andrew Carr\(^1\), Richard Gray\(^1\), Jennifer Hoy\(^1\), Basil Donovan\(^3\), Margaret Hellard\(^4\), Andrew E. Grulich\(^5\), Christopher K. Fairley\(^6\), Martin Holt\(^3\), David J. Templeton\(^1\), Teng Liaw\(^1\), James McMahon\(^1\), Rebecca J. Guy\(^1\), for the TAIPAN Advisory Group

1. University of New South Wales, Sydney, NSW, Australia, 2. Burren Institute, Melbourne, VIC, Australia, 3. St. Vincent’s Hospital, Sydney, NSW, Australia, 4. The Alfred Hospital, Melbourne, VIC, Australia, 5. Monash University, Melbourne, VIC, Australia, 6. RPA Sexual Health, Camperdown, NSW, Australia, 7. Monash Health, Melbourne, VIC, Australia

Background: Considerable public health resources have been dedicated to implementing HIV ‘treatment as prevention’ in an effort to reduce new infections. Although promising, no large-scale studies have yet evaluated the community-level impact of treatment as prevention on direct measures of HIV incidence among gay and bisexual men (GBM). This study assessed the temporal relationship between community viremia and HIV incidence among GBM living in New South Wales and Victoria, Australia’s most populous states.

Methods: For 2012-2017, we established a longitudinal cohort of HIV-positive (n=12,200) and HIV-negative (n=45,719) GBM using data from a targeted sentinel surveillance system of 49 sexual health clinics, general practices, community HIV-testing sites and hospitals. Among GBM with diagnosed HIV, annual prevalence of viremia was calculated for each patient’s last viral load test of a calendar year (≥2 RNA copies/mm\(^3\)) while mathematical modelling was used to estimate the proportion of HIV-positive GBM living with undiagnosed HIV infection (assuming 100% viremia); these outcomes were combined to estimate ‘community viremia’. A correlation coefficient was calculated to assess the temporal relationship between community viremia and HIV incidence, which was directly measured among HIV-negative sentinel surveillance patients using the repeat testing method. To account for the introduction of HIV pre-exposure prophylaxis (PrEP) in 2016, the analysis was repeated for the 2012-2015 period only.

Results: HIV viremia among diagnosed GBM decreased from 27.9% in 2012 to 3.7% in 2017 (p<0.001) while the proportion living with undiagnosed HIV decreased from 10.0% to 8.4% (p=0.01). As shown in Figure 1, annual community prevalence of HIV viremia decreased from 28.6% in 2012 to 12.8% in 2017 (p<0.001) while HIV incidence decreased from 0.88/100 person years in 2012 to 0.22/100 person years in 2017 (p<0.001). The correlation coefficient between annual community prevalence of viremia and HIV incidence from 2012 to 2017 was 0.94 (p<0.001) and for 2012 to 2015 was 0.90 (p<0.001).

Conclusion: Decreasing community viremia among GBM was strongly associated with decreasing HIV incidence, including before the implementation of PrEP. Our findings justify the significant investment in HIV treatment initiatives, highlighting that these should be sustained as key elements of HIV prevention.

COMMUNITY ART INCREASES VIRAL SUPPRESSION AND ELIMINATES DISPARITIES FOR AFRICAN MEN

Ruanne V. Barnabas\(^1\), Heidi van Rooyen\(^1\), Stephen Aslim\(^1\), Alastair van Heerden\(^2\), Deenan Pillay\(^3\), Adam Spiro\(^1\), Torin Schaafsma\(^4\), Meighan Krows\(^1\), Kombi Sausi\(^5\), Nsika Sithole\(^1\), Bosco Turumureba\(^1\), Peter Ehrenkranz\(^6\), Jared Baeten\(^7\), Connie L. Celum\(^8\), for the DO ART Study Team


Background: Community-based HIV testing, same-day ART start, and decentralized monitoring and ART refills could increase viral suppression, particularly among priority groups who engage less in clinic-based HIV care, such as men who are more likely to have detectable HIV viral load.

Methods: We conducted a multi-site, household randomized trial of community-based ART compared to clinic services in rural and peri-urban areas of Sheema District, Uganda, and Kwazulu Natal, South Africa - the Delivery Optimization for ART (DO ART) Study. Community-based HIV testing was conducted at home and in mobile vans. People living with HIV (PLWH) who were not on ART with CD4>100 cell/mL were eligible for randomization to: 1) same-day community-based ART start with quarterly monitoring and ART refills through mobile vans, 2) ART start at the clinic with monitoring and refills through mobile vans in the community (hybrid approach); or 3) clinic-based ART (standard of care). The primary outcome was HIV viral suppression at 12 months, assessed by modified intent to treat analysis using regression analysis; testing first for superiority and then non-inferiority (relative 5%) if not superior.

Results: Between May 2016 and March 2019, 1,531 PLWH not on ART were randomized: 708 (46%) were men and 36% were <30 years. Retention at 12 months was 95%. Compared to standard clinic care, community-based ART increased viral suppression (63% vs. 74%, RR=1.18, 95% CI: 1.07-1.29) and the hybrid approach was non-inferior (63% vs. 68%, RR=1.08, 95% CI: 0.98-1.19, p=0.005 for non-inferiority). Both community strategies significantly increased viral suppression among men: community-based ART (73%, RR=1.34, 95% CI: 1.29-1.39, p<0.001 for non-inferiority) and the hybrid approach was superior (75%) in the community ART arm compared to 54% for men and 73% for women in the clinic arm.

Conclusion: Among PLWH who were not on ART, community-based HIV testing, same-day ART initiation, mobile van monitoring and ART resupply, significantly increased viral suppression compared to clinic-based ART. The UNAIDS 90-90-90 goal of 75% suppression was met for men and women in the community-based ART arm, eliminating disparities in viral suppression by gender. Combining decentralized ART initiation and refill is an effective strategy to increase viral suppression which should be implemented and evaluated in different contexts and populations who are not virally suppressed.

IN VIVO MODELS FOR THE EVALUATION OF NOVEL HIV CURE INTERVENTIONS

J. Victor Garcia-Martinez, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Animal models have contributed extensively to biomedical investigation and specifically to virtually all areas of HIV research. Animal models provide a...
complex substrate for the evaluation of novel therapeutic interventions at very early stages that would not be suitable for testing in humans. They allow for exquisite control of variables that are normally impossible to control in human clinical studies such as the strain of virus, inoculum dose, and the timing and route of exposure. In addition to the evaluation of the success of any given intervention, they permit a very complete analysis of its mechanism of action, it’s possible risks such as toxicity and it’s benefits regarding efficacy all in a highly reproducible and reliable manner. Because animal models infected with HIV and treated with antiretroviral therapy can establish HIV persistence in vivo, they provide a unique tool for the evaluation of novel approaches to reverse latency. Furthermore, they allow for the evaluation of novel approaches for the killing of latently infected cells that have been reactivated. Currently, two animal models have been used for the majority of the published research in HIV CURE: non-human primates and humanized mice. There are significant differences between these two models that make them highly complementary to each other. This lecture will review the implementation of both models for HIV cure and provide recent examples of how both models synergize to provide helpful insight into the reproducibility and efficacy of novel interventions aimed at finding an HIV CURE.

53 TOWARD DURABLE CONTROL OF HIV-1 WITH eCD4-Ig
Michael Farzan, The Scripps Research Institute, La Jolla, CA, USA
eCD4-Ig is an exceptionally broad HIV-1 entry inhibitor that uniquely neutralizes all of the 270 HIV-1, HIV-2 and SIV isolates it has been tested against, in every case with IC50 values < 10 μg/ml. eCD4-Ig’s breadth and potency derives from the fact that it closely and simultaneously mimics the HIV-1 receptor CD4 and the HIV-1 coreceptor CCR5. Consistent with this breadth, eCD4-Ig is much harder to escape than broadly neutralizing antibodies (bNAb). To date, full escape has not been observed either in cell culture or rhesus macaques and viruses which partially escape eCD4-Ig in both cases pay high costs. Adeno-associated virus (AAV)-expressed eCD4-Ig functions as an effective vaccine alternative, and protects rhesus macaques from repeated high-dose viral challenges which are both SHIV-AD8 and SIVmac239. Unlike bNAb and other multispecific antibody-inhibitors, eCD4-Ig markedly improves the endogenous ADCC activity of patient sera. It does so by altering the conformation of the HIV-1 Env, allowing otherwise dormant V3 and CD4i antibodies to bind Env. To determine whether eCD4-Ig could suppress an established infection, six SHIV-AD8-infected rhesus macaques were placed on combined anti-retroviral therapy (ART) 12 weeks after infection and inoculated with AAV-eCD4-Ig 42 to 50 weeks post-infection. ART was subsequently lifted and viral loads and eCD4-Ig concentrations where monitored for now two years. We observed that relatively low concentrations of AAV-expressed eCD4-Ig (3-19 μg/ml) prevent viral rebound of an established SHIV-AD8 infection after ART cessation all six macaques, albeit with sporadic viral ‘blips’ observed in most animals. Macaques “functionally cured” in this manner can provide an ideal platform to monitor the impact of latency-reversing agents on the reservoir of latently infected cells, and to determine if an entry inhibitor with potent ADCC activity can itself change the rate of reservoir decay. Stable HIV-1 remissions may also be appealing and useful to humans, for example limiting transmission from individuals who cannot or will not use conventional ART, enabling long-term drug holidays, and providing a backstop for an imperfect sterilizing cure. Efforts to increase the robustness and consistency of these functional cures will be described.

SYPHILIS CAUSES STILLBIRTH: PENICILLIN IS PREVENTION
Melanie Taylor, WHO, Geneva, Switzerland
WHO estimates 660,000 cases of mother-to-child transmission of syphilis (congenital syphilis) occurred in 2016, resulting in 350,000 adverse birth outcomes inclusive of over 200,000 stillbirths and neonatal deaths. By comparison, UNAIDS estimates approximately 180,000 new cases of HIV occurred in 2016 among children ages 0-14 years. Although over 90% of countries include screening of pregnant women for syphilis in national antenatal care guidelines, efforts to ensure high screening coverage have seen limited improvement, resulting in static estimates of congenital syphilis in the setting of stable or increasing syphilis prevalence among general and high-risk populations of adults. In 2016, WHO estimated 66% coverage of syphilis screening among pregnant women with an estimated global syphilis prevalence in this group of 0.69% (0.70% in 2012). In 2014, WHO launched the initiative “Elimination of Mother-to-Child Transmission of HIV and syphilis” (EMTCT). While 14 countries have been validated by WHO for this achievement, high burden countries in several regions are challenged to achieve the WHO EMTCT criteria of 95% coverage of antenatal care, syphilis testing and treatment of infected pregnant women with benzathine penicillin. Limited national prioritization and stakeholder engagement have resulted in lower coverage of syphilis screening as compared to HIV screening in pregnant women. Recent global shortages of benzathine penicillin have challenged treatment coverage as this medication is currently the only WHO-recommended treatment for pregnant women with syphilis. Newer technologies including rapid syphilis tests and rapid dual HIV/syphilis tests have offered the opportunity for same-visit testing and treatment of syphilis. The rapid dual HIV/syphilis test offers numerous advantages to separate tests and can be purchased at a similar price to that of a single HIV test. Implementation of the rapid dual HIV/syphilis tests can result in the immediate equalization of syphilis screening coverage to that of HIV among pregnant women. Studies to evaluate alternative treatment regimens for syphilis that could be appropriate for use in pregnant women are underway.
Sex causes pregnancy, HIV infection and bacterial sexually transmitted infections (STI). Every year, women aged 15–49 years will experience about 63.8 million new infections caused by Chlamydia trachomatis (chlamydia) and 37.1 million caused by Neisseria gonorrhoeae (gonorrhoea). These estimated incidence rates are highest in southern sub-Saharan Africa and Oceania regions and in women under 25 years. About 2.2 million women aged 15-24 years are living with HIV infection and they are at higher risk of chlamydia and gonorrhoea than HIV-uninfected women. Most of these infections are clinically silent and undiagnosed. The high prevalence of STI in pregnant women in some countries could pose risks to the fetus and newborn. Among pregnant women in South Africa, Botswana, Brazil, and Papua New Guinea, chlamydia prevalence of 10-20% has been observed, with gonorrhoea prevalence of 5-10% in South Africa and Papua New Guinea and 1-2% in Botswana and Brazil. Chlamydia and gonorrhoea, when transmitted during labour, can cause neonatal conjunctivitis and chlamydia can cause neonatal pneumonia. During pregnancy, chlamydia and gonorrhoea have also been associated with other adverse outcomes, including preterm birth, premature rupture of membranes, low birth weight and perinatal death. These associations are not consistent, however; they are subject to confounding and biases in selection and measurement. Chlamydia and gonorrhoea in pregnancy do not seem to increase the risk of HIV mother-to-child transmission. Further research is needed to understand the causal role of chlamydia and gonorrhoea at different stages of pregnancy, and to understand biological mechanisms and the role of other co-infections and interactions with the vaginal microbiota. To prevent adverse pregnancy outcomes, robust evaluation of interventions is needed. In a cluster-randomised trial in Rakai, Uganda, presumptive antimicrobial treatment versus syndromic management reduced infection prevalence and several adverse outcomes, but resulted in overtreatment. There are no completed randomised trials of antenatal screening for C. trachomatis and/or N. gonorrhoeae globally. Near-patient molecular diagnostics will make screening in low- and middle-income settings more feasible. A cluster crossover trial in Papua New Guinea comparing near-patient screening with syndromic management will end in December 2020 and planned trials in China, Ethiopia, and South Africa will add to the evidence base.

56 MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B: CAN IT BE ELIMINATED?
Yusuke Shimakawa, Institut Pasteur, Paris, France
Viral hepatitis, the 7th leading cause of death worldwide, is now integrated into the United Nations Sustainable Development Goals. Consequently, the WHO developed a global strategy to eliminate viral hepatitis as a public health threat by 2030, aiming to reduce the incidence of chronic infection with hepatitis B virus (HBV) by 90% and its mortality by 65%. To achieve these elimination goals, it is essential to prevent perinatal mother-to-child transmission (MTCT) of HBV. Compared to horizontal transmission, MTCT is associated with an increased risk of developing chronic HBV infection, and also with an elevated risk of liver disease progression in those who became a chronic carrier. Moreover, a successful implementation of infant vaccination program over the last decades using a combined vaccine (pentavalent: DTP-hepB-Hib) at 6-10-14 weeks of life effectively prevented horizontal transmission of HBV but not MTCT; this may lead to a change in HBV epidemiology with an increase in the relative contribution of MTCT among new infections. In order to prevent MTCT, the WHO recommends that, in addition to at least two doses of infant vaccine, all neonates should receive the first dose of monovalent hepatitis B vaccine as soon as possible after birth, preferably within 24 hours (birth dose vaccine: HepB-BD). However, this strategy is not well implemented, particularly in sub-Saharan Africa, because many African countries have not yet integrated HepB-BD in the national immunization program. Moreover, even the countries that started HepB-BD face logistical challenges for its timely administration due to high frequency of child birth outside health facilities. Recently, there is accumulating evidence, particularly from Asia, suggesting the efficacy and safety of peripartum antiviral prophylaxis using nucleos(t)ide analogues in pregnant women with high HBV DNA levels, in addition to neonatal immunoprophylaxis with HepB-BD and hepatitis B immune globulin (HBIG). This additional strategy, combined with high HepB-BD coverage, may certainly accelerate the elimination of HBV MTCT, if these evidence-based interventions are carefully tailored to women living in low- and middle-income countries where the access to HBV DNA test or HBIG is still severely limited.

57 BEYOND THE STIGMA: A SORELY NEEDED PERSPECTIVE ON HSV
Anna Wald, University of Washington, Seattle, WA, USA
HSV-1 and 2 infections are common across the globe with recent prevalence estimates of 3709 million cases of HSV-1 (including 140 million cases of genital HSV-1 infection) and 417 million cases of HSV-2 infection. Women are at higher risk and acquire HSV-2 at a younger age than men. Prevalent HSV-2 increases risk of HIV acquisition 2-3 fold. An estimated 14,000 infants contract neonatal HSV infection each year, a frequently fatal disease. The risk of transmission to the newborn is highest if a woman acquires genital herpes toward the end of pregnancy. Current standard of care is to treat women with recurrent genital herpes with suppressive antivirals toward the end of pregnancy; although this approach may reduce cesarean sections, it has had no effect on the incidence of neonatal herpes. The risk of neonatal herpes in infants born to women with established infection is very low. Implementation of control strategies is hampered by lack of evidence-based interventions. Patient management is limited by lack of commercial accurate serologic assays; only partial effectiveness of antiviral for HSV in reducing the risk for sexual transmission, and persistent stigma associated with this infection. While resistance to currently available therapies occurs almost exclusively among immunocompromised patients, alternative therapies for such patients are inadequate and no new drugs have been developed for several decades. A number of vaccines are in development, mostly aimed at therapeutic use. Lack of knowledge about immune correlates of protection complicates the evaluation of candidate vaccine products. However, elimination of HSV infections is likely to be achieved only through prophylactic immunization.

58 REFLECTIONS ON THE UK EPIDEMIC
Valerie Delpech, Public Health England, London, UK
For the third year running, reports of new HIV diagnoses among men and women fell dramatically in the England largely driven by a decline in new diagnoses among gay, bisexual and other men who have sex with men (GBM) residing in London. A CD4 back-calculation model indicates that transmission among GBM has fallen since 2012 — from 2,800 new infections (95% credible interval [CrI] 2,600 to 3,000) that year, to 800 (CrI 500 to 1,400) in 2018 (a 71% drop). Over this period the estimated number of GBM with undiagnosed infection more than halved to 3,600 — with an overall prevalence of 88 per 1,000. In contrast the prevalence of HIV among men and women who acquired HIV heterosexually is overall low (1.1 per 1,000) and greater among black Africans (36 per 1,000). Furthermore, in 2018 about two-thirds of heterosexuals diagnosed were born abroad and half probably acquired HIV abroad. Overall an estimated 3,200 heterosexuals were unaware of their infection in 2018, the majority were women.

The fall in transmission is a success story of combination prevention in the making. Universal and free access to testing and treatment to all citizens is at the core of this success, together with a dedicated HIV sector. Targeted prevention and testing began early in the response. Substantial increases in testing across all groups occurred in the past decade. HIV tests by GBM at STI clinics increased from 61,000 to 165,000 and a doubling of repeat testers to over 40,000.

Treatment guidelines have recommended the early initiation of treatment since 2015. By 2016, >80% of people newly diagnosed begin treatment within 3 months (regardless of gender or sexuality) compared to 53% in 2014. The proportion reaches 90% in certain high throughput clinics in London. Test and Treat strategies have led to the exceedance of the UNAIDS 90:90:90 target across all populations (these were 93:97:97 in 2018).

Scaling up of PrEP is relatively recent with informal use since 2015. By 2018 over 15,000 GBM were receiving PrEP through an STI clinic across England – with demand outstripping supply (uptake among other higher-risk persons remains very low). The expected introduction of a large-scale national PrEP programme is likely to accelerate the decline in HIV incidence provided test and treat strategies are sustained at high levels for all communities.

59 30-PLUS YEARS OF HIV IN RAKAI: THE EPIDEMIC RECEDES
Joseph Kagaayi, Rakai Health Sciences Programme, Kalisizo, Uganda
HIV was first documented in Rakai, Uganda in the early 1980s. For over 30 years, the Rakai Health Sciences Program (RHSPI) tracked the epidemic, and in 1994, established the Rakai Community Cohort Study (RCCS) among 10,000-20,000 residents ages 15-49 residing in agrarian/trading communities. In 2011, hyper-endemic fishing communities were added. A trial of sexually transmitted infection control for HIV prevention (1994-1999), nested in the RCCS, did not reduce HIV incidence. However, secondary data analyses showed that higher
viral load (VL), early and late stages of HIV infection, and uncircumcised men were key drivers of the epidemic. The protective effect of safe male circumcision (SMC) was later confirmed in three trials, one of which was nested in the RCCS. Reduction of VL with ART became the basis for treatment-as-prevention. Since 2004, with PEPFAR/CDC Uganda support, RHSP has scaled-up combination HIV interventions (CHI). RHSP now leads implementation in 12 districts, overseeing 161 clinics with over 110,000 persons on ART and over 250,000 circumcisions to-date. Recently, we evaluated trends in SMC and ART coverage, VL suppression, sexual behaviors, and HIV incidence and prevalence in 30 agrarian/ trading and four fishing communities. In agrarian/trading communities, HIV prevalence was 15.9% in 1994 and incidence was 1.5/100 person-years. Between 2004-2016, ART coverage rose from 0% to 69%; VL suppression rose to 75%; SMC coverage increased from 15% to 59%. Except for delayed sexual debut among adolescents (15-19), we did not observe other changes in sexual behaviors. Between 2004 and 2016, HIV incidence declined by 42% (1.17 to 0.66/100 person-years) while prevalence remained relatively stable. In fishing communities, ART coverage increased from 16% to 82%; VL suppression rose from 34% to 80% and SMC increased from 35% to 65% between 2011 and 2016. HIV incidence declined by 48% (3.43 to 1.59/100 person-years). Despite these reductions, HIV incidence remains above epidemic control rates. Ongoing epidemiological/phylogenetic studies in the RCCS suggest that in-migration and hard-to-reach persons contribute to ongoing transmissions. In conclusion, CHI reduced HIV incidence, but challenges remain. The RCCS has proved invaluable for discovery, intervention testing, and evaluation of real-world impact on HIV incidence. By combining research with intervention delivery, each informing the other, RHSP been able to translate science into population-level impact.

**60** BATTLING HIV IN THE US RURAL SOUTH

Leandro A. Mena, University of Mississippi Medical Center, Jackson, MS, USA

The South’s disproportionate burden of HIV and health care disparities is driven in part by many socioeconomic, cultural and structural factors. This talk will describe challenges to HIV prevention and care especially in the rural South as well as promising strategies aiming to promote equitable access to HIV services throughout the region.

**61** HOW DO WE STOP THE BAND FROM PLAYING ON IN THE US?

Carlos Del Rio, Emory University, Atlanta, GA, USA

Concerted efforts and significant investments in HIV prevention and care resulted in a 69% decline in mortality and a 48% reduction in new diagnoses in the US since the mid-1990s. However, despite over $20B of Federal funding in domestic HIV efforts, new diagnoses have stabilized at about 38,000 for nearly a decade, down only 7.0% from 2012. The US epidemic is not a national epidemic but rather a collection of microepidemics disproportionately affecting racial/ethnic and sexual minorities with 43% of new diagnoses among Blacks, 69% attributed to male-to-male sexual contact and 52% occurring in the Southern States. If current rates persist, 41% of black MSM and 22% of Hispanic MSM in the US will be diagnosed with HIV during their lifetimes. On February 5, 2019, at the State of the Union Address, the President announced the intention to End the US will be diagnosed with HIV during their lifetimes. On February 5, 2019, at the State of the Union Address, the President announced the intention to End the HIV epidemic in the US by reducing new infections by 75% within 5 years. However, despite over $20B of Federal funding in domestic HIV efforts, HIV incidence remains above epidemic control rates. Ongoing epidemiological/phylogenetic studies in the RCCS suggest that in-migration and hard-to-reach persons contribute to ongoing transmissions. In conclusion, CHI reduced HIV incidence, but challenges remain. The RCCS has proved invaluable for discovery, intervention testing, and evaluation of real-world impact on HIV incidence. By combining research with intervention delivery, each informing the other, RHSP been able to translate science into population-level impact.

**62** PREVENTING HIV AMONG PEOPLE WHO INJECT DRUGS: PLUS ÇA CHANGE, PLUS ÇA MÊME CHOSE

Steffanie A. Stratthdee, University of California San Diego, San Diego, CA, USA

In 1997, I presented at CROI on a new HIV outbreak that I helped identify among people who inject drugs (PWID) in Vancouver, Canada, where HIV incidence peaked at 18.6 per 100 person years. The response was to expand needle exchange programs (NEPs), medication for opioid use disorder (MOUD) and mobile HIV testing. Later, Vancouver opened North America’s first supervised injection facility (SIF) and adopted a policy of HIV treatment as prevention (TasP). HIV incidence among PWID plummeted and no social harms associated with its NEP or SIF were documented. In contrast, except for a 2-year period, US Congressional law prevented the use of federal funds to support NEPs until 2015. The US is now in the midst of one of its most serious opioid epidemics with several injection drug use-associated HIV outbreaks, over 40,000 new HCV infections each year and co-occurring epidemics of overdose, endocarditis and syphilis. What has been done to prevent HIV outbreaks among PWID? This presentation will identify missed opportunities and in some cases, progress made to prevent HIV outbreaks in rural settings. For example, a modeling study estimated that if Scott County, IN had launched an earlier response, 200 HIV infections could have been prevented. In W. Virginia, ongoing HIV outbreaks in Huntington and Charleston are exacerbated by restrictions and/or closure of NEPs and an effort to make them illegal, alongside a moratorium on new methadone programs. In these and other U.S. states, structural barriers to accessing MOUD are the rule rather than the exception, although innovations like hospital-based MOUD programs show promise. Across the US, only one (underground) SIF exists. As we approach the 4th decade of the HIV pandemic, we know how HIV is transmitted among PWID and their networks. A plethora of scientific evidence shows that harm reduction programs can avert HIV epidemics. Yet at the federal level, most funding from the U.S. Office of National Drug Control Policy is spent on law enforcement/interdiction and little on prevention of drug use, which could have important downstream effects. Preventing HIV and co-occurring syndemics among PWID necessitates addressing the structural drivers of addiction including homelessness, unemployment, lack of health insurance and cycles of incarceration. The US needs to abandon its war on people who use drugs and treat addiction as a medical condition rather than a moral failing.
with an enzymatically inactive ORF21 protein we show that the tyrosine kinase function of ORF21/TK is not required for the progression of the lytic replication in tissue culture, but that it is essential for the phosphorylation and activation to toxic moieties of the antiviral drugs zidovudine and brivudine. In addition, we identify several tyrosine kinase inhibitors, approved for clinical use against human malignancies, which potently inhibit not only ORF21/TK kinase function, but also viral lytic reactivation and the development of KSHV-infected endothelial tumors in mice. The most potent inhibitors of KSHV TK autophosphorylation, KSHV reactivation and KSHV-dependent tumor formation in a xenograft model were dasatinib, irinotecan, and ponatinib.

Conclusion: Since the identified kinase inhibitors target both cellular tyrosine kinases supporting productive viral replication and the KSHV lytic kinase, these drugs (dasatinib, irinotecan, ponatinib), which are already approved for clinical use, may be suitable for repurposing for the treatment of KSHV-related tumors in AIDS patients or transplant recipients.

65LB A ROLE FOR IRON METABOLISM AND FERROPTOSIS IN KAPOSI SARCOMA HERPESVIRUS PATHOGENESIS

Ramya Ramaswami, Jean Gustin

Background: Iron is an essential element for normal cellular function, and many tumor cells satisfy their high iron requirement via altered expression of proteins that regulate iron metabolism. While iron fuels tumor growth, it presents a paradox: how to maintain redox homeostasis and resist ferroptosis, a ROS-reliant and iron-dependent form of regulated cell death. Many tumor types resist the ferroptotic cascade via increased expression/activity of antioxidant ferroptosis suppressor pathways (FSPs). To date, two complementary but non-redundant pathways have been identified: a canonical glutathione (GSH)-dependent pathway and, more recently, a novel FSP that relies on ubiquinol (the reduced form of CoQ) to prevent lethal lipid peroxidation. Our goal is to determine how the oncogenic Kaposi sarcoma herpesvirus (KSHV) manipulates host iron metabolism and antioxidant defense to promote Kaposi sarcoma (KS) tumorigenesis while resisting ferroptosis.

Methods: Lymphatic endothelial cells (LEC) de novo-infected with KSHV-BAC16 were used for this study. Expression of host genes involved in iron metabolism and ferroptosis resistance was evaluated by RNA-seq, qPCR, immunoblot, FACS and IFA. Cellular iron content was measured by ICP-MS. Markers of pro-antioxidant status (e.g., ROS, GSH) were measured via quantitative colorimetric assay. Susceptibility to ferroptosis was evaluated using selective inducers and inhibitors, and measured via cell viability and lipid peroxidation assays.

Results: Our data indicate that KSHV manipulates the host iron regulon to promote iron acquisition and an iron-responsive growth phenotype. However, despite these changes, infected cells do not succumb to ferroptosis. Notably, KSHV significantly upregulates the expression of xCT, the small subunit of system xC- that functions as the upstream node of the GSH-dependent FSP. Chemical inhibition of xCT induces ferroptotic death only in KSHV-infected LEC, suggesting that enhanced xCT function is central to the ability of infected cells to resist ferroptosis. KSHV also upregulates the oxidoreductase FSP1 (formerly AIFM2), the key component of the novel CoQ-dependent FSP, identifying a second ferroptosis escape mechanism in infected cells.

Conclusion: We have identified unique vulnerabilities in KSHV-infected cells that reflect the delicate pro/antioxidant balance required to facilitate growth and survival. Our work suggests that selective induction of ferroptosis in KSHV-infected cells represents a promising anti-KS strategy.

66 GENE EXPRESSION PATTERNS IN SKIN VS GASTROINTESTINAL KAPOSI SARCOMA LESIONS

Ramya Ramaswami, Takanobu Tagawa, Vishal Kopaar, Kathryn Lurain, Anna Serquina, Anaïda Wildel, Irene Ekvede, Robert Yarchoon, Joseph Ziegelsbauer

Background: Kaposi sarcoma (KS), caused by Kaposi sarcoma herpesvirus (KSHV), is a multifactorial tumor characterized by abnormal vasculature and proliferation of KSHV-infected spindle cells. KS involves the skin (sk) but can also affect the gastrointestinal tract (gi) in severe cases. Little is known about host and viral gene expression differences in patients with KS lesions. Here, we performed RNA sequencing of skin and gi lesions from KS patients with KS to understand the similarities and differences in the gene expression pattern.

Methods: We obtained fresh skin and gi KS lesions with matched normal skin and gi samples. Total RNA was extracted from samples and RNA expression was analyzed using paired-end RNA-seq. Differential gene expression was measured by comparing KS lesions to normal matched samples. We used programs STAR and DESeq2 to identify differentially expressed genes with a False Discovery Rate cut-off of 0.05.

Results: Six samples were obtained (sk 4 and gi 2) from 5 HIV+ patients with KS. All tumors were stage T1. Only 2 pts had received prior KS therapy. In sk KS, cellular gene networks associated with cell adhesion (extracellular matrix), immune response, angiogenesis, and proteolysis were dysregulated when compared with normal skin. There were 13 cellular genes increased in both sk and gi KS lesions (Figure 1). Of these genes those that were clinically significant included FLT4, which encodes for a receptor of VEGF-C and VEGF-D, and RIOX1, a histone demethylase and potential independent prognostic factor for venous invasion and lymphatic duct invasion in colon cancer. The most expressed viral genes were a mixture of latent and lytic genes in skin KS samples. There were more lytic viral genes detected in gi KS as compared to skin KS, which may be due to more advanced KS or a difference in lytic activation in gi tissues. One patient had both sk and gi KS (with matched normal samples), which demonstrated 19 genes that were strongly increased in both tissues and included cellular genes ADAMTS4, RIOX1, ACAN.

Conclusion: This is one of the first studies comparing sk and gi KS that highlights differences in viral gene and clinically relevant host gene expression between these tissues. By analyzing these gene expression patterns, this ongoing study will improve our understanding of KS pathogenesis.

67LB IMPACT OF VALGANCICLOVIR THERAPY ON SEVERE IRIS–KAPOSI SARCOMA–ATTRIBUTABLE MORTALITY

Patricia Volkow, Beda Daniela Islas Muñoz, Leslie Chávez-Galán, Lucero Ramón-Luindo, Doria Patricia Cornejo Juárez, Judith Cruz-Velázquez

Background: High HHV-8 viral load (VL) has been associated with severe KS lesions in AIDS patients with at least two of the following: pulmonary disease, 30 skin lesions, lymphedema, lymph node involvement, GIT involvement. Exclusion criteria: other malignant disease, steroid treatment, active Hepatitis B or C, CMV end-organ disease; and APACHE >15. S-IRIS-KS definition: abrupt clinical exacerbation of KS after starting cART and at least 3 of the following parameters: thrombocytopenia, anemia, hypotension, hypoalbuminemia or fever. Experimental group (EG) started valganciclovir 900 mg BID 4 weeks before cART and continued until week 48; control group (CG), two died in the EG (opiod overdose and H1NI pneumonia). Four patients in the EG developed S-IRIS-KS and was excluded. Three patients died due to S-IRIS-KS in the CG, one in the EG. In each visit HHV-VL, HHV-8 VL (ELITe M GB KIT) CD4 and CD8 count by flow cytometry.

Inclusion criteria: AIDS cART naïve patients with at least two of the following: pulmonary disease, 30 skin lesions, lymphedema, lymph node involvement, GIT involvement. Exclusion criteria: other malignant disease, steroid treatment, active Hepatitis B or C, CMV end-organ disease; and APACHE >15. S-IRIS-KS definition: abrupt clinical exacerbation of KS after starting cART and at least 3 of the following parameters: thrombocytopenia, anemia, hypotension, hypoalbuminemia or fever. Experimental group (EG) started valganciclovir 900 mg BID 4 weeks before cART and continued until week 48; control group (CG), two died in the EG (opiod overdose and H1NI pneumonia). Four patients in the EG developed S-IRIS-KS and was excluded. Three patients died due to S-IRIS-KS in the CG, two died in the EG (opioid overdose and H1NI pneumonia). Four patients developed 12 episodes of S-IRIS-KS in the CG (OR of 0.21 per 100 patient-days), two patients, one episode each in the EG (OR 0.03 per 100 patient-days) p=0.007. In multivariate poisson or negative binomial models, higher-baseline CD44 decreased and higher HHV-8 VL increased consistently the risk of S-IRIS-KS; Valganciclovir treatment reduced S-IRIS-KS events (IRR = 0.06, 95%CI 0.004-0.7
68 SURVEILLANCE OF RHESUS MACAQUE TISSUES IDENTIFYING GAMMAHERPESVIRUS INFECTION SITES

Vickie Marshall1, Catherine Brands1, Nazarena Labo2, Vicky Coalert3, Jeffrey D. Lifson4, Denise Whitby1, Claire Deleage1, Gregory Q. Del Prete1

1AIDS and Cancer Virus Program, Frederick, MD, USA

Background: Gammaherpesviruses are a clinically significant cause of cancer and are primarily transmitted via saliva. However, the specific sites of viral replication in oral tissues resulting in salivary shedding are poorly understood. Rhesus macaques (RM) are naturally infected with three gammaherpesviruses: retropoetional fibromatosis herpesvirus (RFHV), an ortholog of KSHV, rhesus lymphocyctovirus (RLCV), closely related to EBV, and rhesus rhadinovirus (RRV). Rhesus macaques have been used as models of gammaherpesvirus-associated malignancies in the context of SHIV/SIV infection and offer an opportunity to study oral biology of gammaherpesviruses in greater detail.

Methods: Oral fluid and oral tissues from 30 RM experimentally infected with SIV or not were collected during necropsy. These included buccal and gingival tissue, parotid, submandibular and sublingual salivary glands; submandibular lymph nodes, adenoid, palate and inguinal tonsil, soft palate and tongue. DNA was extracted and tested by qPCR for RRV, RLCV, and RFHV viral load. In situ hybridization targeting viral DNA was performed, for all 3 viruses, in all tissue types and highly positive tissues were used to phenotype the cells harboring viral DNA.

Results: Rhesus gammaherpesviruses were detected in the oral fluid and oral tissues of all 30 animals examined; many were positive for more than one virus. By qPCR, the highest levels of RFHV were identified in gingiva, tongue, and submandibular lymph nodes while the highest levels of RLCV and RRV were detected in adenoid and palatine tonsil. Using ISH, most infection events for RFHV were detected in adenoid and palatine tonsil. Multiplexing ISH with antibody-based phenotyping revealed a broad range of infected cell types including T-lymphocytes, fibroblasts, epithelial cells, and NK-cells. Certain infected cell types, especially for RFHV, remain unidentified and phenotyping experiments are ongoing.

Conclusion: This is the first study examining RRV, RLCV, and RFHV viral load in rhesus oral tissues and oral fluid and may provide insights into human gammaherpesvirus biology within the oral compartment.

69 CONJUNCTIVAL CANCER IN PEOPLE LIVING WITH HIV: THE SAM STUDY

Tafadzwa G. Dhokotera1, Mazviita Sengwii2, Lisa Bartels3, Frédérique Chammartin4, Serra L. Asangbehi4, Victor Olaga5, Elivira Singh6, Matthias Egger7, Julia Bohlius1

1Institute of Social and Preventive Medicine, Bern, Switzerland, 2National Health Laboratory Service, Johannesburg, South Africa

Background: Conjunctival cancer has been associated with HIV in sub-Saharan Africa but, the evidence on its epidemiology is scarce. According to the 2014 National Cancer Registry (NCR) report, the incidence of eye cancer was 1.13 and 1.25 per 100 000 of the population in males and females respectively. We aimed to determine the incidence of conjunctival cancer amongst people living with HIV (PLWHIV) and the associated risk factors.

Methods: The South African HIV Cancer Match (SAM) study used privacy preserving record linkage to create a large cohort of cancer in PLWHIV from national laboratory and NCR data 2004-2014. We used the ICD-0-3 coding to identify conjunctival cancers. We calculated crude incidence rates of conjunctival cancer and used Cox regression to obtain hazard ratios (HR) of CD4 cell count, age, sex and calendar period, stratified by province.

Results: Over 12 547 950 person-years of follow-up, 3,359 incident conjunctival cancer cases were diagnosed in the SA cohort of 4 766 614 PLWHIV. Approximately 94% (n=1 274) of conjunctival cancers were squamous cell carcinomas. The median age at entry into the cohort was 33 years (Interquartile Range [IQR]: 26-41 years) and 38 years (IQR: 33-44 years) at cancer diagnosis. There was an upward trend in CD4 cell counts across the years from a median of 240 cells/µl at baseline to 294 cells/µl at diagnosis in 2004 to 340 cells/µl in 2014. The crude conjunctival cancer incidence IR was 11.0 per 100 000 persons-year (95% Confidence Interval [CI]: 10.2-11.4).

Conclusion: To our knowledge, this is the largest epidemiological study of conjunctival cancer in PLWHIV ever done. Our results indicate that immunodeficiency as indexed by lower CD4 counts, immune senescence and prolonged UV light exposure (both indexed by age) are strongly associated with conjunctival cancer risk. The decrease in incidence in more recent calendar periods might reflect increased ART coverage across time and initiation of ART at higher CD4 cell counts. Our analysis suggests that effective HIV control is essential for the prevention of conjunctival cancers. We recommend symptom screening and communication of conjunctiva cancer risk to PLWHIV as well as their clinicians.

Table 1: Crude incidence rates of conjunctival cancer per 100,000 person-years and hazard ratios from multi-factor Cox regression model

<table>
<thead>
<tr>
<th>CD4 count (cells/µl)</th>
<th>Incidence rate (IR)</th>
<th>Hazard ratio (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>0.34 (0.13-0.87)</td>
<td>1</td>
</tr>
<tr>
<td>200-350</td>
<td>0.90 (0.50-1.68)</td>
<td>0.54 (0.40-0.72)</td>
</tr>
<tr>
<td>350-500</td>
<td>1.48 (0.72-2.67)</td>
<td>0.75 (0.51-1.14)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>4.22 (2.28-7.99)</td>
<td>1.73 (0.81-3.70)</td>
</tr>
</tbody>
</table>

Age category (years)

| 10-14    | 1.00 (0.60-1.79)   | 1.00 (0.60-1.79) |
| 15-19    | 1.21 (0.92-1.60)   | 1.00 (0.60-1.79) |
| 20-24    | 1.08 (0.72-1.50)   | 1.00 (0.60-1.79) |
| 25-29    | 1.61 (1.04-2.44)   | 1.00 (0.60-1.79) |
| 30-39    | 1.70 (1.13-2.53)   | 1.00 (0.60-1.79) |
| 40-49    | 1.98 (1.31-2.97)   | 1.00 (0.60-1.79) |
| 50-59    | 1.94 (1.29-2.93)   | 1.00 (0.60-1.79) |
| >60      | 1.94 (1.29-2.93)   | 1.00 (0.60-1.79) |

Gender

| Male | 1.00 (0.60-1.79)   | 1.00 (0.60-1.79) |
| Female| 0.99 (0.60-1.79)   | 1.00 (0.60-1.79) |

*Adjusted for CD4 cell count, calendar period, age and sex. Stratified by province of first HIV test.

**Incidence rates per 100,000 person-years.

70 CLEARANCE OF HPV ANAL HIGH-GRADE INTRAEPITHELIAL LESIONS WITH LOW-DOSE POMALIDOMIDE

Mark Polizzotto1, David Van Bockel2, Carmella Law3, Jennifer Roberts4, Susanne Just5, Griselda Buckland6, Simon Comber7, Mary Poynter8, Richard Hillman9, Richard Gilson10, Sarah Pett11, Anthony Kelleher12, John Emery13, for the SPACE Study Group

1 Kirby Institute, Sydney, NSW, Australia, 2St. Vincent’s Hospital, Sydney, NSW, Australia, 3Douglass Hanly Moir Pathology, Macquarie Park, Australia, 4Mortimer Market Centre, London, UK, 5MRC Clinical Trials Unit at UCL, London, UK

Background: People with HIV (PLWH) have an increased risk of anal cancer. This is preceded by high-grade squamous intraepithelial lesions (HSIL). Spontaneous clearance of HSIL is associated with systemic T-cell response to human papillomavirus (HPV) oncogene E6. Pomalidomide may enhance immune responses to HPV and be therapeutic in HSIL.

Methods: This phase II single centre study (NCT3113942) recruited participants with persistent (>12 months) biopsy-proven anal HSIL. Therapy was oral pomalidomide 2mg 21/28 days for 6 months. PLWH were eligible if on ART with persistent (> 12 months) biopsy-proven anal HSIL. Therapy was oral pomalidomide 2mg 21/28 days for 6 months. PLWH were eligible if on ART with persistent (> 12 months) biopsy-proven anal HSIL.

Results: Participants (n=24) had a median age of 35 years (IQR: 30-42) and median CD4 cell count of 428 cells/µl (IQR: 261-601). Analysis of biopsies showed a median of 17.2% (IQR: 7.5-27.3) of HSIL regression at 2 months. At 6 months, 23% (95% CI: 11.7-34.2) of lesions showed HSIL regression. This is consistent with a previous study of 38% HSIL clearance with continuous ART. A significant increase in systemic CD4 T-cell count was observed (p=0.01). Analysis of systemic CD8 T-cell to HPV E6-specific response showed no correlation with HSIL clearance. However, there was a trend towards increased immune response with higher CD4 count and months on ART.

Conclusion: Pomalidomide may be an effective therapeutic option for high-grade anal intraepithelial lesions in PLWH. Further studies are needed to investigate the role of systemic immune response to HPV E6 in HSIL clearance.

* p-value from Cox proportional hazards regression.
Increased Cancer Risk with Lower CD4/CD8 Ratio Among Adults with HIV in NA-ACCORD

Jessica L. Castilho, Aihua Bian, Cathy Jenkins, Chad J. Achenbach, W. C. Matthews, Greer Burkholder, M. J. Gill, Janet Tate, Angel M. Mayor, Mari M. Kitahata, Michael J. Silverberg, Richard D. Moore, Keith M. Sigel, Staci Sudenga, for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA.

Methods: The Authors examined records of 75,161 PLWH who were part of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). They used Cox proportional hazards regression to evaluate time to first cancer diagnosis from cohort entry and with ≥1 CD4/CD8 ratio in 12 NA-ACCORD cohorts between 1998-2016. Cancer outcomes were validated in each cohort. Risk of cancer and 6-month-lagged CD4/CD8 ratio were evaluated in multivariable, time-varying Cox proportional hazards models. The models included time-varying covariates like time-varying CD4/CD8 ratio, age, race, hepatitis C virus coinfection, and smoking. The models also included time-varying factors like time-varying depressive symptoms and time-varying mood disorders.

Results: Among 75,161 PLWH, there were 5046 incident cancer diagnoses. Most frequent cancers were lung cancer (n=714), non-Hodgkin lymphoma (NHL, n=459), Kaposi sarcoma (KS, n=440), and anal cancer (n=375). Median age at cohort entry was 43 years, 90% were male, and 44% were white. The median CD4/CD8 ratio during the observation period was 0.49 (interquartile range: 0.27-0.79). Adjusted hazard ratios for CD4/CD8 ratio and any cancer and specific cancers are shown in the Figure. For any cancer and specific cancers, non-linear CD4/CD8 ratio was inversely associated with cancer risk in adjusted models (p<0.01).

Conclusion: Low CD4/CD8 ratio was consistently associated with increased cancer risk, independent of CD4 count and HIV RNA. Further research into the causes of CD8 cell inflation and persistent immunologic disturbance in PLWH is needed. CD4/CD8 ratio may serve as useful clinical biomarker for cancer risk in PLWH.

Figure: Hazard ratios for 0.50 and 0.25 onto the 0.75 of the 6-month lagged CD4/CD8 ratio for all cancers and for specific cancers, adjusting for sex, race, age, hepatitis C virus coinfection, lagged CD8 cell count, and lagged HIV RNA.

Whole-Body PET Imaging of the HIV Reservoir Using Radiolabeled VRC01

Timothy J. Henrich, Denis Beckford-Vera, Enrique Martinez- Ortiz, Maya Aslam, Cassandra Thanh, Shreya Kumar, I-Wei Katherine Wu, Rebecca Hoh, Robert Flavell, Youngho Seo, Marion Pardons, Nicolas Chomont, John R. Mascola, Steven G. Deeks, Henry VanBrocklin.

Methods: PET-MRI imaging using 89Zr-VRC01 (100 uCi) was performed on 5 viremic participants (plasma HIV-1 RNA ranging from 3,459 to 789,705 c/mL), 4 ART-suppressed participants (duration of ART ranging from 3.5 to 280 months), and 5 uninfected controls. PET-MRI imaging was performed 2h, 6h, 24h, 72h (day 3), and, in a subgroup of 6 participants, 122h (day 6) following a single 1 mcg injection of 89Zr-VRC01. Radiotracer maximum and mean standard uptake values (SUVmax, SUVmean) adjusted for blood pool background signal were quantified for various lymphoid and other anatomical regions of interest.

Results: Adjusted 89Zr-VRC01 SUVs were significantly higher in inguinal and axillary lymph nodes, nasal-associated lymphoid tissue (NALT), and bone marrow in viremic participants compared with uninfected controls (all P<0.05). SUVmax (NALT, bone marrow) and SUVmean (inguinal lymph node) were significantly higher in ART-suppressed individuals compared with uninfected controls, and generally lower than in viremic participants. The greatest differences between SUVs in HIV-infected and control participants were observed 72h after tracer injection, although differences in tracer uptake in inguinal lymph node tissue were observed up to 6 days following tracer injection (Figure). 89Zr-VRC01 inguinal lymph node SUVmax in viremic and ART-suppressed participants positively correlated with the frequency of p24

Whole-Body PET Imaging of the HIV Reservoir Using Radiolabeled VRC01
expressing cells measured by flow cytometry in fine needle aspirates (p=0.017).
89Zr-VR01 tracer uptake in lymphoid tissues was lower in participants who were on suppressive ART for longer periods of time.

**Conclusion:** HIV envelope-specific PET imaging was able to detect differences between HIV-infected individuals, including those on suppressive ART, and uninfected participants. Importantly, PET tracer uptake correlated with measures of HIV protein expression in tissue. These data suggest that PET imaging of HIV-infected cells has the potential to localize and quantify multiple anatomical HIV reservoirs in a wide range of HIV persistence and curative studies.

**73 ANTIGEN-DRIVEN CLONAL SELECTION SHAPES THE FATE OF HIV-INFECTED CD4+ T CELLS IN VIVO**

Francesco R. Simonetti1, Hao Zhang2, Garshash Soroosh3, Subal A. Beg4, Jiayi Duan5, Kyle Rhodehouse6, Christopher L. Nobles7, Jun Lai8, Rebecca Hoh9, Steven G. Deeks4, Frederic Bushman3, Janet Siliciano1, Robert Siliciano1, John F. Mellors2, for the ACTG A5321 team

1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2University of Pennsylvania, Philadelphia, PA, USA, 4University of California San Francisco, San Francisco, CA, USA

**Background:** Although proliferation of infected CD4+ T-cells is a major mechanism of HIV persistence, the causes of this phenomenon remain unclear. We hypothesized that recurrent antigenic exposure contributes, via clonal selection, to the expansion and maintenance of HIV-infected cells.

**Methods:** We enrolled 10 HIV+ CMV+ donors on ART. PBMCs were briefly stimulated with CMV lysates, GAG peptides or αCD3/28 antibodies. We sorted responding (CD40L+CD69+) and non-responding memory (CD40L-CD69-) CD4+ T-cells. Single genome sequencing was used to identify proviruses. To study HIV-infected clones, we sorted cells in small pools at limiting dilutions and subjected to whole genome amplification. Proviruses from Ag-specific clones were analyzed by IPDA, integration site and full-length sequencing. We used TCR sequencing to study VDJ rearrangements in sorted cells and infected clones. A viral outgrowth assay (VOA) was used in one donor to identify clones carrying infectious proviruses.

**Results:** PBMC stimulation yielded the expected frequencies of CMV- and GAG-specific CD4+ T-cells (mean 2.8% and 1.1%, respectively). Cells responding to non-specific CD3/28 stimulation (mean 33%) were used as a control. Proviruses in CMV-specific cells showed a higher proportion of identical sequences (0.73 vs 0.26, p<0.0001) and higher clonality (mean Gini 0.6 vs 0.2, p=0.0002) than the non-specific control. GAG-specific cells had detectable but less abundant identical sequences. Clonal proviruses were confirmed by integration site analysis. Some clones had integrants in genes previously identified in other individuals on ART, such as BACH2, STAT5B and MKL1. TCR sequencing confirmed a higher clonality of CMV-specific cells compared to GAG-specific and non-responding memory cells (mean clonality 0.2 vs 0.05 vs 0.03, respectively). Most clones carried defective proviruses (hypermutation, deletions, inversions). In one individual, the VOA from CMV-specific cells identified the same isolate in 4 wells that matched identical DNA sequences from CMV-specific cells collected 8 months previously, suggesting the persistence of a CD4 clone selected over time in response to CMV and that harbored an infectious provirus.

**Conclusion:** We provide in vivo evidence that clonal expansion of HIV-infected cells is common for CMV- and GAG-specific CD4+ T-cells, demonstrating that responses to antigens represent selective forces affecting the persistence of both defective and infectious proviruses.

**DISTINCT CHROMOSOMAL SITE CONFIGURATION IN HIV-1 ELITE CONTROLLERS**

Chenyang Jiang1, Ce Gao2, Xiaoming Sun3, Xiaodong Lian4, Stephane Hua5, Joshua Chevalier1, Kevin Einkauf1, Eric Serrao1, Alan N. Engelman1, Mary Carrington1, Bruce D. Walker1, Mathias Lichterfeld1, Xu G. Yu1, 1Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, 2Brigham and Women's Hospital, Boston, MA, USA, 3dana-farber Cancer Institute, Boston, MA, USA, 4University of California San Francisco, San Francisco, CA, USA

**Background:** HIV-1 elite controllers (EC) represent a rare group (< 0.5%) of infected individuals who maintain undetectable viral loads in the absence of antiretroviral therapy (ART). However, the distinguishing features of proviral reservoir cells in these individuals are unclear.

**Methods:** Matched integration site and proviral sequencing (MIP-Seq) was applied to PBMC from 11 EC to investigate chromosomal integration sites (IS) of intact HIV-1 proviruses. Chromatin accessibility and gene expression in autologous CD4+ T-cells were measured by ATAC-Seq and RNA-Seq. CD4+ T-cells from 12 EC and 11 HIV-1 negative individuals (HIVN) were infected with a HIV-1 construct, followed by chromosomal IS analysis.

**Results:** In total, 92 IS of intact proviruses were identified in EC, of which 33 were at unique chromosomal locations. Remarkably, we noted that a significantly larger proportion of intact proviruses from EC were located in non-genic, centromeric satellite DNA, compared to 73 unique (100 in total) intact proviral sequences from long-term ART-treated individuals (unique IS: 21% vs. 0%, p=0.0002; all IS: 17% vs. 0%, p<0.0001). Moreover, in comparison to ART-treated patients, IS of intact proviruses from EC were atypically enriched in genes encoding for members of the Zinc Finger Protein family, particularly for KRAB-ZNF on chromosome 19, which contain constitutive heterochromatin (unique IS: 22% vs. 2%, p=0.0091; all IS: 40% vs. 1%, p<0.0001). In addition, we identified significantly increased chromosomal distances from IS of intact proviruses to the most proximal host gene transcriptional start sites (median: 29.3 kb vs. 9.4 kb, p=0.0002) and to accessible chromatin (median: 73.1 kb vs. 8.8 kb, p=0.0004) in CD4+ T-cells from EC, relative to ART-treated patients. Furthermore, >120,000 HIV-1 IS from in vitro infected CD4+ T-cells from EC and HIVN demonstrated that satellite DNA (0.04%-0.12%) and KRAB-ZNF genes (0.49%-0.85%) were infrequently targeted, irrespective of the study cohort.

**Conclusion:** Integration sites of intact proviruses in EC show features of deep latency, likely as the result of selection mechanisms that preferentially eliminated proviruses integrated in chromosomal regions more permissive to viral transcription. This highly distinct chromosomal integration site configuration in EC represents a structural correlate of natural viral control that eradication strategies may have to induce in order to promote a long-term drug-free remission of HIV-1 infection.

**INTACT PROVIRAL DNA LEVELS DECLINE IN PEOPLE WITH HIV ON ANTIRETROVIRAL THERAPY**

Rajesh T. Gandhi1, Joshua C. Cyktor2, Ronald Bosch3, Hanna Mar4, Gregory Laird5, Albine Martin4, Ann Collier5, Sharon Riddler2, Bernard J. Macatangay2, Charles Rinaldo2, Joseph J. Eron6, Robert Siliciano7, Deborah McMahon2, John W. Mellors1, for the ACTG A5321 team

1Massachusetts General Hospital, Boston, MA, USA, 2University of Pittsburgh, Pittsburgh, PA, USA, 3Harvard T.H. Chan School of Public Health, Boston, MA, USA, 4‘Acceleriv Diagnostics, Baltimore, MD, USA, ‘University of Washington, Seattle, WA, USA, 5University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 1Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** The intact proviral DNA assay (IPDA) is a new, more-specific ddPCR-based measure of the replication-competent HIV reservoir. Little is
known, however, about whether intact proviral DNA levels decline over time on ART and whether the levels correlate with other measures of HIV persistence or with immune activation.

**Methods:** Participants in ACTG A5321 with chronic HIV and well documented virologic suppression on ART had the following measurements performed on blood samples: intact proviral DNA, total proviral DNA (sum of defective, hypermutated and intact proviruses), total HIV DNA by qPCR targeting 3’ integrase, cell-associated HIV RNA (CA-RNA), plasma HIV RNA single copy assay (SCA), T cell activation, and inflammation (IL-6, IP-10, sCD14, sCD163, neopterin, TNF-alpha, hscCRP). Testing was performed at median of 7.1 yr after ART initiation (time point 1) and again a median of 3.7 yr later (time point 2).

**Results:** Fifty participants (26% female) were evaluated. Intact proviral DNA levels declined significantly between time point 1 (n=50) and time point 2 (n=48): median of 57 and 41 copies/million CD4 cells, respectively; p<0.001 (Figure). By contrast, total proviral DNA was stable: median of 551 and 580 copies/million CD4 cells, respectively. The estimated (median) half-life of decline for intact proviral DNA (n=44 participants) was 6.5 yrs (95% CI 4.5, 11.2), whereas that for total proviral DNA was 22.9 years (95% CI, 11.1 to 60.9). Six participants had decline in intact proviral DNA to undetectable levels. Higher on-ART intact proviral DNA levels correlated with higher on-ART total HIV DNA (r=0.48), higher CA-RNA (r=0.46) and higher SCA (r=0.39) (time point 1; all p-values ≤0.005). No associations were seen between on-ART intact proviral DNA levels and on-ART T cell activation or inflammation.

**Conclusion:** In people on long-term ART, intact proviral DNA levels decline significantly (half-life 6.5 yr), whereas total proviral DNA remains stable over the same time period (half-life 22.9 yr). A subset of individuals had a decline in intact proviral DNA to undetectable levels. The overall decline in intact proviruses implies that cells containing replication-competent proviruses are being lost. Defining the mechanisms involved should inform strategies to accelerate HIV reservoir depletion. The more dynamic nature of the intact proviral landscape, compared with total proviral HIV DNA, supports the use of the IPDA to assess the impact of interventions targeting the HIV reservoir.

77 DELAY IN VIRAL REBOUND WITH TLR7 AGONIST, N6-LS, AND PGT121 IN SHIV-INFECTED MACAQUES

Denise C. Hsu1, Decha Silsorn2, Rawiwan Imerboin2, Amarendra Pegu1, Dutadsane Inthawong2, Jumpol Sopanparn2, Alexandra Schuetz2, James Demarest3, Merlin L. Robb4, John R. Mascola4, Tomas Geletuza5, Richard A. Koup1, Dan Barouch1, Nelson L. Michael4, Sandhya Vasani4

1US Military HIV Research Program in Thailand, Bangkok, Thailand, 2Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, 3NIH, Bethesda, MD, USA, 4VIV Healthcare, Research Triangle Park, NC, USA, 5US Military HIV Research Program, Silver Spring, MD, USA, 6Gilead Sciences, Inc, Foster City, CA, USA, 7Beth Israel Deaconess Medical Center, Boston, MA, USA

**Background:** Toll-like receptor (TLR)-7 agonist and PGT121 administration have previously delayed viral rebound and induced SHIV remission after antiretroviral therapy (ART) interruption in macaques that started ART 7 days post SHIV-SF162P3 infection. We evaluated the impact of TLR-7 agonist and dual broadly neutralizing antibodies (bnAb) on viral rebound in SHIV-infected macaques.

**Methods:** Male rhesus macaques (n=16), pre-screened to exclude protective MHC alleles, were inoculated at wk0 with SHIV-11T7pdN34 intrarectally. ART (tenofovir, emtricitabine and dolutegravir) was initiated on Day14. Active arm (n=8) animals received oral GS-986, every 2 weeks from wk14-32 and intravenous N6-LS and PGT121 every 2 weeks from wk24-32 unless anti-drug antibodies (ADA) developed. ART was ceased when plasma levels of N6-LS and PGT121 were <0.25mg/mL. Control animals (n=8) received intravenous saline. Plasma SHIV RNA was assessed by qPCR (limit of detection 10 copies/mL) and soluble markers of immune activation by multiplex assay using Luminex.

**Results:** All animals were SHIV-infected with median SHIV RNA of 5.7 (range 4.1-6.8) log10 copies/mL on day14. After ART initiation on day14, SHIV RNA became undetectable in all animals by wk8 and remained undetectable until ART interruption. Due to varying ADA, animals received 7-10 doses of GS-986, 2-5 doses of PGT121 and 2-5 doses of N6-LS. At 24hrs post GS-986 dosing, plasma levels of IFNα, IL-1RA, IL-2, IL-6, IL-10, IL-15, MCP-1, MIP-1b, TNF, GM-CSF, IL-13 and MIP-1a increased significantly and viral blips were not detected. In the active arm, %Ki-67+ NK cells also increased at wk24 when compared to wk14 (p<0.031).

Total HIV DNA levels in PBMC prior to ART interruption were not significantly different between arms. Median time to viral rebound was 6 weeks in active...
arm and 3 weeks in control arm (p=0.024, Figure 1). There was no significant difference in post rebound peak or set-point viremia between groups.

**Conclusion:** Administration of GS-96 and dual bNAbs was associated with a modest delay in viral rebound. The effect of timing of ART initiation on seeding of the viral reservoir likely influenced the ability to achieve remission. Evaluating this strategy in humans is warranted.

![Figure 1: Viral rebound dynamics post antiretroviral treatment interruption (ART).](image)

**78LB COMBINED ACTIVE AND PASSIVE IMMUNIZATION IN SHIV-INFECTED RHESUS MONKEYS**

**Dan Barouch**, 1 Nee Mercado, 1 Abishek Chandrashekar, 1 Erica Borduchi, 1 Joseph Nikolol, 1 Maria Pau, 1 Hanneke Schuitemaker, 1 Merlin L. Robb, 1 Nelson L. Michael, 1 Rosmarie Geleziunas, 1

1 Beth Israel Deaconess Medical Center, Boston, MA, USA, 2 Janssen Prevention and Vaccines, Leiden, Netherlands, 3 Henry M Jackson Foundation, Rockville, MD, USA, 4 Walter Reed Army Institute of Research, Silver Spring, MD, USA, 5 Gilead Sciences, Inc, Foster City, CA, USA

**Background:** Our group and others have previously reported that therapeutic immunization can result in post-rebound virologic control in SHIV-infected rhesus monkeys following ART discontinuation, and that administration of broadly neutralizing antibodies (bNAbs) can delay or prevent viral rebound. The potential of combined active and passive immunization as an HIV-1 cure strategy has not previously been evaluated.

**Methods:** 49 rhesus monkeys were infected with SHIV-SF162P3 and initiated ART (TDF/FTC/DTG) on day 9 of infection. Following 24 weeks of continuous suppressive ART, animals received 4 immunizations with Ad26/MVA vaccines at weeks 24/36/48/60 (N=12), 5 infusions of 10 mg/kg PGT121 every 2 weeks from weeks 64-72 (N=12), both Ad26/MVA vaccines and PGT121 (N=10), or sham controls (N=15). All groups except the sham controls received 10 doses of 0.15 mg/kg of the TLR7 agonist vesatolimod (VES) by oral gavage (every 2 weeks from weeks 50-72). At week 86, ART was discontinued and viral rebound was monitored for 140 days.

**Results:** Ad26/MVA vaccination resulted in increased magnitude and breadth of SHIV-specific cellular and humoral immune responses. PGT121 infusion resulted in 14 weeks of therapeutic antibody levels followed by a decline to undetectable levels prior to ART discontinuation. VES administration led to activation of multiple cellular immune subsets including CD4+ T lymphocytes. Following ART discontinuation, 100% (15 of 15) of sham controls exhibited rapid viral rebound, and all animals in this group remained viremic by day 140 following ART discontinuation. 100% (12 of 12) of the Ad26/MVA + VES vaccinated animals also rebounded, but 3 animals demonstrated post-rebound virologic control to undetectable levels. In contrast, only 66% (8 of 12) of PGT121 + VES treated animals and 60% (6 of 10) of Ad26/MVA + PGT121 + VES treated animals rebounded (P=0.016, Fisher’s exact test compared with sham controls). Moreover, only 40% (4 of 10) of Ad26/MVA + PGT121 + VES treated animals were viremic by day 140 following ART discontinuation (P=0.001, Fisher’s exact test compared with sham controls).

**Conclusion:** Combined active and passive immunization with TLR7 stimulation resulted in both delayed viral rebound and post-rebound virologic control following ART discontinuation in SHIV-infected rhesus monkeys that initiated ART during acute infection. This multi-pronged approach represents a novel HIV-1 cure strategy.

**79LB COMBINATION IL-15 THERAPY IN A SHIV NHP MODEL**

**So-Yon Lim**, 1 Christa E. Osuna, 1 Jina Lee, 1 Daniela Silva-Ayala, 1 Pratik Vikhe, 1 Elsa Chen, 1 Stephanie Lundingren, 1 Margaret Eliot, 1 Dane Schalk, 1 Nancy Schutz-Darken, 1 Michael S. Seaman, 1 Jeffrey T. Saffir, 1 R. Brad Jones, 1 Douglas Nixon, 1 James Whitney, 1

1 Beth Israel Deaconess Medical Center, Boston, MA, USA, 2 Wisconsin National Primate Research Center, Madison, WI, USA, 3 NantKwest, Culver City, CA, USA, 4 Weill Cornell Medicine, New York, NY, USA

**Background:** Latent reservoirs of replication-competent HIV-1 persist in patients on antiretroviral therapy (ART) and represent the major obstacle to HIV eradication efforts. Considerable effort has been directed to develop and evaluate novel remission strategies to enhance virus-specific immune responses in ART-suppressed patients.

**Methods:** We conducted 2 studies in SHIV-infected ART-suppressed rhesus macaques (RM) to evaluate the IL-15 superagonist, N-803 to enhance virus-specific effector cells, in conjunction with broadly neutralizing antibodies (bNAbs) (N=2074 and 3BN117). Thirty-six RMs were rectally infected with SHIV-AD8. RMs received ART at ~50 days post infection (Study 1, n=20 and Study 2, n=16) and virologic suppression was maintained for 65 or 60 weeks PI for each study, respectively. In Study 1, ART-suppressed monkeys received 6 doses of N-803 alone (n=5), 2 doses of 10-1074 alone (n=5), a combination of N-803 and 10-1074 (n=5), or vehicle control (n=5). In Study 2, ART-suppressed RMs received 6 doses of N-803 and 3 doses of both 10-1074 and 3BN117 (n=8) or the vehicle control (n=8). Plasma SHIV RNA levels were measured and viral DNA were quantified in PBMC, colon and lymph node (LN) biopsies taken pre- and post- treatment. Modulation of immune populations, including CD8 and NK cells, were monitored longitudinally. After monitored washout of bNAbs in plasma, ART was discontinued.

**Results:** In both studies, blood NK cells showed peak activation at 48hrs post 803 administration throughout the dosing period. Memory T cells were preferentially activated by N-803, and CD8+ T cells demonstrated more robust expansion during the dosing period. No immune activation of PBMC was associated with bNAb treatment. We observed no change in integrated SHIV DNA between pre- and post- treatment timepoints in either PBMC or LN tissues (Study 1). In Study 1, plasma viral rebound kinetics in RMs treated with either N-803 or 10-1074 alone, or in combination, were comparable to the control group after ART discontinuation. However, 3 of 5 combination treated RMs showed durable control of viremia after initial low-level rebound. In Study 2, 6 of 8 combination-treated (N-803/bNAb) RMs exhibited durable control of viremia beyond week 25 following initial low-level rebound.

**Conclusion:** Repeated co-dosing of N-803 and bNAbs is safe and may facilitate long-term viral control and remission in the absence of ART.

A MEDEILLIAN RANDOMIZATION ANALYSIS OF PROTEIN BIOMARKERS AND CVD IN PERSONS WITH HIV

**Cavan Reilly**, 1 James Pankow, 1 Jason V. Baker, 2 Álvaro H. Borges, 2 Mark Polizzotto, 1 Shweta Sharma, 1 Sandra Safó, 1 for the INSIGHT Study Group

1 University of Minnesota, Minneapolis, MN, USA, 2 Hennepin County Medical Center, Minneapolis, MN, USA, 3 Rigshospitalet, Copenhagen, Denmark, 4 Kirby Institute, Sydney, NSW, Australia

**Background:** Treated HIV+ persons have excess risk for CVD yet the mechanisms explaining this remain poorly understood. Here we used a Mendelian randomization (MR) approach to assess causality of circulating proteins on CVD risk among participants in INSIGHT trials.

**Methods:** We identified participants in 4 clinical trials conducted by INSIGHT (FIRST, ESPRIT, SMART and START) who experienced a clinical event (composite outcome of AIDS, serious non-AIDS including CVD, and death) and individually matched them (1:2) with study-specific controls who did not. Baseline plasma samples were used to measure protein levels using 5 panels made by Olink (panels: CVD2, CVD3, immune response, cardiometabolic and inflammation). Genome-wide genotypic data was available for all. Proteins that passed quality control were screened for an association with the CVD outcome (MI, coronary revascularization, stroke, CVD death) while controlling for matching, demographics, hypertension, diabetes and study specific treatment group effects using a 5% significance level. Proteins associated with CVD outcomes were then tested for an association with genetic variants within 5Kb of the corresponding protein-coding gene while controlling for matching, demographics and study. Significant SNPs (family-wise p<5% for each protein) were used to construct haplotypes. The number of copies of the most common haplotype was used as an instrumental variable in a linear MR analysis (with a 5% level test). If only a single significant SNP was detected, that SNP was used as an instrument. It can be demonstrated that this protein screening approach controls the family-wise error rate at 5% across all MR tests.
Results: This analysis included 1493 participants (500 cases; 131 with CVD) with a mean follow-up of 6 years. Of the 459 distinct proteins represented at least once on the panels, 389 passed quality control measures. Of these proteins, 89 were associated with CVD. Of these 89, 38 were associated with at least 1 SNP in the corresponding gene. MR analysis detected IL6Ra, AXL, CHI3L1, SCGB3A2, GASE6 and IL1RL2 as potential causal factors that impact CVD outcomes (replicating a previous finding for IL6Ra among HIV-people). Table 1 summarizes these associations of proteins/SNPs with CVD risk.

Conclusion: Application of MR methods demonstrated potential causal effects of 6 proteins on CVD outcomes among a global population. These proteins warrant further study as interventional targets.

RISKS OF METABOLIC SYNDROME, DIABETES, AND CARDIOVASCULAR DISEASE IN ADVANCE TRIAL

Andrew Hill1, Kaitlyn M. McCann2, Victoria Pilkington2, Michelle A. Moorhouse3, Simiso Sokhela4, Alinda Vos5, Willem D. Venter3, Rulan Griesel1, Gary Maartens1, Godspower Akpomiemie2, Willem D. Venter1, Michelle A. Moorhouse2, Phumla Simxadi3
1University of Cape Town, Cape Town, South Africa, 2Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 3Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 4University Medical Center Utrecht, Utrecht, Netherlands

Background: In the ADVANCE trial, more patients taking first-line TAF/FTC+DTG developed clinical obesity compared to TDF/FTC+DTG and TDF/FTC/EFV. Common associations with obesity include type 2 diabetes, cardiovascular disease (CVD), and metabolic syndrome. This analysis aimed to quantify these risks using standard risk algorithms.

Methods: In the ADVANCE trial, 1,053 treatment-naïve patients in South Africa (99% black, 59% female) were randomized to 96 weeks of TAF/FTC+DTG, TDF/FTC+DTG, or TDF/FTC/EFV. Weight, lipids, fasting glucose, and blood pressure (BP) were measured at baseline and week 48, and used to calculate 10-year risks of CVD and type 2 diabetes using the Framingham, QRISK, and QDIABETES equations. Participants included in the analysis if they were between the age of 25-84 years and had complete laboratory data for all parameters in risk equations. Treatment emergent metabolic syndrome was calculated at week 48 using the International Diabetes Federation definition and differences between groups were tested using a two-sample test of proportions.

Results: Of 658 participants in the TDF/FTC+DTG arm, 473(72%) had metabolic syndrome. Changes from baseline to week 48 are shown in Table 1. The percentage change in weight from baseline to 48 weeks was similar between the arms (p=0.939). The percentage change in BMI from baseline to 48 weeks was not significantly different by CYP2B6 metaboliser genotype in women (p=0.082) or men (p=0.732). The percentage change in limb fat on DXA from baseline to 48 weeks differed significantly by CYP2B6 metaboliser genotype in women (p=0.004), with highest percentage increase in extensive metabolisers, but not in men (p=0.680). Percentage change in trunk fat on DXA from baseline to 48 weeks was not significantly different by CYP2B6 metaboliser genotype in women (p=0.082) or men (p=0.732). The percentage change in weight from baseline to 48 weeks was similar between CYP2B6 extensive metabolisers in the EFV/TDF/FTC arm and the DTG/TDF/FTC arm.

Conclusion: In Africans starting EFV-based ART, CYP2B6 metaboliser genotype was associated with weight gain and, in women, with changes in limb fat. The similar weight gain observed between CYP2B6 extensive metabolisers in the EFV/TDF/FTC arm and the DTG/TDF/FTC arm suggests off-target effects (e.g. mitochondrial toxicity) impairing weight gain in EFV slow/intermediate metabolisers could explain the greater weight gain observed with DTG in African trials.

CYP2B6 GENOTYPE AND WEIGHT-GAIN DIFFERENCES BETWEEN DOLUTEGRAVIR AND EFAVIRENZ

Rualen Griesel1, Gary Maartens1, Simiso Sokhela2, Godspower Akpomiemie2, Willem D. Venter1, Michelle A. Moorhouse2, Phumla Simxadi3
1University of Cape Town, Cape Town, South Africa, 2Wits Reproductive Health and HIV Institute, Johannesburg, South Africa

Background: Two African trials reported more weight gain with dolutegravir (DTG) than efavirenz (EFV), especially in women. EFV is toxic to mitochondria and is associated with lipostrophy. We hypothesised that CYP2B6 metaboliser genotype, which predicts EFV exposure, would determine amount of weight gain and fat distribution in patients starting EFV-based ART.

Methods: Participants enrolled in the EFV/TDF/FTC arm of the ADVANCE trial who consented to genetic testing were included. CYP2B6 metaboliser genotype was classified as extensive, intermediate, and slow. Outcomes included changes in weight gain and trunk and limb fat on DXA from baseline to week 48 by CYP2B6 metaboliser genotype.

Results: Of 787 participants, 478 were randomised to TAF/FTC+DTG, 405 to TDF/FTC+DTG, and 278 to TDF/FTC/EFV. Weight gain was compared between CYP2B6 extensive metabolisers in the EFV/TDF/FTC arm and the DTG/TDF/FTC arm.

Conclusion: In Africans starting EFV-based ART, CYP2B6 metaboliser genotype was associated with weight gain and, in women, with changes in limb fat. The similar weight gain observed between CYP2B6 extensive metabolisers in the EFV/TDF/FTC arm and the DTG/TDF/FTC arm suggests off-target effects (e.g. mitochondrial toxicity) impairing weight gain in EFV slow/intermediate metabolisers could explain the greater weight gain observed with DTG in African trials.
83 CHANGES IN BODY MASS INDEX AND THE RISK OF CARDIOVASCULAR DISEASE: THE D:A:D STUDY
Kathy Petoumenos1, Locadiah Kuwanda2, Lene Ryom1, Amanda Mocroft2, Peter Reiss3, Stephane De Wit4, Christian Pedrini5, Andrew N. Phillips6, Camilla Ingrid Hatleberg7, Antonella D’Arminio Monforte8, Rainer Weber9, Caroline Sabin1, Jens D. Lundgren1, Matthew Law10, for the D:A:D Study Group
1Kirby Institute, Sydney, NSW, Australia, 2University of Copenhagen, Copenhagen, Denmark, 3University College London, London, UK, 4University of Amsterdam, Amsterdam, Netherlands, 5Vrije Universiteit Brussel, Brussels, Belgium, 6Nico University Hospital, Nice, France, 7Azienda Ospedaliera San Paolo, Milan, Italy, 8University of Zurich, Zurich, Switzerland

Background: Several studies have shown an increase in weight in HIV-positive people receiving some contemporary antiretrovirals (ARV). We assess the effect of changes in body mass index (BMI), from different baseline BMI levels, on the risk of cardiovascular disease (CVD) and diabetes mellitus (DM).

Methods: We followed D:A:D study participants on ARV therapy from their first BMI measurement (baseline) to the first endpoint or earliest of 1/2/2016 or 6 months after last follow-up. The endpoints were CVD (composite of myocardial infarction/stroke/invasive cardiovascular procedure) and DM. Participants were stratified according to their baseline BMI as <20, 20-24.9, 25-29.9 and >30 kg/m2. BMI was lagged by 1 year, and changes from baseline BMI were calculated for each participant, with values carried forward. Poisson regression models were used, adjusted for baseline BMI and key confounders that did not lie on the causal pathway for each outcome, with BMI change fitted as a time varying covariate.

Results: We included 43,011 participants with 2,104 CVD and 1,583 DM events over 365,287 and 354,898 person years of follow up (rate:CVD 5.8/1000 (95% confidence interval (CI) 5.5–6.0); DM 4.5/1000 (95% CI 4.2–4.7)). Participants were largely male (74%) with baseline mean age of 40 years and baseline median BMI of 23.0 (IQR: 21.0-25.3). Risk of CVD by change in BMI from baseline, stratified by baseline BMI strata are shown in Figure 1a with little evidence of an increased rate of CVD with a decrease in BMI of more than 2 kg/m2, especially in those with a baseline BMI<20 kg/m2. There was also some evidence of an increased rate of CVD with an increased BMI in any baseline BMI strata. Overall results apply to HIV-positive people with increased weight while receiving contemporary ARV. We assess the effect of changes in body mass index (BMI), from different baseline BMI levels, on the risk of cardiovascular disease (CVD) and diabetes mellitus (DM).

Conclusion: While increases in BMI across all levels of baseline BMI were not associated with an increased risk of CVD, such changes were consistently associated with increased risk of DM. There was also some evidence of an increased risk of CVD with a decrease in BMI. The extent to which these results apply to HIV-positive people with increased weight while receiving contemporary ARVs is uncertain.

Figure 1. Risk of CVD (a) and BMI (b) by BMI change within baseline BMI strata

84 LOSARTAN TO REDUCE INFLAMMATION AND FIBROSI ES EN Points IN HIV DISEASE (LIFE-HIV)
Jason V. Baker1, Julian Wolfson2, Gary Collins1, Caryn G. Morse3, Frank S. Rhame1, Andelikhe Liappis2, Stacey Rizza2, Zelalem Temesgen4, Charalampos Mystakelis5, Steven G. Deeks6, James Neaton2, Timothy Schacker2, Irini Sereti6, Russell Tracy7

1Hennepin Healthcare Research Institute, Minneapolis, MN, USA, 2University of Minnesota, Minneapolis, MN, USA, 3NIHDD, Bethesda, MD, USA, 4Allina Health, Minneapolis, MN, USA, 5Washing DC VA Medical Center, Washington, DC, USA, 6Mayo Clinic, Rochester, MN, USA, 7University of California San Francisco, San Francisco, CA, USA, 8University of Vermont, Burlington, VT, USA

Background: Persistent inflammation and incomplete immune recovery among persons with HIV are associated with increased disease risk. Angiotensin receptor blockers (ARB) have been shown to down-regulate inflammation and fibrosis, in part via inhibition of NFκB and TGFβ pathways, respectively. We hypothesized that the ARB losartan would reduce inflammation, inhibit fibrosis, and concurrently improve immune recovery.

Methods: Treatment effects of oral losartan (100mg) versus placebo were investigated in a randomized (1:1), double-blind, placebo-controlled trial, among persons with HIV of age ≥50 years, receiving ART, with plasma HIV RNA <200 copies/mL and a CD4+ count ≥600 cells/μL. Blood was collected at baseline and months 1, 3, 6, 9, and 12. Inflammation and fibrosis biomarkers (Table) were measured using ELISA, electrochemiluminescence, and immunoblotting, and T-cell and monocyte phenotypes were assessed with flow cytometry among a subset of participants. Baseline-to-month 12 changes in (log2-transformed) biomarkers and (untransformed) cell phenotypes were compared between the losartan and placebo arms using linear mixed models.

Results: One hundred eight participants were randomized (n=52 to losartan; n=56 to placebo). 97% had a month 12 visit and 99% of expected visits were completed overall. Median age was 57 years, baseline and nadir CD4+ count were 408 and 120 cells/μL; 96% were male, 56% white, 20% current smokers, 26% taking lipid-lowering medication, and 49% taking an integrase strand transfer inhibitor. The table reports baseline levels of blood inflammation and immune measures, as well as the treatment effect of losartan versus placebo. Losartan treatment was associated with an improvement in any of these measures, nor with CD8+ T-cell memory subsets and activation (data not shown). Losartan reduced systolic and diastolic blood pressure by 6 and 5mmHg, respectively, and raised serum creatinine by 0.05mg/dL (p<0.01 for all). Losartan was not associated with more serious adverse events.

Conclusion: Among older persons with HIV and viral suppression, losartan did not improve blood measures of inflammation, immune activation, fibrotic activity, nor T-cell immune recovery. Losartan treatment is unlikely to reduce inflammation associated co-morbidities among persons with HIV infection to a clinically meaningful degree, beyond the established benefits from lowering blood pressure.

Table: Blood measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Losartan (n=52)</th>
<th>Placebo (n=56)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>0.81 (0.77, 1.30)</td>
<td>1.04 (0.77, 1.41)</td>
<td>0.04</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>119 (100, 120)</td>
<td>133 (105, 126)</td>
<td>0.07</td>
</tr>
<tr>
<td>E-DAYAL (mg/L)</td>
<td>0.03 (0.01, 0.07)</td>
<td>0.03 (0.01, 0.07)</td>
<td>0.50</td>
</tr>
<tr>
<td>M-Mammography (%)</td>
<td>22 (15, 31)</td>
<td>16 (9, 25)</td>
<td>0.02</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m2)</td>
<td>135 (120, 150)</td>
<td>133 (120, 150)</td>
<td>0.77</td>
</tr>
<tr>
<td>HIVRNA (log10 copies/mL)</td>
<td>4.1 (3.7, 4.4)</td>
<td>4.1 (3.8, 4.4)</td>
<td>0.61</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>28.0 (27.0, 28.9)</td>
<td>28.1 (27.0, 28.9)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Conclusion: Losartan treatment was not associated with an improvement in any of these measures, nor with CD8+ T-cell memory subsets and activation (data not shown). Losartan reduced systolic and diastolic blood pressure by 6 and 5mmHg, respectively, and raised serum creatinine by 0.05mg/dL (p<0.01 for all). Losartan was not associated with more serious adverse events.

Conclusion: Among older persons with HIV and viral suppression, losartan did not improve blood measures of inflammation, immune activation, fibrotic activity, nor T-cell immune recovery. Losartan treatment is unlikely to reduce inflammation associated co-morbidities among persons with HIV infection to a clinically meaningful degree, beyond the established benefits from lowering blood pressure.

85 EFFECTS OF HIV INFECTION AND IMMUNE REGULATION ON LONGITUDINAL LUNG FUNCTION DECLINE
Jing Sun1, Jacqueline Astemborski2, Sarath Raju3, M. Brad Drummond4, Robert H. Brown5, Shrut H. Mehta6, Richard D. Moore7, Meredith C. McCormack8, Gregory D. Kirk9, for the Study of HIV Infection in the Etiology of Lung Disease (SHELD) cohort
1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA, 3University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
Background: People living with HIV (PWH) have higher prevalence of lung function abnormalities compared to demographically and behaviorally similar people without HIV (HIV-). However, high quality longitudinal data describing the impact of HIV and of immune dysregulation on lung function decline over prolonged observation by age remains limited.

Methods: Data from the Study of HIV Infection in the Etiology of Lung Disease (SHIELD) cohort was used to evaluate the role of HIV and aging on lung function decline. Pre-bronchodilator FEV1 was repeatedly measured by spirometry at semiannual visits from 2009 to 2017 using ATS standards. HIV serostatus, HIV RNA, CD4 and CD8 counts were measured either in study or routine clinical visits. Time-varying CD4 nadir was defined as lowest CD4 observed up until each visit. Linear regression with generalized estimating equations, adjusted for age at entry, race, gender, current smoking status, and life-time pack-years, was used to evaluate longitudinal change in annualized FEV1 by HIV serostatus, CD4, CD8, and CD4 nadir.

Results: Of 1156 HIV- and 1168 HIV+ participants with 8314 person-years of follow-up, median age at entry was 50 years, 85% were black, 65% male, 79% current smokers, median cigarette exposure was 19 pack-years, and median % predicted FEV1 was 90%. Among PWH, 38% had CD4 <200, 59% had detectable HIV RNA, 78% had CD4<CD8<0.8. At entry, PWH had 133 ml lower FEV1 compared to HIV- (p<0.001). FEV1 declined significantly faster among PWH before age of 50, but declined at similar rate after age of 50 (Table 1). Within the subset with available data (N=1518), PWH with immune dysregulation (CD4:CD8<0.8) had lower (-120ml, p<0.01) and faster decline (-6ml per year faster, pinteraction=0.02) of FEV1 compared to HIV-. PWH with CD4 nadir<200 also had lower (-159ml, p<0.01) and faster decline (-6ml/year faster, pinteraction=0.02) of FEV1 compared to HIV- adjusted for current CD4 and covariates.

Conclusion: Among these participants with heavy tobacco exposure, lung function was significantly lower among PWH compared to HIV- and declined more rapidly in PWH than HIV- in those age <50. Low CD4 nadir (independent of current CD4) and immune dysregulation had a significant impact on lung function decline, irrespective of age. This finding suggests that HIV may manifest with impaired lung function in earlier ages. It also addresses the importance of achieving immune regulation in order to preserve lung function among PWH.

Table 1: Marginal estimation of maximum FEV1 over time by HIV serostatus and stratified by age groups in SHIELD.

<table>
<thead>
<tr>
<th>Age at entry</th>
<th>HIV serostatus</th>
<th>Coef.*</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Age at 50</td>
<td>-1.18</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Age at 25</td>
<td>-1.13</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BIC/FTC/TAF POSTEXPOSURE PROPHYLAXIS PROTECTS MACAQUES AGAINST RECTAL SHIV INFECTION

Elena Bekerman1, Stephanie W. Cox1, Scott McCallister1, Tomas Cihlar1, Christian Callaert1
1Gilead Sciences, Inc, Foster City, CA, USA

Background: Current guidelines recommend 4 weeks of daily ARVs for post-exposure prophylaxis (PEP) after an HIV exposure, though the optimal duration of PEP is not known. An effective short-course regimen could simplify HIV prevention after an exposure, or provide an option for event-driven post-exposure prophylaxis (PrEP) as a simplified alternative to long-term daily regimen. Here, we evaluated PEP/PEP regimens with Emtricitabine(FTC)/Tenofovir Alafenamide(TAF) combined with different doses of Bictegravir(BIC) in a non-human primate model of SHIV exposure.

Methods: A pharmacokinetic study was conducted in rhesus macaques with varying amounts of BIC + FTC/TAF (20/200 mg) to select BIC dose. Two efficacy studies were performed with 6 to 8 repeat low dose SHIV162P3 rectal challenges 2 weeks apart to minimize residual drug exposure. Two oral dosages of ARVs were administered at different times relative to virus exposure. In Study 1, BIC/FTC/TAF (25/200/25mg) or FTC/TAF (200/25mg) was given at -2h/+24h or -4h/+48h (n=6), +2h/+48h (n=6), or +48h/+72h (n=6 or 5). Follow-up Study 2 tested 100mg BIC in combination with FTC/TAF, (100/200) mg given at +6h/+30h, +12/+36h, +24h/+48h, +48h/+72h or FTC/TAF (200/25mg) at +6h/+30h or +12/+36h (n=6 each). A Kaplan-Meier survival analysis was conducted and a log-rank test was used to compare time to infection relative to placebo controls.

Results: After 8 virus challenges in Study 1, BIC/FTC/TAF (25/200/25mg) protected 6/6 animals in the +2h/+48h group, 1/6 animals in the +48h/+72h group and 0/6 animals in the +4h/+48h group (Table 1). BIC/FTC/TAF alone protected 5/6 animals in the +2h/+48h group, 1/6 in the +4h/+48h group and 0/5 in the +4h/+72h group. After 6 virus challenges in Study 2, BIC/FTC/TAF (100/200/25mg) protected 5/6 animals in the +6h/+30h group, 6/6 animals in the +12/+36h, 4/6 animals in the +24h/+48h, and 3/6 animals in the +
+48h/+72h group (Table 1). In contrast, FTC/TAF (200/25mg) protected 3/6 animals in the +6h/+30h group and 4/6 animals in the +12/+36h group.  

**Conclusion:** Two doses of FTC/TAF + BIC (100mg) initiated up to 24h after rectal virus exposure were protective in a SHIV/macaque model. FTC/TAF + BIC (25mg) provided similar protection to FTC/TAF alone and were only efficacious when used as -2/+24h regimen. These results provide support to further study FTC/TAF + BIC (100mg) as a simplified event-driven PEP regimen.

### 88 ON-DEMAND HIV POST-EXPOSURE PROPHYLAXIS BY TAF/EVG VAGINAL INSERTS IN MACAQUES

**Table 1.** Results of NHB PReP PEP Studies with B/F/TAF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1 Film Challenges</th>
<th>2 Film Challenges</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study 1 (8 challenges)</td>
<td>Study 2 (8 challenges)</td>
<td></td>
</tr>
<tr>
<td>FTC/TAF (25/200/25)</td>
<td>-5 to +47h</td>
<td>-5 to +47h</td>
<td>0.9</td>
</tr>
<tr>
<td>B/F/TAF (25/200/25)</td>
<td>-5 to +47h</td>
<td>-5 to +47h</td>
<td>0.75</td>
</tr>
<tr>
<td>F/TAF (25/200/25)</td>
<td>-5 to +47h</td>
<td>-5 to +47h</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Significantly different (p<0.05) with exceptions noted. P<0.01.

**Methods:** Normal cycling pigtail macaques (n=11) were exposed vaginally to SHIV162P3 once-weekly for 13 weeks. Six macaques received TAF/EVG inserts (20/16 mg) and 5 received a placebo. Inserts were placed in the posterior vagina near the cervix 4 hours after each SHIV exposure. Insertion was monitored weekly by serology and RT-PCR of SHIV RNA in plasma. The concentrations of TAF, TFV, and EVG in plasma and TFV-DP in PBMCs were measured at 4 hours in a second group of 6 macaques that received the same TAF/EVG inserts once-weekly for 13 consecutive weeks.

**Results:** Four of the 5 macaques that received placebo inserts became infected with SHIV after a median of 4 challenges (range 2-13). In contrast, all 6 macaques that received TAF/EVG inserts 4h after SHIV exposure remained protected after 13 challenges and a 20-week follow-up period (p=0.009; log-rank test). The calculated PEP efficacy of TAF/EVG inserts was 49.4%. Of the 78 plasma samples collected 4h post insert dosing, EVG was only detected in 1 sample (15 ng/ml); none had detectable TFV or TAF. Conversely, TFV-DP was detected in 42/59 PBMC samples; median level in samples with detectable TFV-DP was 147.5 [range=15-993] fmol/10^6 cells.

**Conclusion:** Vaginal administration of a single TAF/EVG insert several hours after virus exposure fully protected macaques against SHIV infection, thus increasing flexibility and expanding our established window of protection to 4 hours before or after sex. The observed high levels of TFV-DP in PBMCs by topical delivery of TAF is unique and may have contributed to protection. Our data support the clinical development of TAF/EVG inserts for on-demand PReP/PEP for HIV prevention.

89LB WEEKLY ORAL ISLATRAVIR PROVIDES EFFECTIVE PEP AGAINST IV CHALLENGE WITH SIVMAC251

**Background:** Islatravir (ISL, MK-8591, EFdA) is a novel nucleoside reverse transcriptase translocation inhibitor with robust antiviral activity and has demonstrated efficacy as weekly oral PEP in the SHIV/Rhesus macaque (RM) rectal challenge model for doses ranging from 0.1 mg/kg to 3.9 mg/kg. We tested ISL’s efficacy as post-exposure prophylaxis (PEP) in the SHIV/RM IV challenge model.

**Methods:** 12 RM were challenged IV with 10 AID50 of SIVmac251. After 24h, 6 animals received 3.9 mg/kg ISL and 6 animals served as untreated controls. Treated animals in Stage I received a total of 4 weekly oral doses of ISL and were monitored for SHIV infection for 7wk after the 4th dose of ISL. In Stage II, 3 uninfected animals from Stage I were challenged as in Stage I and beginning 24h after 3 weekly oral doses of ISL at 3.9 mg/kg was initiated. Animals were monitored for 7wk after the 3rd dose of ISL. Uninfected animals entered Stage III and were similarly challenged and treatment initiated at 24h with 2 weekly oral doses of ISL at 3.9 mg/kg and animals monitored for 7wk after the 2nd dose of ISL. Finally in Stage IV, uninfected animals were challenged IV and 4 hours later treated with a single oral dose of ISL at 3.9 mg/kg and followed for 7wk. Animals were monitored for infection using RT-PCR and proviral DNA amplification. Virus-specific antibody responses were measured using a commercial assay. Plasma ISL levels as well as ISL-triphosphate (ISL-TP) levels in PBMCs were measured longitudinally.

**Results:** All untreated control animals were viremic 7 days after IV challenge with SIVmac251. 6/6 treated animals were completely protected in Stages I-III (Fisher’s exact test P=0.0002). ISL-TP levels became undetectable in PBMCs 3 weeks after the last ISL oral dose. In Stage IV, two of 6 animals became infected with wild type SIVmac251, one with viremia at day 14 (ISL-TP < 0.02 pmol/10^6 PBMCs) and another at day 49 (Fisher’s exact test P=0.06).

**Conclusion:** As few as 2 weekly oral doses of ISL at 3.9 mg/kg given 24h after IV challenge with SIVmac251 completely prevented infection. However, a single ISL dose 24h after IV challenge failed to provide statistically significant protection. As the ISL-TP T1/2 in human PBMCs (79-214 hr) is substantially longer than RM (50 hr), it is conceivable that a single low oral dose given within 24 hours of HIV exposure may provide effective PEP. These results support the potential utility of ISL as a simplified PEP agent.

90 PHASE I PLACEBO-CONTROLED SAFETY, PK, AND PD STUDY OF MB66 ANTI-HIV AND ANTI-HSV FILM

**Background:** Monoclonal antibodies (mAbs) show promise as multipurpose prevention technology. The MB66 intravaginal film contains 10 mg each of anti-HIV (VRC01) and anti-HSV (HSV8) mAbs to provide protection against two incurable viral infections.

**Methods:** The active film or vehicle control film was randomly assigned at 1:1 ratio to 29 healthy sexually abstinent women who were instructed to insert film daily for 7 days. Visits and clinical sampling occurred predose at 1, 4, 24 hrs after the 1st dose and 24 hrs, 6-10 days after the 7th dose. Cervicovaginal lavage samples (CVLs) were assayed by Luminex for 16 cytokines at 1, 4, 24 hrs after the 1st dose and 24 hrs, 6-10 days after the 7th dose. There were 45 AEs; 19 were deemed related to study product, but were balanced between active and placebo film (p=1.0). There were no serious AEs(SAEs) and no significant differences in levels of proinflammatory cytokines,
Nugent Scores, vaginal pH between Active and Placebo film groups (ps > 0.10).
Acceptability and willingness to use the product were judged to be high by post-use ACASI questionnaire. Concentrations of VRC01 and HSV8 increased significantly in vaginal secretions following insertion of Active film. Antibody levels in TearFlo samples peaked at 1 hr post-dosing (median: 33.5 µg/mL) but remained significantly elevated at 24 hours post 1st and 7th film. (median: ~1.8 µg/mL). In light of an estimated dilution factor of 35 for the TearFlo samples, the extrapolated VRC01 concentrations range from 63-1,225 times IC50 for VRC01 (~1 µg/mL). CVLs from the active film group, collected 24 hr after 1st film and 7th films, significantly neutralized all 3 HSV strains and HSV-2.

Conclusion: Repeated doses of MB66 film was safe and tolerated. Significant HIV-1 and HSV-2 neutralization (ex vivo) was observed at 24 hrs, 7 films. Antibody levels in vagina had concentrations consistent with protection for up to 24 hrs.

91 NEAR-PERFECT ACCURACY OF A REAL-TIME URINE TENOFOVIR TEST COMPARED TO LAB-BASED ELISA

Matthew A. Spinelli1, Warren Rodrigues2, Guohong Wang1, Michael Vincent3, David Glidden1, Randy Stalter3, Patricia A. Defechereux1, Madeline Deutsch1, Gandhi1, for the Partners PrEP and IBrEATHe

1University of California San Francisco, San Francisco, CA, USA, 2Abbott Labs, Abbott Park, IL, USA, 3University of Washington, Seattle, WA, USA, 4Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya

Background: Therapeutic drug monitoring measures adherence to tenofovir (TFV)-based PrEP more accurately than self-report but has not been available at the point-of-care (POC) until now. We developed an ELISA using a highly-selective antibody to TFV in urine and previously validated it against spectrometry-based methods with high accuracy. We have now developed a lateral flow immunoassay (LFA) using this antibody, which permits testing at the POC. A cut-off for the LFA of 1,500 ng/ml was previously selected from a directly observed therapy study to accurately classify recent dosing. The objective of this analysis was to compare a novel POC test for PrEP to laboratory-based ELISA in diverse patient populations.

Methods: Urine samples were analyzed using the ELISA and POC LFA test from two cohorts of PrEP users taking tenofovir disoproxil fumarate/emtricitabine: the Partners PrEP Study, which recruited heterosexual men and women, and the IBrEATHe Study, which recruited transwomen using estrogen and transmen using testosterone hormone therapy. We calculated the sensitivity and specificity of the POC test compared to laboratory-based ELISA at a cut-off of 1,500 ng/ml.

Results: Overall, 684 urine samples were tested from 324 participants in the two cohorts. In Partners PrEP, 454 samples from 278 participants (41% cisgender women) were tested; the median age was 33 years (interquartile range [IQR] 28-39). In IBrEATHe, 231 samples from 46 individuals (50% transwomen) were tested; the median age was 31 (IQR 25-40). Overall, of the 505 samples with tenofovir (TFV) levels greater than or equal to the cut-off using lab-based ELISA, 505 of the POC test results were also positive, yielding 100% sensitivity. Of the 179 samples with TFV levels below the cut-off, 178 were negative with the POC test, yielding 99.4% specificity. The accuracy of the POC LFA was 99.8% compared to ELISA.

Conclusion: In 324 women and men (both cisgender and transgender) taking PrEP, the sensitivity, specificity, and accuracy of a novel POC test for urine TFV all exceeded 99% when compared to a lab-based ELISA method. Given the association of low urine TFV levels with HIV seroconversion events, the simplicity of using the LFA, and its expected low cost, this POC test is a promising tool to support adherence to PrEP that could be widely scalable to real-world clinical settings. Adherence support using this POC test should be evaluated in a randomized controlled trial.

LONGER-TERM SAFETY OF F/TAF AND F/TDF FOR HIV PRÉP: DISCOVER TRIAL WEEK-96 RESULTS

Onyema Ogbugu1, Daniel Podzamczer2, Laura C. Salazar3, Keith Henry4, David M. Asmuth5, David Wohl6, Richard Gloison3, Yongwu Shao4, Ramin Ebrahimi6, Christoph Carter7, Moupali Das7, Scott McCallister8, Jason M. Brunetta7, Gitte Kronborg9, Christoph D. Spinner11

1Yale University, New Haven, CT, USA, 2Hospital Universitario de Bellvitge, Barcelona, Spain, 3Hoag Medical Group, Newport Beach, CA, USA, 4Hennepin Healthcare Research Institute, Minneapolis, MN, USA, 5University of California Davis, Davis, CA, USA, 6University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 7University College London, London, UK, 8Gilead Sciences, Inc, Foster City, CA, USA, 9Maple Leaf Medical Clinic, Toronto, ON, Canada, 10Hvidovre Hospital, Hvidovre, Denmark, 11University Hospital Klinikum rechts der Isar, Munich, Germany

Background: In DISCOVER, a multinational, double-blind, randomized controlled trial, F/TAF compared to F/TDF demonstrated noninferior efficacy for HIV prevention and improved bone mineral density (BMD) and renal safety biomarkers at week (W) 48. We now report W96 safety outcomes.

Methods: We evaluated renal and lipid parameters and weight changes in participants on F/TAF vs F/TDF through W96. BMD was evaluated in a substudy and also examined in younger participants (age <25 yrs) who are still accruing bone mass. We also examined glomerular function, proteinuria, and biomarkers of proximal tubular injury (PTI: B2M/Cr, RBP/Cr) in participants ≥50 yrs of age and those with moderate renal impairment (eGFR 60–<90 mL/min).

Results: Among 5387 participants evaluated, unlike those on F/TDF (n=2693), F/TAF users had significantly increased BMD, with the magnitude of between-group differences increasing between W48 to W96 (Table 1). Participants <25 yrs had greater declines in BMD on F/TDF with a greater magnitude of difference between groups than those ≥25 yrs. Overall, F/TAF users had increases in eGFR and declines in UPCR and PTI biomarkers. Older participants on F/TDF had a greater magnitude of decline in eGFR and a greater increase in UPCR and PTI markers compared to younger F/TDF users. Similarly, those with eGFR 60–<90 mL/min had greater statistically significant changes in PTI markers, if on F/TDF compared with those with eGFR ≥90 mL/min. Those on F/TDF had a smaller weight increase than those on F/TAF through W96, whereas those on F/TAF had decreases in lipids at W48 and W96. Those on F/TDF had a smaller weight increase than those on F/TAF through W96 (Table 1).

Conclusion: These DISCOVER data allow for the largest single-variable comparison of the two tenofovir prodrugs without underlying HIV infection and in the absence of third antiretroviral agents. Overall, those on F/TAF had increased BMD compared to declines in those on F/TDF, with more pronounced differences in younger participants. Older participants on F/TDF and those with impaired renal function had more adverse impact on renal biomarkers. Lipid and weight changes were consistent with the known lipid-lowering and weight suppressive effects of TDF, respectively. F/TAF is a safe, longer-term option for PrEP, with certain subgroups experiencing a greater magnitude of benefit in BMD and renal biomarkers.
93 INITIATING PrEP DURING ACUTE HIV INFECTION: WHAT IS THE RISK FOR ARV DRUG RESISTANCE?

Donn J. Colby, Chanjjaporn Pondel1, Tippawan Panmap1, Prapapiphan Plodkratok1, Rapee Trichaviroj2, Carlo Sacdalan1, Eugène Kroon1, Siriwat Niyomsuwan3, Nittaya Phanuphak1, for the RV254/SEARCH010 Research Group

Background: Prior to PrEP initiation, a single anonymous test was done on pooled samples. The presence of drug resistant mutations was determined through the use of next generation sequencing (NGS) on PrEP users who initiated PrEP between 2013-2016.

Methods: A cross-sectional study of patients who initiated PrEP between 2012 and 2016 was performed. A total of 1,942 patients initiated PrEP, and we had ARV drug resistance data on 1,862 patients. ARV drug resistance was tested using NGS.

Results: ARV drug resistance data were available for 6 cases: 3 cases had single mutations, 1 case had double mutations, 1 case had triple mutations, and 1 case had quadruple mutations.

Conclusion: ARV drug resistance was identified in 6 out of 1,862 PrEP users who initiated PrEP between 2012 and 2016. The risk for ARV drug resistance is low, but it is important to monitor for drug resistance early after PrEP initiation.

94 PEPFAR DREAMS INTERVENTION AMONG ADOLESCENT GIRLS AND YOUNG WOMEN IN RAKAI, UGANDA

Hadija Nakawooya1, Victor Semujjiga2, Dorean Nabukalu1, Anthony Ndayaboko, Tom Lutal1, Fred Nalugoda1, Ronald H. Gray3, Maria Wawer1, Steven J. Reynolds4, Joseph Wamya1, Gertrude Nakigozi, Godfrey Kigozi1

Background: In 2016, the Presidents Emergency Plan for AIDS Relief (PEPFAR) initiated the DREAMS (Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe) programs in 10 sub-Saharan African countries including Uganda to reduce risk of HIV and domestic violence in adolescent girls and young women aged 15-24 (AGYW).

Methods: We identified girls aged 15-24 years who participated in Rakai community cohort study (RCCS) surveys between June 2016 - August 2019 and provided information on HIV risk behaviors and were tested for HIV. Risk behaviors were sexual debut, being sexually active, having non-marital sexual partners, transactional sex, alcohol use and condom use with non-marital partners.

Results: A total of 1945 AGYW participated in the RCCS; 979 (50.3%) aged 15-19 years of whom 40.3% (397) had participated in the DREAMS programs. Among women aged 20-24, receiving ≥5 ST sessions was associated with a significant reduction in alcohol use (aPRR 0.23, 95% CI=0.10 -0.52). Among girls aged 15-19, ≥ 10 sessions of ST were associated with significant reduction in sexual debut (aPRR 0.55, 95% CI=0.36 -0.86) and being sexually active (aPRR 0.54, 95% CI=0.36 -0.93), sexual debut, being sexually active, having non marital sexual partners, transactional sex, alcohol use and condom use with non-marital partners.

Conclusion: DREAMS programs assessed were; participation in any DREAMS programs, stepping stones (ST) a participatory intervention for HIV prevention and strengthening relationship skills, combined social economic approaches (CSEA), HIV testing and counseling (HTC). Generalized linear models was used to estimate prevalence rate ratios (PRR) and 95% CI associated with risk behavior outcomes.

95 STING IN THE TAIL: HOW DNA TRIGGERS IMMUNE RESPONSES TO VIRAL INFECTIONS

Zhijian (James) Chen, University of Texas Southwestern, Dallas, TX, USA
The presence of DNA in the cytoplasm is a danger signal that alerts the host immune system to eliminate microbial infections, but inappropriate activation of this pathway by self DNA can also lead to autoimmune and autoinflammatory diseases. My talk will focus on our discoveries of cyclic GMP-AMP synthase (cGAS) as an innate immune sensor for cytosolic DNA and microbial pathogens, including HIV. Upon binding DNA, cGAS converts GTP and ATP into cyclic GMP-AMP (cGAMP), which functions as a second messenger that binds and activates the ER endonuclease, KHNYN, that is required for antiretroviral activity. We solved a structure at near-atomic resolution, respectively, using cryo-electron microscopy. An extensive panel of SERINC5 mutants were tested for the ability to inhibit HIV-1 infectivity and localisation to the plasma membrane. The SERINC structures reveal a novel protein fold comprised of ten transmembrane helices organised into two subdomains and bisected by a long diagonal helix. Clusters of conserved residues and a lipid binding groove highlight potential functional sites. Extensive structure-based mutagenesis scan identified surface-exposed regions and the interface between the subdomains, as critical for SERINC restriction activity. The same regions are also important for viral sensitisation to neutralising antibodies, directly linking SERINC5 restriction activity with the remodelling of HIV-1 envelope glycoprotein. SERINC variants, which were not surface exposed, were unable to inhibit HIV-1 infectivity arguing that the protein must be located at the plasma membrane to exert its antiviral activity. Our structures and extensive functional data provide the first insights at the molecular level of SERINC proteins and their ability to restrict HIV-1 infection.

99 NEUROHIV IN THE GLOBAL CONTEXT: ADVANCING THE CONTINUUM OF CARE AND ACHIEVING EQUITY
Kiran T. Thakur, Columbia University, New York, NY, USA
Though significant advancements have been made in the field of neuroHIV, neurological and mental health conditions remain major contributors to morbidity and mortality worldwide, particularly in resource-limited settings. In this talk, we will discuss how HIV impacts brain health throughout the lifespan with a discussion on the current global epidemiology of neuroHIV (including the global epidemiology of HIV neurocognitive disorder, CNS opportunistic infections, mental health disorders, etc). We will also identify epidemiological knowledge gaps, specifically highlighting gaps in resource-limited settings. We will discuss discoveries and achievements in neuroHIV since the beginning of the HIV epidemic and will highlight the importance of brain health in the HIV care continuum model. We will then discuss important facets of neurological care across the lifespan with a discussion on pediatric neuroHIV including HIV-associated neurocognitive effects in children and the impact of in-utero exposure to maternal HIV and antiretroviral medications. We will discuss neurological conditions amongst adolescents and adults, as well as gender-related issues in neurological and mental health. We will then focus on the chronic neurological care of people living with HIV, and discuss the impact of HIV on our growing global aging population. We will discuss the growth in dementia and stroke burden worldwide, and the “double burden” of traditional risk factors for cerebrovascular disease and cognitive decline and HIV infection. We will then discuss the current neurological care areas which specifically impact people living with HIV including access and availability of high quality neurological care and mental health resources, the availability of high quality drugs such as antiepileptic medications, access to diagnostic testing including laboratory infrastructure needs, and neurorehabilitation resources. We will focus on how to address disparities in care in vulnerable populations, and the associated stigma in people living with HIV with neurological conditions. We will identify mechanisms to reduce the burden of neurological conditions in people living with HIV worldwide, with an emphasis on improving access and quality of care over the coming decade. Finally, we will emphasize the importance of focusing on brain health as major priority in HIV care in the coming years.

100 HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS AND AGING IN THE GLOBAL SETTING
John Joska, University of Cape Town, Cape Town, South Africa
HIV remains highly prevalent in sub-Saharan Africa with nearly 1.5 adults aged 15–49 years infected in South Africa (SA). Although SA also has the largest antiretroviral (ART) program globally, with >2 million PLWH accessing care, a significant proportion of individuals remain ART naïve. The result is two sub-populations- one at high risk of the effects of immunocompromise, and the other living with chronic HIV and the emerging problems of aging. Despite early reports that clade C was less neuro-virulent, regional data suggest that HIV tat variants are not neuroprotective. The presence of neurocognitive impairment is likely impacted by education, early life adversity, neurologic and
psychiatric co-morbidity and delays in entering care. ART neurotoxicity is not well understood at a population level, but the up-coming programmatic switch to first-line dolutegravir from efavirenz in SA may help. HAND is not routinely recognized or diagnosed in routine clinical care. Screening tools such as the IHDS and CAT-rapid have been validated in South Africa, with comparable sensitivity and specificity to the USA, but few providers are comfortable using them. Other tools, such as the Community Screening Instrument for Dementia have been used widely across multiple resource-limited settings, but in older persons. Other challenges to diagnosis include the risk of over-diagnosis, especially of mild HAND, the assessment of functional impairment, and the detection of co-morbidities. There are no effective adjuvant treatments for HAND. Effective viral control is key, with CSF escape likely very uncommon. Thoughtful psycho-education, treatment support, and possibly patient-tailored medication management and problem-solving strategies may help. HIV infection in persons >60 years is common and will become a growing problem. Neurodegenerative disorders, including Alzheimer's and Vascular dementia, are prevalent in older South Africans. The contribution of HIV infection to morbidity is not well understood, even in well-resourced settings. A life-span, patient-centered approach may afford the best outcomes: improving early education, the effects of poverty, managing mid-life risk factors, early HIV diagnosis, and effective ART will probably reduce the disease burden substantially. If one is honest, current Alzheimer treatments are only modestly effective and unaffordable in low-resource settings. We will have to look for cheaper, disease-modifying treatments.

101 HIV AND MENTAL HEALTH: THE IMPACT OF THE COMORBIDITY IN RESOURCE-CONSTRAINED SETTINGS

Bibiola D. Oladeji, University of Ibadan, Ibadan, Nigeria

There is a complex bi-directional relationship between HIV infection and mental health. It is well recognized worldwide that the prevalence of mental disorders including depression, anxiety disorders, and substance use disorders is higher in people living with HIV (PLHIV) compared to the general population. Reported prevalence estimates of mental and substance use disorders in PLHIV in low- and middle-income countries (LMIC) range between 19% and 50%, with depression being the commonest. This increased risk is often mediated by a mix of factors which could be biological-related the virus and its treatment, psychological-related stigma and coping, and as well as behavioral-related to adherence to medication and retention in care. The presence of mental disorders in PLHIV is often associated with an increased risk of HIV disease progression, poor adherence to antiretroviral therapy and excess mortality. An often overlooked and less well researched aspect of this relationship is the higher risk of HIV amongst people with serious mental disorders such as bipolar affective disorders, schizophrenia and schizoaffective disorders. Patients with comorbid mental disorders and HIV are more likely to delay HIV treatment initiation and more likely to engage in HIV risk behaviors and hence are potential drivers for the continued spread of the virus especially in parts of sub-Saharan Africa with high HIV prevalence rates. Whilst mental health services have become widespread in HIV care and support services in high-income countries (HIC), low- and middle-income countries (LMIC) are bearing a disproportionate burden of the HIV infection are still lagging behind in developing appropriate services to meet the mental health needs of PLHIV. Health systems in low- and middle-income countries are commonly overburdened and characterized by poor human and financial resources which are particularly worse for mental health care. Adoption of a stepped care, task sharing approach is likely to be the most viable option. However, research evidence for the most appropriate models that can deliver effective and cost-effective integrated care in LMIC is still sparse. Meeting the UNAIDS 90-90-90 goal will require commitment to expanding culturally appropriate mental health services for PLHIV, especially in LMICs, that include prevention of transmission of the infection in people with mental disorders, early identification of mental disorders in PLHIV and the provision of evidence-based care.

102 CEREBROVASCULAR DISEASE AND HIV IN THE GLOBAL SETTING: DATA FROM ASIA AND BEYOND

Felicia C. Chow, University of California San Francisco, San Francisco, CA, USA

Stroke is the second leading cause of death worldwide. An estimated 1 in 4 25-year-olds globally will have a stroke during their lifespan. The largest burden of stroke (over 75% of stroke mortality and 80% of disability-adjusted life years) is shouldered by low- and middle-income countries (LMIC) where, in sharp contrast to high-income countries (HIC) that have been experiencing a decline in stroke incidence, stroke rates are steadily rising. Furthermore, strokes in LMIC occur at a younger mean age, affecting individuals during the peak of their productivity. This global stroke crisis poses a major threat to many of the same regions of the world where HIV prevalence is high. This presentation will focus on cerebrovascular disease in persons living with HIV (PLWH) in Asia, with its exceedingly high global lifetime risk of stroke, and sub-Saharan African (SSA), which has seen a rapid acceleration in stroke rates. We will review available data on the epidemiology of HIV-associated stroke in LMIC, drawing attention to similarities and differences in stroke risk factors, pathogenesis, and outcomes between LMIC and HIC. One recurring theme is the strong association between HIV and stroke in younger age groups and, similar to in the general population in LMIC, a younger age at diagnosis of first-time stroke in PLWH, underscoring the pivotal role that HIV plays in stroke in the young. We will also discuss the implications of increased cerebrovascular risk in PLWH on cognitive impairment and potential differences in the contribution of cerebrovascular dysfunction to cognitive health between women and men living with HIV. Finally, with the overall paucity of data on cerebrovascular disease in PLWH from LMIC, we will underscore gaps in knowledge where research efforts should be focused.

103 GLOBAL ELIMINATION OF HEPATITIS B VIRUS

Gilles Wandelcer, University of Bern, Bern, Switzerland

Chronic hepatitis B virus (HBV) infection affects 250 million persons worldwide and is the most important cause of liver cirrhosis and cancer. In 2017, the World Health Organization outlined specific targets along the prevention and care cascade to be met if the elimination of HBV as a global health threat was to be achieved. Among the proposed core interventions, global service coverage of the HBV vaccine birth dose, as well as the uptake of testing and antiviral therapy remain largely insufficient. This presentation will highlight the key determinants of global HBV elimination and discuss the main challenges that will be faced during the implementation of prevention and care interventions. It will also insist on the importance of addressing logistic and sociocultural barriers, especially in resource-limited countries where the HBV burden is highest. As many of the challenges expected to arise on the road to HBV elimination are similar to those experienced during the fight against HIV, it will be critical to learn the lessons from the past 30 years and avoid making the same mistakes. Recent improvements in the understanding of the HBV life cycle and the development of promising treatment modalities to achieve the functional cure of HBV have helped move HBV elimination up the global political agenda. However, HBV elimination will only be achieved if these scientific achievements are accompanied by the rapid uptake of HBV vaccination, testing and treatment. To succeed, HBV elimination efforts will heavily rely on innovative public health strategies, education and political will.

104 ADAPTING THE IMMUNE RESPONSE TO CURE HEPATITIS B

Barbara Rehermann, NIH, Bethesda, MD, USA

Approximately 257 million people worldwide are chronically infected with the hepatitis B virus (HBV). About 900,000 people die from HBV-related liver failure and/or hepatocellular carcinoma each year, which makes HBV more deadly than HIV and malaria. Unfortunately, the incidence of HBV-related mortality is projected to increase further in the coming decades. The goal of curative treatments for chronic HBV infection is a functional cure, defined as sustained loss of hepatitis B surface antigen (HBsAg) with or without anti-HBsAg antibodies. Clearance of HBsAg is a durable endpoint and associated with improved long-term clinical outcome. Unfortunately, nucleos(t)ide analogues are not sufficient to achieve cure, because they do not eliminate the covalently closed circular HBV DNA nor the HBV DNA that has integrated into the human genome. Treatment with pegylated IFNalpha can achieve this cure, albeit only in a minority (2-10%) of chronically HBV infected patients. Its immunomodulatory effects are thought to be important in this process. Although we understand many features of acute self-limited hepatitis B and natural and vaccine-induced immunity, our understanding of immune response in chronic hepatitis B is still limited. One of the keys to curing chronic infection lies in a better understanding of innate and adaptive immune responses in early childhood and the first two decades of life. New insights are emerging that HBV induces innate immune cell maturation and T-helper type 1 cell differentiation (trained immunity) in early life and that an age-related increase in inflammation contributes to changes in disease activity during later life. This presentation will review the role of innate and adaptive immune responses in the control of acute HBV infection, their
 modulation during the distinct clinical phases of chronic infection and immune therapeutic strategies to induce a functional cure.

105 HEPATITIS B VIRUS: NEW AGENTS
Raymond T. Chung, Harvard University, Cambridge, MA, USA
The goals of hepatitis B virus (HBV) treatment are to: 1) achieve sustained suppression of HBV replication, 2) decrease liver injury and 3) prevent cirrhosis, liver failure, hepatocellular carcinoma (HCC) and death. Currently available FDA-approved therapies have been able to deliver on each of these clinical goals, using well-tolerated nucleos(t)ide analogues with high barriers to resistance. However, they are limited in their ability to yield functional cure (loss of HBsAg with or without anti-HBs seroconversion). Hence, there remains a large unmet clinical need.

The ultimate clinical goal is to achieve functional cure of HBV with a finite course of treatment. However, there are many challenges to HBV functional cure. Most importantly, like HIV, HBV has a latent form, covalent closed circular DNA (cccDNA), a highly stable episomal form of the HBV genome that serves as the template for new HBV transcription in the nucleus. Moreover, a fraction of HBV DNA is also integrated into the host genome, and there is evidence that a portion of integrated HBV DNA, particularly HBsAg, can be transcribed. These stable forms are largely untouched by current therapies. There is also evidence that in chronic hepatitis B (CHB), the adaptive virus-specific immune response becomes exhausted, further contributing to chronicity.

The latest therapies in the pipeline seek to achieve HBsAg loss using approaches that target other, discrete steps in the HBV lifecycle as well as modulate the immune environment essential for clearance. Novel antiviral therapies in clinical development include entry inhibitors, capsid assembly modifiers to block assembly and possibly replenishment of cccDNA, RNA interference (siRNA) to block viral protein production, and nucleic acid polymers to block HBsAg release. Immunomodulatory therapies include strategies both to stimulate innate and adaptive responses and to block inhibitory pathways. The targeting of the adaptive immune response may be particularly critical, since functional cure observed during spontaneous resolution of acute hepatitis B (A HBsAg loss, AHB seroconversion) is heavily dependent on a brisk T cell response. In this regard, success using an anti-PD-1 approach has been observed in early studies of these agents in chronic hepatitis B. It is likely that some combination of these novel treatment approaches and existing approved agents will be necessary to achieve functional cure.

106 THE MATHEMATICS OF HEPATITIS B CURE
Alan S. Perelson, Los Alamos National Laboratory, Los Alamos, NM, USA
Current therapies for HBV infection generate a sterilizing or functional cure in a very small fraction of treated individuals. Thus, many new therapeutic approaches are under preclinical and clinical development. Here I will show how insights into these new therapies and HBV biology can be gained by mathematically modeling some of the accumulating experimental data.

For example, by blocking new infections with the entry inhibitor Myrcludex B (Myr-B), one can gain insight into the lifespan of HBV-infected hepatocytes. Analysis of viral load decay after initiation of Myr-B therapy suggests that there may be heterogeneity in the lifespan of HBV-infected cells in vivo, with some infected cells living much longer than others and producing less virus. As another example, I will show how new mathematical models are able to provide quantitative insights into the effects of monotherapy using a capsid inhibitor (CI) and combination therapies of a CI with a nucleic acid analog. Lastly, I will discuss how modeling is providing new estimates of the plasma half-life of HBsAg (as well as that of other species such as HBV DNA and ALT) which may inform therapeutic progress and duration of therapy need to achieve a functional cure.

107 DRUG-DRUG INTERACTIONS: THE UPS AND DOWNS OF ANTIRETROVIRALS PLUS CONTRACEPTIVES
Kimberly K. Scarsi, University of Nebraska, Omaha, NE, USA

Over half of individuals living with or at risk for HIV are of childbearing potential and in need of effective contraception to prevent unintended pregnancies. One barrier to effective hormonal contraception is drug–drug interactions (DDIs) between antiretrovirals (ARVs) and hormones. Interpreting the clinical impact of ARV-hormone DDI data is complicated by an inadequate understanding of hormone pharmacology, including the therapeutic range of different contraceptive products. For example, efavirenz decreases progestin exposure by 10–85%, depending on the progestin studied and the route of administration, yet the clinical impact of this reduction was not realized until subdermal contraceptive implants were scaled-up in combination with efavirenz-based antiretroviral therapy (ART). Specifically, data from a large cohort in Kenya described a 3-fold increase in the risk of pregnancy when progestin-releasing subdermal implants were combined with efavirenz-based ART, yet this excess risk was not observed with depot medroxyprogesterone or oral contraceptives. In addition, some data describe modestly lower ARV exposure when combined with hormones, suggesting the potential for bidirectional ARV-hormone DDIs. To investigate DDIs during ART development, first, one study is conducted between the ARV and a combination of oral contraceptives in healthy volunteers. DDI information from that study is then extrapolated across contraceptives. This approach assumes that all types of exogenous progesterins and estrogens have a similar pharmacokinetic disposition and that the route of administration does not influence the DDI potential of the combination. Recently, studies of non-oral hormones have observed differences in the extent of ARV-hormone DDIs compared to oral studies. Further, individual characteristics, including pharmacogenetics, are emerging as important determinants of the magnitude of DDIs. Taken together, applying a single oral DDI study across diverse populations, different hormones, and variable routes of administration greatly simplify the complex nature of these DDIs. As the field enters an era of HIV treatment and prevention with non-oral ARVs and ARV-hormone multi-purpose technologies to simultaneously prevent both HIV and pregnancy, there lies a critical gap in our understanding of how existing DDI data will extend to these new products across diverse patient populations.

108 CONTRACEPTIVE IMPLANT ROLLOUT IN SOUTH AFRICA
Gregory Petro, University of Cape Town, Cape Town, South Africa
This presentation describes the importance of long acting reversible contraception using the example of the roll-out of contraceptive implants in South Africa.

109 CONTRACEPTION AND HIV RISK: A CONUNDRUM NO MORE
Renee Heffron, University of Washington, Seattle, WA, USA
This talk will provide state-of-the-art evidence on why we have come to understand that injectable depot medroxyprogesterone acetate does not impact women’s susceptibility to HIV infection. It will also examine reasons why data from recent studies have had conflicting results, discuss biologic changes elicited by contraceptive initiation that are relevant for women’s health beyond HIV susceptibility, and point out consequential questions in this domain that are remaining to be addressed.

110 THE STATE OF SRHR & HIV SERVICES FOR CISGENDER WOMEN: A COMMUNITY PERSPECTIVE
Wame Jallow, International Treatment Preparedness Coalition, Gaborone, Botswana

Globally, 19.1 million of the 36.9 million people living with HIV are cisgender women and girls. Countries are failing to meet commitments to the 2016 United Nations Political Declaration on Ending AIDS among adolescent girls and young women (ages 15 to 24), including reducing new HIV infections to below 100,000 per year by 2020, eliminating gender inequalities and all forms of gender-based abuse and violence, encouraging and supporting leadership of young people, scaling up comprehensive sexual and reproductive health education, and protecting their human rights.

In 2018, a potential safety signal associating peri-conception dolutegravir (DTG) use with neural tube defects (NTDs) was reported. It cast a harsh spotlight on chronic problems: access to and quality of essential sexual and reproductive health rights and services for women and girls at risk for or living with HIV - particularly among those ages 14–49. The policy and access fallout from the DTG signal – including national sex-based treatment restrictions for women and adolescent girls - has underscored that they must be essential stakeholders in design, development, implementation, delivery and oversight of HIV research, guidelines, policies and services.

In sub-Saharan Africa, which is home to the world’s highest HIV rate and the lowest prevalence of contraception, access to and quality of essential sexual and reproductive health rights and services are complicated by a range of gender, social, economic, geographic, provider-level, structural and other barriers, limited choices, and lack of information — especially for younger, unmarried and rural women. A survey to assess the current status of sexual and reproductive
111 RECENT ADVANCES IN THE DIAGNOSIS, TREATMENT AND PREVENTION OF TUBERCULOSIS
Gavin Churchyard, The Aurum Institute, Johannesburg, South Africa

Recent advances in the diagnosis, treatment, and prevention of tuberculosis (TB) will be summarized and the importance of these advances for people with HIV discussed. Gaps in current knowledge that need to be addressed to accelerate progress towards ending the TB epidemic will be identified. A roadmap for TB related presentations at CROI will be presented.

112 ENGINEERING VACCINE IMMUNITY
Shane Crotty, La Jolla Institute for Allergy and Immunology, La Jolla, CA, USA

Understanding the immunology of helper T cells, germinal centers, and the human naive B cell repertoire to enable better vaccine design. Most vaccines provide protection from infection through the generation of neutralizing antibodies (nAbs). The repertoire of naive B cells is the starting material from which nAbs eventually arise. Immunization strategies are increasingly targeting precise B cell specificities to mimic nAbs generated during natural infection, in an effort to maximize the potency of the vaccine-elicited Ab response. An understanding of the human B cell specificities capable of immunogen recognition can aid in immunogen design and inform decision-making for clinical trial advancement. We have developed strategies to probe for antigen-specific B cells in the human naive B cell repertoire (Science 2016, Science Translational Medicine 2018, CDI 2018, and Science 2019).

Germinal centers (GCs) are the engines of affinity maturation and are the critical source of memory B cells and long-lived plasma cells. GCs are entirely dependent on T follicular helper (Tfh) CD4 T cells (Immunity 2019). Helping B cells and antibody responses is a major function of CD4 + T cells. It has been 10 years since the publication of B6c as the lineage defining transcription factor for T follicular helper (Tfh) differentiation and the requirement of Tfh cells as the specialized subset of CD4 + T cells needed for germinal centers and related B cell responses. A great deal has been learned about Tfh cells in the past 10 years. Using longitudinal tracking of GCs in draining lymph nodes, using fine needle aspirates (FNAs), we found that two independent methods of slow delivery immunization of rhesus monkeys (RM) resulted in larger GCs, more robust and sustained GC-Tfh cell responses, and GC B cells with improved Env-binding. These GC-associated cell differences correlated with the development of ~20- to 30-fold higher titers of tier 2 HIV nAbs in animals immunized via slow delivery modalities. By analyzing IgV gene usage, we were able to determine that slow delivery immunization enhances HIV neutralizing antibody and GC responses via modulation of immunodominance (Cell, 2019). Slow delivery immunization therefore engages the immune system in unique ways, and novel strategies to accomplish slow delivery immunization in human vaccines will be discussed.

113 IL-6 BLOCKADE DECREASES INFLAMMATION AND INCREASES CD127 EXPRESSION IN HIV INFECTION
Benigno Rodriguez1, Zhengyi Chen1, Curtis Tatsuoka1, Scott F Sieg1, Alan Landay2, Grace A. McComsey1, Brian Clagett1, Chris T. Longenecker1, Carey Shive1, Keith W. Crawford1, Daniela Moisit1, Michael L. Freeman1, Nicholas Funderburg1, Leonard Cabrese1, Michael M. Lederman1

1Case Western Reserve University, Cleveland, OH, USA; 2Rush University, Chicago, IL, USA; 3NAID, Rockville, MD, USA; 4The Ohio State University, Columbus, OH, USA; 5Cleveland Clinic, Cleveland, OH, USA

Background: Interleukin-6 (IL6) is a key inflammatory mediator in treated HIV infection. In vitro, we have shown that IL6 drives cell cycling and blocks responsiveness to interleukin-7 (IL7). In vivo, plasma levels of IL6 are linked to cardiovascular risk and other end-organ complications. We hypothesized that blocking IL6 signaling in vivo could attenuate these effects.

Methods: HIV-infected persons with suppressed viremia and CD4 T cell counts >350 were enrolled in a 2x2 crossover trial of 3 monthly IV doses of the anti-IL6 receptor monoclonal antibody tocilizumab (TCZ) and matching placebo. T cell subpopulations, expression of markers of activation, senescence, cycling, and survival were quantified by flow cytometry. Soluble vascular, metabolic, and inflammation indices were measured by ELISA. Significance of treatment-induced changes was assessed by Wilcoxon signed-rank test. Mixed effects models were fitted to generate effect estimates and for covariate adjustment.

Results: Thirty-four participants were enrolled; 29 continued treatment through the crossover visit at week 20. Two discontinued due to adverse events: grade 3 rash and neutropenia. Both resolved without treatment. IL-6 receptor blockade by TCZ led to a profound decrease in plasma C-reactive protein (CRP) (-2037 ng/mL, p<0.001) and a dramatic increase in plasma IL-6 (42 pg/mL, p<0.001). PD-1 expression on naïve (-2%, p<0.001) and central memory (-3%, p<0.01) CD4 T cells decreased significantly; this was accompanied by a significant decrease in naïve CD4 T cell cycling (Ki-67 expression, -0.2%, p=0.01) and by a significant increase in IL-7 receptor (CD127) expression on naïve (0.7%, p=0.02) and terminally differentiated (3%, p=0.03) CD8 T cells, as well as a significant decrease in soluble IL7 receptor-1, soluble CD14, soluble CD40, and p-selectin. E-selectin, adiponectin. Most lipid species in plasma including oxidized LDL increased with TCZ. Lp-PLA-2 also increased moderately.

Conclusion: Blockade of IL-6 activity markedly decreases soluble markers of inflammation and indices of CD4 T activation/regulation that have been linked to morbidity in treated HIV infection. TCZ enhances expression of the IL7 receptor CD127 on some CD8 subpopulations, which may explain decreased plasma IL7 levels. The combination of these effects may result in reduced turnover and dysfunction of T cells in treated HIV infection.

114 NEUTRALIZING ANTIBODIES AND TRMs PROVIDE ENHANCED AND DURABLE RESISTANCE AGAINST HIV
Prabhus Arunachalama1, Tyshena P. Charles1, Vineett Iqoja1, Satish V. Bollimpalli1, Madeleine K. Scott2, Shakti Gupta2, Shankar Subramanian3, Purvesh Khatri1, Pamela A. Kozlowski1, Cynthia Derdeyn1, Eric Hunter1, David Masopust1, Rama R. Amar1, Bali Pulendran2, for the Emory Consortium for Innovative AIDS Research

1Stanford University, Stanford, CA, USA; 2Emory Vaccine Center, Atlanta, GA, USA; 3University of Minnesota, Minneapolis, MN, USA; 4University of California San Diego, La Jolla, CA, USA; 5Louisiana State University, New Orleans, LA, USA

Background: A broadly cross-reactive neutralizing antibody response is necessary to prevent infection from diverse strains of HIV. Induction of such broadly neutralizing antibodies by vaccination has been challenging but current approaches can induce autologous neutralizing antibodies (nAbs) in various animal models. Here we tested if vaccine-induced nAbs alone or in combination with cellular immune responses can protect rhesus macaques (RMs) against intravaginal challenges with the autologous strain of virus representative of circulating HIV-1 strains.

Methods: We immunized three groups of RMs as follows: group 1 with a trimeric envelope protein (BG505 SOSIP.664) adjuvanted with the TLR7/8 ligand 3M-052, alone to induce nAbs; group 2 with a heterologous viral vector regimen expressing SIVmac239 Gag to induce tissue-resident memory CD8 T cells (TRMs, which traffic to and reside in mucosal tissues), as well as with BG505 SOSIP.664/3M-052 as in group 1; and group 3 as controls with 3M-052 alone. One month after the final protein vaccination, we challenged the animal models. Here we tested if vaccine-induced nAbs alone or in combination with cellular immune responses can protect rhesus macaques (RMs) against intravaginal challenges with the autologous strain of virus representative of circulating HIV-1 strains.

Methods: We immunized three groups of RMs as follows: group 1 with a trimeric HIV envelope protein (BG505 SOSIP.664) adjuvanted with the TLR7/8 ligand 3M-052, alone to induce nAbs; group 2 with a heterologous viral vector regimen expressing SIVmac239 Gag to induce tissue-resident memory CD8 T cells (TRMs, which traffic to and reside in mucosal tissues), as well as with BG505 SOSIP.664/3M-052 as in group 1; and group 3 as controls with 3M-052 alone. One month after the final protein vaccination, we challenged the animal models. Here we tested if vaccine-induced nAbs alone or in combination with cellular immune responses can protect rhesus macaques (RMs) against intravaginal challenges with the autologous strain of virus representative of circulating HIV-1 strains.
from group 2 following necropsy, and were stimulated ex vivo with cognate Gag peptides to reactivate TRMs. The impact of TRM activation was analyzed by CITE-seq single-cell RNA sequencing to identify a possible mechanism(s) by which the TRMs enhanced protection.

**Results:** The protein and HIV immunizations were immunogenic as measured by high autologous nAb titers and Gag-specific T cell responses, respectively. Following 10 weekly vaginal challenges with SHIV-BG505, protection was observed in both immunization groups: 53.3% and 66.7% in groups 1 and 2, respectively. A nAb titer above ~300 represented the primary correlate of protection in group 1 animals. Surprisingly, in group 2, nAb response was not the primary correlate. A majority of the protected animals had nAb titers <300 suggesting that the TRMs reduced the nAb threshold associated with protection. Furthermore, protection observed in group 2 was durable as these animals resisted six additional challenges five months later with the same virus. Ex vivo restimulation of TRMs in vaginal tissues revealed rapid induction of local antiviral immunity.

**Conclusion:** TRMs can reduce nAb threshold and provide durable protection against HIV.

**B**

**Protection**

**C**

**Correlate of protection**

**D**

**Durability of protection**

**Results:** Significant anti-HIV Gag activity (range: 8%-50% killing) by bulk NK cells was exclusively detected in half of all PLWH, while killing of BCLs pulsed with the CEF peptide pool, or killing of MHC-devoid KS62 cell lines, was comparable between PLWH and HD. NK cells from half of EC had detectable HIV Gag-specific cytotoxic activity and displayed the most robust responses. Strikingly, 35% of all tested NKCL (n=165) generated from 22 PLWH (59% NKCL from 8 ART, 18% MCIKL from 14 UT) showed positive responses to HIV (at least twice above killing of unstimulated and above killing of self-peptide-pulsed B-LCL). Reactive NKCL displayed anti-HIV Gag cytotoxic activity up to 43% specific lysis and anti-HIV Env cytotoxic activity up to 87% specific lysis, within the range of robust cytotoxicity normally found against tumor cells. Phenotypic analysis indicated antigen-specific memory was associated with increased NKG2C and CD57 expression. Accordingly, NKG2C receptor blockade and pulsing with single HIV-derived peptides that bind HLA-E indicated memory NK cell responses likely depend on an HLA-E-dependent recognition mechanism.

**Conclusion:** Collectively, our work presents the first mechanistic evidence for HIV-specific memory NK cells induced by HIV infection in humans. These data suggest that HIV-specific responses mediated by NK cells may have the potential to be harnessed for curative or other therapeutic interventions.

**116 EFFICACIOUS RHCMV/SIV VECTORS ELICIT BROADLY CROSS-REACTIVE SIV-SPECIFIC CD8+ T CELLS**

Benjamin N. Bimmer1, Shaheed Abdulhaqq, Abigail Ventura1, Eric McDonald, Daniel Douke1, Scott Hansen1, Jonah Sacha1, Louis J. Picker1

1Oregon Health and Sciences University, Portland, OR, USA, 2NIH, Bethesda, MD, USA

**Background:** RHCMV68-1/SIV vaccines demonstrate a profound ability to protect against SIV challenge, with half of all vaccinated rhesus macaques clearing viremia shortly after infection. A hallmark of RHCMV68-1 vaccines is the induction of CD8 T cells that are non-classically restricted, either by MHC-II or MHC-E molecules. MHC-E restricted cells are necessary for RHCMV68-1 mediated protection, and characterizing these unconventional cells is essential to understand the unique immune response and to improve vaccine efficacy.

**Methods:** We developed novel single-cell methods to isolate and characterize MHC-E restricted CD8 T cells. CD8+ T cells from RHCMV68-1/SIV vaccinated rhesus macaques were stimulated with antigen in vitro (epitopic peptides or autologous SIV-infected CD4+ T cells) and responding cells were isolated on the basis of surface trapped TNF-a and CD69 expression. Next, we performed single cell RNA-seq (scRNA-seq) using the 10x Genomics platform, which enables simultaneous capture of transcriptome data and TCR clonotype from individual cells. As validation, full length TCR alpha/beta pairs were synthesized and used to transduce CD8 T-cells from SIV-naive macaque, which were used in similar recognition assays.

**Results:** We characterized MHC-E restricted TCR clonotypic hierarchies from four RHCMV68-1/SIV vaccinated rhesus macaques over more than 2 years. In each animal, a small number of broadly cross-reactive TCRs represents the entire MHC-E restricted response to SIV-infected cells, with a single clone recognizing up to 7 distinct epitopes. TCR alpha/beta transductants replicated the in vivo pattern of antigen recognition. While these TCRs are specific, we further demonstrate the peptide/MHC avidity of these MHC-E restricted clones is significantly lower than conventional MHC-II clones.

**Conclusion:** These data indicate that the broad, MHC-E restricted epitope recognition is accomplished by a small number of T cell clones using highly cross-reactive TCRs with low functional avidity relative to classical responses. These results provide insight into the mechanisms underlying RHCMV/SIV vector efficacy and demonstrate a novel set of methods that could be used to study any T cell population.

**117 PD-1 BLOCKADE AT TIME OF ART WITHDRAWAL FACILITATES EARLY POST-PEAK VIRAL CONTROL**

Afam Okoye1, Derick M. Dueli2, Benjamin Varco-Merth1, Morgan Chaunza2, Matthew Ldei1, Hannah Behrens1, Jeremy Smedley1, Michael K. Arxheim1, Scott Hansen1, Steven G. Deeks2, Nicolas Chomont3, Jeffrey D. Lifson4, Sharon R. Lewin2, Louis J. Picker1

1Oregon Health and Sciences University, Portland, OR, USA, 2University of California San Francisco, San Francisco, CA, USA, 3Centre de Recherche du CHUM, Montreal, QC, Canada, 4Frederick National Laboratory for Cancer Research, Frederick, MD, USA, 5Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia

**Background:** Previous studies evaluating the ability of PD-1 blockade to reduce viral reservoirs in SIV+ monkeys on ART have failed to demonstrate significant
therapeutic benefit. Here, we evaluated whether PD-1 blockade, around the time of ART discontinuation, could facilitate induction of long-term post-ART control of SIV replication through the functional enhancement of SIV-specific T cells around the time of viral rebound. To address this, we initiated PD-1 blockade in SIV-infected rhesus macaques (RM) receiving ART, starting prior to ART release, with low antigen exposure, or at time of ART release with high antigen exposure.

Methods: 30 RM were IV inoculated with 200 ffu of SIVmac239 and after 12 days began receiving ART (tenofovir/emtricitabine/dolutegravir). After sustained virus suppression (<15 RNA copies/ml), RM were randomized into 3 groups: A) immunotherapy (n=10 each) that received: A) 9 biweekly doses of a rhesusized anti-PD1 mAb at 3mg/Kg starting 45 days prior to ART release (low antigen exposure); B) 6 biweekly doses of anti-PD1 starting 3 days prior to ART release (high antigen exposure); or C) an isotype control mAb at the same dosing frequency as Group A. Plasma viral loads (pvl; RNA copies/ml) were quantified by qRT-PCR and T cell dynamics assessed by flow cytometry.

Results: Anti-PD1 induced increases in CD4+ and CD8+ memory T cell proliferation but no effect on the frequency of viral blips in the low antigen exposure group vs. controls prior to ART release, suggesting PD-1 blockade did not induce SIV production. Following ART release, all RM rebounded within 17 days except for 1 RM in Group B that rebounded at day 31, indicating PD-1 blockade did not affect time to virus rebound. Moreover, rebound pvl peaked by day 21 post-ART at 4.5 logs in Group A, 4.8 logs in Group B and 4.8 logs in Group C. However, by day 2 post-ART, we observed a ~2 log reduction of pvl in both anti-PD1 treatment groups A and B relative to Group C controls (2.5 logs and 2.6 logs vs. 4.5 logs, respectively). RM are continuing to be followed to determine long-term pvl set points.

Conclusion: PD-1 blockade had no effect on reactivation and early spread of virus following ART release, but maintaining PD-1 blockade following ART release appears to facilitate early control of virus replication, likely by enhancing the functional activity of SIV-specific T cells expanding in response to SIV replication.

118 TRACKING AND PREDICTING REBOUND IN SHIV-INFECTED INFANT MACAQUES AFTER LONG-TERM ART

Veronica Obregon-Perko1, Katherine Bricker2, Ferzan Uddin1, Laura Rotolo1, Daryll Vanover1, Philip Santangelo3, Stella Berendam1, Genevieve Foulois4, Shan Liang5, Thomas Vanderford6, Katharine J. Bar1, George Shaw7, Guido Silvestri6, Sallie Permar1, Ann Chahroudi8

1 Emory University, Atlanta, GA, USA, 2Georgia Institute of Technology, Atlanta, GA, USA, 3Duke Human Vaccine Institute, Durham, NC, USA, 4Yerkes National Primate Research Center, Atlanta, GA, USA, 5University of Pennsylvania, Philadelphia, PA, USA

Background: Breastfeeding transmission accounts for the majority of new pediatric infections and commits infants to lifelong ART, as interruption is typically followed by return of replication and repopulation of reservoirs. A better understanding of the anatomic origin and kinetics of viral rebound during analytical treatment interruption (ATI) could inform the development of alternatives to ART-based strategies to achieve long-term viral remission in the pediatric population.

Methods: At 4 wks old, 10 thalas macaques were orally-administered SHIV, CH505:375H.DCT and placed on daily ART at 8 wpi. ART was interrupted after 1 yr in a subset of animals (n=6) to assess viral rebound. Blood and tissue were collected throughout the study for flow cytometry and viral measurements. For whole-body ImmunoPET, macaques were infused with 68Ga-labeled PGT145 F(ab) and imaged by PET/CT. Scans were done once on long-term ART and twice weekly following ATI.

Results: Median viral loads at peak infection and just prior to ART were 5x105 and 1x105 copies/ml, respectively. During ATI, rebound viremia was detected within 10-24 d, with variable peak viral loads that reached levels seen at ART initiation. Post-treatment control within 4 wks of rebound was seen in 1/2 Mamu A01+ macaques. Various parameters were evaluated for their ability to predict time to viral rebound. In our model, we did not see an association between PD-1 expression on CD4+ T cells and time to rebound, as previously reported for HIV-1 infection. SHIV-DNA and -RNA persistence in blood, lymph node, and colorectal CD4+ T cells was also evaluated. Just prior to ATI, the highest levels of SHIV-RNA were found in the colorectal compartment, suggesting this region could be an early site of viral reactivation following ART interruption. Indeed, longitudinal imaging of SHIV Env expressing cells in tissues by ImmunoPET before and immediately following ATI showed an expansion of infected cells in the GI tract prior to SHIV RNA reaching detectable levels in the plasma. A similar trend was observed in the lungs, where tissue-resident macrophages have been found to be the principal target cells of infection.

Conclusion: This work provides novel insight into the kinetics, anatomic origin, and predictors of viral rebound in a pre-clinical NHP model of pediatric HIV infection. Our preliminary data implicates the GI tract as a key site to be studied for the development of remission strategies and one to be monitored in HIV-infected children being considered for ATI.

119 PERIPHERAL BLOOD SIV/HIV ORIGINATES FROM INFECTED CELLS IN TISSUES

Leticia Kuri Cervantes1, Maria B. Pumpens1, Marcus Buggert2, Meagan Watkins3, David S. Khoury4, Kevin McCormick5, Felicity Mampe6, Emily Lindemuth1, Ian Frank1, Max G. itkina7, Miles Davenport4, Brandon F. Keele8, Katharine J. Bar9, Ronald Vezey10, Michael R. Betts11

1 University of Pennsylvania, Philadelphia, PA, USA, 2Karolinska Institute, Stockholm, Sweden, 3Tulane University, Metairie, LA, USA, 4Kirby Institute, Sydney, NSW, Australia, 5NIH, Frederick, MD, USA

Background: HIV and SIV infected CD4 T cells localize primarily to lymphoid and mucosal tissues, where they constitute >90% of infected cells in chronic infection. While largely assumed, it remains to be established if peripheral blood (PB) viremia originates from these tissues, or from infected cells directly within the vasculature. Here we assessed in thalas macaques (RM) and humans the potential contribution of tissue-based virus production to plasma viremia (VL).

Methods: Four RM were infected i.v. with barcoded SIVmac239, and treated with the lymphocyte migration inhibitor FTY720 daily from day 7 or 28 until day 90. PB and lymphoid tissue (LT) samples were collected for cell and virus quantification. In parallel, we collected PB and thoracic duct lymph (TDL) from 11 HIV+ donors (3 viremic, 8 ART) and assessed VL in each compartment. Viral phylogeny was characterized by SGS gp160 env sequencing of plasma and TDL.

Results: In the FTY720-treated RM we observed near complete redistribution of circulating CD4 T cells into tissues within 7 days of FTY720 treatment (pre-FTY720: 513±283 CD4 T cells/µl, post-FTY720: 5±2 CD4 T cells/µl). Despite the absence of PB CD4 T cells, all animals, regardless FTY720 administration, had peak and set point plasma VL similar to historical controls. Barcode sequencing of cell-associated virus from LT and plasma virus during FTY720 treatment revealed substantial overlap in the dominant virus populations replicating in the LT and circulating in plasma. Together, these results suggest that the circulating plasma virus originated from tissues. We next assessed paired TDL and plasma from HIV+ donors. HIV RNA copies were higher in TDL vs. PB (p=0.0137; up to 10-fold higher in viremic), and the virus populations were phylogenetically indistinguishable between the compartments. Based upon the differential VLs, and incorporating viral clearance rate, plasma volume, and lymph output we calculated that ~50% of plasma virus originates from thoracic duct output, in some individuals reaching a 100% contribution.

Conclusion: Our results indicate that HIV infected cells within LT and non-LT, rather than the vasculature, are the major source of PB viremia. A large proportion of this viremia is maintained through thoracic duct lymphatic efflux, indicating that virus released from infected cells in tissues travels through lymphatics into PB.

120LB CD4+ T-CELL DEPLETION IN AFRICAN GREEN MONKEYS DOES NOT ALTER DISEASE PROGRESSION

Egidio Brocca-Cofano1, Paola Sette1, Ranjit Sivanandham1, Cui Ling Xu2, Adam J. Kleinman1, Sindhuja Murali Kilapandal Venkatraman3, Haritha Annapureddy1, Colin McAndrews4, Tammy Dunsmore5, Jacob Brenchley2, Jacob D. Estes1, Cristian Apetrei1, Ivona Pandrea1

1 University of Pittsburgh, Pittsburgh, PA, USA, 2NIAD, Bethesda, MD, USA, 3Oregon Health and Sciences University, Portland, OR, USA

Background: Massive and persistent CD4+ T cell depletion is a hallmark of HIV infection, being associated with impairment of cellular immunity and opportunistic infections. The contribution of CD4+ T cell depletion to HIV-associated gut dysfunction is unknown. African Green Monkeys (AGMs), a species that do not progress to AIDS, partially recover mucosal CD4+ T cells during chronic infection and maintain gut integrity. We assessed the impact of prolonged experimental CD4+ T cell depletion on the gut integrity and natural history of SIV infection in AGMs.

Methods: Six AGMs were infected intravenously with 300TCID50 SIVab. All animals received an anti-CD4 antibody intravenously every three weeks,
starting from 21 days post infection (dpi). Plasma viral loads (PVLs), absolute counts, proliferation and activation status of T cells, systemic and local immune activation and inflammation, gut integrity, and cardiovascular disease onset were monitored throughout the follow-up.

**Results:** Complete ablation of CD4+ T cells in blood and greater than 90% depletion in intestine and lymph nodes was achieved. PVLs peaked at 107 viral RNA copies/ml at 10 dpi, followed by a 4-log decrease by 28 dpi. PVLs were lower compared to SIV-infected historical AGM controls and were even undetectable in some CD4-depleted AGMs. No significant changes in T cell immune activation and proliferation levels occurred in the CD4-depleted AGMs. A transient increase of the inflammatory cytokines and chemokines (IL-1Ra, Rantes, Eotaxin, MCP-1, I-TAC, MIP-10) occurred only during acute infection but was resolved prior to chronic infection. Absence of gut damage was observed in situ and through the testing of iFABP, Zonulin, and sCD14 which remained stable during the follow up. sCD163 transiently increased during acute infection.

**Conclusion:** Despite a major and persistent (over 1 year) depletion of CD4+ T cells in blood and tissues, AGMs remained healthy and did not progress to AIDS. Gut integrity was maintained in spite of profound CD4+ T cell loss. As such, our results suggest that CD4+ T cell depletion, in the absence of increased inflammation and immune activation is not a determinant factor for SIV-related gut dysfunction. Our results also indicate that AGMs’ AIDs-resistance is independent of the CD4+ T cells.

121 INFERIORITY OF SHORT DURATION SOFOSBUVIR-VELPATASVIR FOR RECENT HCV (REACT STUDY)

Gail Matthews1, Sanjay Bhagani1, Marc van der Valk1, Jürgen K. Rockstroh1, Christine Thurnheer1, Arthur Kim2, Jordan J. Feld2, Julie Bruneau3, Edward Gane4, Margaret Hellard5, Tanya Applegate6, Marianne Martinello6, Kathy Petoumenos6, Gregory J. Dore7, for the REACT Study Group

1Kirby Institute, Sydney, NSW, Australia, 2Royal Free Hospital, London, UK, 3Academic Medical Center, Amsterdam, Netherlands, 4University of Bonn, Bonn, Germany, 5University Hospital of Bern, Bern, Switzerland, 6Massachusetts General Hospital, Boston, MA, USA, 7University Health Network, Toronto, ON, Canada, 8Centre de Recherche du CHUM, Montreal, QC, Canada, 9University of Auckland, Auckland, New Zealand, 10Burnet Institute, Melbourne, VIC, Australia

**Background:** Shortened duration therapy for acute and recently acquired HCV infection has been shown to be highly effective in several small non-randomised studies with direct-acting antiviral agents (DAAs), however guidelines remain conservative in their recommendations with no currently approved regimens for this indication.

**Methods:** The REACT study was an NIH-funded multicentre international, open-label, randomised, phase 4 non-inferiority trial examining the efficacy of sofosbuvir/velpatasvir for recently acquired HCV infection, 6 weeks sofosbuvir/velpatasvir was inferior to 12 weeks. Final analysis of the full randomised dataset will be completed October 2019.

122 INDIVIDUAL AND POPULATION-LEVEL IMPACT OF HCV TREATMENT AMONG PEOPLE WHO INJECT DRUGS

Javier Cepeda1, David L. Thomas2, Rachel E. Gicquelais3, Jacquie Astemborski3, Gregory D. Kirk3, Shruti H. Mehta4

1University of California San Diego, San Diego, CA, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA, 3Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** The availability of highly curative direct acting antivirals (DAAs) has led to calls for elimination of HCV as a public health priority. Specifically, a key target is a 65% reduction in HCV-associated mortality by 2030. Mathematical models have predicted that dramatic scale-up of DAAs can achieve this ambitious target, however this has not been assessed empirically. We evaluate temporal trends in individual and population-level liver disease burden (as a proxy for HCV-related mortality) in a community-based cohort of people who inject drugs (PWID) in Baltimore in the context of expanding DAAs use.

**Methods:** From 2005-2018, we collected 11,471 liver stiffness measurements (LSM) using transient elastography from 1,668 PWID who were HCV antibody positive. At the individual-level, we estimated the impact of DAAs on LSM using generalized linear mixed modeling after adjusting for age, sex, race, time, alcohol use and HCV status. To assess population-level impact, we used segmented regression to determine changes in the proportion of the population with cirrhosis (LSM ≥ 12.3 kPa) within and between two periods (before and after 2015) based on presumed scale-up of DAAs in the community.

**Results:** Overall, 69% were male, mean age was 48, 33% were HIV co-infected, and 14% had cirrhosis at baseline. Only 2% reported ever receiving HCV treatment in 2014 which increased to 41% by 2018. After adjusting for confounders, PWID who reported receipt of DAA had significantly lower LSM (-0.88 kPa 95%CI: -0.91 kPa, -0.86 kPa, p<0.0001) compared to PWID who had not received DAAs. HIV/HCV co-infected PWID had significantly higher LSM, especially among those who not HIV virally suppressed (1.14 kPa, 95%CI: 1.08 kPa, 1.20 kPa, p<0.0001) compared to PWID who were HIV negative. At the population-level, we observed a significant rise in the proportion with cirrhosis within the cohort from 2005-2014 (mean log odds of cirrhosis increased each year by a factor of 0.13, p<0.006); however from 2015-2018, the proportion with cirrhosis declined (mean log odds decreased each year by a factor of 0.53, p=0.003, see figure).

**Conclusion:** Expansion of DAAs in the PWID community appears to have led to declines in liver disease progression at the individual and population level. Increasing access to all HCV infected persons, particularly those at greatest risk of liver disease progression will be critical to achieving HCV elimination targets.

123LB LARGE HIV OUTBREAK AMONG PEOPLE WHO INJECT DRUGS, WEST VIRGINIA, 2018–2019

Robert P. McClung1, Nivedha Panneer2, Amy Atkins1, Sheryl Lyss1, Senad Handanagic1, Mi Chen1, Michael Kilkenny1, Kyle T. Bernstein2, Vicki Hogan3, Carolyn Wright1, Erica Thomasson2, Kara Willenburg5, David Wills3, Alexandra M. Oster1, for the West Virginia Bureau of Public Health (BPH), Centers for Disease Control and Prevention (CDC), Washington, DC, USA, 2West Virginia Department of Health and Human Resources, Charleston, WV, USA, 3CDC, Atlanta, GA, USA, 4Marshall University, Huntington, WV, USA, 5Marshall University, Huntington, WV, USA

**Background:** In January 2019, the West Virginia Bureau for Public Health (BPH) identified an increase in HIV diagnoses among people who inject drugs (PWID) in Cabell County, which has experienced high rates of substance use disorder in recent years. Responding to HIV clusters and outbreaks is one of four pillars of the federal Ending the HIV Epidemic initiative and can be used to guide activities supporting the other pillars (diagnose, treat, prevent). BPH, Cabell-Huntington Health Department, and CDC collaborated to conduct a robust investigation and response.
125 NEWBORN TESTING REVEALS HIGH HCV SEROPREVALENCE IN PREGNANT WOMEN FROM NEW YORK STATE

Linda M. Styer1, Erica Miller1, Jean Rock1, Lea Krein1, Monica Martin1, Dhanushki Samarayanayake1, Shu-Yin Leung1, Michele Gaggana1, Colleen Flanagan1, Monica Parker1

1 New York State Department of Health, Albany, NY, USA, 2 University at Albany, Albany, NY, USA

Background: Hepatitis C virus (HCV) infections in New York State (NYS) have been rising among young adults due to increased injection drug use. In 2018 in NYS (excluding NYC), 6% of new female cases were in women of childbearing age (15–44 yrs old). Increased HCV infections in this age group are concerning as 6% of HCV RNA-positive pregnant women will transmit HCV to their baby. To plan effective public health actions, accurate HCV prevalence rates among pregnant women are needed; however, many HCV infections go undiagnosed and unreported. Babies passively acquire maternal IgG antibodies. Therefore, testing newborn blood for HCV antibodies can reveal mom’s serostatus. Our goal was to perform a large-scale HCV serosurvey of pregnant women in NYS by testing newborn dried blood spots (DBS) using a high-throughput, low-cost Luminex HCV immunoassay.

Methods: All DBS submitted to NYS’s newborn screening program over 6 wks were sampled by punching a 3mm circle into microplates. Aggregate data on birth weight, gestational age and mother’s county of residence were recorded, and samples were blinded. A generic patient code was included to identify duplicate samples. HCV antigen-coupled beads were used to test eluted blood for HCV antibodies using a low-cost (<$0.80/well) Luminex-based immunoassay in 384-well plates. Repeated median fluorescence intensity (MFI) >1000 was considered HCV antibody reactive.

Results: Of the 29,323 DBS sampled, 25,571 (87%) were from unique babies born to mothers residing in NYS. Of these, 18,581 (73%) were tested. 148 DBS were HCV antibody reactive, for an overall NYS seroprevalence of 0.8%. Multiple DBS collected on different days were tested from 1409 individuals, 31 with repeat HCV reactive results, 1376 with repeat non-reactive results and 2 with discordant results close to the MFI cutoff. Premature birth (26%) and low birth weight (26%) were twice as common in babies born to HCV seropositive mothers than seronegative mothers (p < 0.001). HCV seroprevalence in Central (2.1%) and Western/Finger Lakes (1.5%) regions, where multiple counties are designated rural, was 3–4 times higher than the rest of NYS and similar to high rates observed in other U.S. rural regions. For the year, we estimate that ~1800 babies will be born to HCV antibody positive women in NYS.

Conclusion: Newborn DBS testing using a Luminex-based immunoassay is an effective way to assess HCV burden among pregnant women.

124 HCV TRANSMISSION AMONG MSM: EXTERNAL INTRODUCTIONS COULD COMPLICATE MICRO-ELIMINATION

Jelle Koopsen1, Edyth Parker1, Colin Russell1, Thijs J. Van De Laar1, Elske Hoornenborg1, Marc Van Der Val1, Janke Schinkel1

1 Academic Medical Center, Amsterdam, Netherlands, 2 OLVG, Amsterdam, Netherlands, 3 Public Health Service Amsterdam, Amsterdam, Netherlands

Background: Elimination of HCV has become a target with the introduction of highly effective direct antiviral agents (DAAs). In the Netherlands, new HCV infections including frequent reinfestions almost exclusively occur in MSM. It is unclear whether unrestricted access and high uptake of DAAs is sufficient to eliminate HCV in high-risk populations such as MSM. This study presents historic trends and current dynamics of HCV among Amsterdam in the Netherlands on the basis of data collected between 1994 and 2019.

Methods: We analyzed surveillance data, including HIV-1 polymerase data, reported to BPH through November 2019; links were identified at ≤0.005 nucleotide substitutions/site. Outbreak cases were defined as HIV diagnoses during January 1, 2008 – October 9, 2019 among 1) PWID linked to Cabell County, 2) their sex or injecting partners, or 3) people with linked sequences. We estimated transmission rate and timing of infections via molecular clock phylogenetic analysis and identified suspected recent infections based on initial viral load and CD4+ cell count, report of last negative HIV test, or presence in a molecular cluster. State, federal, and local partners implemented a comprehensive response.

Results: We identified 81 cases, a 2.285% increase above the 2015–2017 annual average of 2 cases. Most people were male (58%), aged 20–39 years (74%), and white (91%). Almost all (99%) were PWID; many (73%) reported unstable housing. In all, 69 (85%) had ≥1 measure of recent HIV infection. Among 45 people with an available HIV-1 sequence, 41 (91%) were in a large molecular cluster with 35/41 (85%) inferred transmissions occurring after January 1, 2018. Estimated transmission rate in the molecular cluster was 78 per 100 person-years. A comprehensive response feature activities from all four pillars (figure).

Conclusion: Evidence of rapid transmission in this outbreak—the largest relative increase over baseline in the United States since the large 2015 outbreak in rural Scott County, Indiana—galvanized robust collaboration among federal, state, and local partners. Response interventions supported diagnosis, treatment, and prevention (including expansion of preexposure prophylaxis and syringe services); many activities are now being expanded in other counties statewide. Cluster and outbreak response requires increased coordination and creativity to improve service delivery to vulnerable communities.
126 HEPATOCELLULAR CARCINOMA RISK AMONG PERSONS WITH HIV IN NORTH AMERICA, 1996-2015

Jing Sun1, Keri N. Althoff1, H. Nina Kim1, Mari M. Kitahata2, Chad J. Achenbach1, Gypsamber D’Souza3, Marina Klein4, Bryan Lau1, Joseph Lim1, Vincent Lo Re5, Julia L. Marcus6, Angel M. Mayor7, Michael J. Silverberg8, Gregory D. Kirk1, for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2University of Washington, Seattle, WA, USA, 3Northwestern University, Chicago, IL, USA, 4McGill University, Montreal, QC, Canada, 5Yale University, New Haven, CT, USA, 6University of Pennsylvania, Philadelphia, PA, USA, 7Harvard University, Cambridge, MA, USA, 8University Central del Caribe, Bayamon, Puerto Rico, 9Kaiser Permanente, Oakland, CA, USA

Background: People living with HIV (PWH) are often co-infected with HBV and HCV, leading to increased risk of hepatocellular carcinoma (HCC). HCC risk may have changed in the current era of potent combination antiretroviral therapy (ART). We assessed temporal trends in HCC among PWH, comparing HCC rates by viral hepatitis infection status, risk populations, and HIV disease severity in the North America AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

Methods: We examined 3 calendar periods: early- (1996-2000), mid- (2001-2005), and modern- ART (2006-2015). HCC diagnoses were identified and validated through cancer registries or medical records. HBV and HCV infection were confirmed by serologic and/or virologic test and categorized as ever, never infected, or missing. CD4 counts were measured at entry of each calendar period or the beginning of cohort-specific cancer diagnosis ascertainment. HIV RNA viral load (vL) was measured two years before HCC diagnosis or before the end of cancer diagnosis ascertainment. Poisson regression models estimated HCC incidence rates (IR) and rate ratios (aIRR), adjusted for age, sex, race, and viral hepatitis infection status, risk populations, and HIV disease severity by calendar periods were calculated.

Results: Of 109,283 HIV patients with 723,441 person-years (pys) of follow-up, 20% were HCV co-infected, 6% HBV co-infected, 2% triple-infected, 45% developed HCC. PWH who had HBV and/or HCV co-infection were more likely than HIV-monoinfected PWH to develop HCC and did so at earlier ages. From 1996 to 2015, HCC IR increased from 0.28 to 0.75/1000 pys. As compared to HIV-monoinfected PWH, HCV mono-infected persons, PWH co-infected with HBV and/or HCV had substantially greater age-related cumulative incidence of HCC in all 3 periods (Figure). Higher HCV vL (>500 copies/mL) and lower CD4 counts (<500 cells/mL) were associated with higher HCC risk (aIRR: 2.2, 95% CI: 1.8-2.7 and aIRR: 1.2, 95% CI: 1.0-1.4, respectively). People who injected drugs had higher HCC risk compared with men who had sex with men (aIRR: 2.0, 95% CI: 1.3-2.9), even after controlling for viral hepatitis co-infection.

Conclusion: HCC rates among PWH increased significantly over time. Patients with viral hepatitis co-infection, lower CD4, higher HIV vL, or HIV transmission through injection drug use had higher HCC risk. These findings suggest the importance of HIV viral suppression and treatment of viral hepatitis among PWH in the ART era in order to reduce HCC risk.

127 HIV/HCV VS HCV: PLASMA AND LIVER VIRAL DYNAMICS AND IP-10 LEVELS

Ashwin Balagopal1, Jaiprasath Sachithanandham2, Julia Leep-Lazar3, Jeffrey Quinn4, Kenneth Bowdren4, Kathleen M. Ward1, Stephanie Katz1, Mark Sulkowski1, 1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: HIV/HCV co-infected people have worse liver disease progression than HIV mono-infected people. Interferon-free therapies have yielded high rates of sustained virologic response after 12 weeks, but shorter therapy has not been uniformly successful in HIV/HCV co-infection. We compared how quickly the liver is cleared of infection with interferon-free therapy in HIV/HCV co-infection and HCV mono-infection.

Methods: We enrolled 10 people with chronic genotype 1a HCV infection without cirrhosis in a clinical trial of Sofosbuvir and Velpatasvir for 12 weeks; 5 people had virologically suppressed HIV on antiretrovirals. Participants underwent liver biopsies at baseline and on day 4 or 7 after treatment initiation; single-cell laser capture microdissection was performed to quantify the proportion of infected hepatocytes. Plasma viral kinetics and IP-10 levels were measured over the first two weeks.

Results: The median (range) age of participants was 55.5 (28, 66), 5/10 were female, and 8/10 were Black. The median (range) liver stiffness was 6.5 kPa (4.1, 8.6). The median (range) baseline plasma HCV RNA levels was 6.36 log10 IU/mL (5.68, 7.93). The median (range) proportion of HCV-infected cells was 8% (1%, 10%) at baseline and 1% (<0.3%, 7%) at second biopsy: baseline proportions and the change in proportion of infected cells correlated closely with baseline plasma HCV RNA levels (r=0.89, 0.88). The median (range) percent change in proportion of infected hepatocytes within the first week was -89.4% (-70.0, -97.7). There were no differences in plasma or liver HCV kinetics between HIV+ and HIV- at baseline or later. Median (range) IP-10 levels at baseline were 369 pg/mL (175, 479) and did not differ significantly by HIV status; however, day 1 and day 14 IP-10 levels were significant higher among HIV+ participants (p<0.05 for both).

Conclusion: HIV/HCV co-infected persons have rapid clearance of intrahepatic HCV, similar to HCV mono-infected persons; despite having abundant infection. However, residual immune activation appears to persist despite virologic suppression of both viruses. While this may not have different implications for virologic cures, there may be persistent effects on liver disease progression in HIV/HCV co-infection.
128 CLINICAL PREDICTORS OF LIVER FIBROSIS PRESENCE & PROGRESSION IN HIV-ASSOCIATED NAFLD

Lindsay T. Fourman1, Takara L. Stanley1, Meghan Feldpausch1, Julia Purdy1, Isabel Zheng1, Chelsea S. Pan1, Julia Aepfelbacher1, Colleen Buckless1, Andrew Tsao1, Kathleen E. Corey1, Raymond T. Chung1, Martin Torriani1, David E. Kleiner2, Catherine K. Adhu3, Kimberly K. Scarsi6

1Massachusetts General Hospital, Boston, MA, USA, 2NIH, Bethesda, MD, USA

Background: Nonalcoholic fatty liver disease (NAFLD) – ranging from steatosis to steatohepatitis to fibrosis – is a major cause of liver disease in HIV. While simple steatosis is regarded as relatively benign, hepatic fibrosis has been linked to all-cause and liver-specific mortality. The natural history of NAFLD in HIV, including which patients are likely to develop clinically overt disease, is not well known. In the current study, we leverage liver biopsy samples from a clinical trial of HIV-associated NAFLD to identify predictors of fibrosis presence and progression.

Methods: We recently completed a randomized trial of the growth hormone-releasing hormone analogue tesamorelin to treat NAFLD in HIV. In this study, we found that tesamorelin reduced liver fat and prevented fibrosis progression. Sixty-one participants with HIV and NAFLD were randomized to tesamorelin or placebo for 12 months. NAFLD was defined as hepatic fat fraction (HFF) ≥ 5% by magnetic resonance spectroscopy in the absence of active hepatitis B or C or excess alcohol consumption. Individuals with cirrhosis were excluded. Participants underwent liver biopsy at baseline and 12 months; histologic evaluation was performed by a single expert pathologist blinded to treatment and biopsy order.

Results: Among 58 participants with baseline biopsies, 43% had hepatic fibrosis (stage 1, 36%; stage 2, 40%; stage 3, 24%). Fibrosis was associated with greater visceral fat content at baseline (284 ± 91 cm2 vs. 212 ± 95 cm2, P = 0.005), but not subcutaneous fat or BMI. While HFF did not differ between groups, individuals with fibrosis had higher NAFLD Activity Score (3.6 ± 2.0 vs. 2.0 ± 0.8, P < 0.0001), ALT (41 ± 30 U/L vs. 23 ± 8 U/L, P = 0.002), and AST (44 ± 27 U/L vs. 24 ± 10 U/L, P = 0.0003). Among 24 participants randomized to placebo with paired liver biopsies, 38% had progression of fibrosis over 12 months. Higher visceral fat content at baseline (306 ± 119 cm2 vs. 212 ± 89 cm2, P = 0.04) was the only clinical predictor of fibrosis progression, which remained significant upon adjusting for BMI, HFF, and NAS Score. Age, sex, race, duration of HIV, and CD4 count did not relate to fibrosis presence or progression.

Conclusion: High rates of liver fibrosis presence and progression were observed in a cohort with HIV and NAFLD. Individuals with greater visceral fat content at baseline were more likely to have baseline fibrosis and progression of fibrosis, suggesting that these patients should be closely monitored and targeted for intervention.

130LB SAFETY AND EFFICACY OF DTG VS EFV AND TDF VS TAF IN PREGNANCY: IMPACT 2010 TRIAL

Lameck Chinula1, Sean S. Brumme1, Lauren Ziemia1, Lynda Strainich-Chibanda2, Anne Coletti, Chelsea Krofie1, Patrick Jean-Philippe3, Lee Fairlie1, Tiahonna Membro, Deo Wabwiri, Risa M. Hoffman4, Paul E. Sax5, Jeffrey S. Stringer6, Judith S. Currier7, Shahin Lockman1

1University of North Carolina Project – Malawi, Lilongwe, Malawi, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3University of Zimbabwe, Harare, Zimbabwe, 4FH360, Durham, NC, USA, 5Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, 6DAIDS, NIAID, Rockville, MD, USA, 7Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 8Merckère University–Johns Hopkins University Research Collaboration, Kampala, Uganda, 9University of California Los Angeles, Los Angeles, CA, USA, 10Brigham and Women’s Hospital, Boston, MA, USA, 11University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: We compared the safety and virologic efficacy of dolutegravir (DTG) – entecavir (FTC)/tenofovir alafenamide fumarate (TAF) vs. DTG + FTC/tenofovir disoproxil fumarate (TDF) vs. efavirenz (EFV)/FTC/TDF in pregnant women with HIV-1 in 9 countries were randomized 1:1:1 to start open-label DTG + FTC/TAF, DTG + FTC/TDF, or EFV/FTC/TDF at 14-28 weeks of pregnancy. Safety outcomes were compared between all arms were a) composite adverse pregnancy outcome

129 DOLUTEGRAVIR-CONTAINING ART DOES NOT REDUCE ETONOGESTREL IMPLANT CONCENTRATIONS

Rena Patel1, Randy Stalter1, Maricianah Onono2, Evelyn Brown3, Lilian Adeojo4, Catherine K. Adhu3, Kimberly K. Scarsi6

1University of Washington, Seattle, WA, USA, 2Kenya Medical Research Institute, Nairobi, Kenya, 3University of Washington in Kenya, Nairobi, Kenya, 4NIH, Bethesda, MD, USA, 5Jaramogi Oginga Odinga Teaching & Referral Hospital, Kisumu, Kenya, 6University of Nebraska Medical Center, Omaha, NE, USA

Background: Concomitant use of efavirenz-containing antiretroviral therapy (ART) is now the preferred first-line regimen for women of reproductive potential. However, DTG’s drug-drug interactions with hormonal contraceptives have been narrowly evaluated thus far, and understanding any potential for interactions between subdermal implants and DTG is important as countries pursue national rollout of DTG-containing ART.

Methods: We conducted a prospective, open-label pharmacokinetic study among women of reproductive potential in Kisumu, Kenya. Women were either HIV-positive, virologically suppressed, and receiving DTG-containing ART for at least 30 days prior to enrollment, or HIV-negative and not receiving any antiretrovirals (control group). An ENG 68mg subdermal implant was placed as part of routine clinical care and women were enrolled in this study within 2 weeks of implant placement. Blood samples were drawn at 2, 4, 8, 12, 16, 20, and 24 weeks after study entry. We analyzed plasma ENG concentrations using a validated LC-MS/MS assay (range 25-30,000 pg/mL). We describe per visit ENG concentrations using median (range) and compare the concentrations per visit between DTG-containing ART and the control groups using geometric mean ratio (GMR; 90% confidence interval) and the Wilcoxon rank sum test.

Results: All women were black African. The median age was 35 and 25 years, and weight was 62.5 ± 39.0 kg in the DTG-containing ART and control groups, respectively. Women in the DTG-containing ART group were on this ART for a median of 6.7 (range 4.3-8.3) months prior to study enrollment. ENG plasma concentrations for the DTG and control groups were 692 (470-589) and 588 (277-1050) pg/mL, respectively, and decreased to 456 (250-720) and 268 (136-496) pg/mL by week 24, respectively (Table). ENG exposure in the DTG-containing ART group was 19-54% higher compared to controls (all p<0.05).

Conclusion: In the first of its kind study, we observed modestly higher ENG concentrations among women using DTG-containing ART vs. HIV-negative women. Our findings suggest that no detrimental drug-drug interactions exist with concomitant use of ENG implants and DTG. DTG-containing ART represents a preferable alternative to efavirenz-containing ART for women already using or desiring an ENG implant.

Table: Etonogestrel plasma concentrations (pg/mL) among DTG-containing ART and HIV-negative groups at each study visit

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>ENG Concentration (pg/mL)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>620 (470-890)</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>609 (510-770)</td>
<td>0.88</td>
</tr>
<tr>
<td>4</td>
<td>600 (486-732)</td>
<td>0.95</td>
</tr>
<tr>
<td>6</td>
<td>595 (484-671)</td>
<td>0.95</td>
</tr>
<tr>
<td>8</td>
<td>595 (490-680)</td>
<td>0.95</td>
</tr>
<tr>
<td>10</td>
<td>595 (490-680)</td>
<td>0.95</td>
</tr>
<tr>
<td>12</td>
<td>595 (490-680)</td>
<td>0.95</td>
</tr>
<tr>
<td>14</td>
<td>595 (490-680)</td>
<td>0.95</td>
</tr>
<tr>
<td>16</td>
<td>595 (490-680)</td>
<td>0.95</td>
</tr>
<tr>
<td>18</td>
<td>595 (490-680)</td>
<td>0.95</td>
</tr>
<tr>
<td>20</td>
<td>595 (490-680)</td>
<td>0.95</td>
</tr>
<tr>
<td>22</td>
<td>595 (490-680)</td>
<td>0.95</td>
</tr>
<tr>
<td>24</td>
<td>595 (490-680)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

* Only m21, 20, and 12 participants’ samples were available for study visit weeks 16, 20, and 24, respectively, at the time of this manuscript analysis.
(preterm delivery [PTD] < 17 weeks, small for GA [SGA] < 10th centile, stillbirth [SB]; b) maternal grade 3 or 4 adverse event (AE) through 14 days postpartum; and c) infant grade ≥ 3 AE through 28 days. Neonatal death (NND, < 28 days) was also evaluated.

**Results:** We randomized 643 women: 217 to DTG+FTC/TAF, 215 to DTG+FTC/TDF, and 211 to EFV/FTC/TDF. Baseline medians were: GA 21.9 weeks, HIV RNA 903 cp/mL, CD4 count 466 cells/μL; 83% took ART prior to entry (median 6 days). Median antepartum follow-up was 17.4 weeks. Delivery HIV RNA, available for 605 (94.1%) women, was < 200 cp/mL, in 398 of 407 (97.5%) in the combined DTG arms vs 182 of 200 (91.0%) in the EFV/FTC/TDF arm (difference 6.5% [95% CI 2.0%, 10.7%]; p = 0.005). Pregnancy outcomes were available for 640 (99.5%). Fewer women in the DTG+FTC/TAF arm (24.1%) had an adverse pregnancy outcome than in DTG+FTC/TDF (32.9%, p = 0.043) or EFV/FTC/TDF (32.7%, p = 0.047) arms. Although SB was more frequent with DTG+FTC/TAF (3.7%) and DTG+FTC/TDF (5.2%) than EFV/FTC/TDF (1.9%) (all-by-arm p-values ≤ 0.05; post-hoc), NND was more frequent with EFV+FTC/TDF (4.8%) than DTG+FTC/TAF (1.0%, p = 0.019) or DTG+FTC/TDF (1.5%, p = 0.053). Combined SB or NND rates were similar by arm (post-hoc analysis). At least one grade ≥ 3 AE occurred in 148 (23.0%) women and 105 (17.0%) infants (all-by-arm p-values ≤ 0.05). Two babies were diagnosed with HIV at < 14 days, one each in DTG+FTC/TAF and DTG+FTC/TDF arms (maternal delivery HIV-1 RNA 58,590 and <40 cp/mL, respectively).

**Conclusion:** DTG-containing ART started at GA 14-28 weeks had superior virologic efficacy at delivery to EFV/FTC/TDF. DTG+FTC/TAF had the lowest composite frequency of adverse pregnancy outcomes. Maternal and infant AE outcomes were similar by arm.

<table>
<thead>
<tr>
<th>Table: IMPACT 2018 maternal virologic efficacy outcomes and pregnancy and maternal infant safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Arm</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Delivery [mg/m²]</td>
</tr>
<tr>
<td>355/595 (97.5%)</td>
</tr>
<tr>
<td>355/595 (97.5%)</td>
</tr>
<tr>
<td>355/595 (97.5%)</td>
</tr>
</tbody>
</table>

**POC EID vs central lab testing: Results from a step-wedge RCT in Kenya and Zimbabwe**

Emma Sacks1, Rhoderick Macheke1, Bernard Ochuka1, Haurowi Mafaune1, Addmore Chadambuka1, Collins Otiengo1, Agnes Mahomva1, George Githuka1, Jean-Francois Lemaire1, Flavia Bianchi1, Jennifer Cohn1, Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA, 2African Society for Laboratory Medicine, Gaborone, Botswana, 3Zimbabwe Ministry of Health and Child Care, Harare, Zimbabwe, 4Ministry of Health, Nairobi, Kenya

**Background:** Despite WHO recommendations for early infant virologic diagnostic testing (EID) of HIV-exposed infants (HEI), in 2017, only 50% of HEI in 21 high-priority countries received an EID test in the first 2 months of life. This study builds on a United-funded, 9-country point-of-care (POC) EID implementation project that sought to improve access to EID and reduce turnaround time from sample collection to results availability. This randomized stepped-wedge trial evaluated the effect of POC EID compared to standard-of-care conventional central lab-based testing on timely receipt of results in HEI. The study was conducted over two years, in two countries, Kenya and Zimbabwe. In each country, 18 health facilities were randomly selected from the list of project sites to serve as study sites. Study sites were randomized to one of four time points to transition from conventional EID testing to POC EID testing. HIV-exposed infants were eligible for inclusion if they presented for EID testing at the 4-8 week time-point recommended by the WHO. The study was powered to detect at least a 50% increase in the proportion of caregivers receiving HIV test results by 12 weeks of infant age after introduction of POC, assuming a design effect of 2.

**Results:** Overall 412 women were randomised at a median of 10d postpartum (IQR, 6-20d; at enrolment median age 27y; median duration of prenatal ART 21w; 100% VL<1000 and 88% <50 c/mL); baseline characteristics did not differ by arm. Attendance at the allocated service within 3m of referral per protocol was higher in AC (77%) vs PHC (68%); 90% completed the final study visit at 24m postpartum with no difference by arm. For the primary endpoint, 16% and 29% of women in AC experienced a cumulative incidence of VL>1000 c/mL by 12m and 24m, compared to 23% and 37% in PHC, respectively (HR=0.71; 95%CI=0.50-1.01; p=0.056; Figure). For the secondary endpoint, 32% and 44% of women in AC had VL>50 c/mL by 12m and 24m, compared to 42% and 56% in PHC, respectively (HR=0.69; 95%CI=0.52-0.92; p=0.009). Findings were unchanged in per protocol analyses and across a priori demographic and clinical subgroups. Infant HIV testing, MTCT, breastfeeding duration, family planning use, and other outcomes were similar between AC and PHC arms.

**Conclusion:** Postpartum referral to DSD models such as “Adherence Clubs” is associated with an approximately 30% reduction in elevated VL and may be an important part of strategies to improve women’s virologic outcomes on ART.
133 A RANDOMIZED TRIAL OF POINT-OF-CARE EARLY INFANT HIV DIAGNOSIS IN ZAMBIA

Carla J. Chibwesha1, Katie Mollan1, Catherine Ford2, Aaron Shibemba1, Pooja Saha1, Benjamin H. Chi1, Lloyd Mulenga3, Mildred Lusaka2, Felistas Mbewe2, Jeffrey S. Stringer1

1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2University of North Carolina in Zambia, Lusaka, Zambia, 3University Teaching Hospital, Lusaka, Zambia

Background: Early infant HIV diagnosis (EID) requires molecular methods historically limited to central labs. As a result, many HIV-exposed infants either have no access to EID or must wait months for a result. Point of care (POC) EID offers a potential solution.

Methods: We conducted a POC EID trial at 6 clinics in Lusaka, Zambia. HIV-exposed infants were randomly allocated between 4–12 weeks of life to: (a) POC EID – same-day testing with Alere q or (b) Offsite EID – testing of dried heel prick samples at a central lab with Roche COBAS. The trial provided a safety net by testing an archived sample if off-site EID results did not return within 4 weeks. HIV-infected infants were referred for immediate antiretroviral therapy (ART). Our primary outcome was defined as being alive, in care, and virally suppressed (viral load <200 copies/mL) at 12 months.

Results: Between Mar 2016 and Nov 2018, we randomized 4,000 HIV-exposed infants at a median age of 6 (IQR 6-7) weeks to POC EID (1,989) or Offsite EID (2,011). Most mothers (94%) reported ART for PMTCT. Eighty-one (2.0%, 95%CI 1.6-2.5%) infants were diagnosed with HIV. Every infant in the POC arm received a same-day result, while the median time to diagnosis in the Offsite arm was 27 (IQR 22-30) days. The majority of infants randomized to Offsite EID relied upon the trial’s diagnostic safety net (Fig. 1a). ART initiation was high in both arms (Fig. 1b), but adverse outcomes were common. Among 81 HIV-infected infants, there were 15 (19%) deaths, 15 (19%) follow-up losses, and 30 (38%) virologic failures (1 viral load <200 copies/mL) at 12 months.

Conclusion: Despite the success of Zambia’s PMTCT program, high rates of vertical transmission were observed. POC EID eliminated diagnostic delays and resulted in rapid ART initiation but this did not translate to treatment success at 12 months. As countries consider whether to adopt POC EID, they will need to weigh the costs of new technology against the costs of improving existing EID services. Most importantly, substantial investments are needed to strengthen pediatric HIV treatment programs.

134LB POPULATION-LEVEL HIV-FREE INFANT SURVIVAL IN THE SEARCH TRIAL

Shalika Gupta1, Jane Kabambe2, Gabriel Chaminde3, Norton Sang4, Dalsone Kwasiima2, Douglas Black4, Laura B. Balzer1, James Aiyeku4, Craig R. Cohen1, Elizabeth A. Bukusi5, Moses R. Kamya6, Diane V. Havlir7, Maya P. Petersen1, Theodore Ruel1

1University of California Berkeley, Berkeley, CA, USA, 2Infectious Diseases Research Collaboration, Kampala, Uganda, 3University of California San Francisco, San Francisco, CA, USA, 4Kenya Medical Research Institute, Nairobi, Kenya, 5University of Massachusetts Amherst, Amherst, MA, USA, 6Makerere University College of Health Sciences, Kampala, Uganda

Background: Universal test and treat (UTT) strategies could reduce vertical transmission of HIV by diagnosing women living with HIV earlier and improving care delivery. We evaluated the effect of universal HIV testing and a patient-centered HIV care model on vertical transmission and HIV-free survival in the SEARCH Trial.

Methods: At baseline, 32 communities in rural Uganda and Kenya (total population ~350,000) received population level HIV testing (90% coverage) and were randomized to: 1) intervention: immediate ART, annual population level testing, and patient-centered HIV care (including welcoming staff, flexible hours, and facilitation between antenatal care and HIV clinic); or, 2) control: HIV-care per national guidelines. Pregnant women were offered immediate ART in both arms. After 3 years, we repeated population-level testing including children <3 years and ascertained births and deaths. In pre-specified analyses, we compared HIV-free survival (% of infants alive and HIV uninfected) and vertical transmission (% of living infants with HIV infection) between study arms among infants born to a) all women with known HIV+ status by year 3; and, b) the subset of women with known HIV+ status at baseline using cluster-level targeted maximum likelihood estimation.

Results: There were 1,417 births to 1,332 women with known HIV+ status by year 3; outcomes were ascertained in 76% of infants in intervention and 78% in control. The proportion (95%CI) with HIV-free survival was higher and vertical transmission was lower in the intervention versus control: 3.3% (1.0-5.6%) in the intervention died or became HIV-infected by year 3 versus 6.4% (4.7-8.0%) in the control (Relative risk 1.03; 95%CI 1.00, 1.06; p=0.04). Vertical transmission was 1.8% (0.2-3.3%) in the intervention versus 4.4% (2.7-6.1%) in the control (p=0.04). Of 1,230 births to 1,158 women with known HIV+...
status at baseline, vertical transmission was 0.5% (0-1.3%) in the intervention, compared to 3.7% (2.4-5.1%; p<0.001) in the control.

**Conclusion:** Universal testing and a patient-centered care delivered via government clinics reduced 3 year population-level HIV infection/mortality among infants by over 50% and reduced vertical transmission to 0.5% among women with known HIV, progress toward the elimination of vertical transmission.

### 135 PREDICTORS OF THE PERSISTING VIREOUS RESERVOIR IN VERY EARLY TREATED INFANTS

**Maria Pazimadis**, Bianca Da Costa Dias, Sizanani Mncube, Renate Strehlau, Iyanh Shen, Stephanie Shiu, Faezeh Patel, Megan Burke, Karl Techmaur, Shayne Loubser, Elaine J. Abrams, Caroline Tiemessen, for the LEOPARD Study Team

1 National Institute for Communicable Diseases, Johannesburg, South Africa, 2 Empliwini Service and Research Unit, Johannesburg, South Africa, 3 Columbia University Medical Center, New York, NY, USA, 4 University of the Witwatersrand, Johannesburg, South Africa

**Background:** The size of the persisting viral reservoir while receiving antiretroviral therapy (ART) has consistently been shown to be smaller when ART is initiated at a younger age in perinatally-acquired HIV infection. However, there are only limited data on predictors of the proviral DNA reservoir in very early treated infants.

**Methods:** Sixty-three confirmed HIV-infected neonates recruited at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa, who had been identified <48 hours after birth were included. Viably- preserved PBMCs collected pre-treatment, and at 1, 3, 6 and 12 months after ART initiation, were tested if sufficient sample was available. To quantify the proviral DNA reservoir, a semi-nested real-time quantitative hydrolysis probe (TaqMan) PCR assay was designed to detect and quantify total HIV-1 subtype C proviral DNA. The assay was designed to target the integrase gene of HIV-1 subtype C. We conducted six replicates to allow detection to a level of one copy/9.1x105 cells. Multivariable Generalized Estimating Equation (GEE) regression models were used for statistical analysis.

**Results:** Thirty-one (49.0%) infants initiated ART <48 hours of birth and the remaining 32 infants at median of 7 days (all received daily nevirapine prophylaxis prior to ART start). Three-quarters were infected despite their mothers having received ART during pregnancy and, for 25%, mothers had received no ART prior to delivery. At all post-ART time points, infant HIV-1 DNA was significantly associated with concurrent HIV-1 RNA levels (viral load [VL]) (Spearman ρ = 0.645, p < 0.0001). If VL was not targeted, the median HIV-1 DNA was 1.56 log copies and 23.1% had <10 DNA copies detected. Whereas, at VL <50, 51-399, 400-999 and >1000 RNA copies/ml, median HIV-1 DNA was 1.56 log copies and 23.1% had <10 DNA copies detected. Where VL <50, 51-399, 400-999 and >1000 RNA copies/ml, median HIV-1 DNA was 1.56 log copies and 23.1% had <10 DNA copies detected.

**Conclusion:** Age at starting ART, combined with other maternal and infant factors, predict the size of the pool of proviral DNA in very early treated infants.

---

### 136 LONG-TERM OUTCOMES: EARLY VERSUS DEFERRED ART IN CHILDREN LIVING WITH HIV

**Ngampiyaskul**, Thanyawee Puthanakit, Jiratchaya Sophonphan, Wipaporn Natalie Songtaweesin, Thairattana Jariyapong, Thanyawee Puthanakit, Jitnat Ananworanich, for the PREDICT and Resilience Study Group

1 Chulalongkorn University, Bangkok, Thailand, 2 HIV–NAI, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, 3 National Centre for HIV/AIDS Dermatology and STDs, Phra Nakhon, Cambodia, 4 Khon Kaen University, Khon Kaen, Thailand, 5 Chiang Rai Prachanukroh Hospital, Chiang Rai, Thailand, 6 Nakomping Hospital, Chiang Mai, Thailand, 7 Prapokklao Hospital, Chanthaburi, Thailand, 8 New York State Psychiatric Institute, New York, NY, USA, 9 Henry M Jackson Foundation, Bethesda, MD, USA

**Background:** WHO antiretroviral treatment (ART) guidelines currently recommend initiating ART in HIV infected children at any CD4 count, as soon as possible after diagnosis. The objective of this study was to describe long term treatment outcomes after a decade of follow up, among children in the PREDICT study who did not have rapidly progressive HIV, and were randomized to early versus deferred treatment strategies.

**Methods:** The PREDICT study was a multicentre, randomised trial in Thailand and Cambodia. ART naïve HIV-infected children aged 1-12 years with CD4 15-24% and no advanced HIV symptoms were randomly assigned (1:1) to start ART at study entry (early treatment) or when CD4 < 15% (deferred treatment, standard of care at that time). The long-term endpoints were virological suppression, cumulative probability of virological treatment failure, defined as plasma HIV RNA > 1000 copies/ml, and immunological status. Cumulative failure probability was calculated using the Kaplan-Meier method; formal comparisons between group were made using chi-square, log rank test, Mann_Whitney U tests.

**Results:** From March 2006 to September 2008, 300 Thai and Cambodian children were enrolled, with a median age of 6-4 (IQR 3-9) years, and median baseline CD4 of 19% (IQR 16-22). As of July 2019, 230 (77%) participants remained in the study (132 Thai, 98 Cambodian), 19 withdrew, 2 died and 47 were lost or referred out at median of 12.9 (10.4-15.4) years. The median age at last visit was 16.7 years (IQR 14.3-18.6). Current antiretroviral regimens were 75.2% NNRTI-based, 20.4% PI-based and 4.4% others. Among adolescents with HIV, 86.3% in the early arm and 77.9% in the deferred arm had plasma HIV RNA < 50 copies/ml (p = 0.09); 88.9% in the early arm and 76.1% in the deferred arm had CD4 > 500 cells/mm3 (p = 0.01). However, the 10 year cumulative probability of virologic failure was higher among adolescents in the deferred (34.3% [95%CI 24.8-46.1] versus early treatment group 22.8% [95%CI 16.1-31.7] [P = 0.07]).

**Conclusion:** Leveraging this randomized study conducted when early ART was not the standard of care, it demonstrates that amongst children with slow progressor, a decade of ART could not overcome the lower CD4 count at ART start. The longer lasting poorer CD4 recovery and higher virological failure mandates prompt diagnosis and ART initiation in children.

Table 1: Long term outcomes among HIV-infected adolescents with early or deferred antiretroviral treatment initiation strategies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=130)</th>
<th>Early (n=117)</th>
<th>Deferred (n=13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment (years)</td>
<td>6.7 (3.9-9.1)</td>
<td>6.4 (3.6-7.9)</td>
<td>6.4 (4.2-6.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>CD4 % at enrollment</td>
<td>21 (18-23)</td>
<td>20 (12-22)</td>
<td>21 (18-23)</td>
<td>0.18</td>
</tr>
<tr>
<td>Age at ART initiation (years)</td>
<td>7.0 (4.9-12.1)</td>
<td>6.4 (3.6-7.9)</td>
<td>9.7 (7.0-22.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At last visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>16.7 (14.3-18.4)</td>
<td>16.5 (14.3-18.3)</td>
<td>16.0 (16.3-18.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Character of ART (years)</td>
<td>9.6 (7.6-10.7)</td>
<td>9.5 (7.5-11.2)</td>
<td>7.0 (5.9-9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>On first line ART regimen</td>
<td>178 (79%)</td>
<td>91 (78%)</td>
<td>87 (77%)</td>
<td>0.89</td>
</tr>
<tr>
<td>CD4 %</td>
<td>36 (25.6-34)</td>
<td>31 (27.3-35)</td>
<td>27 (20.3-32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)</td>
<td>725 (538-912)</td>
<td>801 (618-995)</td>
<td>672 (511-996)</td>
<td>0.002</td>
</tr>
<tr>
<td>HIV RNA (copies/ml)</td>
<td>1095 (395)</td>
<td>1051 (98)</td>
<td>1138 (139)</td>
<td>0.24</td>
</tr>
<tr>
<td>10 year probability of virologic failure</td>
<td>27.7 (21.3-34.7)</td>
<td>23.8 (20.6-31.5)</td>
<td>38.5 (28.4-48.6)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

---

### 137 ANTIMICROBIAL PROPHYLAXIS AMONG AFRICAN ADULTS ON ART: RESULTS OF A RANDOMIZED TRIAL


1 WHO, Lilongwe, Malawi, 2 University of Malawi, Blantyre, Malawi, 3 Dignitas International, Zomba, Malawi, 4 Blantyre Malaria Project, Blantyre, Malawi, 5 University of Maryland, Baltimore, MD, USA, 6 Dignitas International, Blantyre, Malawi, 7 Blantyre Malaria Project, Blantyre, Malawi, 8 Dignitas International, Blantyre, Malawi, 9 University of Maryland, Baltimore, MD, USA, 10 Dignitas International, Zomba, Malawi

**Background:** Before widespread antiretroviral therapy (ART) use in sub-Saharan Africa, studies demonstrated that daily trimethoprim-sulfamethoxazole (TS) prophylaxis reduced morbidity and mortality among HIV-infected adults, predominantly by preventing malaria and diarrhea in this population. Routine
administration of TS prophylaxis has continued with expanded access to ART throughout sub-Saharan Africa. However, the public health benefit has not been definitively evaluated. We designed a clinical trial to evaluate the impact of TS prophylaxis on morbidity and mortality among HIV-infected Malawian adults following good response to ART. If beneficial, we also aimed to determine if this is due to TS antibacterial and/or antimalarial properties.

**Methods:** We conducted a randomized, controlled, open label, phase 3 trial of continued standard of care prophylaxis with daily TS compared to discontinuation of TS and starting weekly chloroquine (CQ) prophylaxis or discontinuation of TS prophylaxis. The study randomized 1,499 HIV-infected adults (1:1:1) ratio with nondetectable viral load and CD4 count >250/mm³. The primary endpoint events were death and WHO Stage 3 and 4 events. We compared virologic, immunologic and clinical responses to ART among study arms.

**Results:** Among 2219 persons screened, 1499 were enrolled. 4956 ppy were accrued, and 1249 (83%) completed the study. 24 deaths were reported, 10 in TS group, 6 in CQ group, and 8 in no prophylaxis group. The primary endpoint rate was lower in TS group compared to no prophylaxis, but this result was not significant (Table 1). When WHO Stage 2 events are added to the primary endpoint rate per 100 ppy for each group, TS group had a lower rate of events compared to no prophylaxis and to CQ. Groups did not differ regarding secondary endpoints of virologic failure, low CD4 cell count, or adverse events. Participants on TS prophylaxis experienced fewer malaria episodes than those on no prophylaxis and equivalent episodes compared to CQ prophylaxis. Participants on TS experienced fewer suspected or confirmed bacterial infections than those on no prophylaxis or CQ.

**Conclusion:** Following immune reconstitution, TS prophylaxis continued to provide benefit in terms of prevention of non-severe bacterial infections and malaria, and was safe and well tolerated. Continuation of TS prophylaxis should be considered based on comprehensive analyses of cost and risk/benefit alongside other public health interventions aimed to improve outcomes in this population.

**Table 1:** Event rates and analysis by Pearson regression for efficacy endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TS arm (per 100 ppy)</th>
<th>CQ arm (per 100 ppy)</th>
<th>No prophylaxis arm (per 100 ppy)</th>
<th>Rate ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>9.7 (2.7)</td>
<td>10.6 (3.2)</td>
<td>14.0 (4.5)</td>
<td>0.68 (0.43, 1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>WHO Stage 3 &amp; 4</td>
<td>10.9 (2.8)</td>
<td>11.4 (3.2)</td>
<td>15.0 (5.0)</td>
<td>0.72 (0.47, 1.08)</td>
<td>0.10</td>
</tr>
<tr>
<td>Malaria</td>
<td>63 (2.8)</td>
<td>69 (3.0)</td>
<td>75 (3.2)</td>
<td>0.85 (0.65, 1.12)</td>
<td>0.22</td>
</tr>
<tr>
<td>Bacterial</td>
<td>21 (1.2)</td>
<td>24 (1.5)</td>
<td>33 (1.9)</td>
<td>0.81 (0.50, 1.34)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

**139 PREDICTORS OF TUBERCULOSIS INFECTION IN MDR-TB HOUSEHOLD CONTACTS ≥15 YEARS OLD**

Soyeon Kim1, Amita Gupta1, Xingye Wu1, Michael D. Hughes1, Rodney Dawson1, Vidya Mave1, Nagalingeswaran Kumarasamy1, Elizabeth Smith1, Roxana Rustomjee1, N. Sarita Shah1, Anneke Hesseling1, Susan Swindells1, Gavin Churchyard1, for the A5300/I2003 PHENIX Feasibility Study Team

**Background:** HIV-exposed uninfected infants (HEU) in TB endemic settings are at increased risk of TB infection and disease. However, the optimal prophylaxis regimen among HEU has not been definitively established. The study investigated the impact of isoniazid (INH) prophylaxis in HEU among pregnant women in TB-endemic countries.

**Methods:** From 10/2015–4/2016, ACTG and IMPAACT networks conducted AS300/I2003, a cross-sectional observational study of adults with pulmonary MDR-TB and their HHCs, in high TB-burden countries in preparation for a randomized trial. Among HHCs ≥15 years of age without TB disease, index case (IC), household (HH), HHCs, and TB exposure characteristics were evaluated for association with TB infection based on interferon gamma release assay (IGRA) status (QuantiFERON Gold/Gold-in-Tube) and MDR-TB status. HHs ≥15 years have previously been reported on. Logistic regression using generalized estimating equations was used for testing.

**Results:** 278 ICs enrolled at 16 sites in 8 countries had 712 HHCs ≥15 years of age. 36% of ICs were TB-infected and 10% had unknown TB status. 54 (8%) HHCs ≥15 years were TB-infected and 436 (64%) female (16 pregnant). 601 had determine, 4 indeterminate, and 22 NO IGRA results. Factors independently predictive (p≤0.05) in multivariable models are shown in the Table. Of 686 HHs with determine IGRA results, 471 (69%, 95% confidence interval: 65-73%) were positive; prevalence varied with age: 59% in TS <25, 76% in 25 ≤<50, and 68% ≥50 (p<0.001). Cautions on Ctx, smear status, and duration of IC TB treatment were not associated with HHC TB infection prevalence. TB infection prevalence increased when a HHC had self-reported or a medical history of COPD/asthma (33% vs 69%, p=0.039), spent more nights/week with the IC (61%, 68%, 70% for 0-2, 3-5, 6-7 nights, respectively, p=0.05) but not by sleeping proximity. Compared to HHCs never incarcerated and not substance or alcohol users (66%), HHCs previously incarcerated had the highest prevalence of TB infection (55%); HHCs never incarcerated using substances or alcohol were also more likely to have TB infection (84%) (p<0.001). Smoking in the household (77% vs 64%, p=0.02) and lower quality exterior wall materials (see definition in Table) were associated with increased TBI prevalence (77% vs 67%, p=0.009).

**Conclusion:** Over 2/3 of HHCs age≥15 in HHs of adult MDR-TB patients had evidence of TB infection, confirming the importance of household contact investigation. HHCs with lower quality homes and HHCs highly exposed to IC, ever incarcerated or currently using substances or alcohol, or with COPD/asthma require particular attention to identify all TB infected HHCs.
140 DIAGNOSTIC AND THERAPEUTIC CHALLENGES ARISE WITH EARLY HIV INFECTION ON PrEP

Michael J. Peluso1, Monica Gandhi1, Susa Coffey2, Heather Hartig1, Susan P. Buchbinder1, Michael P. Busch1, Christopher D. Pilcher3, Hyman Scott4, Stephanie E. Cohen1, Darpun Sachdev5, Pierre Crouch6, Diane V. Havlir2, Steven G. Deeks1, Timothy J. Henrich1, Sulggi Lee1

1University of California San Francisco, San Francisco, CA, USA, 2San Francisco Department of Public Health, San Francisco, CA, USA, 3Vitalant Research Institute, San Francisco, CA, USA, 4San Francisco AIDS Foundation, San Francisco, CA, USA

Background: The impact of PrEP during HIV acquisition may alter reservoir establishment, viral load set points, and immune responses. Some individuals on PrEP may remain negative by screening assays while still becoming infected. Characterization of such individuals is needed to define how to diagnose early infection in this context.

Methods: Working with the San Francisco Department of Public Health, we identified individuals with early HIV infection, many of whom were on PrEP. The estimated date of detected infection (EDDI) was calculated; standard diagnostic and resistance testing was performed.

Results: 58 participants (all men) with early HIV enrolled from 2015-2019. Most had sex with men (87%); median (IQR) age was 30 (25-37) years; pre-ART CD4 508 (355-680); log plasma HIV RNA 5.1 (4.1-5.7); time between EDDI and ART 29 (20-91) days. Among 24 with PrEP exposure, 13 (54%) reported prior use (> 10 days pre-diagnosis), 6 (25%) active use (≤10 days pre-diagnosis), and 5 (21%) recent use (20-91) days. Among participants randomized to deposit contracts, 24 (14%) made a baseline deposit, and 2 (1%) made a 3-month deposit. In intent-to-treat analyses focus on those on active PrEP and those positive at PrEP initiation (n=11, Table). HIV Ab screening was positive in only 4/11 (36%). HIV RNA was detected in all cases, although 100 copies/mL in one and <20 copies/mL in two. Of these, two had a newly positive Ab/Ag test, with cell-associated (CA)-DNA not detected and CA-RNA 117 copies/10^6 cells. The second had a negative Ab/Ag test and analysis of 25M PBMCs did not show CA-DNA or CA-RNA despite transiently detectable HIV RNA on clinical assays. Of the 8/11 who could have genotypic resistance testing, three had M184V/I mutations, with two. Of these two, one had a newly positive Ab/Ag test, with cell-associated (CA)-DNA not detected and CA-RNA 117 copies/10^6 cells. The second had a newly positive Ab/Ag test and an estimated date of detected infection (EDDI) was calculated; standard diagnostic and resistance testing was performed.

Conclusion: Increasingly widespread PrEP use may result in distinct and challenging presentations of HIV infection. We present the largest case series of early (or pre-existing) HIV on PrEP, with resultant blunting of immune responses and viral loads. Those presenting with delayed evidence of infection may be continued on PrEP, resulting in suboptimal treatment and development of resistance. In some cases, diagnostic uncertainty will arise regarding whether infection was prevented or established with a more limited reservoir. Further  

141 A RANDOMIZED TRIAL OF INCENTIVES AND DEPOSIT CONTRACTS TO PROMOTE HIV RETESTING

Dalsone Kwarisimia1, Alex Nydababakira1, Kara Marson2, Carol S. Camlin3, Diane V. Havlir1, Moses R. Kamya4, Harshita Thirumurthy4, Gabriel Chamie2

1Infectious Diseases Research Collaboration, Kampa, Uganda, 2University of California San Francisco, San Francisco, CA, USA, 3Makerere University College of Health Sciences, Kampala, Uganda, 4University of Pennsylvania, Philadelphia, PA, USA

Background: Retesting for HIV in high-risk populations is critical for identifying newly infected persons and promoting prevention services. Whether standard financial standard incentives and less costly deposit contracts can increase retesting for HIV among at-risk adults is unknown.

Methods: In a peri-urban Ugandan community, we recruited persons at-risk for HIV from selected venues (bars, sites of commercial sex work, and transport hubs) and referred them for clinic-based HIV testing. HIV-negative adults (18-59 years old) with self-reported risk (either >1 partner, HIV-infected partner, sexually transmitted infection, or payment/receipt of compensation for sex) were enrolled. Participants were randomized to either: (1) no incentive (control); (2) cash incentives (US$7) for retesting at 3 and 6 months (total $14); or (3) deposit contracts that leveraged loss aversion: participants could voluntarily deposit $5.50 at baseline and 3 months that would be returned with interest (total US$7) upon retesting at 3 and 6 months respectively (total $14) or lost if participants failed to retest. The primary outcome was retesting for HIV at both 3 and 6 months.

Results: A total of 524 participants were randomized to either no incentive (N=180), incentives (N=172), or deposit contracts (N=172). Participants’ median age was 25 years (IQR: 22-30), 44% were women, and median weekly income was US$13.60 (IQR: $8.16-21.76). Baseline characteristics were similar across arms. Among participants randomized to deposit contracts, 24 (14%) made a baseline deposit, and 2 (1%) made a 3-month deposit. In intent-to-treat analyses, the proportion of participants who retested for HIV at both 3 and 6 months was higher in the incentive arm (52%) than either the control arm (18%, p<0.001) or the deposit contract arm (16%, p<0.001; Figure). Among those in the deposit contract arm who made a baseline deposit, 83% retested at 3 and 6 months respectively (total $14) or lost if participants failed to retest. The primary outcome was retesting for HIV at both 3 and 6 months.

Conclusion: Offering financial incentives to high-risk adults in Uganda resulted in significantly higher HIV retesting. Deposit contracts to help individuals follow through on a commitment to retesting had low uptake and overall did not increase retesting rates.
COMMUNITY-BASED HIV TESTING IN URBAN KENYA: A STRATEGY TO REACH MEN AND YOUTH

Hong-Ha M. Truong1, A. Rain Mocello1, David Ouma2, Dena Bushman3, Kevin Kadee4, Eric AttingA1, Dancun O. Obunge1, Elizabeth A. Bukusi5, Francesca Odhiambo1, Craig R. Cohen1
1University of California San Francisco, San Francisco, CA, USA, 2KEMRI-UCSF, Kisumu, Kenya, 3Kenya Medical Research Institute, Nairobi, Kenya

Background: Some countries are struggling to reach the UNAIDS testing target, especially among men and youth. Randomized controlled trials and HIV testing services (HTS) have successfully conducted community-based hybrid HTS in urban settings in East Africa to identify persons unaware of their HIV-positive status and achieve testing saturation. We implemented a hybrid HIV testing approach in an urban slum setting in Kisumu, Kenya.

Methods: The Community Health Initiative (CHI) conducted community mapping, household census, multi-disease community health campaigns (CHCs) and home-based tracking in Obunga in 2018. To encourage participation by men and youth, health and counseling services tailored for them were provided. HTS eligibility (not previously diagnosed HIV-positive, aged >=15 years, sexually-active <15 years) and antiretroviral therapy (ART) initiation were based on 2018 national guidelines. We calculated the previously unidentified fraction (PUF), a new metric, as the proportion of newly identified PLWH out of all previously identified and newly identified PLWH.

Results: CHI reached a total of 23,584 persons; 21,364 enumerated residents and 2,220 nonresidents. There were 22,685 persons engaged through CHCs and tracking. Of 12,768 HTS-eligible persons, 12,407 (97%) accepted testing, of whom 3,917 (32%) were first-time testers. First-time testers were more likely to be men (AOR=1.1; p<0.03) and adolescents aged 15-19 years (AOR=2.8; p<0.01). There were 100 newly identified PLWH out of 1,247 total HIV-positive persons, representing an 8.0% PUF. The PUF was higher among men (9.8%) and youth aged 15-24 years (13.1%). Ninety-four percent of newly diagnosed persons initiated same-day ART.

Conclusion: The community-based hybrid HIV testing approach was implemented successfully for the first time in an urban setting characterized by a high risk, impoverished and highly mobile population. CHI identified persons previously unaware of their HIV-positive status and achieved testing saturation. Innovative approaches that make HIV testing more accessible and acceptable to the community, in particular men and youth, are critical for reaching individuals who might otherwise be reticent to take up standard facility-based testing services. An approach focused on identifying persons unaware of their HIV-positive status in combination with monitoring the PUF has the potential to achieve the UNAIDS 90-90-90 target.

RIFAMPENTINE PHARMACOKINETICS AND SAFETY IN PREGNANT WOMEN WITH AND WITHOUT HIV ON 3HP

Jyoti S. Mathad1, Radioka M. Savić2, Paula Britto3, Lubbe Wiesner4, Ellen Townley1, Nahida Chakhtoura2, Sarah Bradford5, Sandesh Patil6, Tichaona Vhembo7, Dominique Lepinsasse8, Deborah Langat9, Peerawong Werrarak10, Portia Kambhunzi11, Amita Gupta12, Kelly E. Dooley13, 1Weill Cornell Medicine, New York, NY, USA, 2University of California San Francisco, San Francisco, CA, USA, 3Harvard T.H. Chan School of Public Health, Boston, MA, USA, 4University of Cape Town, Cape Town, South Africa, 5NIAID, Bethesda, MD, USA, 6Institute of National Child of Health and Human Development, Bethesda, MD, USA, 7FHI 360, Durham, NC, USA, 8Byramjee Jeejeebhoy Government Medical College, Pune, India, 9University of Zimbabwe, Harare, Zimbabwe, 10GHESKIO, Port-au-Prince, Haiti, 11Kenya Medical Research Institute, Kericho, Kenya, 12Siriraj Hospital, Bangkok, Thailand, 13University of North Carolina Project–Malawi, Lilongwe, Malawi, 14Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: Weekly isoniazid (900mg) and rifapentine (900mg) for 12 weeks (3HP) has similar efficacy to 6 months of daily isoniazid (6H) as TB preventive therapy. We compared treatment completion rates and effectiveness of 3HP vs. 6H and the effectiveness of 3HP given annually vs. once among HIV-positive people. (NCT02980016)

Methods: HIV-positive people in South Africa, Ethiopia and Mozambique aged ≥2 years, without active TB and on antiretroviral therapy (ART) for ≥3 months or ineligible were randomized 9:9:2 to periodic (annual) 3HP (p3HP), 3HP, or 6H. Participants in the 3HP/p3HP and 6H arms were followed for 24 and 12 months, respectively; all were seen monthly for the first three months of each participation year. Medication doses were directly observed at dispensing visits and otherwise self-administered. Participants in the 6H arm were dispensed 3 months treatment at month 3. Participants were screened for TB with symptoms, chest X-ray and sputum culture after 12 and 24 months. Completion of the initial treatment course in the combined 3HP/p3HP arms vs. 6H was compared using all counts. TB incidence and all-cause mortality over 12 months was compared in the 3HP and 6H arms, and TB incidence, all-cause mortality, and permanent discontinuation of 3HP for adverse events over 24 months was compared in the p3HP and 3HP arms.

Results: Between November 2016 and November 2017, 4593 participants were screened, 4027 enrolled and 4014 analysed. The median age was 41 years (19.0%-18.0%), 70% were female, 38% were QuantiFERON-TB GOLD Plus positive, 63% and 15% were from South Africa, Ethiopia and Mozambique, respectively. Treatment completion in the combined 3HP (n=3610) and 6H (n=404) arms was 90.4% versus 50.5% (risk ratio: 1.79; 95%CI:1.62-1.79). TB incidence and mortality by study arm are shown in the table. TB incidence and mortality from month 0 to month 12 was similar in the 3HP and 6H arms. TB incidence over 24 months and from month 12 to month 24 was similar in the p3HP (n=1808) and 3HP (n=1802) arms. Over 24 months, TB incidence among QuantiFERON Plus positive participants, incidence of rifampicin resistant TB, and mortality were similar in the p3HP and 3HP arms. Treatment discontinuation in the p3HP and 3HP arms was 1.2% vs. 6.6% (OR2.11, 95%CI:0.95-5.02).

Conclusion: Treatment completion was higher in the 3HP arms vs. 6H. In high TB transmission settings, annual 3HP did not provide additional benefit to people receiving ART.

Table 1: TB incidence and mortality by study arm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time period (Months)</th>
<th>Events/px (H)</th>
<th>Events/px (6H)</th>
<th>HR (3HP vs 6H)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB incidence</td>
<td>0-12</td>
<td>10</td>
<td>55/808</td>
<td>15/202</td>
<td>1.60 (1.30-2.40)</td>
<td>0.001</td>
</tr>
<tr>
<td>TB incidence</td>
<td>13-24</td>
<td>20</td>
<td>15/114</td>
<td>7/110</td>
<td>1.90 (1.20-2.90)</td>
<td>0.003</td>
</tr>
<tr>
<td>TB incidence</td>
<td>25-36</td>
<td>20</td>
<td>14/114</td>
<td>6/110</td>
<td>2.10 (1.20-3.60)</td>
<td>0.003</td>
</tr>
<tr>
<td>Tuberculosis mortality</td>
<td>0-12</td>
<td>0</td>
<td>3/382</td>
<td>2/378</td>
<td>1.00 (0.35-2.80)</td>
<td>0.99</td>
</tr>
<tr>
<td>Tuberculosis mortality</td>
<td>13-24</td>
<td>0</td>
<td>3/382</td>
<td>2/378</td>
<td>1.00 (0.35-2.80)</td>
<td>0.99</td>
</tr>
<tr>
<td>Tuberculosis mortality</td>
<td>25-36</td>
<td>0</td>
<td>3/382</td>
<td>2/378</td>
<td>1.00 (0.35-2.80)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

144LB
Background: Pregnancy increases the risk of progressing from latent tuberculosis infection (LTBI) to active TB. A 3-month TB-prevention regimen of weekly isoniazid and rifapentine (3HP) shows excellent safety and adherence in non-pregnant people, including those with HIV. We hypothesized that the pharmacokinetics (PK) of rifapentine (RPT) in pregnant women taking 3HP would be comparable to non-pregnant adults and well-tolerated.

Methods: IMPAACT 2001 is a Phase I/II study evaluating the PK and safety of 3HP among pregnant women with or without HIV, who had LTBI or a household contact with active pulmonary TB (NCT02653259). Sites were in Haiti, Kenya, Malawi, Thailand, and Zimbabwe. Cohort 1 had dosing and PK sampling in the 2nd and 3rd trimesters; Cohort 2 in the 3rd trimester and postpartum. Isoniazid and RPT were provided at standard doses of 900 mg weekly. PK samples were collected with the 1st (predose, 0.5h, 1h, 2h, 4h, 8h, 12h, 24h, 48h, 72h post-dose) and 12th doses (predose, 1h, 4h, 24h, 48h post-dose). Primary objectives were to estimate the population PK of RPT during pregnancy and post-partum using non-linear mixed effects modeling, and to describe maternal-infant safety outcomes.

Results: We enrolled 50 pregnant women, 25 per cohort. Twenty women had HIV; all were taking efavirenz (EFV)-based antiretroviral therapy (median CD4: 510 cells/mm³). All women completed the 3HP regimen. There were no drug-related SAE and no cases of active TB in women or their infants. There was one maternal and fetal death by abruptio placentae from trauma. Among women without HIV, oral clearance (CL/F) of RPT was 36% lower during pregnancy (1.24 L/h) than post-partum (1.68 L/h), with an area under the concentration-time curve (AUC) of 736 and 618 mg*hr/L, similar to historical non-pregnant controls. In women with HIV, CL/F was the same during pregnancy and postpartum (1.60 vs. 1.61 L/hr), which was 34% higher (p<0.001) compared to pregnant women without HIV, resulting in a lower AUC of 512 mg*hr/L.

Conclusion: Pregnancy does not appear to increase RPT clearance; thus, there is no need for dose adjustment of 3HP in pregnancy. Among women with HIV taking EFV, however, clearance of RPT was higher than expected during pregnancy. Exposures remained in the expected therapeutic range. Initial tolerability and safety results from this small trial are encouraging, given limited options for TB prophylaxis in pregnancy, but larger studies will be needed to characterize its safety in pregnancy definitively.

Figure 1: Increased clearance of RPT in HIV-infected vs. HIV-uninfected pregnant women

145 NO HIV INCIDENCE INCREASE IN FIRST-TIME BLOOD DONORS WITH 12-MONTH DEFERRAL FOR MSM

Eduard Grebe1, Edward P. Notari2, Roberta Bruhn1, Claire Quine1, Mars Stone1, Sonia Bakkour1, Hong Yang1, Debra Kessler1, Rita Reik1, Michael P. Busch1, Susan Stramer1, Simone Glynn1, Alan Williams1, Brian Custer1, for the U.S. FDA

Transfusion Transmissible Infections Monitoring System

Vitalant Research Institute, San Francisco, CA, USA; 1American Red Cross, Washington, DC, USA; 1FDA, Silver Spring, MD, USA; 1New York Blood Center, New York, NY, USA; 1OneBlood, St Petersburg, FL, USA; 1National Heart, Lung, and Blood Institute, Bethesda, MD, USA

Background: In 2015, the FDA published revised guidance that recommended a change in donor deferral policy for men who have sex with men (MSM) from indefinite to one year. The Transfusion Transmissible Infections Monitoring System (TTIMS) has monitored HIV, HBV and HCV infections in four blood collection organizations since 2015, representing approximately 60% of the US blood supply. We evaluated HIV-1 incidence changes in first-time blood donors following the implementation of the new MSM deferral policy using biomarkers of recent infection.

Methods: We utilized an algorithm to identify recent HIV infections amongst 5.7 million first-time donors (NAT-positive/Ab-negative or by applying the LAg Avidity EIA and viral load testing to seropositive donations). We derived a context-specific mean duration of recent infection using a novel Bayesian method and a false-recent rate, and utilized these parameters to estimate incidence rates and incidence rate differences in first-time donors during the 15-month TB periods preceding and following the deferral policy implementation, as well the entire post-implementation period through end 2018. We used Poisson regression models to identify demographic covariates of incidence.

Results: Overall HIV incidence in first-time donors in the 15 months prior to the MSM deferral policy implementation was estimated at 2.63 cases/100,000PY (95% CI: 1.44–3.81), in the 15 months after at 3.19 (1.94–4.43) and in the entire period after at 2.59 (1.71–3.48). Incidence differences were not statistically significant for either comparison. The figure shows incidence difference estimates by sex, age group, race/ethnicity and public health region. Of these, only the Western region showed a marginally significant increase, which becomes non-significant when the post period is expanded to include all available data. Bivariant and multivariable Poisson regression models using data from the entire TTIMS period showed that MSM deferral policy was not a significant correlate of incidence, although male sex (risk ratio 5.0, 95% CI: 2.8–9.5), age 18-24 (RR: 4.3; 1.5–18.3), black race (RR: 10.1), 5.8–17.9), Hispanic ethnicity (RR: 2.6, 1.3–5.0) and Southern region (RR: 2.0, 1.4–7.9) were significant.

Conclusion: There is no evidence that the implementation of a 12-month MSM deferral policy resulted in increased HIV incidence in, and therefore transfusion transmission risk from, first-time blood donors in the United States.

146 EXPLAINING RACIAL DISPARITIES IN VIRAL SUPPRESSION AMONG MSM LIVING WITH HIV

Justin R. Knox1, Jodie L. Guest2, Jeb Jones2, Eric Hall1, Nicole Luisi1, Jennifer Taussig1, Mariah Valentine-Graves2, Eli Rosenberg1, Travis Sanchez1, Patrick S. Sullivan1

1Columbia University Medical Center, New York, NY, USA; 2Emory University, Atlanta, GA, USA; 3State University of New York at Albany, Rensselaer, NY, USA

Background: National surveillance has documented consistent racial disparities at each step of the HIV treatment cascade, culminating in HIV-infected black men who have sex with men (MSM) having a 30% lower level of viral suppression compared to white MSM. Modifiable reasons for these racial disparities remain unclear. Nearly all supporting data for these findings are from clinical cohorts. Community-based studies that sample people living with HIV are not subject to the bias of selecting on those more likely to be engaged in HIV care, and thus are critical to understand causes of these disparities and to
identify targets for interventions. We examined factors associated with racial disparities in baseline viral suppression in a community-based cohort of black and white MSM living with HIV in Atlanta, GA.

Methods: Baseline visits occurred from June 2016-July 2017 when laboratory and behavioral survey data were collected. Explanatory factors for racial disparities in viral suppression that were assessed included: sociodemographics, psychosocial variables and biological factors. Poisson regression models with robust error variance were used to estimate prevalence ratios (PR). We first estimated the unadjusted black/white PR for lack of viral suppression. Factors were individually added to that model and those that diminished the adjusted PR for race by greater than or equal to 10%, were considered to meaningfully attenuate the racial disparity. All variables that met this criterion were included in a multivariable model.

Results: Overall, 26% (104/398) of participants were not virally suppressed at baseline. Lack of viral suppression was significantly more prevalent (PR=1.62; 95% CI: 1.05–2.50; p<0.001) among black MSM (33%; 69/206) than among white MSM (19%; 36/192). Adjustment for the following explanatory factors diminished the adjusted PR for race: age (-19%), ART coverage (through health insurance, a government program or a pharmaceutical company drug program) (-16%), income (-12%), housing stability (-11%), and marijuana use (-10%). In a multivariable model, these factors cumulatively diminished the PR for race by 38%, and it was no longer statistically significant (adjusted PR=1.10 (95% CI: 0.76–1.59)).

Conclusion: Relative to white MSM, black MSM living with HIV in Atlanta were less likely to be virally suppressed. However, this disparity was attenuated when accounting for explanatory factors, many of which can be targeted or modified by policy and individual-level interventions to help reduce racial disparities.

EXPLOSIVE HIV AND HCV EPIDEMICS DRIVEN BY NETWORK VIREMIA AMONG PWID

Steven J. Clipman1, Shrutti H. Mehta1, Aylur K. Srikrishnan2, Katie J. Zook1, Priya Duggal1, Shobha Mohapatra1, Shanmugam Saravanan1, Vandormael2, Joel Miller3, Anna Bershteyn4, Edward Wenger1, Diego F. Cuadros5, Frank Tanser6, Adam N. Akullian1, Alain Vandormael2, Joel Miller3, Anna Bershteyn4, Edward Wenger1, Diego F. Cuadros5, Frank Tanser6

1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2YR Gaitonde Center for AIDS Research and Education, Chennai, India, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: While much attention has focused on the US opioid crisis, misuse of opioids is rapidly becoming a global epidemic with >80% of drug seizures in Asia/Asia in part due to increased use of opioids to manage pain and expansion of heroin trafficking routes. Little is known about the drug using networks in these settings which contribute to HIV/HCV transmission.

Methods: 2512 people who inject drugs (PWID) in New Delhi, India were recruited (2017-19) into a cohort by a chain referral approach. Index participants were asked to name and recruit people they injected with in the past month (egocentric network of the index). Each recruit was asked to name and recruit their recent injection network members (egocentric network of recruit; sociometric network of index). Biometrics were used to identify duplicates and cross-network linkages. Participants underwent a survey and blood draw semi-annually. Blood was tested for HIV and HCV antibodies, HIV RNA and HCV RNA. Network viral load was calculated as the number of egocentric network members with HIV RNA>150 copies/ml. Poisson regression was used to identify predictors of incident HIV.

Results: At baseline, 36.9% had HIV infection of whom only 7.4% were virologically suppressed; HCV prevalence was 65.1%; recent heroin and other opioid use were 26.6% and 95.3%, respectively. Among 1,066 with at least one follow-up as of 9/1/19, 96 seroconversions were observed in 370 person-years (p-y) (HIV incidence: 25.9 per 100 p-y); 64 HCV antibody seroconversions were observed in 188 p-y (primary HCV incidence: 34.0 per 100 p-y). Of 96 incident HIV cases, 74% were directly connected to at least one viremic person in their egocentric network (Figure). In multivariable analysis adjusting for recent needle sharing and injection frequency, HIV incidence increased by 23% per unit increase in egocentric network member with detectable HIV RNA (incidence rate ratio [IRR]: 1.23; p<0.01); further, every increased step in the path between a participant and a sociometric network member with detectable HIV RNA decreased HIV incidence by 37% (IRR: 0.63; p<0.01).

Conclusion: We observed explosive HIV and HCV epidemics among PWID in New Delhi, largely driven by exposure to viremic individuals in both egocentric and sociometric networks, highlighting the importance of achieving broad viral suppression in order to curb transmission. Expanding treatment and prevention efforts in such disenfranchised populations will be critical for epidemic control.
men 30–34 years, IRR=2.30, 95% CI, 1.24–4.26; and increased by 50% among women 30–34 years, IRR=1.51, 95% CI, (1.09-2.05).

Conclusion: HIV-1 incidence shifted older over a 14-year period during scale-up of HIV treatment and prevention in a hyperepidemic South African cohort. The aging risk of HIV acquisition will require expanding demographic targets for HIV prevention beyond the youngest cohorts in high burden settings.

150 RAPIDLY DECLINING HIV INCIDENCE AMONG MEN AND WOMEN IN RAKAI, UGANDA

Gertrude Nakigozi1, Larry W. Chang2, Steven J. Reynolds3, Fred Nalugoda1, Godfrey Kigozi1, Thomas C. Quinn4, Ronald H. Gray1, Alice R Kisakye5, Anthony Ndyama6, Robert Ssesembaga7, David Serwadda2, Maria Wawer1, Joseph Kagaayi1, Mary K. Grabowski6, for the Rakai Health Sciences Program

Rakai Health Sciences Program, Kalisizo, Uganda, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA, 3NIAID, Baltimore, MD, USA, 4Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: We previously reported on declines in HIV incidence associated with the scale-up of voluntary medical male circumcision (VMMC) and antiretroviral therapy (ART) at CD4 counts of <500 in 30 communities continuously surveyed between 1994 and 2016 in the Rakai Community Cohort Study (RCCS). Prior analyses showed a 42% reduction in HIV incidence by 2016 relative to the period prior to VMMC and ART availability with greater declines observed among men than women (54% vs. 32%). We report here on HIV incidence following the implementation of universal test and treat in 2016.

Methods: Population-level trends in HIV incidence among RCCS study communities were assessed between April 1999 and May 2018. Trends in HIV incidence based on observed seroconversion, self-reported male circumcision, and self-reported ART use were assessed using data collected over 13 surveys. Viral loads among all HIV-positive persons were assessed at three surveys, including the two most recent surveys. Relative changes in HIV incidence at each survey after 2006 was compared to the mean HIV incidence before 2006 (i.e., before scale-up of VMMC and ART) using multivariate Poisson regression models and are reported as adjusted incidence rate ratios (adjIRR) with 95% confidence intervals (CI).

Results: 37,283 individuals participated, including 19,645 initially HIV-negative persons who contributed at least one follow-up visit. There were 992 HIV incident cases detected over 107,297 person-years of follow-up. By 2018, HIV incidence was 0.43 per 100 person years (py), a decline of 58% relative to the period prior to VMMC and ART availability (adjIRR=0.42; 95CI:0.31-0.57). Recent incidence declines were most pronounced among women whose incidence fell from 0.83 per 100 py to 0.48 per 100 py between the final two surveys (adjIRR=0.63; 95%Ct:0.41-0.98) and by 59% since the period prior to VMMC and ART availability (adjIRR=0.41; 95CI:0.28-0.60). Viral load suppression levels in 2018 improved modestly compared to the prior survey, increasing from 76% to 80% overall, from 79% to 85% among women, and from 67% to 71% among men. Prevalence of male circumcision continued to increase with 65% coverage among all men.

Conclusion: HIV incidence is rapidly declining among women and men with the continued scale-up of ART and VMMC in Rakai. Sustained investment and targeted efforts to achieve increased levels of viral load suppression and male circumcision coverage could potentially eliminate transmission in this African setting.
Methods: We conducted a cohort study of adult (aged ≥21) members of Kaiser Permanente in Northern or Southern California, or Mid-Atlantic States (DC, MD, VA), during 2000-2016. PWH were frequency-matched 1:10 to uninfected adults on age (2-year groups), sex, race/ethnicity, medical center, and calendar year. We used abridged life tables to estimate the average number of total and comorbidity-free years of life remaining at age 21 by calendar era. Comorbidity-free years were prior to diagnosis of any of 6 common comorbidities: cardiovascular disease, respiratory disease, renal disease, liver disease, cancer, or diabetes. For 2014-2016, we also estimated life expectancy for PWH with early ART initiation (i.e., with CD4 ≥500).

Results: Among 39,000 PWH and 387,785 matched uninfected adults, there were 2,661 and 9,147 deaths, with mortality rates of 1,303 and 390 per 100,000 person-years, respectively. In 2000-2003, overall life expectancy at age 21 was 37.6 and 57.9 years for PWH and uninfected adults, respectively, corresponding with a gap of 20.3 years (95% CI: 18.4-22.1; Figure). Overall life expectancy for PWH increased to 55.5 years in 2014-2016, narrowing the gap to 7.3 years (6.1-8.6). PWH with early ART initiation had a life expectancy at age 21 of 59.4 years in 2014-2016, further narrowing the gap compared with uninfected adults to 3.4 years (0.9-5.8). In 2000-2003, the expected number of comorbidity-free years remaining at age 21 was 11.0 and 26.1 years for PWH and uninfected adults, respectively, with PWH being diagnosed with comorbidities 15.1 years (13.7-16.4) earlier than uninfected adults. This gap persisted in 2014-2016, with comorbidity-free life expectancy at age 21 of 13.3 and 29.3 years for PWH and uninfected adults, respectively (16.1-year gap, 15.1-17.1), and no improvement for PWH with early ART initiation.

Conclusion: Overall lifespan has continued to increase for PWH in care, and only a 3-year gap remains relative to uninfected adults. However, PWH have 16 fewer healthy years than uninfected adults, with diagnoses of common comorbidities beginning at age 34, and no improvement over time or with early ART initiation. Greater attention to comorbidity prevention for PWH is warranted.

152 LOW-LEVEL VIREMIA DURING ART AND THE RISK OF DEATH, AIDS, AND SERIOUS NON-AIDS EVENTS

Olof Elvström,1 Gaetano Marrone2, Patrik Medstrand1, Carl Johan Treutiger3, Anders Sonnerborg4, Manus Gisslen5, Per Bjorkman1
1 Lund University, Lund, Sweden, 2 Karolinska Institute, Stockholm, Sweden, 3 Södersjukhuset, Stockholm, Sweden, 4 Karolinska University Hospital, Stockholm, Sweden, 5 Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Background: The impact of low-level viremia (LLV) during ART is unclear. We explored the associations between LLV and mortality, AIDS, and serious non-AIDS events (SNAE) using a population-based cohort.

Methods: All adults in the nationwide Swedish InfCare HIV register who started combination ART (cART) 1996-2017 were included if ≥2 viral load results (VL) were available ≥6 months after cART initiation. Participants were grouped into 3 categories: virologic suppression (<50 c/mL), LLV (50-999 c/mL), and high-level viremia (HVL, ≥1000 c/mL). Viremia was handled as a time-varying covariate; reclassification was only possible to a higher viremia stratum. In a separate analysis, LLV was divided into 2 subcategories: LLV 50-199 c/mL and 200-999 c/mL. Cox proportional-hazard models were fitted to determine the associations between viremia category and all-cause death, first AIDS condition, and first SNAE (cardiovascular disease, non-AIDS cancer, thromboembolism, pulmonary hypertension, renal and liver disease). The multivariable analysis included sex, age at start of cART, CD4 count and VL before ART, country of birth, injection drug use, exposure to mono and/or dual ART prior to cART, treatment interruptions, and an interaction term between viremia category and time.

Results: In total, 6,956 participants were included, with a median follow-up of 5.7 years (49,986 person years). LLV occurred in 953 (14%) subjects; at the end of follow-up, 4,177 (60%) had virologic suppression, 339 (5%) had LLV 50-199 c/mL, 258 (4%) had LLV 200-999 c/mL, and 2,182 (31%) had HVL. LLV was associated with increased all-cause mortality compared to virologic suppression, adjusted hazard ratio (aHR) 2.2 (95% confidence interval [CI] 1.3-3.6). When analyzed separately, LLV 50-199 c/mL had an aHR of 2.2 (95% CI 1.3-3.8) and LLV 200-999 c/mL of 2.1 (95% CI 0.95-4.7). All-cause mortality was also independently associated with higher age, male sex, lower CD4 counts, injection drug use, and treatment interruptions. Overall, LLV was not linked to increased risk of AIDS and SNAE, but in a subanalysis, LLV 200-999 c/mL was significantly associated with SNAE, aHR 2.1 (95% CI 1.2-3.8).

Conclusion: In conclusion, patients with LLV during ART were at increased risk of death. LLV 200-999 c/mL was associated with SNAE when compared to virologic suppression. Our study adds to mounting evidence that persistent LLV may be associated with increased risk of adverse events.

153 USING SYSTEMS BIOLOGY TO UNDERSTAND THE MECHANISMS OF VACCINE EFFICACY

Bali Pulendran, Emory University, Atlanta, GA, USA

For more than a century, immunologists and vaccinologists have existed in parallel universes. Immunologists have for long reveled in using ‘model antigens’, such as chicken egg ovalbumin or nitrophenyl hapten, to study immune responses in model organisms such as mice. Such studies have yielded many seminal insights about the mechanisms of immune regulation, but their relevance to humans has been questioned. In another universe, vaccinologists have relied on human clinical trials to assess vaccine efficacy, but have done little to take advantage of such trials for studying the nature of immune responses to vaccination. The human model provides a nexus between these two universes, and recent studies have begun to use systems biological approaches to study the molecular profile of innate and adaptive responses to vaccination in the human model. Such ‘systems vaccinology’ studies are beginning to provide mechanistic insights about innate and adaptive immunity in humans. Here, we present an overview of such studies, with particular examples from studies with the yellow fever and the seasonal influenza vaccines. Vaccination with the yellow fever vaccine causes a systemic acute viral infection and thus provides an attractive model to study innate and adaptive responses to a primary viral challenge. Vaccination with the live attenuated influenza vaccine causes a localized acute viral infection in mucosal tissues and induces a recall response, since most vaccines have had prior exposure to influenza. Both these vaccines provide a unique opportunity to study innate and antigen-specific memory responses in mucosal tissues and in the blood. Vaccination with the inactivated influenza vaccine offers a model to study immune responses to an inactivated immunogen. Studies with these and other vaccines are beginning to reunite the estranged fields of immunology and vaccinology, yielding unexpected insights about fundamental mechanisms of immune regulation.

154 DECODING THE TRANSCRIPTONAL INFLAMMATORY CASCADES THAT MAINTAIN HIV RESERVOIR

Susan Pereira Ribeiro, Case Western Reserve University, Cleveland, OH, USA
Antiretroviral therapy (ART) has improved the quality of life of HIV-infected subjects. However, the persistence of long-lasting viral reservoir poses a major obstacle for viral eradication. Early HIV infection is characterized by a cascade of inflammatory cytokines followed by a negative feedback loop of anti-inflammatory cytokines, such as IL-10, in order to reestablish homeostasis. Interestingly, viruses have evolved mechanisms that exploit the immunoregulatory function of IL10 for immune evasion, suppression, and tolerance to promote their own survival. As a result, some viruses, as HIV, can persist for life in infected hosts. HIV persists in a small pool of long-lived latently infected quiescent CD4+ T cells and molecular mechanisms that maintain the survival of productively infected cells is not completely understood.

In a cohort of ART-treated HIV aviremic subjects, IL10 was increased in blood and lymph nodes as compared to healthy controls. IL10 producing cells, including T cells, macrophages and B cells were in close proximity to cells with viral DNA in lymph nodes of infected subjects. Importantly IL10 triggered several cellular processes that promoted HIV persistence including the survival of infected cells, the upregulation of several co-inhibitory receptors (Co-IRs) which are involved in the establishment of HIV latency and immune dysfunction; confirming the ex vivo and in vitro gene signatures we also have shown that IL-10 is a potent regulator of TFH differentiation, a major HIV reservoir. Genetic manipulation i.e. in vitro knockout of STAT3, the transcription factor downstream of IL10/IL10R engagement, or functional inactivation of this pathway through the use of a neutralizing antibody to IL10, led to decreased HIV survival, downmodulation of Co-IRs expression and decreased THF frequencies, and consequently led to a significantly lower frequency of HIV infected cells in vitro. These data confirm the role of IL-10 as a trigger for HIV persistence.

In vivo blockade of the IL10 pathway in aviremic chronically infected Rhesus macaques, using an anti-IL10 antibody, led to reversion of all the pathways observed in humans as associated to HIV reservoir maintenance, and resulted in significant decrease on SIV provirus. The NHP pre-clinical data confirmed the safety of this intervention which could be targeted for HIV Cure in humans.

**155 DISSECTING THE DRIVERS OF CHRONIC INFLAMMATION**

Krystelle Nganou, NIH, Bethesda, MD, USA

Immune recovery during HIV infection is profoundly influenced by inflammation, with chronic inflammation being consistently associated to disease progression and poor prognosis. In addition, numerous studies have shown that antiretroviral therapy (ART) does not resolve inflammation.

Therefore, understanding the drivers of chronic inflammation is of considerable interest. This presentation will review current knowledge on the factors known to influence inflammation during ART, such as the HIV reservoir, microbial translocation and co-infections with other viruses. Recent studies on the microbiome will be presented in an effort to clarify whether changes in the microbiome are a cause or consequence of chronic inflammation. Moreover, we will describe how metabolic factors and health risk behaviors also contribute to chronic inflammation in persons living with HIV. Finally, the use of multi-omics approaches and state-of-the-art methodologies will be highlighted as means to unravel the mechanisms underlying chronic inflammation in HIV infection and, ultimately, to identify optimal therapeutic targets.

**156 DEFINING TREATABLE PATHWAYS IN INFLAMMATING: IS IT NICE TO FOOL WITH MOTHER NATURE?**

Michael M. Lederman, Case Western Reserve University, Cleveland, OH, USA

Our host defenses have evolved over millions of years and in general they work pretty well, except when they don’t. In HIV infection, defenses are broadly dysregulated resulting in both a heightened risk of infection and a systemic proinflammatory environment. Thus host defenses and the immune activation and inflammation that mediate these defenses cannot be viewed on a simple two-dimensional scale. These perturbations are improved with antiretroviral therapy, but they are not completely normalized and in particular, inflammatory morbidities persist as does a reservoir of replication-competent virus. If properly monitored, targeted interventions to alter this environment can provide insight as to how immune and inflammatory pathways interact, and thus be prepared to expect the unexpected as these pathways are complex, dynamic and difficult to orchestrate smoothly with the simple yet blunt interventions that we possess.

**157 NOVEL ANTIRETROVIRAL AGENTS: TRANSFORMING THE CARE OF PEOPLE WITH HIV**

Rajesh T. Gandhi, Massachusetts General Hospital, Boston, MA, USA

In this state-of-the-art overview, we will discuss new approaches to treating HIV, including agents with novel mechanisms of action; long-acting medications; and innovative delivery systems. We will review novel options for optimizing treatment of HIV for a broad array of patients, including those initiating therapy for the first time and those who have multi-drug resistant virus. And we will highlight treatments that are on the horizon but that have the potential to transform the care of people with HIV.

**158 PEDIATRIC AND ADOLESCENT ART: A ROAD LESS TRAVELLED**

Carolyn Bolton Moore, Centre for Infectious Disease Research in Zambia, Lusaka, Zambia

Over the last three decades, advances in antiretroviral therapy and improvements in overall clinical management and service provision have dramatically reduced both morbidity and mortality in children with HIV across the globe. However, in general, outcomes remain much poorer than those seen in adults and data from both the developing and developed world show that children have consistently lower rates of viral suppression than adults. Adherence to ART is critical for optimal treatment outcomes. Proper adherence to treatment results in viral suppression, improved symptoms, fewer opportunistic infections and less chance of viral resistance. Barriers to poor adherence are diverse and those affecting young children may differ significantly from those largely affecting older children and adolescents. Developing more palatable, child-friendly formulations of ART which do not require specialized cold chain management is likely to significantly increase adherence amongst younger children. But improving treatment outcomes in older children and adolescents likely requires a multi-pronged approach combining innovative behavioral interventions, stigma reduction strategies and simplification of treatment regimens. Several strategies for reducing and simplifying antiretroviral therapy for adolescents and children are currently under investigation and aim to maximize adherence, reduce toxicity, preserve future treatment options, and reduce costs. Development of pediatric formulations of antiretroviral drugs have historically lagged 10-15 years behind that of adult versions of the drugs, partly as a result of diminishing markets for these drugs in wealthier countries and partly due to the complexity of the physiological and developmental changes associated with childhood and adolescence. Over the past few years, various efforts have enabled better alignment and agreement on key principles in pediatric drug development and research including defining dosing by weight bands, applying innovative study designs, synergizing work across research networks to achieve common goals, including adolescents in adult trials and the establishment of a global prioritized research agenda. However, despite these advances, accelerating the pediatric agenda and prioritizing new/more effective agents and formulations remains a priority. Keeping up the momentum, and finding new momentum, is key to ending the epidemic and allowing our children and adolescents to be happy, healthy and free of HIV.

**159 METABOLIC COMPLICATIONS OF HIV AND ITS THERAPIES**

Jordan E. Lake, University of Texas at Houston, Houston, TX, USA

This talk will discuss the contributions of current ART agents and combinations to metabolic disease, including the potential impact of weight gain on co-morbid conditions, and possible interventions to mitigate metabolic complications of ART.

**160 GETTING IT RIGHT: PRACTICAL APPROACHES TO ADHERENCE WITH MODERN ARVs**

Jose R. Castillo-Mancilla, University of Colorado Denver, Denver, CO, USA

Along with the remarkable advancements in antiretroviral therapy (ART), new paradigms have emerged on the importance of adherence. Early studies with older antiretrovirals (ARVs) proposed that >95% adherence was required to achieve and maintain virologic suppression, which led to the concept that an undetectable HIV viral load (VL) was equivalent to full adherence. However, the potency and favorable pharmacology of the new ARVs have allowed for more forgiveness to missed doses; with recent studies demonstrating that the “minimal” level of ART adherence required to sustain viral suppression may range between 80-85% (and as low as 75%). While advantageous, achieving viral suppression despite variable ART adherence has de-emphasized the focus
on adherence in clinical practice, limiting our understanding of its consequences at the individual (i.e., biological, virological) and population (i.e., transmission) levels. This is essential to maximizing the benefit of ART and controlling the HIV epidemic, since maintaining an undetectable HIV VL (mainly driven by adherence) is indispensable for the U=U (Undetectable=Untransmittable) strategy to be effective, and because adherence remains a lifelong challenge. However, despite its critical importance, we currently lack a gold-standard measure to quantify ART adherence. In response to this gap, several innovative methods and strategies to objectively measure ART adherence have emerged in recent years. These include: a) pharmacologic methods that inform about cumulative adherence and recent dosing by quantifying drug concentrations in plasma, urine, hair and dried blood spots; b) advances in electronic medication dispensers that monitor pill-taking behavior, and; c) digital pills that confirm medication ingestion. These novel methods have proven more accurate than self-report, can predict adverse clinical outcomes (i.e., viremia), and provide real-time adherence information that can lead to actionable interventions during a routine clinical visit. Moreover, pharmacologic methods can assess individual pharmacokinetic differences not captured by HIV VL monitoring or other adherence measures. This symposium talk will address these and other questions by exploring the benefits and potential risks of forgiveness of modern ARVs (including long-acting agents), evaluating the pearls and pitfalls of existing and new ART adherence measures, and providing the audience with some practical strategies for integrating these tools into clinical practice.

161 GLOBAL EPIDEMIOLOGY OF HEPATITIS C
Yvan J. Hutin, WHO, Geneva, Switzerland
In 2017, WHO published its Global Hepatitis Report, which described the status of the viral hepatitis epidemic in 2015, at the baseline of the Global Health Sector Strategy (GHSS) on viral hepatitis that aims for elimination. In 2020, 4 years into the strategy, we can reflect on what is known and what is unclear in terms of incidence, prevalence, and mortality of HCV infection. With respect to incidence, using a model from the Centre for Data Analysis (CODA), WHO estimated that in 2015, 1.75 million new infections occurred. Surveillance for acute hepatitis C and age-specific seroprevalence suggests that in most countries, the incidence has been on the decline. However, a reoccurrence of transmission because of injection drug use, unsafe health care or unsafe practices among men who have sex with men is always possible. This calls for enhanced case reporting of acute hepatitis to describe trends and risk factors for infection. With respect to prevalence, on the basis of a CODA systematic review of biomarker surveys adjusted with modeling, WHO estimated that 71 million persons were living with HCV in 2015. This number is decreasing because of curative treatments. Also, the heterogeneity of prevalence needs to be better characterized so that testing and treatment policies can be adapted. A limited number of high-prevalence countries (> 2-5%) faced substantial morbidity and mortality that require testing in the general population. However, most infections are located in settings where prevalence is under 2% and where focused testing may be more cost-effective. Given this heterogeneity, local biomarker surveys and data on the prevalence of HCV infection in subgroups being tested are needed to guide testing and treatment policies. Finally, on the basis of death certificates and attributable fractions, WHO estimated that in 2015, about 400,000 persons died from the sequelae of HCV infection, including cirrhosis and hepatocellular carcinoma. While on average HCV-associated mortality is increasing worldwide, there are differences. In countries where transmission occurred many decades ago, mortality already started to decrease. In countries where transmission took place more recently, mortality is still increasing or in some cases, may not even have started to increase. Therefore, sequelae surveillance is needed to describe baseline mortality trends so that we can better predict the impact of testing and treatment.

162 MODELING AND EXAMPLES OF HCV ELIMINATION: POSSIBILITIES, ACHIEVEMENTS, AND NEXT STEPS
Natasha Martin, University of California San Diego, San Diego, CA, USA
The WHO viral hepatitis elimination strategy set ambitious targets for reducing HCV incidence and mortality by 2030. Modeling indicated these targets could be achieved at global, national, and local levels through scaling-up interventions to prevent and treat HCV. However, differences in transmission risks and historical or on-going epidemiology highlight the need for setting-specific strategies, and local data to understand these differences. Indeed, a recent modeling study indicated unsafe injecting practices among people who inject drugs will contribute to ~43% of incident HCV infections globally from 2018-2030, but varying considerably by country. In Pakistan, where transmission is highly disseminated the contribution is low, whereas in the U.S. the contribution is high due to the ongoing opioid crisis thus requiring combination harm reduction and treatment strategies. Where are we now? Several countries are implementing ambitious national elimination strategies, with interim evaluations occurring. In Egypt, from 2014 to 2018, ~2.5 million people were treated, yet an even greater number were undiagnosed. In 2018, Egypt initiated the world’s largest HCV screening program, aiming to screen the entire population (101 million); 50 million were screened in the first 6 months. In Georgia, >54,000 people were treated between 2015 and February 2019 and a recent interim dynamic modeling analysis predicted the country was on track to achieve both WHO targets by 2030. In Australia, unrestricted access to direct-acting antivirals since 2016 led to widespread treatment uptake, with modeling indicating the country is on track for elimination. What is still needed? Despite progress in a few countries, the vast majority are not on track to achieve elimination. Political commitment and funding for harm reduction interventions, which additionally prevent HCV and overdose, are urgently needed. Interventions to increase diagnoses will be required as the diagnosed and untreated pool dwindles. Strategies to reduce cost are still required and will be setting-specific. For example, in Pakistan, modeling indicates full elimination requires a national screening program, which could require annual expenditure of 9% of the health budget even with a simplified treatment algorithm and low DAA costs. Integration strategies could reduce costs. Robust local data systems will enable modeling to inform efficient elimination strategies and evaluation of elimination progress across the next decade.

163 VERTICAL HEPATITIS C TRANSMISSION: DÉJÀ VU ALL OVER AGAIN?
Ali Judd, University College London, London, UK
Vertical transmission of HIV and hepatitis B virus (HBV) is preventable, and risk is reduced through routine antenatal screening coupled with treatment during pregnancy for all women with HIV and those with high HBV viral loads. This approach is a “double dividend” for HIV, as it provides the opportunity for pregnant women to receive treatment for their own health, while at the same time preventing vertical transmission. The number of new HCV infections in children is declining, but the global incidence of chronic hepatitis B is still largely driven by vertical and early childhood infections, and challenges remain in implementing HIV and HBV prevention and treatment strategies in pregnant women and infants in some high burden countries. There are important differences between vertical transmission of HCV, and HIV and HBV, most notably that HCV is not associated with high infant mortality (unlike HIV), there is no vaccine (unlike HBV), and HCV is curable (unlike HIV and HBV). Efforts are being made to scale up HCV treatment worldwide, and there are ambitious HCV elimination goals. However, pregnant and breastfeeding women and their infants have been left behind in the HCV elimination agenda, as no direct acting antivirals are licensed for use in these groups. This is partly due to uncertainty regarding optimal test and treat strategies, with a weak evidence base, and many countries know little about the epidemiology of HCV in pregnant women due to the scarcity of universal antenatal HCV screening. In this talk the evidence for the effect of HCV on pregnancy and neonatal outcomes, risk of vertical transmission, potential interventions to prevent transmission, safety profiles of DAs, screening and linkage to care for mothers and HCV diagnosis and treatment for children, will be reviewed. Key gaps in knowledge and areas for future research will be identified. There is a need to improve our understanding of the potential benefits associated with routine HCV screening and treatment in these vulnerable populations, to ensure that the double dividend approach of treatment and prevention is used in the most effective way. Fast-forwarding to the future, if we are serious about HCV elimination then we cannot neglect the potential opportunities of universal antenatal screening to treat mothers and prevent vertical transmission. We need to learn from our experience with HIV and HBV and accelerate our response. Otherwise, will it be déjà vu all over again?

164 HEPATITIS C TREATMENT ON A SHOESTRING
Isabelle Andrieux-Meyer, Drugs for Neglected Diseases Initiative, Geneva, Switzerland
Despite the effective diagnostic & therapeutic tools available to eliminate hepatitis C, WHO reported that only 5M people with HCV, out of 71 million
infected, had received treatment by the end of 2017. Of these, 2.5M people were treated in Egypt, 1.8M in high-income countries, and a tiny fraction (0.7M) in the rest of the world. In Egypt, a 2018 campaign aimed to screen 53M people and treat 2.2M HCV patients. This is facilitated by locally produced DAAAs priced below 1% of the US price, following government rejection of DAA patents. After agreements signed between DAA patent holders and generic manufacturers, DAA prices decreased spectacularly by over 99%, from $120,000 in 2013 to $20 for 12 weeks of the same curative treatment. However, most low- and middle-income countries eligible for the lowest generic DAA prices ended up paying $750-1,000, which does not support test and treat strategies. High and middle-income countries excluded from licensing agreements used different strategies to decrease DAA prices and implement elimination programs. In Brazil, the threat of patent rejection and local DAA production initiatives supported government pricing negotiations, resulting in the lowest prices offered by originator companies. The Malaysian government opted to grant a compulsory license to import affordable generic sofosbuvir at $237 per course, compared to $11,200 with sofosbuvir. Australia paved the way with “Netflix” type agreements aimed at reduced prices based on volumes to support test and treat programs. As demonstrated by countries on track for HCV elimination, the main challenges are detecting the 80% of people unaware of their status and providing universal access to DAAAs, essential to halt HCV transmission. Simplification of HCV models of care and DAA affordability are key determinants for countries to launch elimination programs.

**POSTER ABSTRACTS**

**165 HIV-1 CAPSID-NUCLEAR ENVELOPE INTERACTIONS THAT FACILITATE NUCLEAR IMPORT**

Mohamed Husen Munshi1, Ryan C. Burdick1, Wei-Shau Hu1, Vinay K. Pathak1
1National Cancer Institute, Frederick, MD, USA

**Background:** HIV-1 must enter the nucleus and integrate its DNA into host genome for successful infection. However, the mechanism by which the viral complex docks at the nuclear envelope (NE) and enters the nucleus is not well understood. Although CA is known to play a critical role in nuclear import, the CA determinants that influence NE docking and viral complex translocation through the nuclear pore have not been defined. To identify the critical CA determinants, we developed quantitative live-cell imaging assays to study the NE docking and nuclear import of single viral complexes.

**Methods:** A high-throughput live-cell imaging assay was developed to study NE docking and residence times of single viral complexes labeled with either HIV-1 integrase-superfolder green fluorescent protein (sfGFP), APOBEC3F-yellow fluorescent protein (A3F-YFP) or Cyclophilin A-red fluorescent protein (CypA-DSRed). The amount of CA associated with viral complexes was quantified using a newly developed direct CA label (GFP-CA); CA was also detected by immunostaining with anti-CA antibody. Infectivity was determined in HeLa cells, and the CEM-SS and MT4 T cell lines.

**Results:** Using high-throughput live-cell imaging, we identified CA mutants M10I, M10V and I15V that exhibited longer NE residence times compared to wild-type viral complexes in a CypA-dependent manner. Additionally, the M10 mutant complexes that entered the nucleus had longer NE residence times compared to WT, but only for the CypA-dependent nuclear import pathway. Analysis of virions labeled with CypA-DSRed also indicated that most viral complexes lost CypA-DSRed prior to nuclear import. CA mutants did not show infectivity defects in HeLa cells but were defective in T cell lines. Direct labeling of CA (GFP-CA) indicated that the CA levels of WT and mutant viral complexes were similar; however, CA detection using anti-CA antibody suggested differences in mutant viral complexes that reduced anti-CA antibody binding as a result of differences in conformation or host protein binding.

**Conclusion:** We have identified CA determinants that play a critical role in NE docking and nuclear import in a CypA-dependent manner. We propose a model in which CypA stabilizes the initial interaction of the viral core with NE but does not enter the nucleus with the viral core. These studies provide valuable insights into the interactions between the viral complex and the NE that result in stable docking and nuclear import.

**166 REPORTER VIRUSES WITH PROTEIN BARCODES TO ANALYZE HIV LATENCY ESTABLISHMENT**

Eun Hye G. Kim1, Maria C. Bermúdez-González1, Michael Schoutsaert1, Ana Fernández-Sesma1, Luíbértas C. Mulder1, Lara Manganaro2, Viviana A. Simon1
1Icahn School of Medicine at Mount Sinai, New York, NY, USA, 2Istituto Nazionale Genetica Molecolare, Milan, Italy

**Background:** Studies of HIV latency establishment at the single cell level have been hampered by difficulties to identify CD4+ T cells that harbor transcriptionally silent proviruses. HIV molecular clones encoding reporter proteins, whose expression is either dependent or independent of HIV LTR promoter, have been powerful tools to dissect mechanisms of HIV persistence. To better support multi-dimensional analyses such as those carried out by Mass Cytometry (CyTOF), we have generated HIV dual reporter viruses that carry cell membrane expressed protein barcodes.

**Methods:** To detect the LTR independent expression of affinity tags such as chimeric protein VS-NEGFR or the GFP reporter protein, a PKG promoter driven reporter cassette was cloned into the envelope frame of HIV molecular clone pLAI2. In addition, for the assessment LTR-dependent expression, reporters HSA-mCherry were cloned upstream of an internal ribosomal site followed by nef. VS-NEGFR and HSA, in contrast to GEP or mCherry, are both expressed at the plasma membrane of the cell making the reporters easily accessible to membrane probes and magnetic bead enrichment approaches.

**Results:** Primary human CD4+ T cells from six different donors were stimulated with IL-2, IL-15 or CD3/CD28 and infected with the different dual reporter viruses. Cells were analyzed by flow cytometry after 3, 4 and 5 days to determine the optimal conditions and select the most informative time points and donors. The reporter virus HIV-GKO previously described by the Verdin lab was used as reference. Mock infected and HIV infected cells were analyzed by CyTOF. We used a customized CyTOF antibody panel, which captures 30 different markers allowing the discrimination of different CD4+ T populations including CD4+ T memory cells with stem cell like properties (CD4+ Tscm) and CD4+ Tregs. Markers for determining cellular features such as proliferation, activation and cell cycle were also included. CyTOF experiments were performed at the Human Immune Monitoring Center of the Icahn School of Medicine.

**Conclusion:** Our preliminary data indicate that our dual reporter viruses allow accurate detection of both LTR silent and LTR active proviruses with minimal promoter interference. We will expand on the existing viruses to generate panels of barcoded reporter viruses to test the influence that viral genes, such as integrase and Vpr, have on latency establishment and maintenance in specific primary human CD4+ T cell populations.

**167 Gag DETERMINANTS OF SPECIFIC GENOME PACKAGING IN HIV-1 AND HIV-2**

Jonathan Rawson1, Olga A. Nikitachik1, ‘Xayathed Somoulay1, Jennifer A. Yoo1, Vinay K. Pathak1, Wei-Shau Hu1
1National Cancer Institute, Frederick, MD, USA

**Background:** Genomic packaging of HIV is controlled by the HIV-1 Gag protein. Gag drives this process by binding to the packaging signal in the 5’ untranslated region of genomic RNA. However, Gag also binds cellular RNAs, and the mechanism by which Gag selectively packages the viral genome remains poorly understood. It was previously observed that HIV-1 and HIV-2 exhibit a striking difference: HIV-1 Gag efficiently packages HIV-2 RNA, but HIV-2 Gag does not package HIV-1 RNA. We hypothesized that studies of these non-
reciprocal interactions would lead to the identification of novel HIV packaging determinants.

Methods: HIV-1-based Gag chimeras were constructed that contained the entire HIV-2 nucleocapsid (NC) domain or just the two zinc fingers of HIV-2 NC. The chimeras were transfected into 293T cells, and Gag expression, particle release, and maturation were examined. Single virion analysis, a technique in which individual particles are analyzed by fluorescence microscopy, was performed to determine packaging efficiencies for HIV-1 or HIV-2 RNA. 

Results: The chimeras did not affect Gag expression or particle release but did slightly impair Gag processing. Surprisingly, both chimeras packaged HIV-1 RNA into ~70% of particles, a modest reduction relative to wild-type (WT) HIV-1 (~95%). However, when HIV-1 and HIV-2 RNAs were co-expressed and competed for packaging, both chimeras strongly preferred to package HIV-2 RNA. In contrast, WT HIV-1 Gag packaged HIV-1 and HIV-2 RNAs with similar efficiencies. We further found that the chimeras replicated in MT-4 cells, although with delayed kinetics compared to WT HIV-1. When re-passaged, the chimeras replicated significantly faster, indicative of adaptation. Putative adaptive mutations in Gag were identified by PCR and sequencing. One single amino acid substitution was found in the first zinc finger of HIV-2 NC and represents a switch from an HIV-2 to an HIV-1 residue at this position. This mutation alone significantly improved chimeric replication.

Conclusion: Our findings provide new insights into the mechanistic basis of selective genome packaging in HIV-1 and HIV-2. These studies may inform future efforts to develop antivirals targeting RNA packaging and have implications for the possible emergence of HIV-1/HIV-2 recombinants in co-infected individuals.

169LB MULTI-OMICS ANALYSES REVEAL IMMUNOMETABOLIC REPROGRAMMING-DEPENDENT HIV-1 REPLICATION

Haitao Guo1, Qi Wang1, Li Wang1, Khader Ghneim2, Elena Rampanelli2, Carolina Garrido1, Rafick-Pierre Sekaly3, Merlin L. Robb3, Leigh Anne Eller3, David M. Margolis1, Xian Chen1, Lishan Su1, Jenny P. Ting1
1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2Case Western Reserve University, Cleveland, OH, USA, 3Walter Reed Army Institute of Research, Silver Spring, MD, USA

Background: Human Immunodeficiency Virus type 1 (HIV-1)-infected individuals show metabolic alterations of CD4 T cells through unclear mechanisms. The nucleotide-binding, leucine-rich-repeat-containing protein NLRX1 is a novel host factor required for HIV-1 infection. Whether NLRX1 has an interaction with the immunometabolism to promote HIV-1 infection of CD4 T cells is an intriguing question.

Methods: First, we silenced NLRX1 expression in human primary CD4 T cells by short hairpin RNA and assessed HIV-1 replication in those cells compared with the control cells. Second, we used quantitative mass spectrometry to profile the altered protein expression resulted from HIV-1 infection of Jurkat T cells, followed by an analysis of differentially expressed proteins between NLRX1-silenced cells and the control cells. Third, we conducted metabolic assays to compare the differently induced oxidative phosphorylation (OXPHOS) and glycolysis by HIV-1 infection in NLRX1-silenced T cells vs the control cells. Fourth, we used the inhibitor and activator of OXPHOS to modulate HIV-1 replication in both primary CD4 T cell culture and human CD4 T cell-reconstituted mouse model. Finally, we analyzed the RV217 transcriptomic study of HIV-1 patients to search the association between immunometabolic pathways and HIV-1 viremia.

Conclusion: NLRX1 facilitates HIV-1 replication in both human primary CD4 T cells and human CD4 T cells-reconstituted mice. Quantitative proteomics and metabolic analyses reveal that NLRX1 enhances OXPHOS and glycolysis during HIV-1 infection of CD4 T cells to promote viral replication. Inhibition of OXPHOS by an FDA-approved drug, metformin, suppresses HIV-1 replication in primary CD4 T cells and in humanized mice. Potentiating OXPHOS by resveratrol restored the deficiency of HIV-1 replication in NLRX1-silenced T cells. The role of OXPHOS during HIV-1 infection in patients is supported by the transcriptome profiling of CD4 T cells from 22 male and 15 female HIV-1 patients residing in Asia and Africa. HIV-1 viremia positively correlates with NLRX1 expression and poor outcomes are associated with elevated OXPHOS.

Conclusion: NLRX1 promotes HIV-1 replication in CD4 T cells by inducing immunometabolism OXPHOS and glycolysis. Inhibition of OXPHOS by metformin suppressed HIV-1 replication in both primary human CD4 T cells and humanized mice. OXPHOS is positively correlated with HIV-1 viremia in HIV-1 patients. This study uncovers a T cell OXPHOS pathway as an unappreciated target for HIV-1 therapy.

170LB HIGH-RESOLUTION PARTICLE STRUCTURE OF IMMATURE HIV-2

Nathaniel L. Talledge1, Huixin M. Yang1, Luiza Mendonca1, Ke Shi1, Hideki M. Alhara1, Wei Zhang1, Louis M. Mansky1
1University of Minnesota, Minneapolis, MN, USA

Background: Immature retroviruses like human immunodeficiency virus type 1 (HIV-1) are known to possess an unusual degree of irregularity, with Gag proteins forming a hexagonal lattice that drives assembly and release of particles lacking icosahedral symmetry, and creating a lattice this is substantially incomplete. Immature virus particle structure can provide important clues to the nature of virus particle assembly in cells.

Methods: In this study, we sought to decipher key structural details of immature retroviral morphology of HIV-1 and the less pathogenic HIV-2 by obtaining high-resolution structures using cryo-electron microscopy (cryo-EM). In particular, we sought to identify a structural basis for our preliminary observations indicating that distinct differences in immature particle morphology are observed between HIV-1 and the less pathogenic HIV-2. In particular, key phenotypic features that distinguish HIV-2 immature particles include a larger average particle size as well as a nearly complete Gag lattice.

Results: Structural comparison at 5.5 Å resolution between published HIV-1 and that of our HIV-2 cryo-EM reconstructions emphasizes the importance of the capsid (CA) C-terminal domain (CTD) and spacer peptide 1 (SP1) regions in forming hexameric assemblies of CA in the intermolecular contacts of the overall lattice structure (including critical residues at the dimeric and trimeric intermolecular interfaces). In conjunction to the cryo-EM analyses, we solved
a 1.98Å crystal structure of HIV-2 CACTD and found a unique extra alpha helix (H12) at the C-terminal region, which was not previously observed in the domain structures of HIV-1 or other retrovirus CA proteins. Fitting of the HIV-2 CACTD into the reconstruction map confirmed critical contact interfaces of Gag proteins, and emphasized the importance of the co-factor mositol hexakishosphophate (IP6) at the six-fold symmetry interface. The presence of H12 in CA may contribute to the stability of the hexameric interactions in the HIV-2 immature Gag lattice.

**Conclusion:** Taken together, our observations provide important clues for explaining the observed morphological differences between immature HIV-1 and HIV-2 particles. These differences may help explain differences virus virulence.

### 171 B CELLS DIRECT RS-TROPIC HIV INFECTION OF CCR5<sup>NEG</sup> NAIVE CD4+ T CELLS

**Abigail D. Gerberick, Nicolas Sluis-Cremer<sup>1</sup>, Paolo A. Piazza<sup>1</sup>, Charles Rinaldo<sup>1</sup>, Giovanna Rappocciolo<sup>1</sup>, Diana Campbell Delucia<sup>1</sup>**

1University of Pittsburgh, Pittsburgh, PA, USA

**Background:** Naive CD4 T (TN) cells are an important reservoir of latent, replication-competent HIV. CD4 TN isolated from peripheral blood are resistant to direct infection with RS-tropic HIV in vitro because there is negligible expression of CCR5 on the cell surface. Paradoxically, RS-tropic virus has been isolated from TN cells from HIV-infected individuals on antiretroviral therapy. We assessed whether antigen presenting cells (APCs) - B cells and dendritic cells (DCs) - mediate trans infection of RS-tropic HIV to TN cells in the absence of global T cell activation.

**Methods:** Total CD4 T cells, CD4 TN cells, B cells and monocytes were purified from PBMCs of seronegative donors by magnetic microbead separation. B cells were activated by CD40L and IL4, and DCs were differentiated from monocytes by GM-CSF and IL4. B cells and DCs were pulsed with 10-3 moi RS-tropic HIVBaL and cultured with TN or total CD4+ T cells at a 1:1 ratio. As a control, we exposed TN or total CD4 T cells to 10-1 moi of HIVBaL in the absence of B cells or DC (i.e., cis infection). Cell phenotype was assessed by flow cytometry and viral replication by HIVp24 production before and after stimulation with anti-CD3/CD28 Ab or PMA/PHA. We quantified total HIV DNA in the TN and total CD4 T cell populations from 2 HIV nonprogressors (NPs).

**Results:** After 12 days of incubation, there were low levels of p24 in the B cell-TN co-cultures (n=10), indicative of productive infection, but not in the DC-TN co-cultures. In contrast, both B cells and DC could efficiently HIV trans infect total CD4 T cells. As expected, TN were refractory to direct, cis infection with HIVBaL. Phenotypic analysis of the TN cells revealed that they maintained a CCR5neg phenotype. B cell-TN co-cultures exposed to anti-CD3/CD28 Ab or PMA/PHA resulted in high-levels of p24 production, whereas no virus expression was recovered from the DC-TN co-cultures. We previously demonstrated that APCs derived from NPs cannot trans infect CD4 T cells, which prompted us to quantify the HIV DNA reservoir in TN and total CD4 T cells isolated from 2 NPs. We detected HIV DNA in the total CD4 T cells but not in the TN of both NPs.

**Conclusion:** B cells, but not DCs, efficiently trans infect CCR5neg TN cells with RS-tropic HIVBaL. No HIV DNA was detected in DC-TN cells from NPs, consistent with the notion that APCs derived from NPs cannot trans infect CD4 T cells. B cell-mediated HIV trans infection of CD4 TN cells could be a key mode to establish early HIV reservoir.

### 172 TFR REDUCE HIV-1 INFECTED TFH IN VITRO IN AN IL-2 DEPENDENT MANNER

**Matthew T. Ollerton<sup>1</sup>, Elizabeth Connick<sup>1</sup>**

1University of Arizona, Tucson, AZ, USA

**Background:** Follicular CD4+ T cells (TFH) are highly permissive to HIV-1 infection and a major reservoir of HIV-1 in lymphoid tissues. Follicular regulatory CD4+ T cells (TRF) limit TFH numbers and function in vitro and in vivo. We hypothesized that TRF inhibit HIV-1 replication in TFH.

**Methods:** TFH (CD3+CD4+CXCR5+CD25-) isolated from tonsils of individuals at low risk for HIV were spinoculated with the GALT reporter virus NLEN61, labeled with the proliferation dye VPD450, and co-cultured 1:1 with autologous TRF (CD3+CD8-CD45RA-CD25+) or TFH (control) for 5 days in Advanced R-10 media and 10 IU/ml IL-2. Percent GFP+VPD450+ TFH were determined by flow cytometry. Live VPD450+ TFH were isolated on a cell sorter, and total and integrated HIV DNA were quantified using QPCR. Cell counts were measured using counting beads. In some experiments, 0, 10, 30, or 100 IU/ml of IL-2, or blocking antibodies to TGF-beta, CD39, or IL-10 at 10 µg/ml were added. IL-2 supernatant concentrations were measured by ELISA. Statistical analyses were performed using non-parametric Wilcoxon matched-pairs test and Spearman’s correlation.

**Results:** In comparison to control co-cultures, TRF reduced TFH numbers (p=0.023; n=14), %GFP+ TFH (p=0.001; n=14), total HIV DNA (p=0.016; n=7), and integrated HIV DNA (p=0.016; n=7). Blocking TGF-beta, CD39, and IL-10 did not reverse TRF inhibition of %GFP+ TFH. IL-2 increased TFH viability in a dose dependent manner (r=0.946 p=<0.0001), but did not promote TFH proliferation. Compared to control co-cultures, %GFP+ TFH were reduced in TRF co-cultures with 10 IU/ml and 30 IU/ml IL-2, while no inhibition was detected in TRF co-cultures without IL-2 or with 100 IU/ml IL-2 (See Figure). TFH cell counts followed the same pattern. IL-2 supernatant concentrations were lower in TRF co-cultures compared to control co-cultures with 10 IU/ml (median, 1.0 vs 5.0 ng/ml; p=0.031) and with 30 IU/ml (median, 5.3 vs 121 ng/ml; p=0.156), but not with no IL-2 (median, 0 vs 0; p=0.999) or 100 IU/ml IL-2 (median, 67.39 vs 56.0 ng/ml; p=0.813).

**Conclusion:** IL-2 promoted TFH viability and HIV-1 associated GFP expression in vitro. TRF reduced HIV-1 producing TFH at low, but not high or absent concentrations of IL-2. Consumption of IL-2 in cell foliculies may be one mechanism by which TRF reduce HIV-expressing TFH in vivo.
174 THE ARYL HYDROCARBON RECEPTOR NEGATIVELY REGULATES HIV REPLICATION IN TH17/TH22 CELLS
Debashree Chatterjee1, Yuwei Zhang1, Huicheng Chen1, Tomas Raul Wiche Salinas1, Yasmine Small1, Jean-Pierre Routy1, Petronela Ancuta2
1Université de Montréal, Montreal, QC, Canada, 2McGill University Health Centre, Glen site, Montreal, QC, Canada, 3Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada
Background ART fails to restore the depletion of Th17-polarized CCRI6+CD4+ T-cells in PLWH. Novel Th17-targeted HIV remission/cure strategies are needed to restore Th17-mediated mucosal immunity. Autoimmunity studies demonstrated the existence of pathogenic and non-pathogenic Th17 cells and identified the aryl hydrocarbon receptor (AhR) as a marker of non-pathogenic Th17 cells. AhR is a ligand-dependent transcription factor that regulates the expression of several genes (IL-22, IL-10, integrin β7) and is involved in proteasomal degradation via its E3 ubiquitin ligase activity. We hypothesized that AhR negatively regulates HIV replication in non-pathogenic Th17 cells.
Methods: PBMC of ART-treated PLWH (n=8; median CD4 counts: 598, plasma viral load < 40 HIV-RNA copies/ml) and uninfected controls (n=5) were used in this study. Total/CCRI6+CCR6-memory CD4+ T-cells were isolated by magnetic/flow cytometry sorting. Cells of uninfected donors were stimulated via CD3/CD28, exposed to HIV, and cultured 9 days. Viral outgrowth assay (VOA) was performed with cells of ART-treated PLWH. AhR silencing was performed using CRISPR/cas9, with efficacy evaluated by T7 endonuclease assay and Western blotting. AhR agonist (FICZ) and antagonist (CH223191) were used. Cell viability/proliferation, HIV replication, cytokines, and gene expression were quantified by ELISA, flow cytometry and/or real-time PCR.
Results: AhR mRNA/protein expression was induced by T-cell receptor triggering. CRISPR/cas9-mediated AhR silencing significantly inhibited IL-22, IL-17A, IL-10 and integrin β2 expression (p<0.01) and increased viral replication upon infection in vitro (n=3; p=0.0084). Similarly, CH223191 significantly down-regulated IL-22, IL-17A, IL-10, production (p<0.001); increased wild type HIV replication (p=0.0016), as well as HIV DNA integration/transcription upon single-round infection with HIV-WSV pseudotyped viruses (n=5; p=0.001); and increased >2-fold HIV reactivation in VOA (n=7). At the opposite, FICZ significantly increased IL-22 and IL-10 production and inhibited viral replication in vitro and reactivation in VOA.
Conclusion: Our results identify the AhR as a novel negative regulator of HIV replication in Th17/Th22-polarized cells thus raising the interest in testing natural/synthetic AhR agonists/antagonists for HIV remission/cure strategies.

175 ANTI-HIV ACTIVITIES OF THE 12 INTERFERON-ALPHA SUBTYPES
Aexandra Tauzin1, Armando Espinosa1, Olivia Blake2, Fabrizio Mammano3
1INSERM, Paris, France
Background: The human genome encodes for 12 different interferon (IFN)-alpha subtypes, which share a common receptor on target cells, and trigger similar signaling cascades through Jak-STAT pathways. Several studies have collectively shown that this apparent redundancy may be justified by specific properties of the different IFN subtypes. Accordingly, the sets of genes induced by different IFN subtypes do not completely overlap, and different viruses, including HIV, are differently sensitive to individual subtypes.
Methods: We have measured the inhibition of HIV replication by the 12 IFN-alpha subtypes in primary T-lymphocytes and in a T-cell line using a multiple cycle replication assay. We have then measured the efficacy of inhibition on specific steps of the HIV replication cycle, including viral entry, reverse transcription, integration and budding. In parallel, we have measured the impact of IFN-alpha subtypes on cell proliferation, whose modification could indirectly participate in the overall antiviral effect.
Results: Working with primary T-lymphocytes and a T-cell line, we have first confirmed the differential potencies of the 12 IFN-alpha subtypes on HIV replication. The order of potency was similar in the two experimental settings, suggesting the induction of similar sets of antiviral genes. Using dedicated assays, we found that some subtypes act more potently on the early steps of HIV replication, while others target more efficiently the late steps.
Conclusion: Our findings support the notion that different genes with anti-HIV potential are induced by the different IFN subtypes. They allow us to identify those characterized by potent direct antiviral effect with minimal perturbation of cellular proliferation. Our study also prompts the search for new anti-HIV factors, targeting specific steps of virus replication.

176 LOOP 1 OF HUMAN APOBEC3C REGULATES THE ANTIVIRAL ACTIVITY AGAINST HIV-1
Ananda A. Jaguva Vasudevan1, Zeli Zhang1, Kannan Balakrishnan2, Christoph Gertzen1, Ignacio G. Bravo1, Gerald G. Schumann1, Dieter Häussinger1, Holger Gohlke1, Carsten Münk1
1Heinrich Heine University Hospital, Düsseldorf, Germany, 2Heinrich Heine University Düsseldorf, Düsseldorf, Germany, 3IRD, Montpellier, France, 4Paul Ehrlich Institut, Langen, Germany
Background: The APOBEC3 (A3) family of single stranded DNA deaminases defends hosts from Human immunodeficiency virus (HIV)-1 lacking viral infectivity factor (vif) (HIV-1Δvif). A3 catalyzes the dC to dU deamination in the viral DNA/genome, causing hypermutation that abrogates the virus. Human APOBEC3C (hA3C) is known as a strong restriction factor of Vif-deficient Simian immunodeficiency virus (SIVΔvif), but exhibits a weak inhibition against HIV-1Δvif. The reason for this specificity of A3C's antiviral function remains unknown.
Methods: Experiments were performed in cell culture using virus infections, expression of APOBEC3 proteins, biochemistry to study protein DNA interaction and enzyme activity, which were complemented with structural protein modelling and gene evolution studies.
Results: We report that residues in loop 1 of A3C govern their anti-HIV-1 activity to the level compared to that of A3G. We identified that exchanging WE to RK in loop 1 in A3C drastically enhances A3C's deamination activity. Molecular modeling and EMSA experiments demonstrated that A3C-WE-RK interacts with ssDNA substrate stronger than that of wild-type, which consecutively facilitates catalytic function. As the RK residues are naturally presenting in A3F at the equivalent position, we swapped them with WE and found a marginal decrease in HIV-1Δvif inhibition. The gain-of-function A3C variant also exhibited stronger LINE-1 restriction capacity but RK-WE exchange did not drastically disarm A3F.
Conclusion: Loop 1 of human A3C restriction factor was identified as a novel protein-nucleic acid domain that binds DNA and thereby drastically gains in antiviral activity against HIV-1.

177.7 IFITM3 REDUCES RETROVIRAL ENV FUNCTION AND IS COUNTERACTED BY GLYCOGAG
Yadvinder S. Ah1, Diborah Yimer1, Guoli Shi1, Salih Majdoul1, Kazi Rahman1, Alan Rein1, Alex A. Compton1
1National Cancer Institute, Frederick, MD, USA
Background: The interferon-induced transmembrane (IFITM) proteins are known for inhibiting the entry of a wide array of viruses into host cells. Furthermore, if IFITM3 is present in virus-producing cells, it reduces the fusion potential of HIV-1 viruses, but the mechanism is poorly understood.
Methods: To describe the antiviral mechanism of IFITM3 and to discover modes of viral evasion, we took advantage of a murine leukemia virus (MLV)-based pseudotyping system. By controlling IFITM3 and envelope (Env) levels in virus-producing cells, we found that IFITM3 potently inhibits MLV infectivity when Env levels are limiting.
Results: Loss of infectivity was associated with defective proteolytic processing of Env and lysosomal degradation of the Env precursor. Ecotropic and xenotropic variants of MLV Env, as well as HIV-1 Env and vesicular stomatitis virus glycoprotein (VSV-G), are sensitive to IFITM3, whereas Ebola glycoprotein is resistant, suggesting that IFITM3 selectively inactivates certain viral glycoproteins. Furthermore, endogenous IFITM3 in human and murine cells negatively regulates MLV Env abundance. However, the negative impact of IFITM3 on virion infectivity is greater than its impact on Env incorporation into virions, suggesting that IFITM3 also impairs Env function. Finally, we demonstrate that the presence of glycosylated Gag (glycoGag), the only accessory protein encoded by MLV, confers resistance to the IFITM3-mediated loss of infectivity. GlycoGag has previously been shown to counteract another antiviral transmembrane protein known as SERINC. Importantly, glycoGag rescues virus infectivity in the presence of IFITM3 without enhancing Env incorporation, indicating that glycoGag counteracts the cryptic function of IFITM3 which acts on Env function. This represents the first description of a viral auxiliary protein displaying the capacity to antagonize or enable viral evasion of IFITM3.
Conclusion: Overall, we demonstrate that IFITM3: (i) impairs virion infectivity by decreasing Env quantity and Env function, (ii) glycoGag confers virions with resistance to IFITM3 and, (iii) the antiviral activities of IFITM3 and SERINC3/5 may be linked. We are now testing whether the antiviral function of IFITM3 is maintained in SERINC5 knockout cells and whether other retroviral accessory proteins, such as HIV-1 Nef and EUV S2, also exhibit the capacity to counteract IFITM3.

178 SEQUENCE CHANGES CAUSING REV ACTIVITY DIFFERENCES IN HIV-1 PRIMARY ISOLATES

Patrick E. Jackson1, Jordan Holsey1, Godfrey Dzivhuhvo1, David Rekosh1, Marie-Louise Hammarskjöld1
1University of Virginia, Charlottesville, VA, USA

Background: The HIV-1 Rev-Rev Response Element (RRE) regulatory axis is required for the nucleocytoplasmic export of intron-containing viral mRNAs, an essential step in viral replication. A viral protein, Rev, binds to the RRE, an RNA structure found on incompletely spliced viral mRNAs, multimerizes, and recruits cellular factors to export the transcript. We previously described two Revs from primary isolates which display markedly different levels of activity. The high-activity, 9-G, and low-activity, 8-G, Revs differ by a total of 29 amino acids spanning across all domains including the bipartite oligomerization domain (OD), arginine rich motif (ARM), and nuclear export site (NES) (see Figure). Here, we define key residues causing differential activity.

Methods: Chimeric Revs were generated by exchanging regions between 8-G and 9-G sequences. Rev activity was determined using a recently described assay. Two constructs were created: an HIV vector modified to produce two fluorescent proteins in a Rev-dependent or Rev-independent fashion, and a murine stem cell virus vector producing different Revs and a third fluorescent marker. Both constructs were packaged and used to co-transduce lymphoid cells. Rev activity was determined by measuring relative intensity of the fluorescent markers.

Results: 9-G Rev displayed about 4-fold greater activity than 8-G Rev (p<0.001). Chimeric Revs created by exchanging the turn or link, the c-terminus, a block including the ARM and second OD, or the NES did not show changes in functional activity. However, exchanging a block including the n-terminus and the first OD with four amino acid changes in N-OD was sufficient to determine activity, such that a 9-G N-OD in an 8-G background was as active as unmodified 9-G Rev (p=0.55), and vice versa. A single variation at position 24 was tested as this has been shown to affect activity in NL4-3. The 9-G Q24R mutant had a 50% reduction in activity (p=0.001) but the 8-G R24Q mutant did not show increased activity, demonstrating an additional role for the other three amino acid changes.

Conclusion: The large difference in Rev-RRE activity between these primary isolates is due to four amino acid changes. Some of these residues have been implicated in Rev monomer stabilization while others may affect dimer-dimer interaction. Rev activity changes in another lentivirus are associated with clinical disease progression. Activity variation in HIV Rev may also play a role in clinical disease, such as in the establishment of latency.
compensatory mutations next to this codon or reverted this codon to WT. Computational analyses revealed a severe disruption in a RNA secondary structure of variants containing this mutated codon. Importantly, the disrupted RNA structure was restored when this codon was reverted to WT or new mutations were introduced in the proximity.

**Conclusion:** We show here that codon usage of the HIV-1 env strongly impact the replication capacity of the virus. Moreover, synonymous recoding of HIV-1 env gene has identified, in the gp41 coding region, an evolutionary conserved local RNA secondary structure that may be essential for virus viability. Disruption of this structure leads to severe reduction in mRNA translation and virus replication capacity.

**181 GENETIC IDENTITY AND BIOLOGICAL PHENOTYPE OF EARLY TRANSMITTED FOUNDER HIV-1 VIRUSES**

Ashokkumar Manickam1, Aanand Sonawanne1, Shambhu G. Aralaguppe2, Srikantin Tripathy1, Ujjwal Neogi1, Luke Elizabeth Hanna1

1National Institute for Research in TB, Chennai, India; 2Karolinska Institute, Stockholm, Sweden

**Background:** Among the repertoire of transmitted viral variants, only a small proportion of the viruses (transmitted founder (TF) viruses) are successful in establishing infection. It is widely believed that the early immune response to HIV infection is likely to be an essential factor in determining the clinical course of the disease. Thus, a better understanding of the characteristics of TF viruses and their role in early infection will throw light on the features that bestow these variants with the unique advantage of successfully establishing infection, and contribute significantly to the design and development of a protective HIV vaccine.

**Methods:** Patient-derived 250 envelope glycoprotein, gp120 were cloned in pMN-K7-Luc-IRESSs-NetDgp120 to obtain chimeric viruses. Samples were obtained from eight infants who had recently infected with HIV through mother-to-child transmission and two adults who acquired infection through the heterosexual route and were in the chronic stage of the infection. 65 out of 250 clones tested were found infectious and analyzed for genetic identity and biological phenotype of virus variants such as per-particle infectivity, response to neutralizing antibody (nAb), Maraviroc (MVC) and Interferon alpha (IFN-a).

**Results:** Based on the genotypic and phenotypic analysis, we identified 10 TF variants to neutralizing antibody (nAb), Maraviroc (MVC) and Interferon alpha (IFN-a). Reduced number of potential N-linked glycosylation sites and higher infectivity to neutralizing antibody (nAb) was observed for the TF viruses.

**Conclusion:** The negative strand of the HIV-1 genome encodes a highly hydrophobic antisensope protein (ASP) with ~30% efficiency. Altogether, these two assays demonstrate the presence of budding virions. Indeed, 324.6 captured HIV-1 particles with efficiency similar coefficient 76%, suggesting that ASP might be incorporated in the membrane of budding virions. These studies provide a new robust method for quantification of ASP associated CA during nuclear import using live-cell imaging.

**Methods:** We developed a method to directly label CA with green fluorescent protein (GFP) in infectious viral complexes, determined virus infectivity in HeLa and CEM-SS cells, characterized GFP-CA core incorporation and stability by sucrose gradient fractionation and Western blot, and quantified the core-associated CA during nuclear import using live-cell imaging.

**Results:** The GFP-CA labeling method is highly efficient and results in >96% of the virions being fluorescently labeled. Importantly, the GFP-CA labeling resulted in only a ~2-fold loss of virus infectivity in HeLa and CEM-SS T cells, indicating that GFP-CA-labeled viral complexes are infectious. Sucrose-gradient fractionation of virions indicated that GFP-CA was incorporated into viral cores and did not affect the core stability. Moreover, analysis of infected HeLa cells indicated that GFP-CA-labeled cores can efficiently associate with the nuclear envelope and enter the nucleus. We analyzed the amount of GFP-CA associated with viral cores docked at the nuclear envelope just before and after their translocation into the nucleus. No significant loss of GFP-CA was observed in the viral nuclear complexes compared to those at the nuclear envelope, indicating that uncoating does not occur during nuclear import.

**Conclusion:** These studies provide a new robust method for quantification of CA associated with viral complexes and will facilitate studies of HIV-1 post-entry events. Our results do not support the model that viral core uncoating occurs during nuclear import.

**182 THE HIV ANTISENSE PROTEIN ASP IS A TRANSMEMBRANE PROTEIN OF THE VIRAL ENVELOPE**

Zahra Gholizadeh1, Yvonne Affram1, Juan C. Zapata1, Hongshuo Song1, Rui Li1, Maria Iglesias-Ussel1, Krishana Ray1, Olga Latinnovic1

1University of Maryland, Baltimore, MD, USA

**Background:** The negative strand of the HIV-1 genome encodes a highly hydrophobic antisensope protein (ASP) with ~30% efficiency. Humoral and cellular immune responses against ASP show that it is expressed in vivo, but its role remains unknown. We studied ASP expression in chronically infected myeloid and lymphoid cell lines, its impact on viral replication, and ASP sequence evolution during natural infection.

**Methods:** Flow cytometry was performed on Millipore Guava flow and analyzed with FlowJo. Confocal microscopy was performed with Zeiss LSM 800 and analyzed with Zen Blue. Fluorescence Correlation Spectroscopy (FCS) was performed with ISS Q2 confocal microscope and ISS VistaVision. Longitudinal sequences were downloaded from the Los Alamos HIV database and were aligned using GeneCutter.

**Results:** Using a monoclonal antibody (324.6) against an epitope mapping between two transmembrane domains of ASP, we detected ASP in the nuclei of all infected cell lines. Confocal microscopy showed a polarized nuclear distribution of ASP, and accumulation in areas containing actively transcribed chromatin. PMA treatment caused translocation of ASP to the cytoplasm and cell membrane. Cell surface detection of ASP without membrane permeabilization shows extracellular exposure of the 324.6 epitope. We found that ASP and gp120 co-localize on the membrane of PMA-treated cells (Manders overlap coefficient 76%), suggesting that ASP might be incorporated in the membrane of budding virions. Indeed, 324.6 captured HIV-1 particles with efficiency similar to anti-gp120 VRC01. Also, FCS showed that 324.6 binds single virions in solution with ~30% efficiency. Altogether, these two assays demonstrate the presence of ASP on the surface of HIV-1 virions. ASP knock-out HIV-1 particles displayed a ~50% reduction in replication rate compared to wildtype virus. Longitudinal sequence analysis shows that during natural infection viruses with intact ASP preserve the ORF, and viruses with early stop codons in ASP undergo deletion or recombination events that restore the ORF.
Conclusion: ASP is a transmembrane protein found on the surface of productively infected cells, and on the envelope of mature HIV-1 virions. Knocking out ASP expression reduced viral replication. Preservation or restoration of functional ASP ORF during natural infection indicates that ASP may provide a selective advantage to HIV-1.

184 HIV ADAPTATION FOLLOWING VERTICAL TRANSMISSION
Jennifer Currenti1, Abha Chopra1, Mina John2, Shay Leary2, Elizabeth McKinnon1, Eric Alves3, Mark Pilkington3, Ramesh Ram3, Becker Law3, Francine Noel1, Simon Malail1, Joseph Conrad4, Spyros Kalams4, Silvana Gaudieri5
1University of Western Australia, Crawley, Australia, 2Murdoch University, Murdoch, Australia, 3Royal Perth Hospital, Perth, Australia, 4Vanderbilt University, Nashville, TN, USA, 5GHE5000, Port-au-Prince, Haiti

Background: Human immunodeficiency virus (HIV) can adapt to an individual's T cell immune response via genetic mutations that affect antigen recognition and impact disease outcome. In vaccine design, it is vital to understand this complex host-viral interaction including the mechanisms that underpin viral adaptations that subvert/alter the immune response. In this study, we assign the putative replicative cost and immune benefit of specific HIV adaptations in the unique setting of vertical HIV transmission. Single cell transcriptomics of antigen-specific T cells was also utilised to further delineate the dynamics of specific adaptations that may reflect a novel mechanism of adaptation. These results could be used to inform vaccine designs and cure strategies to combat the issue of immune adaptation.

Methods: Specifically, we utilised a deep sequencing approach to determine the HIV quasispecies in 26 mother/child transmission pairs where the potential for founder viruses to be pre-adapted is high. The resultant sequences and previously determined viral adaptations for specific host genotypes were used to generate adaptation scores for the transmitted virus. We used intra-cellular cytokine staining to assess specific antigen-specific T cell immune responses and single cell technologies to compare T cell receptor (TCR) repertoire and transcriptome data for a specific HIV epitope in which adaptation is associated with continued immune recognition.

Results: We showed that the dynamics of HIV adaptations following transmission provides insight into the in vivo replicative cost associated with specific adaptations with limited evidence for reversion of adaptations in non-selective environments suggestive of extensive compensatory networks. The antigen-specific T cell responses in the child overall suggested the immune response to the heavily pre-adapted HIV strains may focus on sub-dominant T cell epitopes as evidenced by de novo adaptation following transmission. Interestingly, there was evidence of cross-reactive T cells to the adapted and non-adapted form of an epitope at the TCR family level for the mother/child pair, but this did not extend to the α/β CDR3. Unsupervised clustering of scRNAseq data separated cells stimulated by the adapted and non-adapted forms, with common differentially expressed genes upregulated in both the mother and child.

Conclusion: Such targets will be important in the development of a therapeutic vaccine for individuals that have an established reservoir of adapted virus.

Methods: Eleven ART-treated people living with HIV (PLWH; median CD4 counts: 606 cells/ml; age: 57 years; time since infection: 242 months; aviremia under ART: 216 months) were hospitalized at the CRCHUM Phase I Clinic a Friday afternoon for 40 hours. Starting the next morning, blood was collected/processed every 4 hours for 24 hours before food intake. Polychromatic flow cytometry allowed cell counting/phenotypic analysis on fresh blood. Plasma levels of cortisol/melatonin and markers of mucosal barrier impairment (FABP2, LBP) were measured by ELISA. PBMC were frozen. HIV DNA/RNA were quantified by qPCR on sorted CD4+ T-cells.

Results: The memory naïve/regulatory T-cell counts showed daily variations, with maximal counts observed 20:00-4:00 (nadir 12:00). The expression of the HIV co-receptors CCR5/CXCR4, gut-homing molecules CCR6/integrin α7, and the immune checkpoint PD-1 on memory T-cells showed similar maximal expression 20:00-4:00. Pro-inflammatory non-classical monocyte counts were similarly high 8:00-00:00 but dropped significantly at 4:00. Plasma FABP2 levels peaked at 4:00, while LBP levels significantly dropped at 4:00. Daily variations in plasma cortisol (peak 4:00-8:00) and melatonin (peak 4:00) levels were observed. HIV-DNA reservoirs were stable. HIV-RNA levels in CD4 T-cells collected at night were higher compared to morning.

Conclusion: Daily variations in the blood T-cell/myeloid compartments, mucosal permeability markers, HIV transcription, and melatonin/cortisol levels, were observed in a cohort of aviremic ART-treated PLWH. These findings provide a rationale for studying the role of the circadian clock machinery in regulating residual HIV transcription under ART.

185 DAILY IMMUNOLOGICAL/VIROLOGICAL VARIATIONS IN AVIREMIC ART-TREATED HIV PARTICIPANTS
Debashree Chatterjee1, Tomas Raul Wiche Salinas1, Yuwei Zhang1, Delphine Planas1, Amelie Cattin8, Augustine Fert1, Etienne Moreira Gabriel1, Laurence Raymond Marchand1, Josee Girouard2, Nicolas Cermakian3, Daniel E. Kaufmann1, Jean-Pierre Routy1, Petronela Ancuta1
1Université de Montréal, Montreal, QC, Canada, 2McGill University Health Centre Research Institute, Montreal, QC, Canada, 3McGill University, Montreal, QC, Canada, 4McGill University Health Centre, Glen site, Montreal, QC, Canada, 5Centre de Recherche du CHUM, Montreal, QC, Canada

Background: Biological functions fluctuate in a circadian manner to align with environmental changes. In healthy uninfected individuals, variations in T-cell trafficking are documented in the blood, with nadir CD4 counts in the morning. Daily variations are also observed for plasma cortisol and melatonin, two regulators of immune functions. HIV infection is associated with profound alterations in CD4 T-cell homeostasis and chronic immune activation. HIV transcription is regulated by BMAL1, a circadian clock master regulator. However, daily variations in immunological/virological parameters during ART-treated HIV infection remain unknown.

Methods: We showed that the dynamics of HIV adaptations following transmission provides insight into the in vivo replicative cost associated with specific adaptations with limited evidence for reversion of adaptations in non-selective environments suggestive of extensive compensatory networks. The antigen-specific T cell responses in the child overall suggested the immune response to the heavily pre-adapted HIV strains may focus on sub-dominant T cell epitopes as evidenced by de novo adaptation following transmission. Interestingly, there was evidence of cross-reactive T cells to the adapted and non-adapted form of an epitope at the TCR family level for the mother/child pair, but this did not extend to the α/β CDR3. Unsupervised clustering of scRNAseq data separated cells stimulated by the adapted and non-adapted forms, with common differentially expressed genes upregulated in both the mother and child.

Conclusion: Such targets will be important in the development of a therapeutic vaccine for individuals that have an established reservoir of adapted virus.

Methods: Eleven ART-treated people living with HIV (PLWH; median CD4 counts: 606 cells/ml; age: 57 years; time since infection: 242 months; aviremia under ART: 216 months) were hospitalized at the CRCHUM Phase I Clinic a Friday afternoon for 40 hours. Starting the next morning, blood was collected/processed every 4 hours for 24 hours before food intake. Polychromatic flow cytometry allowed cell counting/phenotypic analysis on fresh blood. Plasma levels of cortisol/melatonin and markers of mucosal barrier impairment (FABP2, LBP) were measured by ELISA. PBMC were frozen. HIV DNA/RNA were quantified by qPCR on sorted CD4+ T-cells.

Results: The memory naïve/regulatory T-cell counts showed daily variations, with maximal counts observed 20:00-4:00 (nadir 12:00). The expression of the HIV co-receptors CCR5/CXCR4, gut-homing molecules CCR6/integrin α7, and the immune checkpoint PD-1 on memory T-cells showed similar maximal expression 20:00-4:00. Pro-inflammatory non-classical monocyte counts were similarly high 8:00-00:00 but dropped significantly at 4:00. Plasma FABP2 levels peaked at 4:00, while LBP levels significantly dropped at 4:00. Daily variations in plasma cortisol (peak 4:00-8:00) and melatonin (peak 4:00) levels were observed. HIV-DNA reservoirs were stable. HIV-RNA levels in CD4 T-cells collected at night were higher compared to morning.

Conclusion: Daily variations in the blood T-cell/myeloid compartments, mucosal permeability markers, HIV transcription, and melatonin/cortisol levels, were observed in a cohort of aviremic ART-treated PLWH. These findings provide a rationale for studying the role of the circadian clock machinery in regulating residual HIV transcription under ART.

186 WITHDRAWN

187 HIGH-THROUGHPUT SINGLE-MOLECULE SEQUENCING TO CHARACTERIZE AB-RESISTANT HIV/SHIV
Sung Hee Ko1, Divya Kilam1, Mangaiarkarasi Asokan1, Dylan Westfall2, Amy Ransier1, Sam Darko1, Daniel Douek2, Richard A. Koup1, John R. Mascola1, James Mullins1, El A. Buritz1
1NIH, Bethesda, MD, USA, 2University of Washington, Seattle, WA, USA

Background: Although HIV-specific broadly-neutralizing antibodies (bNab) can suppress viremia in ART-naive people, clinical use of bNabs is limited by neutralization-resistant viruses that may be too rare for detection before bNab infusion. Novel assays to track the dynamics of rare viruses after bNab infusion
may inform future bNAb treatment approaches, and may also allow a better understanding of HIV evolution in response to humoral immune pressure.

**Methods:** We optimized high-throughput, single-copy HIV env sequencing methods to study samples taken in bNAb infusion trials. Virion RNAs were reverse-transcribed with or without the addition of 8-nucleotide unique molecule identifiers (UMIs), followed by PCR. Pacific Biosciences single-molecule, real-time (SMRT) technology was used to obtain full-length env sequences. Sequence data were analyzed using standard and custom software tools. Errors arising in the sequencing process were quantified using data obtained from HIV molecular clones and HIV-infected patient plasma virus samples.

**Results:** Initial studies demonstrated concordance of non-UMI-based SMRT sequence data with Sanger sequence data obtained in parallel from three HIV-infected participants. A non-UMI-based approach was then used to study samples from SHIV-infected macaques treated with bNAb VIRG07-523LS. We observed pronounced changes in env sequences after VIRG07-523LS infusion, with predominance of entirely new env clades and a relative loss of species clustering with pre-infusion virus. Selection of amino acid variants at several positions associated with resistance to CD4-binding-site antibodies was observed. Using plasmid HIV clones, we found that most of the error in the sequencing process was generated during the PCR and sequencing steps. We found that the use of UMIs reduced errors to a rate consistent with error rate of the RNA reverse transcription step alone. The number of unique sequences obtained after UMI-based analysis was comparable to the input template number, and reconstruction experiments showed that the use of UMIs substantially eliminated sequencing errors.

**Conclusion:** High-throughput, single-copy HIV env sequencing can reveal genetic changes that occur within large virus populations after bNAb infusion. The incorporation of UMIs in full-length env sequencing greatly improves accuracy, providing a robust method to study dynamics of Ab-resistant HIV.

---

**188 ANALYSIS OF COMPARTMENTALIZATION OF HIV-1 IN BONE MARROW**

**Thuy T. Nguyen**, Jena Honeycutt, Christopher Nixon, Oksana Zakharchova, Christopher Evans, Joann D. Kuruc, Ben Murriel, Cynthia L. Gay, Douglas D. Richman, J. V. Garcia

1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2Karolinska Institute, Stockholm, Sweden, 3Laboratory of Experimental Medicine, Institute for Molecular Medicine, University of California San Diego, La Jolla, CA, USA

**Background:** HIV infection results in hematological disorders frequently observed in the late stages of disease. Little is known about the virus in the bone marrow (BM). We evaluated the compartmentalization of HIV in BM from participants not on antiretroviral therapy (ART).

**Methods:** Full HIV env was sequenced from BM and peripheral blood (PB) plasma using PacBio technologies. High-quality consensus sequences (FLEA software) were used to build phylogenetic trees (FastTree v2.1.11) and assessed for compartmentalization by distance-based tests a) genetic diversity with the average pairwise distance (APD), b) divergence using a test for panmixia, c) Wright’s measure of population subdivision (Fst), d) nearest-neighbor statistics and tree-based tests a) Simmonds Association Index, b) Slatkin-Maddison, c) correlation coefficients (MEGA7, HYPHY v 2.3.14). Viral tropism was determined at 2.5% of false-positive rate (https://coreceptor.geno2pheno.org/). Compartmentalization was established when results from phylogeny and compartmentalization analyses were concordant.

**Results:** Paired PB and BM samples were collected from 3 participants. Participant 1 was ART-naive. Participants 2 and 3 were ART-experienced but stopped treatment 12 and 2 months before sample collection, respectively. Participant 3 self-discontinued his ART multiple times. The medians [IQR] log10 CD4+ T cell count was 1.78 [2.65] in BM vs 2.94 [2.0] in PB.

**Conclusions:** We demonstrated viral compartmentalization and the presence of CCR5-tropic virus in the BM. HIV-1 compartmentalization has been previously shown in the central nervous system and correlated with neurocognitive impairment suggesting that compartmentalization in other tissues might have pathogenic consequences.
191 FOLICLE MORPHOLOGY AND HIV RNA DISTRIBUTION IN SPLEEN OF HIV+ and whether follicular dendritic cells (FDCs) are present and trap HIV particles. Germinal centers (GC), whether F harbor high concentrations of HIV RNA+ cells, (SLT) of these mice is lacking. We assessed whether HIV+ DRAGA mice develop high viral loads, HIV-specific antibodies, and B cell follicles. Knowledge of follicle

**Background:**

Importantly, high viral loads in platelets were correlated with patient clinical status and parameters over >3 years.

**Conclusion:** Altogether, our results reveal that platelets act as a neglected transient shelter for infectious HIV in the blood of HIV-infected cART-suppressed patient. Platelets carrying HIV establish an alternative pathway for HIV dissemination in immunodeficiency with familial or congenital or acquired disorders, for whom no efficient treatment is available yet. Furthermore, HIV contained in platelets can potentially fuel the tissue-macrophage reservoir we recently described in cART-suppressed patients (Ganor, Real et al., Nat Microbiol, 2019) in a process inhibited by the therapeutic anti-platelet agents.

**Methods:** Infectious HIV content in platelets was quantified by qPCR, FISH-flow, microscopy, and reporter cell assays using platelet-rich plasma (PRP) from 78 HIV-infected cART-treated adult patients. The capacity of platelet containing HIV to propagate infection was evaluated by culturing human primary macrophages with PRP with or without the platelet activation-blocker Abciximab (anti-integrin alpha(IIb)/beta(3) Fab). The presence of HIV in platelets was correlated with patient clinical status and parameters over >3 years.

**Results:** We demonstrate that platelets from HIV-infected patients shelter infectious HIV in vivo, despite successful viral suppression by the combined antiretroviral therapy (cART) and in strong correlation with low blood CD4+T-cell counts (<350cells/microL). Patient platelets carrying HIV can propagate infection to macrophages in vitro in a process prevented by blocking platelet-macrophage interaction with Abciximab. Comparative phylogenetic analyses of virus found in peripheral blood and platelet samples prior to and >1 year after cART initiation indicate that viruses contained in platelets do not originate from a latent reservoir established prior to therapy. Moreover, 88% of viremically suppressed patients sheltering HIV in platelets are immunological nonresponders and fail to restore a proper immune status over >1 year of cART with a >50-fold higher likelihood than patients without HIV in platelets (OR: 56, 95%CI: 4.3-719.2, p=0.002).

**Conclusion:** Overall, our results reveal that platelets act as a neglected transient shelter for infectious HIV in the blood of HIV-infected cART-suppressed patients. Platelets carrying HIV establish an alternative pathway for HIV dissemination in immunodeficiency with familial or congenital or acquired disorders, for whom no efficient treatment is available yet. Furthermore, HIV contained in platelets can potentially fuel the tissue-macrophage reservoir we recently described in cART-suppressed patients (Ganor, Real et al., Nat Microbiol, 2019) in a process inhibited by the therapeutic anti-platelet agents.

**Methods:** DRAGA (HLA-DR4.HLA-A2.Rag1KO.IL2RgKO.NOD) mice (n=17) were infused with HLA-matched human hematopoietic stem cells (hHSCs) from cord blood and 7 were infected with HIV at 4-10 months post-hHSC infusion. Snap frozen spleens were stained with antibodies to human CD20, CD4, IgG, Kii6, FDC, and mouse FDC and analyzed by microscopy. HIV RNA was detected by NASPace, %CD4 and %FDC by quantitative image analysis, plasma viral load by a modified Abbott RealTime HIV test and HIV-specific p24 and gp41 antibodies by ELISA. Non-parametric tests were used for analysis.

**Results:** No GC (IgD+Ki67+ regions) were seen in DRAGA spleen; IgD+ and Ki67+ cells were dispersed throughout F (CD20+ area). Human FDCs were not detected in any mice. Mouse FDCs were found throughout the F in contrast to normal mouse where FDCs localize in GC. %FDC+ area tended to be higher in HIV+ vs HIV- spleens (median 6% vs 2.9%; p=0.06). Many CD4+ cells localized within F (median, 70% in HIV- and 50% in HIV+; p=0.07). In 4 mice sacrificed at 4 months post HIV infection, more HIV RNA+ cells were located in F than extralymphoid regions (median, 128 ± 14 cells/mm²), but differences disappeared when adjusted for CD4. In these mice, first HIV-specific IgM and then IgG antibodies were detected in plasma over time. HIV RNA particles colocalized with FDC in these animals, but not in 3 acutely infected animals (<16 days).

**Conclusion:** DRAGA mice lack canonical GC in spleen, possibly because of incompatible signaling between mouse FDCs and human lymphocytes. Despite this, they produce HIV-specific and class-switched antibody. In chronic infection, HIV RNA+ cells are concentrated in F (likely due to high numbers of CD4+ cells rather than heightened permiscosity) and HIV RNA+ particles are associated with mouse FDC (likely bound via human antibody). Thus, the DRAGA mouse model recapitulates some key aspects of HIV disease in SLT. This knowledge is important in the use of the DRAGA mouse model in HIV immunopathogenesis studies.

192 PERMANENT CONTROL OF HIV-1 PATHOGENESIS IN EXCEPTIONAL ELITE CONTROLLERS

** Cristina Galvez, Concepcion Casado, Maria Pernas, Laura Taraccon-Diez, Carmen Rodriguez, Victor Sanchez-Merino, Mar Vera, Rebeca S De Fabio-Bernal, Alberto Merino-Mansilla, Jorge Del Romero, Ramon Lorenzo-Redondo, Ezequiel Ruiz-Mateos, Maria Salgado, Javier Martinez-Picado, Cecilio Lopez-Galindez**

**1 Instituto Cajal for AIDS Research, Badalona, Spain, 2Institute of Health Carlos III, Madrid, Spain, 3Institute of Biomedicine of Seville, Seville, Spain, 4Centro Sandoval, Madrid, Spain, 5Northwestern University, Chicago, IL, USA**

**Background:** Elite controllers (EC) represent a small subset of HIV-1-infected people able to spontaneously control viral replication. However, natural virological suppression and absence of immune dysfunction are not always long-term sustained. Exceptional EC (EEC) are HIV-1 subjects who maintain the EC characteristics without disease progression for more than 10 years.

**Methods:** We analyzed three EEC from the Sandoval Health Center in Madrid, diagnosed between 1988 and 1992, who without antiretroviral treatment have never shown signs of clinical progression. A comprehensive clinical, virological, and immunological study has been performed.

**Results:** The three EEC studied, diagnosed for more than 25 years, simultaneously exhibited previously described EC characteristics as ≥3 host protective alleles, low levels of total HIV-1 DNA (<20 copies/10⁶ CD4+ T-cells), absence of viral transcription, without evidence of replication-competent viruses (<0.025 Infectious Units Per Million). This was consistent with high levels of defective genomes, and strong cellular HIV-1-specific immune response with a high poly-functionality index (>0.50). Inflammation levels of EEC (measured as plasma levels of hsPCR, β2-microglobulin, D-Dimer, IL-6 and sCD163) were similar to HIV-1 negative donors. Remarkably, they showed 8-fold lower genetic diversity (<0.01 s/n) in env gene than transient EC, and an exceptional lack of viral evolution.

**Conclusion:** We postulate that these EEC should be considered unique cases of spontaneous functional HIV-1 cure. Low genetic diversity and lack of viral evolution distinguish these individuals from other EC. The combined non-functional HIV-1 reservoir, extremely low viral diversity and an HIV-1-specific immune response seems to be key to mimic these cases of spontaneous functional cure in future eradication strategies.
LACK OF DONOR-DERIVED SUPERINFECTION IN HIV+ TO HIV+ KIDNEY & LIVER TRANSPLANTATION

Tania S. Bonny1, Charles Kirby2, Craig Martens3, Christine Durand1, Niraj Desai1, Sander S. Florman3, Diane M. Brown1, Dorry Segev1, Aaron Tobian1, Andrew D. Redd1
1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2NIH, Bethesda, MD, USA, 3Mt Sinai School of Medicine, New York, NY, USA

Background: HIV+ to HIV+ organ transplantation offers HIV-infected patients a unique treatment option for end-stage kidney and liver disease. One of the primary concerns for these surgeries, however, is the risk of HIV superinfection (HIV-SI), which occurs when an HIV+ individual becomes infected with a new distinct HIV strain.

Methods: HIV+ to HIV+ kidney and liver transplant recipients were followed in a prospective observational study (NCT02602262). Peripheral blood mononuclear cells (PBMCs) were collected from recipients (14=kidney and 8=liver) and their respective donors (n=14) at the time of transplant (week 0) and followed post-transplant (spanning from weeks 13 to 104 post-transplant). Serum taken during a viremic episode from one recipient due to antiretroviral therapy (ART) non-adherence three years post transplant was also evaluated. HIV proviral DNA from PBMC and viral RNA from the serum sample were extracted, amplified, and sequenced using a site-directed next generation sequencing (NGS) assay for both the reverse transcriptase region of pol and the env coding region. Phylogenetic analyses of recipient HIV sequences from one or more time points post transplant and/or with their corresponding donor sequences revealed the donor and recipient pol and env sequences clustered separately, thereby indicating no evidence of HIV-SI in all patients examined (n=18). In the serum taken during the viremic episode (viral load=2,080,000), only recipient virus sequences could be detected (total amplicons analyzed: recipient gp41=154,852, pol=74369; donor gp41=89,304, pol=51,715). Phylogenetic analysis was performed for each biomarker using multiple linear regression analysis. Results were obtained for all biomarkers in 770,558 individuals across 3 multi-ethnic HIV+ cohorts.

Conclusion: This study monitoring recipient HIV sequences for up to two years post-transplant reveals no evidence of sustained donor-derived HIV-SI, even in one recipient following temporary ART non-adherence. These findings suggest that HIV-SI may not be a significant clinical concern in well-monitored ART.

HIV SUPERINFECTION AMONG MSM AND TGW IN SUB-SAHARAN AFRICA: HPTN 075

Philip J. Palumbo1, Yinfeng Zhang1, Mariya V. Sivay1, Xu Guo1, Vanessa Cummings1, Erica Hamilton1, Wairimu Chege1, Arthur Ogendo1, Noel Kayange1, Ravindra Pancheria1, Karen Dominguez1, Ying Qin Chen1, Theodorus Sandfort1, Susan H. Eshleman1, for the HPTN 075 Study Team
1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 3TH6, Durham, NC, USA, 4DAIDS, NIH, Bethesda, MD, USA, 5KEMRI-Centre for Global Health Research, Kisumu, Kenya, 6Malawi College of Medicine-Johns Hopkins University Research Project, Blantyre, Malawi, 7University of the Witwatersrand, Soweto, South Africa

Background: HIV superinfection (SI) occurs when an infected person is infected with a new, distinct HIV strain. High rates of HIV SI have been reported among men who have sex with men (MSM). The HIV Prevention Trials Network (HPTN) 075 study evaluated the feasibility of recruiting and retaining MSM in sub-Saharan Africa in clinical trials. We used next-generation sequencing (NGS) to assess SI among MSM and transgender women (TGW) enrolled in the HPTN 075 study.

Methods: HPTN 075 participants had quarterly visits with up to 12 months follow-up. The HPTN 075 study included 72 participants who were HIV-infected at enrollment (ENR+); 28 had a 12-month sample with a viral load >400 copies/mL. Twenty-one of 329 acquired HIV during the study (seroconverters); 17 (52.4%) had a sample from >30 days after the first HIV-positive visit (range: 38-316 days). HIV RNA was extracted using the ViroSeq HIV-1 Genotyping System. NGS was performed using the MiSeq System (env and pol regions). Phylogenetic analysis was used to identify and characterize SI events.

Results: Sequencing results were obtained for 27/28 ENR+ participants (one failed analysis) and for 11/17 seroconverters (6 failed analysis). Three cases of SI were identified: these included one (3.7%) of 27 ENR+ participants and two (18.2%) of 11 seroconverters. The incidence of SI among seroconverters (30.3/100 person-years [py]) was higher than among ENR+ participants (3.6/100 py; p=0.08) and was significantly higher than the rate of primary HIV infection in the HPTN 075 cohort (6.96/100 py; p=0.046). In one case, subtype C was present at enrollment and an inter-subtype recombinant strain was detected 369 days later (env subtype F2, pol subtype C); both strains were present at the follow-up visit. In the other two cases, the viral strain present at seroconversion shifted entirely to a new strain. In one case, the subtype C strain present at seroconversion was replaced with an inter-subtype recombinant strain 181 days later (env subtype A1, pol subtype C). In the other case, the subtype C strain present at seroconversion was replaced with a different inter-subtype C strain 184 days later.

Conclusion: This study revealed a high incidence of SI in a cohort of MSM and TGW from sub-Saharan Africa. The incidence of SI was higher than the incidence of primary infection, and involved new infection with inter-subtype recombinant HIV strains in two of three cases.

GENETIC DETERMINANTS OF hsCRP, D-DIMER, AND IL-6 IN 3 MULTIETHNIC HIV COHORTS

Brad Sherman1, Xiaojun Hu1, Kanal Singh2, Lillian Haine3, James Neaton3, Jens D. Lundgren4, H. Clifford Lane5, for the INSIGHT Study Group
1Frederick National Laboratory for Cancer Research, Frederick, MD, USA, 2NIAID, Bethesda, MD, USA, 3University of Minnesota, Minneapolis, MN, USA, 4Rigshospitalet, Copenhagen, Denmark

Background: Elevations in IL-6, D-dimer, and hsCRP, are associated with increased incidence of comorbid disease & mortality among HIV+ individuals (PLWH). Prior studies suggest a genetic basis for these biomarker elevations among certain ethnicities. We performed a genome-wide associated study (GWAS) using 3 HIV+ cohorts to identify single nucleotide polymorphisms (SNPs) associated with elevations in these 3 biomarkers in PLWH.

Methods: 7,192 participants across 3 established multi-ethnic HIV+ cohorts (START, SMART, ESPRIT) were studied. Baseline levels of hsCRP, D-dimer and IL-6 were measured & SNPs identified using a custom Affymetrix Axiom SNP array with 770,558 probes. Five ancestral ethnic groups were assigned (African, American, European, South and East Asian). Principal component (PC) analysis was used to account for population stratification, and single variant analysis was performed for each biomarker using multiple linear regression analysis.
models incorporating the first 10 PCs, gender, age, CD4 count, HIV viral load, BMI, smoking (missing in ESPRIT) and biomarker related traits (CVD, diabetes, Hepatitis B & C) at baseline as covariates for combined and ethnicity-specific cohort samples. To increase power, a fixed-effects meta-analysis was conducted with inverse variance weighting for all samples, and those from the 3 largest ethnic ancestry groups (African, n=1732, American, n=645, European, n=4675).

**Results:** Allele frequencies varied by genotyped ethnicity, but associations between each biomarker and allele frequency did not, therefore results from the cross-cohort meta-analyses are cited. 22 SNPs within 3 gene loci (CRP, HNF1A and APOE) reached genome-wide significance (GWAS, P < 5 x 10^-8) for hsCRP. 3 SNPs within 2 gene loci (coagulation factors F3 and F5) reached GWS for D-dimer; and 27 SNPs within 1 locus (IL6R) reached GWS for IL-6. (Fig. 1a,b,c). These loci have been previously described in non-HIV populations, mostly from studies of individuals of European descent.

**Conclusion:** Multiple SNPs were associated with elevations in hsCRP, D-dimer, and IL-6 in HIV+ individuals from 3 ethnically diverse cohorts. These findings support the hypothesis that host genetics partially contribute to chronic inflammation in this population and identify potential targets for intervention.

**Figures:** Manhattan plots of cross-cohort meta-analyses results for genetic associations with a. hsCRP, b. D-dimer, and c. IL-6. levels. loci are labelled by the closest gene. Each point represents one SNP and is colored by chromosomal location (x-axis) and log10(SNP) (y-axis). The dashed red line represents genome-wide significance (P = 5 x 10^-8) and SNPs meeting this threshold are colored red.

### 196 ABNORMAL IMMUNOMETABOLISM AND GENE ACCESSIBILITY IN ALVEOLAR MACROPHAGES IN HIV

**Sara C. Auld**1, Jolyn Fernandes1, Mariam Ahmed1, Neel R. Gandhi1, Samantha Yeligar1, Bashar Statkevich1

**Emory University, Atlanta, GA, USA**

**Background:** People with HIV, including those who are on antiretroviral therapy (ART) with an undetectable viral load, have an elevated risk of infectious and non-infectious pulmonary diseases, which persist even after immune reconstitution with ART. In the setting of HIV, alveolar macrophages serve as a viral reservoir and exhibit derangements in antioxidant balance and innate immune function. We sought to determine whether alterations in immunometabolism, which have been implicated in other pulmonary diseases, support the hypothesis that host genetics partially contribute to chronic inflammation in this population and identify potential targets for intervention.

**Methods:** We enrolled 10 participants for a research bronchoscopy study in Atlanta, GA. Five participants with HIV were matched by age, sex, race and smoking status with five participants without HIV. Participants had no major medical comorbidities and those with HIV were on ART for ≥ 18 months with a CD4 count ≥ 350 cells/μl and undetectable viral load. Bronchoalveolar lavage was performed and alveolar macrophages were washed and isolated before plating for analysis of mitochondrial bioenergetics using Agilent Seahorse XF96 and chromatin accessibility using ATAC-seq.

**Results:** Compared to participants without HIV, participants with well-controlled HIV demonstrated impaired alveolar macrophage oxygen consumption rates and mitochondrial bioenergetics across multiple domains, including basal and ATP-linked respiration (Figure). In parallel, ATAC-seq analysis identified 803 genes with significantly greater chromatin accessibility in participants with HIV than in those without HIV. Of those genes, 19 are known to have a critical impact on mitochondrial homeostasis, with functions ranging from mitochondrial RNA processing to free radical scavenging, including mitochondrial transcription termination factor-4 (MTERF4), superoxide dismutase 2 (SOD2), cathepsin B (CTSB), and Methionyl-TRNA Synthetase 2 (MARS2).

**Conclusion:** In people with HIV, we identified alterations in alveolar macrophage mitochondrial bioenergetics and chromatin accessibility for multiple genes associated with mitochondrial function. These alterations in alveolar macrophage function, in the face of ART and immune reconstitution, suggest that mitochondrial derangements may contribute to the elevated risk of pulmonary disease in people with HIV.

**197 IMPACT OF EARLY ART ON CD8 T CELLS IN MESENTERIC LYMPH NODES DURING SIV INFECTION**

**Alexis Yero**1, Omar Farnos2, Henintsoa Rabezanahary2, Ghita Benmadid-Laktout3, Julien Clain4, Gina Racine4, Jerome Estaquio5, Mohammad-Ali Jenabian6

1 Université du Québec à Montréal, Montréal, QC, Canada; 2 CHU de Québec-Université Laval, Quebec, QC, Canada

**Background:** CD8 T-cells play a pivotal role in clearance of HIV-infected cells, such that CD8 exhaustion contributes to their dysfunction and, consequently, viral persistence. Mesenteric lymph nodes (MLNs), which drain the large and small intestine, are critical sites for the induction and maintenance of gut mucosal immunity. However, the dynamics of CD8 T-cells in MLNs is less known due to the lack of accessibility to these tissues in human. Thus, we assessed CD8 T-cell dynamics in MLNs vs blood in SIV-infected rhesus macaques (RMs) following early antiretroviral therapy (ART) initiation.

**Methods:** 32 female Chinese RMs were enrolled including 25 intravenously SIVmac251-infected animals. Nine monkeys were treated at day 4 post-infection with a cocktail of antiretroviral drugs. Furthermore, 5 RMs after ART interruption (8-10 weeks post-ART initiation) and 4 untreated chronically infected were also studied. Peripheral blood and mechanically isolated cells from MLNs were analyzed by flow cytometry.

**Results:** Acute SIV infection was associated with decreased CD4/CD8 ratio and increased memory CD8 T-cell immune-activation (CD39/HLA-DR), exhaustion (PD1) and immunosuppressive CTLA-4 expression in both blood and MLNs which were all normalized by early ART initiation. Notably, MLN CD8 T-cells had consistently higher levels of immunosuppressive CTLA-4 and CD39 expression compared to matched blood samples in acute phase. Furthermore, acute SIV infection resulted in the expansion of FoxP3+ CD8 Tregs in both blood and MLNs, while early ART decreased CD8 Tregs only in blood. Helios+ thymic CD8 Tregs were also increased in both tissues in acute infection which were normalized by ART. Analyzing the trafficking of CD8 T-cells by assessing the expression of chemokine receptors, we found that the acute SIV infection resulted in decreased CCR6+ but not CCR3+ expressing CD8 T-cells in both MLNs and blood, which was recovered following early ART. ART interruption was associated with increased HLA-DR+ CD8 T-cells and decreased CCR6+ CD8 T-cells within MLNs.

**Conclusion:** Early ART initiation during acute infection normalized CD8 frequencies and their markers of immune activation and function in both MLNs and blood, but elevated levels of suppressive CD8 Tregs persists despite early ART in MLNs. This could be of great importance regarding immune surveillance of SIV persistence despite ART.

**198 ENHANCED MUCOSAL IMMUNITY AND SIV SUPPRESSION AFTER MESENCHYMAL STEM-CELL TRANSFER**

**Marina Guedes Weber**1, Lauren Hiraod, Abigail Mendel, Clarissa Rocha, Joy E. Walters1, Juan Arredondo2, Bipin Balan1, Sonny Elizalde1, Smita Iyer1, Alice Tarantal1, Amir Kol1, Satya Dandekar2

1 University of California Davis, Davis, CA, USA; 2 University of Palermo, Palermo, Italy
**Background:** Despite the presence of HIV-specific responses, HIV reservoirs persist and pose obstacles for cure. Early pathogenic effects of HIV infection in secondary lymphoid tissues including the gut contribute to ineffective anti-viral immunity, which are not repaired by ART. MSC secrete immuno-modulatory molecules and have beneficial effects in clinical studies. Using the SIV model of AIDS, we tested the hypothesis that systemic MSC administration will modulate antigen presentation and enhance anti-viral immunity at mucosal sites and lead to better viral suppression and increased immune recovery.

**Methods:** Rhesus macaques with chronic SIV infection were administered with MSC by adoptive transfer and compared with SIV-infected and SIV-negative animals without MSC treatment. Virologic, immunologic, transcriptomic, metabolomic, and microbiota analyses were performed. SIV RNA loads in plasma and tissue samples were determined by RT-PCR and RNAseq. Changes in the T and B cell subset distribution and activation was measured by flow cytometry. SIV-specific cellular and humoral (SIV Env antibodies by ELISA) responses were measured and changes in the gene expression (RNAseq) were performed.

**Results:** MSC-treated animals had decreased SIV viral loads that correlated with increased levels of activated B cells, SIV-specific CD8+ T cells and SIV Env-specific antibodies in peripheral blood compared to untreated controls. In the gut and lymph nodes, SIV RNA-positive cells were relocated to germinal centers and majority of them were PD1+. In contrast, SIV+ cells were dispersed in lamina propria. Transcriptional analysis revealed enhanced immune networks supporting anti-viral immunity. Increased prevalence of Lactobacillus and enhanced Linoleic acid metabolism was detected.

**Conclusion:** Collectively, our data support the hypothesis that MSCs enhance the virus-specific cellular and humoral immune responses by correlating SIV+ cells to the lymphoid follicles and improving antigen presentation and activating immune cell networks. Thus, MSC can be used for reviving or tooling mucosal immunity in HIV infection for viral clearance.

**199 IDENTIFYING CENTRAL COMPONENTS OF THE HIV-1+ PREGNANCY IMMUNE NETWORK**

**Alexander Cocker**<sup>1</sup>, Sarah Dermont<sup>1</sup>, Waheed Khan<sup>1</sup>, Nesrina Imami<sup>1</sup>, Mark Johnson<sup>1</sup>

<sup>1</sup>Imperial College London, London, UK, <sup>2</sup>Chelsea and Westminster Hospital, London, UK

**Background:** Successful pregnancy is reliant on the acceptance of a semi-allogeneic fetus, meaning the systemic regulation of the immune system to maintain tolerance is important. In complicated pregnancies changes in both frequency and activation of peripheral leukocytes have been found. HIV-1 positive women have increased incidence of preterm labour suggesting HIV-1 infection disrupts immunological interactions relevant to the regulation of immunological balance in pregnancy, though this has not been explored in depth. We aimed to identify central leukocyte populations in HIV-1 positive and negative pregnancy immune networks that were shared or discordant which may impact on systemic immune regulation.

**Methods:** Freshly isolated peripheral blood mononuclear cells from uncomplicated ART treated HIV-1 positive pregnant (PP, n=21) and HIV-1 negative pregnant (NP; n=36) women were analysed using flow cytometry and ELSpot assays. Natural killer (NK) cells, monocytes (Mo), dendritic cells (DC), and both classical and non-classical T-cell subsets were identified, while IFNγ, IL-2, IL-10 and granulyme B functional responses against influenza, Epstein-Barr and Cytomegalovirus were quantified. Cytometry acquisition was optimised for longitudinal comparison between samples. Non-parametric correlation networks of the resulting 500+ parameter group datasets were generated and analysed to determine network centrality measures and compare group networks using R packages. The top 50 Strength (number of significant associations) and Betweenness (times passed through in shortest paths between all other interacting parameters) centrality measures were compared.

**Results:** Mo PD-L1 expression was identified as highly central by both measures in both groups, suggesting this pathway of interaction shapes the pregnant immune system. CD40-L expression on CD4 and CD8 T-cell subsets and PD-L1 on CD8 T cells had high Strength scores in both groups, while NGK2A and CD11b expression on NK cells as well as CD56bright NK subset frequency had high Betweenness scores in NP and PP women. However, the PP group had more high Strength scoring T-cell parameters, predominantly CD38 expressing T cells, suggesting these activated T cells are more influential in the HIV-1 positive pregnancy network.

**Conclusion:** Our work highlights shared immune components that may be key regulators of pregnancy tolerance and has identified parameters uniquely impacted by HIV-1 that may negatively influence the pregnancy immune network.

**200 CXCR5+ NK CELLS IN THE LYMPH NODE ARE ASSOCIATED WITH CONTROL OF SHIV INFECTION**

Sheikh A. Rahman<sup>1</sup>, James M. Billingsley<sup>2</sup>, Chris C. Ibegbu<sup>1</sup>, Sadia J. Rahman<sup>1</sup>, R. Paul Johnson<sup>1</sup>, Steven E. Bosinger<sup>1</sup>, Rama R. Amar<sup>1</sup>, Vijayakumar Velu<sup>1</sup>,<sup>2</sup>

<sup>1</sup>Yerkes National Primate Research Center, Atlanta, GA, USA, 2Emory University, Atlanta, GA, USA

**Background:** Natural killer cells (NKs) play an essential role in antiviral immunity; however, their function in lymph nodes (LN) during chronic HIV/SIV infection is not fully elucidated. LN follicles constitute major reservoir sites for HIV/SIV persistence. Cure strategies could benefit from the characterization of CXCR5+ NK cells able to access/eliminate HIV reservoirs.

**Methods:** Here we studied the phenotype, distribution and function of CXCR5+ NK cells in the LN of SHIV-naive and chronic SHIV1157ipd3HIV-infected (>14 weeks PI) rhesus macaques (RM) and their association with plasma viral RNA levels. Flow cytometry was used for phenotypic analysis, function (IFN-γ, TNF-a, CD107a) was assessed by intracellular staining and in vitro target cell killing experiments. Immunohistochemistry was performed to identify the location of NK cells in B cell follicles.

**Results:** We found that prior to infection, a significant proportion of NK cells (~15%) expressed CXCR5. Following infection, the frequency of CXCR5+ NK cells was significantly higher in chronic SHIV-infected RM. Phenotypically CXCR5+ NK cells express higher levels of FcγRIIa and FcγRIIIa compared to CXCR5- NK cells, which might be important for ADCC function. The CXCR5+ NK cells demonstrated enhanced polyfunctionality with higher production of IFN-γ, TNF-a and CD107a when stimulated with mitogen. Immunohistochemistry analysis confirmed the presence of NK cells in LN follicles. Transcriptional profiling (RNA-seq) of sorted CXCR5+ and CXCR5- NK cells from SHIV-infected RM revealed that CXCR5+ NK cells are activated and express increased levels of cytolytic markers (perforin, granulyme B, granulysin and CD107a), suggesting that these cells have a higher capacity to kill. Gene set enrichment analysis of CXCR5+ cells additionally showed elevated transcripts associated with cell activation, TNF-α, interferon signaling and apoptosis. Importantly, the frequency of CXCR5+ NK cells correlated inversely with plasma SHIV viral RNA levels and exhibited a significant negative association with germinal center Tfh cells.

**Conclusion:** Chronic SHIV infection is characterized by accumulation of NK cells within LN follicles and suggest that CXCR5+ NK cells could play an important role in controlling SHIV infection. Cure strategies should focus on inducing these cells for sustained HIV remission.

**201LB THE ROLE OF CD101 IN HIV/SIV PATHOGENESIS AND MAINTENANCE OF THE VIRAL RESERVOIR**

Timothy Hoang<sup>1</sup>, Zachary Strongin<sup>2</sup>, Gregory K. Tharp<sup>1</sup>, Justin L. Harper<sup>1</sup>, Zhan Zhang<sup>1</sup>, Steven E. Bosinger<sup>1</sup>, Deanna Kulp<sup>1</sup>, Mirko Paiardini<sup>1</sup>

<sup>1</sup>Emory University, Atlanta, GA, USA

**Background:** HIV infection results in depletion of CD4+ T cells, induction of systemic inflammation, and exhaustion of antiviral responses, all features that are not normalized during ART and implicated in promotion of viral persistence. CD101 is a surface glycoprotein that has been linked to highly suppressive TRegs and defining “terminally exhausted” CD8+ T cells during chronic infection. Here, we sought to understand implications of CD101 expression on CD4+ T cells during SIV infection and mechanisms leading to SIV persistence.

**Methods:** 28 rhesus macaques (RMs) were infected with SIVMac239 and started ART 42 d.p.i. Samples were collected longitudinally for flow cytometric and RNAseq analysis. Latency and Reversion Assay (LARA) was used for latency induction and integrated HIV was measured by qPCR.

**Results:** At 14 d.p.i. CD101+ CD4+ T cells were preferentially depleted, as compared to other CD4+ memory subsets (p<0.001). CD101+ CD4+ T cells remained significantly lower than CD101- CD4+ T cells in blood and tissues up to 42 d.p.i. (p<0.001). Reconstitution of CD101+ CD4+ T cells was delayed compared to CD101- CD4+ T cells after ART. In SIV+ RMs on ART for >1 year, PD-1 and CTLA-4 were upregulated in CD101+ as compared to CD101- CD4+ T cells (p=0.0156 and p=0.0078, respectively). We also detected higher levels of cell cycling (p=0.0078) in the CD101+ CD4+ T cells, suggesting that...
these cells may persist through homeostatic proliferation and replenish the reservoir via clonal expansion. RNAseq showed that CD101+ CD4+ T cells were transcriptionally distinct and in a more terminally differentiated state, aligning with reports stating that CD101+ PD-1+ CD8+ T cells were "terminally differentiated." Using LARCA, we detected similar levels of integrated HIV-DNA in CD101+ and CD101- CD4+ T cells. Interestingly, and consistent with their higher co-expression of PD-1/CTLA-4 and transcriptional profile, p24 gag expression within CD101+ CD4+ T cells was significantly lower at 7 dpi., suggesting that HIV-infected CD101+ CD4+ T cells progress to a latent state more readily.

**Conclusion:** Altogether, these data identify CD101+ CD4+ T cells as a cell subset that (i) is preferentially depleted during early SIV infection, (ii) leads to the establishment of immune exhaustion, and (iii) preferentially enter latency. As such, CD101+ CD4+ T cells could be vital contributors to the HIV reservoir and targets of future therapeutic approaches.

**202 IMMUNE CONTROL OF LIVE ATTENUATED-HIV INFECTION AND DISEASE IN BLT5-HUMANIZED MICE**

Shivkumar Biradar1, Moses Bityli2, Robbie B. Mailliard1, for the Bityli Lab Group

**Background:** We recently demonstrated the robust development of human lymphoid and myeloid cells in immunodeficient mice, achieved through co-transplantation of bone marrow-derived human hematopoietic stem cells (hHSCs), liver, thymus, and spleen (BLTs). Importantly, unlike other earlier mouse models, BLTS-humanized (hBLTS) mice exhibit lymphoid tissue with proper development of B cell follicles, a major site of the latent HIV reservoir. Therefore, we hypothesize that hBLTS mice with complete human immune cell repertoire and lymphoid tissue architecture will provide an improved model for studying HIV immunity.

**Methods:** To generate hBLTS mice, NSG mice were engrafted with autologous hHSCs via intravascular injection, and with human hematopoietic lymphoid tissues (fetal thymus, liver and spleen) via kidney capsule transplant. Reconstitution and characterization of human immune cells was determined through flow cytometry. Wild type and Nef-deleted HIV strains were used to infect the hBLTS mice. Blood samples were analyzed by flow cytometry and qRT-PCR to measure impact on the human immune cell populations and HIV viral load, respectively. Lymphoid tissue pathology was examined via immunohistochemistry.

**Results:** We demonstrated successful reconstitution of functionally active T Cells (αβ and γδ T cells), NK cells, and antibody-secreting B cells in hBLTS mice, along with the formation B cell follicles within lymphatic tissues. We were able to generate differentially matured and functionally polarized human dendritic cells from bone marrow of hBLTS mice. We found that the BLTS model also could successfully support HIV infection that could be controlled by antiretroviral therapy. Infection of hBLTS mice with live-attenuated (Nef-deleted) HIV resulted in the establishment of long-term aviremia (below detection limit). Moreover, CD4+ T cell counts were maintained in Nef-deleted HIV infected mice at levels similar to uninfected hBLTS mice. Viral control in these mice was concurrent with induction of human antiviral immune responses and reduced lymphoid tissue pathology compared to that found in hBLTS mice infected with wild type HIV.

**Conclusion:** The immune system of the hBLTS mouse effectively recapitulates that of the human immune system, and therefore provides a robust model for investigating human immunity to HIV. Furthermore, this model provides a means to evaluate novel HIV immunotherapeutic approaches in vivo.

**203 FLTL3-MEDIATED EXPRESSION OF PLASMACYTOID DCS CONTROLS HIV INFECTION IN HUMANIZED MICE**

Tram Pham1, Oussama Meziane1, Mohammad Alam Miah1, Olga Volodina2, Chloé Colas1, Kathie Bélanger1, Yuan Li1, Frédéric Dallaire1, Tibor Kele1, Jean V. Guimond1, Sylvie Lesage3, Cheolho Cheong1, Elie Haddad4, Eric A. Cohen5, Brianna Scott2, Christy M. Anderson2, Sara Gianella4, Masato Nakazawa2, Gemma Caballero2, Laura Layman1, Sara Gianella2, Laura Layman1, M. Nakazawa2, G. Caballero2, L. Layman1, S. Gianella2

**Background:** We previously showed that detectable Cytomegalovirus (CMV) DNA was associated with increased activation of CD4+ T cells and with a slower decay of HIV DNA in people starting antiretroviral therapy (ART) during early HIV infection. Here, we investigate changes in HIV DNA molecular diversity associated with CMV DNA in the setting of early ART.

**Methods:** We obtained at least 3 longitudinal peripheral blood mononuclear cell (PBMC) samples from 37 individuals starting ART during early HIV infection and who reached virologic suppression (<50c/ml, no viral blips) within a median of 3 months of the estimated date of HIV infection (IQR: 2.6-6.8). In each PBMC sample (N=120), levels of HIV, CMV and Epstein-Barr Virus (EBV) DNA were measured by digital droplet (dd)PCR. Deep Sequencing of HIV DNA C2-V3 env was performed using the MiSeq Illumina platform. Cleaned mapped reads were obtained after iterative read mapping and quality filtering using an in-house pipeline. The HIV DNA molecular diversity (Shannon Entropy) was computed for 99 samples. A linear mixed-effect regression model was used to analyze the effect of detectable CMV or EBV DNA on HIV DNA molecular diversity and its change from ART initiation (baseline) to the end of follow-up (approximately 30 months).

**Results:** Participants had a median of 515 (IQR: 363-732) CD4+ T cells/ul at baseline and were followed for a median of 29 months (IQR: 18-39) while on suppressive ART. Overall, 19 (51%) participants had detectable CMV DNA during follow up, while 18 did not. Entropy levels at the time of ART initiation did not differ by CMV status (p=0.2). However, entropy levels were more likely to increase during ART for participants who exhibited CMV shedding and to decrease for those who did not (see Figure), and this change in entropy was significantly different for the 2 groups (interaction p<0.05). Such a relationship was not found for EBV (EBV by time interaction; p=0.66).

**Conclusion:** In addition to slower HIV DNA decay and increased CD4+ T cell activation, we now observe increasing HIV DNA molecular diversity during early ART in the setting of subclinical CMV replication. Taken together, these observations suggest that subclinical CMV DNA shedding might affect HIV infection.
persistence by promoting HIV replication at low levels during early ART. Future studies with anti-CMV therapeutics could help determine the underlying mechanisms and if causal associations exist.

205 GUT MICROBIOTA FACILITATES HIV ACQUISITION IN THE GUT
Angela Wahl1, Cara Richardson1, Wenbo Yao1, Allison Rogala1, R. Balfour Sartor1, J. V. Garcia1
1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Resident microbiota protect the gut from pathogenic organisms. However, gut microbiota can facilitate the transmission and pathogenesis of viruses. The gut is a significant site of HIV acquisition in infants (via breastfeeding) and adults (via receptive anal intercourse) and a primary site of HIV replication and CD4+ T cell depletion. The effect of gut microbiota on HIV acquisition risk, pathogenesis, and disease progression is unknown.

Methods: It is not possible to perform the direct experimentation that is needed to establish gut microbiota’s role in HIV acquisition and infection in humans. Bone marrow/liver/thymus (BLT) humanized mice have been extensively utilized to study HIV acquisition, pathogenesis and prevention strategies in vivo. To examine the role of gut microbiota in HIV acquisition risk, we constructed germ-free BLT mice and BLT mice colonized with gut microbiota. First, we rederived the immunodeficient NSG mouse strain germ-free. Next, we constructed germ-free BLT mice and BLT mice colonized with gut microbiota. The germ-free status of mice was monitored by the National Gnotobiotic Rodent Resource Center with Gram stain, culture and PCR. BLT mice colonized with gut microbiome were also constructed. To directly evaluate the effect of gut microbiota on HIV acquisition risk after oral exposure, germ-free BLT mice (n=8) and colonized BLT mice (n=10) were exposed to HIV via oral gavage. HIV-RNA levels were monitored longitudinally in the peripheral blood plasma of mice weekly by real-time PCR analysis. At necropsy, we also measured HIV-DNA levels in tissues.

Results: Following a single oral HIV exposure, HIV-RNA was detected in the plasma of 4/10 colonized BLT mice. Remarkably, no HIV-RNA was detected in the plasma of germ-free BLT mice. Given that breastfed infants are repeatedly exposed to HIV, we administered a second dose of HIV to BLT mice with a negative HIV viral load. Following a second HIV exposure, 5/6 colonized BLT mice became positive for HIV. In sharp contrast, only 2/8 germ-free BLT mice became positive for HIV. Overall, gut microbiota significantly increased oral HIV acquisition of colonized BLT mice (9/10 vs 2/8, p=0.01).

Conclusion: To our knowledge, these results provide the first direct evidence that gut microbiota facilitate HIV acquisition.

206 KYNURENINE PATHWAY ACTIVITY REMAINS ABNORMAL DESPITE VERY EARLY ART INITIATION
Samuel R. Schnittman1, Amelia Deitchman1, Gabriele B. Beck-Engeser1, HaeLee Ahn1, Vanessa A. York1, Heather Hartig1, Rebecca Hohl1, Frederick M. Hecht1, Jeffrey N. Martin1, Steven G. Deeks1, Francesca Aveveka1, Peter W. Hunt1
1University of California San Francisco, San Francisco, CA, USA

Background: Despite early ART initiation, ART-suppressed people living with HIV (PLWH) remain at higher risk for tuberculosis (TB) and infection-related malignancies than the general population. The immunologic pathways that remain abnormal in this setting—and may plausibly drive these complications—are unclear.

Methods: PLWH maintaining ART-mediated viral suppression >1 year and HIV-negative controls, all CMV+ and enriched for HIV risk factors, were sampled from a study of influenza vaccine response. PLWH were stratified by timing of ART initiation (within 6 months of HIV infection [early ART] vs. later), and among later initiators, by nadir CD4 count (>350, 200-350, <200 cells/mm3). Plasma kynurenine/tryptophan (KT) ratio (by LC-MS) and both sTNFR2 and sCD14 (by ELISA) were assessed before vaccination. Between-group differences adjusted for age, sex, # lifetime male sexual partners, and ART type were assessed by linear regression, transforming biomarkers as necessary.

Results: A total of 164 PLWH and 41 HIV-negative participants were enrolled. Median age was 54 years and 91% were men. Of HIV-negatives, 56% were MSM, 41% had >100 lifetime male sexual partners, and 15% had distinct IDU. Of the PLWH, 34 were early ART initiators and the remainder had a range of nadir CD4 counts: >350 (n=32), 200-350 (n=43), and <200 cells/mm3 (n=55). Median duration of viral suppression was 8 years (IQR 7-11 years). Compared to HIV-negatives, PLWH with later ART initiation had higher KT ratio, sCD14, and sTNFR2 after adjustment for age and sex, but only KT ratio and sCD14 remained abnormal in the early ART initiators (see figure). Both efavirenz use (P<0.001) and # lifetime male sex partners (P=0.03) were associated with higher sCD14, but not KT ratio or sTNFR2. After additional adjustment for EFV use and # male sex partners, early ART initiators continued to have a mean 22% higher KT ratio (P=0.001), but not sCD14 (+7%, P=0.11), than HIV-negative controls.

Conclusion: While PLWH initiating ART in the first 6 months of infection appear to restore near-normal levels of many immune activation markers that predict morbidity and mortality, the kynurenine pathway of tryptophan catabolism—a biomarker of indoleamine 2,3-dioxygenase-1 (IDO) activity—remains abnormal. As IDO confers adaptive immune defects and contributes to TB and cancer pathogenesis in animal models, the persistent induction of this pathway in PLWH with early ART initiation may plausibly contribute to persistent risks of these complications in this setting.

207 TREHALOSE INHIBITS HIV IN CD4+ LYMPHOCYTES AND MACROPHAGES BY 2 DISTINCT MECHANISMS
Pratima Rawat1, Simson Hon1, Carmen Teodorof-Diedrich1, Stephen A. Spector1
1University of California San Diego, La Jolla, CA, USA, 2University of California Davis, Davis, CA, USA

Background: We previously showed that induction of autophagy through the inhibition of mTOR inhibits HIV replication. However, inhibition of mTOR may have cellular effects other than autophagy that could affect HIV infection. Here, we examined trehalose, a naturally occurring glucose mTOR-independent inducer of autophagy, to determine the effects on HIV replication.

Methods: Human macrophages (MO) and CD4+ T lymphocytes (T-cells) treated with trehalose with or without HIV infection were assessed for cytotoxicity by LDH release assay and viral replication by p24 ELISA. Autophagy proteins were assessed by immunoblotting, qRT-PCR and fluorescence microscopy combined with assessment of LC3B lipidation. Viral entry was measured by intracellular p24. Data were analyzed using the Student paired T-test and one-way Anova.

Results: Pretreatment of T-cells and MO with trehalose resulted in a dose dependent inhibition of HIV reaching ~90% inhibition at 100mM in both cell types without cytotoxicity. Trehalose induced autophagic flux in T-cells and MO as indicated by increased LC3B lipidation and LC3B–II accumulation following treatment with the autophagic flux inhibitor bafilomycin. Inhibition of HIV was at least partially dependent on induction of autophagy since knockdown of ATG5 by siRNA significantly increased p24 release by 42% and 47% in trehalose-treated HIV-infected T-cells and MO. Surprisingly, trehalose also decreased HIV entry into T-cells and MO in a dose dependent manner reaching...
Background: Foreskin cells were allowed to migrate out of isolated epidermal sheets and qRT-PCR. AMPs alpha defensin 1, beta defensin (bDEF) 1, bDEF2, bDEF4, Lysozyme C, PLA2G2a, and Reg3g were assayed by ELISA.

Methods: We isolated fecal MVs from 12 healthy and 12 SIV-infected rhesus macaques (RM, Macaca mulatta) and co-cultured these MVs with isolates of SIV-infected RM. Among AMPs, bDEF1 showed a significant downregulation among MV miRNA profiles differ significantly after SIV infection. Ninety-three of the precise mechanisms by which fecal MVs differentially regulate the behavior of translocating bacteria will inform the development of therapeutics aimed at impeding microbial translocation.

Results: hSIV env gag p24 expression. CD4 downregulation expressed 2% mCherry, 13% p24 and absolute CD4 downregulation. These data demonstrate that the naturally occurring sugar, trehalose, at doses safely achieved in humans inhibits HIV through two mechanisms: 1) decreased entry through the down-regulation of CCR5 in T-cells, and a 4.6-fold decrease in CD4 expression (p=0.002) but no significant change in CCR5 expression in MO.

Conclusion: These data demonstrate that the naturally occurring sugar, trehalose, at doses safely achieved in humans inhibits HIV through two mechanisms: 1) decreased entry through the down-regulation of CCR5 in T-cells, and decreased CD4 expression in both T-cells and MO; and 2) degradation of intracellular HIV through the induction of mTOR independent autophagy. These findings demonstrate that cellular mechanisms can be modulated to inhibit HIV entry and intracellular replication using a naturally occurring, non-toxic sugar. Trehalose may be a useful adjunct in the maintenance of patients who achieve an HIV functional cure.

208 FECAL MICROVESICLES UNIQUELY INFUENCE TRANSLOCATING BACTERIA AFTER SIV INFECTION
Alexander Ortiz1, Jacob K. Flynn1, Jason Brenchley1
NIH, Bethesda, MD, USA

Background: Microbial translocation contributes to persistent inflammation in both treated and untreated HIV infection. Although translocation is due in part to a disintegration of the intestinal epithelial barrier, there is a bias towards the translocation of Proteobacteria. In murine models, epithelial-derived microvesicles (MVs) have been shown to influence bacterial gene expression and growth. We hypothesize that intestinal epithelial MVs biologically differ after HIV infection, which may contribute to biased translocation.

Methods: We isolated fecal MVs from 12 healthy and 12 SIV-infected rhesus macaques (RM, Macaca mulatta) and co-cultured these MVs with isolates of translocated bacterial species. Viable bacteria that had translocated were isolated from mesenteric lymph nodes, livers, and spleens obtained from end-stage, SW-infected RM, cultured under aerobic and anaerobic conditions, and identified by MALDI-TOF or 16S rDNA sequencing. Bacterial growth was kinetically assayed by spectrophotometer. MV miRNA profiles were assessed by human miRNA Array cards and qRT-PCR. AMPS alpha defensin 1, beta defensin (bDEF) 1, bDEF2, bDEF4, Lysozyme C, PLA2G2a, and Reg3g were assayed by ELISA.

Results: Utilizing a non-human primate model of AIDS, we observed that MV miRNA profiles differ significantly after SIV infection. Ninety-three of 100 differentially expressed miRNAs displayed upregulated expression, with miR-425 and -484 showing significant upregulation in MVs derived from SIV-infected RM. Among AMPS, bDEF1 showed a significant downregulation among MVs from SIV-infected RM. Several bacterial species showed dose-dependent growth sensitivity upon MV co-culture. Notably, Lactobacillus salivarius showed significantly accelerated growth when co-cultured with MVs derived from SIV-infected animals while Klebsiella pneumoniae displayed stunted growth. These data demonstrate that the naturally occurring sugar, trehalose, at doses safely achieved in humans inhibits HIV through two mechanisms: 1) decreased entry through the down-regulation of CCR5 in T-cells, and a 4.6-fold decrease in CD4 expression (p=0.002) but no significant change in CCR5 expression in MO.

Conclusion: These data demonstrate that the naturally occurring sugar, trehalose, at doses safely achieved in humans inhibits HIV through two mechanisms: 1) decreased entry through the down-regulation of CCR5 in T-cells, and decreased CD4 expression in both T-cells and MO; and 2) degradation of intracellular HIV through the induction of mTOR independent autophagy. These findings demonstrate that cellular mechanisms can be modulated to inhibit HIV entry and intracellular replication using a naturally occurring, non-toxic sugar. Trehalose may be a useful adjunct in the maintenance of patients who achieve an HIV functional cure.

209 CHARACTERISATION OF POTENTIAL HIV TARGET MYELOID CELLS IN FORESKIN EPITHELIA
Bokani Nleya1, Yamkela Qumulo1, Nobomi Donsa1, Christen Da Costa1, Kyle O’hagan1, Clive M. Gray1, Nyaradzo T. Chigorimbo-Tsikiwa1
1University of Cape Town, Cape Town, South Africa

Background: The human foreskin is an immunologically active tissue containing both lymphoid and myeloid cells. The foreskin has been shown to play an important role in HIV infection as its complete removal during MMC has been shown to reduce the risk of HIV acquisition by up to 60%. CD4+/CCR5+ Langerhan’s cells (LCs) and macrophages are known to be resident in both inner and outer foreskin tissue and are potential HIV target cells. To better understand whether foreskin-derived myeloid cells are promiscuous to HIV-1, we exposed foreskin macrophages from the inner and outer foreskins were identified using a multiparameter flow panel: CD207, CD1a, CD80/86, HLA-DR, CD11c, CD209, CD206, CD14, CCR5, CD169 and zombie (live/dead). Ex-vivo HIV challenge assays were set up using migratory cells and HIV infection was detected using reporter genes, GFP and mCherry as well as p24 antibody.

Results: Tissue resident LCs and macrophages were isolated. LCs (4.8 x 105) were more abundant than macrophages (9.4 x 105), with averages of 5% and 0.009% of the entire cell population respectively. Both migrating CD11c+ and CD206+ LCs and CD209+ and CD163+ macrophages expressed higher levels of CD80/86 (p=0.006) and HLA-DR (p=0.02) relative to cells that remained in the tissue co-expressing these surface antigens (p=0.015). HIV exposed CD11c+ LCs and macrophages expressed 2% mCherry, 13% p24 and absolute CD4 downregulation.

Conclusion: LCs and macrophages that migrate from foreskin epidermal sheets express high levels of maturation and activation markers CD40, CD80/86 and HLA-DR, they are therefore activated and susceptible to HIV infection as evidenced by reporter gene (mCherry) and p24 expression. CD4 downregulation also indicates HIV infection.
**IMPACT OF PENILE CIRCUMCISION ON HIV SUSCEPTIBILITY MARKERS IN THE URETHRA**

Ronald M. Galiwango, Daniel Park, Sanja Huibner, Abigail Onos, Malika Azz2, Kelsey Roach, Aggrey Anok1, James Ninamute, Yahaya Isabirie1, Deo Male1, Godfrey Kigozi1, Aaron Tobian1, Jessica L. Progd1, Cindy M. Lia1, Rupert Kaul1, for the Rakai Immuno Biomarker Research Group 1University of Toronto, Toronto, ON, Canada, 2George Washington University, Washington, DC, USA, 3Rakai Health Sciences Program, Kalisizo, Uganda, 4Johns Hopkins University School of Medicine, Baltimore, MD, USA, 5Western University, London, ON, Canada

**Background:** Penile circumcision (PC) reduces HIV risk by approximately 60%. This may relate to the stochastic reduction in susceptible foreskin tissue and/or alterations in the coronal sulcus (CS) microbiome and associated inflammatory cytokines/chemokines, particularly levels of IL-8. However, it is also possible that circumcision mediates protection through effects on the urethral microbiome and immune milieu. Therefore we performed a prospective analysis of the impact of PC on the microbiome and immune milieu of both the urethra and CS.

**Methods:** HIV-negative, STI symptom-free adult Ugandan men (n=51) undergoing elective PC were enrolled. Swabs were collected from the urethra and either the inner foreskin (pre-PC) or CS (post PC) at baseline and 6 months after PC. Multiplex ELISA quantified chemoattractant chemokines (IL-8, MIP-1β), proinflammatory cytokines (IL-1α, IL-1β) and an epithelial integrity biomarker (E-cadherin). Bacterial abundance was assessed by 16S RNA qPCR and sequencing. The intra-individual impact of PC was assessed using the paired Wilcoxon test.

**Results:** At baseline the urethra was enriched for IL-8, MIP-1β and E-cadherin, while the inner foreskin was enriched for IL-1α, IL-1β with a greater total bacterial abundance (median 27,100 vs. 1,200, gene copies/swab, p=0.001). Anaerobes made up 49% of inner foreskin bacteria, but only 26% of urethral bacteria. PC did not alter urethral IL-8 (median 1058 vs. 818 pg/ml at 12 months and baseline, respectively; p=0.057) or other chemokines/ cytokines, and urethelial E-cadherin increased (155,750 vs. 111,928 pg/ml, p=0.012), suggesting reduced epithelial integrity; urethral total bacterial abundance and anaerobe abundance dropped by 5-fold and 7-fold, respectively. In contrast at the CS, where there were dramatic reductions in E-cadherin (900 vs. 15,843 pg/ml, p<0.001) and most proinflammatory chemokines/ cytokines (eg: IL-8, 3 vs. 34 pg/ml; p<0.001). IL-1α was increased post-PC at the CS coupled with a 14-fold reduction in total bacterial abundance (p=0.004) and 200-fold reduction in anaerobes (p<0.001).

**Conclusion:** PC had no impact on urethral immunology and may have reduced epithelial integrity despite some reductions in total bacterial load and anaerobes; in the CS there was enhanced epithelial integrity, near total loss of anaerobes and dramatic immune alterations. This suggests that HIV protection post-PC is mediated through removal of inflamed, HIV-susceptible inner foreskin tissues rather than via the urethra.

**MEDICAL MALE CIRCUMCISION DISCIPLINES THE PENIS: UNDERSTANDING HIV SUSCEPTIBILITY**

Cosnet L. Rametse1, Micheal Mndini1, Sibulelo Mollie1, Kyle O'hagan1, Nyaradzo T. Chigorinbo-Tsikwa1, Gianguido C. Cianci1, Thomas Hope1, Clive M. Gray1 1University of Cape Town, Cape Town, South Africa, 2Northwestern University, Chicago, IL, USA

**Background:** The male foreskin is the main site of HIV entry in heterosexual men as evidenced by the effective protection incurred upon its removal following voluntary medical male circumcision (VMMC). However, the biological mechanism by which circumcision confers this protection remains poorly understood. To understand changes to skin barrier function after VMMC, we measured transepithelial water loss (TEWL) and hydration status in the glans, foreskin and shaft before and after (glans & shaft only) VMMC as in vivo measures for skin barrier integrity. The lower TEWL and higher hydration status equates with more intact skin barrier integrity.

**Methods:** Hand-held vapometers and moisture meters SC & D, designed to measure water loss and content in the skin (and used extensively in dermatology and the cosmetic industry), were used to quantify TEWL (n=45 adult males), surface hydration in the stratum corneum and water content in the skin (n=31 adults) of the glans, inner foreskin and penis shaft before VMMC. These in vivo proxy measurements for skin integrity were then made two weeks after circumcision. First-pass urine samples were tested for common curable sexually transmitted infections (STIs): Chlamydia trachomatis, Neisseria gonorrhoea, Trichomonas vaginalis & Mycoplasma genitalium.

**Results:** To date, we show that 20-25% men have an asymptomatic STI. In males who were STI negative prior to circumcision, the inner foreskin and glans had higher TEWL readings compared to the shaft, whereas the surface hydration and water content were the same across all anatomical sites. Two weeks after circumcision, the TEWL readings in the glans significantly decreased (from a median of 27.6 to 17 g/hr/m²) to match the shaft readings and the hydration content also decreased in all three sites but especially surface hydration in the shaft (from a median of 48 to 28 au, p=0.0061). Comparing men who were STI positive (n=9) versus STI negative at the time of VMMC, there was lower TEWL in the glans in the presence of an STI (median of 26 vs 9 g/hr/m², p=0.033), but no differences in the hydration status.

**Conclusion:** Our data show that prior to VMMC, the inner foreskin and glans had lower skin barrier integrity which increased soon after circumcision in STI negative males, but not in those with an asymptomatic STI. This finding has implications for understanding how MMC disciplines penile tissue and gives insight into how HIV acquisition may be prevented after circumcision.
Background: Antiretroviral therapy (ART) effectively suppresses HIV levels in plasma. While HIV levels at mucosal surfaces generally also fall to undetectable levels, several groups have described detectable HIV shedding in the anogenital tissues of ART-treated individuals, and the immune correlates of HIV shedding in the context of effective ART are not well understood. Because mucosal inflammation drives increased HIV shedding in ART-naïve individuals, we hypothesized that anorectal HIV shedding in ART-treated men would be associated with activated mucosal CD4+ T cells.

Methods: Fifty-four HIV-infected, ART-treated men who have sex with men were recruited from Toronto, Canada. Anal swabs were used to test for HIV RNA levels by RT-PCR. High-resolution anoscopy was performed to collect anal biopsies, and lymphocytes isolated from collagenase-treated biopsies were stained for flow cytometric analysis. Markers included: CD38/HLA-DR (immune activation), CD25/FoxP3 (Tregs), CCR6 (Th17), CCR5 (HIV co-receptor) and CCR7/CD45RA (memory subsets). HIV shedders and non-shedders were compared by Mann-Whitney (SPSS).

Results: Fifteen (27.8%) of 54 ART-treated men had detectable anorectal HIV shedding despite plasma HIV suppression, albeit at low levels (median 206 copies/swab). Surprisingly, HIV shedders did not have increased levels of activated (CD38+HLA-DR+) CD4+ T cells (p=0.401). However, we observed differences in anorectal CD4+ T cells memory subsets: HIV shedders had significantly higher proportion of central memory cells (CCR7+/CD45RA-; Shedders= 34.5%, Non-shedders= 17.9%; p=0.004). All other mucosal memory subsets were enriched in HIV non-shedders, including terminally differentiated cells (CCR7-/CD45RA+; p=0.024). No other mucosal T cell differences were observed between HIV shedders and HIV non-shedders.

Conclusion: An increased proportion of central memory cells (TCM), but not of activated mucosal CD4+ T cells, was associated with HIV shedding. This suggests that non-inflammatory mechanisms, such as the homeostatic proliferation of latently infected cells, may be driving mucosal HIV shedding in ART-treated individuals. While the low-level HIV shedding that we observed is unlikely to contribute to sexual transmission of HIV, understanding immune correlates of compartmentalized HIV production in ART-treated individuals may help to optimize strategies for HIV eradication.

Background: The female reproductive tract is one of the most common sites of initial HIV transmission yet we lack a detailed understanding of the cells that are most susceptible to infection. One challenge involves the extensive remodeling of host cells by HIV, rendering it difficult to classify infected cells into traditional T cell subsets.

Methods: We exposed specimens of endometrial biopsies and PBMCs from the same donors to a CCR5-tropic transmitted/founder HIV-1 reporter virus, and conducted an extensive phenotypic analysis of uninfected and infected cells using CyTOF. Using bioinformatics analyses of the resultant high-dimensional single-cell datasets, we were able to characterize the subsets of cells that were most susceptible to HIV infection independent of remodeling.

Results: Memory CD4+ T cells were almost exclusively targeted for infection in both the tissue and blood specimens, but those from the endometrium were significantly more susceptible (p<0.01). While a diverse array of endometrial memory CD4+ T cells were targeted for infection, only a small subset of the unstimulated PBMC-derived CD4+ T cells could be infected. In-depth analyses of the features of the endometrial memory CD4+ T cells targeted for infection revealed preferential infection of T effector memory (Tem) cells polarized towards the Th1 and Th2 lineages, as well as preferential infection of T resident memory (Trm) and T follicular helper (Tfh) cells. Upon infection, HIV interfered with the TCR signaling apparatus by downregulating CD4, CD45R0, CD28, and ICOS, and upregulated BIRC5 promoting survival of infected cells. Infection also upregulated the chemokine receptors CCR7 and CXCR3 and the tissue retention receptor CD69 while downregulating expression of the CD49d integrin.

Conclusion: These data suggest that unique phenotypic features of memory CD4+ T cells in the genital tract renders these cells highly susceptible to infection by HIV-1, and that upon infection the virus remodels the cell in a manner than undermines TCR signaling while promoting survival and enhancing migration to other lymphoid sites via modulation of homing receptor expression.

Background: Understanding the molecular mechanisms underlying the role of the vaginal microbiome in HIV acquisition risk is an essential step toward safer and more effective HIV prevention. We hypothesized that the resident microbiota regulates micro(mi)-RNAs that can interfere with host pathways exploited by the virus. miRNAs are endogenous short non-coding RNA molecules that are stably carried in circulation by extracellular vesicles and exert post-transcriptional epigenetic regulation with emerging significance in HIV infection. Their role in the anti-viral mucosal barrier function is unknown.

Methods: The study utilized 112 cervicovaginal specimens from healthy reproductive-age women collected during the luteal phase of the menstrual
cycle. All subjects were confirmed negative for sexually transmitted infections at the time of sampling. Vaginal microbiota was classified by Nugent scores and microbiome sequencing. Levels of miRNAs were quantified in extracellular vesicles isolated from the cervicovaginal secretions using the EdgeSeq global transcriptome platform. Differential expression (DE) was determined using Bioconductor DESeq2. miRNA target prediction was performed using miRNAtap Bioconductor package.

Results: Cervicovaginal miRNA profiles varied by both Nugent score categories (0-3 scores – normal, 4-6 – intermediate, and 7-10 – bacterial vaginosis, BV) and by metagenome classification. Higher microbiome diversity was associated with higher number of significantly dysregulated miRNAs (373 in BV versus 119 in Nugent 4-6 compared to Nugent 0-3, FDR<0.1, p<0.01). The miRNAs dysregulated by BV overlapped with 66% of the miRNAs which were up or down regulated in G. vaginalis-dominated compared to L. crispatus-dominated metagenomes. The gene ontology predictions based on BV-dysregulated miRNAs identified enrichment for 88 genes previously validated as part of the HIV-host interactome facilitating infection. Gene clusters identified with highest stringency included proteasome and chaperonin pathways, virus entry receptor clusters, host signaling pathways downstream of NF-κB, TNFα, T-cell receptor and the MAPK cascade. Highest enrichment scores were achieved for the TCP-1 ring complex which interacts with the HIV Vif.

Conclusion: We identified miRNAs regulated by vaginal dysbiosis that may facilitate immune imbalance and cellular pathways associated with HIV risk.

217 LONG-TERM SEX DIFFERENCES IN OUTCOMES FOLLOWING ACUTE HIV-1 INFECTION
Sophie Novelli1, Pierre Delobel1, Olivier Bouchaud1, Yeroneique Avettand-Fenoël1, Pascale Faillaire1, Sylvie Abe1, Faouzi Souala1, François Raify1, Pillarxo Catalan1, Laurence Weiss1, Laurence Meyer1, Cécile Goujard1, for the ANRS PRIMO Cohort Study Group

1INSERM, Le Kremlin-Bicêtre, France, 2Toulouse University Hospital, Toulouse, France, 3Hôpital Avicenne, Bobigny, France, 4Necker Hospital, Paris, France, 5CHU de Angers, Angers, France, 6CHU Fort de France, Fort de France, Martinique, 7CHU de Rennes, Rennes, France, 8CHU de Nantes, Nantes, France, 9Hôpital Bicêtre, Le Kremlin-Bicêtre, France, 10Georges Pompidou European Hospital, Paris, France

Background: Women have shown more favorable immunovirological characteristics than men around seroconversion. Here we investigated whether differences persisted under long-term antiretroviral therapy (ART) in individuals treated since acute and early HIV-1 infection (AHI).

Methods: Data was obtained for 262 women and 1783 men enrolled in the French multicenter ANRS PRIMO cohort between 1996 and 2017. We modelled the viral response, long-term immune recovery and total HIV DNA decay in the 143 women and 1126 men who initiated ART within the first three months of infection. Analyses were performed separately for men and women.

Results: The 1269 participants were mostly white (85%). The median age at AHI diagnosis was 36 years (IQR: 29–44). The median ART duration was 62 months (IQR: 20–87). Mean pre-ART viral loads were lower in women than men, 5.2 and 5.8 log10 copies/mL respectively (P = 0.001). After ART initiation, women more rapidly achieved viral suppression (HIV RNA < 50 copies/mL) than men (age and pre-ART viral load adjusted hazard ratio: 1.33, 95% confidence interval 1.09 - 1.69). They also experienced a faster increase in CD4+ T-cell count and CD4/CD8 ratio during the first two months of treatment. Baseline sex-related differences in CD4+ T-cell counts were more pronounced with increasing age. This led to a sustained mean difference of +99 to +168 CD4+ T-cells/µL depending on age between women and men at 12.5 years of ART. CD4/CD8 ratio of women was persistently higher than that of men by a mean of 0.31. With long-term ART, women and men achieved similar levels of total HIV DNA (mean estimate at the last modelling point: 1.9 log10 copies/109 PBMCs after 70 months of ART for both sexes).

Conclusion: ART initiated within 3 months of AHI was associated with a larger immunological benefit in women. This benefit was sustained and more pronounced under very long-term ART, which may give women additional protection from adverse clinical outcomes and premature ageing.

218 PERSISTENT IMMUNE ACTIVATION IN HIV-1—TREATED SUBJECTS COMPARED WITH NON-HIV CONTROLS
Sophie Novelli1, Camille Lecroux1, Jacques Reynes1, Agnes Villemant1, Laurent Blum2, Asma Essat2, Yeroneique Avettand-Fenoël3, Odile Lautanay2, Jean-Michel Molina1, Cécile Goujard1, Christine Bourgeois1, Laurence Meyer1

1INSERM, Le Kremlin-Bicêtre, France, 2CHU de Montpellier, Montpellier, France, 3Hôpital Beaujon AP-HP, Clichy, France, 4Centre Hospitalier René Dubos, Pontoise, France, 5Necker Hospital, Paris, France, 6Chocin Hospital, Paris, France, 7Hôpital Saint-Louis, Paris, France, 8Hôpital Bicêtre, Le Kremlin-Bicêtre, France

Background: Non-AIDS events under antiretroviral therapy (ART) are attributed to persistent low-grade inflammation. The magnitude of this inflammation is still discussed, partly because there is no standard value for "basal inflammation". Here we compared the inflammation profile of HIV-infected patients under long-term suppressive ART to 2 well-characterised HIV-uninfected groups, at low and high risk of HIV acquisition.

Methods: HIV participants followed since acute/early HIV infection (AHI) in the ANRS PRIMO cohort were selected if treated for ≥36 months with sustained HIV RNA<50 copies/mL and available frozen samples. Sex and age-matched controls were sampled from the ANRS IPERGAY trial of pre-exposure prophylaxis among men who have sex with men at high risk for HIV infection, and the ANRS COHVAC cohort, a long-term safety cohort of volunteers in preventive HIV-1 vaccine trials. Participants with HBV or HCV infection were excluded. We compared the three groups on plasma levels of ten biomarkers: non-specific markers of inflammation (usCRP, IL6, TNFα, sTNFRII), and markers associated with monocyte activation (sCD14, sCD163, CXCL10), gut epithelial dysfunction (I-FABP, IL17) or fibrosis (hyaluronic acid). We also measured plasma ultraviolet HIV RNA and total HIV DNA in blood. Analyses were performed separately for men and women.

Results: 150 PRIMO subjects (108 men and 42 women) were matched with 141 COHVAC participants (100 men, 41 women) and 102 IPERGAY men. The median age was 47 years. Among PRIMO subjects, 89% had CD4 counts >500 cells/µL and 64% had an undetectable ultrasensitive viral load after a median of 6 years of ART. Smoking and alcohol use were less frequent in COHVAC participants than in the other groups. After adjusting for age, smoking, alcohol use, and body mass index, both HIV-infected men and women had higher levels of sCD14, sCD163, CXCL10, gut epithelial dysfunction (I-FABP, IL17) or fibrosis (hyaluronic acid). We also measured plasma ultraviolet HIV RNA and total HIV DNA in blood. Analyses were performed separately for men and women.

Conclusion: After a median of 6 years under ART, HIV-infected participants maintained high levels of monocyte activation and gut epithelial dysfunction.

219 SOCS PROTEINS AND JAK-STAT PATHWAY DYSREGULATION IN SIV-INFECTED SUPPRESSED MACAQUES
Erandi E. Velarde De La Cruz1, Lingyun Wang1, Anna Aldovinii

1Boston Children’s Hospital, Boston, MA, USA
220 EFFECT OF HIV SUPPRESSION ON CYTOKINES IN BLOOD AND SEMINAL PLASMA

Stephen A. Rawlings1, Felix Torres2, Andrea Lisca2, Leonid Margolis2, Sara Gianella3, Christophe Vanyouville4

1University of California San Diego, La Jolla, CA, USA, 2NIH, Bethesda, MD, USA

BACKGROUND: HIV infection disrupts the cytokine network and it remains disrupted after HIV is suppressed by ART. Characterization of this continuing disruption in genital secretions is important for understanding the mechanisms of HIV sexual transmission. Therefore, we undertook to determine the cytokine network in individuals longitudinally sampled before they began antiretroviral therapy (ART) and after achieving suppression of HIV RNA.

METHODS: Concentrations of 34 cytokine/chemokines were measured by multiplex-bead assay in longitudinal blood and seminal plasma from 20 men with HIV from a well-studied cohort with banked blood and seminal samples when viremic and suppressed. We used Partial Least Squares Discriminant Analysis (PLS-DA) to visualize the difference in cytokine pattern between the time points and rank the relative importance of cytokines for determining suppression status. Any cytokines with Variable Importance on PLS Projections (VIP) scores exceeding 1 were deemed important in predicting suppression status and were subsequently tested using Wilcoxon Signed Rank Tests.

RESULTS: Baseline characteristics of our cohort included median age of 33 years (IQR 27–41), median CD4+ T cell count 702/μL (range 324–997), and median pre-ART HIV viral loads in blood log10 4.7 (range 2.8–6.6). Significant overlap of the PLS-DA projections in blood suggested no significant difference in the overall cytokine network after suppression of viremia, even though individual cytokines changed in line with published findings from other studies. However, the projections are significantly different in seminal plasma, highlighting the importance of immune activation in this compartment. When tested individually, four cytokines were significantly different across time points in seminal plasma (MIG, IL-15, and IL-7p < 0.001; TFN-α p = 0.019), while only two were significantly different across time points in blood (MIG and IP-10, both p = 0.006).

CONCLUSION: Our study demonstrates that viral suppression with ART has the most significant decrease in the inflammatory milieu in seminal plasma, while the overall effect on the network of cytokines in the blood is weaker.

These results identify specific changes in the cytokine networks in semen and blood—consistent with prior reports—as the immune system acclimates to chronic, suppressed HIV infection and they highlight the utility of novel statistical methods in the analysis of large data sets of cytokine measurements.
vascular and coagulation pathways, rather than in innate immune activation or microbial translocation, previously associated with greater risk of comorbidities in obese PWH remains to be determined.

**222 RESIDUAL IMMUNE ACTIVATION IN AFRICANS ON ART PREDICTS CD4 RECOVERY AND VIREAL REBOUND**

**Stefanie Kroese**, Theresa M Rossouw, Helen Steel, Ferdinand Wit, Cissy Kityo, Margaret Swale, Sulaimon Akanmu, Kishorchandra Mandaliya, Marleen de Jager, Pascale Ondoa, Peter Reiss, Tobias F. Rinke de Wit, Neeltje A. Kootstra, Raph L. Hamers, for the PanAfrican Studies to Evaluate Resistance (PASER)

**1** Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; **2** University of Pretoria, Pretoria, South Africa; **3** Joint Clinical Research Centre, Kampala, Uganda; **4** Lusaka Trust Hospital, Lusaka, Zambia; **5** University of Lagos, Lagos, Nigeria; **6** University of Nairobi, Nairobi, Kenya; **7** Mulmmed Hospital, Pretoria, South Africa; **8** Academic Medical Center, Amsterdam, Netherlands

**Background:** There are limited data on the clinical implications of persistent chronic immune dysregulation in HIV-1-infected African populations on suppressive antiretroviral therapy (ART). We investigated the prognostic value of elevated plasma immune biomarkers, during suppressive ART, in predicting impaired CD4 T-cell recovery and virological rebound during 6 years of follow-up.

**Methods:** In a multi-country African adult cohort, we measured 8 selected systemic biomarkers (IL-6, IP-10/CXCL10, MCP-1/CCL2, MIG/CXCL9, LBP, CRP, sCD163, and sCD14) in 398 participants with suppressed plasma HIV-RNA (<50 cps/mL) after 12 months of non-nucleoside reverse-transcriptase inhibitor-based ART. We estimated associations between each of the month-12 biomarkers and 2 long-term outcomes: 1) CD4 T-cell recovery, using a multivariable linear mixed model; and 2) virological rebound (defined as single HIV-RNA>1000 cps/mL), using multivariable interval-censored survival analysis.

**Results:** 229 participants (58%) were female, median age was 37 years (IQR 33-43), and country of origin was Kenya (n=92), Nigeria (n=57), South Africa (n=65), Uganda (n=121) and Zambia (n=63). Median CD4 T-cell count rose from 291 cells/μL (IQR 216-395) at month 12 to 458 cells/μL (IQR 340-602) at month 72. Participants with elevated levels of sCD14 (coefficient -83.38, 95%CI -163.49 to -32.27; p=0.041), IP-10 (aOR 4.67; 95%CI 1.47 to 14.79), MIG (-34.78, 95%CI -67.27 to -2.29, p=0.036), and CRP (-28.49, 95%CI -45.95 to -11.04, p=0.001) were more likely to experience impaired CD4 T-cell recovery. From month 12 after ART initiation onwards, we recorded 1148 person-years of follow-up, with 47 events of virological rebound (incidence rate of 40.9, 95%CI 30.8-54.5, per 1000 person-years). Risk of virological rebound was increased for participants with an elevated IP-10 level (hazard ratio [HR] 1.81 per log₂ pg/mL unit increase, 95%CI 1.03-3.18; p=0.038), and reduced for those with an elevated MCP-1 level (HR 0.25 per log₂ pg/mL unit increase, 95%CI 0.07-0.87; p=0.030). None of the other biomarkers were significantly associated (figure).

**Conclusion:** Persistent systemic inflammatory and immune activation during suppressive ART was associated with impaired long-term CD4 T-cell recovery and virological rebound; the counterintuitive MCP-1 association requires further investigation. Further research needs to explore the potential for adjunct therapies targeting relevant inflammatory pathways.

**223 HIV-RELATED MICROBIOME, PREVIOUS IMMUNODEFICIENCY, AND EXCESS METABOLIC RISK**

**Marco Gelpi**, Beate Vestad, Simon H. Hansen, Kristian Holm, Nina Drivsholm, Alexandra Goetz, Hedda Hoel, Nikolai Kirkby, Birgitte Undegaard, Anne-Mette Lebech, Jan Gerstoft, Jens D. Lundgren, Johannes R. Hov, Susanne D. Nielsen, Marius Troseid

**1** Rigshospitalet, Copenhagen, Denmark; **2** Oslo University Hospital, Oslo, Norway; **3** University of Oslo, Oslo, Norway; **4** Hvidovre Hospital, Hvidovre, Denmark

**Background:** We aimed to identify an HIV-related microbiota signature, independent of sexual preferences and demographic confounders, to assess a possible impact of the microbiome on metabolic comorbidities.

**Methods:** 405 HIV-infected and 111 uninfected individuals, stratified to sexual behaviour (men who have sex with men, MSM and non-MSM), were included from the COCOMO study. Stool samples were analyzed using 16S rRNA sequencing. Hypotheses were tested using regression models adjusting for known confounders.

**Results:** Microbiota alterations in HIV-positive MSM and uninfected MSM were largely overlapping. After filtering out MSM-associated microbiota traits and adjusting for relevant confounders, we identified an HIV-related dysbiosis, consisting of lower biodiversity, increased relative abundance of Gammaproteobacteria and Desulfovibrionaceae and decrease in several Clostridia (Figure 1). HIV-related dysbiosis was associated with previous immunodeficiency (low nadir CD4), elevated microbial translocation markers (soluble CD14 and LPS-binding protein, p<0.05), and a 2-fold (adjusted Odds Ratio (aOR) 1.97 [1.12; 3.46]) increased excess risk of metabolic syndrome, the latter driven by increase in Desulfovibrionaceae and decrease in several Clostridia of the Lachnospiraceae and Ruminococcaceae families (Butyrivibrio, Coprococcus-2, Lachnospiraceae UCG-001 and CAG-56). In individuals with a history of AIDS, this microbiota profile was associated with 8-fold (aOR 8.14 [1.74; 38.07]) excess risk of metabolic syndrome and 6-fold (aOR 6.71 [1.35; 33.50]) excess risk of abdominal obesity.

**Conclusion:** HIV infection was associated with altered bacterial composition, independently of sexual behaviour and demographic factors. HIV-related dysbiosis was associated with increased risk of metabolic syndrome, particularly in individuals with previous severe immunodeficiency. The excess metabolic...
risk was driven by increased Desulfovibrionaceae, H2S-producing bacteria with toxic effects on the gut epithelium, and decrease of potentially butyrate-producing Clostridia. As outgrowth of Desulfovibrio and reduction in Clostridia have been shown to trigger metabolic alterations in immunodeficient mice, our findings suggest a potential interplay between HIV-related dysbiosis, previous immunodeficiency and future risk of metabolic comorbidities.

**Conclusion:** Our integrative analyses suggested that altered gut microbiota with related functional capacities are associated with disrupted plasma metabolite profiles in HIV-infected women.

**Figure 1** HIV infection, gut bacterial genera and host plasma metabolites.

**A.** Plasma metabolite profiles and HIV infection. Three-dimensional Partial Least Squares Discriminant Analysis (PLSDA) scores plot by HIV status, based on 53 plasma metabolites.

**B.** Correlation between four HIV-associated bacterial genera and plasma metabolites. Red and green plots depict bacterial genera which showed increased and decreased relative abundance in HIV-uninfected individuals. The glycerophospholipid column represents total glycerophospholipid, the acylcarnitine column represents total acylcarnitine, and the phosphatidylcholine column represents total phosphatidylcholine.

**225 ART REVERSES LOSS OF DIVERSITY & RICHNESS OF INTESTINAL MICROBIOME IN HIV+ NAIVE**

Angelica I. Cruz-Lebron1, Ramona M. Johnson1, Danielle Labbato1, Theresa O. Rodgers2, Julia C. Kosco3, Grace A. McComsey4, Alan D. Levine1

1Case Western Reserve University, Cleveland, OH, USA, 2University Hospitals Cleveland Medical Center, Cleveland, OH, USA

**Background:** Changes in the intestinal microbiome, known as dysbiosis, and its metabolites promote inflammation and systemic immune activation in persons living with HIV, which may contribute to the persistence of HIV during ART.

**Methods:** To define the major factors that drive dysbiosis we contrasted the diversity and composition of the fecal microbiome of persons living with HIV before beginning ART (HIV+ naive; 13 patients) with those on ART (57 patients) for 133 months (HIV+ ART+) by16S rRNA sequencing. Results were compared to the microbiome in 55 healthy HIV-uninfected controls.

**Results:** Overall, 76% were males of median age of 44. Groups were similar in demographics. HIV+ ART+ had a median CD4 count of 685 and 88% had HIV-1 RNA of < 20. Principal component analysis (PCA) of the intestinal microbiome at the phylum level reveals that b-diversity of the microbial composition in HIV+ naive and HIV+ ART+ individuals is similar and quite distinct from the uninfected controls. Individual a-diversity, as measured by the Shannon index, and richness, reported by the Chao-1 index, are decreased in HIV+ naive patients (p = 0.009) and are partially reversed after ART treatment. However, the balance in the abundance of the core microbiota, Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, and Verrucomicrobia, distinguishes HIV+ naive from HIV+ ART+ individuals. The HIV+ naive population exhibits decreased Firmicutes, Proteobacteria, and Verrucomicrobia, distinguishes HIV+ naive from HIV+ ART+ individuals. The HIV+ naive population exhibits decreased Firmicutes, Proteobacteria, and Verrucomicrobia, distinguishes HIV+ naive from HIV+ ART+ individuals.

**Conclusion:** These results indicate that HIV reduces the diversity and breadth of microbes in the intestine and that after ART, the diversity of the microbiota...
increases due to an undergrowth of Bacteroidetes and excess colonization by Actinobacteria and Firmicutes.

226 MICROBIOTA MODULATES HIV TARGET-CELL LEVELS AT SITES OF MUCOSAL HIV ACQUISITION

Angela Wahl 1, Baolin Liao 1, Cara Richardson 1, Morgan Chateau 1, Wenbo Yao 1, Allison Roggja 1, R. Balfour Sartor 1, J. V. Garcia 1

1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Most HIV infections are acquired at the mucosa of the gut or female genital tract (FGT). Given that resident microbiota regulate mucosal immune homeostasis, we hypothesized that microbiota modulates HIV target cell levels at these sites of HIV transmission which could affect HIV acquisition, pathogenesis, persistence, and PrEP efficacy.

Methods: We used bone marrow/liver/thymus (BLT) humanized mice to examine the effect of microbiota on HIV target cell levels in the gut and FGT. The systemic presence of human immune cells in BLT mice including the gut and FGT is well documented. Specifically, we bioengineered germ-free (GF) BLT humanized mice using rederived GF immunodeficient NSG mice. GF NSG mice were implanted with human thymus/liver tissue and transplanted with autologous stem cells in a GF surgical isolator. The GF status of mice was determined using bone marrow/liver/thymus (BLT) humanized mice to construct GF NSG humanized mice colonized with microbiome were also constructed. To directly evaluate the effect of microbiota on HIV target cell levels in the gut and FGT, we quantitated the number of human CD4+ T cells and myeloid cells in both models with flow cytometry. We also quantitated the number of CCR5+ CD4+ T cells and activated (HLA-DR+CD38+) CD4+ T cells in the gut. We analyzed the small intestine (S), cecum (C), and large intestine (L) intraepithelial (IEL) and lamina propria (LPL) layers separately.

Results: Numbers of human CD4+ T cells were higher in the SIEL (p=0.0001), SLPL (p=0.0009), CIEL (p=0.0232), LIEL (p=0.0005), and LPL (p=0.0015) of colonized BLT mice compared to GF BLT mice. Numbers of CCR5+ CD4+ T cells were consistently higher in the gut of colonized BLT mice (SIEL p=0.0002, SLPL p=0.0401, CIEL p=0.0004, LIEL p=0.0005, LPL p=0.0022). The presence of microbiome also resulted in higher numbers of activated CD4+ T cells in the SIEL (p=0.0071), SLPL (p=0.0279), and CIEL (p=0.0364), higher numbers of human myeloid cells were observed in the SIEL (p=0.0015) and SLPL (p=0.0005) of colonized BLT mice. In the FGT, the presence of microbiome resulted in higher numbers of human CD4+ T cells (p=0.0079) but had no effect on human myeloid cell levels.

Conclusion: Our results provide direct evidence that microbiota modulate HIV target cell levels and in particular, CD4+ T cell levels at key mucosal sites of HIV acquisition.

227 KEY FEATURES OF GUT-MICROBIAL DYSBIOSIS IDENTIFIED IN ALCOHOLIC HIV-1 PATIENTS

Richa Singhal 1, Kendall Stocke 1, Smrita Ghare 2, Manicka Vadhanam 3, Dmitry Lioznov 4, Elena Blokhina 2, Evgeny Krupitsky 2, Kaku So-Armah 3, Natalia Gnatienko 5, Jeffrey H. Same 6, J. V. Garcia 1, Kendall J. Bryant 1, Robert L. Cook 6, Matthew Freiberg 7, Shirish A. Barve 3

1University of Louisville, Louisville, KY, USA, 2First Pavlov State Medical University of St Petersburg, St Petersburg, Russia, 3National Institute for Alcohol Abuse and Alcoholism, Bethesda, MD, USA, 4University of Florida, Gainesville, FL, USA, 5Vanderbilt University, Nashville, TN, USA

Background: Heavy alcohol drinking and HIV-1 infection are independently associated with the development of gut-microbial dysbiosis and increase in intestinal permeability and microbial translocation. These gut-associated events are major pathogenic factors driving local and systemic inflammation and development of comorbidities. Significantly, the combinatorial effects of HIV-1 infection with a history of heavy alcohol consumption have not been determined. We will evaluate the qualitative and quantitative changes occurring in the gut microbiome (dysbiosis) associated with heavy alcohol consumption in people living with HIV (PLWH).

Methods: Fecal samples were obtained from 102 participants in the St PETER (Russia) HIV and alcohol use cohort (RCHIV-Alc). Metagenomics analysis of the 16S rRNA gene was done by amplification of V3-V5 regions, on the Illumina MiSeq platform. Operational taxonomic units (OTUs) tables profiling microbiome were generated using QIIME. Important statistical analyses included LEfSe (Linear discriminant analysis Effect Size), Pearson's correlation, and multivariate analysis, Mann-Whitney U test and ANOVA with Tukeys correction. Cytokine levels were determined using the MSD platform.

Results: Metagenomics analysis revealed that as compared to control, RCHIV-Alc patients showed a major loss of butyrate producing bacteria. This loss correlated with a decrease in microbial diversity and F/B ratio along with an increase in immune activation and inflammation markers sCD14, IL6 and MIP-1β (Table 1A,B). Further, LEfSe analysis determined that there was a significant enrichment of pathogenic Enterobacteriaceae (LDA score > 1.5, p < 0.05), only in very heavy alcohol drinking RCHIV-Alc patients with an AUDIT score ≥20 (Table 1A). Significantly, this enteroracerbiaceae also resulted in a decrease in microbial diversity and CD4+ counts along with a concomitant increase in viral load and TNFα, IFNγ, IL-6, IL-8, MCP-1, MIP-3α and sCD14(Table 1B).

Conclusion: The study identifies a significant loss of butyrate producing bacteria in RCHIV-Alc patients. Notably, in a subset of HIV patients with very heavy alcohol use (AUDIT score ≥20) the gut microbial dysbiosis is further characterized by a significant enrichment of “pro-inflammatory” Gram negative bacteria represented by Enterobacteriaceae. These findings identify the characteristics of gut microbial dysbiosis occurring in response to the combinational effects of alcohol and HIV-1 infection that can adversely affect HIV-1 pathogenesis.

Table 1A: Significant features of gut-microbial dysbiosis in RCHIV-Alc patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>sCD14</th>
<th>IL6</th>
<th>MIP-1β</th>
<th>sCD14/IL6</th>
<th>sCD14/MIP-1β</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 1B: Significant features of gut-microbial dysbiosis in RCHIV-Alc patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>sCD14</th>
<th>IL6</th>
<th>MIP-1β</th>
<th>sCD14/IL6</th>
<th>sCD14/MIP-1β</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>RCHIV-Alc versus Normal</td>
<td>-0.05</td>
<td>0.49</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Preventella is related to a dysregulation of IFN and T-cell response in HIV infection

Claudia Pinacchio 1, Giuseppe P. Innocenti 1, Letizia Santinelli 1, Eugenio Nelson Cavallari 2, Federica Frasca 2, Carolina Scagnolari 2, Guido Antonelli 3, Claudio M. Mastromarino 4, Gabriella d’Ettore 5

1Sapienza University of Rome, Rome, Italy

Background: Altered interplay between gut mucosa and dysbiotic microbes during HIV infection has been linked to chronic immune dysfunction, commonly characterized by high levels of IFN-1 and immune activation markers as well as by a severe depletion of Th17 T cells in the gastrointestinal tract. We hypothesized that a specific gut microbial communities imbalance in HIV-infected individuals could affect the antiviral defense and T cell immunity.

Methods: Ten HIV-infected subjects on long-term suppressive combined antiretroviral therapy (cART) underwent endoscopic procedures and blood collection. Lamina propria lymphocytes were isolated from five different intestinal sites (e.g. terminal ileum, cecum, ascending, transverse, and descending colon). Phylum, Family, Class, Order and Genus identification was performed on bacterial 16S ribosomal DNA sequences obtained from fecal samples collected for all patients. Measurements of CD4 and CD8 T cell activation (CD38+, HLA-DR+) and IFNγ and IL-17 expression on both CD4+ (Th1, Th17) were performed by flow cytometry. Gene expression level of IFNβ, IFN receptor 1 (IFNAR1) and the well-known interferon Stimulator Gene (ISG), Myxovirus resistance gene a (MxIA), was also evaluated in both anatomical sites by RT/real-time PCR. Nonparametric t-tests were used for statistical analysis.

228 PREVENTELLA IS RELATED TO A DYSREGULATION OF IFN AND T-CELL RESPONSE IN HIV INFECTION
Results: Fecal microbiota analyses confirmed that all HIV-1 individuals showed a distinct pattern of gut microbiota composition characterized by elevated levels of the genus Prevotella (relative abundance of 6.10%). Abundance of Prevotella was directly correlated with CD4+38+ (CD4+DR+ and CD4+38+DR+) in both peripheral blood and gut (p<0.05 for all these measures). Additionally, the same trend was observed for the activated CD8+ T cell subsets in both compartments. By contrast, Prevotella levels were inversely associated with the frequencies of Th17 T cells in blood (R=−0.454, p=0.00005) and in gut compartment (R=−0.284, p=0.011). Notably, higher levels of IL-17A (R=−0.662, p=0.042), IL-22 (R=−0.774, p=0.012), and IFNAR (R=−0.662, p=0.042), were associated to lower abundance of the genus Prevotella in the gut mucosa.

Conclusion: Our findings suggest that abundance of the genus Prevotella could affect gut mucosal type IFN pathways and modify T cell response in HIV-infected subjects.

229 ANTIINFLAMMATORY EFFECT OF METFORMIN ON MICROBIOTA IN NONDIABETIC PEOPLE WITH HIV

Stéphane Isnard1, John Lin1, Brandon Fombuena1, Thibaut V. Varin1, André Mareette2, Delphine Planas2, Mériem Messaoudene1, Bertrand Routy3, Claude P. Van Der Ley4, Ido Kema4, Petronela Ancuta3, Jonathan Angel5, Jean-Pierre Marette2, Ranieri Verin2, Giuseppe P. Innocenti1, Claudia Pinacchio1, Stéphane Isnard1

Background: People living with HIV (PLWH) on antiretroviral therapy (ART) remain at increased risks of inflammatory comorbidities. Metformin, an anti-diabetic drug with anti-aging effect, was shown to decrease inflammation by improving glucose metabolism and changing gut microbiota composition in diabetic people. Herein, we report results from the LILAC (CHR/CTN PT027) clinical trial evaluating the effect of 12 weeks of metformin on blood/gut inflammation and gut microbial composition in PLWH on ART.

Methods: A total of 22 non-diabetic (Hba1c<6%) PLWH, on ART with viral load <50 copies/ml for more than 3 years and CD4/CD8 ratio ≥0.7, received 12 weeks of metformin (850 mg bid). Blood and stools were collected at baseline (V1), after 6 weeks (V2), and after 12 weeks (V3). Soluble CD14 was measured in plasma. DNA was extracted from stools and 16S rRNA sequenced. Bacterial microbiota composition variations were analyzed using LeFSe. Serum short chain fatty acids (SCFA) were measured by LC-MS. The beneficial Akkermansia muciniphila, enriched in stools of diabetic people initiating metformin, was quantified by qPCR.

Results: CD4+ T-cell count, CD4/CD8 and HbA1c levels did not vary between visits, however plasma sCD14 levels decreased at V2 and V3 compared to V1. Bacterial alpha diversity tended to increase at V2 and V3. However, we observed a significant increase of Escherichia/Shigella and Lachnoclostridium and a decrease of Collinsella abundance at V2 compared to V1. The abundance of Lachnospiraceae, which are specialized in butyrate production, was increased at V3 compared to V1. Accordingly, we found increased serum butyrate/iso-butyrate levels at V2 and V3 compared to V1. No differences were observed for other SCFA propionate, succinate and methylofanalate. A. muciniphila abundance remained stable between visits.

Conclusion: A 12-week metformin therapy in non-diabetic PLWH on ART decreased plasma levels of the inflammation marker sCD14 in association with an enrichment of butyrate-producing bacteria in stools and increased serum butyrate levels. To confirm our study findings, a longer metformin treatment is needed in non-diabetic PLWH.

230 FUNCTIONAL RESTORING OF GUT BARRIER AFTER MODULATION OF INTESTINAL MICROBIOTA

Letizia Santinelli1, Ranieri Verin1, Giuseppe P. Innocenti1, Claudia Pinacchio1, Eugenio Nelson Cavallari1, Gabriella De Girolamo1, Anna Maria Pronio1, Guido Antinori1, Giancarlo Coccarello1, Carolina Scaglione1, Vincenzo Vulli1, Claudio M. Mastromarino1, Giacomo Rossi1, Gabriella d’Etterre1

1Sapienza University of Rome, Rome, Italy, 2University of Liverpool, Liverpool, UK, 3University of Camerino, Camerino, Italy

Background: A complex series of events starting from enterocytes modifications, mucosal immune dysfunction, damage to the intestinal epithelial barrier, microbial translocation, and chronic systemic immune activation, contribute to HIV disease progression. This study aimed to verify whether the modulation of microbiota plays a role in restoring the intestinal barrier integrity focusing on cellular morphology, cellular apoptosis machinery and mitochondrial restoring.

Methods: 10 Caucasian cART-treated HIV+ patients and 10 healthy age and gender matched controls were recruited at the Department of Public Health and Infectious Diseases, Sapienza University of Rome (Italy). HIV+ participants received for six months two saches, each containing 450 × 109 billion bacteria, two times a day of Vivomix®. All patients underwent to pancoloscopy and blood sampling before (T0) and after 6 months of probiotic supplementation (T6). Cellular morphology, cellular apoptosis machinery and mitochondrial restoring were analyzed in mucosal biopsies taken from different colonic tracts of intestine at T0 and T6.

Results: After the probiotic administration, sections of intestinal mucosa showed an improvement of epithelial integrity and a reduction of diffuse interstitial inflammatory infiltrate. The rate of enterocytes, undergoing apoptosis both in epithelium and intestinal crypts, was significantly reduced at T6 (p=0.04). Mitochondria number and size differed from the 2 groups of patients (p>0.05): samples taken at T6 showed significant increased number of mitochondria and the levels of these organelles were similar to healthy samples (p>0.05). Ultrastructural morphological data regarding mitochondria were confirmed by mtDNA evaluation at T6 that indicated an increase concentration of mitochondria in all tested patients (p<0.005) and a similar trend for CYTC concentration (p<0.005), with substantial reduction of HSHP60 and 70 m-RNA expression in mucosal biopsies (p<0.005). LPS and cCK18 plasma levels significantly decreased at T6 (p<0.05).

Conclusion: The modulation of intestinal microbiota ameliorates histopathological alterations characterizing HIV enteropathy, reducing inflammatory cells infiltration, villous blunting and widening, vacuolated enterocytes, crypt hyperplasia. All these data are in accord with a decrease in LPS and cCK18 plasma levels after probiotic supplementation, respect to levels that were observed at baseline.

231 CELLULAR STRESS BIOMARKERS ARE ASSOCIATED WITH MARKERS OF MICROBIAL TRANSLOCATION

Carol Vinton1, Carly E. Starke1, Alejandro Ortiz1, Ornella Sorinto1, Kenneth Knox1, Irini Sereti1, Jason Brenchley1

1NIH, Bethesda, MD, USA, 2University of Arizona, Tucson, AZ, USA

Background: Microbes and microbe components that translocate from the lumen of the GI tract can directly stimulate the immune system and contribute to inflammation. Given that microbial translocation occurs in many chronic diseases, defining reliable biomarkers that reflect microbial translocation is essential for proper inflammatory diagnoses. Host proteins produced in response to microbial antigenic stimulation are often used as surrogates of microbial translocation; however, many of these can be produced in response to self-proteins produced by dead and dying cells. We measured levels of biomarkers associated with GI damage, innate immune responses, and cell death associated proteins in cohorts of HIV-infected individuals and SIV-infected and infected pigtail and rhesus macaques to identify potentially confounding contributors to microbial translocation biomarkers.

Methods: We measured plasma levels of sCD14, HMGB1, RAGE, IFABP, and zonulin by ELISA in human and non-human primates (NHPs). Our cohorts consisted of 38 ARV-naive and treated HIV-infected human patients; 9 pigtail macaques (PTs) and 12 rhesus macaques (RMs) longitudinally pre-SIV and during acute and chronic infection; and an unmatched cohort of 6 chronically SIV-infected RMs and 6 SIV-uninfected and infected pigtail and rhesus macaques to identify potentially confounding contributors to microbial translocation biomarkers.

Results: We measured plasma levels of sCD14, HMGB1, RAGE, IFABP, and zonulin by ELISA in human and non-human primates (NHPs). Our cohorts consisted of 38 ARV-naive and treated HIV-infected human patients; 9 pigtail macaques (PTs) and 12 rhesus macaques (RMs) longitudinally pre-SIV and during acute and chronic infection; and an unmatched cohort of 6 chronically SIV-infected RMs and 6 SIV-uninfected RMs.

Results: We observed significant reductions in systemic levels of sCD14 and RAGE post-ARV in HIV-infected individuals. sCD14, HMGB1, and IFABP levels increased in chronically SIV-infected NHPs relative to their pre-infection plasma levels. Surprisingly, both sCD14 and zonulin levels decreased longitudinally, prior to acute-SIV infection. No markers strongly associated with sCD14 consistently in all three groups. In humans, sCD14 associated most strongly with HMGB1 plasma levels. However, in NHPs, sCD14 only correlated with RAGE levels in the RM cohort. The strongest association between markers within the NHP cohort was between RAGE and IFABP (P<0.0001).

Conclusion: Our data suggest that cellular proteins which are secreted during generalized cellular stress, and which specifically induce sCD14 production may contribute to elevated levels of sCD14 observed in HIV/SIV-infected individuals.
These cellular stress biomarkers, specifically RAGE and IFABP may be released into circulation due to epithelial barrier damage.

**232 CMV SEROPOSITIVITY AND MICROBIAL TRANSLOCATION IN HIV ELITE CONTROLLERS**

Rayoum Ramendra, Stéphane Isnard, John Lin, Brandon Fombuena, Jing Ouyang, Franck P. Dupuy, Yonglong Zhang, Malcolm Finkelman, Ido Kema, Cécile Tremblay, Nicole Bernard, Jean-Pierre Routy, for the Canadian Cohort of Ouyang, Franck P. Dupuy, Yonglong Zhang, Malcolm Finkelman, Ido Kema, Cécile Tremblay, Nicole Bernard, Jean-Pierre Routy, for the Canadian Cohort of Ouyang, Franck P. Dupuy, Yonglong Zhang, Malcolm Finkelman, Ido Kema, Cécile Tremblay, Nicole Bernard, Jean-Pierre Routy, for the Canadian Cohort of.

**Background:** Elite controllers (EC) are people living with HIV (PLWH) who maintain plasma viral load below 50 copies/ml without antiretroviral therapy. However, EC present with chronic inflammation and remain at increased risk of developing non-AIDS comorbidities. Microbial translocation is a contributor to chronic inflammation and CMV co-infection has been recently linked to increased gut damage. We previously reported that CMV seropositivity was associated with elevated epithelial gut damage and microbial translocation in ART-treated PLWH and HIV-uninfected controls. As Canada has one of the lowest CMV co-infection prevalence in the world, we evaluated the link between CMV seropositivity, microbial translocation, and inflammation among EC.

**Methods:** Study samples were collected from 37 EC (25 CMV +, 12 CMV-). By HLA typing, we categorized participants with/without protective HLA alleles (B*27, B*57, B*58, n=16). We measured CD4 and CD8 T-cell counts, anti-CMV IgG and anti-EBV IgG titers, markers of epithelial gut damage REG3a and I-FABP, markers of microbial translocation LPS, sCD14 and B-D-Glucan (BDG), as well as total IgG, IgM, IgA, IL-1B, IL-6 and kynurenine/tryptophan.

**Results:** As expected, participants with protective HLA alleles had higher CD4 T-cell count compared those without protective alleles (p=0.03). Plasma levels of markers of epithelial gut damage and microbial translocation were similar among EC with and without protective HLA alleles. CMV seropositive and seronegative EC presented with similar age, male/female ratio, and CD4 T-cell counts. Conversely, CMV seropositive EC had elevated CD8 T-cell counts (p<0.001), I-FABP (p=0.04), LPS (p=0.02), BDG (p=0.02), IL-1B (p=0.001), IL-6 (p<0.001), and kynurenine/tryptophan ratio (0.002) compared to CMV seronegative EC. Moreover, anti-CMV IgG titers were also associated with plasma levels of I-FABP (r=0.48, p=0.02), sCD14 (r=0.3; p=0.05), LPS (r=0.42, p=0.04), BDG (r=0.69, p<0.001), IL-1B (r=0.52, p=0.01), and IL-6 (r=0.37, p=0.05). Conversely, anti-EBV IgG titers and total IgG, IgM, IgA were not associated with these markers.

**Conclusion:** Markers of epithelial gut damage, microbial translocation, and inflammation were higher in CMV seropositive EC, irrespective of protective HLA alleles. CMV co-infection emerges as an important contributor to gut damage and microbial translocation and may contribute to non-AIDS comorbidities in EC.

**234 GUT BARRIER PROTECTANT INTESTINAL ALKALINE PHOSPHATASE IS REDUCED IN PEOPLE WITH HIV**


**Background:** Gastrointestinal (GI) microbial translocation in people with HIV (PWH) is associated with systemic immune activation and inflammation. The intestinal brush border enzyme intestinal alkaline phosphatase (IAP) is important for maintaining healthy GI barrier function. IAP promotes intestinal homeostasis by regulating the pH of the gut luminal surface via bicarbonate secretion and by detoxifying lipopolysaccharides (LPS). After IAP dephosphorylates the lipid moiety of LPS, the modified LPS is no longer active to induce proinflammatory responses through TLR4 and subsequent MyD88-dependent signaling pathways in the gut. IAP is reduced in human diseases in which intestinal dysbiosis has been implicated, such as inflammatory bowel disease and diabetes mellitus. Furthermore, exogenously administered IAP reversed intestinal inflammation and metabolic syndrome in animal models. We hypothesized that IAP would be lower in PWH given the known intestinal damage and dysbiosis in PWH.

**Methods:** IAP activity was measured in fluid from the terminal ileum collected by colonoscopy in 30 participants with chronic HIV and 6 controls without HIV. For IAP activity, luminal fluid is mixed with phosphate assay reagent containing p-nitrophenyl phosphate followed by determining optical density at 405nm. All participants did not have known GI disease, and participants with HIV were treated with stable ART > 6 months and had suppressed HIV RNA.

**Results:** In PWH, IAP activity was significantly lower compared to controls (6.25±3.69 (mean±SD) vs 10.98±2.10, p=0.0069). Proinflammatory IL-1β tended to be higher in the intestinal fluid of PWH compared to controls (33.16±7.55 vs 5.97±2.96 pg/mg protein, p=0.099). BMI (27.3±4.3 vs 26.9±4.2 kg/m², p=0.83), and HbA1c (5.5±0.3 vs 5.5±0.4 %, p=0.86) were similar between the groups. Peripheral CD4+ cell count was 729±234 cells/µL in PWH.

**Conclusion:** We demonstrated significantly lower IAP in the terminal ileum of PWH compared to uninfected controls, which has not been reported previously. This novel finding of reduced IAP in PWH may provide additional insight into the pathogenesis of intestinal barrier dysfunction and its associated comorbidities in PWH. Future studies are needed to further elucidate the role of IAP in HIV-associated GI dysfunction and the potential use of exogenous IAP to reduce LPS-mediated inflammation in PWH.
235 IMPACT OF INTRAVENOUS HEROIN AND HIV ON GUT INTEGRITY AND IMMUNE ACTIVATION

Corrilynn O. Hileman1, Emily Bowman2, Janelle Gabriel3, Aaron Kettelhut4, Julia C. Kosco1, Danielle Labbato3, Theresa D. Rodgers1, Cheryl A. Smith1, Nicholas Funderburg1, Grace A. McComsey1

1MetroHealth Medical Center, Cleveland, OH, USA, 2The Ohio State University, Columbus, OH, USA, 3University Hospitals Cleveland Medical Center, Cleveland, OH, USA

**Background:** Altered gut integrity and translocation of microbial products appear to be central in HIV-related immune activation. Opioid use may promote similar changes in gut permeability potentially augmenting immune activation in HIV-infected opioid users. Injection as a route administration may also heighten inflammation. Excess immune activation may increase risk of co-morbid metabolic conditions and contribute to the increased risk of mortality in people with HIV who inject opioids.

**Methods:** HIV+ and HIV- heroin users and HIV+ and HIV- never heroin users were prospectively enrolled. Never users were matched to HIV+ heroin users by sex, age and CD4+ count (HIV+ only). Soluble markers of systemic inflammation, monocyte activation, gut integrity and microbial translocation were quantified by ELISA. ANOVA and multivariable linear regression were used to compare markers between groups and to test for effect modification by HIV status.

**Results:** 100 enrolled (19 HIV+ Heroin+; 38 HIV- Heroin+; 19 HIV+ Heroin-; 24 HIV- Heroin-). Groups were similar except HIV+ Heroin+ had lower trunk fat (p<0.01) and lower current (p=0.02), but similar nadir CD4+ counts. HIV+ groups were more likely to be Hispanic (p<0.01), have active hepatitis c (p<0.01) and be current smokers (p<0.01). Overall, median age was 42 years and 75% were men. For HIV+ groups, median known duration of HIV was 13 years and all but 3 had HIV-1 RNA <200 copies/mL. For Heroin+ groups, 96% were current smokers; 49% also used cocaine and 11% used methamphetamine. Active heroin use was associated with higher soluble tumor necrosis factor alpha receptors-I and –II (sTNF-RI and –II), high sensitivity C-reactive protein (hsCRP), D-dimer, soluble CD14 (trend only), soluble CD163, LPS binding protein (LBP) and beta-D-glucan independent of HIV status, age, sex, race, trunk fat, hepatitis c and smoking. HIV was only associated with sCD14 and LBP, with other putative measures of gut barrier integrity. Surfactant D appeared to be associated with sTNFRI (rho: 0.39, P=0.03) and IL-6 (rho: 0.58, P=0.002).

**Conclusion:** IV heroin use is associated with immune activation and altered gut integrity. Although not statistically significant, some markers were higher in HIV+ than HIV- heroin users which may portend higher risk of poor outcomes.

236 VALGANCICLOVIR EFFECTS ON GUT AND PULMONARY EPITHELIAL BARRIER MARKERS IN TREATED HIV

Sabrina Sevilla1, Gabrielle B. Beck-Engeser1, Vanessa A. York1, Rebecca Hoh1, Steven G. Deeks2, Jeffrey N. Martin3, Barbara L. Shacklett3, Laurence Huang1, Ma Somsouk4, Peter W. Hunt5

1University of Nevada—Reno, Reno, NV, USA, 2University of California San Francisco, San Francisco, CA, USA, 3University of California Davis, Davis, CA, USA

**Background:** The CMV drug valganciclovir broadly suppressed markers of innate and adaptive immune activation in a trial of people living with HIV (PLWH) with incomplete CD4 recovery during antiretroviral therapy (ART). As CMV replicates in and is shed from gut and pulmonary mucosa, we hypothesized that valganciclovir might affect soluble markers of gut and pulmonary epithelial barrier function.

**Methods:** Plasma was assessed from a placebo-controlled trial of valganciclovir (900mg daily for 8 weeks) among 30 HIV/CMV co-infected individuals with incomplete ART-mediated CD4 recovery and high CD8+ T cell activation (>10% CD38+ HLA-DR+ CD8+ T cells). Markers of gut barrier dysfunction (sCD14, LPS binding protein [LBP], intestinal fatty acid binding protein [I-FABP], B-D-glucan, and regenerating islet-derived protein-3a [Reg3a]) and pulmonary barrier dysfunction (clara cell secretory protein [CC16], surfactant D) were assessed every 4 weeks. Changes from baseline at each timepoint were compared between arms with linear mixed models, log-transforming variables and normalizing to the baseline interquartile range (IQR) to facilitate comparisons between biomarkers.

**Results:** Among 14 valganciclovir-treated and 16 placebo-treated PLWH, most (93%) were men. 9 (30%) had detectable plasma HIV RNA levels, and median CD4 count was 190 cells/mm³. At baseline, there were significant correlations between sCD14 and both I-FABP and B-D-glucan (rho: 0.19-0.21, P<0.05), but not with other putative measures of gut barrier integrity. Surfactant D appeared to be associated with sTNFRI (rho: 0.39, P<0.03) and IL-6 (rho: 0.58, P=0.002). In the valganciclovir arm, sCD14 declined by over a quartile from baseline, an effect that persisted for 4 weeks after treatment cessation and was significantly greater than placebo at weeks 4 and 12 (see Table). LBP also appeared to decline by over a quartile in the valganclovir arm through week 12. Less consistent changes were observed in other markers of gut and pulmonary barrier dysfunction.

**Conclusion:** Treating asymptomatic CMV for 8 weeks in PLWH with incomplete ART-mediated CD4 recovery significantly reduces sCD14 and LBP, without clear effects on more specific markers of microbial translocation and epithelial barrier function. Given high within-subject variability for some of these analytes and the potential for greater effects with longer treatment duration, a longer and larger trial of treating asymptomatic CMV infection is required to definitively test these hypotheses in vivo.
237 LIPID ABNORMALITIES MAY CONTRIBUTE TO ALTERED MACROPHAGE PHENOTYPE IN PEOPLE WITH HIV

Emily Bowman 1, Brian Richardson 1, Manjusha Kulkarni 1, Aaren Kettelhut 1, Janelle Gabriel 1, Morgan Cichon 1, Kenneth Riedl 1, Subha Raman 1, Susan L. Koleta 1, Cheryl A. Cameron 1, Mark Cameron 1, Nicholas Funderburg 1, 2

1The Ohio State University, Columbus, OH, USA, 2Case Western Reserve University, Cleveland, OH, USA

Background: Lipid abnormalities in HIV infection may contribute to atherosclerosis and increased cardiovascular disease (CVD) risk. Macrophages accumulate in arterial walls and produce factors that contribute to vascular inflammation. The relationships among lipids and macrophage phenotype in people with HIV (PWH) are unclear.

Methods: Coronary artery calcification (CAC) in people with (n=40) and without (n=15) HIV was quantified by computed tomography scanning. PBMCs from HIV+ART+ (n=20) and HIV- donors (n=20) were cultured for 5 days in medium containing 20% autologous serum to generate monocyte derived macrophages (MDMs). Concentration and composition of serum lipids was measured by mass spectrometry. MDM transcriptomes and differential gene expression (DGE) were analyzed using our R Bioconductor pipeline. Foam cell formation was assessed by Bodipy staining. Immune activation was assessed by flow cytometry.

Results: PWH (ages 27-67) had significantly increased CAC scores compared to people without HIV (ages 25-70) (CAC=9.1 ± 2.5, p=0.010). Traditional risk factors and systemic inflammation/immune activation were more prevalent among people with HIV (PWH) for the first time and determine its relationship to HIV-specific factors and systemic inflammation/immune activation. We sought to investigate FCP in people with HIV (PWH) for the first time and determine its relationship to HIV-specific factors and systemic inflammation/immune activation.

Methods: FCP was evaluated as a continuous variable and by thresholds.

Conclusion: Fecal calprotectin (FCP), a biomarker of gastrointestinal inflammation, is used in the diagnosis and management of inflammatory bowel disease. HIV infection severely damages gut-associated lymphoid and epithelial tissues leading to gut inflammation, microbial translocation and systemic inflammation/immune activation. We sought to investigate FCP in people with HIV (PWH) for the first time and determine its relationship to HIV-specific factors and systemic inflammation/immune activation.

Methods: FCP-naive to ART, ART-treated and uninfected controls were prospectively enrolled. Stool samples were collected and FCP was measured by ELISA. Plasma biomarkers of inflammation/immune activation were also measured. FCP was evaluated as a continuous variable and by thresholds. Spearman correlations were used to investigate associations with FCP.

Results: 101 PWH (83 ART-naive, 18 naive) and 89 uninfected controls were enrolled. ART-treated were older than naive (51 vs 31 years; P=0.006), but sex and race were similar (overall 78% males, 66% blacks). All but one ART-treated had HIV RNA <200 copies/mL, CD4 counts for treated and naive were 683 and 410 cells/µL, resp. Controls had a median age of 37 yrs (78% males, 22% blacks). There was a difference (P=0.001) in FCP among the 3 groups with the highest median (25th, 75th %ile) FCP in ART-naive [144 (33, 262) µg/g] followed by ART-treated (78 (36, 141) µg/g) and then controls (41 (21, 89) µg/g). Fig. 56% of ART-naive had FCP >100 µg/g vs 37% in treated and 19% in controls (P=0.0003).

In PWH, high-sensitivity C-reactive protein (hs-CRP) measured by ELISA. Plasma biomarkers of inflammation/immune activation were also measured. FCP was evaluated as a continuous variable and by thresholds. Spearman correlations were used to investigate associations with FCP.

Results: Among PWH and controls, at baseline, there were no statistically significant differences in concentrations of total lipids. With the exercise intervention, changes in total triacylglycerol (TAG) levels significantly differed among people with and without HIV (unadj-p=0.006, adj-p=0.078). Tags tended to decrease in PWH (Change: -4.5 [-14.1, 6.2]), but significantly increased in controls after 24 weeks of exercise (% Change: 14.7 [6, 24]). Concentrations of TAG species (Table) composed of long chain fatty acids increased among uninfected controls but not PWH (unadj-p=0.001-0.036, adj-p=0.10-0.12) from baseline to week 24. Total diacylglycerols (DAGs) increased in PWH from baseline to week 24 (% Change: 6.1 [0, 12.5]), but decreased in controls (% Change: -5.1 [-12.7, 3.2]) (unadj-p=0.03, adj-p=0.2). Baseline to week 24 changes in specific DAGs composed of palmitic acid (16:0), palmitoleic acid (16:1), and stearic acid (18:0) varied by serostatus, with increases in PWH (unadj-p=0.009-0.03; adj-p=0.10-0.12) and non-significant decreases in controls (Table). The change in concentrations of lysophosphatidylcholine (LPC) species composed of saturated fatty acids (LPC FA(15:0;16:0;17:0)) also differed by serostatus, with increases in PWH and decreases among controls (unadj-p=0.02-0.05; adj-p=0.12-0.21; Table).

Conclusion: Although exploratory, the effects of exercise on the plasma lipidome may differ among people with and without HIV, potentially due to underlying alterations in lipid processing and fatty acid oxidation in PWH.

239 FECAL CALPROTECTIN IS ELEVATED IN HIV AND RELATED TO SYSTEMIC INFLAMMATION

Allison Ross Eckard 1, Nancy L. Hagoed 1, Heather Y. Hughes 1, Mary Ann O’Riordan 1, Danielle Labbato 1, Sarah E. Scott 1, Grace A. McComsey 1, 2

1Medical University of South Carolina, Charleston, SC, USA, 2University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Background: Fecal calprotectin (FCP), a biomarker of gastrointestinal inflammation, is used in the diagnosis and management of inflammatory bowel disease. HIV infection severely damages gut-associated lymphoid and epithelial tissues leading to gut inflammation, microbial translocation and systemic inflammation/immune activation. We sought to investigate FCP in people with HIV (PWH) for the first time and determine its relationship to HIV-specific factors and systemic inflammation/immune activation.

Methods: Plasma biomarkers of inflammation/immune activation were also measured. FCP was evaluated as a continuous variable and by thresholds. Spearman correlations were used to investigate associations with FCP.

Results: 101 PWH (83 ART-naive, 18 naive) and 89 uninfected controls were enrolled. ART-treated were older than naive (51 vs 31 years; P=0.006), but sex and race were similar (overall 78% males, 66% blacks). All but one ART-treated had HIV RNA <200 copies/mL, CD4 counts for treated and naive were 683 and 410 cells/µL, resp. Controls had a median age of 37 yrs (78% males, 22% blacks). There was a difference (P=0.001) in FCP among the 3 groups with the highest median (25th, 75th %ile) FCP in ART-naive [144 (33, 262) µg/g] followed by ART-treated (78 (36, 141) µg/g) and then controls (41 (21, 89) µg/g). Fig. 56% of ART-naive had FCP >100 µg/g vs 37% in treated and 19% in controls (P=0.0003).

In PWH, high-sensitivity C-reactive protein (hs-CRP) measured by ELISA. Plasma biomarkers of inflammation/immune activation were also measured. FCP was evaluated as a continuous variable and by thresholds. Spearman correlations were used to investigate associations with FCP.

Results: Among PWH and controls, at baseline, there were no statistically significant differences in concentrations of total lipids. With the exercise intervention, changes in total triacylglycerol (TAG) levels significantly differed among people with and without HIV (unadj-p=0.006, adj-p=0.078). Tags tended to decrease in PWH (Change: -4.5 [-14.1, 6.2]), but significantly increased in controls after 24 weeks of exercise (% Change: 14.7 [6, 24]). Concentrations of TAG species (Table) composed of long chain fatty acids increased among uninfected controls but not PWH (unadj-p=0.001-0.036, adj-p=0.10-0.12) from baseline to week 24. Total diacylglycerols (DAGs) increased in PWH from baseline to week 24 (% Change: 6.1 [0, 12.5]), but decreased in controls (% Change: -5.1 [-12.7, 3.2]) (unadj-p=0.03, adj-p=0.2). Baseline to week 24 changes in specific DAGs composed of palmitic acid (16:0), palmitoleic acid (16:1), and stearic acid (18:0) varied by serostatus, with increases in PWH (unadj-p=0.009-0.03; adj-p=0.10-0.12) and non-significant decreases in controls (Table). The change in concentrations of lysophosphatidylcholine (LPC) species composed of saturated fatty acids (LPC FA(15:0;16:0;17:0)) also differed by serostatus, with increases in PWH and decreases among controls (unadj-p=0.02-0.05; adj-p=0.12-0.21; Table).

Conclusion: Although exploratory, the effects of exercise on the plasma lipidome may differ among people with and without HIV, potentially due to underlying alterations in lipid processing and fatty acid oxidation in PWH.
240 LONG-TERM ELEVATED IL-6 AND D-DIMER AFTER DELAYED ART INITIATION IN THE START TRIAL

Jason V. Baker1, Birgit Grund2, Shweta Sharma2, Keith Henry1, Jennifer Hoy1, Stefan Esser1, Silvia Nozza2, Kiat Ruxrangthan2, Adam Rupert1, H. Clifford Lane3, Jens D. Lundgren4, James Neaton2, for the INSIGHT START Study Group.

Background: Inflammation and coagulation are associated with disease risk among persons with HIV. ART reduces inflammation, but whether time of initiation during infection affects this reduction has not been studied experimentally. We report on the interleukin-6 (IL-6) and D-dimer trajectories in the immediate versus deferred arms of the START trial.

Methods: In participants randomized to immediate (CD4>500 cells/µL) vs. deferred (CD4 <350 cells/µL) ART initiation, IL-6 and D-dimer levels were measured from stored plasma specimens at baseline, month 8, and annually up to 7 years. Mean changes from entry and from start of ART in log2-transformed concentrations are positively correlated with several markers of systemic inflammation/immune activation, and negatively with CD4. FCP may serve as a useful biomarker to monitor gastrointestinal inflammation and associated systemic inflammation/immune activation in HIV.

Results: In participants randomized to immediate (CD4>500 cells/µL) vs. deferred (CD4 <350 cells/µL) ART initiation, IL-6 and D-dimer levels were measured from stored plasma specimens at baseline, month 8, and annually up to 7 years. Mean changes from entry and from start of ART in log2-transformed concentrations are positively correlated with several markers of systemic inflammation/immune activation, and negatively with CD4. FCP may serve as a useful biomarker to monitor gastrointestinal inflammation and associated systemic inflammation/immune activation in HIV.

Conclusion: Compared to immediate ART, deferral of ART was associated with higher levels of IL-6 and D-dimer over at least 5 years. During the first 2 years of ART treatment, despite viral suppression in both groups, biomarker levels were higher in the deferred compared to immediate group. Follow-up continues in START to determine the clinical consequences of excess inflammation from delayed diagnosis and treatment.

241 NON-AIDS-DEFINING EVENTS IN HIV CONTROLLERS VS ART-CONTROLLED PATIENTS

Carmelita Audrey Manto Kuidjo1, Alicia Castro Gordon2, Cécile Goujard2, Laurence Meyer1, Olivier Lambotte1, Asma Essat1, Arnoo Shallykova1, Farouky Boufassa1, Nicolas Noel1, for the ANRS CO21 CODEX and CO6 PRIMO Study Groups.

Background: HIV controllers (HICs) are rare persons living with HIV who spontaneously maintain low or undetectable viremia. Low-grade chronic inflammation persisting in this population could lead to higher rates of non-AIDS defining events (nADEs) than in patients who achieve low or undetectable viremia on antiretroviral therapy (ART).

Methods: From the ongoing multicenter ANRS CODEX cohort, we enrolled 315 HIV controllers with a known HIV-1 infection ≥5 years, with at least 5 consecutive viral loads (VL) below 400 HIV RNA copies/ml in the absence of ART. The ongoing multicenter ANRS PRIMO Cohort enrolls HIV-1 infected patients diagnosed during primary infection (≤3 months). From this latter cohort, we included 328 patients who initiated ART ≤1 month after the diagnosis, with undetectable VL ≤12 months following ART initiation and for at least 5 years (“ART-subjects”). Incidence rates (IR) of first nADEs, i.e. malignancies, cardiovascular, pulmonary, hepatic, psychiatric or bone events were compared between HICs and ART-subjects; potential determinants were assessed by using Cox regression models.

Results: The most common events observed in the 2 cohorts were non-AIDS related infections (36.9%), psychiatric (17.2%), cardiovascular (6.8%), and malignancies (6.1%), with no statistically significant differences in distribution between the 2 cohorts. Two and 4 non-AIDS related deaths were observed among HICs and ART subjects, respectively. All-cause nADEs incidence rates were 2.8 per 100 person-years (py) and 5.3 per 100 py among HICs and ART subjects, respectively (Hazard Ratio HR=0.53 [95% Confidence Interval 95%CI), 0.40-0.71]. After adjustment for the cohort, demographic and immunological characteristics, the only other factor associated with all cause nADEs occurrence was age 36-43 (vs. 18-29) years at beginning of control (HR=1.56 [95%CI, 1.06-2.30]). Baseline CD4 T-cell count or nadir, CD4/CD8 ratio, history of viral blips, HBV/HCV co-infection and tobacco use, were not associated with an increased risk of nADEs.

Conclusion: HICs, defined on the basis of ≥5-year period of spontaneous viral control, experienced two times less nADEs than virologically suppressed patients on ART. Age was the only other factor independently associated with nADEs occurrence, irrespective of immune or virologic parameters. These results do not argue in favor of expanding the indication for ART for HICs subjects but rather a case-by-case approach considering clinical outcomes such as nADEs besides immune activation.

242 TOTAL HIV DNA LEVELS DO NOT PREDICT NON-AIDS-DEFINING EVENTS

Colline Wong1, Ashley McKhann1, Carlee Moser1, Alan Landay1, Michael M. Lederman1, Sara Gianella1, Jonathan Z. Li1.
Background: Despite antiretroviral therapy (ART), individuals with HIV maintain an HIV reservoir with high levels of systemic inflammation and are more likely to have non-AIDS-defining events compared to those without HIV. We performed a case-control study of AIDS Clinical Trials Group (ACTG) participants to assess the relationship of HIV reservoir size with levels of systemic inflammation, viral co-infections, and risk of non-AIDS-defining events.

Methods: Participants were ART-naive at the time of enrollment, maintained plasma HIV-1 RNA levels <400 copies/mL after ART initiation, and were part of a long-term ACTG follow-up cohort. Cases were defined as participants who had a non-AIDS-related event (Mi, stroke, non-AIDS-defining malignancy, serious bacterial infection, or death from a non-AIDS-defining event). Controls were identified and matched based on age, sex, baseline CD4+ T-cell count, and ART regimen. PBMCs and plasma specimens were collected from both 1 year after ART initiation and at the pre-event time point, and analyzed for levels of IL-6, sCD14, interferon γ (IFN-γ), inducible protein 10 (IP10), sTNFR-I, sTNFR-II, D-dimer, CMV, and EBV DNA and antibody levels. T-cell phenotyping was performed by flow cytometry. Total HIV DNA levels in PBMCs were measured by qPCR. Adjusted and unadjusted conditional logistic regression analyses were performed to determine if HIV DNA levels predicted the occurrence of non-AIDS-defining events.

Results: Samples from 102 cases and 201 controls at year 1 and from 65 cases and 110 controls pre-event were included. Total HIV DNA levels at either 1 year after ART initiation or pre-event were not predictive of non-AIDS-defining events, supporting sTNFrII as the primary endpoint of ACTG studies of lortemovir and anti-CMV vaccine.
2.96, 95% Confidence Interval [CI] 1.30-6.74), cancer (OR 1.83, CI 1.11-3.02), and dyslipidemia (OR 4.02, CI 2.90-5.58).

**Conclusion:** Pre-treatment immune injury may persist as assessed by T4/T8 which may not resolve even with prolonged viral suppression and may have clinical consequences in aging PWH.

**Figure:** Percent of participants with T4/T8 ≥ 0.7 by baseline age group and year of follow-up, the HIV Outpatient Study, n = 1,910.

---

245 SYSTEMIC AND VASCULAR INFLAMMATION PREDICT COMORBIDITIES IN TREATED HIV INFECTION


1University College Dublin, Dublin, Ireland, 2Mater Misericordiae University Hospital, Dublin, Ireland, 3Rush University Medical Center, Chicago, IL, USA

**Background:** Although inflammation and immune dysfunction are implicated in pathogenesis of comorbidities in treated people with HIV (PWH), whether an immune risk profile can predict PWH at higher risk of comorbidity is unclear.

**Methods:** In the UCD Infectious Diseases cohort study of PWH on anti-retroviral therapy, we measured 24 biomarkers using bead-based quantitative ELISA, covering pathways of systemic inflammation (hsCRP, IL6, TNFR1,2, TNFα), innate immune activation (SCD14, SCID13, MCP1, MIP1, SCD40), endothelial function (P-selectin, Eselectin, sICAM, sVCAM), coagulation (D-dimer, vWF) and intestinal permeability (IL18, LBP). Principal component analysis was performed followed by unsupervised hierarchical clustering to partition subjects into biomarker derived clusters. Logistic regression assessed association between clusters and prevalent comorbidities (CVD, kidney, liver, hypertension, dyslipidemia). Data are median[IQR] or odds ratio (OR) [95%CI].

**Results:** We included 99 PWH, age 41 (36, 48) years; 44% male; 54% African; 93% with HIVVL<40cps/ml, duration of ART 7.1 (2.3, 10.8) years. We observed 3 distinct clusters, two characterized by higher inflammation; cluster 2 (19%), only cluster 3 was associated with prevalent comorbidities (CVD, kidney, liver, hypertension, dyslipidemia). Data are median[IQR] or odds ratio (OR) [95%CI].

**Conclusion:** We have identified distinct inflammatory pathways in treated PWH that predict prevalent co-morbidities. That these patterns, characterized by pathways including systemic and vascular inflammation remain associated with clinical outcomes even after correction for CMV and CD4:CD8 ratio suggest a number of distinct pathways contributing to co-morbidities in PWH.
**247 INCREASED GUT AND BLOOD CD4+ T-CELL EXHAUSTION IN IMMUNOLOGICAL NONRESPONDERS**

Kristina B. Lervik¹, Malin H. Meyer-Myklestad², Asle W. Medhus¹, Marius Lund-Iversen¹, Birgitte Stiksrud¹, Dag Kvale¹, Anne Ma D. Riise¹, Dag Henrik Reikvam¹, Kjetil Taskén¹

¹Oxol University Hospital, Oslo, Norway, ²University of Oslo, Oslo, Norway

**Background:** Immunological non-responders (INR) have increased inflammation and non-AIDS related morbidity. We hypothesized that their insufficient immune recovery is associated with a gut-induced exhausted T cell phenotype.

**Methods:** Blood samples and mucosal biopsies from terminal ileum and sigmoid colon were collected from Caucasian men: 19 INR (ART>4 years with HIV RNA <50 copies/ml and CD4 count <400 cells/µl for <3.5 years); 20 immunological responders (IR) (ART>4 years with HIV RNA <50 copies/ml and CD4 count >600 cells/µl for >3.5 years) matched on nadir CD4 count and age; and 20 age-matched healthy HIV-negative controls (HC). Peripheral blood and lamina propria mononuclear cells were analyzed with a multi-color flow cytometry panel to investigate the expression of the exhaustion markers PDL1 and TIM3 in additional to T cell surface markers CD3, CD4, CD8, CD45RA, CD45RO, CD45RA/RO, CD25, CD38, CD127, HLA DR and the gut homing marker integrin β7. Immunohistochemistry was applied to detect PDL1 ligand 1 (PD-L1).

**Results:** INR had increased fractions of PD1+ and TIM3+ CD4+ T cells compared with IR and HC both in blood (p<0.01) and gut (p<0.05). PD1 and TIM3 expression in blood and gut both correlated negatively with systemic CD4/CD8 ratio. In the blood, but not in the gut, INR had more activated (def.: CD45RAneg) gut-homing B/High CD4+ T cells than both IR and HC (p<0.05), but these cells did not display more exhaustion markers than activated non-gut homing CD4+ T cells. Immunohistochemistry staining of gut biopsies showed that neither INR nor IR expressed PD-L1.

**Conclusion:** INR have a more exhausted CD4+ T cell pool than IR, both in blood and gut, supporting the hypothesis that T cell exhaustion may be a contributor to insufficient immunological response to ART. The higher prevalence of blood activated gut-homing CD4+ T cells in INR implies an enhanced stimulation and activation CD4+ T cells in the gut of INR compared with IR, but this feature is not associated with differential expression of PD-L1.

**248 NOVEL MECHANISM OF HIV-1 ELITE CONTROL BY ENRICHING GUT DIPEPTIDES AS CCR5-ANTAGONIST**

Ujjwal Neogi¹, Maika Spirk¹, Flora Mikaeloff¹, Ashokkumar Manickam¹, Anoop T. Ambikar¹, Kamleendra Singh¹, Jan Vesterbacka², Anders Sonneberg²

¹Karolinska Institute, Stockholm, Sweden, ²University of Missouri St Louis, St Louis, MO, USA

**Background:** A small subset (<0.5%) of HIV-1 positive individuals, the “Elite Controllers” (EC), controls viral replication for a long duration of time without receiving antiretroviral therapy. Due to the lack of data from well-controlled clinical EC cohorts, the mechanisms by which EC can control the virus remain mostly unknown. Transcriptomics analysis of blood cells has shown that CCR5 was downregulated in EC compared to viremic progressors (VP). Here we used untargeted plasma and fecal metabolomics to identify the metabolicomic signature in EC followed by in vitro and ex vivo mechanistic studies.

**Methods:** Blood and fecal material were collected from EC (n=14), matched HIV-negative (HC, n=12) and VP (n=16). Untargeted metabolomics was performed by Ultra-High-Performance Liquid Chromatography/Mass Spectrometry/Mass Spectrometry (UHPLC/MS/MS). Microscale thermophoresis (MST) was performed to describe the peptide-protein interactions. Viral infection and release assays were performed in TZMBl-cell lines and primary CD4+ T-cells, respectively. The significance was considered p<0.05 and false discovery rate <0.1.

**Results:** In total 825 biochemicals were identified in feces and 950 biochemicals in plasma of which 485 and 294 biochemicals had group effects identified by ANOVA in fecal and plasma samples respectively. The top 30 metabolites important for group separation identified by random forest analysis were part of lipid metabolism, nucleotide metabolism, and amino acid metabolism. However, among the 19 identified peptides 79% (15/19) were significantly enriched in EC compared to HC and VP in feces. Of these, 47% (7/15) were significantly enriched in the plasma of EC compared to VP. We synthesized these seven dipeptides in amide forms (DP-am) and performed MST with protease and gp120 proteins. The DP-am binds to gp120 but not to the protease.

This was further supported by infection assays in TZMBl cell lines which gave an EC₅₀ ranging from 3.5µM to 49.1µM in HIV-1 subtype B and C. CCR5-tropic viruses but not CCR4-tropic viruses. The viral release assay showed significantly low released measured by p24 in presence of DP-am.

**Conclusion:** We posit that the enriched dipeptides act as CCR5-antagonist that efficiently controls viral replication in EC, and this mechanism contributes to the efficient HIV elite control status.

**249 OVERT GUT IL-32 ISOFORM EXPRESSION DURING TREATED HIV INFECTION: REGULATION BY IL-17A**

Etienne Moreira Gabriel¹, Tomas Wiche Salinas¹, Mohamed El-Far², Etienne Larouche-Antcl³, Annie Gosselin¹, Madeleine Durand¹, Jean-Pierre Routy¹, Cécile L. Tremblay¹, Petronela Ancuta¹

¹Centre de Recherche du CHUM, Montreal, QC, Canada, ²McGill University, Montreal, QC, Canada

**Background:** The interplay between intestinal epithelial cells (IEC) and Th17 cells is key for mucosal immunity homeostasis. HIV infection provokes intestinal barrier function impairment and chronic immune activation, which are not normalized by antiretroviral therapy (ART). Such alterations coincide with the overexpression of IL-32, a newly described cytokine, with multiple isoforms. IL-32 overexpression was predictive of the loss of viral control in HIV slow progressors and associated with non-AIDS co-morbidities such as cardiovascular disease (CVD). The role of specific IL-32 isoforms in HIV pathogenesis remains poorly investigated. Here, we quantified the expression of IL-32 isoforms in the colon and blood of ART-treated people living with HIV (ART+PHLV), and explored the regulation of IL-32 expression by the Th17 hallmark cytokine IL-17A.

**Methods:** Matched PBMC and sigmoid colon biopsies were available from n=17 ART+PHLV (median age: 55 years; CD4 counts: 679 cells/µl; time on ART: 72 months) and n=5 age-matched HIV-uninfected controls. The HT-29 IEC line was used to study the modulation of IL-32 expression upon exposure to recombinant TNF-α and/or IL-17A, the Th17-agonist Poly I:C, or the HIV N4L3.3B or THRO strains. IL-32a, β, γ, ε, and δ mRNA expression was measured by real-time RT-PCR. IL-32 protein production was measured in cell-culture supernatant and cell lysates by ELISA.

**Results:** Our results reveal a significant increase in IL-32 mRNA expression, specifically IL-32β and γ, in colon biopsies and PBMC of ART+PHLV compared to uninfected controls. IL-32 mRNA expression, especially IL-32β, and γ was induced by exposure of HT-29 cells to recombinant TNF-α, Poly I:C, and HIV THRO strain. IL-32 mRNA levels positively correlated with intracellular IL-32 protein expression, but no soluble IL-32 was detected in cell culture supernatants indicative that IL-32 protein expression in IEC is mainly intracellular. Of note, recombinant IL-17A significantly decreased IL-32 mRNA/protein expression induced by TNF-α and Poly I:C, supporting an immune-regulatory role played by IL-17A.

**Conclusion:** Our results document the overexpression of specific IL-32 isoforms in colon biopsies and PBMC of ART-treated PHLV and point to the negative consequences of mucosal Th17 paucity, in line with our discovery that IL-17A acts as a negative regulator of IL-32 isoforms with pro-inflammatory and/or antiviral features.
250 DISTINCT INTERFEROMES ASSOCIATE WITH CHRONIC HIV PATHOGENESIS IN THE GUT

Stephanie Dillon1, Kejun Guo2, Guanan Shen1, Harry Smith3, Miranda E. Kroehl4, Katerina Kecheil1, Cara Wilson5, Mario Santiago1
1University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Background: Type I Interferons (IFN-Is) protect against early HIV infection, but were linked to pathogenesis during the chronic stages. Previously, we showed that IFNβ, but not IFNα, was upregulated in the colon of chronically infected people with HIV (PWH) relative to uninfected persons (PMID29762170). To gain understanding on how IFNβ may influence chronic gut HIV pathogenesis, we profiled the transcriptome of uninfected gut CD4 T cells exposed to dominant IFNα subtypes or IFNβ in vitro. This analysis revealed a set of IFN-stimulated genes (ISGs) upregulated by all IFN-Is tested (core ISGs) and genes specifically induced by IFNβ (βISGs). Here, we evaluated these 2 gene sets in chronic, untreated HIV-1 infection.

Methods: Colon biopsies (previously collected with informed consent) from 19 untreated, chronically infected PWH (median VL 26000 HIV-1 RNA/ml; median CD4 count 429 cells/μl) and 13 uninfected controls were transcriptomically profiled using RNAseq. Differential gene analysis was conducted using edgeR and correlations between ISGs and clinical/immunological parameters tested using linear regression models adjusted for age and gender and corrected for multiple comparisons. Significance was established at FDR <5% for all analyses.

Results: Of 246 core ISGs, 51% were significantly altered in PWH vs. controls. Of these 126 altered core ISGs, 89% were upregulated in PWH. Upregulated core ISGs included genes linked to innate sensing (e.g. IRF9 3.9x; NLRC5 3.5x), immune activation (e.g. CD38 2.4x) and exhaustion (e.g. LAG3 6.2x). Majority (78%) of altered core ISGs positively correlated with gut IFNβ transcripts and genes specifically induced by IFNβ (βISGs). Here, we evaluated these 2 gene sets in chronic, untreated HIV-1 infection.

Conclusion: Our data reveals a complex picture of how IFNβ may promote HIV pathogenesis in the gut. While IFNβ is associated with increased core ISG expression linked to inflammation, immune activation and exhaustion, it is also linked to decreased expression of genes with potential anti-inflammatory properties. These data could guide IFN-1 blockade strategies to reduce chronic inflammation in PWH.

Figure 1: Overexpression of IL-32β and α forms in the sigmoid colon biopsies of ART-treated PLWH compared to uninfected participants.

Etienne Moreira Gabriel et al., CRIO2020

251 OPPOSING ASSOCIATIONS OF NK AND MZ B CELLS IN RECTAL EXPLAN MODEL OF HIV INFECTION

S. Abigail Smith1, Praveen Kumar Amanuel2, Phillip M. Murray3, Cassie Grimsley-Ackerley1, Rama R. Amara1, Collen F. Kelley1
1Emory University, Atlanta, GA, USA, 2Yerkes National Primate Research Center, Atlanta, GA, USA

Background: Our understanding of innate immune cells in human rectal mucosal tissues (RM) and their contributions to promoting or restricting HIV transmission is limited. Studies focused on systemic responses or utilizing PBMC are not suitable proxies for mucosal responses. Here, we utilized the rectal explant model to elucidate associations between RM innate cell subsets and HIV-1 BAL replication ex vivo.

Methods: Plasmacytoid dendritic cells (pDCs); CD1c+ myeloid DCs; neutrophils; macrophages; natural killer cells (NK); Marginal Zone-like B cells (MZBs); gd T cells; and mucosal-associated invariant T cells were quantified in RM from 69 HIV-negative men aged 18-65 years by flow cytometry. Associations between these cell subsets and HIV replication (p24 production over days 3-18) in ex vivo RM explant challenge experiments from the same study participants were examined. Hierarchical Stochastic Neighbor Embedding (HSNE) analysis was used to compare MZB and NK from blood and RM. From the explant supernatants, longitudinal production of 22 cytokines were quantified via LegendPlex analysis.

Results: In RM, pDCs were the least abundant innate cell subset (p=0.001), while MZB and NK cells were most abundant (p<0.01). There was an inverse correlation between the percentage of NK cells in RM and p24 production in parallel RM explants (r=-0.36, p=0.005); but there was a positive correlation between MZB cells and HIV replication (r=0.69, p<0.0001). No other innate subset was associated with p24 production. Comparison of RM blood and MZB and NK subsets illustrated quantifiable differences (Figure). Of the 22 cytokines quantified, IL17A, IFNg, IL10, IP10, GMCSF, Granzyme A (GzA), Granulysin, and Perforin, were positively correlated with HIV replication (p<0.01 for all). Detection of IL17A, IFNg, IL10, and GMCSF on day 3 positively correlated with HIV replication (p<0.01 for all).

Conclusion: Our data demonstrate novel associations between MZB and NK cells and p24 production in RM, highlighting their potential importance in HIV replication, and that RM NK activity is likely mediated by GzA, Granulysin, and Perforin. Our data also underscore the critical importance of pro-inflammatory cytokines IL17 and IFNg early in mucosal HIV infection. Defining the innate cells subsets and their effector mechanisms that facilitate or hinder HIV infection in RM could identify new targets for biomedical interventions.

Figure 1: Hierarchical Stochastic Neighbor Embedding (HSNE) analysis of blood (red) and rectal mucosal-resident (blue). Marginal Zone-like B cells (left, CD20+; HLA-DR+, CD4+); and Natural Killer cells (right, CD16+/+, CD56+/+)

252 IgA PRESERVATION IN GUT IN SIVagm INFECTION IS ASSOCIATED WITH INFLAMMATION CONTROL

Philippe Rasche1, Cyril Planchais2, Beatrice Jacquelin1, Marie Lazzerini1, Vanessa Contreras3, Hugo Mouquet2, Nicolas Hout4, Michaela Müller-Trutwin5
1Institut Pasteur, Paris, France, 2INSERM, Le Kremlin-Bicetre, France

Background: Lymph nodes (LN) and intestine are the major HIV reservoirs. During SIVagm infection in African Green Monkeys (AGM), NK cells express CXCR5 and migrate into B cell follicles (BCF) of peripheral LN (pLN) where they efficiently control SIVagm replication. In the intestine, SIVagm replicates at high levels but this does not lead to bacterial translocation and chronic inflammation. IgA is important for the control of bacterial translocation and inflammation in the gut. In this study, we aimed at investigating whether there is a link between...
ALKED DNA METHYLATION OF CCR5 IN SIGMOID MUCOSAL TISSUES OF TRANSGENDER THAI WOMEN

Hence, we propose that the viral control in BCF could help maintaining normal and inflammation in SIVmac infection, with a dramatic loss of intestinal IgA in uninfected MAC (mean=0.54-0.42AU), but strongly decreased in chronically infected (mean=0.51-0.45AU) and non-infected animals (mean=0.49-0.44AU). In acute SIVmac infection, intestinal IgA levels were similar to those of uninfected MAC (mean=0.59-0.49AU), but strongly decreased in chronically infected animals (mean=0.17-0.24AU). Similarly, IgA were decreased in BCF of chronically infected MAC. There was a negative correlation between serum IgA and IgA levels in MAC (p=0.0007; r=0.32) and not in AGM (p=0.72; r=0.072). Conclusions: Our data unravel the involvement of gut IgA titres and inflammation in SIVmac infection, with a dramatic loss of intestinal IgA in SIV-infected MAC while IgA levels in chronic SIVmac infection remain stable. Hence, we propose that the viral control in BCF could help maintaining normal IgA responses and a better control of gut inflammation.

ALTERED DNA METHYLATION OF CCR5 IN SIGMOID MUCOSAL TISSUES OF TRANSGENDER THAI WOMEN

Michael J. Corley1, Alexandra Schuetz2, Alina P. Pang3, Carlo Sacdalan3, Suchada Sukhumvitaya4, Nitya Chomche4, Nisakorn Ratnarat4, Yuwadee Phuangs-nern5, Jintanat Ananworanich6, Eugène Kroon7, Nittaya Phanuphak7, Sandhya Vasani8, Lishowma C. Nkolu9, for the SChEnOCT/RS034 study group1, University of Hawaii, Honolulu, HI, USA, 2Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand, 3Thai Red Cross AIDS Research Center, Bangkok, Thailand, 4US Military HIV Research Program, Silver Spring, MD, USA.

Background: Transgender women (TGW) have a high overall prevalence of HIV. Lifestyle factors including hormone use have been shown to alter epigenetic modifications in TCGW, which may link exogenous factors and altered HIV-related cell gene regulation leading to increased risk of HIV transmission.

Methods: In a pilot study of HIV uninfected Thai volunteers, cross-sectional sigmoid mucosa biopsies were obtained from men who have sex with men (MSM, n=10), cisgender women not on hormonal contraception (CW, n=9), and TGW who had undergone gender affirmation surgery and remained on hormonal therapy (n=3). DNA methylation was measured genome-wide using the HumanMethylationEPIC array on the biopsies. Immunophenotyping of peripheral and mucosal mononuclear cells was performed to assess T cell subsets for CCR5 expression by flow cytometry. Statistical analysis included t-tests, non-parametric tests, and false discovery rate.

Results: Among TCGW, mean age of hormone initiation was 14 years, and sex reassignment surgery 19 yrs. Median duration of hormone use in TGW was 8.5 yrs, with 1/3 using estrogen/progesterone, and 2/3 estrogen only. All TGW reported anal and neovaginal sex and median lifetime sexual partners was significantly higher in TGW compared to CW (p = 0.005). We observed the greatest differences in DNA methylation at 219,788 CpG sites showing absolute mean differences in methylation greater than 5% between TGW and MSM (Δβ-value > 0.05) and significant at FDR adjusted P < 0.05 in sigmoid biopsies. There were fewer differences between TGW and CW (188,833 methylation sites) and even fewer between CW and MSM (5,162 methylation sites). Of known HIV acquisition risk genes, methylation at CpG's at the promoter region of the CCR5 gene were significantly decreased in TGW compared to both CW (p < 0.05) and MSM (p < 0.05). Furthermore, mucosal CCR5+ CD4 T cell frequencies were higher in TGW compared to MSM (p = 0.002), but not different compared to CW (p = 0.419). Notably, methylation levels of CCR5 associated with the frequency of mucosal CCR5+ CD4 T cells (p = 0.018).

Conclusion: The gut mucosal epigenome appears to be altered in TGW compared to CW and MSM Thai volunteers. This occurred at several gene loci including CCR5 that are known to affect HIV susceptibility. Further investigations of biological HIV risk factors specific to TGW are needed to inform additional HIV prevention strategies.

DECREASED EXPRESSION OF MUCOSAL TYPE I IFN RESPONSE IN HIV-INFECTED MSM PATIENTS

Letizia Santinelli1, Alessandra Pierangeli1, Eugenio Nelson Cavallari1, Paolo Gozzo1, Giancarlo Ceccarelli1, Claudio M. Mastroianni1, Raphael Viscidi1, Guido Antonelli1, Gabriella d’Ettorre1, Carolina Scagnolari1

1Sanpienza University of Rome, Rome, Italy, 2Johns Hopkins University, Baltimore, MD, USA.

Background: Innate immunity pathways, especially those related to type I interferon (IFN-I) are involved in Human Papillomavirus (HPV) recognition and clearance. Among HIV-positive patients who have sex with men (MSM), the extremely high incidence of HPV infection is strongly associated with an increased risk of squamous cell carcinoma of the anal canal. We hypothesized that HPV, through evasion strategies adapted to overcome the host immune defense and establish persistent infection, might target different IFN-I genes in HIV-1 infected patients.

Methods: Anal brushings were collected from 86 Caucasian MSM HIV-1 infected patients, from median age of 46 ±11 years, on long-term antiretroviral therapy (ART), attending Policlinico Umberto I Hospital in Rome. Detection of HPV DNA and genotyping were performed by PCR and sequencing. The mRNA levels of IFN alf,aIFN beta, IFN epsilon, an emerging component of innate immune defense and establish persistent infection, might target different IFN-I genes in HIV-1 infected patients.

Results: Anal HPV DNA was detected in 71 MSM patients (83%), with 43% of the cases having a high-risk (HR) HPV genotype, mainly HPV16. Out of 86 patients, 54% showed H5SH/5IL. A decreased mucosal expression of IFN-beta, IFN epsilon, IFNAR1 and IFNAR2 was recorded in HR compared to low-risk (LR) HPV positive and HPV negative patients (Mann-Whitney U test p <0.05 for all genes). There were no differences found on levels of IFN-I components according to the presence or absence of HR. By contrast, the expression of IFN beta, IFN epsilon, IFNAR1 and IFNAR2 was reduced in patients with a persistent HPV infection (18%) compared to those who spontaneously cleared the infection (11%) (Mann-Whitney U test p <0.01 for all genes).

Conclusion: HPV persistent infection may dysregulate IFN-I response and contribute to the establishment of an immunosuppressive microenvironment in mucosal epithelia, which is essential for precarious anal lesions progression.

HIGH-RISK HUMAN PAPILLOMAVIRUS ONCOPROTEINS DYSREGULATE INTERLEUKIN-1 SIGNALING

Hee W. Kim1, Lk Matthew Lam2, Pavithra Rajagopalan2, Devraj Basu2, Elizabeth A. White2

1University of Pennsylvania, Philadelphia, PA, USA.

Background: High-risk human papillomavirus (HPV) infection causes cervical, anogenital, and oropharyngeal cancers that account for ~5% of cancer cases worldwide. The incidence of these AIDS-defining (cervical) or non-AIDS-defining (analo, oropharyngeal) malignancies is increasing among HIV-infected individuals. A mutation in any one of several components of the interleukin-1 (IL-1) signaling pathway predisposes individuals to develop HPV-associated malignancies, suggesting that IL-1 signals restrict either HPV infection or development/progression of HPV-positive neoplasia. IL-1ß is a pro-inflammatory cytokine and the IL-1 pathway is subject to complex regulation.

The purpose of the study was to define the effects of high-risk HPV E6 and E7 oncoproteins on IL-1-related gene expression and signaling.

Methods: We used several models to assess HPV oncoprotein-dependant changes in the IL-1 pathway. First, we compared human keratinocites engineered to express high-risk HPV E6/E7 to negative controls. Complementary experiments used HPV-positive and HPV-negative head and neck squamous cell carcinoma (HNSCC) cell lines. Finally, we employed a panel of HPV-positive and HPV-negative patient-derived xenografts (PDX). In each model we measured the levels of IL-1 signaling-related transcripts, the response of cells to IL-1 and the production of IL-1 upon exposure to the inflammasome-activating agent nigericin.

Results: In both cell lines and PDXs, the presence of HPV oncopogens was associated with decreased expression of IL1B and increased expression of...
256 25-HYDROXYCHOLESTEROL INHIBITS HERPESVIRUSES BY ACTIVATING INFLAMMATORY PATHWAYS

Anna Sergiunia, Takeshi Tagaya, Joseph Ziegelbauer1 1National Cancer Institute, Bethesda, MD, USA

**Background:** Kaposi’s Sarcoma Herpesvirus (KSHV/HHV-8) expresses several viral proteins during latency and lytic replication cycle that block innate immune responses. It is therefore of interest to study antiviral approaches that can tip the balance and help the host mount an effective immune response. Recently, we have described how 25-hydroxycholesterol (25HC), a derivative of cholesterol, can block KSHV de novo infection of primary endothelial cells (HUVEC) at a post-entry step and decreases expression of viral genes. We wanted to determine whether 25HC inhibits other gammaherpesviruses. More importantly, we aimed to study how 25HC exerts its antiviral effect.

**Methods:** To test the antiviral effect of 25HC against Epstein-Barr Virus (EBV), another oncogenic gammaherpesvirus (often co-infecting certain cancers with KSHV, e.g. PEL), we performed de novo infection of primary B cells with 25HC treatment and measured apoptosis using flow cytometry. We also quantitated EBV viral transcript levels using RT-qPCR. To characterize the gene regulatory pathways triggered by 25HC, we performed RNA sequencing (RNA-Seq) of HUVEC treated with 25HC and de novo infected with KSHV. Validation was performed by RT-qPCR. Single and combinatorial siRNA knockdown of candidate target genes screened from RNA-Seq analysis were performed to identify which genes were required for the antiviral activity of 25HC.

**Results:** We found that 25HC increased apoptosis in EBV-infected cells, decreasing the number of EBV-transformed lymphoblastoid cell lines (LCLs). 25HC downregulated an RNA Pol III-transcribed EBV transcript, but not an RNA Pol II EBV transcript. RNA-Seq showed global suppression of KSHV viral gene expression with treatment of 25HC. On the other hand, 25HC increased Type I interferon-stimulated genes (ISGs), including inflammatory cytokines and chemokines. Using single and combinatorial siRNA-mediated knockdown, we found that depletion of certain candidate genes resulted in recovery of viral gene expression, validating their contribution towards the antiviral effect of 25HC in KSHV.

**Conclusion:** 25HC rendered EBV-infected B cells unable to form LCLs. RNA-Seq data showed induction of inflammatory cytokines due to 25HC treatment. Loss-of-function experiments confirmed their role in the antiviral activity of 25HC. Our studies aim to elucidate how we can augment these intrinsic antiviral activities.

258 INTEGRATED ANALYSIS OF MULTICELLULAR IMMUNE DYNAMICS DURING HYPERACUTE HIV INFECTION

Samuel W. Kazer1, Toby P. Aicher1, Daniel M. Muema2, Vincent N. Miao3, Carly G. Ziegler1, Sarah K. Nyquist1, Amber D. Moodley1, Krista Dong1, Zaza Ndlovu1, Thumbi Mungu1, Bruce D. Walker, Alex K. Shalek1

1Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, 2KwaZulu-Natal Research Institute for TB and HIV, Durban, South Africa, 3MIT Institute for Medical Engineering & Science, Cambridge, MA, USA, 4University of KwaZulu-Natal, Durban, South Africa

**Background:** Development of effective vaccines and therapeutics is facilitated by understanding the earliest moments of infection. Studies in [HIV] models have characterized the quality and duration of the interferon-stimulated gene (ISG) response in acute infection. However, longitudinal immune responses to acute HIV infection are underexplored. Moreover, contributions and interactions of different cell subsets are unknown. Here, we longitudinally profile multicellular immune responses in hyper-acute HIV infection detected in Fiebig Stage I.

**Methods:** High-throughput single-cell RNA-seq was performed on peripheral immune cells throughout acute HIV-1 infection (pre-infection, HIV detection – 1 year) on 4 FRESH participants (Dong, The Lancet, 2018). Cell subsets were identified by unsupervised clustering analyses. Shared and cell subset specific immune responses were elucidated using a gene-module discovery approach. Modules were tested for significant changes in expression.
over time and qualitatively compared across individuals. Celluar features of 2 participants who later develop spontaneous control of HIV were also described.

Results: Across all individuals we profiled >39,000 single cells. Onset of viremia induced conserved ISG responses integrated across multiple lymphocyte and myeloid lineages, wherein monocytes and natural killer (NK) cells significantly contributed to the cytokine milieu. Otherwise obscured in bulk analyses, we describe a second layer of responses following ISG upregulation: pro-inflammatory T cell differentiation, prolonged monocyte MHC-II upregulation, and persistent NK cytolytic killing. Predicting upstream drivers, we propose both shared and cell subset specific intra- and inter-cellular regulation by several key cytokines. Two participants who later develop viremic control associated with elevated frequencies of proliferating cytotoxic cells following HIV detection, inclusive of a previously unappreciated proliferating NK cell subset.

Conclusion: We present an experimental and computational framework to longitudinally characterize multicular responses in viral infection at high-resolution in humans. Applied to hyper-acute HIV infection, our approach reveals both cooperative and cell subset specific immune responses with temporal resolution. We nominate cell subsets and signaling pathways to perturb in future vaccines and therapeutics and highlight the importance of monocytes and NK cells in driving coordination and potentially influencing clinical trajectory.

259 UNCOUPLED CELLULAR AND PLASMA MARKERS OF MONOCYTE ACTIVATION IN EARLY HIV INFECTION
Montse Jiménez1, Lucia Pastor Palomo1, Víctor Urrea1, Nuria Izquierdo-Useros1, Javier Martinez-Picado1, Inacio Mandomando3, Chenjerai Jairoce3, Bonaventura Clotet1, Jorge Carrillo1, Denise Naniche2, Julià Blanco1, Montse Jiménez1

Plasma HIV viremia peaked at one month after infection and remaining at high levels during the first year of infection. Furthermore, CD16+ monocytes showed significantly higher levels of Siglec-1, suggesting that CD16+ and Siglec-1+ monocytes were activated by different pathways.

Conclusion: Early monocyte activation and plasma IFN-a levels showed similar dynamics during PHI. In contrast, CD16 expression significantly increased after 6 months of infection and was uncoupled from plasma sCD14 and sCD163 levels. Considering the role of activated monocytes in cardiovascular disorders and aging of the innate immune system, an early treatment may potentially reduce monocyte activation, resulting in long-term clinical benefit.

260 IMMUNOLOGICAL AND CYTOKINE CHANGES IN BLOOD AND GUT MUCOSA FROM PHI BY AN EARLY ART
Nuria Climent1, Juan Ambrosioni1, David Nicolas2, M.J. Maleno1, L. Miralles1, Carmen Hurtado1, Marta Subirana1, Carmen Ligerot1, Cristina Rodriguez De Miguel1, Josep Llach2, Michael Meulbroek2, Sonosoles Sanchez-Palomino1, Jose M. Mira2, Montserrat Plana1, for the Hospital Clinic PHI Investigators

During PHI, the frequency of these monocytes were significantly increased in untreated CHI patients compared to HIV-uninfected individuals (p<0.005). During PHI, CD16– monocytes showed significantly increased in untreated CHI patients compared to HIV-uninfected individuals (p<0.005). Considering the role of activated monocytes in cardiovascular disorders and aging of the innate immune system, an early treatment may potentially reduce monocyte activation, resulting in long-term clinical benefit.

Methods: Patients started an intensified ART consisting on abacavir/lamivudine/dolutegravir regimen during 48 weeks plus darunavir-boost and maraviroc the first 12 weeks. Rectoscopies were done at w0 and w48. Immunological subsets in blood (PBMC) and rectal tissue (MMC) were compared between w0 and w48 and between cases (Fiebig I-II, n=6) and controls (Fiebig III-IV, n=11) by multi-parametric flow cytometry. The analysis of 25 cytokines on rectal fluid was performed using Luminex assay. Clinical Trials NCT02588820.

Results: At w48, all except one patient in the controls had undetectable plasma VL. At w48, a higher increase of blood CD4+ T cells was observed in cases (from 39.35% to 47.47% p<0.031) than in controls (from 36.50% to 36.10%, p<0.05). CD4/CD8 ratio was also higher in cases both in PBMCs and in MMCs. ART highly decreased activated CD68+ T cells in both cases (from 24.3% to 12.6%, p=0.0131) and controls (from 30.1% to 7.5%, p<0.004) from PBMCs and MMCs (from 39.55% to 22.80% in cases, p=0.0087 and from 52.8% to 36.9% in controls, p=0.004). Concerning naive CD4+ and CD8+ T cells, higher percentages were seen in cases with respect to controls even before initiation of ART and were maintained at week 48. Moreover, CD8+ TCM cells were higher in cases before and after ART (p<0.014 and p<0.005, respectively). At mucosal tissue, percentage of macrophages (CD11c+ CD163+) was higher in controls than in cases (p=0.009) at w0 and decreased in controls (p=0.006) at w48. In general, a decrease of pro-inflammatory cytokines, such as IL-8, occurred mainly in cases at w48 (721.4 vs 485.5, p=0.008). In addition, levels of Th1 (IFN-γ, IL-12, MIP-1β), Th2 (IL-4, IL-10) and Th17 cytokines and chemokines decreased similarly in both cases and controls at w48.

Conclusion: An extremely early and intensified ART in PHI patients allowed good immunological reconstitution, decreased immune activation and reduced inflammatory profile in different body compartments.

261 IDENTIFICATION OF BROADLY NEUTRALIZING ANTIBODIES FROM SHIV-INFECTED CHINESE MACAQUES
Nan Gao1, Yanxin Gai1, Linda Meng1, Chu Wang1, Tiejun Gu1, Wei Wang2, Xiaojun Li1, Thomas B. Kepler1, Chuan Qin1, Xianghui Yus, Feng Gao1

Single memory B cells were sorted with a pair of HIV-1 Env V2 single-antibodies and infected with SHIV-infected rhesus macaques. Understanding how bnAbs develop in SHIV-infected non-human primates (NHPs) will have important implications in use of rhesus macaques to study efficacy of HIV-1 vaccines.

Methods: Single memory B cells were sorted with a pair of HIV-1 Env V2 differentiating baits from a SHIV1157p3d3H-infected rhesus macaque which showed broad neutralization activity in plasma after 6 years of infection. Paired variable heavy and light chains were amplified from the same B cells.
The recombinant IgG proteins were expressed in Expi293 cells. Neutralization activity was determined using 17 hard-to-neutralize tier-2 viruses on TZM-bl cells.

**Results:** 48Abs were expressed and 12 of them were found to bind HIV-11157yp120. Six (J003, J033, J030, J038, J040 and J044) from the same lineage (VH4-2’01F and VK1-2001 F) neutralized 2-12 viruses. Among them, J038 and J033 had the broadest neutralizing activities, neutralizing ~70% of 17 tier-2 viruses. Both Abs also had the highest somatic mutation rate (~20%) and 18 amino acids in the HCQR3 region. Inferred UCA of the J033 lineage Abs had no neutralization activity, indicating the broad neutralization activity was obtained during the lineage maturation. No Abs from other lineages neutralized any of 17 tier-2 viruses. Epitope mapping with CAP45 mutants showed that N160A/T162A (deletion of a glycosylation site) and K169E mutants rendered the virus fully resistant to both mAbs, similar as human V2-target bAbs. Both J038 and J033 bound deglycosylated gp120 at much reduced levels, confirming that neutralization mediated by both Abs depends on glycosylation in V2. Analysis of the viral sequences showed that the three mutations (I165L, K171R and V172A) together in V2 rendered the virus more resistant to both Abs, suggesting viruses with these mutations had escaped from this lineage of Abs.

**Conclusion:** Similar bnAbs as those identified in humans can be elicited in rhesus macaques during natural SHIV infection. Further characterization the maturation pathway of these bnAbs by comparing to bnAbs with the similar specificities in humans will provide unprecedented insight into mechanisms of bnAb development in NHPs.

---

**POLY/AUTOREACTIVITY AND BROAD NEUTRALIZATION ARE DETERMINED BY DIFFERENT MUTATIONS**

**Xiaojun Li,1 Dongmei Liao,2 Zhengyang Li,2 Shobhit Srivastava,2 Jixi Li,2 Laurent Verkoczy1, Feng Gao1**

1Duke University, Durham, NC, USA, 2Fudan University, Shanghai, China, 3San Diego Biomedical Research Institute, San Diego, CA, USA

**Background:** Nearly half of broadly neutralizing antibodies (bAbs) are polyreactive and/or auto-reactive (poly/auto-reactive). Some of them, like CH103, gain poly/auto-reactivity during bnAb maturation. However, whether poly/auto-reactivity and broad neutralization are governed by the same mutations during bnAb maturation is not well understood.

**Methods:** Mutations in Ab pairs differing in poly/auto-reactivity within the CH103 lineage were individually introduced back into the Ab from each pair with less (or no) poly/auto-reactivity. Recombinant Abs were expressed and purified from transfected Expi293 cells. Neutralization activity against HIV-1 was determined using the TZM-bl assay. Poly/auto-reactivity was analyzed by their ability to bind HEP-2 cells, host proteins and UBE3A. Positions and properties of mutations were analyzed using Swiss-Model.

**Results:** Poly/auto-reactivity became detectable for intermediate antibody 1 (IA1) and mature bnAbs during evolution of the CH103 lineage. There were 2, 17 and 11 amino acid (aa) differences between IA2/IA1, IA3/IA1, and CH103/CH106 Abs, respectively. Each of these aa differences was introduced into the Abs without (IA2 or IA3) or weak (CH103) poly/auto-reactivity, and they had little effects on neutralization. The IA2 variable heavy (VH) N605 mutant Ab and the CH103 VH E656 mutant Ab reacted to HEP-2 and many host proteins and dsDNA, while the IA2 VH E646K mutant Ab was only reactive to histone. The poly/auto-reactivity analysis using ~9000 human proteins showed that the IA2 N605 mutant Ab is poly/auto-reactive, while the E64K mutation did not render IA2 poly/auto-reactive. The UBE3A binding analysis of all mutants showed that only the VH E646K mutation in IA2 and IA3 as well as the VH E656 and VH E454 mutations in CH103 rendered their parental Abs reactive to UBE3A. Structure modeling showed all those mutations were in VH CDR2 or upstream of VL CDR2 but the aa substitutions were not thought to affect binding to HIV-1 Env. However, aa charge changes in the VH and VL CDR2 regions may play an important role in increased poly/auto-reactivity.

**Conclusion:** Development of poly/auto-reactivity during maturation of the bnAb CH103 lineage is determined by several somatic mutations not required for developing broad neutralization. The charge changes in the CDR2 regions of VH and VL mini-genes may play an especially important role in specifying poly/auto-reactivity in this bnAb lineage.

---

**POLYFUNCTIONAL ANTIBODY RESPONSE TO SHORT-SCHEDULE EBOLA VACCINE IN HIV+/− SUBJECTS**

Dominic Paquin-Proulx1, Michael A. Elder1, Aljawahrah Alrubayyi1, Jack N. Hutter2, Leigh Anne Eller3, Lucy Ward4, Janice Rusnak4, Callie Bounds4, Georgi Shukarev5, Viki Bockstal5, Kerstin Luhn5, Macaya Douoguih5, Cynthia Robinson6, Julie Ake7

1Henry M Jackson Foundation, Silver Spring, MD, USA, 2Walter Reed Army Institute of Research, Silver Spring, MD, USA, 3Henry M Jackson Foundation, Bethesda, MD, USA, 4Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense, Frederick, MD, USA, 5Janssen Prevention and Vaccines, Leiden, Netherlands, 6Walter Reed Army Institute of Research, Bethesda, MD, USA

**Background:** Ebola outbreaks occur in areas with a higher prevalence of HIV infection that may impact vaccine efficacy as ART-treated HIV+ subjects have been shown to generate lower responses to other vaccines. Non-neutralizing functions of antibodies may contribute to protection from Ebola virus infection, but it is unclear if HIV modulates these responses after vaccination. Antibody functionality was explored in HIV− and HIV− subjects following an accelerated Ebola vaccination schedule that is not intended for licensure.

**Methods:** Polyfunctional antibody effector functions were examined following IM administration of 1x108 Inf U MVA-BN-Filo (dose 1) followed by 5x1010 vp Ad26.ZEBOV IM 14 days later in ART-treated HIV+ and HIV− adults in the US. Plasma samples from days 1, 36, and 380 were used to evaluate antibody dependent cellular phagocytosis (ADCP), complement deposition (ADCD), and induction of NK cell cytokine production by flow cytometry.

**Results:** 40 HIV− and 20 HIV+− subjects received the heterologous vaccine schedule and 15 individuals received placebo (10 HIV− and 5 HIV+). The vaccine was well tolerated and binding antibodies were detected to the Ebola
glycoprotein in all vaccinees after completion of the 2-dose regimen. Significant increases from baseline in effector antibody responses were observed at day 36 (peak) in HIV+ and HIV- subjects. Placebo subjects had no response. At day 36, there was no significant difference between HIV+ and HIV- subjects in effector antibody functions but responses in HIV+ subjects tended to be lower. Responses declined in both populations by day 380, see figure 1. The majority of subjects in both populations (HIV-infected 50%, HIV-uninfected 50%) show polyfunctional capability, defined as 2 or more effectors, at day 380. Lower antibody polyfunctionality in HIV-infected subjects was not associated with the CD4 to CD8 ratio. Given the small sample size, definitive conclusions about any observed differences can not be made.

Conclusion: Polyfunctional antibody effector functions were significantly increased from baseline in response to an accelerated Ebola vaccination schedule in HIV+ and HIV- subjects. Although responses declined in both populations, at least 2 antibody effector functions persisted in the majority of subjects until day 380.

**IMMUNE RESPONSES TO THERAPEUTIC VACCINES AND IMMUNE CHECKPOINT INHIBITORS IN VACCINE-INDUCED ANTI-HIV RESPONSES**

Miguel A. Marin1, Alba Ruiz1, Esther Jimenez-Moyano1, Dan Ouchi2, Oscar Blanch-Lombarte2, Daniel Gorman3, Ruth Penya1, Richard Barnard4, Christian Manzano5, Tomas Hanke6, Christian Brandt1, Bonnie J. Howell7, Bonaventura Clotet1, Beatriz Mothe1, Julia G. Prado1

1IrsiCaixa Institute for AIDS Research, Badalona, Spain, 2Merck & Co, Inc, Kenilworth, NJ, USA, 3Merck & Co, Inc, Upper Gwynedd, PA, USA, 4IDIBAPS, Barcelona, Spain, 5The Jenner Institute, Oxford, UK, 6Merck & Co, Inc, West Point, PA, USA

**Background:** To attain the control or elimination of HIV-1 infection it is critical to delineate immune interventions capable of boosting or reinvigorating HIV-1-specific CD8+ T-cell responses. Immune interventions, including therapeutic vaccines or immune checkpoint inhibitors (ICIs), have been postulated to achieve this goal. However, the potency of combining both immune interventions has not yet been tested. Here, we assessed ex vivo the impact of ICIs on vaccine-induced HIV-1 CD8+ T-cell responses in samples from a vaccine trial conducted in early-treated HIV-1 infected individuals.

**Methods:** We selected PBMCs of individuals from the BCN01 (NCT01712425) trial receiving early treatment and a ChAdV63.HIVconsv/MVA.HIVconsv prime-boost regimen (Et; n=12). For comparison, we selected PBMCs from early treated not vaccinated individuals (Et; n=13) and chronically treated individuals (Chro; n=11). PBMCs were CFSE-stained and stimulated with an HIV-1 peptide pool in the presence of anti-PD-1, anti-TIM-3, anti-PD-1+TIM-3 or isotype antibodies. After seven days, we quantified the frequency of CFSE-, IFNγ+ and HLA-DR+/CD38+ responses and the plasma activity of the 4 HIV-1/TB individuals with high baseline BP score clustered with CD4 binding site and membrane-proximal external region targeting bnAbs.

**Results:** Our results suggest that active TB enhances anti-HIV-1 antibody response, possibly leading to the emergence of bnAbs that target conserved envelope domains. Dissecting mechanisms that account for the enhanced HIV-1 neutralization in HIV-1 cases with TB could be leveraged in the generation of a more effective humoral response in HIV-1 vaccination and treatment.

**RESULTS:** The blockade of PD-1 in Etvac boosted the frequency of vaccine-induced HIV-1-specific CD8+ T-cell responses in terms of proliferation (p=0.004), IFNγ production (p=0.04), and HLA-DR+/CD38+ expression (p=0.004). These results were consistent for anti-PD-1+TIM-3 in the absence of response to anti-TIM-3. In Et, ICI did not have any effect while Chro individuals showed an increase in the frequency of HIV-1-specific CD8+ responses upon PD-1 or PD-1+TIM-3 inhibition.

**Conclusion:** Characterizing “EXCEPTIONAL” CONTROL AMONG HIV ELITE CONTROLLERS

Michael J. Peluso1, Peter Burbele2, Shreya Kumar1, Sadie Munter1, Rebecca Hohl1, Sulgii Lee1, Peter W. Hunt2, Rachel L. Rutishauser1, Timothy J. Henrich1, Steven G. Deeks1

1University of California San Francisco, San Francisco, CA, USA, 2NIH, Bethesda, MD, USA

**Background:** Mycobacterium tuberculosis (TB) is an integral component of complete Freund’s adjuvant which is known to augment antibody production. We hypothesized that active TB disease enhances the development of HIV-1 broadly neutralizing antibodies (bnAbs) in people living with HIV-1.

**Methods:** We compared anti-HIV-1 antibody response among treatment-naive plasma samples from 15 HIV-1 patients with active pulmonary TB (HIV-1/TB) and 16 HIV-1 only infected individuals. Ability to inhibit 12 different tier 1 and 2 HIV-1 variants of diverse subtypes in the TZM-bl neutralization assay was used to estimate a neutralization breadth and potency (BP) score. Total IgG and cytokine levels were estimated using multiplex Lumienx based assays. Neutralization heatmaps were used to identify potential targeted HIV-1 envelope epitopes. Comparisons were done using the Wilcoxon rank-sum and Fischer’s exact tests.

**Results:** HIV-1/TB and HIV-1 only infected individuals had similar baseline plasma virus levels (p=0.33) and CD4 counts (p=0.40). HIV-1/TB individuals had a significantly higher BP score (0.59 ± 0.05, range 0.34-0.98) than the HIV-1 only group (0.43 ± 0.02, range 0.25-0.59, p=0.006). Four of the HIV-1/TB but none of the HIV-1 only infected individuals had a similar or higher BP score as that observed among 2nd generation bnAbs (BP score range 0.71-0.98, p=0.04). Neutralization BP score correlated with the total plasma IgG (r = 0.51, p=0.003), but not with baseline viral load, absolute CD4 count, IL-6, soluble CD163 or MCP-1 concentrations. After completing TB treatment and starting HIV-1 therapy, HIV-1/TB (0.68 ± 0.07, n= 6, range 0.28-0.88) as compared to HIV-1 only infected subjects (0.57 ± 0.07, n= 8, range 0.34-0.82) still had higher neutralizing capacity, but the difference was not statistically significant (p=0.56).

**Conclusion:** The plasma activity of the 4 HIV-1/TB individuals with high baseline BP score clustered with CD4 binding site and membrane-proximal external region targeting bnAbs.

**Results:** Our results suggest that active TB enhances anti-HIV-1 antibody response, possibly leading to the emergence of bnAbs that target conserved envelope domains. Dissecting mechanisms that account for the enhanced HIV-1 neutralization in HIV-1 cases with TB could be leveraged in the generation of a more effective humoral response in HIV-1 vaccination and treatment.
Background: Studies of “elite controllers” (ECs) might lead to novel approaches for HIV cure. We characterized the clinical, immunologic and virologic characteristics of ECs with very low reservoirs (“exceptional controllers”). Such individuals may prove to be models for a functional cure.

Methods: We systematically applied a clinical case definition to identify ECs within the SCOPE cohort. A related ART-treated cohort (n=80) was used for comparison. We measured CD4 T cell-associated (CA) HIV DNA and RNA using PCR from median 9M PBMCs, HIV-specific antibody responses using luciferase immunoprecipitation systems (LIPS), and T cell responses using flow cytometry. We stratified the sample by reservoir size and compared clinical outcomes, antibody response, and T cell immunophenotypes. Exceptional controllers were defined as ECs with no detectable HIV DNA. Clinical progression was defined as loss of virus control or CD4 decline requiring ART.

Results: 96 individuals met our case definition. Median CA DNA and CA RNA was 1.5 (0-7.6) and 99 (4.8-317) copies/10^6 cells, respectively. These levels were significantly lower than those on ART (CA DNA 10.8 and CA RNA 2138 copies/10^6 cells, p<0.001 for both). CA DNA levels highly correlated with CA RNA levels (0.74, p<0.001). CA DNA levels were associated with antibody levels targeting matrix (r=0.30, p=0.008), integrase (r=0.26, p=0.03), and protease (r=0.27, p=0.02), but not envelope, or measures of T cell activation. 22 (23%) met our virologic definition of exceptional control. Exceptional controllers were more likely to have a protective HLA allele (B*27 or 57; p=0.002) and less likely to progress clinically (18% vs 49%, p=0.02). Compared with the rest of the EC cohort, exceptional controllers had lower antibody levels to matrix (p=0.007), integrase (p=0.007), and protease (p=0.02), but comparable levels of T cell activation. In a logistic regression model, exceptional control was associated with presence of protective HLA alleles (6.8 fold effect, p=0.002).

Conclusion: We identified a subset of controllers with very low HIV DNA and RNA levels, low HIV antibody levels, and lower risk of clinical progression. These individuals are enriched for certain HLA alleles, arguing that CD8+ T responses mediate control. Such individuals may not need ART and might prove to be a model for a “functional cure” or remission.

269 HIGH FREQUENCY OF CD8 ESCAPE MUTANTS IN ELITE CONTROLLER AS NEW OBSTACLE TO HIV CURE
Maria Ángeles Navarrete1, Marcel García1, Ricardo Ramos2, Africa Holguín3, Clara Restrepo1, Alfonso Caballero1, Juan Carlos López-Bernaldo2, Francisco Javier De La Hera1, Carlos Barros3, Manuel Fernández3, Vicente Estrada3, Miguel Górgolas Hernández-Mora1, José M. Benito2, Norma Rallón1
1Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain, 2Parque Científico de Madrid, Madrid, Spain, 3Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain, Fundación Jiménez Díaz, Madrid, Spain, 4Hospital General Universitario Gregorio Marañón, Madrid, Spain, 5Hospital Universitario de Móstoles, Madrid, Spain, 6Hospital Universitario Clínico San Carlos, Madrid, Spain

Background: The shock and kill strategy to purge the reservoir has failed likely as a consequence of several obstacles. The existence of escape mutations in regions of the HIV proviral sequence coding for epitopes of CD8 immune response has been postulated as one of the reasons for this failure. Herein, we have analyzed the frequency of these mutations in two different groups of HIV patients with complete viral suppression: patients on successful cART and elite controller patients.

Methods: Twenty HIV patients were included: 7 elite controllers (EC) and 10 non-controller patients on successful cART (TX). CD4 resting memory cells were immunomagnetically purified and total genomic DNA was extracted. The entire Gag gene was amplified by nested PCR and a pair-end sequencing run on a MiSeq system was performed. Sequences were mapped and aligned to the consensus HXB2 sequence. Optimal Gag epitopes of CD8 immune response were predicted for each patient based on their HLA class I haplotype (A, B, C). The prevalence of mutated epitopes as well as its impact on HLA recognition were calculated for each patient.

Results: EC and TX groups were matched for age, years of HIV diagnosis and CD4 T-cell counts. TX patients had been on cART for a median of 129–16 years. The whole HIV-Gag sequence was successfully amplified and sequenced in all patients. The median number of CD8 Gag epitopes predicted for EC and TX patients were 74–7 and 76–12, respectively. Of note, the prevalence (%) of mutated CD8 epitopes was 75(46–100) and 54(48–74) in EC and TX respectively (p=0.432). Moreover the frequency (%) of mutated peptides with a significant impact reducing HLA recognition was similar in both groups (50(33–50) in EC and 41(19–52) in TX, p=0.552).

Conclusion: Our results show a high prevalence of mutations in HIV-Gag epitopes of CD8 T-cell response not only in the HIV reservoir of patients with successful cART-mediated control, but also in patients with spontaneous HIV
control in whom control is reached at an early stage of infection. Indeed, many of these mutations have a potential negative impact on antigen recognition. These findings support the role of existence of escape mutations as another obstacle to purge the HIV reservoir. This could provide a proof of concept challenging the current HIV cure strategies based on reservoir reactivation.

270 ASSOCIATION OF POLYFUNCTIONAL CMV-SPECIFIC T CELLS WITH FRAILTY IN HIV-INFECTED MEN

Weiyong Zhang1, Jay Bream2, Sean X. Leng3, Tricia Nilles4, Huifen Li5, Joseph B. Margolick6
1Johns Hopkins University, Baltimore, MD, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: Cytomegalovirus (CMV) infection is associated with both HIV infection and frailty. CMV-specific T cell responses correlated differently with immune activation and inflammatory markers, depending on donor HIV and frailty status; and the proportion of CD4 T-cells producing IL-2 in response to CMV predicted onset of frailty. Here, we studied T-cell production of IFN-γ and TNF-α as well as IL-2 as predictors of a) onset of frailty in nonfrail men, and b) stability of frailty in frail men, in HIV+ and HIV- men who have sex with men.

Methods: CMV-specific T cell responses of 42 men (22 virologically suppressed HIV+ and 20 HIV-) were assessed by flow cytometric analysis of production of IFN-γ, TNF-α, and IL-2 in response to overlapping peptide pools spanning 19 CMV open reading frames. Frailty was assessed semiannually using the Fried criteria. To explore the relationship between cytokine-producing T cells and onset (in nonfrail men) and stability (in frail men) of frailty, men were categorized into tertiles of percentages of these cells. Times to onset or loss of frailty were compared by tertiles using Kaplan-Meier estimators and the nonparametric log-rank test.

Results: Cytokine production by T cells fell into three main patterns: IFN-γ+TNF-α+IL-2- (median: 5% vs 58% of CD4 vs CD8 cytokine-producing cells), IFN-γ+TNF-α-IL-2- (15% vs 34%), and IFN-γ+TNF-α+IL-2+ (11% vs 5%). IFN-γ+TNF-α-IL-2+ CMV-specific T cells were detected in only one man. Percentages of these subsets of cells did not differ significantly by HIV and frailty status. Over a median follow-up of 7 years, for HIV+ men onset of frailty was associated with higher percentages of IL-2+ CD4 cells also producing IFN-γ and/or TNF-α, and of IFN-γ+TNF-α-IL-2- CD4 T cells (p<0.001). In contrast, for HIV+ men, onset of frailty was associated with lower percentages of the latter cells (p<0.05). Lower percentages of these cells were associated with remaining frail for all men (p=0.05 for HIV- and p=0.06 for HIV+ men).

Conclusion: Percentages of IFN-γ+TNF-α-IL-2- producing CMV-specific T cells did not differ significantly by HIV and frailty status. However, high percentages of IFN-γ+TNF-α-IL-2- CD4 T cells predicted onset of frailty in HIV+ men. Moreover, low levels of these cells predicted both onset of frailty among HIV+ men, and maintenance of frailty in both HIV+ and HIV- men. Thus, this T cell subset may play different roles in onset and maintenance of frailty in HIV+ and HIV- men.

272 VULNERABLE TARGETS IN HIV-1 POL FOR ATTENUATION-BASED VACCINE DESIGN

Doty A. Ojwach1, Tarylee Reddy1, Daniel MacMillan1, Vladimir Novitsky1, Zabrina Brumme2, Mark Brockman3, Thambi Ndungu4, Jaclyn Mann5
1University of KwaZulu-Natal, Durban, South Africa, 2Medical Research Council, London, UK, 3Simon Fraser University, Burnaby, BC, Canada, 4Harvard T.H. Chan School of Public Health, Boston, MA, USA, 5Simon Fraser University, Vancouver, BC, Canada

Background: Identification of viral immune escape mutations that compromise HIV’s ability to replicate may aid rational attenuation-based vaccine design. Focussing cytotoxic T cell (CTL) responses on several epitopes where CTL escape compromises viral replication may delay escape and/or attenuate the virus. We investigated immune-mediated attenuation in Pol, specifically reverse transcriptase (RT)-integrase.

Methods: We generated 487 recombinant viruses encoding RT-integrase from individuals with chronic (n = 406) and recent (n = 81) HIV-1 subtype B infection and measured their in vitro replication capacities (RC) using a GFP-reporter T-cell assay. A codon-by-codon analysis was performed to identify amino acid changes associated with altered RC and mutagenesis experiments were performed to validate the effect of these mutations on RC.

Results: The polymorphisms V241I, I257V, P272K and E297K in RT and I201V in integrase, respectively uncommon polymorphisms occurring in or adjacent to optimally-described HLA-restricted CTL epitopes, were statistically associated with the most pronounced decreases in RC, while RT polymorphisms E68K and A158S (both in CTL epitopes) were associated with modestly reduced RC. A subset of sequences (n=89) were mutated at the RT-integrase stop codon (*849Q), leading to the usage of a stop codon 17 residues downstream. These extended integrase sequences were significantly associated with reduced RC. Our mutagenesis experiments confirmed that RT mutants A158S, V241, I257V as well as the integrase mutation *849Q significantly and negatively impact RC.

Conclusion: In summary, the length of integrase influences Pol RC and RT-integrase variants in viral domains of the RT palm (158S) and RT thumb (241I and 257V) represent potential vulnerable targets for an attenuation-based vaccine. The relevant RT-integrase epitopes spanning these residues could be utilised in a vaccine construct to stimulate the CD8+ T cell responses, and in the event that the virus escapes these specific responses, this is likely to be accompanied by a replicative fitness cost.

272 ASSOCIATION OF HIV AND HOST GENETIC VARIANTS IN ANTIRETROVIRAL THERAPY NAIVE PERSONS

Migle Gabrielaite1, Adrian G. Zucco2, Marc Bennedeb1, Christina Ekenberg1, Virginia L. Kan2, Giota Touloumi3, Linos Vandekerckhove4, Dan Turner5, James Neaton6, H. Clifford Lane7, Jens D. Lundgren1, Rasmus L. Marvig1, for the INSIGHT START Trial Group
1Righospitalet, Copenhagen, Denmark, 2George Washington University, Washington, DC, USA, 3University of Athens, Athens, Greece, 4HIV Cure Research Center, Ghent University, Ghent, Belgium, 5Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, 6University of Minnesota, Minneapolis, MN, USA, 7National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

Background: HIV-1 genetic diversity allows the virus to adapt and escape the host’s immune response; conversely, certain sections of the host genome affect the replicative rate of the virus. The molecular specificity of the interplay between viral genetic escape and host genomic control remains poorly defined. Here, we associated viral genetic data with recently reported host genetic data from a demographically diverse cohort of ART naive HIV+ participants in the Strategic Timing of AntiRetroviral Treatment (START) trial.

Methods: Two 3.6 kb amplicons (HIV-1 HB2X genome regions 1.485-5.058 and 5.967-9.517) from viral genomes from plasma samples were sequenced on Illumina platform. Sequence alignment and single nucleotide polymorphism (SNP) calling were performed with BWA and Vardict software, respectively, using HBX2 genome as reference. Associations between HIV-1 SNPs and human HLA types, respectively, were estimated with logistic regression models adjusting for age, sex, and genetic structures in the viral and human population captured by principal component analysis. Bonferroni correction was used to set significance cut-offs.

Results: Human and viral genetic data was combined for 2,035 trial participants. Viral populations showed large diversity across the cohort (most common subtypes were B and C). We identified 1,461 HIV-1 SNPs for association analysis against 398,349 human SNPs and observed significant human SNP associations for a total of 7 HIV-1 SNPs (p<8.6•10-11; see figure). All 408 associated human SNPs were in the HLA gene region. While the strongest association was observed in parg 1514C→A; rs41293883; P=2.34•10-44), 4 out of 7 significant HIV-1 SNPs were in nef (Nef downregulates CD4 and MHC class I molecules). Furthermore, we identified 15 imputed HLA alleles which were significantly associated with one or more of the 7 identified HIV-1 SNPs (p<7.9•10-5) using dominant logistic regression model. Most significant associations were 1514C→A HIV-1 SNP with B*57:01 (p=9.99•10-5) and C*06:02 (p=5.42•10-6) alleles, respectively.

Conclusion: These data suggest that human immunotypes impose selection on viral genotypes through viral epitope specificity. Alleles of HLA (B*57:01 and C*06:02) observed here to be associated with viral epitope selection have previously been found to be associated with viral load in the same cohort. Hence, the present finding provides independent confirmation of a genuine biological effect of variations in HLA gene region.
**273 CXCR5 EXPRESSION ON HUMAN CD8+ T CELLS IS TIGHTLY REGULATED BY EPIGENETIC MECHANISMS**

Funsho Ogunshola1, Werner Smidt2, Veron Ramusaran2, Thumbi Ndungu2, Bruce D. Walker1, Tulio de Oliveira1, Zaza Ndisho2

1Africa Health Research Institute, Mtubatuba, South Africa, 2University of KwaZulu-Natal, Durban, South Africa, 3Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

**Background:** CD8+ T cells located in B cell follicles play an important role in viral and tumor control. However, only a small subset of CD8+ T cells called follicular CD8+ T cells express CXCR5, the chemokine receptor required for cell migration into B cell follicles. We investigated why most LND8+ T cells lack CXCR5 expression, and why there is reduced CXCR5 expression on CDX5+CD8 T cells (FC8Bs) relative to GCTfh.

**Methods:** We FACs-sorted CXCR5+CD8+ (FC8Bs), CXCR5-CD8+ (non-FC8Bs), naive CD8+ T cells and GCTfh from lymph nodes of HIV-1 infected individuals and performed RNA-sequencing (RNA-Seq). DNA methylation was used to profile methylation pattern of the CXCR5 gene and the Assay for Transposase-Accessible Chromatin using Sequencing (ATAC-Seq) was used to quantify accessible genes and to identify epigenetic modules governing CXCR5 expression.

**Results:** RNA-Seq data analysis of FC8B and non-FC8B identified 43 gene among the most differentially expressed genes (FDR<0.01) that are associated with epigenetic gene regulation. DNA bisulfite treatment and sequencing showed that 70% of Cpg islands in CXCR5 gene were methylated whereas FC8B had less than 7% methylation levels at equivalent sites. ATAC-Seq analysis revealed a closed chromatin conformation at the CXCR5 TSS in non-FC8Bs whereas FC8Bs had open chromatin at equivalent sites. Furthermore, analysis of nucleosomal footprinting around the CXCR5 TSS revealed greater nucleosomal occupancy in FC8Bs compared to GCTfh, computational simulation indicated that the presence of nucleosomes at the TSS interfered with transcription efficiency resulting in attenuated expression of the CXCR5 gene.

**Conclusion:** We show that DNA methylation coupled with chromatin compaction at TSS prevent CXCR5 gene expression in non-FC8Bs and greater nucleosomal occupancy down-modulate CXCR5 expression levels in FC8Bs. Together, these data provide insights into both the underlying molecular mechanisms that repress CXCR5 in non-FC8Bs and the molecular mechanisms responsible for the low CXCR5 expression in FC8Bs, with implications for HIV cure strategy or eradication of B cell-derived tumors.

---

**274 ADDITIVE DETRIMENTAL EFFECT OF B*35/39 TYPES IN A LARGE MEXICO/CENTRAL AMERICA COHORT**

Humberto Valenzuela Ponce1, Maribel Soto-Nava1, Irma Saulle1, Salomé Valentina Iba1, Claudio Fenizia1, Francesca Vichi, Sergio Lo Caputo2, Daria Trabattoni2, Mario Clerici2

1University of Milan, Milan, Italy, 2University of Bari, Bari, Italy

**Background:** Polymorphism within the human leukocyte antigen (HLA) class I loci represents the strongest genetic modifier of HIV disease progression. In a cross-sectional Mexico/Central America (MEX/CAM) cohort, we have described both canonical and novel associations between specific HLA and HIV disease progression, from which the B*35 and B*39 subtypes featured several risk associations, including the Amerindian B*35:12/14 and B*39:01/05/06 alleles. As more than 6% of the MEX/CAM cohort expressed two alleles of the B*35 and/or B*39 subgroups, we investigated HLA additive effects and in the context of B*35-PX/PY grouping with HIV disease progression.

**Methods:** HLA sequence-based typing was performed on 3213 chronically HIV-1 clade B-infected, ART-naive individuals from Mexico (n=1679), Guatemala (n=418), Nicaragua (n=254), Honduras (n=402), Panama (n=316), Belize (n=102), and El Salvador (n=42). Univariate and multivariate analyses were performed using the Generalized Linear Model (GLM) to evaluate additive effects between B*35/39 subtypes or between B*35-PX/PY groups. Associations were adjusted by age, gender and location of recruitment, included as possible confounders in multivariate analyses. For B*35-PX/PY analyses, only HLA-B heterozygous individuals were compared in order to exclude confounding effects resulting from HLA homozygosity.

**Results:** Both in univariate and multivariate analyses, expressing one or two copies of any B*35 or B*39 subtype (B*39:02 being the exception) was associated to significantly higher plasma viral load (pVL) and lower CD4 counts (in all cases p<0.05). pVL and CD4 linear regression coefficients were one-fold larger in individuals that co-expressed 2 copies of any B*35/39 in comparison with subjects that expressed 1-cop of any B*35/39, suggesting an additive detrimental effect. We confirmed the B*35-PX group association with poor HIV outcome (both with pVL and CD4), but also observed that B*35-PY alleles were associated to significant lower CD4 counts. Given its similarity with other PX members (B*35:02/03), the Amerindian B*35:12 allele represents a putative new member of the established B*35-PX HIV risk group.

**Conclusion:** Our results suggest an additive detrimental effect between B*35/39 subtypes, highly frequent in the Mesoamerican mestizo population. Our results also challenge the B*35-PX/PY hypothesis, indicating that PY alleles can be disease-susceptible and also that differences exist in disease associations within PX/PY grouping.

---

**275 NATURAL RESISTANCE TO HIV-1 CORRELATES WITH IFNA-CONTROLLED STEROL METABOLISM**

Mara Biasin1, Irma Saulle1, Salomé Valentina Iba1, Claudio Fenizia1, Francesca Vichi, Sergio Lo Caputo1, Daria Trabattoni2, Mario Clerici2

1University of Milan, Milan, Italy, 2University of Bari, Bari, Italy

**Background:** Interferon-stimulated genes (ISGs) that are able to interfere with viral replication through the modulation of cholesterol metabolism. We therefore verified if natural resistance to HIV-1 infection in HIV-exposed seronegative (HESN) subjects is at least partially dependent on a peculiar regulation of sterol biosynthesis pathway mediated by IFN-induced CH25H expression.

**Methods:** Peripheral blood mononuclear cells (PBMCs) and monocyte-derived macrophages (MDMs) isolated from 15 sexually-exposed HESN, their HIV+ partners and 15 healthy controls were analyzed for: 1) percentage of IFNa-producing plasmacytoid Dendritic Cells (pDCs); 2) RNA expression of factors involved in lipoprotein signaling and cholesterol metabolism by Real Time PCR; 3) susceptibility to HIV-1 infection by p24 viral antigen quantification.

**Results:** The increase in IFNa-producing pDCs in both unstimulated and in vitro HIV-infected PBMCs from HESN was coupled with an augmented expression of cholesterol-25-hydroxylase (CH25H) (HESN vs HC: p<0.001 in both cases). The expression of several genes involved in cholesterol metabolism (LXR, ABCA1, SCARB, HMGCS1, PPARg) was modulated as well (>3 fold) in unstimulated as producing plasmacytoid Dendritic Cells (pDCs); 2) RNA expression of factors involved in lipoprotein signaling and cholesterol metabolism by Real Time PCR; 3) susceptibility to HIV-1 infection by p24 viral antigen quantification.

**Conclusion:** The observation that CH25H, an oxysterol-producing enzyme, is up-regulated in HIV-exposed cells from HESN, is particularly intriguing.
276 **BASELINE INDUCIBLE HIV p24 INFORMS VIRAL CONTROL DURING INTERFERON-α MONOTHERAPY**

Livio Azzoni1, Emmanouil Papasavvas1, Pablo Tebas2, Karam Mounzer3, Jay Kostman1, Ian Frank2, Bonnie J. Howell4, Daria Hazuda4, Daniel Holder4, Nicolas Kostman3, Ian Frank2, Bonnie J. Howell4, Daria Hazuda4, Daniel Holder4, Nicolas Chomont6, Costin Tomescu6, Michael R. Betts6, Leticia Kuri Cervantes6, Luis J. Montaner1

1Wistar Institute, Philadelphia, PA, USA, 2University of Pennsylvania, Philadelphia, PA, USA, 3Philadelphia FIGHT, Philadelphia, PA, USA, 4Merck & Co, Inc, West Point, PA, USA, 5Université de Montréal, Montreal, QC, Canada

**Background:** Pegylated (peg) IFNα monotherapy after ART interruption results in increased HIV control in association with NK cell activation. The relationship between inducible or other HIV proviral reservoir measures with subsequent time to rebound during ART interruption and Peg IFN-α monotherapy are unknown.

**Methods:** 13 individuals randomized to arm 1 of the BEAT-HIV study (NCT02227277: HIV VL < 50 copies/ml on ART, CD4 count > 450/μl) receiving 1 μg/kg of peg-IFNα-2b (Pegintron, Merck) for 20 weeks, interrupting ART at week 4 and resuming it upon viremia (VL > 50 copies/ml, bi-weekly evaluations) or at week 20. P24 SIMOA (IP24) was measured in CD4+ T cells cultured for 16-hour with medium or PMA/ionomycin using single molecule array (SIMOA). Intact, S-defective, 3' defective and total proviral DNA were measured by Accelvir, Inc. on CD4+ T cells; integrated HIV proviral DNA was assessed using Alu-gag RT-PCR on CD4+ T cells. Time to viremia was first VL > 50 copies/ml after stopping ART. HIV-specific responses in PBMC: a) T cell - 6-hour cultures of PBMC with of gp120-coated CEM NKres targets. Multicolor flow cytometry was used to assess HIV-specific degranulation and cytokine production. Associations were tested with Pearson or Spearman tests, and linear regression models.

**Results:** 12 of 13 participants became viremic during ART interruption, one remained suppressed and was imputed to week 20. IP24 was positively associated (p<0.05) with time to viremia (effect estimate 0.362; p = 0.029; Adj R2 = 0.305), first detected VL (Fig 1), and Fc receptor-dependent expression of intracellular MIP1β in CD56dim/CD57neg NK cells, but not with T-cell responses to Gal peptides. Proximal measures were correlated to each other, as expected, but not with time to viremia or level of first VL measured.

**Conclusion:** In vitro-inducible HIV proteins (i.e.: p24 SIMOA), but not total proviral HIV DNA measures, are associated with level of first viral load and time to viremia during peg-IFNα-2b monotherapy. In contrast to expectation that higher latent reservoirs would lead to shorter time to viremia, the immune correlates measured are consistent with NK ADCC response and chemokine responses contributing to viral control off ART.
**Background:** HIV aging contribute to inflammaging (chronic low-grade systemic inflammation) and immune senescence (accelerated aging of the immune system). Immune dysfunction, in the form of impaired antibody (Ab) responses to vaccines such as influenza (flu) vaccination, is observed in aging and HIV infection. Given the central role of IL-21 in Ab responses we hypothesized that administration of IL-21 as a flu vaccine adjuvant in aged, ART treated, SIV+ RM would result in significant improvement in the quality of pTfh and B cell function alongside improved germinal center reactions, resulting in improved Ab responses to vaccination. **Methods:** In this study flu vaccination was administered with (N=4) and without (N=4) subcutaneous IL-21 in a prime, boost, boost series at 3-month intervals to old ART treated, SIV+ (IV SIVmac239) RM. IL-21 was given (50µg/kg) on d-2, d0, d5 post each vaccine dose. Blood was collected on d0, d5, d14 and d42; and lymph node tissue was collected on d14 after each vaccine dose. Serum was analyzed for flu Ab titers, and PBMC with multicolor flow cytometry using panels for detailed phenotypic characterization of peripheral blood T follicular helper (pTfh) cells and CD4 memory populations. **Results:** In results analyzed to date, pre-prime H3N2 HAI titers of controls (mean=1.55) did not differ from IL-21 treated animals (mean=1.100). Titers increased significantly (p=0.0018) in IL-21 treated animals from 1:100 at baseline to 1:283 post boost 1 (PB1) and were significantly higher (P=0.00001) than the PB1 control mean titer of 1:60 (Fig. 1A). We did not observe baseline differences in pTfh frequency between groups (Fig. 1A). IL-21 treated animals had significant (p=0.0118) expansion of pTfh, as measured by the fold change of pTfh frequency from day of Boost 1 (B1) to 14 days PB1, correlating with H3N2 HAI titers 14 days PB1 (R2=0.6978, P=0.0193, Fig. 1B). We also observed that the frequency of PD+ pTfh cells was significantly higher (p=0.0188) in IL-21 treated animals (mean=27%) compared to controls (mean=16.7%) on the day of B1 and correlated with H3N2 HAI titers 14 days PB1 (R2=0.728, P=0.0146). **Conclusion:** These findings suggest IL-21 has a significant adjuvant effect, improving flu vaccine titers in old, ART treated, SIV+ RM. As no baseline pTfh differences were observed, these results highlight that IL-21 may be directly or indirectly inducing a shift in pTfh cell kinetics and phenotype, warranting further investigation as a potential vaccine adjuvant.

---

**Background:** Immunological synapse is required for Natural Killer (NK) cells to kill viral infected cells. HIV infection promotes the appearance of dysfunctional NK cells with diminished capacity to kill infected cells. Thus, new tools to reinvigorate and redirect NK-mediated immune effector functions will help to eliminate HIV. **Methods:** We have developed bispesific gold nanoparticles (BiAb-AuNPs) containing two different polarized antibodies at their surface. BiAb-AuNPs were prepared by conjugating AuNPs with IgG anti-HIVgp120 (A32) and IgG anti-CD16 (3G8) antibodies following a novel controlled, linker-free and polarizing conjugation method. Validation was performed by transmission electron microscopy (TEM), UV-Vis Spectroscopy, Dynamic Light Scattering (DLS) and Zeta-potential measurements. The ability of BiAb-AuNPs to promote specific cell contacts was evaluated by flow cytometry and confocal microscopy. Functionality of BiAb-AuNPs was measured by ADCC assays and cytotoxicity assays performed in tonsil histocultures after ex vivo infection with HIV (n=8). In addition, the killing of viral reactivated cells promoted by BiAb-AuNPs was assessed in a primary cell model of HIV latency (n=5). In all assays we included irrelevant bispesific BiAb-AuNPs as a control. **Results:** BiAb-AuNPs increased the number of NK HIV+CD4 T cells doublets by over 7-fold compared to control medium (median %doublets 16.0% vs. 2.5%) (p=0.0143; paired t test). Direct contact zipped by BiAb-AuNPs was confirmed by confocal microscopy. In addition, BiAb-AuNPs increased the percentage of NK cells producing IFN-γ and CD107a (median 22.5% vs. 4.9% of medium control) (p<0.05; Friedman test) and triggered a potent cytotoxic response against HIV-expressing cells (median 29.1% vs. 14.9% or 12.7% for irrelevant BiAb-AuNPs and A32, respectively) (p=0.0133 for both comparisons; Wilcoxon test). Moreover, BiAb-AuNPs entered tonsil blocks, measured by the loss of detection of CD16 molecules in NK cells (p<0.0078; Wilcoxon test) and significantly impacted HIV infection in this lymphoid tissue, reaching up to 50% of reduction

---

**Background:** Overexpression of immune-checkpoint receptors (IRs) has been associated with T-cell exhaustion and overall dysfunction in HIV. CD4 T-cells expressing IRs (e.g. PD-1, CTLA-4, LAG-3) enrich for integrated provirus and likely contribute to viral persistence during ART suppression. We identified a class of IRs, buytophilins (BTNIs), with high homology to B7 family members (e.g., PD-1-L1 and PD-L2) and the capability to modulate T-cell activation and HIV expression. We postulate BTNIs can be exploited to induce both latent virus reaction and/or T-cell function and serve as novel immunomodulatory targets for HIV cure research. **Methods:** An aptamer screen was performed to identify proteins enriched on primary CD4 T-cells infected with HIV. Target enrichment was confirmed by flow cytometry as well as immuno-pulldown in CD4 T-cells from ART-suppressed donors using qPCR and ELISA. Functional assays were performed using recombinant BTN proteins or antibodies to demonstrate the impact of target modulation on HIV latency reversal and T-cell activation. Viral reactivation in a human latency model was measured by GFP or luciferase reporter virus and T-cell activation was evaluated concomitantly via IFN-γ release in the culture supernatant. **Results:** BTN immune checkpoint receptors were identified as cell surface proteins overexpressed on in vitro infected HIV+ CD4 T-cells relative to uninfected cells as determined by aptamer screen and flow cytometry. Antibody-pulldowns in CD4 T-cells from ART-suppressed participants demonstrated BTN3A-expressing cells enrich for HIV integrase RNA (4 of 8 participants), LTR DNA (4 of 4), and p24 protein (5 of 8). Recombinant BTN-Fc fusion proteins inhibited activation of human CD4 T-cells following anti-CD3 antibody stimulation, verifying pathway function. In contrast, BTN3A-specific antibodies enhanced T-cell activation and reactivated HIV in response to anti-CD3 antibody; an activity blocked by recombinant BTN3A-Fc proteins. Novel antibodies were generated against three BTN3A protein isoforms using yeast display and characterized for modulation of HIV latency and T-cell activation. Work is ongoing to evaluate Gal-specific CD19 T cell response +/- BTN antibodies. **Conclusion:** This data collectively implicates BTN3A family members as putative immune targets for HIV transcriptional regulation or T-cell activation. This novel finding warrants further investigation to determine if therapeutically modulating BTNs can impact the latent viral reservoir.
in some cases (p=0.0131; Wilcoxon test). Furthermore, BiAb-AuNPs enhanced the killing of latent-HIV-infected cells after viral reactivation, inducing a median of 51.5% killing (p=0.0163; One sample t test).

**Conclusion:** BiAb-AuNPs are a novel molecularly-targeted nanotool that potentiates NK-immune response against HIV.

### 281 INTERFERON-Α MODULATES THE HOST GLYCOSYLATION MACHINERY DURING TREATED HIV INFECTION

Leila B. Giron1, Florent Colomb1, Emmanuel Papasavvas1, Livio Azzoni1, Xiangfan Yin1, Alitzel Anzurez2, Matthew Fair1, Karam Mounzer3, Jay Kostman4, Pablo Tebas1, Ulla O’Doherty5, Qin Liu4, Michael R. Betts3, Luis J. Montaner1, Mohamed Abdel-Mohsen1

1Wistar Institute, Philadelphia, PA, USA, 2Philadelphia FIGHT, Philadelphia, PA, USA, 3University of Pennsylvania, Philadelphia, PA, USA

**Background:** A comprehensive understanding of host factors modulated by the key antiviral cytokine interferon-α (IFNα) is imperative for harnessing its beneficial effects while avoiding its detrimental side-effects, during chronic diseases such as HIV infection. Cytokines modulate host glycosylation, and the host glycome (circulating glycans and cell-surface glycans) plays a critical role in mediating several cellular processes and immunological functions. However, the impact of IFNα on host glycosylation machinery has never been characterized.

**Methods:** We assessed the impact of pegylated IFNα2α therapy on circulating IgG glycomes and isolated CD8+ T and NK cell-surface glycomes of 18 HIV-monoinfected individuals on suppressive antiretroviral therapy, using capillary electrophoresis and lectin microarrays. Plasma levels of sCD14 and sCD163 were measured by ELISA. CD8+ T cell and K562-stimulated NK cell phenotypes were profiled using flow cytometry. Integrated HIV DNA in CD4+ T cells was measured by qPCR. Wilcoxon test and Spearman’s correlations were used for statistical analysis. False discovery rates (FDR) were calculated to account for multiple comparisons.

**Results:** Interactome analysis highlighted significant interactions that support a model in which a) IFNα increases the proportion of pro-inflammatory, bisected GlcNac glycans (known to enhance FcγR binding) within the IgG glycome (FDR<0.02), which in turn b) increases inflammation (as measured by sCD14 and sCD163; p<0.03), which c) leads to lower levels of CD8+ T cell functionality (perforin, Eomes, and TNFα expression) but higher degradation (CD107) (p<0.02, Figure). IFNα-mediated induction of bisected GlcNac associated with a poor reduction of HIV integrated DNA (p=0.02, rho=-0.8). Examining cell-surface glycomes, IFNα increases the levels of T antigen (Gal-GalNAc) on CD8+ T cells (FDR=0.01). This association is lower with CD8+ T cell functionality (perforin, Eomes, T-bet, and IFNγ upon K562 stimulation (p=0.048, rho>0.8).

**Conclusion:** IFNα causes host glycomic alterations that are known to mediate inflammatory responses. These alterations are associated with mainly detrimental, but also beneficial, consequences of IFNα on innate and adaptive immune functions. Manipulating glycan-lectin interactions may represent a strategy to enhance the impact of IFNα on immunity while avoiding its detrimental side-effects.

### 282 PHASE I/II RANDOMIZED STUDY: THERAPEUTIC DENDRITIC CELL VACCINE PLUS PEGYLATED INF-Α

Lorna Leal1, Elvira Couto Jaime1, Yolanda Romero1, L Miraless1, Tania González2, M.J Maleno1, Blanca Parío1, Pich Judit3, Nuria Climent4, Sonsoles Sánchez-Palomino5, Carlos Nicolau1, Jose M. Gatell3, Felipe García1, Montserrat Plana1, for the DCV-3/RIVAC04 Study Group

1Hospital Clinic of Barcelona, Barcelona, Spain, 2IDIBAPS, Barcelona, Spain, 3ViiV Healthcare, Madrid, Spain

**Background:** A double-blind placebo-controlled randomized therapeutic vaccine trial with myeloid derived-dendritic cells (MD-DC) loaded with heat-inactivated autologous HIV-1 (HIAH) plus pegylated interferon-α (pIFN) in HIV-1 chronic infected patients on antiretroviral treatment (ART) to achieve functional cure was performed.

**Methods:** 36 patients on successful ART with CD4+ ≥450 cells/mm3 were randomized: 1:1:1:1 and 29 received at w0, 2 and 4 an ultrasound-guided inguinal intranodal dose of: 1) vaccine (V) 107 MD-DC pulsed with 1010 HIAH (n=8); 2) V plus 3 doses of pIFN (VpIFN) at w4, 5 and 6 (n=8); 3) placebo (P) (n=7); and 4) P plus 3 doses of pIFN (PpIFN) at w4, 5 and 6 (n=8). ART was interrupted (ATI) at week 4. The primary end-points were safety and proportion of patients with undetectable VL 12w after ATI (w16). Secondary end-points were DVL set-point (set-point ATI-preART), and HIV-1 specific T cell responses (IFN-γ, Elispot) (w16-w0).

**Results:** All participants were male. The procedure was safe and well tolerated. All patients had detectable VL at w16. DVL set-point (log10_mean (SE) copies/ml) was: 1) V 0.20 (0.21) 2) VpIFN -0.44 (0.38) 3) P -0.19 (0.23) 4) PpIFN -0.17 (0.20) (p=0.37). A decrease >1log in VL set-point was seen in 0.3, 1 and 0 patients in V, VpIFN, P and PpIFN, respectively (p=0.05 and p=0.06 for the differences between VpIFN vs V, and VpIFN vs PpIFN, respectively). At baseline, HIV-1 specific T-cell responses were lower in vaccines vs placebo groups (mean (SE) 900 (200) vs 2259 (535) SFC/10⁶ PBMC, p=0.028). No significant differences in DHIV-1 specific T-cell responses were observed between vaccine and placebo groups (p=0.09). No effect on T cell responses was observed with pIFN administration. A trend to significative negative correlation between DVL and DHIV-specific T-cell responses (w16-w0) was observed in vaccine and not in placebo groups (r=-0.56, p=0.09; r=-0.28, p=0.43; vaccine and placebo groups, respectively).

**Conclusion:** The combination of a MD-DC therapeutic vaccine and pegIFNα was safe. A very modest decrease in VL was observed in vaccine recipients and was correlated with an increase of HIV-1 specific T-cell responses. Clinical trial.gov EudrACT 2015-001795-22

### 283 PERSISTENT ANTIVIRAL EFFECT INDUCED BY TYROSINE KINASE INHIBITORS

Lorena Vigón1, Sara Rodríguez-Morad1, Elena Mateos1, Valentin Garcia1, Juan Ambrosioni1, Virginia Sandonis1, Guiomar Bautista1, Pilar Pérez-Romero1, José Alcami Pertejo1, Juan Luis Steegmann1, Jose M. Miro1, Vicente Planelles1, María Rosa López-Huertas1, Mayte Coiras1

1Institute of Health Carlos III, Madrid, Spain, 2Hospital Ramon y Cajal, Madrid, Spain, 3IDIBAPS, Barcelona, Spain, 4Hospital Universitario 12 de Octubre, Madrid,
Tyrosine kinase inhibitors (TKIs) are used in clinic to treat chronic myeloid leukemia (CML). TKIs should be taken for life but some patients stop treatment due to antileukemic deep molecular response (DMR). Some TKIs may also induce a potent immune response against CMV and our group described an inhibition of HIV infection in vitro and in vivo. Many mechanisms define TKIs activity against HIV: 1) cytostatic effect and inhibition of cytokine-dependent proliferation, possibly affecting reservoir establishment and replenishment 2) maintenance of SAMHD1 antiviral activity 3) sustained cytoxic activity to control the growth of cancerous cells even after withdrawal. Objectives: 1) to analyze cytoxic effect in CML patient cell populations during TKI treatment and after withdrawal; 2) to determine the susceptibility to HIV infection of CD4 T cells from CML patients off TKI treatment.

Methods: PBMCs from CML patients on TKI treatment for avg. 3.8±0.5y (dasatinib n=20; imatinib n=11; nilotinib n=9; bosutinib n=5; ponatinib n=1), CML patients off TKI treatment for avg. 2.3±0.3y due to DMR (last TKI: dasatinib n=4; imatinib n=7; nilotinib n=6) and healthy donors (n=30) were analyzed by flow cytometry. IFNγ synthesis was analyzed by flow cytometry and proportional integration by Alu-qPCR.

Results: 1) Active NK cells CD56+CD16+CD107a+ were increased >6-fold in patients on treatment with all TKIs except imatinib, compared to control. This population remained >5-fold enhanced after withdrawal; 2) CD8±TCRgd+lymphocytes were increased >2-fold in patients on treatment and remained >3-fold greater in patients off treatment. 3) Synthesis of IFNg in response to in vitro CMV pp65 peptide was increased >2-fold in CD8+CD69+ T cells from patients off treatment. However, no CD8 reactivation was detected in patients on treatment probably due to the potent cytostatic effect of TKIs. 4) In vitro treatment with TKI dasatinib and IL-15 increased >2.5-fold the IFNg secretion from NK cells. 5) PBMCs from patients off treatment showed <12-fold proviral integration after in vitro infection

Conclusion: TKIs induce mechanisms with antiviral activity that may be used against HIV infection. Populations of active NK cells and IFNg-secreting CD8 cells may persist in CML patients even after treatment withdrawal; 2) to determine the susceptibility to HIV infection of CD4 T cells from CML patients off TKI treatment.

284 RATIONAL DONOR FECAL MICROBIOTA TRANSPLANTATION IN HIV (REFRESH STUDY)

Sergio Serrano-Villar, Alba Talavera, Nadia Madrid-Elena, José A. Pérez-Molina, María José Gosalbes, Shrish Budre, Alejandro Vallejo, Ryan J. Elliott, Fernando Dronda, Carolina Gutiérrez, María J. Vivancos-Gallego, Javier Martínez-Sanz, Sabina Herrera, Raquel Ron, Santiago Moreno, 1Hospital Ramón y Cajal, Madrid, Spain, 2Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain, 3FISABIO, Valencia, Spain, 4OpenBiome, Cambridge, MA, USA

Background: It is unknown whether oral fecal microbiota transplants (FMT) can affect the gut microbiota and systemic immunity of HIV-infected individuals.

Methods: Thirty ART-treated HIV-infected subjects with a CD4/CD8 ratio <1 were allocated to receive either weekly oral fecal microbiota capsules or placebo for 8 weeks (10 capsules at week 0; 5 capsules/week from weeks 1-7). Three stool donors were selected from a universal donor stool bank based on bacterial abundance of Fecalibacterium and Bacteroides (high) and Prevotella (low) and high fecal butyrate concentrations. We assessed 48-week safety and efficacy, including changes in CD4/CD8 T cells, microbiota engraftment using illumina 16S rDNA sequencing, T cell activation/senescence, inflammation (sCD14, sCD163, STNF-2), bacterial translocation (LTA, LBP) and intestinal damage (FABP2) markers.

Results: Twenty-nine participants, with a mean CD4 count of 641±286 cells/μL completed the 48-week follow-up. FMT was well tolerated, with no grade 3-4 related adverse events. No significant changes were observed in CD4/CD8 T-cells, in T-cell activation/senescence or levels of the inflammation/bacterial translocation markers. Significant between-group differences were observed in FABP2, with higher fold change decrease at week 4 in the FMT arm (0.52 vs. 0.95, p=0.045), Alfa diversity significantly and incrementally increased until week 6 in the FMT arm (FMT vs. placebo arm, p=0.013) and returned to baseline levels at week 48. Unifrac distance trajectories indicated mild engraftment of donor’s microbiota that persisted until week 36 and greater engraftment among the 4 subjects who had received antibiotics in the 12-week period before FMT. LEfSe analyses showed an incremental engraftment of different taxa in the active arm, being Lachnospiraceae family and Faecalibaculum, Faecalibacillus, Fusiformiaceae, Anaerostipes and Ruminococcus genus the taxa more robustly engrafted across time-points.

Conclusion: Repeated oral capsular FMT was safe in HIV-infected subjects on ART and introduced incremental compositional changes in the microbiota. While it is unclear whether this strategy will help to attenuate systemic inflammation, our results indicate that manipulation of the gut microbiota using a non-invasive and safe strategy of FMT delivery is feasible.
**286LB ENHANCED COMPLEMENT ACTIVITY DOES NOT IMPROVE PROTECTION IN SHIV-CHALLENGED MACAQUES**

David A. Spencer¹, Benjamin Goldberg², Jérémy Duflo³, Timothée Bruel³, Olivier Schwartz³, Margaret Ackerman¹, Ann J. Hessell¹

¹Oregon Health and Sciences University, Portland, OR, USA, ²Dartmouth College, Hanover, NH, USA, ³Institut Pasteur, Paris, France

**Background:** Fc modified bNAbs are being developed for prophylactic and therapeutic treatment of HIV. Extended half-life and reduced immunogenicity modifications have proven effective, but attempts to improve bNAb efficacy by enhancing affinity for Fcg receptors alone have not worked in SHIV-challenged macaques. In this model, ablating FcγR binding reduced protection, but the role of complement appeared limited. We hypothesized improving bNAb Fc-mediated complement activity and increasing affinity for FcgR would strengthen protection.

**Methods:** We developed 10 Fc variant bNAbs with site mutations designed to increase CDC activity, Cfq binding, and FcgR affinity and evaluated each for binding to FcgRs, Cfq and infected cells plus functional CDC, ADCC and ADCP activity. MPER targeting 10E8v4 that weakly neutralizes SHIVSF162P3 (IC₅₀ 30 mg/ml) and mediated complement activity in vitro, but does not mediate ADCC was selected for macaque studies. Protection was evaluated with a single high dose intrarectal SHIVSF162P3 challenge 3 days after 5 mg/kg mAb infusion. Groups of 6 macaques received either unmodified 10E8v4, 10E8v4-LALA (Complement/FcgR dual knockout), 10E8v4-ETF, (-2-fold enhanced complement deposition, viral lysis, and CDC, increased affinity for FcgRs with no ADCC or increased ADCP), or a control mAb. Blood draws monitored viremia, mAb kinetics, and neutralizing titers.

**Results:** Unexpectedly, mean plasma viral loads (PVL) were elevated in the ETFE group compared to unmodified 10E8v4 (P<0.0001) and LALA groups (P=0.0070). Viremia was starkly increased in multiple lymphoid and gut tissues in the ETFE group, over unmodified 10E8v4 (P<0.0001), LALA (P=0.0270), and control (P<0.0001) groups. ETFE mutations led to lower serum concentrations and neutralizing titers at challenge and reduced serum half-life. Higher doses of 10 and 20 mg/kg ETFE or unmodified mAb led to comparable PVL, suggesting neutralizing titers may mitigate effects of increased complement. Mechanistic studies show splenocytes treated with sub-neutralizing ETFE increased infection over controls dependent on the presence of monocyte derived DCs.

**Conclusion:** Our studies imply enhancing CDC in vitro may not predict in vivo function and supports evidence that increased affinity for FcgRs may not enhance protection. Implications of complement asosmulation of HIV inhibiting effector cell function warrant further study. Importantly, consequences seen here of modulating complement in HIV infection may forewarn clinical safety and therapeutic trials with modified Fc bNAbs.

**287 THE RV144 VACCINE PRIMED IgG4 AND V1V2-ADCP RESPONSES IN HIV BREAKTHROUGH INFECTIONS**

Thembi Mdluli¹, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackerman⁵, Merlin L. Robb⁶, Nelson L. Michael⁷, Sandhya Vasan⁸, Michael A. Eller⁹, Thembi Mdluli², Jérémy Duflo³, Dominic Paquin-Proulx¹, Bonnie Slike¹, Gina Donofrio¹, Sorachai Nityanaphan², Punnee Pitsutthitium³, Supachai Berks-Ngam⁴, Margaret Ackman
MUCOSAL T AND B CELL RESPONSES INDUCED BY ALVAC-HIV/AIDSVAX B/E
LATE BOOST STRATEGIES

Alexandra Schuett1, Srisawat Akapirat1, Michael A. Eller2, Yuwadee Phuang-ngern2, Punnee Pitsitsitthithum3, Sorasound Nitayaphan4, Sunwat Chariyalertsa5, Nittaya Phanuphak6, Carlos A. Diazgranados7, Jerome H. Kim8, Merlin L. Robb9, Nelson L. Michael1, Robert J. O’Connell3, Sandhya Vasan3, for the RV306 Study Group

1US Military HIV Research Program in Thailand, Bangkok, Thailand, 2Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, 3US Military HIV Research Program, Silver Spring, MD, USA, 4Mahidol University, Bangkok, Thailand, 5Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand, 6SEARCH, Bangkok, Thailand, 7Sanofi Pasteur, Swiftwater, PA, USA, 8International Vaccine Institute, Seoul, South Korea

Background: The majority of HIV-1 infections occur across mucosal surfaces, hence mucosal immune responses including CTL, T-helper cells and IgA-secreting plasma blasts (PB) are part of the initial defense against infection. RV144 is still the only vaccine trial that demonstrated modest efficacy; however, mucosal responses were not characterized. Here we assess mucosal immune responses elicited after the ALVAC-HIV/AIDS/AXV B/E prime boost regime used in RV144 followed by additional late boost strategies.

Methods: Sigmoid biopsies were collected two weeks after final vaccinations, either after the RV144 regimen, or after late boosts at 12, 15 or 18 months (mo) with ALVAC-HIV and/or AIDSVAX B/E. TH023- and Gag-specific CD4 and CD8 T cell responses as well as B cell responses were assessed by flow cytometry. Vaccine-specific IgG and IgA was measured in rectal secretions by binding antibody ELISA.

Results: Mucosal TH023- and Gag-specific T cell responses were readily observed with TNFa as the predominant cytokine produced followed by IFNg and IL-2. After the RV144 regimen, 30% of vaccine recipients developed TH023-specific CD4 T cell TNFa responses, which increased after the late boosts to 63% (12mo), and 100% (15/18mo). Similarly, the magnitude of TH023-specific CD4 T cell TNFa responses increased with a delayed boost interval from 0.01% post RV144, to 0.09% at 12mo, 0.98% at 15mo and 0.92% at 18mo boosts (p=0.007 by Kruskal-Wallis). Additionally, magnitude of mucosal TH023-specific CD8 T cell TNFa responses increased with later boost intervals (post RV144: 0.12%, 12mo: 0.09%, 15mo: 0.58%, 18mo: 0.83%; p=0.03 by Kruskal-Wallis). This is in contrast to univariate peripheral responses that were mainly CD4-mediated, appeared already after the RV144 regimen and were maintained after the late boosts. Although vaccine-specific IgG was not detected in rectal secretions, an increase in mucosal IgA-producing PB was observed with increasing late boost intervals (post RV144: 8.6%, 12mo: 7.7%, 15mo: 17.4%, 18mo: 17.0%; p=0.04 by Kruskal-Wallis).

Conclusion: Late boosts with ALVAC-HIV and/or AIDSVAX B/E induce robust mucosal vaccine-specific CD4 and CD8 T cell responses and increase the frequency of mucosal IgA-producing PB. These responses differ in quality and kinetics from peripheral responses, highlighting potentially different mucosal mechanisms in contributing to the defense against HIV-1 after vaccination.
TARGETING HIV ENV TO CD40 LEADS TO HIV-SPECIFIC POLYCLONAL B CELLS IN HUMANIZED MICE

Veronique Godot1, Colas Tcherakian1, Lorrain Gil2, Iliai Cervera-Marziali3, Hugo Mouquet4, Guangming Li5, Liang Cheng5, Jean Daniel Lelievre2, Giuseppe Pantaleo6, Mireille Centlivre2, Sandy Zurawski3, Gerard Zurawski3, Pierre Milpied1, Lishan Su1, Yves Levy1
1INSERM, Paris, France, 2Vaccine Research Institute, Créteil, France, 3INSERM, Strasbourg, France, 4Baylor Institute for Immunology Research, Dallas, TX, USA, 5University of California Davis, Davis, CA, USA, 6University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Challenges in the development of HIV-1 vaccines are to more accurately direct protective immune responses and develop appropriate animal models. Methods: Mice with a functional human immune system (HIS) were immunized with either anti-CD40 mAb in which the Fcgamma receptors are fused to the HIV-1 envelope protein (gp140ZM96) (anti-CD40 gp140) with Cpg-B (w0, w3, w5) (CD/CD group) or Nycax K Cpx vaccine encoding gp140ZM96 with Cpg-B (w0) followed by two injections of anti-CD40 Env gp140 with Cpg-B (w3, w5) (N/CD group). B- and T-cell responses were studied at w6 in blood and spleens and compared to control animals (PBS or Cpg-B only, C group). BCR diversity was analyzed by single cell RNA sequencing (scRNAseq).

Results: As compared to C group, anti-CD40 Env gp140 vaccine induced a sustained CD40 expression on myeloid DCs and B cells. In both vaccine groups, gp140ZM96-specific CD4+ memory T cells and IgG-switched B cells were elicited at w6. Among these cells, gp140ZM96-specific IgG+ B cells were induced in the spleen and blood with a higher frequency in the N/CD group than in controls (840.8 and 77.5 EC 50, respectively) at 5 weeks post boost (1028 and 450 SFC/10^6 PBMC, respectively; mean of 6 animals). Specific antibody titers against Clade C Env proteins were also greater in anti-CD40 group (1700 and 202 EC 50, respectively) than in controls (840.8 and 77.5 EC 50, respectively) at 5 weeks post boost. Magnitude of the cellular response after a second boost was correlated to the durability of the response measured 30 weeks after immunization.

Conclusion: Altogether these results exhibited that CD40 targeting influences the early immune events within the draining LN then leading to stronger T and B cells responses. We also demonstrate that CD40 targeting in presence of adjuvant significantly improves vaccine immunogenicity without requiring priming with different types of vaccine or targeting strategy. The safety and efficacy of the CD40-targeted vaccine justify further development for future human clinical trials.

HARNESSING ORIGINAL ANTIGENIC SIN FOR PREVENTING MTCT OF HIV

Ashley N. Nelson1, Maria Dennis1, Jesse F. Mangold1, Katherine N. Li1, Riley J. Mangan1, George Shaw2, Katharine J. Bar3, Barton F. Haynes2, M. Anthony Moody1, Justin Pollara1, Koen Van Rompay1, Kristina De Paris4, Sallie Permar2
1Duke University School of Medicine, Durham, NC, USA, 2Duke Human Vaccine Institute, Durham, NC, USA, 3University of Pennsylvania, Philadelphia, PA, USA, 4University of California Davis, Davis, CA, USA, 5University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Progress towards the elimination of pediatric HIV infection via mother to child transmission (MTCT) is limited by several factors, including inconsistent access and maternal adherence to ART. The development of a maternal vaccine that can synergize with current ART prophylaxis could overcome implementation challenges impeding achievement of an HIV-free generation. Both the epitope specificity of HIV envelope (Env)-specific antibody responses and autologous virus neutralization have been implicated in MTCT
risk of HIV. Our goal was to evaluate the immunogenicity of a heterologous vaccine regimen to boost autologous HIV Env-specific antibody responses in SHIV-infected, ART-suppressed, female rhesus macaques (RMs).

**Methods:** Twelve female RMs were infected intravenously with SHIV.C.CH505.375H.dCT, and began a daily ART (TDF, FTC, dolutegravir) regimen at 12 weeks post-infection (wpi). Two weeks after ART initiation, RMs received 3 intramuscular doses of HIV b.63521/1086.c gp120 (n=6; vaccine group) or RSV (n=6; placebo group) vaccine with a TLR agonist adjuvant (StR8C) monthly. ART was discontinued after 12 weeks and RMs were monitored for viral rebound. Binding and functional antibody responses were also measured.

**Results:** HIV Env vaccination in the setting of ART did not delay viral rebound. HIV Env gp120 vaccinated RMs exhibited peak antibody binding responses at 20 wpi (2 weeks post 2nd immunization), with enhanced IgG responses against b.63521 and 1086.c vaccine immunogens; as well as the challenge virus Env, SHIV.C.CH505. Plasma autoantibody titers (CH505.TF) neutralization was similar between the two groups upon treatment interruption, while ADCC responses were markedly boosted in Env vaccinated animals. Vaccinated RMs exhibited greater breadth in IgG antibody responses against various Env epitopes, with V3- and V1V2-specific responses against both the vaccine and challenge virus antigens.

**Conclusion:** In conclusion, vaccination of SHIV-infected RMs in the setting of ART can boost IgG responses against the original infecting antigen, SHIV.C.CH505, and Env-specific antibody responses previously associated with low risk of MTCT. Our results suggest that a vaccine regimen administered to HIV-infected pregnant women could boost previously identified humoral correlates of reduced MTCT risk in humans.

---

**295**

**TBK-1-DC VACCINE INDUCES POLYFUNCTIONAL T CELLS AND CONTROL OF HIV-1 IN THE BLT MOUSE**


**Background:** Strain 68-1 rhesus cytomegalovirus (CMV) vaccine vectors expressing simian immunodeficiency virus (SIV) antigens (RhCMV/SIV) prime broadly-targeted, unconventionally MHC-II- and MHC-E-restricted CD8+ T cell responses that strongly control SIV replication in vaccinated rhesus macaques (RM). However, RM express many more MHC-II and MHC-E alleles than humans, and it remains unclear if the unprecedented cellular immunity and control of SIV observed in RhCMV/SIV-vaccinated RMs is due to the unique immunogenetics of RM or species-specific functions of RhCMV itself. In contrast to RMs, Mauritian cynomolgus macaques (MCM) exhibit reduced genetic diversity with immunogenetics that more closely resemble those of humans. However, 68-1 RhCMV was unable to elicit unconventionally restricted CD8+ T cells in MCM suggesting a species barrier for viral vector function.

**Methods:** To determine if non-classical T cell priming and protection against mucosal SIV challenge is restricted to RhCMV vaccination of RM or a universal phenomenon, we constructed a '68-1 like' cynomolgus CMV expressing SIV antigens (CyCMV/SIV). We vaccinated eight MCM with CyCMV/SIV and monitored multiple immune parameters in the animals including transgene-specific CD4+ and CD8+ T cell responses in blood and BAL. We challenged the eight vaccinated MCM and eight unvaccinated controls with repeated, limited-dose, intrarectal SIVmac239 to assess vaccine-mediated protection.

**Results:** CyCMV/SIV vaccinated MCM generated unconventionally, MHC-II- and MHC-E-restricted T cell responses comparable to RhCMV/SIV vaccinated rhesus macaques. Upon challenge with SIVmac239, 50% of CyCMV/SIV vaccinated MCM stringently controlled SIVmac239 replication, defined as no plasma viremia and the development of T cell responses against SIV proteins absent from the vaccine. Acquisition and subsequent control of SIV was confirmed by cell-associated viral loads and adoptive transfer to naive MCM of tissue biopsies from CyCMV/SIV-protected animals.

**Conclusion:** Thus, we have confirmed the distinct immunologic and protective phenotype induced by CMV vaccines in a second nonhuman primate species with immunogenetics reflective of humans, indicating that these results are not unusual species-specific traits of RM or RhCMV and that 68-1 like HCMV/HIV vaccines might similarly recapitulate unconventional T cell restriction and protect against HIV.

---

**297LB**

**SUPERIOR PROTECTION AGAINST SHIV INFECTION BY SAME SITE DNA-PROTEIN COMBINATION**

Barbara K. Felber, Zhongyan Lu, Yintao Hu, Antonio Valentin, Margherita Rosati, Joshua A. Weiner, Xiaoying Shen, Georgia Tomaras, Celia C. Lebranche, David Vezzon, George Shaw, Guido Ferrari, Margaret Ackerman, Barton F. Haynes, George N. Pavlakis

1National Cancer Institute, Frederick, MD, USA, 2Dartmouth College, Hanover, NH, USA, 3Duke University, Durham, NC, USA, 4National Cancer Institute, Bethesda, MD, USA, 5University of Pennsylvania, Philadelphia, PA, USA
Background: We compared immunogenicity and protective efficacy of an HIV vaccine comprised of DNA (env and gag) and Env proteins by co-administration of DNA and Protein in the same muscle or by separate administration of the DNA and Protein components in contralateral sites.

Methods: Female rhesus macaques (20 animals/group) were immunized with a 6-valent vaccine including DNA plasmids expressing membrane-anchored gp145 Env sequentially isolated from a HIV-1 infected individual (CH305). The DNA was delivered by IM injection followed by in vivo electroporation. The vaccine also included a gp120 Env protein component matching the sequences encoded by the plasmid DNA and adjuvanted in GLA-SE. The DNA and protein vaccine components were administered in the same anatomical sites ('Co-administration') or in contralateral sites ('Separate Administration') After 6 vaccinations in 4-month intervals, the macaques were challenged by weekly intravaginal exposures with low dose T/F tier-2 SHIV CH305 stock.

Results: Only macaques in the co-administration vaccine group were protected against SHIV CH305 acquisition, with a 67% risk reduction per exposure after 15 weekly IVAG challenges. Macaques in the co-administration group developed higher Env-specific humoral and cellular immune responses. Non-neutralizing Env antibodies, ADCC and antibodies binding to Fc-gamma Receptor IIa were associated with decreased transmission risk. These data suggest that simultaneous recognition, processing and presentation of DNA + Env protein in the same draining lymph node play a critical role in the development of protective immunity.

Conclusion: Co-immunization of DNA + Protein in the same muscle is superior for inducing protective immune responses against repeated tier-2 SHIV challenge. The advantage of co-immunization vaccine regimens targeting Env immunogens to the same draining LN could also be beneficial to other vaccine modalities and other pathogens.

Dolutegravir increases B cells and resting memory B cells in RV254

Supannee Buranapraditkul1, Eugene Kroon2, Hiroshi Takata3, Suthat Chottanapund4, Carlo Sacdalan2, Duanghathai Suttichom5, Ratchapong Kanaparch6, Somporn Tipsuk7, Khunthalee Benjapornpong5, Bessara Nuntapin5, Merlin L. Robb8, Jintanat Ananworanich9, Sandhya Vasan5, Lydie Trautmann9, for the SEARCh010/RV254/SEARCH013/RV304 Study group

1Chulalongkorn University, Bangkok, Thailand, 2SEARCH, Bangkok, Thailand, 3Henry M Jackson Foundation, Silver Spring, MD, USA, 4Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, 5Henry M Jackson Foundation, Bethesda, MD, USA

Background: Early initiation of antiretroviral therapy (ART) in acute HIV infection (AHI) could help preempt evasion and damage of the immune system by HIV. Use of the integrase inhibitor Dolutegravir (DTG) and 2NRTIs is the new standard regimen. However, the influence of these drugs on the recovery of immune cells in blood and lymph node (LN) tissue has not been well studied. To address this, we assessed differences in B cell populations in Thai participants randomized to switch from 2NRTI+EFV to 2NRTI+DTG.

Methods: Cryopreserved peripheral blood mononuclear cells (PBMCs) and lymph node mononuclear cells (LNMCs) from 27 AHI treated Thai participants enrolled in the RV254 cohort were analyzed. Participants were grouped based on ART regimen: those randomized to switch from 2NRTI+EFV to 2NRTI+DTG (n=13; 6-22 mos EFV followed by 9-20 mos DTG) and those who remained on 3TC/TDF/EFV (n=14; range 6-22 mos). Eighteen uninfected individuals (HV−) enrolled in RV304 were included for comparison. B cells were characterized by flow cytometry.

Results: The frequencies of CD19+ B cells were significantly decreased in PBMCs but not LNMCs of 2NRTI+EFV treated compared to HIV− participants (p<0.05), but were recovered in those who switched to DTG. The frequencies of resting memory B cells (RM; CD21+CD27+IgG+CD20+) were significantly decreased in both PBMCs and LNMCs of the 2NRTI+EFV group (Fig 1a), whereas the frequencies of tissue-like memory B cells (TLM) were significantly increased compared to HIV− participants (p<0.05; Fig 1b). 2NRTI+DTG treated participants had recovered frequencies of RM B cells, but lower frequencies of TLM and activated memory B cells (AIM) compared to HIV− participants and non-switched EFV-treated participants (p<0.05; Fig 1c).

Conclusion: Our data show that switching from 2NRTI+EFV to 2NRTI+DTG could aid in recovery of B cell populations in the blood and LN, although the number of LNMC samples in the 2NRTI+DTG group in the present study limits definitive conclusions for this compartment. We observed higher frequencies of B cells and RM B cells in both PBMCs and LNMCs after switching from 2NRTI+EFV to 2NRTI+DTG. Further, 2NRTI+DTG treated participants had fewer AM and TLM B cells, the latter of which have an exhausted phenotype. These data suggest that switching from EFV to DTG may be beneficial to limit activation and exhaustion in the B cell compartment of participants who initiated treatment in AHI.

Characterizing Antibody Responses in ART-Treated Individuals

Andrew B. Wilson1, Yangxin Ren1, Eva M. Stevenson2, R. Brad Jones3, Rebecca Lynch2

1George Washington University, Washington, DC, USA, 2Weill Cornell Medicine, New York, NY, USA

Background: Although suppression of HIV has become possible through antiretroviral therapy (ART), ART-treated individuals must maintain therapy to avoid rebound from a viral reservoir. Strategies to limit or clear this reservoir are urgently needed. Research has shown that individuals infected for longer prior to receiving ART harbor greater reservoir diversity, but may also have higher anti-HIV antibody titers. The roles that infection length and viral diversity play in the humoral response must be further studied to inform approaches to clearing infection. Here, we aim to clarify a role, if any, for autologous antibodies in these treatments by characterizing their function in individuals on different lengths of ART.

Methods: Plasma was collected from 8 HIV+ males on ART. Bulk IgG was isolated and normalized concentrations were tested for binding to gp41 and gp120 proteins. IgG was then tested for breadth and potency of neutralization against a global HIV panel as well as autologous outgrowth viruses derived from each individual.

Results: Binding against gp41 was highly correlated with gp120, and these binding titers were correlated with neutralization potency against the global panel. On average, participants exhibited low-potency neutralization of 8 of 12 viruses on the panel. Interestingly we did not observe potent autologous neutralization of outgrowth virus, and in fact 2 of 8 people harbored completely resistant virus at the highest level of IgG tested. 5 of the 8 individuals had a documented HIV-negative date, and therefore antibody functionality could be correlated to estimated length of infection before ART and duration of ART. We observe that length of infection is not correlated with autologous neutralization, but we do observe a trend toward more potent neutralization of the global panel by individuals infected for longer periods of time.

Conclusion: Our findings agree with published studies of untreated individuals that length of infection is related to neutralization breadth. By contrast, we found that duration of ART treatment was not associated with differences in neutralization — either heterologous or autologous. Overall, these data suggest that the inducible reservoir is relatively resistant to autologous antibodies whether the individuals are ART-suppressed early or late after diagnosis.

Near Normalization of Immune Activation in PLWH on Long-Term Suppressive ART

Óscar Brochado Kith1, Lidorio Martinez2, Juan Berenguer3, Luz M. Medrano4, Juan González-García5, Pilar Garcia-Broncano5, María Á. Jimenez-Sousa1, Ana Carrero2, Victor Hontanon3, M Ángeles Muñoz-Fernández2, Juan Carlos López-Bernald5, Amanda Fernández-Rodriguez2, Salvador Resino1

1Institute of Health Carlos III, Madrid, Spain, 2University Hospital Gregorio Marañón, Madrid, Spain, 3La Paz University Hospital, Madrid, Spain, 4Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: In HIV-infected patients, chronic immune activation and inflammation persist after suppressive combination antiretroviral therapy
(cART). We compared gene expression and biomarkers in peripheral blood between HIV-infected patients on long-term suppressive cART (HIV-group) and age-matched healthy controls (HC-group).

Methods: Cross-sectional study of 22 subjects in HIV-group with HIV-RNA <50 copies/mL and cART >1 years’ follow-up. RNA-seq was performed from peripheral blood mononuclear cells (PBMCs). Thirteen T-cell subsets were evaluated by flow-cytometry and 32 plasma biomarkers by immunoassays. All p-values were corrected by the false discovery rate (q-values).

Results: Only the serine/arginine repetitive matrix 4 (SRRM4) gene was differentially expressed between HIV and HC groups (q-value<0.05 and fold-change>2). However, 147 differentially expressed genes were found with a more relaxed threshold (p-value<0.05 and fold-change>1.5). Sixty-seven of these, with values of variable importance in projection (VIP)>1, were selected for pathway analysis. Significant ribosome-related pathways were represented by six ribosomal genes (RPS: S27, RPS27, L18A, RPL18A, L8, RPL8, L26, RPL26), L4 (RPL4), and S21 (RPS21), all of them downregulated in the HIV-group. T-cell subset and plasma biomarkers were also analyzed, but none of them were significant (q-value>0.05). However, non-corrected p-values showed higher values of CD4+ Treg cells (CD4+CD25+CD127-/low), MCP-1, and sVEGF-R1 in the HIV-group (p-values<0.05). Correlation patterns between RNA-seq expression and peripheral biomarkers (T-cells and plasma) were different between HC and HIV groups.

Conclusion: Immune activation and inflammatory biomarkers were close to normalization in HIV-infected patients on long-term suppressive cART, compared to HC group. However, residual alterations remained at the gene expression of PBMCs, which still reveal the impact of HIV infection in these patients.

301 REVERSION OF CD4+ T-CELL EXHAUSTION MEDIATED BY PLASMACYTOID DENDRITIC CELLS
M Reyes Jimenez-Leon1, M. Carmen Gasca-Capote1, Macarena Lopez-Verduqui1, Laura Tarazon-Diez1, Maria Trujillo Rodriguez1, Cristina Roca1, Nuria Espina1, Alicja Gutierrez-Valencia1, Pompeyo Viciana1, Luis Lopez-Cortes1, Ezequiel Ruiz-Mateos1
1Institute of Biomedicine of Seville, Sevilla, Spain

Background: T-cell exhaustion is not reverse by effective ART. T-cell exhausted cells have been associated with HIV persistence during ART. The plasmacytid dendritic cells (pDCs) sense viral and bacterial products through Toll-like receptors (TLR)-7 and -9 and translate this sensing in IFN-a production and T-cell polarization. It is unknown whether pDCs can reverse T-cell exhaustion in HIV-infected patient on long-term suppressive ART. The aim of the present study was to analyze, through a pDC/T-cell co-culture, whether pDCs after stimulation with different TLR agonist were able to reverse T-cell exhaustion.

Methods: Patients on suppressive ART (ART, n=5) were compared with healthy donors (HD, n=5) and viremic patients naïve for ART (VIR, n=4). pDCs, CD4+ and CD8+ T-cells were isolated from 450mL of whole blood using negative selection. After pDCs overnight stimulation with HIV inactivated with aldritol (AT-2, HIV), CpG-A, CpG-C, and GS9620 or no stimuli, stimulated pDCs were cocultured for 6h with autologous CD4+ or CD8+ T-cells. The expression of (AT-2-HIV), CpGA, CpGC, and GS9620 or no stimuli, stimulated pDCs were cocultured for 6h with autologous CD4+ or CD8+ T-cells. The expression of PD1, TIGIT, TIM3 or LAG3 were increased ex vivo and in vitro by multiparametric flow cytometry.

Results: Ex vivo the expression of PD1, TIGIT, TIM3 or LAG3 were increased in several CD4+ T-cell memory subsets from ART compared to HD (e.g. PD1+TIGIT+TIM3+LAG3+CD4+CD45RA-CD27+, p=0.002). After the coculture, we observed a trend to decrease in the expression of these markers after AT-2 and CpG-A pDC stimulation (p=0.047 and p=0.06, respectively). This reversion in CD4+ T-cell exhaustion phenotype was specially patent after CpG-C and GS9620 pDC stimulation with normalization compared to HD (p=0.117, p=0.037, respectively). This decrease of CD4 T-cell markers exhaustion occurs at a much higher rate in the polyfunctional ability of different CD4+ T-cell subsets in terms of cytokine production (e.g.: CD107a+IL2-IL17a+INF-γ+TNFα+CD45RA+CD27-) expression were significantly increased in ART respect HD after CpG-C and GS9620 stimulation p=0.037, respectively.

Conclusion: The modulation of the pDCs through TLR agonists reverses CD4+ T-cell exhaustion in HIV-infected patients on ART. These results may have important implications in the reduction of deleterious effect of pDCs and T-cells causing non AIDS events and may decrease HIV-reservoir levels.

302 CD8+ SUBSET-DEPENDENT OVEREXPRESSION OF TIGIT AND TIGIT+TIM3 BY HIV DESPITE ART
Oscar Blanch-Lombarte1, Esther Jimenez-Moyano1, Dan Ouchi1, Adam Pelletier1, Aarti Tallal1, Ashish Sharma1, Ruth Penya1, Judith Dalmat1, José R. Santos1, Rafick-Pierre Sekaly2, Bonaventura Clotet1, Julia G Prado1
1InciCiva Institute for AIDS Research, Badalona, Spain, 2Case Western Reserve University, Cleveland, OH, USA, 3Fundació Lluita Contra la Sida, Badalona, Spain

Background: The expression of inhibitory Receptors (iRs) blocks CD8+ T-cell activity in HIV-1 infection. Consequently, the control of iRs is critical for recovering CD8+ T-cell function. The alterations of iR expression by HIV-1 infection are not fully delineated but are essential to identify future immunotherapeutic targets. With this aim, we performed a high-dimensional cytofluorimetric analysis of iRs, CD39, and CD8+ lineage markers in early and chronically suppressed HIV-infected individuals.

Methods: We selected PBMCs from early (t=24) and chronically HIV-infected individuals with longitudinal samples in a median of 3 (t=31) and 10 years (t=52) on suppressive cART (n=24). For comparisons, we selected PBMCs from healthy seronegative individuals (HC, n=24). We stained PBMCs using antibodies for iRs (TIGIT, PD1, LAG3, and TIM3), CD39, and CD8+ T-cell lineage (CD3, CD8, CD45RA, CCR7, and CD27). We analyzed multivariate datasets by FlowVa, SPICE, and R package. Also, we performed an unsupervised KNN algorithm for cell clustering and tSNE for visualizing single-cell data.

Results: Based on the expression levels of iRs and lineage markers, we identified 23 cellular clusters. From this analysis, we observed a remarkable heterogeneity of CD8+ T-cells and detected four clusters with significant differences across C31 and C52 individuals (p<0.05). These four clusters were high on TIGIT expression and one of them was also high on TIM3 expression. Moreover, differentiated clusters had additional lineage markers indicative of memory or effector-like features. We confirmed the overexpression of TIGIT at a single level or combined with TIM3, LAG3, and CD39 in C31 and C52 by combinatorial profiling with SPICE. Single TIGIT was elevated on CM and TM (p<0.05) and TIGIT+TIM3 on CM and E (p<0.05). The combinations of four iRs, including TIGIT+TIM3 with LAG3 or CD39, were upregulated on CM or E (p<0.05). Also, we found a correlation between CD8 counts and the absence of iR expression in C32 (r=0.51, p<0.05).

Conclusion: HIV-1 infection drives irreversible overexpression of TIGIT alone or co-expressed with TIM3, and LAG3 or CD39 in a CD8+ cell subset-dependent manner. These results point towards the targeting of TIGIT in combination with TIM3, and LAG3 or CD39 to regain CD8+ T-cell subset specific function in HIV-infected individuals on cART.

303 DYNAMICS OF HIV-SPECIFIC T CELLS ON DURABLE ART DIFFER BY ANTIGEN RECOGNIZED & BY SEX
Eva M. Stevenson1, Adam R. Ward1, Thomas R. Dilling1, John W. Mellors2, Rajesh T. Gandhi1, Deborah McMahon1, Joseph J. Eron1, Ronald Bosch1, Christina Lalama1, Joshua C. Cyktor3, R. Brad Jones1, for the A5321 Team
1Well Cornell Medicine, New York, NY, USA, 2George Washington University, Washington, DC, USA, 3University of Pittsburgh, Pittsburgh, PA, USA, 4Massachusetts General Hospital, Boston, MA, USA, 5University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 6Harvard University, Cambridge, MA, USA

Background: T-cell responses to HIV decay in the early stages of ART, with a half-life of 39 weeks. We previously demonstrated a direct correlation between levels of cell-associated HIV DNA (CA-DNA) and magnitudes of HIV-specific T-cell responses targeting early gene products nef/Tat/Rev in the ACTG A5321 cohort. These results suggested that ongoing interactions with HIV-infected cells may shape HIV-specific T-cell responses in individuals on long-term ART; however, little is known about the dynamics of these responses.

Methods: We previously performed IFN-γ ELISPOT assays on PBMCs from 49 participants (11 female) at study entry (on-ART timepoint 1): median (IQR) yrs on ART 7 (4, 8). We measured responses to pools of overlapping 15-mer peptides spanning the HIV gene products Gag, Env, Pol, Nef/Tat/Rev, as well as CMV pp65. Here, we applied this same assay to batched samples from week 24 & week 168 post-entry. Relationships were assessed between these responses and virologic/immunologic & clinical data provided by the ACTG.

Results: HIV-specific T-cell responses were stable on durable ART, with magnitudes differing by gene product & by sex (Figure). Responses exhibited
long median half-lives, which also differed by sex: Gag 32.4yrs (F 75.1yrs, M 3.7yrs); Env 3.5yrs (F 2.5yrs, M 1.1yrs); Pol 12.3yrs (F no decay, M 6.0yrs); Nef/Tat/Rev 6.9yrs (F 3.3yrs, M 6.5yrs). F vs. M participants exhibited higher magnitudes of responses longitudinally for all HIV gene products, but not for CMV, before and after controlling for pre-ART HIV RNA & CD4 count (all p<0.05). Higher levels of CA-DNA at study entry were associated with lesser decay of Nef/Tat/Rev-specific responses between weeks 24 & 168 (r=0.36, p=0.03, r=0.34, p=0.06 controlling for pre-ART HIV RNA & CD4 count). Correlations were not observed between: (i) CA-DNA & T-cell responses to other HIV gene products (p>0.1), nor (ii) between the slopes of decay of any HIV-specific T-cell responses and CA-DNA, plasma HIV-RNA, %CD38+HLA-DR+ T-cells, age, or PD-1 expression. **Conclusion:** Overall, HIV-specific T-cell responses were stable, demonstrating long half-lives, which differed by sex. Females also displayed higher magnitudes of HIV-specific T-cell responses. This result may help explain previous findings that females have a lower residual viremia in this cohort. Higher CA-DNA at study entry correlated with slower rates of decay in Nef/Tat/Rev-specific T-cell responses on long-term ART, consistent with some level of ongoing recognition of infected cells.

**304 EXPRESSION PROFILING OF HIV LATENTLY INFECTED CELLS VIA NANOSTRING AND MASS CYTOMETRY**

**Hannah S. Sperber**, Tong cui Ma', Nadia R. Roan', Satish K. Pillai

**Vitalant Research Institute, San Francisco, CA, USA, 1Gladstone Institute of Virology and Immunology, San Francisco, CA, USA**

**Background:** The main barrier to an HIV cure is the latent HIV reservoir. Long-lived HIV latently-infected cells remain invisible to the host immune system and persist during antiretroviral therapy. In this study, we characterized latently-infected cells by implementing combined transcriptomic and proteomic profiling to identify unique expression signatures and reliable biomarkers that can be exploited to target and eliminate the latent reservoir.

**Methods:** Primary CD4+ T cells were purified from six healthy donors and were infected with a dual-reporter HIV construct that enables the isolation of HIV latently-infected and productively-infected cells by flow cytometry. The populations were then characterized using NanoString hybridization and fluorescence-based digital counting technology allowing for simultaneous detection of 770 mRNA and 30 protein targets, and mass cytometry (CyTOF), measuring 40 surface proteins. Target expression levels were compared between populations using false discovery rate (FDR<0.1), cellular pathways and causal relationships were deciphered using Ingenuity Pathway Analysis.

**Results:** The latent population displayed significant upregulation of CD73 protein and IL8 mRNA, and significant downregulation of CD39 mRNA compared to productively-infected cells and controls. Protein expression levels of T cell activation markers including CD25, PD-1, OX40, CD127, and GITR did not significantly differ between productively- and latently-infected cells, while ICOS, an inducible T cell costimulator, was significantly increased on latently-infected cells. The ‘Pathogen defense’ pathway was significantly suppressed in both HIV infected cell populations compared to uninfected controls. ‘Antigen processing’ was strongly suppressed in the latent population. Transcription factors FOXP1, FOXD1, and FOXJ1 were discovered as the top three master regulators in latent cells.

**Conclusion:** Our data suggest that HIV latently-infected cells exhibit distinct molecular features associated with an anergic and/or hypoxic T cell state, and may subvert antigen processing to remain immunologically invisible. FOXD1 and FOXJ1 likely repress HIV transcription in latently-infected cells through inhibition of NFκB and NFAT complexes. Our results warrant validation in vivo using clinical samples from ART-suppressed HIV-infected individuals, and mechanistic exploration ex vivo using targeted gene knockouts.

**305 EPIGENOMIC CHARACTERIZATION OF A PRIMARY CELL MODEL OF HIV LATENCY**

**Barclay T. Pace**, Stuart R. Jefferys', Joel Parker', Raghuramanaraju, Brian D. Strahl', David M. Margolis', Edward P. Browne

**1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA**

**Background:** Transcriptional silencing of HIV in CD4 T cells generates a reservoir of latently infected cells that can reseed infection after interruption of therapy. As such, these cells represent the principal barrier to curing HIV infection, but little is known about the characteristics or regulation of the latent reservoir.

**Methods:** To further our understanding of the molecular mechanisms of latency, we employed a primary cell model of HIV latency in which infected cells adopt heterogeneous transcriptional fates with a subset of infected cells establishing viral latency. We characterized this model using assay of Transposon-Accessible Chromatin sequencing (ATACseq).

**Results:** We observed that loss of viral gene expression is a stable and heritable phenotype that is maintained through multiple rounds of stimulation and expansion, suggesting a role for epigenetic maintenance of latency. Using ATACseq we found that cells in which latency is established exhibit a significantly more closed chromatin conformation, both within the HIV genome and across the host cell genome, indicating that latency is correlated with a global process of epigenomic modification and heterochromatin expansion. We also observed that latency reversing agents (LRAs) induced distinct patterns of chromatin opening in both the HIV and host cell genomes. Furthermore, we observed that latently infected cells exhibited elevated levels of specific repressive histone modifications, including H3K27me3.

**Conclusion:** Altogether, these data demonstrate that latency establishment in primary CD4 T cells occurs preferentially in a subset of cells that exhibit expanded H3K27me3-associated heterochromatin, and that viral silencing is connected to global cellular epigenomic reprogramming. A deeper understanding of this process will likely lead to new therapeutic strategies for blocking the initiation or maintenance of latency.
306 SINGLE-CELL ANALYSIS SHOWS MOLECULAR SIGNATURES OF HIV LATENCY IN PRIMARY CELL MODELS

Sushama Telwatte1, Mauricio Montano1, Rachel S. Resop1, Emilie Battivelli1, Sara Moron-Lopez1, Eric Verdin1, Warner C. Green1, Alberto Bosque1, Joseph K. Wong1, Steven A. Yuki1
1University of California San Francisco, San Francisco, CA, USA, 2Gladstone Institutes, San Francisco, CA, USA, 3George Washington University, Washington, DC, USA, 4The Buck Institute for Research on Aging, Novato, CA, USA, 5San Francisco VA Medical Center, San Francisco, CA, USA

Background: Primary cell models have greatly advanced our understanding of HIV latency. However, it is unclear what mechanisms underlie latency in these primary cell models. We hypothesized that molecular signatures can distinguish uninfected, latently- and productively-infected populations in these models.

Methods: We assessed 4 primary cell models (blood CD4T cells: models from labs of Eric Verdin, Alberto Bosque, and Warner Greene; tissue/tonsillar CD4T cells: model from Warner Greene). Single cells from each model (2 donors) were FACS-sorted into 96-well plates and multiplex RT-qPCR (BiomarkHD) was used to quantify 88 human RNAs previously implicated in HIV infection/latency and 8 HIV targets (LTR, gag, pol, nef, MTI-2, U3-PolyA, and the IPDA assays for Env&Gag). We compared HIV-unexposed, HIV-exposed but uninfected, and latently -/+ productively-infected populations from each model to identify genes with ≥2-fold difference in median expression levels and P<0.05(*) or FDR-corrected P<0.05(**).

Results: As expected, multiple HIV targets(**) distinguished uninfected, latently-infected, and productively-infected cells. Each model differed in the cellular factors that distinguished populations, with some differences between donors. Compared to HIV-unexposed cells, latently-infected cells from the Verdin model showed higher expression of CXCR4(**), POLR2A(**), AP0BEC3G(*), and STING(*), while latent cells from the Bosque model expressed higher levels of CGAS(**), and latent tonsillar cells from the Greene model showed higher expression of CDK7, PBAF, RIG-I, and MDAS(* for all). Compared to HIV-exposed but uninfected cells, latently-infected cells showed: 1) less CR35(*), CD35(*), and NF-KBIA(*), but higher CD25(*) expression in the Verdin model; 2) less Cyclin L2(*) and more BCL6(*) in the Bosque model; and 3) no difference (except HIV targets**) in blood cells from the Greene model. Relative to productively-infected cells, latently-infected cells upregulated CTLA-4, BCL-11B, NFATC1, CDK7, HTATSF1, PAF-1, and PBAF expression (** for all) in the Verdin model, and exhibited lower expression of CD28, CTLA-4, PD-1, BCL-6, FAS, Sp1, POLR2A, CREBBP, G9a, STAT1, and IRF9 (?) for all in the Greene tonsillar model.

Conclusion: Our single cell analysis reveals multiple cellular factors that distinguish latently-infected cells from uninfected and productively-infected cells, that may provide a molecular signature necessary to discriminate this population in vivo.

307 PROVIRAL/HUMAN GENOMIC CROSSTALK IN CELLULAR MODELS FOR HIV INFECTION

Ulrike C. Lange1, Christoph P. Schwarz2, Julia K. Bliek1, Thomas Walther1, Roxane Verdi1, Carine M. Van Lint1, Joachim Hauber1
1University Medical Center Hamburg–Eppendorf, Hamburg, Germany, 2Heinrich-Heine University Freiberg, Germany, 3Vrije Universiteit Brussel, Brussels, Belgium

Background: Chronic HIV-1 infection is characterized by accumulation of proviral sequences in the genome of HIV target cells. Integration of viral-derived DNA is found at preferential loci, suggesting site-specific crosstalk between viral sequences and human genes. This crosstalk has been postulated to play a role in emergence of clonal infected cell populations. The molecular nature of this phenomenon is unclear. Paucity of HIV-infected cells in chronically infected individuals and lack of markers for HIV reservoir cells preclude functional studies in primary patient-derived cells.

Methods: CRISPR/Cas9-based homologous recombination was used to target HIV-derived reporter sequences to genomic sites in T cell-derived immortalized cells. Clonal lines were generated and multiple screening steps used to verify correct targeting. Cell models were analyzed for LTR inducibility and epigenetic regulation/transcriptomic effects of LTR activity.

Results: We have established a workflow to generate cellular models for HIV infection that recapitulate proviral integration at selected genomic loci. Using this workflow, we have derived several BACH2 HIV-1 reporter models that mimic integration of proviral DNA in the DBT Domain and CREBBP (BACH2) locus, which has been associated with recurrent integration and HIV-reservoir maintenance in chronically infected patients. We show that LTR transcriptional activity is repressed in BACH2 integral regions associated with proviral-DNA integrations in vivo. This repression is not observed if proviral-sequences are targeted to regions that do not correlate with sites observed in patients. We demonstrate that these findings are reflected in epigenetic modifications on LTR regulatory regions. Furthermore, to study genome-wide effects of proviral/human crosstalk at the BACH2 locus, we have undertaken transcriptome analysis in different BACH2-HIV-1 models in latent as well as LTR-activating conditions for which results will be presented.

Conclusion: Our workflow is an adaptable tool for functional studies of proviral/human crosstalk. We show features of such crosstalk for the BACH2 locus, indicating that clustered BACH2 proviral integrations in vivo might be due to site-specific effects on LTR activity.

308 DIFFERENTIAL DECAY OF INTACT AND DEFECTIVE PROVIRUS IN INDIVIDUALS ON SUPPRESSIVE ART

Michael J. Peluso1, Peter Bacchetti2, Kristen D. Ritter2, Subal A. Beg3, Jun Lai1, Jeffrey Martin1, Peter V. Hunt1, Timothy J. Heinrich1, Janet Siliciano1, Robert Siliciano1, Gregory Laird3, Steven G. Deeks3
1University of California San Francisco, San Francisco, CA, USA, 2Gladstone Institutes, San Francisco, CA, USA, 3Acceleron Diagnostics, Baltimore, MD, USA, 4Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: The latent HIV-1 reservoir is established early in the course of infection and persists despite suppressive antiretroviral therapy (ART). The relative stabilities of the intact and defective HIV genomes over time during effective ART have not been fully characterized. Understanding variability in the rate of change of the reservoir size, correlates of this variability, and factors associated with rapid decay is likely to be useful in the design and interpretation of HIV cure interventions.

Methods: We used the intact proviral DNA assay (IPDA) to estimate the rate of change of intact and defective proviruses in HIV-infected adults on suppressive ART over several years. We used linear spline models with a knot at seven years; these included a random intercept and slope up to the knot. We also estimated the influence of covariates on levels at the start of suppression and rates of change.

Results: We studied 81 individuals for a median of 7.3 (IQR 5.9-9.6) years. In a model allowing for a change in the rate of decline, we found evidence for more rapid declines in intact genomes from initial suppression through seven years (16.0% per year decline; CI -23.0%, -8.4%) followed by a slower rate (3.6% per year; CI -8.1%, +11%). The estimated half-life of the reservoir was 4.0 years (CI 2.6-7.9) until year seven and 19.0 years (CI 8.2-infinite) thereafter. Intact provirus declined at a faster rate than defective proviruses (p<0.001). There was substantial variability between individuals in the rate of decline until year seven. In multivariate models, individuals with higher CD4+ T-cell count nadir values had a faster rate of decline. A subset of individuals (n =7) were estimated to have very rapid declines (>30%) per year.

Conclusion: These results demonstrate a non-linear decay of viral genomes over time. Intact proviral genomes decay more rapidly than defective ones. The mechanism for this difference is not clear, but could involve cells with intact genomes experiencing increased cytopathic effects or enhanced immune targeting due to virus protein production. These findings provide evidence that the biology of the replication-competent (intact) reservoir differs from that of the replication-incompetent (non-intact) pool of proviruses.
DISTINCT HIV RESERVOIR MEASURES CORRELATE WITH DEFECTIVE BUT NOT INTACT PROVIRAL DNA

Emmanouil Papasavvas,1 Livio Azzoni,1 Brian Ross,1 Matthew Fair,1 Amelie Pagliuzza,1 Steven Lada,1 Guoxin Wu,1 Paul Zuck,1 Pablo Tebas,1 Karam Mounzer,1 Jay Kostman,1 Douglas D. Richman,1 Nicolas Chomont,1 Bonnie J. Howell1,2 Luis Montaner1

1Wistar Institute, Philadelphia, PA, USA, 2Université de Montréal, Montréal, QC, Canada

Background: A major priority for HIV cure strategies remains how best to measure persistence of HIV despite suppressive antiretroviral therapy (ART) in chronic HIV infection. Several assays have been developed to measure the HIV reservoir. We assessed the association between five distinct HIV measures on ART (intact and defective pro-viral DNA, integrated HIV DNA, integrated HIV Gag and Pol, and inducible RNA or p24).

Methods: Peripheral blood mononuclear cells (PBMC) from 20 HIV+ subjects chronically suppressed on ART at <50 HIV-1 copies/mL were assessed for a) intact and defective pro-viral DNA by IPDA (Accelevir), b) integrated HIV DNA by Alu-gag PCR, c) integrated HIV Gag and Pol by droplet digital PCR (ddPCR) following pulsed-field gel electrophoresis (PFGE), and d) latency re-activation in vitro measured by both cell-associated tat/ne induced limiting dilution assay (TILDA), and by HIV p24 single molecule array (Simoa). Spearman tests were used to test relationships between HIV measures.

Results: HIV DNA measures assessed by Alu-gag PCR or PFGE/ddPCR as well as in vitro latency re-activation assessed by TILDA or HIV p24 Simoa were positively associated with each other (e.g. HIV DNA measures assessed by Alu-gag PCR and in vitro latency re-activation assessed by TILDA: p = 0.025, spearman’s rho=0.541). On the other hand, intact proviral DNA did not correlate with any HIV measure. However, hypermutated and/or S’ deleted pro-viral DNA was positively associated with integrated HIV DNA assessed by Alu-gag PCR (p < 0.001, spearman’s rho=0.909) and total gag by PFGE/ddPCR (p < 0.008, spearman’s rho=0.741), as well as with in vitro latency re-activation by HIV p24 Simoa (p = 0.044, spearman’s rho=0.627).

Conclusion: Alu-gag PCR or PFGE/ddPCR HIV DNA measures, as well as induced HIV p24 in HIV+ subjects chronically suppressed on ART best reflect hypermutated and/or deleted rather than intact pro-viral DNA.

RISK AND PREVALENCE OF RESIDUAL VIREMIA AFTER cART IN RESOURCE-LIMITED COUNTRIES

Sivaporn Gatechompol1, Anchalae Avhingsongson1, Lu Zheng1, Yajing Bao1, Stephen J. Kerr1, Nagalineswaran Kumara1, James G. Hakim1, Frank Maldarelli1, Rob Garelick1, Jeffrey D. Lisson2, Mina C. Hosseinipour1, Joseph J. Eron1, Kiat Ruxrungtham1 for the ACTG NWCS 425 Team

Background: To our knowledge, this is the first study to compare residual viremia in long-term virally suppressed PWVH between US and LMIC. The prevalence of residual viremia between both groups were not different and more than half of the participants had detectable viremia. Higher baseline HIV RNA was independently associated with residual viremia.

A NOVEL DDPCR PROTOCOL TO ESTIMATE COPY NUMBERS OF POTENTIALLY INTACT HIV-1 PROVIRUS

Claire Levy1, Sean Hughes1, Pavitra Roychoudhury1, Daniel B. Reeves1, Chelsea Amstuz1, Haiyang Zhu1, Meei-Li Huang1, Yulun Wei1, Marta E. Bull1, Noah A. Cassidy1, Dana Lehman1, Jan McClure2, Robert Coombs1, Keith Jerome1, Florian Hladik1

1University of Washington, Seattle, WA, USA, 2Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Accurately quantifying the replication-competent HIV reservoir is essential for evaluating the efficacy of HIV cure strategies. Ideally, this should be achieved by a rapid turn-around high-throughput assay suitable for a clinical setting.

Methods: We designed a multiplex ddPCR protocol to quantify potentially intact provirus in CD4+ T cells in ART-suppressed people living with HIV (PWLVH). Our multiplex ddPCR targets 5 regions in the HIV genome across 2 ddPCR assays, each with 2 unique and 1 common target. We chose the 5 targets by selecting conserved sequences but with documented deletions from the LANL database. Multiplex ddPCR allows us to assess potentially intact (“intact”) proviral genomes by quantifying the number of droplets positive for each of 3 targets. We developed a gentle DNA isolation method for cell and tissue samples, and also mathematically corrected for residual shearing, measured by two RPP30 targets. We normalized results to number of T cells, quantified by RPP30 (all cells) minus copies of a region in TRD that is deleted during TCR rearrangement and quantifies non-T cells.

Results: Our method results in minimal shearing of DNA isolated from blood samples (mean: 90% un-sheared, SD: 6%), has a low limit of detection (96.1 copies/million T cells by probe analysis with 95% confidence), and high sensitivity (detection: 1-5 copies/million, specificity 100%, n=150 negative control tests) and reproducibility (CV of positive control aliquots tested 23x over 1 year: 42.8%). The final estimate of intact provirus is the lower of the 2 assays. In blood CD4+ T cells from 14 ART-suppressed PLWH, we measured HIV by QVQO (range: 0.08-3.49 infectious units/million) and ddPCR (0-1,900 copies/million, undetectable in 2/14 samples). ddPCR averaged 99.2x (range: 0-557x) higher than QVOA. Longitudinal CD4+ T cell samples from 6-8 blood draws over 4.5-10 years in 20 ART-suppressed PLWH showed median reservoir half-lives of 35 months (range: 22-∞), consistent with previous studies. To relate the mucosal tissue reservoir to HIV shedding, we tested 6 pairs of cervical biopsies (ddPCR) and vaginal secretions (HIV RNA). 3/6 were positive for intact provirus in tissues.
and viral RNA in secretions, 2/6 were negative for both, and 1/6 was positive by ddPCR but negative for viral RNA.

**Conclusion:** Our protocol to quantify potentially intact HIV provirus is specific, sensitive, reproducible, and applicable to cell and tissue samples.

### 312 QUANTITATIVE HIV-1 SPECIFIC ANTIBODIES AS PREDICTORS OF BLOOD HIV-1 DNA LEVELS

**Margaret McManus**, 1 Brad Karalius, 1 Kunjal Patel, 1 Deborah Persaud, 1 Katherine Luzuriaga, 1 for the Pediatric HIV/AIDS Cohort Study

**University of Massachusetts, Worcester, MA, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA**

**Background:** Antiretroviral therapy (ART) reduces HIV-1-related morbidity and mortality in children but does not prevent the establishment of a persistent replication-competent HIV-1 reservoir. Achieving low reservoir size is favorable for HIV-1 eradication efforts and sustained virologic remission. We evaluated the utility of using HIV-quantitative antibodies as a screening test for low circulating cell-associated HIV-1 DNA levels in children and adolescents with perinatal HIV-1 infection.

**Methods:** This study utilized 514 longitudinally-collected plasma specimens from 61 perinatally-infected study participants living with HIV and enrolled in the Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol (PHACS AMP). We included participants who achieved sustained virologic suppression (VS) with HIV-1 plasma levels <400 copies/mL at or before 5 years of age on ART and maintained virologic control (allowing for isolated viral loads ≥400 copies/mL). Antibody levels to HIV-1 envelope (gp160, gp41), gag (capsid, p24; matrix, p17), RT (p66/p51), and integrase (p31) were quantified by ELISA; PBMC HIV-1 DNA levels were measured by droplet digital PCR. Receiver operator curve (ROC) analyses and the random forest model were used to identify the most predictive antibodies for low HIV-1 DNA levels (<100 and <10 copies per million PBMCs). We also utilized ROC analysis to inform the stepwise building of a GEE model for low HIV-1 DNA levels that included all antibody levels as predictors.

**Results:** Among the 13 children with VS by 1 year of age, antibodies to p17, p24, and RT decreased throughout follow-up and antibodies to gp160 and gp41 were low and remained low; antibodies to p31 were either exceedingly low or undetectable (Figure). In contrast, among the 48 children with late VS after 1 year of age (between 1-5 years), antibody levels to all six HIV-1 proteins were high and remained high or increased longitudinally. The stepwise model suggested that gp41 and gp160 were useful predictors of low HIV-1 DNA levels; c-statistics including all antibodies ranged from 0.75 to 0.77. The random forest method also identified gp41 and gp160 as important predictors of low HIV-1 DNA area under the curve estimates using all HIV-1-specific antibodies ranged from 0.70 to 0.81.

**Conclusion:** HIV-1 antibody levels to gp41 and gp160 may be useful to identify virologically-suppressed children on ART with low circulating cell-associated HIV-1 DNA levels for inclusion in clinical trials aimed at remission.

![Figure. LOESS trajectories of ELISA results by antibody and age at sustained virologic suppression](image)

### 313LB LONGITUDINAL QVOA AND IPDA MEASUREMENTS IN CD4 T CELLS FROM ART-SUPPRESSED DONORS

**Shane Falcinelli**, 1 Jenna Read, 1 Ross Murtagh, 1 Sam Raines, 1 Morgan Dewey, 1 Nancie Archin, 1 David M. Margolis

1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

**Background:** The intact proviral DNA assay (IPDA) is a novel method to quantify intact, latent provirus using minimal cell input relative to the gold standard quantitative viral outgrowth assay (QVOA). As IPDA sensitivity may be affected by viral diversity, prior to implementation in experimental medicine trials it is critical to evaluate the relationship between IPDA and QVOA measurements across different participants. As latent provirus can decay over time, a comparison of the IPDA to QVOA longitudinally is also needed.

**Methods:** We conducted the IPDA on stored resting CD4 T cells from a cohort of 68 ART-suppressed individuals in whom QVOA had been measured. In 25 of these individuals, we performed the IPDA on two to six longitudinal samples, with matched QVOA data. Longitudinal sampling spanned a range of 1 to 33 years after ART initiation.

**Results:** The IPDA moderately correlated with QVOA measurements (Spearman r = 0.661, p < 0.0001). For 4/68 participants, no IPDA signal was observed despite moderate QVOA levels. For longitudinal measurements, there was significant interparticipant variability in the correlation between QVOA, intact DNA, and defective DNA measurements. In general, however, we observed a significant decay of both IPDA and QVOA measurements in the first 1 to 4 years following ART initiation. After 4 years of ART, both IPDA and QVOA measurements generally remained stable or decayed more slowly. Packaging Signal (PS)- and Rev Response Element (RRE)-defective proviral DNA frequency tracked with intact and QVOA changes (or lack thereof) in most participants (17/25). However, in some participants there appeared to be expansion and/or decay of defective DNA species over time (8/25).

**Conclusion:** This study provides a key comparison of QVOA and IPDA measurements longitudinally in a large cohort of ART-suppressed participants. In general, intact proviral DNA measurements correlated with QVOA measurements over time; some correlation was also seen in measurements of defective DNA species. The precision of correlation of IPDA with QVOA may vary across individuals. The recent description of proviral clones that contract and expand over time may explain some changes seen in IPDA over time. These findings suggest an advantage for the IPDA over traditional single-target assays that measure predominantly defective DNA. The utility of IPDA to monitor cure interventions designed to deplete persistent infection deserves further study.

### 314 HIV TRANSCRIPTION PROFILE IN BLOOD, GUT, LIVER, AND GENITAL TRACT IN SUPPRESSED WOMEN

**Sara Moron-Lopez**, 1 Grace Xie, 2 Peggy Kim, 1 Joseph K. Wong, 1 Jennifer C. Price, 1 Najwa Elnachef, 1 Ruth Greenblatt, 1 Phyllis Tien, 1 Nadia R. Roant, 1 Steven A. Yukl

1University of California San Francisco, San Francisco, CA, USA, 2Gladsome Institutes, San Francisco, CA, USA, 3San Francisco VA Medical Center, San Francisco, CA, USA

**Background:** Sex-specific differences affect various aspects of HIV infection. However, few studies have quantified levels of HIV infection or expression in tissues from women. Here, we measured the extent of HIV infection and progression through the HIV transcriptional blocks in blood, gut, liver, and genital tissues from HIV-infected ART-suppressed women.

**Methods:** Peripheral blood mononuclear cells (PBMC), liver, gut (ileum, colon, rectosigmoid), and genital tract biopsies ( cervix, endometrium), and endocervical curettage (ECC) samples were collected from 5 women with plasma HIV RNA <200 copies/ml (median 10.4 years). Total and intact (IPDA) cell-associated HIV DNA and levels of read-through, initiated (TAR), S' elongated, polyadenylated, and multiply-spliced HIV transcripts were measured by dPCR. Phenotyping of immune cells was conducted by qIF. Results were analyzed using the Wilcoxon signed-rank test.

**Results:** Total HIV DNA was detected in all tissues, with levels being comparable between the gut, liver and genital tract tissues. Intact HIV DNA was detected in PBMC, ileum, colon and cervix. HIV transcriptional initiation (TAR RNA per provirus) tended to be higher in PBMC and endometrium than in ileum, colon, rectosigmoid, cervix, and ECC (p = 0.06), and higher in rectum than either ileum or colon (p = 0.06). Likewise, levels of elongated HIV transcripts per provirus were comparable in PBMC and endometrium, but higher than the gut and cervical samples (p = 0.06). Polyadenylated HIV transcripts were detected in...
PBMC from all 5 individuals but were rarely detected in the tissues. Multiplexed HIV transcripts were detected in PBMC from 2 of 5 individuals, but not detected in any tissue. The phenotypes of CD4+ T cells were distinct between the blood, genital tract, and gut.

**Conclusion:** The gut, liver, and genital tract are all sites of HIV persistence in women. The female genital tract contains a large pool of HIV-infected cells, with HIV DNA levels/million tissue cells that are similar to the gut. HIV-infected cells in the blood and endometrium showed higher levels of HIV transcription per provirus, while much lower levels were observed in the gut, cervix and liver. These results suggest tissue-specific differences in the mechanisms that govern HIV latency, with greater suppression of HIV transcription in most tissues than blood. Therapies aimed at disrupting latency, such as latency-reversing or latency-silencing agents, will be required to penetrate into multiple tissues and affect different blocks to HIV transcription.

### 315 INTACT PROVIRUSES FROM NAIVE AND EFFECTOR MEMORY T CELLS MATCH PERSISTENT VIREMIA

**Katie Fisher**1, Bonnie Hiener1, Bethany A. Horsburgh1, Timothy E. Schlub2, Eunok Lee1, Vincent Mocella1, John-Sebastian Eden1, Susanne Von Stockenstrom1, Jeffrey M. Milush1, Rebecca Hoh1, Remi Fromentin1, Nicolas Chomont1, Steven G. Deeks5, Frederick M. Hecht1, Sarah Palmer1

1The Westmead Institute for Medical Research, Westmead, NSW, Australia, 2University of California San Francisco, San Francisco, CA, USA, 3Northwestern University, Chicago, IL, USA, 4University of Minnesota, Minneapolis, MN, USA, 5Merck & Co, Inc, West Point, PA, USA

**Background:** Genetically intact, and potentially replication competent, proviruses are a likely source for viremia during antiretroviral therapy (ART). Identifying the CD4+ T cell subsets that harbour these proviruses within different anatomic sites is important for future eradication strategies.

**Methods:** Near full-length proviral sequences were obtained from naïve (NV), central (CM), transitional (TM) and effector memory (EM) CD4+ T cells (sorted based on their expression of CD45RA, CD27 and CC chemokine receptor 5) which were isolated from both the peripheral blood (PB, 13 participants) and lymph nodes (paired LN, 5 participants), using the Full-Length Individual Proviral Sequencing Assay (FLIPS). Proviral sequences were identified as genetically intact if they lacked inversions, stop codons/hypermutation, insertions, deletions or frameshifts. Genetically intact proviruses from 10 participants were compared to on-therapy plasma RNA (p6-RT region obtained by single-genome sequencing (SGS)).

**Results:** We sequenced 1913 proviruses, and genetically intact proviruses were found in all cell subsets except for LNEM (n=3). We found that the infection frequency of genetically intact proviruses differed across the subsets in both PB and LN (P<0.001). In PB, the order of intact genomics was found to be EM=TM/ NV>CM (all P<0.02), while in the LN the trend was NV>CM>TM>EM, with evidence for NV>CM (P=0.01). All 22 intact LN sequences were genetically unique. For the subsets that had more than 10 genetically intact DNA sequences (PBEM, PBNV and LNNV), we compared the genetically intact proviruses obtained by FLIPS to the on-therapy plasma RNA p6-RT sequences obtained by SGS. PBEM had the highest frequency of genetically intact DNA sequences matching 100% to the on-therapy RNA sequences (13/23, 57%). This was followed by PBNV, with 6/19 (32%) DNA sequences matching RNA, and LNNV, with 3/16 (19%) DNA sequences matching RNA.

**Conclusion:** The distribution of genetically intact proviruses differs between PB and LN. For the five participants with paired PB and LN cells available, HIV cells had the highest frequency of intact proviruses in LN. In PB, however, the highest levels of intact genomes were found in EM cells. PBEM, PBNV and LNNV also had a high frequency of genetically intact proviruses matching to on-therapy plasma RNA p6-RT sequences, suggesting that the intact proviruses within these T cell subsets from different anatomic sites may contribute to ongoing viremia during ART.

### 317 LACK OF COMPARTMENTALIZATION IN THE LATENT RESERVOIR OF BLOOD AND LYMPH NODES

**Charles Kirby**1, Jada Hackman2, Alyssa R. Martin1, Alexandra M. Bender1, Kyungyun J. Kwon1, Craig Martens1, Michael J. Baile1, Niraj Desai1, Sander S. Florman1, Dorry Segev1, Aaron Tobian2, Christine Durand1, Robert Siliciano1, Andrew D. Redd2

1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2NIH, Bethesda, MD, USA, *NIAID, Hamilton, MT, USA, *National Cancer Institute, Frederick, MD, USA, *Mt Sinai School of Medicine, New York, NY, USA

**Background:** There are conflicting reports on the similarity of the HIV-1 latent reservoir (LR) in the lymph node (LN) compared to the peripheral blood (PB). Characterizing the composition and any possible differences in anatomical compartments remains a crucial step in understanding the barriers to HIV cure.

**Methods:** HIV+ individuals on ART with suppressed viral loads who were undergoing solid organ transplantation consented to have LN removed at the time of transplant, and PB and LN mononuclear cells (MC) were collected and isolated (n=10). CD4+ cells from matched PBMC and LNMC samples were plated in a novel quantitative viral induction assay (QVIA). Sequence data was obtained from positive wells using a validated site-directed next-generation sequencing based assay that amplified the gag-p1 region of the viral envelope to identify the prominent induced viral variants (>2.5% of amplicons; Illumina Inc.). Subjects who had sequences obtained from >75% of the positive wells in both compartments were used to examine for compartmentalization. Neighbor-joining trees of all prominent patient sequences were inferred (Geneious prime), and identical variants were classified as ‘replicates’. A Bayesian model (UPMBayes) was used to estimate the relative size of the LR for each participant, as well as the proportion of the LR made up by each variant for their respective compartments. Compartmentalization was assessed on samples using a Hudson based test for panmixia (non-parametric) and a branch length tree correlation coefficient (parametric).

**Results:** In four individuals with sufficient sequences, a median of 29 induced variants were identified in PB (IQR:27.8-21.3), as compared to 26 in LN (IQR:23.8-21.3). The estimated frequency of latently infected cells was 10.4% of induced proviruses per million cells (IPPMC) in PB (IQR:16.5-2.5) and 6.4 IPPMC in LN (IQR:13.2-6.8). Replicant variants and variants with unique sequences were found in both compartments in all patients. The estimated proportion of the LR made up of variants that were replicated in the patient’s matched
compartment varied between compartments and between patients (median % LR shared for PB=37.1% (IQR=40.1-20.5%) and LN=42.4% (IQR=57.9-29.8%); Figure). There was no significant compartmentalization between PB and LN across all patients.

**Conclusion:** These data provide further evidence of intermingling and limited compartmentalization between the LN and PB, and support previous data that the LR found in the blood can be a good representation of the LR in the lymph node.

![Figure](image)

**Figure:** Neighbor-joining tree of distinct and replicate viral gag41 prominent species between PB and LN compartments from induced viral RNA populations from One person with positive vDNA of one representative patient. Bar graph coloring shows percent of the LR made up by each variant. Multiple sites shared between sites are shown with matched colors, solid grey sequences were detected only in PB, and striped grey were found only in LN. The percentage shared variants for this patient is PB=93.986%, LN=54.096%.

### 318 CHARACTERIZATION OF CD8+ TRM TOWARD THE CONTROL OF THE HIV RESERVOIR IN CERVIX

**Nuria Massana**1, Jon Cantero, Judith Grau-Exposito, Laura Luque-Ballesteros1, Josep Castellví2, Laura Mahallí-Barachina1, Cristina Centeno-Mediavilla1, Vicenc Falco1, Maria J. Buzari, Meritxell Genesca1

1 Vall d’Hebron Research Institute, Barcelona, Spain, 2 Hospital Universitario de la Vall d’Hebron, Barcelona, Spain

**Background:** In tissues, resident memory CD8+ T cells (TRM) are most likely necessary to eliminate remaining cellular HIV-1 reservoirs. However, TRM signature includes expression of molecules associated to exhausted phenotypes during chronic viral infections. Here we addressed the functional capacity of CD8+TRMs from the cervical mucosa of HIV-infected women on ART to determine the most effective phenotypes at limiting viral persistence.

**Methods:** CD8+ T cells from cervical tissues were phenotyped based on CD69 expression to determine TRM signature (n=6-9). Frequency and activation of CD103+/-CD8+TRM subsets were compared between healthy (n=9) and ART-suppressed HIV+ women (n=18). In a subset of these patients, we determined total vDNA in blood and cervix (n=7). A functional assay was established to determine suppression of viral reactivation by CD8+TRM in ART-suppressed HIV+ women.

**Results:** Cervical CD69+CD8+ T cells protein profile was compatible with >90% belonging to bona fide CD8+TRMs, as determined by CCR7, S1PR1, T-bet, Eomes, CCR2 and CD161 compared to non-CD8+TRMs, and less frequently CXCR3, CCR5, and CD103+/-CD8+TRM subsets were compared between healthy (n=9) and ART-suppressed HIV+ women (n=18). In a subset of these patients, we determined total vDNA in blood and cervix (n=7). A functional assay was established to determine suppression of viral reactivation by CD8+TRM in ART-suppressed HIV+ women.

**Conclusion:** Alterations of the CD8+ T cell compartment within the cervical mucosa remain in HIV+ women even after several years of effective ART-suppression. The association between higher proportion of CD8+TRMs in cervix and less proviral HIV-1 DNA, together with data showing higher control of virally-reactivated infected cells by CD8+TRMs, indicates that these cells may be critical to control persisting virus in tissues.

### 319 FACTORS ASSOCIATED WITH VIREAL CONTROL AFTER STRUCTURED TREATMENT INTERRUPTION

**Nikolaus Jilg**1, Behzad Etemad2, Ruth Dele-Oni2, Colline Wong2, Jesse Fajnzylber2, Abbas Mohammadi3, Evgenia Aga3, Ronald Bosch1, Daniel R. Kuritzkes3, Ian Frank4, Jeffrey Jacobson2, Jonathan Z. Li2

1 Massachusetts General Hospital, Boston, MA, USA, 2 Brigham and Women’s Hospital, Boston, MA, USA, 3 Harvard T.H. Chan School of Public Health, Boston, MA, USA, 4 Hospital of the University of Pennsylvania, Philadelphia, PA, USA, 5 Case Western Reserve University, Cleveland, OH, USA

**Background:** ACTG A5068 was a RCT of people with chronic HIV infection (18% females) receiving continuous ART versus intermittent structured treatment interruptions (STIs) with or without administration of a therapeutic HIV vaccine. In the CHAMP study, HIV post-treatment controllers (PTCs) were clustered among individuals who were subjected to STIs prior to a prolonged analytical treatment interruption (ATI). We aimed to identify virologic determinants of post-treatment control in the participants of A5068 who underwent multiple STIs.

**Methods:** A5068 participants in the STI arms underwent two short (~4 weeks) STIs (STI 1 and 2) and a subsequent extended ATI. Both STI 1 and 2 were followed by 16 weeks of antiretroviral therapy. We compared plasma viral load (pVL) dynamics after each STI between PTCs and post-treatment non-controllers (NCs). Single-genome sequencing (SGS) of the pol region from plasma HIV RNA was performed for 6 PTCs and 7 NCs. Confirmatory long-range SGS of the pol-env region was performed for a subset of time points. Viral diversity was calculated by the average pairwise distance at one time point and viral divergence was calculated by the average pairwise distance between sequences of different time points.

**Results:** pVLs were significantly lower during STI 2 compared to STI 1 for both PTCs (n=6) and NCs (n=27). For both the first and second STI, PTCs had significantly lower peak pVLs compared to NCs (median pVL [Q1, Q3] for PTCs vs. NCs at the first STI: 1,270 [1,036, 5,593] vs. 37,506 [1,643, 66,579] HIV-1 RNA copies/mL, p=0.001; and second STI: 199 [<50, 424] vs. 14,562 [7,870, 33,031] HIV-1 RNA copies/mL, p=0.001). An algorithm that used a combination of peak pVL<10,000 HIV-1 RNA copies/mL during STI 1 and peak pVL<1,000 HIV-1 RNA copies/mL during STI 2 accurately predicted that all 6 PTCs would achieve HIV control and that 26/27 NCs would not. In addition, we have generated >500 plasma HIV single-genome sequences for the PTCs and NCs during the STIs and ATI. Among all participants, higher plasma HIV diversity during STI 1 predicted higher viral diversity in ATI (Spearman r=0.67, p=0.02). Increasing viral divergence from STI 1 to ATI was associated with a higher peak pVL at ATI (Spearman r=0.69, p=0.02).

**Conclusion:** In participants undergoing STIs, lower peak pVLs during the first two short STIs may predict post-treatment control. Emergence of divergent viral populations during the third TI may compromise the ability to achieve viral control.
Results: We find that the vaccine reduced reactivation of latent virus by 4-fold (95% CI [2.8]), and boosted the avidity of antiviral immune responses by 17-fold when alone [5, 67] and 210-fold [30, 1400] when combined with the TLR7 agonist. In the context of later initiation of antiretroviral therapy only (9 vs. 1 week after infection), the TLR7 agonist reduced latent reservoir reactivation by 8-fold [4, 16], but also slightly increased target cell availability (1.5-fold). The antibody boosted immune response avidity 8-fold [3,16] and displayed no detectable synergy with the TLR7 agonist. In humans, the TLR7 agonist alone, TLR7+ vaccine, and TLR7+ antibody are expected to lead to control of rebound in some patients (~5%, ~55%, ~90% respectively), but often after a high peak viral load. Heterogeneity in rebound time and peak/setpoint viral loads between some patients (~5%, ~55%, ~90% respectively), but often after a high peak viral load.

Conclusions: Overall, our results provide a framework for understanding the relative contributions of different mechanisms of preventing viral rebound and highlight the multifaceted roles of TLR7 agonists for HIV/SIV cure.

321 FREQUENCY OF POSTTREATMENT CONTROL VARIES BY ART RESTART AND VIRAL LOAD CRITERIA

Jesse Fajnzylber, Radwa Sharaf, Evgenia Aga, Ronald Bosch, Jeffrey M. Jacobson, Elizabeth Connick, Daniel Skiest, Michael Sneller, Ronald T. Mitsuyasu, Keith Henry, Tae-Wook Chun, Ann Callier, Frederick M. Hecht, Jonathan Z. Li, for the CHAMP Study Team

Background: Clinical trials including an analytic treatment interruption (ATI) are vital to evaluating the efficacy of strategies for HIV remissions. Determining the optimal ART-restart criteria that minimizes exposure to high-level viremia and maximizes detection of post-treatment controllers (PTCs) remains challenging. We present an interactive online tool for predicting viral rebound timing in ATI trials and describe the impact of PTC definitions on PTC frequency estimates.

Methods: The interactive viral rebound calculator (http://jonathanlab.bwh.harvard.edu/rebound-calculator/) was created with a pooled analysis of plasma viral loads (pVLs) of >700 participants from 10 ATI trials. The tool allows the user to set the ART restart criteria based on a single or multiweek pVL criteria and to customize results by the timing of ART initiation, ART regimen, and pVL frequency (default is the CHAMP study criteria: pVL<400 cps/mL at ≥2/3 time points for ≥24 wks post-ATI). No significant differences were observed by current patterns of drug use, with pVL frequencies of intact proviruses ranging from 1.95 to 2.44 log 10 per 106 CD4+ T cells, respectively; P=0.0011. In multi-variable linear regression adjusting for demographics and drug use, NTIs were strongly associated with higher intact provirus (coef= 0.576; P=0.026).

Conclusions: Our interactive calculator provides the first interactive tool for estimating viral rebound outcomes and supporting the design of ATI trials. A multi-week ART restart criteria of 1,000 pVL provides high sensitivity and specificity for PTC detection. However, the expected frequency of PTC identification in ATI trials can vary dramatically by the definition of post-treatment control.

322 NONSTRUCTURED TREATMENT INTERRUPTIONS CONTRIBUTE TO LATENT HIV-1 RESERVOIR IN PWID

Gregory D. Kirk, Shruti H. Mehta, Jacque Astemborski, Kristen D. Ritter, Gregory Laird, Robert Siliciano

Background: Persons with a history of injecting drugs (PWID) often struggle to maintain stable viral suppression and experience ART non-structured treatment interruptions (NTIs). Injecting drugs has been associated with increased inflammation and alterations in T cell homeostasis. However, the long-term effects of NTIs or of injection drug use on the HIV-1 latent reservoir have not been defined.

Methods: We performed the intact proviral DNA assay (IPDA) on 108 HIV-1+ adult participants of the ALIVE cohort who at a minimum were on suppressive ART with plasma HIV-1 RNA <50 copies/mL at the time of sampling and at the study visit 6 months prior; a minimum of 5 HIV RNA measurements (2.5 years of observation) was required. Participants were selected based on self-report of current drug use: active heroin use (n=28), active cocaine use (n=23), combined cocaine and heroin use (n=29), and no reported drug use (n=28). Participants were further selected to include those with a history of stable viral suppression (n=36) and those with past periods of viremia due to NTIs (n=72).

Results: Participants were 71% male, 96% black, and median age was 53 years. No significant differences were observed by current patterns of drug use, with median frequencies of intact proviruses ranging from 1.95 to 2.44 log 10 per 106 CD4+ T cells across groups, values comparable to those seen in other cohorts not selected based on illicit drug use (Figure, Panel A). However, we did observe notably higher intact provirus frequency among persons who had experienced NTIs (Figure, Panel B) compared to those with stable suppression (mean 2.15 vs. 1.50 log 10, per 106 CD4+ T cells, respectively; P=0.0011). In multi-variable linear regression adjusting for demographics and drug use, NTIs were strongly associated with higher intact provirus (coef= 0.576; P=0.026).

Conclusion: We found no apparent long-term effect of injecting drugs on latent reservoir size as measured by IPDA. However, we found a notable increase in reservoir size for those with past periods of viremia due to NTIs compared to those with a history of more stable viral suppression. Our data have important implications for the field. First, they support the inclusion of PWID with stable suppression in cure studies. Second, they demonstrate that a history of viremia due to NTIs may have lasting effects on the size of the reservoir, and as such, virologic history should be considered when designing or analyzing HIV-1 cure studies.
323 PRESENCE MACROPHAGE-TROPIC HIV-1 VARIANTS FOLLOWING ANALYTIC TREATMENT INTERRUPTION

Viviane M. Andrade1, Carla Mavian2, Dunja Babic1, Thaisa Cordeiro Alvarado1, Mark Sharkey1, Labelle Barrios1, Christian Branders1, Judith Dalmau1, Michael S. Seaman1, Marco Salemi2, Javier Martinez-Picado1, Mario Stevenson1, Lisa Frenkel4, Sarah Palmer2, Linos Vandekerckhove1

1University of Miami, Miami, FL, USA, 2University of Florida, Gainesville, FL, USA, 1HIV Cure Research Center, Ghent University, Ghent, Belgium, 4Seattle Children’s Research Institute, Seattle, WA, USA

Background: HIV-1 persists in cellular reservoirs that can replenish viremia if antiretroviral therapy (ART) is interrupted. Therefore, insight into the nature of these reservoirs may be revealed from the composition of recrudescing viremia following treatment cessation. Most attention has focused on the CD4+ T cell reservoir in patients on ART. We hypothesize that macrophages also serve as a viral reservoir under ART. To assess this, we examined the composition of rebound viremia in individuals undergoing an analytic treatment interruption (ATI). Specifically we examined whether post-ATI viremia harbored viral variants that exhibited a highly macrophage-adapted phenotype.

Methods: A total of 55 HIV-1 full-length envelopes were isolated by single genome amplification from plasma of six individuals who underwent ATI. Isolated env sequences were used to construct recombinant, infectious HIV-1 molecular clones. The recombinant viruses were assessed for the ability to fuse and replicate within primary macrophages. To determine whether macrophages were a source for macrophage-adapted HIV-1 variants, immunoprecipitation of plasma-containing virions was performed using a macrophage-specific marker (CD14). To assess whether macrophage-tropic viruses identified in post-ATI viremia originated from macrophages prior to treatment interruption, we inferred time-scaled phylogenies, through Bayesian phyloanatomy framework using a robust estimate of intra-host evolutionary rate in the envgene (7.53 10^-3 nt substitutions/site/year).

Results: Macrophage-tropic viruses were identified at low frequency in a library of recombinant viruses constructed with individual envelope genes that were obtained from plasma of six individuals undergoing analytic treatment interruption (ATI). Macrophage-tropic viruses could also be enriched from post-ATI plasma using macrophage-specific (CD14) but not CD4+ T cell-specific (CD3) antibodies, suggesting that macrophage-tropic viruses had a macrophage origin. Phylogenetic relationships indicated that the establishment of macrophage-tropic HIV-1 variants predated ATI in 4 out of 6 study participants.

Conclusion: Collectively, these data suggest that macrophages are a viral reservoir in HIV-1-infected individuals on effective ART and contribute to viral recrudescence when treatment is interrupted. These findings have implications for the design of curative strategies for HIV-1.

324 THE ELUSIVE SOURCE OF HIV-1 REBOUND AFTER TREATMENT INTERRUPTION

Laurens Lambrechts1, Basiel Cole1, Marie-Angélique D. De Scheerder2, Zoe Boyer1, Ytse Hoppe1, Katie Fisher1, John-Sebastian Eden1, Wim Van Cleeke1, Lisa Frenkel1, Sarah Palmer1, Linos Vandekerckhove1

1HIV Cure Research Center, Ghent University, Ghent, Belgium, 2The Westmead Institute for Medical Research, Westmead, NSW, Australia, 1Ghent University, Ghent, Belgium, 5Seattle Children’s Research Institute, Seattle, WA, USA

Background: Identifying the source of viral rebound during a monitored analytical treatment interruption (ATI) would reveal potential targets for cure strategies. Therefore, we examined the genetic composition of proviral DNA in different subsets from participants on antiretroviral therapy and compared this to rebounding virus after an ATI.

Methods: Eleven participants underwent a monitored ATI and were sampled from different anatomical sites prior to and after the ATI. From the peripheral blood, naïve (TNA), central (TCM), transitional (TTM) and effector (TEM) memory CD4+ T cells were sorted as were CD45 cells from gut-associated lymphoid tissue (GALT). Using single-genome sequencing (SGS) the env region of HIV DNA and plasma-derived RNA was sequenced. In an ongoing study, Full-Length Individual Proviral Sequencing (FLIPS) and Integration Site Loop Amplification (ISLA) assays were performed on the T cell subsets from 2 participants.

Results: For participant STAR10, 87 integration sites (IS) and 113 proviral genomes were sequenced while only 3 unique intact proviruses (3%) were identified. A cluster of 17 identical defective proviruses were linked to an IS (9% of all IS) in STAT5B located in TCM, TNA, TEM and TTM. When comparing the FLIPS to SGS env sequences a 100% match was found between one defective provirus and one plasma HIV RNA sequence after rebound. For participant STAR11, 37 IS and 105 proviral genomes were sequenced yielding 14 intact proviruses (13%) with the highest proportion found predominantly in the TEM subset (n=13, 45%). Four different clusters of identical sequences could be identified of which 2 (n=3 and n=9) consisted of intact TEM sequences with the smaller cluster linked to an IS in ZNF274. A 99% match between 2 env from rebounding plasma RNA and this smaller cluster of intact proviral genomes was identified.

Conclusion: Comparing proviral sequences and their IS to plasma-derived RNA sequences after an ATI reveals additional information in terms of the source of viral rebound. However, this comparison is complicated by multiple factors. For example, we found a plasma-derived RNA sequence obtained during viral rebound matched a defective proviral sequence which highlights the problem of using one HIV RNA subgenomic region for identifying replication-competent virus. In addition, ongoing viral replication during rebound may prevent a 100% match with genetically intact proviral sequences making it challenging to determine the absolute source of rebound.

325 HIV POSTTREATMENT CONTROL DESPITE PLASMA VIRAL EVOLUTION AND Dual INFECTION

Behzad Etemad1, Golnaz Namazi1, Ying Wer1, Nikolaus Höl1, Elmir Esmaeili-Zadeh1, Xin Zhang1, Radwa Sharaf1, Daniel McMillan1, Ronald Bosch2, Evgenia Aqa3, Jeffrey A. Johnson1, Rajesh T. Gandhi1, Zabrina Brumme1, Mary F. Kearney1, Jonathan Z. Li1

1Brigham and Women’s Hospital, Boston, MA, USA, 2China Medical University, Shenyang, China, 3Massachusetts General Hospital, Boston, MA, USA, 4Simon Fraser University, Burnaby, BC, Canada, 5Harvard T. Chan School of Public Health, Boston, MA, USA, 6CDC, Atlanta, GA, USA, 7MGH Institute of Health Professions, Boston, MA, USA, 8NII, Frederick, MD, USA

Background: HIV post-treatment controllers (PTCs) serve as models for sustained HIV remission. These individuals frequently have early HIV rebound before viral control and subsequent periods of intermittent low-level viremia. Little is known about the viral composition during these periods of viremia.

Methods: We extracted longitudinal plasma HIV RNA from PTCs and post-treatment non-controllers (NCs) from AIDS Clinical Trials Group (ACTG) analytic treatment interruption (ATI) trials. Single-genome sequences (SGSs) of HIV-1 pol were obtained at pre- and multiple post-ATI time points (median 90 wkks at the late time point for the PTCs). Sequence analysis included calculations of viral genetic diversity by average pairwise distance (APD), root-to-tip distances, percent of HLA-escape mutations, and panmixia testing.

Results: Despite low plasma viremia, >1200 SGSs were obtained for 20 PTCs and 13 NCs. Early after ATI, chronic-treated NCs had the highest levels of plasma HIV diversity while viral diversity was limited for both early-treated PTCs and NCs. Over time, increasing viral diversity was detected in almost all PTCs, but rates of diversification were significantly slower in PTCs compared to NCs (median 0.05% vs 0.27% per year, p=0.007). PTCs were also able to maintain viral control despite evidence of viral evolution. This included increasing root-to-tip distances of HIV sequences by phylogenetic analysis over time for all PTCs, divergent population structures by the panmixia test in 73% of PTCs, and accumulation of HLA escape mutations in longitudinal sampling for 2 chronic-
EVALUATING BIOMARKERS FOR HIV REBOUND DURING TREATMENT INTERRUPTION

Marie-Angélique D. De Scheerder, Clarissa Van Hecke, Henrik Zetterberg, Dietmar Fuchs, Nele De Langhe, Sofie L. Rutsaert, Bram Vrancken, Marie-Angélique D. De Scheerder, Clarissa Van Hecke, Henrik Zetterberg, Dietmar Fuchs, Nele De Langhe, Sofie L. Rutsaert, Bram Vrancken

1 Ghent University Hospital, Ghent, Belgium, 2 HIV Cure Research Center, Ghent University, Ghent, Belgium, 3 Sahlgrenska University Hospital, Gothenburg, Sweden, 4 Innsbruck Medical University, Innsbruck, Austria, 5 Katholieke University Leuven, Leuven, Belgium, 6 The Westmead Institute for Medical Research, Westmead, NSW, Australia, 7 Istituto Superiore di Sanità, Rome, Italy

Background: Validated biomarkers to evaluate HIV-1 cure strategies are currently lacking, therefore requiring analytical treatment interruption (ATI) in study participants, potentially impacting their health. Here we assessed these patients safety concerns by evaluating viral reservoir size in blood and inflammatory levels in the brain. Furthermore, restriction factor (RF) expression levels and cell-associated (CA) HIV-1 RNA transcripts were assessed as potential biomarkers for predicting viral rebound.

Methods: In the HIV-STAR study, we collected peripheral blood mononuclear cells (PBMC), plasma and cerebrospinal fluid (CSF) from 11 participants at 4 time-points on- and off-treatment to assess these safety concerns and screen potential biomarkers for predicting viral rebound. Total and integrated HIV-1 DNA, CA HIV-1 RNA transcripts and restriction factors (RF) expression were measured. Markers of neuro-inflammation and neuronal injury were measured in CSF and immune activation was assessed in plasma and CSF.

Results: Total HIV-1 DNA, integrated HIV-1 DNA and CA viral RNA transcripts did not differ pre- and post-ATI. Similarly, no significant NfL or YKL-40 increase in CSF was observed between baseline and viral rebound. Furthermore, markers of immune activation did not increase during ATI. Interestingly, RF SLFN11 and APOBEC3G increased after ATI before viral rebound was observed. Similarly, Tat-Rev transcripts were increased preceding viral rebound after interruption.

Conclusion: ATI did not increase viral reservoir size, nor did it reveal signs of increased neuronal injury or inflammation, suggesting that these well-monitored ATIs are safe. Elevation of Tat-Rev transcription and induced expression of RF SLFN11 and APOBEC3G after ATI prior to viral rebound indicates that these markers could be used as potential biomarkers predicting viral rebound.

HIV DIRECTLY INFECTS RESTING MEMORY CD4 T CELLS

Rodrigo Matus-Nicodemos, David R. Ambrozak, Sam Darko, Amy Ransier, Daniel Douek, Richard A. Koup

1 Vaccine Research Center, NIAID, Bethesda, MD, USA

Background: The establishment of the latent HIV reservoir in resting memory CD4 T cells occurs early in infection. Resting CD4 T cells are more difficult to infect than activated CD4 T cells. Therefore, the HIV reservoir is thought to form when HIV infects a few activated CD4 T cells that are resting down. Furthermore, HIV encodes four proteins: Vif, Vpr, Vpu, and Nef, which play an important role for the persistence of HIV. For example, Nef is known to downregulate MHC class I molecules (pMHCs) which prevents the recognition by CD8 T cells. However, the precise timing of expression of these four HIV proteins and the downregulation of their targeted host proteins in resting memory CD4 T cells is unknown.

Methods: We explored this question by direct infection and longitudinal analysis of primary resting CD4 T cells with a CRISPR-cas9 reporter virus in which GFP reports the expression of Nef. We then measured pMHCs by flow cytometry and performed bulk and scRNAseq of sorted GFP+ cells to measure host and HIV mRNAs. We also performed scATACseq to identify the sites of HIV integration to determine their influence on the timing of Nef expression.

Results: We detected resting memory GFP+ cells 3 to 4 days after infection. These GFP+ cells showed low surface levels of pMHCs. By scRNAseq HIV mRNAs were identified in GFP+ cells and they encoded for Nef, Vpr, Vpu, and Nef, which play an important role for the persistence of HIV. For example, Nef is known to downregulate MHC class I molecules (pMHCs) which prevents the recognition by CD8 T cells. However, the precise timing of expression of these four HIV proteins and the downregulation of their targeted host proteins in resting memory CD4 T cells is unknown.

Methods: We explored this question by direct infection and longitudinal analysis of primary resting CD4 T cells with a CRISPR-cas9 reporter virus in which GFP reports the expression of Nef. We then measured pMHCs by flow cytometry and performed bulk and scRNAseq of sorted GFP+ cells to measure host and HIV mRNAs. We also performed scATACseq to identify the sites of HIV integration to determine their influence on the timing of Nef expression.

Results: We detected resting memory GFP+ cells 3 to 4 days after infection. These GFP+ cells showed low surface levels of pMHCs. By scRNAseq HIV mRNAs were identified in GFP+ cells and they encoded for Nef, Vpr, Vpu, and Nef, which play an important role for the persistence of HIV. For example, Nef is known to downregulate MHC class I molecules (pMHCs) which prevents the recognition by CD8 T cells. However, the precise timing of expression of these four HIV proteins and the downregulation of their targeted host proteins in resting memory CD4 T cells is unknown.

Methods: We explored this question by direct infection and longitudinal analysis of primary resting CD4 T cells with a CRISPR-cas9 reporter virus in which GFP reports the expression of Nef. We then measured pMHCs by flow cytometry and performed bulk and scRNAseq of sorted GFP+ cells to measure host and HIV mRNAs. We also performed scATACseq to identify the sites of HIV integration to determine their influence on the timing of Nef expression.

Results: We detected resting memory GFP+ cells 3 to 4 days after infection. These GFP+ cells showed low surface levels of pMHCs. By scRNAseq HIV mRNAs were identified in GFP+ cells and they encoded for Nef, Vpr, Vpu, and Nef, which play an important role for the persistence of HIV. For example, Nef is known to downregulate MHC class I molecules (pMHCs) which prevents the recognition by CD8 T cells. However, the precise timing of expression of these four HIV proteins and the downregulation of their targeted host proteins in resting memory CD4 T cells is unknown.

Methods: We explored this question by direct infection and longitudinal analysis of primary resting CD4 T cells with a CRISPR-cas9 reporter virus in which GFP reports the expression of Nef. We then measured pMHCs by flow cytometry and performed bulk and scRNAseq of sorted GFP+ cells to measure host and HIV mRNAs. We also performed scATACseq to identify the sites of HIV integration to determine their influence on the timing of Nef expression.

Results: We detected resting memory GFP+ cells 3 to 4 days after infection. These GFP+ cells showed low surface levels of pMHCs. By scRNAseq HIV mRNAs were identified in GFP+ cells and they encoded for Nef, Vpr, Vpu, and Nef, which play an important role for the persistence of HIV. For example, Nef is known to downregulate MHC class I molecules (pMHCs) which prevents the recognition by CD8 T cells. However, the precise timing of expression of these four HIV proteins and the downregulation of their targeted host proteins in resting memory CD4 T cells is unknown.
RNAseq analysis identified the expression of a cell-cycle independent form of ribonucleotide reductase, which converts ribonucleotides to deoxynucleotides. Also, the pathway for thymidine synthesis was not active in resting T cells. Thus, using a real-time qPCR assay that distinguishes proviruses with deoxyuracils or thymidines, we found the proviruses in resting T cells had deoxyuracils instead of thymidines. Lastly, we revealed Vpr protected proviruses from an UNA-dependent inactivation mechanism.

Conclusion: We conclude that HIV can directly infect primary resting memory CD4 T cells to establish the reservoir. HIV-infected resting CD4 T cells incorporate deoxyuracils, which is deleterious in the absence of Vpr inhibiting UNG. Finally, we believe the integrated HIV genome persists through transcription and alternatively splicing for mRNAs encoding Nef, Vif, Vpr, or Vpu-Env.

328 ESTABLISHMENT OF THE HIV-1 DNA RESERVOIR MIRRORS THE REPLICATION-COMPETENT RESERVOIR
Olivia D. Council1, Melissa-Rose Abrahams2, Sarah B. Joseph1, Nigel Garrett1, Matthew Moeser2, Shuntai Zhou1, Lynn Tyers2, David Matten1, Colin Anthony1, Sergei L. Kosakovsky Pond1, Nancie Archin1, David M. Margolis1, Salim S. Abdool Karim1, Ronald Swanstrom2, Carolyn Williamson1
1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2University of Cape Town, Cape Town, South Africa, 3University of KwaZulu-Natal, Durban, South Africa, 4Temple University, Philadelphia, PA, USA, 5CAPRISA, Durban, South Africa

Background: All HIV-infected people on ART have a long-lived reservoir. We recently showed that the replication-competent portion of this reservoir originates from viruses circulating near the time of ART initiation, similar to a previous report that examined total viral DNA. Here we examine both the replication-competent reservoir and the viral DNA reservoir in the same set of participants.

Methods: Plasma was collected longitudinally from 16 women in the CAPRISA-002 cohort pre-ART, with PBMCs then collected after 4.8 years (average) of suppressive ART. RNAseq with Primer ID was used to sequence 5 genomic regions from RNA in the pre-ART plasma samples. Outgrowth virus was generated from quantitative viral outgrowth assays (QVOA) using resting CD4+ T cells collected post-ART. PCR was used to generate overlapping half genome amplicons from QVOA-derived viral RNA and from total cellular DNA from the post-ART PBMCs and sequencing using PacBio with barcodes. Phylogenetic trees were constructed using all pre-ART sequences and reservoir sequences. Reservoir entry time was estimated by the phylogenetic relationship between each entry reservoir sequence and the pre-ART sequences.

Results: A median of 10 (range: 4 to 54) reservoir sequences were generated for each participant. In all 5 women with both QVOA and DNA sequences, we did not detect a difference in the timing of establishment of the DNA compared to the replication-competent reservoir (Fishers exact test, all p > 0.05). For the overall cohort (N=16; 4 DNA only, 7 QVOA only and 5 DNA and QVOA), a median of 71% of reservoir sequences were seeded in the year before ART initiation. In one individual where only late viruses had been detected using QVOA, deeper sampling of viral DNA identified a minority of early viruses, consistent with the potential for virus to enter the reservoir when active replication is ongoing.

Conclusion: Viral evolution prior to ART was used to date when both replication-competent viruses and proviral DNA were seeded into the long-lived reservoir. We observed no difference in when these reservoirs formed; both formed predominantly around the time of ART initiation. Our results suggest that the probability an infected cell contributes to the long-lived HIV-1 reservoir is largely determined by the biology of the infected T cell, not the provirus that it carries. In this interpretation a larger population of cells transition to a long-lived state around the time of ART initiation, with some of these cells being nonproductively infected.

329 CD127+ LYMPHOID MEMORY CD4+ T CELLS PREFERENTIALLY SUBJECT TO LATENT HIV INFECTION
Feng Hisao1, Julie Frouard1, Andrea Gramatica1, Guorui Xie1, Roland Schwarzer1, Xiaoyu Luo1, Marieille Cavrois2, Warner C. Greene1, Nadia R. Roan1
1University of California San Francisco, San Francisco, CA, USA, 2Glendale Institute of Virology and Immunology, San Francisco, CA, USA

Background: Lymphoid tissues are a primary site of HIV replication and persistence. We recently demonstrated that tonsil cell memory CD4+ T cells expressing CD127, efficiently fused to HIV but did not allow the fused virus to complete a round of productive infection. Mechanisms that prevent transcription off the viral LTR can prevent completion of the viral life cycle, and also promote HIV latency which is one of the main barriers to an HIV cure. In this study, we set out to better characterize the molecular basis for the block in HIV replication in tissue CD127+ memory CD4+ T cells by considering two main possibilities: post-entry restriction by SAMHD1, or latent infection of these cells by HIV.

Methods: Tonsil cells from uninfected donors were mock-treated or exposed to a CRISPR-tropic HIV reporter virus for 3 days. Multiple populations of memory CD4+ T cells were compared for SAMHD1 expression and infection levels by FACS. These subsets were sorted and quantified for levels of integrated HIV-1 provirus using 2-step Alu-gag PCR with ddPCR. Global expression profiling of the sorted subsets was conducted.

Results: Lymphoid CD127+ mem CD4+ T cells do not exhibit early post-entry restriction by SAMHD1, but rather preferentially undergo latent infection as they harbor high levels of integrated HIV DNA in the absence of reporter gene expression. Relative to other memory CD4+ T cell subsets highly permissive for productive infection, the CD127+ cells preferentially expressed host transcripts associated with cellular quiescence explaining how these cells can preferentially silence the HIV LTR. Latently-infected CD127+ memory cells were reactivated by stimulation through the TCR.

Conclusion: We identify a population of tissue-specific memory CD4+ T cells expressing CD127 that upon exposure to HIV preferentially supports latent infection. Because these cells can undergo IL-7-driven homostatic proliferation and can be reactivated, they may serve as an important reservoir to target for HIV eradication efforts. They also serve as a useful in vitro model of HIV latency that can be used to investigate multiple aspects of latency establishment and maintenance. Although CD127 has not been found to be preferentially expressed on latent cells in vivo, the data presented herein warrant investigation of this receptor as a potential biomarker of latently infected cells residing in tissues.

330 UNPRIMED CD8+ LYMPHOCYTES PROMOTE THE ESTABLISHMENT OF HIV LATENCY IN CD4+ T CELLS
Lavinia Franchitti1, Zhan Zhang1, Jack Yoon1, Mirko Paiardini1, Guido Silvestri1, Deanna Kulpa1
1Emory University, Atlanta, GA, USA

Background: The persistence of HIV infection under ART is due to a reservoir of latently infected cells that remain indefinitely despite suppression of virus replication. Defining the mechanisms responsible for the establishment and maintenance of the HIV reservoir under ART has been the focus of efforts aimed at HIV eradication. Several studies have demonstrated that CD8+ T cells inhibit
virus replication during untreated HIV/SIV infection; however, the mechanisms responsible for this antiviral effect remain poorly understood. **Methods:** We used our primary cell based in vitro model of HIV latency to study the CD8+ T cell mediated suppression of HIV expression. To examine the impact of CD8+ T cells on the establishment of HIV latency, memory CD4+ T cells from HIV naïve donors were infected in vitro and co-cultured with activated CD8+ T lymphocytes (1:1 or 1:3 target:effector ratios) in the presence of the anti-retroviral compound saquinavir. After three days, we assessed intracellular Gag expression on CD4+ T cells by flow cytometry, and quantified the frequency of integrated HIV DNA by qPCR. To assess the role of CD8+ T cells in latency reversal, latently infected CD4+ T cells generated in our in vitro latency model were TCR stimulated in the presence or absence of activated CD8+ T lymphocytes (1:1 or 1:5 target:effector ratios). After three days of activation, we again assessed intracellular Gag expression on CD4+ T cells, and quantified the frequency of integrated HIV DNA. **Results:** In the establishment of HIV latency, we found that HIV expression in CD4+ T cells was reduced when co-cultured with CD8+ T cells an average of 9-fold (p<0.0001) and 18-fold (p<0.0001) at 1:1 or 1:5 ratios respectively, without significantly reducing the frequency of HIV-infected cells (n=21). We also observed a significant suppression of HIV latency reversal, a 6-fold decrease at 1:1 target: effector ratio (p= 0.0156) and 14-fold decrease at 1:5 ratio (p= 0.0156). **Conclusion:** Our studies demonstrated a CD8+ lymphocyte mediated suppression of HIV expression in CD4+ T cells that functions to induce the establishment as well as maintain latency in the presence of activation signaling. Understanding the mechanisms by which CD8+ lymphocytes suppress virus transcription and ultimately promote HIV latency in ART-treated HIV-infected individuals may provide critical insight to support the design HIV eradication approaches.

**331 THE HIV ANTISENSE TRANSCRIPT AST INDUCES VIRAL LATENCY VIA SEVERAL SILENCING PATHWAYS**

Rui Li1, Zahra Gholidaei1, Kaveh Daneshvar2, Michelle Pleet1, Fatah Kashanchi1, Luigi Marchionni1, Alan Mullen1
1University of Maryland, Baltimore, MD, USA, 2Massachusetts General Hospital, Boston, MA, USA

**Background:** The HIV-1 antisense transcript (Ast) induces the establishment and maintenance of HIV-1 latency via recruitment of the Polycomb Repressor Complex 2 (PRC2) to the HIV-1 5'LTR, leading to trimethylation of lysine 27 on histone H3 (H3K27me3), nucleosome assembly and transcriptional silencing. **Methods:** Ast mutants were tested after stable transduction in Jurkat E4 cells. To identify new binding partners, Ast was fused to a streptavidin-binding RNA aptamer, expressed in 293 cells, affinity-purified by streptavidin, and binding proteins identified by mass spectrometry (MS). For RNAseq, differential analysis was performed with edgeR with negative binomial distribution using FANTOMCAT permissive set as reference transcriptome. **Results:** We produced a panel of substitution and deletion mutants. A 376-nt segment at the 5' end of Ast (SAST, from the 3'LTR) mediates binding of Ast to the proviral 5'LTR via sequence homology. We divided the Ast sequence downstream of SAST into four segments (A through D). Substitution of segment A or B reduces Ast function. Substitution of 70nt in segment B containing a putative PRC2-binding motif also reduces Ast activity decreasing H3K27me3 levels at Nuc-1. Concurrent substitution or deletion of segments C and D also impacted Ast activity, suggesting the recruitment of additional factors. We found that Ast interacts with several repressors such as NuRD, CTGF, YY1, TDP-43, forming a complex of ~2MDa. To assess off-target effects of Ast, we found that Ast interacts with several repressors such as NuRD, CTCF, YY1, histone H3 (H3K27me3), nucleosome assembly and transcriptional silencing. **Conclusion:** Our studies identified Ast as an ideal tool for the development of a functional cure. Induction of Ast to greater extent than sense HIV transcripts in response to LRA may explain their limited efficacy in HIV reactivation.

**332 LUNG DOUBLE NEGATIVE T CELLS HARBOR HIV IN ACUTE INFECTION AND DURING LONG-TERM ART**

Oussama Meziane1, Syim Salahuddin1, Tram Pham2, Omar Farnos1, Amelie Pagliuzz1, Nicholas Chomont1, Elaine Thomson1, Ron Olivenstein1, Marianna Orlova1, Erwin Schur1, Eric A. Cohen1, Cecilia Costinuki1, Mohammad-Ali Jenabian1
1Research Institute of McGill University Health Centre, Montreal, QC, Canada, 2Université de Montréal, Montréal, QC, Canada, 3Centre de Recherche du CHUM, Montréal, QC, Canada, 4McGill University Health Centre Research Institute, Montreal, QC, Canada, 5McGill University Health Centre, Glen site, Montréal, QC, Canada

**Background:** The lungs are relatively unexplored reservoirs in the ART era. Double negative (DN) T-cells originate either from the thymus by escaping negative selection, or in the periphery following CD4 downregulation by HIV Nef/Vpu. As circulating DN T-cells have been described as cellular HIV repositories, we undertook a thorough analysis of DN T-cells in the lungs vs blood of ART-treated HIV-infected individuals. **Methods:** 17 long-term ART-suppressed adults (median 9 years) and 8 uninfected controls, both without active respiratory symptoms, were recruited. Bronchoscopies were performed to obtain bronchoalveolar lavage (BAL) fluid, and matched blood was collected. T-cell subsets and HIV p24 were characterized by flow cytometry and HIV-DNA levels were measured by ultrasensitive PCR. To examine DN T-cell dynamics in acute vs chronic infection lung, spleen and blood specimens from 85 HIV-infected BLT humanized mice (hu-mice) were assessed. **Results:** FACs-sorted DN T-cells from BAL harbored HIV-DNA in ART+ adults although HIV-DNA levels were lower in DN vs lung CD4 T-cells. Both HIV+ and HIV- adults had greater CD3+CD4-CD8α-CD8β- cell frequencies in BAL vs blood, while CD3+CD4-CD8α-TCRβ-TCRγδ- cells were only enriched in BAL from HIV+ individuals. In contrast to blood, pulmonary DN T-cells in both HIV+ and HIV- groups displayed mostly an effector memory phenotype (CD45RA-CD28+). However, HIV+ individuals had more activated (HLA-DR+T) DN cells and fewer senescent (CD28-CD57+) and recent thymic migrant (CD31+) lung DN cells. No changes were noted in CCR3+ (lung epithelium homing) DN T-cells within lungs vs blood. Similar to humans, CD3+CD4-CD8α-CD8β- DN T-cells were enriched in BAL vs blood of HIV+ and HIV- hu-mice. Importantly, p24+ DN T-cell frequencies within the lungs were consistently higher than in blood and spleen in both acute and chronic HIV infection of hu-mice. Like in humans, fewer lung DN T-cells in hu-mice had a recent thymic migrant phenotype, suggesting their local expansion within the lungs due to HIV infection. **Conclusion:** Long-term ART-suppressed adults have higher frequencies of DN T-cells in lungs vs blood and exhibit HIV-DNA persistence within their lung DN T-cells. In hu-mice, HIV is seeded within the lung DN T-cells during acute infection. As in HIV infection lung DN T-cells are activated effector memory cells expressing reduced senescence and thymic migration phenotypes vs blood, viral reservoirs are likely to be more active in lungs despite long-term ART.

**333 EFFECT OF TAMOXIFEN ON VORINOSTAT-INDUCED HIV RNA EXPRESSION IN WOMEN ON ART (A3566)**

Eileen P. Scully1, Athe Tsibris2, Evgenia Aga2, Qing Ma3, Kate Starr3, Kathleen E. Squires4, Steven G. Deeks5, Elizabeth Connick5, Monica Gandhi3, Ronald Bosch3, Nancie Archin6, Jonathan Karn7, Daniel R. Kuritzkes2, Rajesh T. Gandhi8, for the ACTG A3566 Study Team
1Johns Hopkins University, Baltimore, MD, USA, 2Brigham and Women's Hospital, Boston, MA, USA, 3Harvard T.H. Chan School of Public Health, Boston, MA, USA, 4University of Rochester, Rochester, NY, USA, 5The Ohio State University, Columbus, OH, USA, 6Merck & Co, Inc, Upper Gwynedd, PA, USA, 7University of California San Francisco, San Francisco, CA, USA, 8University of Arizona, Tucson, AZ, USA, 9University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 10Case Western Reserve University, Cleveland, OH, USA, 11Massachusetts General Hospital, Boston, MA, USA

**Background:** HIV reservoirs differ between men and women but few women have been enrolled in HIV cure trials to date. In vitro and ex vivo data have identified a suppressive role for the estrogen receptor in HIV transcriptional control. ACTG A3566 investigated whether the selective estrogen receptor
modulator tamoxifen enhances HIV transcription in vivo after vorinostat exposure.

Methods: Postmenopausal women with HIV suppression for >1 yr and continuous ART for >=2 yrs were randomized 2:1 to 5 wks of tamoxifen (ArmA) vs observation (Armb); both groups then received 2 doses of 400mg of vorinostat separated by 72 hrs. Primary outcomes were safety in all treated women and change in HIV RNA expression from baseline to 5 hrs after second vorinostat dose in those receiving full study treatment (efficacy group). Total HIV DNA and unspliced cell-associated RNA (caRNA) were measured in 5x10^6 CD4 T cells by qPCR, and spliced HIV envelope transcripts were measured in 106 resting memory CD4 cells by EDITS assay. Single copy assay (SCA) of plasma viremia and histone acetylation by ELISA were measured. Arms were compared by t-tests.

Results: 31 women enrolled in 3 months; median age 57, 58% African American, median CD4 count 688 cells/mm^3, No >=Grade 3 adverse events related to study drugs were seen. 27 women comprised the efficacy group (19 ArmA, 8 ArmB). There was no difference between the groups in the change in HIV expression by caRNA (mean fold change: ArmA 1.2, ArmB 1.5, p=0.6) or in EDITS (mean fold change ArmA 1.5, ArmB 4.3, p=0.12). Following vorinostat, 18 participants had increased histone acetylation; in these women, HIV expression by EDITS also increased (mean fold increase: Overall 2.8; ArmA 1.7, ArmB 7.4; Table 1). There were no changes in HIV DNA or SCA. Targeted plasma concentrations of tamoxifen and vorinostat were achieved.

Conclusion: In post-menopausal women receiving vorinostat, ESRI antagonism with tamoxifen was not associated with a significant change in the magnitude of HIV RNA induction by qPCR or EDITS. Induction of HIV RNA after vorinostat by the EDITS assay was primarily seen in women with increases in histone acetylation which was only observed in 67% of trial participants; this may have limited the ability to detect an effect of tamoxifen. This clinical trial, the first to study HIV latency reversal exclusively in women, was rapidly enrolled and completed, supporting the feasibility of future efforts to investigate sex-specific features of the HIV reservoir.

### Table 1. Changes in HIV expression stratified by change in histone acetylation

<table>
<thead>
<tr>
<th>Overall</th>
<th>ArmA (Baseline vs. Vorinostat)</th>
<th>ArmB (Baseline vs. Vorinostat)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change+</td>
<td>Increase N=18</td>
</tr>
<tr>
<td>EDITS fold change</td>
<td>0.02 (0.00-0.14)</td>
<td>0.44 (0.04-3.19)</td>
</tr>
<tr>
<td>EDITS fold change</td>
<td>1.06</td>
<td>2.95</td>
</tr>
</tbody>
</table>

### 335 ABX464 DECREASES THE TOTAL HIV RESERVOIR AND HIV TRANSCRIPTION INITIATION IN VIVO

Sara Moron-Lopez1, Silvia Bernal2, Jean-Marc Steens3, Joseph K. Wong1, Javier Martinez-Picado1, Steven A. Yuki1

1University of California San Francisco, San Francisco, CA, USA, 2IrsiCaixa Institute for AIDS Research, Badalona, Spain, 3ABIVAX, Paris, France, 4San Francisco VA Medical Center, San Francisco, CA, USA

Background: Antiretroviral treatment (ART) intensification and disruption of latent HIV infection (reversal or silencing) have been suggested as strategies to eradicate HIV. ABX464 (AbiVax) is a novel antiviral that binds to the cap binding complex, interfering with splicing and Rev-mediated export of newly transcribed HIV RNA. ABX464 has been shown to inhibit HIV RNA biogenesis in vitro and delayed viral rebound in a humanized mouse model. We investigated the effect of ABX464 on the HIV transcription profile and total and intact HIV DNA in circulating CD4+ T cells from ART-suppressed participants enrolled in the ABIVAX-005 clinical trial (NCT02990325).

Methods: Eleven participants on suppressive ART were treated daily with 150mg of ABX464 for 4 weeks. Peripheral CD4+ T cells from nine study participants were available for HIV transcription profile and reservoir size analysis. Total HIV DNA, intact HIV DNA (IPDA), and Read-through, total/ initiated, S’elongated, unspliced, polyadenylated and multiply-spliced HIV transcripts were quantified at weeks 0, 4 and 8 using ddPCR.

Results: We observed a significant decrease in the total HIV DNA (p=0.008, median fold-change=-0.8) and a lower median level of intact HIV DNA (p=0.05, median fold-change=-0.8) after ABX464 treatment (wk0 vs. wk4). However, intact HIV DNA increased significantly (p=0.008, fold-change=+1.6) after ABX464 discontinuation (wk4 vs. wk8). After 4 weeks of ABX464 treatment, we observed a decrease in total initiated HIV RNA per million CD4+ T cells and per provirus (HIV RNA/HIV DNA) (p=0.05, median fold-change=0.7; p=0.004, median fold-change=0.5, respectively), a trend towards a decrease in the
S’elongated HIV RNA per provirus \( (p=0.07, \text{median fold-change}=0.5) \), and a lower median level of unspliced HIV RNA \( (p=\text{n.s.}, \text{median fold-change}=0.6) \), but no decrease in polyadenylated or multiply-spliced HIV RNA. However, S’elongated HIV RNA per million CD4+ T cells increased significantly \( (p=0.04, \text{fold-change}=1.4) \) after ABX464 discontinuation (wk4 vs. wk8).

**Conclusion:** In this study, ABX464 had a dual effect of decreasing total HIV DNA (and possibly intact proviruses) and decreasing the amount of HIV transcription per provirus, although these changes were reversed after drug discontinuation. Our data suggest that ABX464 acts as an ART intensifier in vivo. To further characterize its specific mechanism of inhibiting HIV transcription, long-term administration of ABX464 in a larger cohort should be studied.

---

**ATTACKING LATENT HIV WITH CONVERTIBLE CAR-T CELLS, A MODULAR KILLING PLATFORM**


**Background:** Reducing the size of the latent HIV reservoir and controlling subsequent viral rebound by immune engineering could lead to a sustained viral remission in HIV-infected individuals in the absence of ART. CTLs could reduce the size of the reservoir by recognizing and killing reactivated reservoir cells. However, cellular exhaustion and the presence of CTL-resistant viruses may undermine their effectiveness. We have tested a new approach to reservoir reduction where convertibleCAR-T cells (cCAR-Ts) programmed with multiple HIV-specific broadly neutralizing antibodies (bNAbs) are deployed.

**Methods:** cCAR-Ts utilize a mutated, inert form of the NGK2D receptor. Orthogonal MIC ligands that bind to inert NGK2D but not wild-type NGK2D are fused to antibodies to generate bispecific MicAbodies for directing cCAR-T targeting and activation. cCAR-Ts can therefore be readily redirected by altering the antibody component of the MicAbody and furthermore, MicAbodies can be multiplexed. 4 bNAbs were engineered as MicAbodies and tested for their ability to kill tonsil, spleen, or blood cells infected with GFP-tagged R5 or X4-tropic or transmitted/founder viruses. Specificity of infected cell killing was monitored by loss of GFP+ vs GFP- cells. Reactivated CD4 T cells from HIV-infected individuals on ART were assayed for loss of cell-associated viral RNA in the presence cCAR-Ts either armed or not armed with bNAbs. The platform was checked in vivo, in NSG mice model of cancer, by measuring size reduction of cancer tumors.

**Results:** In the presence of bNAb-MicAbodies, CD8 cCAR-Ts effectively killed HIV-infected, but not uninfected, cells from tonsil, spleen and blood. Killing was strictly dependent on the presence of bNAb-MicAbodies targeting HIV Env. Multiplexing of four MicAbodies increased the breadth of killing. cCAR-T cells also reduced by more than half the inducible reservoir present in blood of HIV-infected individuals on ART. Administration of cCAR-T cells in a mice cancer model, demonstrated highly effective in vivo killing.

**Conclusion:** An attractive feature of cCAR-Ts is that is a modular platform that not only allows for multiplexing of MicAbodies, but also targeted delivery of kill switches if needed or cytokines for cCAR-T rejuvenation. This platform could be an important tool for reducing and controlling the size of the latent HIV reservoir.

---

**CAR-T CELLS AT 15 YEARS: PERSISTENCE OF CD4+ ZETA TRANSGENE AND EFFECT ON RESESORV**


**Background:** Despite effective antiretroviral therapy, cellular reservoirs of HIV persist. CD4+ is a chimeric T cell receptor with the intracellular and transmembrane domain of CD4 linked to the zeta signaling chain of the CD3 T cell receptor. The long term persistence of this CAR-T cell therapy was previously estimated.

**Methods:** Fifteen individuals were randomized to 3 groups (cells, IL-2, cells + IL-2) to receive a single infusion of 5-9 x 109 autologous CD4+ gene modified T cells ± subcutaneous IL-2 at 1.2 million IU/m2 for 56 days. Inclusion criteria included CD4≥200, viral load<50, stable HAART for ≥8 weeks. Pheresis and rectal biopsy were performed at baseline and at 13-15 years follow up. Real-time PCR was used to detect and measure the CD4+ transgene and the HIV-1 gag gene in PBMCs and rectal tissues. RNA-seq using HIV-1 Clade B probe was performed on formalin fixed rectal tissue at long term follow up. Total and integrated HIV DNA were measured in PBMCs using a highly sensitive nested PCR assay. Mixed models and ANCOVA were used to assess the effects of treatment arms on CD4, CD4%, CD4:CD8, total and integrated HIV DNA over time.

**Results:** Fifteen persons enrolled (mean age 38.4 ± 7.9 years) and thirteen individuals, 11 males and 2 females, completed the long term follow up (LTFU). Race/ethnicity of the participants included one Asian, four Blacks, two Hispanics and six Caucasians. The median CD4 count on enrollment was 821 (IL-2), 712 (cells) and 822 (cells + IL-2), \( p=0.468 \). At LTFU median CD4 counts were 779, 720 and 1047 respectively, \( p=0.376 \). HIV viral loads were suppressed except in one nonadherent subject at LTFU. No differences by race or sex were seen. There was persistence of CD4+ CAR-T cells 13-15 years post infusion in both PBMC and rectal tissues in all recipients. Rare HIV-RNA+ cells can be identified in the majority of treatment arms and was not statistically different.

**Conclusion:** The CD4+ transgene persisted for 13-15 years in CAR-T cell treated subjects. With the caveat of a trial with a small number of subjects, coupled with intersubject variability, our analysis suggests that there was no statistical difference in baseline to LTFU between arms and that HIV remains present in PBMC and rectal tissue. Furthermore, this is the most mature data set to date to indicate that CAR-T cells are safe for at least 15 years.

---

**PHASE I STUDY OF GENE-MODIFIED CD4+ CELLS AND CD34+ CELLS W/WO BUSULFAN IN HIV+ ADULT**

**Ronald T. Mitsuyasu**, Jay Lalezarli, Bryan Burke, Mollie Barrett, Jeremy Casey, Alison Knoop, Suparna Mishra, Jeffrey Ahlers, Louis Breton, Orit Wolstein, Jeffrey Bartlett, W. David Hardy, Louise Evans, Geoffrey Symonds, James L. Riley, Linda Jagodzinski, Sodsai Tovanabutra, Eunice W. Wolfe, Walter Reed Army Institute of Research, Silver Spring, MD, USA, Quest Clinical Research, San Francisco, CA, USA, Calimmune, Inc, Pasadena, CA, USA, Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** HIV gene therapy could reduce viral load, preserve immunity and mitigate ART toxicities. Safety and feasibility of an anti-HIV-1 dual-gene construct Lvsh5/C46 (Cal-1) in modified, autologous CD4+ T-cells (Ttn) and HSC (HSCtms) was assessed.

**Methods:** PLWH with CD4+ count > 500/mm, and voluntary ART suspension (drug toxicities, treatment fatigue or other reasons) underwent aphereses for CD4+ T-cells and HSC following mobilization, then gene-modified cell infusion. Busulfan pre-conditioning was: none (Cohort 1), 4 mg/kg on Day -2 (Cohort 2) and 3mg/kg (Day -2) to a total AUC exposure of 8,000 μmolar/min at Day -4 (Cohort 3). Subjects were followed for 48 weeks with ART reinitiation if CD4+ count or viral RNA reached safety thresholds, or participant decision. BM aspirates and GALT biopsies were taken at 24 and 48 weeks.

**Results:** 12 participants (4 per cohort) were treated. At 48 weeks, 4 remained off and 8 resumed ART. Only 1 unrelated SAE was reported. Procedure-related AEs included neutropenia, thrombocytopenia, fatigue, nausea, and back pain. One pt in Cohort 1 had Cal-1 marking in PB -3% at wk 4 which was not sustained. All Cohort 2 pts had >1% marking at early time points which was not sustained. Cohort 3 had highest levels of Cal-1 marking at peak and longest persistence. While no association was seen between Cal-1 marking and Ttn persistence, a correlation between Cal-1 marking and Ttn marking could be multiplexed. 4 bNAbs were engineered as MicAbodies and tested for their ability to kill tonsil, spleen, or blood cells infected with GFP-tagged R5 or X4-tropic or transmitted/founder viruses. Specificity of infected cell killing was monitored by loss of GFP+ vs GFP- cells. Reactivated CD4 T cells from HIV-infected individuals on ART were assayed for loss of cell-associated viral RNA in the presence cCAR-Ts either armed or not armed with bNAbs. The platform was checked in vivo, in NSG mice model of cancer, by measuring size reduction of cancer tumors.

**Results:** In the presence of bNAb-MicAbodies, CD8 cCAR-Ts effectively killed HIV-infected, but not uninfected, cells from tonsil, spleen and blood. Killing was strictly dependent on the presence of bNAb-MicAbodies targeting HIV Env. Multiplexing of four MicAbodies increased the breadth of killing. cCAR-T cells also reduced by more than half the inducible reservoir present in blood of HIV-infected individuals on ART. Administration of cCAR-T cells in a mice cancer model, demonstrated highly effective in vivo killing.

**Conclusion:** An attractive feature of cCAR-Ts is that it is a modular platform that not only allows for multiplexing of MicAbodies, but also targeted delivery of kill switches if needed or cytokines for cCAR-T rejuvenation. This platform could be an important tool for reducing and controlling the size of the latent HIV reservoir.
339 HIV-SPECIFIC T-CELL RESPONSES IN AN HIV-POSITIVE COHORT POST ALLO-HSCT
Johanna M. Eberhard1, Mathieu Angin2, Caroline P. Passaes1, Maria Saigado3, Valérie Moncaux4, Gero Hutter5, Pascual Balsalobre6, Mi Kwon7, Jose Luis Diez8, Monique Nijhuis8, Annemarie Wensing9, Javier Martinez-Picado1, Julian Schulze Zur Wiesch1, Aisier Saez-Cirion11, for the iCStem Study Group
1University Medical Center Hamburg—Eppendorf, Hamburg, Germany, 2Institut Pasteur, Paris, France, 3IrsiCaixa Institute for AIDS Research, Badalona, Spain, 4Celastic, Dresden, Germany, 5University Hospital Gregorio Marañon, Madrid, Spain, 6University Medical Center Utrecht, Utrecht, Netherlands

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only medical intervention which has led to HIV cure. While the size of the HIV reservoir sharply decreases after allo-HSCT, the dynamics of the T-cell reconstitution has not been comprehensively described.

Methods: We analyzed the activation and differentiation of CD4+ and CD8+ T-cells, and the breadth and quality of HIV- and CMV-specific CD8+ T-cell responses in 16 HIV-infected patients who underwent allo-HSCT (including 4 individuals who received cells from CCR5D32/D32 donors) to treat their underlying hematological malignancy and remained under antiretroviral therapy (ART).

Results: We found that reconstitution of the CD4+ and CD8+ T-cell compartment was slow and heterogeneous with an initial expansion of activated CD4+ T-cells that preceded the expansion of CD8+ T-cells. Transplanted patients did not achieve full immune reconstitution after allo-HSCT. While HIV-specific CD8+ T-cells disappeared immediately after allo-HSCT, weak ex vivo HIV-specific CD8+ T-cell responses were detectable several weeks after allo-HSCT, and could still be detected at the time of full T-cell chimerism, indicating that de novo priming, and hence antigen expression, occurred during the time of T-cell expansion. These HIV-specific T-cells had limited functionality compared to CMV-specific CD8+ T-cells, and persisted years after allo-HSCT.

Conclusion: In conclusion, immune reconstitution was slow, heterogeneous and incomplete and coincided with de novo detection of weak HIV-specific T-cell responses. The initial short phase of high T-cell activation, in which HIV antigens were present, may constitute a window of vulnerability for the reseeding of viral reservoirs, emphasizing the importance of maintaining ART directly after allo-HSCT.

340 MYCOPHENOLATE MOFETIL FOR DEPLETION OF THE HIV RESERVOIR
Joshua T. Schiffer1, Claire Levy2, Sean Hughes2, Mel Padullo2, Katrina Puckett2, Eric Helgeson2, Robert D. Harrington3, Florian Hladik2
1Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 2University of Washington, Seattle, WA, USA

Background: Recent data suggests that proliferation of latently infected memory CD4+ T cells is essential to the maintenance of the HIV reservoir in individuals who are taking suppressive antiretroviral therapy (ART). Mathematical model projections suggest that curtailing lymphocyte proliferation may accelerate the rate of reservoir clearance. We conducted a clinical trial to test this hypothesis.

Methods: We performed a small (n=4), open-label, non-randomized Phase II clinical trial (NCT03262441) to assess the safety and tolerability of 22 months of low-dose mycophenolate mofetil (MMF) in chronically HIV-infected men on ART suppressed individuals. The TAPT is reported as percent reduction in proliferation compared to serum/participant T cells are exposed to serum from participants after MMF dosing.

Results: The TAPT is reported as percent reduction in proliferation compared to serum/participant T cells are exposed to serum from participants after MMF dosing.

Conclusion: One year of low-dose MMF was safe and well-tolerated in ART suppressed men but did not lower total or intact HIV proviral DNA levels. The anti-proliferative effect waned during the dosing interval, suggesting that higher doses, or more frequent or extended-release dosing may be necessary to lower the HIV reservoir.

341 VIRAL RESERVOIR DISRUPTION WITH PANOBINOSTAT AND IFN-Α: FIRST RESULTS
Ciputra A. Hartana1, Theresa Flynni, Amy Sbrolla1, Carina Barnach1, Jane Blackmer1, Joshua Chevalier1, Pilar Garcia Broncano2, Xu G. Yu3, Rajesh T. Gandhi2, Michael R. Kurtzkes2, Mathias Lichterfeld
1Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, 2Massachusetts General Hospital, Boston, MA, USA, 3Brigham and Women’s Hospital, Boston, MA, USA

Background: Reactivation of viral transcription can sensitize viral reservoir cells to immune-mediated killing which may reduce long-term persistence of virally-infected CD4+ T cells in ART-treated individuals. The ACTIVATE study is an ongoing, prospective, randomized, dose-escalation clinical trial in which the histone deacetylase inhibitor (HDACi) panobinostat is administered as a latency-reversing agent in combination with pegylated IFN-α2a as an innate immune modulator.

Methods: ART-treated participants were randomized to receive three consecutive doses of 5mg (phase I) or 10mg (phase II) of panobinostat alone (Arm A, n=2 participants in stages I and II each), or in combination with one dose of pegylated IFN-α2a (Arm B, n=6 participants in stages I and II each). Before and at multiple timepoints after study drug administration, cell-associated HIV-1 RNA from the CD4+ T cells were quantified using ddPCR; moreover, innate and adaptive immune responses and acetylated H3 expression were analyzed by flow cytometry. HIV-1 DNA was evaluated using the IPDA. Results: Relative to baseline, the expression of acetylated histone H3 increased 1.5 times (p=0.025) on day 4 after 3 doses of panobinostat, an effect that was most visible in naïve, stem cell memory and central-memory CD4+ T cells. In parallel, a significant increase of HIV-1 gene expression relative to baseline levels was seen for TAR transcripts (p=0.0234) and long-LTR transcripts (p=0.0156) in stage II, but not in stage I. The frequency of activated CD38+ NK cells and NKp30+ NK cells increased significantly at day 4 and day 10 from participants receiving IFN-α2a in stages I and II, which was mostly seen in the cytokine producing (CD16- CD56+), cytotoxic (CD16+ CD56+) and immature (CD16+ CD56-) NK cell subsets. Moreover, the proportion of IL-2-producing HIV-1-specific CD4+ T cells increased during treatment with IFN-α2a, while IFN-α secreting CD4+ T cells were reduced. There were no changes in HIV-1 DNA levels among timepoints and between medication arms in both phases. No unexpected or severe clinical adverse events occurred so far.

Conclusion: First results indicate that the medication induces HIV-1 transcription and augments innate and adaptive immune cells. Phase III with 15mg panobinostat administered is ongoing.

342 IAP ANTAGONISM PROMOTES PD-1 BLOCKADE-MEDIATED ELIMINATION OF HIV IN HUMANIZED MICE
Michael Bobardt1, Joseph Kuo1, Udayan Chatterji1, Norbert Wiedemann2, Gregoire Vuagniaux3, Philippe Gallay1
1The Scripps Research Institute, La Jolla, CA, USA, 2Debiopharm, Lausanne, Switzerland

Background: The immune checkpoint programmed cell death protein 1 (PD-1) plays a major role in T-cell exhaustion in cancer and chronic HIV infection. Inhibitor of apoptosis protein antagonists (IAPa) reverse HIV latency and costimulate T-cells through modulation of NF-κB signaling in vitro.

Table 1. Clinical trial participant clinical data and outcomes

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>CD4+ T cells (baseline)</th>
<th>CD4+ T cells (12 months)</th>
<th>HIV proviral DNA (logging/mL)</th>
<th>TAPT (%)</th>
<th>Peak TAPT (%)</th>
<th>TAPT [RANTES]</th>
<th>IFN-α (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>490</td>
<td>392</td>
<td>500</td>
<td>83.9</td>
<td>93.1</td>
<td>1.2</td>
<td>2096</td>
</tr>
<tr>
<td>2</td>
<td>573</td>
<td>460</td>
<td>560</td>
<td>71.7</td>
<td>67.7</td>
<td>0.9</td>
<td>2107</td>
</tr>
<tr>
<td>3</td>
<td>508</td>
<td>293</td>
<td>850</td>
<td>50.6</td>
<td>55</td>
<td>0.2</td>
<td>5894</td>
</tr>
<tr>
<td>4</td>
<td>792</td>
<td>723</td>
<td>830</td>
<td>50.6</td>
<td>55</td>
<td>0.2</td>
<td>5894</td>
</tr>
</tbody>
</table>

Criteria for study continuation at 12 months (0.25 log reduction in total HIV DNA) and MMF was therefore stopped for all participants. Intact HIV DNA levels were undetectable in one participant and remained stable in the remaining participants over one year of MMF. (Table)
Methods: We asked in this study whether a new IAPa would stimulate the potency of an anti-human PD-1 monoclonal antibody (mAb) to reduce HIV loads in humanized mice.

Results: Four weeks of Anti-PD-1 mAb treatment decreased the PD-1+ CD8+ cell population among CD4+ T cells by 22% compared to vehicle, while IAPa co-treatment reduced it by 50%. Anti-PD-1 mAb administration reduced HIV load in blood by 94% with detectable levels in 8 of 8 mice, and addition of the IAPa further enhanced this reduction from 94 to 97% with undetectable levels in 3 of 8 mice. 2 weeks after drug treatment interruption, Anti-PD-1 mAb administration had reduced HIV loads in CD4+ cells also in all tissues analyzed compared to vehicle, including spleen (5.6 to 2 log in viral RNA copies), lymph nodes (5.6 to 1.1 log in viral RNA copies), liver (5.4 to 1.6 log in viral RNA copies), lung (5.6 to 2 log in viral RNA copies), and thymic organoid (5.5 to 1.2 log in viral RNA copies), IAPa further enhanced the anti-PD-1-mediated reduction of HIV tissue loads achieving a >5 log reduction in all tissues analyzed, notably with undetectable levels in some individual organs; spleen (5.6 to 0.2 log in viral RNA copies), lymph nodes (5.6 to 0.2 log in viral RNA copies), liver (5.4 to 0.3 log in viral RNA copies), lung (5.6 to 0.2 log in viral RNA copies), and thymic organoid (5.5 to 0.1 log in viral RNA copies). Following the 4 weeks of in vivo treatments, ex vivo anti-CD3/CD28 stimulation increased the ability to activate CD8+ T cells in infected mice having received in vivo anti-PD-1 treatment by 2.9-fold (5 to 39.6%), and an additional increase by 1.7-fold in mice having received IAPa co-treatment (39.6 to 67.3%).

Conclusion: These findings demonstrate for the first time that an IAPa greatly enhances the effects of an immune checkpoint inhibitor on antiviral immunity resulting in undetectable HIV titers in blood and organs of humanized mice. This suggests that the combination of two distinct classes of immunomodulatory agents constitutes a promising immunotherapeutic approach to cure HIV.

343 IMPACT OF GS-986, PGT121 AND N6-LS ON CNS IMMUNE ACTIVATION IN SHIV-INFECTED MACAQUES

Denise C. Hsu1, Decha Silsorn2, Rawiwan Imerbsin1, Amandara Pegu1, Dutaddee Inthawong2, Jumpol Sopanaporn3, Alexandra Schuetz1, James Demarest1, Merlin L. Bobb4, John R. Mascola5, Ramses Gelezunis6, Richard A. Koup7, Dan Barouch1, Nelson L. Michael1, Sandhya Vasan8, US Military HIV Research Program in Thailand, Bangkok, Thailand, 2Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, 3NIH, Bethesda, MD, USA, 4ViiV Healthcare, Research Triangle Park, NC, USA, 5US Military HIV Research Program, Silver Spring, MD, USA, 6Gilead Sciences, Inc, Foster City, CA, USA, 7Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: Kick and kill strategies using TLR-7 agonist and broadly neutralizing antibodies (bNab) have shown promise in non-human primates, but effects on the central nervous system (CNS) have not been evaluated.

Methods: Rhesus macaques (n=16) were intrarectally inoculated with SHIV-1157pdR68 at wk0 and initiated on ART (TDF, FTC, DTG) on Day14. Active group (n=8) received GS-986 every 2 weeks from wk14 and intravenous N6-LS and PGT121 every 2 weeks from wk24. The development of anti-drug antibodies limited number of bNab administrations. Active group animals received at least 7, 2 and 2 doses of GS-986, PGT121 and N6-LS, respectively. ART was ceased 2 weeks after plasma levels of bNabs <0.25ug/mL. Control animals (n=8) received intravenous saline and ART was ceased at wk40. Plasma and cerebral spinal fluid (CSF) SHIV RNA levels were measured by PCR and soluble markers of immune activation in CSF, suggesting that this strategy may be pursued in humans without impacting CNS activation.

Results: Administration of GS-986, PGT121 and N6-LS did not increase SHIV RNA or markers of immune activation in CSF, and remained similar post GS-986 administration at wk24 and post bNabs prior to ART interruption. At 12 weeks post rebound, CSF IL-2 (p=0.031), and G-CSF (p=0.008) were increased relative to pre-infection levels.

Conclusion: Administration of GS-986, PGT121 and N6-LS did not increase SHIV RNA or markers of immune activation in CSF, suggesting that this strategy may be pursued in humans without impacting CNS activation.
345LB PGT121 AND VESATOLIMOD IN CHRONICALLY TREATED SHIV-INFECTED RHESUS MONKEYS

Dan Barouch1, Noe Mercado1, Abishek Chandrashekar1, Erica Borduchi3, Joseph Nikolola1, Brian A. Carr2, Nathan D. Thomsen2, Tomas Gelezunas2

1Beth Israel Deaconess Medical Center, Boston, MA, USA, 2Gilead Sciences, Inc, Foster City, CA, USA

Background: We have previously reported that administration of the broadly neutralizing antibody PGT121 with the TLR7 agonist vesatolimod (VES) delayed or prevented viral rebound in SHIV-infected rhesus monkeys following ART discontinuation in animals that initiated ART early during acute infection. However, the efficacy of bNAbs has not previously been evaluated in the more clinically relevant model of animals that initiated ART during chronic infection with extended ART suppression.

Methods: 24 rhesus monkeys were infected with SHIV-SF162P3 and initiated daily ART (TDF/FTC/DTG) after 12 months of chronic infection. Following 30 months of continuous daily suppressive ART, animals received 10 infusions of 10 mg/kg PGT121 and 0.15 mg/kg VES (N=8), an Fc-modified version of this antibody GS-9721 and VES (N=9), or sham control (N=7) every 2 weeks. At week 42 following initial antibody dosing, which was 24 weeks after the final antibody and VES doses, ART was discontinued and viral rebound was monitored for 140 days.

Results: PGT121 and GS-9721 infusion resulted in 24 weeks of therapeutic antibody levels without the development of ADA, followed by a decline to undetectable levels prior to ART discontinuation. VES administration led to activation of multiple cellular immune subsets including CD4+ T lymphocytes and increased levels of serum cytokines. Following ART discontinuation, 100% (7 of 7) of sham controls exhibited rapid viral rebound with a median rebound and increased levels of serum cytokines. Following ART discontinuation, 100% (7 of 7) of sham controls exhibited rapid viral rebound with a median rebound and increased levels of serum cytokines. Following ART discontinuation, 100% (7 of 7) of sham controls exhibited rapid viral rebound with a median rebound and increased levels of serum cytokines. Following ART discontinuation, 100% (7 of 7) of sham controls exhibited rapid viral rebound with a median rebound and increased levels of serum cytokines.

Conclusion: In SHIV-infected rhesus monkeys that initiated ART after 1 year of chronic infection and that were virologically suppressed with ART for 2.5 years, administration of PGT121 or GS-9721 with VES prevented viral rebound in 100% (7 of 7) of animals following ART discontinuation. These data suggest therapeutic efficacy of broadly neutralizing antibodies with TLR7 stimulation in targeting the viral reservoir in the rarely used but clinically more relevant model.

347LB SUSTAINED REMISSION IN A 4-YEAR-OLD HIV-INFECTED CHILD TREATED IN FIRST YEAR OF LIFE

Gloria P. Heresi1, Douglas J. Richman2, Roukaya AH Hammoud3, Gilhen Rodriguez4, Norma Perez4, James R. Murphy4

1University of Texas at Houston, Houston, TX, USA, 2University of California San Diego, La Jolla, CA, USA

Background: Very rarely children with vertically acquired HIV and given antiretroviral therapy (ART) soon after birth, then stop ART, have extended periods without detectable HIV in peripheral blood by routine testing. We report a child with intrauterine-acquired HIV, who started on combined antiretroviral therapy at 33 hours of life and remains undetectable over 3 years after discontinuing ART.

Methods: In addition to routine clinical assays, HIV DNA was assayed using droplet digital PCR (ddPCR) for gag and pol using DNA extracted from available CD4 lymphocytes purified by negative selection.

Results: A healthy newborn was born to a mother with no prenatal care and a 6-year history of diagnosed, but untreated HIV infection, with 14,400 HIV RNA copies/ml and 27% CD4 at delivery. The child was started on ART at 33 hours of life. A blood sample submitted for HIV DNA on day of life (DOL) 1 and another for HIV RNA on DOL 2 failed due to technical issues. A DOL 14 sample tested positive for HIV DNA. Because of this finding dried blood spots from DOL 1 from routine newborn screening were tested for HIV DNA with a positive result (CDC). The mother discontinued the child's ART after 1 year. From birth through 4 years old the child remained clinically well with undetectable HIV RNA (<20) by routine laboratory testing, and HIV specific antibodies becoming and remaining negative from 15 months. Testing by HIV ddPCR-DNA was performed at intervals beginning at DOL 114 and were intermittently detected with the most recent one showing <1 copy of gag and pol DNA/million cells.

Conclusion: We present a child with intrauterine-acquired HIV infection, initiation of ART at 33 hours of life who was maintained on ART for 1 year and has remained clinically well through 4 years of age including 3 years without ART. Whether viral control was affected by ART, characteristics of the virus or virus being investigated.
349LB EDITING OF SIV IN NONHUMAN PRIMATES BY CRISPR-CAS9 IN VIRAL RESERVOIRS

Jennifer Gordon1, Tricia H. Burdo1, Pietro Mancuso1, Chen Chen1, Rafal Kaminski1, Mark G. Lewis1, Kamel Khali1

1Temple University, Philadelphia, PA, USA, 2BIOQUAL Inc, Rockville, MD, USA

Background: Antiretroviral therapy (ART) suppresses but does not eliminate replication competent HIV proviral DNA from latently infected cells, thus resulting in viral reactivation upon ART cessation. Therefore, removal of HIV proviral DNA from infected individuals is needed. We have assessed a CRISPR-Cas9 based gene editing strategy for the elimination of the SIV proviral DNA in the rhesus macaque model.

Methods: An all-in-one AAV9 gene therapy vector was constructed to deliver CRISPR-Cas9 plus two gRNA targeting sequences within the S 5' and 3' viral LTRs and the Gag gene to excise the intervening proviral DNA fragment. Ten adult Indian rhesus macaques were i.v. infected with SIVmac239 and then treated daily with a drug regimen of tenofovir, emtricitabine and dolutegravir (1/3.5/2.5mg/kg daily s.q.). Animals were randomized into groups to receive low versus high dose of AAV9-CRISPR-Cas9 in a single i.v. infusion (low dose: 1.4x1010/GC/kg, high dose: 1.4x1011/GC/kg, n=3) as well as control SIV infected animals (n=3).

Results: SIV-infected animals treated with AAV9-CRISPR-Cas9 at both high and low doses showed vivo excision of viral DNA from serial blood and lymph node samples. Results from Sanger sequencing confirmed the precise breakpoint of the viral DNA in samples in which excision was detected. Biodistribution of the AAV9-CRISPR-Cas9 vector was assessed by PCR to detect the presence of the Cas9 gene sequence. DNA and RNA scope were performed on lymph nodes in parallel to detect the AAV9-CRISPR-Cas9 viral vector and expression of the Cas9 gene. Broad excision of SIV proviral DNA was observed in lymph nodes and other tissues known to be viral reservoirs including spleen, gut, and brain. A dose response between low and high doses, as well as temporal distribution between 3 and 6 months, was observed for AAV9-CRISPR-Cas9 SIV viral DNA in the blood.

Conclusion: Here we demonstrate broad SIV DNA excision in viral reservoirs leading to permanent inactivation of SIV proviral DNA in a one shot CRISPR-Cas9 molecule. We observed biodistribution of AAV9-CRISPR-Cas9 in the blood in a dose and time dependent manner for the elimination of SIV DNA. These findings support the utilization of AAV9-CRISPR-Cas9 as a potential therapeutic strategy for in vivo gene editing of HIV proviral DNA from latent tissue reservoirs.

350LB EFFICIENT DELETION OF CCR5 PROVIDES COMPLETE PROTECTION AGAINST HIV IN XENOGRAFT MICE

Daniel Claiborne1, Christian L. Boutwell2, Zachary Detwiler3, Tao Chen1, Radiana Trifonova1, David T. Scadden1, Tony W. Ho1, Todd M. Allen2

1Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, 2CRISPR Therapeutics, Cambridge, MA, USA, 3Harvard University, Cambridge, MA, USA

Background: Hematopoietic stem cell transplant (HSTC) with CCR5d32/d32 defective stem cells has resulted in complete remission of HIV infection in three patients (“Berlin”, “Dusseldorf”, and “Oxford”) that received allogeneic HSTC for co-occurring malignancies. However, the scarcity of HLA-matched, CCR5d32 homozygous stem cell donors represents a significant hurdle to widespread adoption of HSTC for treatment of HIV infection. The ability to effectively delete CCR5 in autologous, mobilized, CD34+ hematopoietic stem progenitor cells (mobilHSCs) would overcome this hurdle and provide a path toward an autologous HSTC cure for HIV infection.

Methods: Guides were screened for editing efficiency by CRISPR-Cas9 ribonuclease (RNase) nuclease of primary human CD4+ T cells. Edited CD4+ T cells were then stimulated and challenged with R5-tropic HIV. A dual guide approach engendered the highest level of CRIS of CRIS editing and complete protection from high titer HIV challenge in vitro and was selected for HSCPC editing and transplant.

Results: Dual guides achieved a 92% CRIS editing frequency in mobilHSCs from an anonymous HIV-negative donor (guide 1: 70%; guide 2: 58%; total: 92%). After transplant into NSG mice, CCR5edit HSCPs displayed slightly delayed but otherwise normal hematopoiesis resulting in human immune cell reconstitution with frequencies of human monocytes, B cells, and T cells comparable to the control sham (GFp guide) edited mice. High frequency CRIS editing was detected in descendant monocytes, B cells, and T cells (median 89%), and the frequency of circulating T cells expressing CCR5 on the cell surface was <0.25% compared to >5% in the sham edited controls. Importantly, CCR5edit mice were completely refractory to challenge with an ID100 of a CR5-tropic HIV (0/5 CCR5edit mice infected) that infected 8/8 control mice. CCR5edit mice further resisted a challenge dose of 50x ID100. In contrast, subsequent intraperitoneal challenge of a CCR5edit mouse with a CXCR4-tropic HIV strain resulted in robust infection and plasma viremia confirming CCR5-specific protection.

Conclusion: These data demonstrate that high frequency CRISPR-Cas9-mediated editing of CCR5 in human HSCPs is achievable and is sufficient to prevent infection during multiple, high dose exposures to a highly pathogenic
strain of HIV. These experiments provide the basis to explore the prevention of systemic HIV rebound in an autologous transplant setting to help guide future clinical approaches to achieve a functional cure.

**351 ANTAGONISM OF PPARG FOR TH17 MUCOSAL IMMUNITY RESTORATION AND HIV-RESERVOIR PURGING**


'Centre de Recherche du CHUM, Montreal, QC, Canada, 'Caprion Biosciences, Montreal, QC, Canada, 'Laval University, Quebec City, QC, Canada, 'Université de Montréal, Montreal, QC, Canada, 'McGill University Health Centre, Glen site, Montreal, QC, Canada

**Background:** The Th17-polarized CCR6+ROTYt+CD4+T-cells are key players in mucosal homeostasis. These cells are preferential targets for HIV/SIV infection at mucosal sites and their depletion/functionional alteration persist despite viral-suppressive antiretroviral therapy (ART) in people living with HIV (PLWH). Moreover, Th17 cells carrying replication-competent HIV persist during long-term ART. Therefore, novel Th17-targeted HIV remission/cure strategies are needed. Considering that PPARY represses ROYt, Th17-specific master regulator and HIV transcription, we hypothesized that PPARγ pharmacological inhibition will enhance Th17-effecter functions and facilitate HIV reactivation from latency.

**Methods:** PBMC from ART-treated PLWH (n=14; CD4 counts >300 cells/µl, plasma viral load <40 HIV-RNA copies/ml) and HIV- (n=8) were used to isolate total/CCR6+/CCR6- memory CD4+T-cells by magnetic and flow cytometry sorting. Cells from HIV- were stimulated via CD3/CD28 for 12 days. Short-long term viral outgrowth assays (VDA) were performed with cells from ART-treated PLWH in the presence/absence of the PPARγ antagonist T0070907 for 12 days. Short-long term viral outgrowth assays (VDA) were performed with cells from ART-treated PLWH in the presence/absence of T0070907 and/or antiretroviral drugs. Cell-associated (CA)/free HIV RNA/DNA and HIV-p24 levels were quantified by real-time PCR, ELISA, and flow cytometry. Transcriptional profiling was performed using the Illumina RNA Sequencing technology. Results were validated by flow cytometry, ELISA and miR29 antagonist.

**Results:** While PPARγ antagonist increased IL-17A and CA HIV RNA levels in cells of ART-treated PLWH, viral outgrowth was unexpectedly inhibited. To define the mechanism of action, RNA-sequencing/transcriptional validations were performed. PPARγ inhibition in CCR6+CD4+T-cells up-regulated transcripts linked to Th17 polarization (ROYt, STAT3, BCL6 IL-17A/IFN-γ), HIV transcription (CDA9, HTATIP2) and restriction (Caveolin-1, TRIM22, TRIM5α, BST2, miR29), and down-regulated transcripts encoding key HIV-dependency factors (CCR5, furin). Moreover, T0070907 increased the antiviral IL-21/miR29 axis. MiR29 antagonist increased HIV replication in the absence but not in presence of T0070907, pointing to miR29-independent antiviral mechanisms.

**Conclusion:** These results provide the rationale for considering PPARγ antagonism as a novel strategy towards Th17-mediated mucosal immunity restoration and HIV-reservoir purging.

---

**352 A JAK1 INHIBITOR SUPPRESSES HIV-1-DRIVEN ABERRANT HOST GENE TRANSCRIPTION**

Yang-Hui Yeh1, Katharine Jenike1, Rachela Calvi1, Jennifer Chiarella1, Ya-Chi Ho1, Yale University, New Haven, CT, USA, ‘Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** More than 50% of the latent reservoir are maintained through clonal expansion. While ART effectively blocks new rounds of infection, HIV-1 promoter remains intact, drives HIV-1 expression and aberrant cancer-related gene expression, and contributes to HIV-1 integration site-related clonal expansion. New therapeutic approaches targeting the clonal expansion of HIV-1-infected cells is required to reduce the size of the latent reservoir. We hypothesize that suppressing HIV-1 transcription can disrupt HIV-1-driven clonal expansion of the infected cells.

**Methods:** We first developed a dual-reporter cell line model and screened a library of 1,430 FDA-approved small molecule compounds to identify HIV-1-suppressing agents. Second, we examined the effect of candidate HIV-1-suppressing agents on HIV-1 transcription and HIV-1-driven aberrant host gene transcription at the integration site. Third, we examined cellular transcriptional landscape of cells treated with candidate HIV-1-suppressing agents to understand how these agents affect host cell environment. Fourth, to understand whether candidate HIV-1-suppressing agents can disrupt the proliferation dynamics of HIV-1-infected cells, we examined the frequency of HIV-1-infected cells upon ex vivo T cell activation with and without ex vivo treatment of candidate HIV-1-suppressing agents.

**Results:** We identified four FDA-approved drugs – JAK1 inhibitor filgotinib, JAK1/2 inhibitor ruxolitinib, spironolactone and guanine synthesis inhibitor mycophenolic acid – which reduce HIV-1-GFP reporter expression in cell line models and HIV-1 RNA transcription in CD4+ T cells from HIV-1-infected individuals. Among them, filgotinib, spironolactone and mycophenolic acid suppress HIV-1-driven aberrant host gene transcription and aberrant oncogenic protein production in a HIV-1 reporter cell line model. Filgotinib alters host transcriptional landscape by changing host RNA processing involving intron retention and RNA splicing. During CD3/CD28 induced T cell activation and proliferation, filgotinib reduces the frequency of cells harboring inducible HIV-1 ex vivo.

**Conclusion:** Filgotinib preferentially reduce the proliferation of HIV-1-infected cells upon T cell activation. HIV-1 suppressing agents serve as a new therapeutic approach to target the clonally expanding HIV-1-infected cells.
**353 DEVELOPMENT OF A PSEUDOVIRUS DELIVERY SYSTEM FOR HIV-1 ELIMINATION**

Jonathan Herskovitz1, Mahmudul Hasan1, Wilson Blomberg3, Insiya Mukadam4, Jatin Machhi4, Maxim Oleniuk4, Kamel Khalili5, Bharesh D. Kevadia1, Benson Edagwa1, Channabasavaiah Gurumurthy1, Howard E. Gendelman1

1University of Nebraska Medical Center, Omaha, NE, USA, 2Cornell University, Ithaca, NY, USA, 3Temple University, Philadelphia, PA, USA, 4Stanford University, Stanford, CA, USA

**Background:** A key challenge in developing successful HIV-1 cure strategies rest in eliminating the integrated provirus from the genomes of infected CD4+ T lymphocytes and monocyte-macrophages. In a first step towards this end, we recently demonstrated success by the sequential use of long acting slow effective release (LASER) ART and CRISPR-Cas9 in achieving viral sterilization from a subset of infected humanized mice. We sought to improve upon the transduction and known immunogenicity of the adeno-associated virus 9 (AAV9; 1012 genome copies/mouse) by generating an HIV-1 pseudovirus enabling both CD4+ and CCR5 receptor targeting. We hypothesize that virus-like particles, bearing antigenic resemblance to HIV but lacking infectivity, will utilize viral glycoprotein-120 (gp120) to specifically deliver curative agents to CD4+ cells.

**Methods:** Viral matrix (HIV-1p17) and capsid (HIV-1p24) were genetically fused to biotinylated peptide (AviTag) and monomeric streptavidin (maxavidin) encoding sequences, respectively, to facilitate encapsulation of bioconjugated payloads. We generated VLPs (figure 1) by pseudo-typing modified lentiviral structural proteins with dual-tropic HIV-189.6 envelope by co-transfection of plasmids in HEK293FT cells. A duplex LTR and gag splicing CRISPR-Cas9 system was inserted via plasmid. Non-gene payloads including streptavidin quantum dots, biotinylated fluorophore and a cabotegravir (CAB) prodrug were independently loaded in the VLPs.

**Results:** VLPs retained the same 150nm size, spherical morphology, and targeting epitope (gp120) expression as native infectious HIV-1 but were replication incompetent. Using our bioconjugation system, streptavidin quantum dots and biotinylated fluorophore were detected in the VLPs at 1.4 and 3.6-fold above baseline measurements. In human PBMC, 57% of monocytes and 9.5% of CD4+ T cells co-localized with fluorescently labeled VLPs. VLPs bearing CRISPR-Cas9 showed gp120-mediated entry and robust excision of proviral DNA from HIV-1 infected CD4+ T cells.

**Conclusion:** HIV-1 VLPs, engineered for loading with bioconjugated theranostic agents, direct payloads to CD4+ cell targets. VLPs specifically delivered proviral DNA excision therapy to HIV-infected T cells supporting the need for their development in HIV-1 cure strategies.

354 ROMIDEPSIN COMBINED WITH PRO-APOTOTIC DRUGS REDUCE INTEGRATED HIV DNA

Youry Kim1, Ajanta Solomons2, Jennifer M. Zerbato3, Paul Cameron3, James McMahon3, Jenny L. Anderson3, Sharon R. Lewin1, 1University of Melbourne, Melbourne, VIC, Australia, 2Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia, 3The Alfred Hospital, Melbourne, VIC, Australia

**Background:** Effective elimination of latently infected cells in people living with HIV (PLWH) on antiretroviral therapy (ART) through activation of HIV transcription will also require the induction of death of the infected cell. Given that HIV proteins, such as envelope and vpr, expressed late in the productive replication cycle, can induce apoptosis of CD4+ T-cells, we hypothesized that using latency reversing agents (LRAs) to induce expression of pro-apoptotic viral proteins combined with pro-apoptotic drugs will enhance the reduction of latently infected cells.

**Methods:** Total CD4+ T-cells were isolated from peripheral blood collected by leukapheresis from PLWH on ART. CD4+ T-cells were treated with pro-apoptotic drugs (the phoshoinositide-3 kinase (PI3K) inhibitors, IPI-443, IPI-3063 and wortmannin or an inhibitor of B-cell lymphoma (Bcl)-2, venetoclax) for 24 hours, followed by treatment with five different latency reversing agents (LRAs; panobinostat, romidepsin, bryostatin, JQ1 or PMA/PHA) for 4 or 24 hours and then the pro-apoptotic drugs alone for a further 48 hours. We measured integrated HIV DNA and cell-associated unspliced (CA-US) HIV RNA by RT-qPCR.

**Results**

The combined treatment of romidepsin with each of the four pro-apoptotic drugs led to a greater decline in integrated HIV DNA versus either romidepsin or pro-apoptotic drug alone. Romidepsin together with 5nM venetoclax showed the greatest decline in integrated HIV DNA. Romidepsin or venetoclax alone resulted in a mean fold change (MFC) in HIV integrated DNA of 0.72 and 0.18, respectively while the combined treatment resulted in an MFC of 0.54. Panobinostat and JQ1 combined with 1μM venetoclax also led to a reduction in HIV integrated DNA (PNB+1μM VNX MFC=0.47; JQ1+1μM VNX MFC=0.60), compared to the decline resulting from each drug alone (PNB MFC=0.71; JQ1 MFC=0.88; 1μM VNX MFC=0.76). We observed increases in CA-US HIV RNA and the ratio of CA-US HIV RNA to integrated DNA following treatment of CD4+ T-cells with all four LRAs as well as each of the pro-apoptotic drugs alone or combined.

**Conclusion:** Using CD4+ T-cells from PLWH on ART ex vivo, reduction of integrated HIV DNA could be significantly enhanced using the combination of romidepsin with either a PI3K or Bcl-2 inhibitor. The addition of a pro-apoptotic drug could potentially provide the “kill” needed for effective “shock and kill”.

355 NOD2 AND TLR8 AGONISTS ENHANCE IL-15-MEDIATED ACTIVATION OF HIV EXPRESSION

Jasmine Kaur1, Jay Lalezari2, Rebecca Hoh3, Steven G. Deeks4, Wade Blair4, Tomas Cihlar1, Jeffrey Murry1

1Gilead Sciences, Inc, Foster City, CA, USA, 2Quest Clinical Research, San Francisco, CA, USA, 3University of California San Francisco, San Francisco, CA, USA

**Background:** The latent HIV reservoir is a barrier to achieving an HIV cure. Individual reservoir-targeting agents have shown potential activity in exploratory clinical trials, but it is likely that activation of HIV expression would enhance and/or accelerate the depletion of the latent reservoir. We previously identified clinically advanced agents that modestly activate HIV expression in cells isolated from ART-suppressed people living with HIV (PLWHIV), including
IL-15 and agonists of multiple pattern recognition receptors (PRRs), such as toll-like receptor (TLR) and Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) agonists. Here we identify combinations of agents that have greater activity than either agent alone.

**Methods:** Peripheral blood mononuclear cells (PBMCs) were isolated from ART-suppressed PLWHIV then treated with various PRR agonists individually or in combination with IL-15. Cytokine production and surface markers of T cell activation were assessed 24 hours after treatment initiation. HIV RNA in culture supernatants and T cell proliferation were quantified following a 4-day treatment with PRR agonists. Wilcoxon matched pair signed rank test and Bliss independence model were used for statistical and synergy analysis, respectively.

**Results:** In PBMCs from 7 ART-suppressed PLWHIV, IL-15 alone induced a 3.9-fold increase in HIV expression relative to control, while NOD2 and TLR8 agonists induced 3.0- and 3.2-fold increases, respectively (geometric means, p < 0.05 for each). In combination with IL-15, NOD2 and TLR8 agonists had the greatest effect, increasing HIV expression 14- and 11-fold, respectively (p < 0.05 for both compared to IL-15 alone). This was not significantly different from that induced by PMA and ionomycin (18-fold). The combination of NOD2 and IL-15 showed the clearest synergy. Correspondingly, both NOD2 and TLR8 agonists increased the levels of cytokines and activation markers produced in response to IL-15 stimulation, but had minimal additional effect on CD4 T cell proliferation.

**Conclusion:** Combining either NOD2 or TLR8 agonist with IL-15 significantly increased HIV expression and, in cells from several donors, approached that observed with the mitogenic activation control. This identifies clinically tested agents capable of robustly inducing HIV. It is important to consider that these combinations can also activate broader immunity and potentially augment immune-mediated reservoir clearance.

**356 HIV-1 GENE EXPRESSION DURING REVERSAL OF LATENCY USING RNA-Seq WITH PROBE ENRICHMENT**

**Philip Tomeszko**1, Silvi Rouskin2, Daniel R. Kuritzkes3, Athie Tsibris1
1Harvard Medical School, Boston, MA, USA, 2MIT, Cambridge, MA, USA, 3Brigham and Women’s Hospital, Boston, MA, USA

**Background:** Transcriptomic analysis of the human and HIV-1 expression profile that is essential for successful reactivation of latently infected cells promises to help inform the next generation of latency reversal agents. However, because of the rarity of latently infected cells, the HIV-1 genome is poorly covered by bulk RNAseq. To address this limitation, we developed an RNAseq method with probe-based enrichment of HIV-1 reads.

**Methods:** Resting, non-naive CD4 T cells were isolated from leukapheresis samples from four HIV-1 Eradication and Latency Study (HEAL) participants. 15 million cells were treated for 24 hours with: 1) unstimulated 2) PMA-ionomycin (iono) 3) romidepsin (rmd) 4) bryostatin (bryo) 5) IL-15 6) rmd/bryo. Total RNA was extracted using Trizol. RNA was poly-A selected and libraries were generated following an adapted Truseq library generation protocol. A custom set of tiling probes was used to enrich HIV-1 and control gene PCR constructs. The unenriched and enriched libraries were sequenced on Nextseq, 40x40 paired-end reads. The reads were aligned to the human transcriptome and HIV-1 genome. A custom script was used to count reads per gene and per region of the HIV-1 genome.

**Results:** For both host control genes and HIV-1, we observed an average ~50-fold enrichment after probe capture (see Figure 1). HIV-1 reads aligned across all regions of the genome. PMA-iono and combination rmd/bryo had the greatest increase in HIV-1 transcription. To test the reproducibility of the probe-enrichment, we performed linear regression on normalized RNAseq reads from cells treated with PMA-iono. We observed a Pearson’s R2 of 0.95 for total RNAseq between two participants and 0.97 for enriched RNAseq between the same participants. We also found evidence of hypermutated HIV-1 RNAseq reads in the enriched samples.

**Conclusion:** Our approach to analyzing host and HIV transcriptomes leverages next-generation sequencing to investigate latency reactivation. Probe-based enrichment allowed RNAseq quantification of HIV-1 reads from resting memory CD4+ T cells without the need for sorting of HIV-infected cell populations. We were able to measure HIV-1 transcription after reactivation from latency using a variety of latency reversal agents and compare HIV-1 gene expression across conditions. Analysis of differential host gene expression will yield insight into host factors necessary for HIV-1 reactivation in latently infected resting memory CD4+ T cells in persons with HIV.

**357 SURFACE ENGINEERING OF EXTRACELLULAR VESICLES TO TARGET HIV PERSISTENCE**

**Pooja Bhardwaj**1, Rafael Kaminski2, Shivani Desai2, Ali Danesh2, Amir Afshari3, Nicholas Yam3, Kamel Khalili2, Archana Gupta2, Satish K. Pilla3
1Vitalant Research Institute, San Francisco, CA, USA, 2Temple University, Philadelphia, PA, USA

**Background:** Current limitations of antiretroviral therapy are driving interest in novel HIV eradication strategies. Extracellular vesicles (EVs) are nano-sized membrane vesicles involved in cell signaling which have shown promise as engineerable therapeutic agents. We used surface display technology to engineer HIV-targeting EVs (HTEVs) that block HIV infection and target infected cells.

**Methods:** EVs were isolated from healthy donor plasma using polymer-based precipitation and column purification. EVs were decorated with single-chain variable fragment (scFv)-C12 fusion proteins targeting the HIV envelope protein. Surface-engineered EVs and HIV particles were fluorescently labeled and incubation reactions were visualized in dual-color channel and single-particle tracking analysis using a Nanomager (ONI). Decorated EVs were incubated for two hours with a GFP-reporter HIV strain at 1:1, 2:1, and 4:1 ratios. Jurkat E6.1 cells and primary human CD4+ T cells were infected via spinoculation. Reporter virus was incubated with no EVs, undecorated EVs, or anti-PD-1 scFv-decorated EVs as negative controls. Jurkat Z101 cells were induced with PMA/TSA to reactivate latent HIVNL4-3-Dgag/pol-GFP reporter virus and then were treated with Texas red-labeled control or anti-HIV-C12 fusion proteins decorated EVs. After 24h, cells were analyzed by flow cytometry. TZM-bl cells were in vitro infected with HIVNL4-3-Dgag/pol-GFP reporter virus and then were treated with Texas red-labeled control or anti-HIV-C12 fusion proteins decorated EVs. Internalization of decorated EVs was assessed after 18h incubation using fluorescence microscopy.

**Results:** Tracking data revealed that HTEVs clustered and moved in tandem with HIV virions, in contrast to negative controls which did not form clusters and tracked independently of virions. HTEVs significantly inhibited HIV infection in Jurkat E6.1 cells (n=3) and CD4+ T cells (n=5 donors) with respect to negative controls (p<0.05, paired t-test). HTEVs efficiently directed EVs into latently-infected, reactivated T lymphoid cells and in vitro HIV-1-infected TZM-bl cells.

**Conclusion:** HTEVs suppress HIV infection and selectively target infected cells ex vivo following latency reversal. HTEVs may facilitate the clearance of the latent HIV reservoir by delivering cytotoxic cargo specifically to infected cells.

**358 IN VITRO MODEL FOR STUDYING T-CELL PROLIFERATION/SURVIVAL DRIVEN BY HIV INTEGRATION**

**Machika Kaku**1, John K. Yoon1, John M. Coffin1
1Tufts University, Boston, MA, USA

**Background:** The latent HIV reservoir is maintained through clonal expansion of T cells containing latent proviruses. Several clusters of HIV integration sites have been identified in a fraction of highly expanded T cell clones from patients on long-term ART. These clusters are characterized by proviruses in few introns in the same orientation as the host target gene. Similar patterns are hallmarks of insertional mutagenesis by oncogenic retroviruses; in these cases the integrated provirus causes aberrant gene expression, leading to cancer if the target gene is a proto-oncogene. The HIV provirus clusters in expanded cell clones likely reflect the alteration of host gene expression to promote growth/survival of the host cell, contributing to the persistence of the latent reservoir during ART, and possibly promoting tumor development in infected cells.
Methods: Primary human CD4+ T cells were infected with an HIV vector and reactivated every other week for 3 months to allow the T cells to proliferate and rest repeatedly. Each donor sample was divided into three independent replicates. Integration site analysis on randomly fragmented genomic DNA after each reactivation event was used to monitor provirus dynamics: clonal expansion of an infected cell was determined by the observation of multiple DNA fragments with different breakpoints and identical HIV-host junction sites from the Illumina sequencing library.

Results: We observed expansion of clones containing specific HIV provirus insertions, supporting our model of T cell expansion during HIV infection. We did not observe expansion of cell with proviruses in the known gene, but we identified large provirus clusters in one small intron of the STAT3 gene associated with extensive clonal expansion. Interestingly, there was a recently reported case of an AIDS-related B cell lymphoma with an HIV integration in the same region and orientation of STAT3.

Conclusion: Although in our pilot experiment we did not observe clonal expansion of cells with proviruses in the genes identified in vivo, we did observe significant expansion of cells that contained a provirus in a small region in the STAT3 gene in each of six replicates from two donors. This in vitro system will be an important tool for identifying new genes that HIV may disrupt to promote proliferation of the host cell to play a direct role in HIV-related cancer.

359B AMINOBLISPHOSPHONATES REVERSE LATENCY IN HIV-SEBAROPOSITIVE INDIVIDUALS

Sara Selitsky1, Matthew Clohosey1, Marie Anne Iannone1, Susana Garcia-Recio1, Jennifer Kirchherr1, Carolina Garrido1, Yinyan Xu1, Shahryar Samir1, Ann Marie1 University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: We hypothesized that aminoblisphosphonates (N-BPs), such as pamidronate (PAM), zoledronate (Zol) and alendronate (ALN), that inhibit the formation of farnesyl phosphoproteins, used for protein prenylation disrupting cell signaling, may induce reversal of HIV latency. Therefore, here we explore their potential as novel latency reversing agents.

Methods: Latency reactivation capacity of N-BPs was analyzed ex vivo in nine HIV-seropositive individuals on suppressive antiretroviral therapy (ART). Resting CD4 T cells were isolated and left untreated or treated with PHA, PAM or Zol, and then cell-associated HIV RNA (caRNA) levels and replication-competent HIV were measured. RNA-seq was used to explore the N-BPs’ mechanism of action, and flow cytometry was used to analyze the ex vivo effect of N-BPs on immune cell activation and proliferation. Longitudinal PBMC (baseline and weeks 2, 24, 48 post intervention) were obtained from the ACTG A5163. This trial examined the effects of weekly dosing of ALN or placebo (PLB) on low bone density associated with HIV and ART. We measured caRNA levels and total HIV DNA levels. A Wilcoxon matched-pairs signed-rank test was used to analyze patient-specific replicate data across treatment types, and a Mann-Kendall test was used to test for trend (in either direction) in HIV DNA levels.

Results: N-BPs induced reactivation of latent HIV ex vivo (Figure 1A) without causing non-specific activation or other significant alterations on peripheral immune cell populations. RNA-seq analysis showed a correlation between pathways altered by N-BP treatment and those altered following HIV infection ($R=0.44, p<0.001$). In vivo administration of ALN induced perturbations of the latent reservoir in 8 of 9 participants analyzed who took ALN, that were not detected in participants who took PLB (N=5). Most importantly, treatment with N-BP ALN resulted in a 2.9 to 49.1-fold decrease in total HIV DNA levels in three of eight participants (Figure 1B), while no changes were detected in the PLB arm.

Conclusion: Three of eight participants received N-BPs and showed significant decrease in total DNA levels. These results support the need for further clinical testing of N-BPs to reduce persistent HIV infection in vivo.

360 PARALLEL HIV RNA INTEGRATION SITE, AND PROVIRAL SEQUENCING IN SINGLE RESERVOIR CELLS

Kevin Einkauf1, Matthew Osborne2, Ho G. Xu1, Matthew Lichterfeld1, 1Brigham and Women’s Hospital, Boston, MA, USA, 2Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: Highly durable latent reservoirs constitute the major barrier to HIV cure. The ability of viral reservoir cells to persist long-term may depend on the proviral sequence, corresponding integration site and HIV gene expression, but technical limitations have hindered efforts to obtain all three features from single reservoir cells. Here, we describe a novel technology that accomplishes this goal.

Methods: PBMC from 2 HIV-infected patients, collected during pre-ART viremia and during suppressive ART, were subjected to a novel assay termed Parallel RNA, Integration Site and Proviral Sequencing (PRIP-Seq). Briefly, PBMC were diluted to single viral reservoir cells, subjected to parallel extraction of cellular DNA and RNA, and exposed to whole-genome (WGA) and whole-transcriptome amplification (WTA). Subsequently, near-full-length proviral sequences, integration sites and the expression of immature and mature HIV RNA transcripts were determined using WGA and WTA products.

Results: Paired HIV RNA expression profiles and proviral sequences were determined for 219 total proviruses. HIV transcription was observed in 35% and 31% of cells containing genome-intact and defective proviruses, respectively. Integration sites were simultaneously obtained for 99 of these sequences. Among proviruses with defined integration sites as well as detectable and intact viral promoter regions (n=34), transcriptionally-silent proviruses were 2.8-fold more frequently located in non-genic/pseudogenic regions and were positioned 2.9-fold further away from proximal host transcriptional start sites relative to transcriptionally-active proviruses. Longitudinal analysis in one patient indicated an enrichment of non-genic/pseudogenic integrations after suppressive ART (21%) as compared to pre-ART levels (0%). This trend was paralleled by a 59-fold reduction in the number of transcriptionally-active intact proviruses, and a 7-fold reduction in the number of transcriptionally-silent intact proviruses per million PBMC after suppressive ART. In comparison, transcriptionally-active and -silent defective reservoirs declined 6-fold and 4-fold, respectively.

Conclusion: Parallel analysis of proviral sequences, integration sites and viral gene expression from single reservoir cells suggests progressive enrichment of transcriptionally-silent proviruses integrated into non-permissive genomic regions during prolonged ART. Future use of PRIP-Seq will allow profiling of the evolutionary dynamics of viral reservoir cells in great detail.

361 SINGLE-CELL ATLAS AND CLONAL EXPANSION DYNAMICS OF CD4+ T CELLS DURING HIV INFECTION

Jack A. Collora1, Delia Pinto-Santini1, Siavash Pasalar2, Ricardo Alfaro3, Carmela Ganoza1, Jennifer Chiarella1, Rachael Calvi1, Javier R. Lama1, Serena S. Spudich1, Ann Duerr1, Ya-Chi Ho1, 1Yale University, New Haven, CT, USA, 2Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 3Association Civil Impacta Salud y Educacion, Lima, Peru

Background: Despite effective antiretroviral therapy (ART), HIV-1 persists in CD4+ T cells as a major barrier to cure. More than 50% of the HIV-1 latent reservoir is maintained by clonal expansion. HIV-1-infected cells undergo clonal...
expansion through antigen-driven proliferation, homeostatic proliferation and integration site-driven proliferation. Targeting clonally expanding HIV-1-infected cells without damaging uninfected cells is required to eliminate the latent reservoir. We constructed a single-cell multiomic atlas of CD4+ T cells from HIV-1-infected individuals during acute HIV-1 infection and after viral suppression at its native status without ex vivo stimulation.

Methods: We obtained paired CD4+ T cells from three HIV-1-infected individuals from the MERLIN cohort during acute infection (within one month of the estimated day of infection) and after suppressive ART (11 months of ART with viral suppression [plasma viral load <200 copies/ml] within the past 6 months). CD4+ T cells from three uninfected individuals were obtained as negative controls. Using ECCTIsEq (Expanded CRISPR-compatible Cellular Indexing of Transcriptomes and Epitopes by sequencing), we captured 1) surface protein expression, including memory phenotypes, activation status and exhaustion markers, 2) transcriptome, 3) HIV-1 RNA and 4) T cell clonality by T cell receptor sequences in the same single cells. We analyzed T cell clonal abundance, repertoire dynamics and clone tracking.

Results: We captured an average of 7,950 single cells, 1,504 genes mapped to human genome and 6,110 T cell clones per sample. Among them, we identified a total of 67 HIV-1-infected cells and 25 expanded CD4+ T cell clones harboring HIV-1-infected cells. We mapped the single-cell atlas of CD4+ T cells from HIV-1-infected individuals which is distinct from that of uninfected individuals. We found upregulation of interferon-stimulated genes and T cell activation, reflecting T cell responses to acute HIV-1 infection. We also identified CD4+ T cell clones that persist despite suppressive ART. Even within the same CD4+ T cell clone, CD4+ T cells exhibit heterogeneous transcriptional profiles.

Conclusion: We captured the cellular environment of HIV-1-infected cells from HIV-1-infected individuals at the native status without ex vivo stimulation. Transcriptional signatures of HIV-1-infected cells may serve as therapeutic targets for HIV-1 cure strategies.

362 TCR SEQUENCING REVEALS CLONAL EXPANSIONS OF INDUCIBLE RESERVOIRS IN SPECIFIC SUBSETS

Pierre Gantner1, Amelie Pagliuzza1, Marion Pardons1, Moti Ramgopal1, Jean-Pierre Routy1, Rémi Fromentin2, Nicolas Chomont1

1Université de Montréal, Montreal, QC, Canada, 2Centre de Recherche du CHUM, Montreal, QC, Canada

Background: Clonal expansions occur in the persistent HIV reservoir as demonstrated by the duplication of HIV genes and/or integration sites reported in several studies. However, these approaches do not permit to phenotypically analyze these expanded clones of infected cells nor the inducibility of the proviruses. We took advantage of the uniqueness of the T-cell receptor (TCR) expressed by a given T-cell clone to unravel the phenotype and dynamics of the inducible HIV reservoir.

Methods: Blood samples from 8 individuals on suppressive ART for at least 2 years were collected longitudinally. Clonotype characterization of HIV-infected cells was determined by combining index single-cell sorting of HIV-infected cells by HIV-Flow (which allows recording the memory phenotype of individual p24+ cells, according to their differentiation status: central, transitional, effector memory cells) with multiplex PCR of the V1-J junction of the TCRbeta chain (including the CD3 region) followed by sequencing. A representative subset of p24- cells was analyzed to determine TCR diversity in the CD4+ T-cell compartment.

Results: We obtained the TCR sequences from 538 p24+ and 346 p24- single-sorted cells. There was no bias in the selection of V and J segments in p24+ cells when compared to p24- cells. Expanded TCR clonotypes were present in 7/8 individuals and accounted for the majority of reservoir cells (median 89%, range 77-100). These expanded clonotypes were maintained over time on ART in 5 individuals and persisted for up to 6 years. The dynamic of the HIV reservoir on ART greatly varied between individuals, with some participants showing a stable repertoire, whereas others displayed emergence of new clonotypes over time. Expanded infected cells were systematically overrepresented in the most differentiated cells (i.e. transitional and effector memory). Nonetheless, these expanded clones were also identified within the central memory compartment from the majority of the participants, albeit at lower frequencies. Importantly, the memory phenotype of these expanded reservoir cells was maintained over time on ART.

Conclusion: Through the repertoire analysis of infected cells, we show that antigen-driven clonal expansion highly contributes to the persistence of the translation-competent HIV reservoir during ART. Our results suggest that infected T cell clonotypes displaying a differentiated phenotype are the progeny of infected central memory cells undergoing clonal expansion during ART.

363 ONLY A FEW HIV-1 INTEGRATION SITES CONFER GROWTH ADVANTAGE TO INFECTED CELLS IN VIVO

John M. Coffin1, Michael J. Bale1, Daria W. Wells1, Shuang Guo1, Brian Luke1, Jennifer M. Zerbato1, Michele Sobolewski1, Twan Sia1, Wei Shao2, Xiaolin Wu1, Frank Maldarelli1, Mary F. Kearney2, John W. Mellors4, Stephen H. Hughes1

1Tufts University, Boston, MA, USA, 2National Cancer Institute, Frederick, MD, USA, 3Leidos Biomedical Research, Inc, Frederick, MD, USA, 4University of Pittsburgh, Pittsburgh, PA, USA

Background: HIV persists during antiretroviral therapy (ART) as proviruses in latently-infected cells that are descendants of a tiny fraction of the CD4+ T cells infected prior to ART initiation. We and others previously reported in vivo selection of cell clones with proviruses integrated in several specific genes, based on analyzing small numbers of integration sites.

Methods: We compared about 380,000 integration sites in PBMC infected ex vivo to sites combined from 32 individuals on suppressive ART for >1 year. The on-ART dataset comprised about 52,000 sites, of which about 31,000 were unique. The two datasets were compared to look for evidence of selection in vivo, and to infer its mechanism.

Results: The overall distribution of unique integration sites was nearly identical between the two datasets. As expected, there was preferential integration in highly-expressed genes (84% of sites) in the ex vivo infected PBMC dataset, and the proviruses were randomly oriented relative to the host gene. By contrast, in the on ART dataset, there was a modest (55%), but significant (P=10^-50), bias for integration in the reverse orientation, which was the result of a weak selection acting on a large number of genes, rather than of strong selection acting on a few genes. Proviruses integrated in three genes (MKL2, BACH2, STAT5B), known to be drivers of cell growth or survival, were enriched in vivo (Table 1) and were preferentially integrated in one or two introns in the same orientation as the gene. We detected three more genes (MKL1, IL2RB, MYB) in which the data also suggest proviral effects on cell growth or survival (Table 1). Taken together, the proviruses in the 6 genes comprised only 2.3% of unique integration sites. Outside of these genes there was no evidence of clustering, orientation bias, or local enrichment of clonally amplified proviruses.

Conclusion: The primary determinant of the distribution of integration sites in persons on ART is their initial distribution, which is subsequently modified only modestly by selection against proviruses in the sense orientation. Proviruses integrated in the sense orientation in any one of 6 genes can enhance cell expansion and/or survival; however, these few selected cells are unlikely to be of major importance to HIV-1 persistence. Other mechanisms driving clonal expansion, for example immune signaling, are more important.

Table 1. Genes in Which Proviruses Can Contribute to Growth and Persistence of Clones

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Size of the In Vivo Sites (in Basepairs)</th>
<th>Size of the In Vitro Sites (in Basepairs)</th>
<th>Size of the Geometric Mean of the In Vitro Sites (in Basepairs)</th>
<th>Size of the In Vitro Sites of the Geometric Mean (in Basepairs)</th>
<th>Number of Sites (in Basepairs)</th>
<th>Percent of Sites (in Basepairs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MKL2</td>
<td>1040a</td>
<td>978</td>
<td>967</td>
<td>953</td>
<td>1040a</td>
<td>100%</td>
</tr>
<tr>
<td>BACH2</td>
<td>304b</td>
<td>294</td>
<td>290</td>
<td>286</td>
<td>304b</td>
<td>100%</td>
</tr>
<tr>
<td>STAT5B</td>
<td>264c</td>
<td>258</td>
<td>253</td>
<td>248</td>
<td>264c</td>
<td>100%</td>
</tr>
<tr>
<td>IL2RB</td>
<td>46d</td>
<td>44</td>
<td>43</td>
<td>40</td>
<td>46d</td>
<td>100%</td>
</tr>
<tr>
<td>MYB</td>
<td>126e</td>
<td>119</td>
<td>116</td>
<td>105</td>
<td>126e</td>
<td>100%</td>
</tr>
<tr>
<td>p24+</td>
<td>1040a</td>
<td>978</td>
<td>967</td>
<td>953</td>
<td>1040a</td>
<td>100%</td>
</tr>
</tbody>
</table>

HIV DYNAMICS AND REPOPULATION OF RESERVOIRS IN THE HUMAN BODY

Antoine Chaillou1, Sara Gianella1, Simon Dellicour2, Stephen A. Rawlings1, Michelli Faria De Oliveira1, Caroline Ignacio1, Magali Porchiola1, Bram Vrancken1, Davey M. Smith1

1University of California San Diego, San Diego, CA, USA, 2Katholieke University Leuven, Leuven, Belgium, 3University of California San Diego, La Jolla, CA, USA, 4Veterans Medical Research Foundation, San Diego, CA, USA

Background: Characterizing HIV persistence and dynamics across the human body is important to develop ways to clear reservoirs. This goal has been hampered by technical difficulties and obtaining fresh tissues.

Methods: Samples were obtained from 6 Last Gift participants, who provided blood ante-mortem and their whole bodies for rapid autopsy within 6 hours of death.
death. Two voluntarily stopped their antiretroviral therapy (ART) before death and 4 remained on ART. HIV reservoirs were characterized by digital droplet PCR and single genome amplification and sequencing of full-length (FL) envelope HIV. Phylogeographic methods reconstructed HIV spread and generalized linear models (GLM) tested for associations between HIV diversity, divergence, predicted tropism, DNA level, and viral dispersal.

**Results:** Across participants, HIV DNA levels ranged from ~0 copies/10^6 cells in the occipital lobe (interquartile range: [IQR] 0–4.6) to 659 copies/10^6 cells in lymph nodes (IQR 580–753), mean ~98 copies/10^6 cells (IQR:23–132) across all tissues. We recovered 603 intact FL env sequences in antemortem blood cells and across 28 anatomical sites (mean of 7 viruses/site, IQR: 5–10), including the central nervous system (CNS). Among the 2 participants stopping ART, viral diversity was lower (<0.01) in blood plasma than in most tissue-derived HIV DNA.

Most of the rebounding intact HIV RNA populations in blood (65% and 80% of variants) were clonal (>99% identical). There was also evidence of clonal expansion within tissues (Fig.), especially gut and genital tract (e.g., 30 identical proviruses observed across 8 tissues in 1 participant). While the main sources of viral dispersal were blood, gut and lymph nodes, our models also revealed viral exchanges within the CNS (Fig.) and from blood toward the CNS. The GLM models revealed that low HIV genetic divergence between sites and high HIV diversity in the recipient sites but not HIV DNA levels were associated with viral exchange.

**Conclusion:** This study found: 1) The emergence of large, clonal, intact HIV RNA populations after stopping ART, which repopulated tissues throughout the body; 2) Multiple sites can act as hubs for dissemination of HIV within the host; 3) Viral exchanges occur within the CNS areas and between the CNS and blood; 4) Viral dynamics are associated with low HIV diversity between sites and high HIV diversity at the recipient site.

---

**365 LONGITUDINAL CHARACTERIZATION OF HIV PROVIRUSES IN PEOPLE ON SUPPRESSIVE ART**

**Annukka Antar**, Katharine M. Jenike, Sunyoung Jang, Danielle Rigau, Daniel B. Reeves, Rebecca Hoh, Jeanne C. Keruly, Richard D. Moore, Joshua T. Schiffier, Barenq Nonyane, Frederick M. Hecht, Steven G. Deeks, Janet Siliciano, Ya-Chi Ho, Robert Siliciano

**Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 3University of California San Francisco, San Francisco, CA, USA, 4University of California San Francisco, San Francisco, CA, USA, 5Yale University, New Haven, CT, USA

**Background:** Clonal proliferation of CD4+ T cells harboring HIV proviruses is a major contributor to HIV persistence despite antiretroviral therapy (ART). Most proviruses are defective, and it is unknown whether cells harboring intact and defective proviruses or those with escape epitopes experience differential rates of clonal expansion and persistence during ART.

**Methods:** To determine whether HIV-specific cytotoxic T lymphocyte (CTL) pressure or differential rates of clonal proliferation shape the HIV provirus landscape during long-term ART, we sequenced 661 near-full-length proviruses from two samples, average 7 years apart, from 8 individuals with suppressed viral loads on ART. 3 of these were elite controllers on ART. The best-defined CTL epitopes based on HLA type were identified in HIV Gag, Pol, and Nef, and each epitope in each provirus was categorized as recognized or not based on its sequence and published data.

**Results:** We found that the provirus landscape of intact and defective proviruses does not change dramatically over time on suppressive ART, although there was a trend towards fewer intact proviruses over time when analyzed by dual primer-probe ddPCR. There was no evidence for longitudinal selection effects in HIV epitopes in Gag, Pol, and Nef. Intact proviruses appear in large clones at least as often as defective proviruses, and proviruses found in large clones are not enriched in escape/unrecognized epitopes. Elite controllers on ART have a similar distribution of defective proviruses and similar proportions of escape and unrecognized epitopes as other individuals on ART. The proportion of proviruses present in large clones increased over time on ART in all participants. Although with small sample sizes, modeling of this data suggests that over time on ART a smaller number of very large infected CD4+ clones come to dominate the observed provirus landscape.

**Conclusion:** We demonstrate that the mechanisms of clonal proliferation in vivo do not activate HIV expression often enough to discern dramatic differences in the types of proviruses found in large clones due to viral cytotoxicity or CTL recognition. Our work suggests that CTL targeting of activated CD4+ T cells expressing HIV genes during long-term suppressive ART shapes the provirus landscape only subtly if at all. Our findings in elite controllers on ART indicate that the drivers of HIV persistence are similar in this population despite stronger, polyfunctional HIV-specific CTLs.

---

**366 IDENTICAL HIV PROVIRUSES ARISE FROM CELL EXPANSION AND INFECTION BY COMMON ANCESTOR**

**Sean Patro**, Aurelie Niyongabo, Shuang Guo, Jason W. Rausch, Michael J. Bale, Andrew Musick, Xiaolin Wu, Liliana Perez-Rodriguez, Wei Shao2, Eli A. Boritz, Steven G. Deeks, Frank Malardelli, Stephen H. Hughes, John M. Coffin, Mary F. Kearney

**1National Cancer Institute, Frederick, MD, USA, 2Leidos Biomedical Research, Inc, Frederick, MD, USA, 3ENAID, Bethesda, MD, USA, 4University of California San Francisco, San Francisco, CA, USA, 5Tufts University, Boston, MA, USA

**Background:** Understanding the mechanisms of HIV-1 persistence during ART is crucial for developing curative strategies. Identical proviral sequences that are observed during ART can result from the proliferation of single infected cells or from genetic bottlenecks leading to viral clones that can spread prior to ART initiation. To investigate the origins of identical proviruses in individuals on ART, we sequenced near-full-length proviruses and determined their sites of integration.

**Methods:** PBMC was obtained from 5 donors on ART and analyzed by Multiple-Displacement Amplification (MDA) Single-Genome Sequencing in which DNA is diluted to a proviral endpoint, subjected to whole genome amplification, and used for both integration site analysis and full-length proviral sequencing. 15 sets of identical sub-genomic sequences (12 in P6-PR-RT, 3 in env) were examined to determine if identical proviruses also had identical integration sites (cell clones), identical proviruses had different integration sites (viral clones), or identical proviruses resulted from some with identical integration sites and some with different sites (both cell and viral clones).

**Results:** Of the 12 sets of identical P6-PR-RT sequences, 3 contained only identical integration sites (4, 2, and 2 MDA wells), 7 contained integration sites observed only once (2-5 MDA wells per set), and 2 contained a combination of identical (19 and 13 MDA wells) and singly-observed integration sites (4 and 2 MDA wells). From the 3 sets of identical env populations, one had integration sites observed only once (7 different sites) and 2 contained a combination of identical (3 and 28 MDA wells) and singly-observed integration sites (1 and 3 MDA wells). Two of the cell clones contained replication-competent proviruses, confirmed by VOA. Within the populations of defective proviruses, near-full length sequence analyses showed that sequences identical in sub-genomic regions were often identical throughout the genome, except for non-overlapping deletions, making it possible to reconstruct the sequence of the shared viral ancestor.

**Conclusion:** The finding that identical proviruses can have different integration sites demonstrates that sub-genomic SGS is not sufficient to identify clones of infected cells and suggests that multiple infected cell clones can be established from the same viral ancestor. Such viral clones can arise from the transmission bottleneck, escape from immune pressure, or selection for drug resistant virus.
367 HIGH-THROUGHPUT SEQUENCING OF INTEGRATED HIV-1 REVEALS NOVEL PROVIRAL STRUCTURES

Kevin W. Joseph1, Elias K. Halvás2, Leah D. Brandt2, Sean Patro3, Jason W. Rausch4, Mary F. Kearney2, John M. Coffin2 and John W. Mellors1

1University of Pittsburgh, Pittsburgh, PA, USA, 2National Cancer Institute, Frederick, MD, USA, 3National Institutes of Health, Bethesda, MD, USA, 4Tufts University, Boston, MA, USA

Background: Efforts to cure HIV-1 infection will require a better understanding of the HIV-1 reservoir but characterizing individual integrated proviruses has remained difficult because of technical challenges related to the rarity of proviruses in CD4+ T-cells. Current approaches for sequencing integration sites using NGS are inefficient (most reads are off-target reads) and restricted read lengths can make it difficult to definitively identify both integration sites and proviral sequences.

Methods: We have developed a novel approach that sequences single HIV proviruses and their 5’ host integration sites by: i) amplifying the whole cellular genome at a proviral end point through multiple displacement amplification; ii) performing long-range PCR that amplifies variable and near-full length proviruses; and iii) performing nullomer-mediated PCR using a linker consisting of nullomer motifs absent in target genomes that markedly enhances specificity for integrated proviral targets. Amplicons can be sequenced by dideoxy (e.g., Sanger) and/or NGS methods.

Results: Amplicons sequenced by NGS utilized >90% of reads on average during consensus generation for both proviral and integration site amplicons. The workflow sequences all but 69 bp of the 3’ LTR of the provirus. Across 5 donors, an average of 78% of HIV-positive MDA reactions yielded the 5’ host-virus junction containing 400-297 bp of flanking host sequence (compared to about 5 nucleotides by standard integrations site analyses) and 13.4% of proviruses were near-full length (determined by sequencing, N=33 out of 247 total proviruses). To date, the assay has been used to characterize a broad set of proviruses in CD4+ T-cell clones from donors on suppressive ART including replication-competent proviruses amplified directly from blood mononuclear cells from donors on suppressive ART; ii) performing long-range PCR that amplifies variable and near-full length proviruses; and iii) performing nullomer-mediated PCR using a linker consisting of nullomer motifs absent in target genomes that markedly enhances specificity for integrated proviral targets. Amplicons can be sequenced by dideoxy (e.g., Sanger) and/or NGS methods.

Conclusion: This novel integrated proviral sequencing assay provides an efficient and high-throughput means of characterizing HIV-1 proviruses that need to be targeted to achieve a cure of HIV-1 infection.

368 CELL PROLIFERATION CONTRIBUTES TO THE INCREASE OF GENETICALLY INTACT HIV OVER TIME

Bethany A. Horsburgh1, Bonnie Hiener2, Katie Fisher3, John-Sebastian Eden2, Eunook Lee4, Susanne von Stockenstrom1, Lina Odevall1, Jeffrey M. Milush5, Teri Liegler3, Rebecca Hoh3, Rémi Fromentin4, Nicolas Chomont4, Steven G. Deeks2, Frederick M. Hecht4, Sarah Palmer6

1The Westmead Institute for Medical Research, Westmead, NSW, Australia, 2Karolinska Institute, Stockholm, Sweden, 3University of California San Francisco, San Francisco, CA, USA, 4Centre de Recherche du CHUM, Montreal, QC, Canada

Background: Effective HIV eradication strategies require an understanding of the mechanisms maintaining persistent HIV during therapy. We examined the role of memory cell proliferation in maintaining genetically-intact proviruses over 4 years of effective therapy.

Methods: Naïve (N), central (CM), transitional (TM) and effector (EM) memory CD4+ T-cells were sorted from the peripheral blood of two participants on long-term ART. Additional sequences from naïve, CM HLA-DR+/DR-, TM HLA-DR+/DR- and EM HLA-DR+/DR- T-cells were obtained 4 years later. Full-length individual proviral sequencing was used to characterise proviruses as intact or defective. Clusters of ≥2 100% genetically identical proviral sequences - indicative of host cell proliferation - were identified.

Results: A total of 287 and 448 sequences were isolated from the first and second time-points, and 34 (12%) and 90 (20%) were considered intact. At both times the frequency of intact genomes differed between cell subsets, EM>TM>CM/N. In each subset, HLA-DR+ cells contained more intact proviruses than HLA-DR- cells. The proportion of intact sequences was significantly higher in intact proviruses compared to defective at the second time point (85% vs 41%, p<0.03), but not the first. There was a significant correlation at the second time point between the proportion of identical sequences overall and the proportion of intact proviruses (R2=0.58-67, p=0.02-0.04). The majority (44/51, 86%) of sequences observed at both time-points were found in cells of the same memory phenotype. The number and size of identical sequence clusters differed depending on activation status. A greater number of identical sequence clusters were derived from HLA-DR+ cells. However, the size of clusters derived from cells of mixed activation status was larger, with 60% of all identical sequences derived from a cluster of both HLA-DR+ and HLA-DR- cells.

Conclusion: Genetically intact proviruses were found most frequently in the more differentiated EM cells. However, the frequency of intact proviruses was increased in each memory cell subset when the cell expressed HLA-DR, highlighting the role of cellular activation in maintaining the reservoir. Moreover, the correlation between cellular proliferation and intact proviruses highlights the importance of host cell proliferation in maintaining HIV over time. These findings demonstrate the importance of limiting cellular activation, differentiation and proliferation in strategies aimed at reducing the reservoir.

369LB WITHDRAWN

370LB ANTIGEN RESPONSIVE CLONES OF CD4+ T CELLS CONTRIBUTE TO THE INTACT LATENT RESERVOIR

Pilar Mendoza1, Julia Jackson2, Thiago Oliveira1, Christian Gaebler1, Victor Ramos1, Mila Jankovic1, Marina Caskey1, Michel Nussenzweig3, Lillian B. Cohn4

1The Rockefeller University, New York, NY, USA, 2Chan Zuckerberg Biohub, San Francisco, CA, USA

Background: Antiretroviral therapy suppresses but does not cure HIV-1 infection due to the existence of a long-lived reservoir of latently infected cells. The long half-life appears to partially result from expansion and contraction of infected CD4+ T cell clones over time. However, the mechanisms that govern this process in vivo are poorly understood.

Methods: To test the hypothesis that expanded clones harboring latent proviruses respond to foreign antigens, we exposed CD4+ T-cells from ART suppressed individuals to overlapping peptide pools from either a negative control protein, HIV-gag or CMV-pp65. Following overnight culture, activated CD4+ T-cells were sorted by cell sorting based on expression of HLA-DR, highlighting the role of cellular activation in maintaining the reservoir. Moreover, the correlation between cellular proliferation and intact proviruses highlights the importance of host cell proliferation in maintaining HIV over time. These findings demonstrate the importance of limiting cellular activation, differentiation and proliferation in strategies aimed at reducing the reservoir.

Table 1.

<table>
<thead>
<tr>
<th>Category</th>
<th>Seq of Identical PIC/DEL Sequences</th>
<th>Seq of Identical Provirus Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. All integration sites obtained were identical</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>B. All integration sites obtained were different</td>
<td>2 (4-atom consensus in each cluster)</td>
<td>1</td>
</tr>
<tr>
<td>C. Combination of identical and different integration sites were observed</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Assuming identity validated using gene-specific integration site PCR with one unique primer. (MA)
Results: The overall frequency of intact and defective proviruses contained within antigen responsive (AIM+) cells varied among individuals. We analyzed all HIV-1 sequences across all groups and identified clones of viral sequences in all participants. Seven of 8 donors harbored intact or defective clones of proviral sequences in antigen responsive cells. The clonal distribution of HIV-1 sequences found in AIM+ cells was significantly different from the negative control in 4 of 6 individuals for whom we obtained sufficient data. Intact sequences from AIM+ cells were identical to replication competent viruses sequenced during outbreak in 2 of 5 donors assayed.

Conclusion: We show that both intact and defective HIV-1 proviruses can persist in clones of CD4+ T cells that respond to CMV and HIV antigens. The data suggests that infected clones of CD4+ T cells may respond to diverse pathogens in HIV-1 infected individuals. Their intermittent exposure to these and other antigens found in the virome and microbe may account for the reported waxing and waning of individual clones of latently infected cells and their persistence over time.

371 SINGLE-CELL ANALYSIS OF IN VIVO HIV RESERVOIR UNCOVERS NOVEL MARKERS OF LATENT CELLS

Jason Neidleman¹, Xiaoyu Luo², Julie Frouard², Feng Hsiao², Grace Xie², Vincent Morcilla³, Katherine Sholtis³, Rebecca Hohl³, Ma Somsouk³, Peter W. Hunt³, Steven G. Deeks³, Nance Archin⁴, Sarah Palmer⁴, Warren C. Greene⁴, Nadia R. Roan⁴
¹University of California San Francisco, San Francisco, CA, USA, ²Gladstone Institutes, San Francisco, CA, USA, ³University of Sydney, Westmead, NSW, Australia, ⁴University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Direct phenotypic analysis of the in vivo latent HIV reservoir is complicated by the need to reactivate these cells ex vivo to identify them, which changes the phenotypes of the latent cells. We used CyTOF to quantitate the levels of 43 different proteins on reactivated cells from ART-suppressed, HIV-infected individuals, and implemented a bioinformatics approach to trace these reactivated cell to its original latent state.

Methods: PBMCs (n=7), rectosigmoid biopsies (n=7), and lymph node aspirates (n=2) from treated individuals were phenotype by CyTOF immediately after cell isolation, or stimulated with PMA/ionomycin or LRsAs and then phenotyped. Reactivated cells were traced back to their original pre-stimulation state using the bioinformatics approach PP-SLIDE (Cavrois et al, Cell Reports 2017). Markers identified as preferentially expressed on latent cells were validated by sorting the cells and then conducting viral outgrowth assays and proviral sequencing.

Results: Latent cells were non-randomly distributed amongst memory CD4+ T cells. Markers preferentially expressed on latent cells included those that were shared between donors (PD1, CCR5, CD2, CD49d, Ox40) and donor-specific ones (CXCR5, TIGIT, CCR6, CD28, CD7). Markers differentially expressed between latent cells in blood vs. tissues, and between latent cells reactivatable by different stimulation methods, were identified. Analysis of longitudinal samples suggested the phenotype of latent cells is stable over time. Multiparameter sorting revealed that donor-shared surface markers identified by CyTOF markedly enriched for latent cells with replication-competent HIV. TH1, already highly enriched for replication-competent HIV, was further enriched by 3 orders of magnitude using such markers. Viral sequence analysis revealed the enriched cells to be largely clonally expanded.

Conclusion: We have validated CyTOF phenotyping of reactivated latent cells paired with bioinformatics analysis by PP-SLIDE as an effective way to chart the in vivo blood and tissue HIV latent reservoir. Our results demonstrate that 1) latent cells are not randomly distributed amongst memory CD4+ T cells, 2) the phenotypes of latent cells are stable over time, 3) LRsA can target different latent cells than PMA/ionomycin, 4) there are shared as well as donor-specific surface markers of latent cells, and 5) sorting of cells based on surface markers identified by CyTOF markedly enriches for clonally-expanded latent cells with replication-competent HIV.

372 INTACT HIV GENOMES ARE ENRICHED IN MEMORY T CELLS WITH SHORT HALF-LIVES

Vincent Morcilla¹, Charlene Bacchus-Souffran², Katie Fisher¹, Xiao Qian Wang³, Bethany A. Horshburg⁴, Timothy E. Schubl⁵, Mark Fitch⁵, Rebecca Hohl⁵, Frederick M. Hecht⁶, Jeffrey Martin⁶, Steven G. Deeks³, Marc Hellerstein¹, Joseph M. McCune³, Peter W. Hunt³, Sarah Palmer¹
¹The Westmead Institute for Medical Research, Westmead, NSW, Australia, ²University of California San Francisco, San Francisco, CA, USA, ³University of California Berkeley, Berkeley, CA, USA

Background: Future HIV curative therapies require a thorough understanding of the distribution of genetically intact HIV within T cell subsets during short-term antiretroviral therapy (ART) and the cellular mechanisms which maintain this reservoir. Therefore, we genetically characterized HIV genomes within T cell subsets from participants on <4 years of therapy.

Methods: Seven participants were treated for <4 years either within 5 months (early, n=4) or after 7 months (late, n=3) of HIV infection. Near-full-length proviral sequences were obtained from naïve (NV), stem-cell memory (SCM), central memory (CM), transitional memory (TM), effector memory (EM), and terminally differentiated (TD) CD4+ T cells. Clusters of ≥2 proviral sequences which were 100% genetically identical and indicative of host cell proliferation were identified. Cellular half-lives were measured by in vivo incorporation of deuterium into genomic DNA within these cell subsets.

Results: A total of 893 sequences were isolated; 585 and 308 from the early and late ART participants respectively. From these 893 sequences, 57 were considered intact (6.4%); 13 and 44 respectively from the early and late ART groups. The proportion of intact sequences across the T cell subsets was different (p=0.03). In the late ART group, the intact sequences were concentrated in cells with shorter half-lives such as TM (6/10 TM cells; median half-life: 95 days) and EM cells (25/10 EM cells; median half-life: 82 days) compared to other subsets with longer half-lives (median half-lives: 162-1107 days for NV, SCM, CM, and TD cells). For the early and late ART groups, a correlation was found where cells with shorter half-lives contained more intact proviruses (p=0.03). For the early ART participants, the clusters of identical sequences were less frequent when compared to the late ART participants (p=0.006). However, the levels of identical sequences contributing to a cluster were highest within EM and TD in all participants (p<0.001).

Conclusion: The distribution of HIV genomes across T cell subsets during short-term therapy after both early and late ART suggests that a short cellular half-life could be a predictor of a higher frequency of intact proviruses. Both TD and EM cell subsets were marked by clusters of identical HIV genomes reflecting cellular proliferation. This indicates that specific cellular mechanisms such as a short half-life and greater proliferative potential, characteristics of EM T cells, contribute to the maintenance of intact HIV.

373 “FALSE ART FAILURE” FROM IDENTICAL HYPERMUTATED HIV NUCLEIC ACID IN PLASMA

Johannes C. Botha¹, Kim Steegen¹, Lucia Hans¹, Alan Karstaedt¹, Sergio Carmona¹, Denasha Reddy¹, Mary F. Kearney¹, John W. Mellors¹, Gert U. van Zyl¹
¹Stellenbosch University, Tygerberg, South Africa, ²National Health Laboratory Service, Johannesburg, South Africa, ³University of the Witwatersrand, Johannesburg, South Africa, ⁴Chris Hani Baragwanath Hospital, Johannesburg, South Africa, ⁵National Cancer Institute, Frederick, MD, USA, ⁶University of Pittsburgh, Pittsburgh, PA, USA

Background: Plasma HIV-1 RNA above the limit of detection of commercial assays on ART arise from incomplete cycles of viral replication as a consequence of inadequate drug exposure and/or drug resistance; or from illogically produced from proviruses in clonally-expanded cells without complete cycles of replication. Most proviruses that persist on ART are defective, including those hypermutated by APOBEC. Although hypermutated proviruses can be transcribed into mRNA and even spliced, their packaging into virus is expected to be very inefficient. Here we report the first instance of false virologic failure on ART arising from cells with hypermutated proviruses.

Methods: A 46 year old female presented with detectable HIV on ART ranging from 439 to 4230 copies/mL. Single genome sequencing (SGS) analysis (p6-Pro-RT) of 4 longitudinal plasma samples obtained over 13 months was performed. To characterize the source of viremia, fractions of plasma after low-(2700 g) and high-speed centrifugation (17 200 g) and cell-associated HIV mRNA (Figure). The only non-hypermutated sequences were from the high-speed plasma pellet (4 of 4) and PBMC HIV DNA sequencing of proviral DNA.

Results: SGS (p6-Pro-RT) revealed multiple, identical hypermutated sequences in all low- and one high-speed plasma pellet(s), and in PBMC HIV DNA (p6-Pro-RT and NFL) and cell-associated HIV mRNA (Figure). The only non-hypermutated sequences were from the high-speed plasma pellet (4 of 4) and PBMC HIV DNA (1 of 10) at the 13 month time point. Sequencing of gag revealed a stop codon at 128 (1 of 10) at the 13 month time point. Sequencing of gag revealed a stop codon at 128 (1 of 10) at the 13 month time point. Sequencing of gag revealed a stop codon at 128 (1 of 10) at the 13 month time point. Sequencing of gag revealed a stop codon at 128 (1 of 10) at the 13 month time point. Sequencing of gag revealed a stop codon at 128 (1 of 10) at the 13 month time point.
large population of cells with identical hypermutated proviruses, i.e. an infected CD4+ T-cell clone that is undergoing cytolysis and release of cellular nucleic acid including HIV DNA and mRNA into plasma. Production of viral proteins and packaging of viral genomes is a highly unlikely source given the hypermutated genome with at least one stop codon in gag-p24. Release of cellular nucleic acids into plasma may be an underappreciated cause of false virologic failure.

374 ART-TREATED SUBJECTS WITH LOW VIRAL RESERVOIR SHOW UNUSUAL HIV LATENCY DISTRIBUTION

Cristina Gálvez1, Victor Urrea1, Susana Benet1, Lucia Bailon2, Andrea Martinez2, Beatriz Mathe1, Judith Dalmaz1, Lorna Leal1, Feliche Garcia1, Javier Martinez-Picado1, Maria Salgado1

1IrsiCaixa Institute for AIDS Research, Badalona, Spain, 2Fundació Lluita Contra la Sida, Badalona, Spain, 3Hospital Clinic of Barcelona, Barcelona, Spain

Background: Small-size viral reservoirs are predominantly found in HIV-1 controllers and individuals treated during acute/early HIV-1 infection. However, other HIV+ subjects could naturally also harbor low viral reservoirs. We have longitudinally measured in cryopreserved CD4+ T cells by ddPCR, including small-size reservoirs in 12 LoViReTs with infectious T cells as well as total HIV-DNA in LoViReTs and controls.

Methods: ddPCR of total HIV-DNA and infectious LoViReTs were recruited as controls.

Results: In 12 LoViReTs, total HIV-DNA was longitudinally measured in cryopreserved CD4+ T cells by ddPCR, including a pre-ART time point. 14 LoViReTs underwent a leukapheresis to measure the replication-competent virus by qVOA (37×10^6 CD4+ T cells), and total HIV-DNA in sorted CD4+ T cell subsets. In 9 LoViReTs with <0.1 infectious units per million (IUPM), total HIV-DNA was measured in rectal and/or lymph node biopsies (LN). Clinically matched individuals with HIV-DNA >50 HIV-DNA copies/10^6 PBMCs were recruited as controls.

Results: LoViReTs harbored significantly lower total HIV-DNA in CD4+ T cells before ART initiation compared to controls (1,051 and 5,995 HIV-DNA copies/10^6 CD4+ T cells respectively, p=0.002) despite comparable pre-ART viral load. These differences became higher after 5 years on ART (16 vs 5-folds decay respectively, p=0.001). 10/14 LoViReTs had undetectable replication-competent virus (IUPM<0.0185) >10 years after ART. Among them, we detected low levels of HIV-DNA in rectum in 6/8 subjects with a median of 57 HIV-DNA copies/10^6 CD4+ T cells (IQR:7-114). In LN, only 3/8 subjects had detectable reservoir (263×10^3-2,112 HIV-DNA copies/10^6 CD4+ T cells). Unexpected HIV reservoir distribution was observed in LoViReTs, being the short-live transitional memory (T TM) and effector memory (TEM) T cells the major contributors to the total reservoir (47% and 29% respectively). TCM presented limited contribution to the HIV reservoir (24%).

Conclusion: LoViReTs individuals have abnormally low HIV reservoirs before ART initiation. 71% of LoViReTs did not have replication-competent virus and harbored limited provirus in tissue sanctuaries after a median of 15 years on ART. A cause of this exceptional low reservoir could be the high contribution of the short-live T TM and TEM cells in the total HIV reservoir. This unique group of individuals are of great interest as trial participants in eradication studies.

375 A NEW LONG-READ NGS METHOD TO SEQUENCE HIV1 INSERTION SITES AND ASSOCIATED PROVIRUSES

Maria Artesi1, Vincent Hahaut1, Basel Cole1, Laurens Lambrechts1, Ambrose Marcais2, Olivier Hermine2, Philip Griebel5, Natasa Arsic5, Dominique Bron6, Carole Charlier5, Linos Vandenkerckhove5, Michel Georges5, Anne Van den Broeke4, Keith Durkin1

1GIGA German Institute of Global and Area Studies, Liege, Belgium, 2University of Liege, Liege, Belgium, 3HIV Cure Research Center, Ghent University, Ghent, Belgium, 4Hopital Necker Enfants Malades, Paris, France, 5University of Saskatchewan, Saskatoon, Canada, 6Institut Jules Bordet, Brussels, Belgium

Background: The HIV-1 reservoir represents a major obstacle to HIV cure, making its exploration a priority, however, this task is complicated by its elusiveness, with only ~0.1% of CD4 T cells carrying integrated HIV-1 DNA. Substantial effort has been expended to determine the patterns of proviral integration in this latent reservoir and simultaneously identify the sequence of the associated HIV-1 proviruses. Recent approaches based on short-read high throughput sequencing allow the sequence of individual proviruses to be linked to the integration site, however, these methods rely on whole genome amplification of isolated HIV-1 genomes, with separate reactions to identify the integration site and sequence the provirus, limiting the number of proviruses one can reasonably interrogate.

Methods: To exploit the potential of long reads we developed Pooled CRISPR Inverse PCR sequencing (PCIP-seq), a method that leverages selective cleavage of circularized DNA fragments carrying HIV-1 proviral DNA with a pool of CRISPR guide RNAs, followed by inverse long-range PCR and multiplexed sequencing on the Oxford Nanopore MinION platform.

Results: We first tested PCIP-seq on 0.1 and 0.01% dilutions of the HIV-1 cell line U1 and demonstrated its utility to examine low proviral loads. We then applied PCIP-seq to CD4 T cells of two HIV-1 patients on long term cART, generating the sequence from hundreds of HIV-1 proviruses and linked this sequence to specific integration sites. We identified proviruses with single nucleotide variants and large deletions as well as intact proviruses. Among these, we found proviruses present in clonally expanded cells mapping to segmentally duplicated regions and satellite repeats of the centromeres of chr13, 14, 21 and 22. Both patients had four integration sites in intron 1 of STAT5B, all in the same transcriptional orientation as the host gene. In addition to HIV-1 we also successfully applied the technique to oncogenic retroviruses HTLV-1 and BLV.

Conclusion: Using long reads, we can simultaneously identify the integration site and track clone abundance while also sequencing the HIV-1 provirus inserted at that position. Methods currently used are labor intensive, costly, and only examine a handful of patients. Using PCIP-seq it is feasible to sequence thousands of bases from hundreds of proviruses in a single experiment, opening the landscape of proviral variation and evolution within, and between large numbers of hosts.

376 COMBINED ASSAYS SHED NEW LIGHT ON HIV-1 PROVIRAL SEQUENCE AND LINKED INTEGRATION SITE

Basel Cole1, Laurens Lambrechts1, Maria Artesi2, Vincent Hahaut1, Wojciech Witkowski1, Ysé Noppe3, Annemieke Dhondt4, Keith Durkin1, Anne Van Den Broeke5, Linos Vandenkerckhove1

1HIV Cure Research Center, Ghent University, Ghent, Belgium, 2GIGA German Institute of Global and Area Studies, Liege, Belgium, 3Université Libre de Bruxelles, Brussels, Belgium, 4Ghent University Hospital, Ghent, Belgium, 5University of Liège, Liège, Belgium

Background: HIV-1 infection remains incurable due to the establishment of a persistent viral reservoir, capable of rebounding upon treatment interruption. Evidence has shown that only a small proportion of this reservoir contains intact proviruses, and these are maintained, at least in part, by clonal expansion. We have generated integration site (IS) data down to single cell level on patients

...
on cART using different approaches, comparing strengths/weaknesses and complementarity of the methods.

**Methods:** Two patients (PT1, PT2) underwent leukapheresis and CD4+ T cells were isolated. DNA was extracted and IS were sequenced using integration Site Loop Amplification (ISLA). DNA from the same extract was analyzed using Pooled CRISPR Inverse PCR sequencing (PCIP-seq), a new long-read NGS method, to generate both IS and adjacent proviral genomes. CD4+ T cells were stimulated, stained for two epitopes of p24, and double positive cells were single-cell sorted. After DNA amplification, near full-length (NFL) proviral genomes and corresponding IS were sequenced. Subsequently, all data were subjected to an in-depth comparison.

**Results:** Using ISLA, we recovered 144 IS for PT1, and 201 IS for PT2. The former displays a limited degree of clonality (7%, 4 clones) while the latter is highly clonal (75%, 13 clones). PCIP yielded 80 IS for PT1 and 161 IS for PT2. Comparison showed that most clonal IS were detected by both ISLA and PCIP, validating the results of PCIP. Moreover, NFL genomes from 4 clones were identified by PCIP in PT2. One of them contained a 115 bp deletion, disrupting the packaging signal. The second one is located in the MLT3 gene, which protein product has been shown to interact with HIV-1 Tat. Importantly, both of these clones were detected using the p24 stimulation assay while the other two, integrated within centromeric regions, were not detected with the assay.

**Conclusion:** Comparing PCIP to ISLA, we show that PCIP is a potent method to retrieve both IS and linked proviral genome. Next to that, we show that while the stimulation assay biases towards proviruses that are translationally competent, it does not bias towards replication competent ones. The fact that the stimulation assay does not reveal intact proviruses in centromeric regions hints to deep latency and the inability of the assay to reactivate these. We conclude that the PCIP yields the most comprehensive overview of proviruses and their associated IS, while the stimulation assay adds functional data on translational competency.

**377 ULTRADEEP ANALYSIS OF PRETHERAPY HIV PREDICTS GENETICALLY COMPLEX RESERVOIRS**

**Kristi Huij1, Junko Hattori1, Valerie F. Bolzt2, Jason W. Rausch3, Wei Shao2, Mary F. Kearney1, John M. Coffin3, Frank Maldarelli1**

**Background:** Measuring the genetic characteristics of HIV populations is essential to understanding the formation of HIV reservoirs that persist during antiretroviral therapy (ART). Analysis of plasma HIV using new next generation sequencing (NGS) approaches using primer ID (ultrasensitive single genome sequencing [uSSG]) and advanced bioinformatic analyses (Boltz et al 2016), yields large HIV sequence datasets with the same, low PCR error and genome sequencing (uSGS) and advanced bioinformatic analyses (Boltz et al 2016), yields large HIV sequence datasets with the same, low PCR error and recombination rate as standard SGS. We used uSSG to determine population parameters (replicating population size, in vivo recombination rate). We also extended the uSSG approach to characterize cell associated (CA) HIV RNA and DNA derived from peripheral blood lymphocytes (PBLs).

**Methods:** Plasma samples were obtained from chronically infected ART naive individuals (N=6) enrolled in HIV studies at the NIH in 2000-2002. uSSG of HIV RT [HXB2ntm 2704-2943 and 3046-3253] using primer ID and the Illumina NGS yielded 400 nt sequences. Replicating population sizes were estimated as previously described (Maldarelli et al 2013) and linkage disequilibrium was calculated using DNASP; recombination rate was calculated directly by measuring the rate at which linked alleles become unlinked. To obtain uSSG sequences from PBL, DNA was sheared (avg 10 kb), and subjected to a linear PCR step to add primer IDs before the uSSG procedure.

**Results:** Longitudinal plasma samples were obtained from chronically infected ART naive individuals (median CD4=498/µl, viral RNA=4.3 log, cps/ml) uSSG from plasma derived HIV resulted in total of 17,172 (median 1,252/patient, range 54-3,165) sequences from 6 subjects from 2 time points. Maximum replicating population sizes exceeded 10^7/person. Viral populations were highly polymorphic, but nearly all polymorphisms were in linkage equilibrium. With a single exception, all linked loci (3-12/patient) became unlinked over short periods (30-413 generations). The measured recombination rate (range 0.004-0.07) is similar to previous estimates (Batorovsky et al 2011) indicating that virtually all sequences were the product of recent recombination events. Analysis of CA HIV from PBL of one patient revealed HIV was readily recovered with 742 DNA sequences, and 946 RNA sequences.

**Conclusion:** Prior to ART, HIV populations are large (>10^4-10^10/person) and compose of variants that undergo frequent recombination. uSSG predicts that viruses rebounding from reservoirs are diverse and likely to have evidence of prior recombination events.

**378 HIV CONTROLLERS HAVE LOW FREQUENCIES OF INTACT PROVIRAL DNA**

**Abena Kwaai1, Caroline Garlisi1, Kristen D. Ritter1, Gregory Laird1, Joel Blankson2, Kristi Huik1, John M. Coffin3, Frank Maldarelli1**

**Background:** Elite controllers or suppressors (ES) are subjects who control viral replication without antiretroviral therapy. Studies using standard DNA PCR assays or the quantitative viral outgrowth assay (QVOA) have shown that these subjects have smaller viral reservoirs than chronic progressors (CP) on antiretroviral therapy (ART). However, standard DNA PCR assays measure both defective and replication-competent virus and the QVOA measures only a fraction of the replication-competent reservoir. The objective of this study was to better approximate the size of the latent reservoir in ES by measuring the frequency of CD4+ T cells that contained intact proviral DNA.

**Methods:** Total and intact proviral DNA was measured in unfraccionated CD4+ T cells from 9 CPs, 8 treatment naïve ES and 2 viemric controllers (VCs, VL < 1000 copies pre-treatment) on ART with the recently described intact proviral DNA assay (IPDA). CD4+ T cells from 5 ES and the 2 VCs on ART were also cultured in the standard QVOA.

**Results:** The median frequency of total provirus was 24.7 per million CD4+ T cells in the ES, 220.1 per million CD4+ T cells in the 2 VCs on ART and 75.6 per million CD4+ T cells in the CPs on ART. The median frequency of intact provirus was 1.2 per million CD4+ T cells in the ES, 2.83 per million CD4+ T cells in the 2 VCs on ART and 36.2 per million CD4+ T cells in the CPs on ART. While the absolute frequencies of total and intact proviral DNA per million CD4+ T cells were significantly lower in ES than in CP, there was no significant difference in the fraction of total proviral DNA that was found to be intact between these 2 subject groups. There was a positive correlation between the frequency of intact proviral DNA and the frequency of latently infected cells as measured by QVOA in the ES and VCs on ART.

**Conclusion:** We show that ES have a median frequency of both intact proviral DNA and total proviral DNA that are more than 1 log lower than the frequencies seen in CPs. These findings suggest that while the absolute frequency of persistent HIV is lower in ES as compared to CP, the relative composition of that pool of persistent proviruses may not differ significantly. Furthermore, this data has implications for HIV cure strategies as it demonstrates that while this small reservoir size may contribute to the control, it is not an absolute requirement as one ES had a higher frequency of intact proviral DNA than all of the CPs in our study.

**379 EARLY THERAPY OF YOUTH WITH ACUTE/RECENT HIV: EFFECT ON HIV DNA & ANTIBODY (ATN 147)**

**Ruth Cortado1, Tara Kerin2, Justine Ceballos3, Eduardo Saad4, Kate Mitchell5, Jasmine Fouquier6, Brenda Andrews7, Manuel Oravos8, Sue Ellen Abdallah9, Robert Bolar10, Rica Flynn10, Brittany Juhlmann10, Mary Jane Rotheram-Borus11, Karin Nielsen-Saines12, Yvonne Bryson13, Abena Kwaa14**

**Background:** Recent studies in adults indicate early potent antiretrovirals (ARV) in acute HIV infection may reduce viral reservoir size, and potentially result in better long-term viral control. There is limited data, however, on the large population of HIV-infected high-risk youth. We hypothesize that the decay of HIV reservoirs and accompanying immune responses are different in youth who have an active thymus and are treated early with potent ARV. As part of a clinical trial, ATN 147, which identified acutely or recently HIV-infected youth (12-24 years), we assessed HIV viral load by HIV RNA PCR, viral reservoirs by DNA ddPCR and HIV antibody at baseline and sequentially for 12-24 months.

**Methods:** ATN CARES enrolled 75 high risk youth in Los Angeles and New Orleans with newly diagnosed HIV infection; i.e., Fiebig 1-3, acute (34%), VL recent (66%). Samples were collected at baseline, 1 & 2 weeks, 1, 2, 4, 8, 12, 18 and 24 months for plasma HIV RNA <200cp/ml (UD), HIV DNA measured by ddPCR on PBMC with primers 5′/661F/2588X. HIV antibody by Western blot (BioRad) was done at baseline for Fiebig staging and 12, and 24 mos. post-treatment. Youth were considered complete responders (CR) if plasma HIV RNA
became undetectable and sustained at <200 copies/ml (UD), partial responders (PR) if HIV RNA became UD with minor blips and non-responder (NR) if HIV RNA never reached UD.

Results: 14 male MSM (mean age 21) reached > 12 mos. of follow-up to date. Eight were CR, 5 PR and 1 NR. Median HIV DNA ddPCR at baseline (N=14) was 457 (SD 852) and decreased to 186 (SD 304) copies/10^6 at 52 weeks (p=0.02). HIV DNA levels remained constant or increased in 3/14; 11 had a decrease and 1 of these had very low levels <4 cp/10^6 at 52 wks. HIV AB measured by Western blot showed a significant decrease in HIV bands resulting in a negative or indeterminate results in 6/14 (43%) at 12 months post ARV Two of these participants were Feibig stage 5 at entry. The median time to UD plasma HIV RNA was 14 wks. (range 3-34) in 13/14 participants. An example of biomarkers in a CR is shown in the figure.

Conclusion: Identification, recruitment, treatment and follow up of high risk U.S. youth with acute/recent HIV is feasible. Early ARV can reduce HIV DNA levels and HIV antibodies in a subset with persistent virus suppression. Youth with lower levels of HIV viral reservoirs are a key target for future evaluation of CURE/eradication strategies including therapeutic vaccination.

380 WIDE ANATOMIC DISTRIBUTION OF HIV-INFECTED CELLS IN INDIVIDUALS WITH COMORBID CANCER

Monica A. Gouzoulis1, Daria W. Wells2, James Q. Virga1, Camille M. Lange1, Kristi Hui1, Shawn Hill2, Stephen M. Hewitt1, Rob Gorelick1, Thomas S. Ulbrick1, Joseph A. Kovacs1, Robert Yarchao1, Xiaolin Wu1, Stephen H. Hughes2, Frank Maldarelli1, NIH, Frederick, MD, USA, 2Leidos Biomedical Research, Inc, Frederick, MD, USA, 3NIH, Bethesda, MD, USA, 4Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: HIV persistence during combination antiretroviral therapy (ART) is the principal challenge preventing viral eradication. We and others reported that HIV infected cells undergo clonal expansion during ART, and we reported that clones of infected cells are present in tissues and in a neoplasm. The tissue distribution of infected cells and their roles in HIV persistence are not well understood. To determine the distribution of clones of infected cells during ART, we analyzed tissues obtained from individuals who underwent autopsy after expiring with comorbid neoplasms.

Methods: Participants (N=2) underwent autopsy after therapy for primary expiring with comorbid neoplasms. We analyzed tissues obtained from the Los Alamos HIV Immunology Database. Integration sites of intact proviruses were analyzed by Matched Integration Site and Proviral Sequencing (MIP-Seq) assays.

Results: We obtained 199 and 89 near full-length intact proviral genomes from ECs and ART-treated individuals. A median of 47 optimal epitopes corresponding to expressed HLA Class I alleles were obtained from the Los Alamos HIV Immunology Database. Integration sites of intact proviruses were analyzed by Matched Integration Site and Proviral Sequencing (MIP-Seq) assays.

Conclusion: EC exhibit low frequencies of CTL escape-associated mutations in intact proviruses, despite the absence of antiretroviral therapy, and serve as a model for cure of HIV-1 infection. Cytotoxic T lymphocytes (CTL) are widely recognized as the immune correlate most closely associated with an elite controller phenotype, but the frequency of CTL-driven mutations in intact proviral sequences from such individuals is unknown.

381 LOW FREQUENCY OF CTL ESCAPE MUTATIONS IN INTACT PROVIRUSES FROM ELITE CONTROLLERS

Xiaodong Lian1, Chenyang Jiang2, Ce Gao3, Joshua Chevalier1, Ben S. Rhee1, Jane Blackmer1, Kevin Einkauf1, Xiaoming Sun1, Mary Carrington1, Bruce D. Walker1, Mathias Lichterfeld3, Xu G. Yu4

1Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, 2National Cancer Institute, Frederick, MD, USA, 3Bigham and Women's Hospital, Boston, MA, USA

Background: Elite controllers (ECs), maintain undetectable plasma virus levels in the absence of antiretroviral therapy, and serve as a model for cure of HIV-1 infection. Cytotoxic T lymphocytes (CTL) are widely recognized as the immune correlate most closely associated with an elite controller phenotype, but the frequency of CTL-driven mutations in intact proviral sequences from such individuals is unknown.

Methods: Single-genome near full-length proviral sequencing was used to analyze the proviral reservoir in 49 untreated ECs with undetectable viral loads for 1-20 years and in 28 HIV-1 patients treated with ART for 2-19 years. Optimal epitopes and escape mutations associated each person's HLA-A, -B, and -C alleles were obtained from the Los Alamos HIV Immunology Database. Integration sites of intact proviruses were analyzed by Matched Integration Site and Proviral Sequencing (MIP-Seq) assays.

Results: We obtained 199 and 89 near full-length intact proviral genomes from ECs and ART-treated individuals. A median of 47 optimal epitopes corresponding to expressed HLA Class I alleles were analyzed in ECs, compared to 49 in ART-treated individuals. Frequencies of defined CTL escape mutations, compared to the intact proviral consensus sequence were higher in ECs relative to ART-treated patients (47.4% vs 37.9%, p=0.0005). Moreover, the proportion of CTL epitopes displaying known escape mutations was lower in ECs than in ART-treated individuals but did not reach statistical significance (5.67% vs 7.32%, p=0.2818). Among individuals carrying the protective HLA B*27 and B*57 alleles, optimal epitopes from EC were more likely to show wild-type sequences (43.5% vs 30.4%, p=0.0013), and less likely to encompass previously defined CTL escape mutations (5.84% vs 17.4%, p=0.0043). Notably, among ECs, intact proviral sequences integrated in centromeric satellite DNA and non-genic DNA tended to exhibit lower frequencies of defined CTL escape mutations, compared to the intact proviral sequences integrated in non-centromeric DNA (p=0.0245) or genic regions (p=0.0254).

Conclusion: EC exhibit low frequencies of CTL escape-associated mutations in intact proviruses, despite the absence of antiretroviral therapy, suggesting either lack of viral replication or effective targeting of mutational intolerant epitopes. The low proportion of CTL escape mutations in intact proviruses integrated in non-genic/centromeric DNA suggests that these sequences were seeded during early disease stages and are among the most ancestral proviruses in a given patient.

382 TH2 CYTOKINES ARE ASSOCIATED WITH HIGHER LEVELS OF INTACT PROVIRUSES ON ART

Joshua C. Cyktor1, Hanna Mar2, Gregory Laird1, Ronald Bosch2, Albine Martin2, Joseph J. Eron1, Bernard J. Macatangay4, Deborah McMahon4, Rajesh T. Gardner1, John W. Mellors1

1University of Pittsburgh, Pittsburgh, PA, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3Accelev Diagnostics, Baltimore, MD, USA, 4University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: TH2 cytokines, such as interleukin (IL)-4 and IL-13, regulate humoral immunity, promote production of neutralizing antibodies, and can suppress Th1 and Th17 responses by upregulating repressors of interferon...
HIV-1 ENVELOPES FROM PERSISTENT VIREMIA ON ART SHOW REDUCED proviruses is undefined, these findings suggest that the dampening effect of the relationship between immune responses and the HIV-1 reservoir. While residual viremia, which likely arises from cells with intact proviruses. This work higher frequencies of cells containing intact proviral HIV-1 DNA but not total DNA (r=0.14, p=0.18) or CA-RNA (r=0.16, p=0.14). IL-1RA, and cell-associated RNA (CA-RNA) from PBMC, intact proviral DNA (IPDA) from methods of plasma HIV-1 RNA by single copy assay (SCA), total HIV-1 DNA and cell-associated RNA (CA-RNA) from PBMC, intact proviral DNA (IPDA) from CD4+ T cells, and plasma levels of IL-1RA, IL-4, IL-10, IL-11, IL-22, and TGFβ. Exploratory cross-sectional analyses assessed the relationship between these cytokines and measures of HIV-1 persistence.

Results: 98 participants (21 females) were evaluated with a median (IQR) age of 46 years (37, 53) and 6.7 (4, 8) years on suppressive ART. Plasma levels of IL-4 were associated with the levels of intact proviral DNA (r=0.26, p=0.07) (Table 1). There was also a trend towards an association of IL-4 levels with SCA HIV-1 RNA (r=0.2, p=0.06) but not total HIV-1 DNA (r=0.14, p=0.18) or CA-RNA (r=0.16, p=0.14). IL-1RA, IL-10, IL-11, IL-22, and TGFβ were not significantly associated with plasma SCA (N=95), total HIV-1 DNA (N=95), CA-RNA (N=90), or IPDA (N=48).

Conclusion: The levels of Th2 cytokines IL-4 and IL-13 are associated with higher frequencies of cells containing intact proviral HIV-1 DNA but not total HIV-1 DNA, whereas other cytokines including IL-10 were not associated with intact or total HIV-1 DNA. There was a weaker association of IL-4 with residual viremia, which likely arises from cells with intact proviruses. This work demonstrates the value of measuring intact proviral HIV-1 DNA when evaluating the relationship between immune responses and the HIV-1 reservoir. While the mechanistic link between IL-4 and IL-13 levels and cells carrying intact proviruses is undefined, these findings suggest that the dampening effect of Th2 cytokines on Th1 and Th17 responses could promote persistence of the HIV-1 reservoir.

| Associations between measures of HIV-1 persistence and Th2 or anti-inflammatory cytokines |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|  | Total HIV-1 DNA | CA-RNA | Plasma SCA | IPDA |
|  | n=95 | n=90 | n=95 | n=48 |
| **IL-4** | 0.14  | 0.15  | 0.14  | 0.10  |
| **IL-10** | 0.04  | 0.07  | 0.04  | 0.03  |
| **IL-11** | 0.14  | 0.17  | 0.15  | 0.16  |
| **IL-13** | 0.05  | 0.15  | 0.14  | 0.16  |
| **IL-1RA** | 0.09  | 0.06  | 0.07  | 0.02  |
| **CCL-22** | 0.04  | 0.07  | 0.02  | 0.09  |
| **TGFβ** | 0.16  | 0.19  | 0.11  | 0.29  |

Table 1 shows Spearman associations (r) of total HIV-1 DNA, cell-associated HIV-1 RNA, plasma HIV-1 RNA by single copy assay, and intact proviral DNA with plasma levels of cytokines.

HIV-1 ENVELOPES FROM PERSISTENT VIREMIA ON ART SHOW REDUCED ANTIBODY SENSITIVITY

Savrina Manhas1, Joseph P. Brooker1, Elias K. Halvas1, John W. Mellors1
1University of Pittsburgh, Pittsburgh, PA, USA

Background: Despite adherence to ART, clinically detectable viremia (HIV RNA >20 copies/ml) persists in some individuals and arises from large, infected cell clones. The mechanisms by which these clones escape immune responses is not defined but envelope (Env) resistance to antibodies (Abs) could contribute. To test this, we assessed the Ab neutralization sensitivity of HIV-1 Envs from 5 donors on ART with non-suppressed viremia despite therapeutic drug levels and no evidence of drug resistance to the current ART regimen.

Methods: Single, full-length Env genes were amplified from plasma by RT-PCR. Amplicons were sequenced, ligated into a mammalian expression vector, and expressed as a pseudovirus (PSV) from HEK293T cells. A luciferase-based assay was used to measure the neutralization sensitivity of the plasma sequence-derived PSVs against a panel of 16 monoclonal antibodies (mAbs) directed to the CD4 binding site (CD4bs); CR01, 3BC117, b12, L5Evh-1s, V1V2 apex (PG9, PG16, PGT145), glycan (2G12), V3-glycan (PGT121, 101074, PGT128), gp120-gp41 interface (PGT151), the membrane-proximal external region (MPER) of gp41 (10e8, 4e10, and 25f), and a tri-specific antibody (6v9/PGDM1400x10E8) directed to the CD4bs, V1V2 apex, and MPER binding sites.

Results: 40 unique Envs from 5 donors (R-09, C-03, C-02, T-13, F-07) were assessed. In general, the Envs tested were more resistant to CD4bs, Gp41, and Apex mAbs but more sensitive to V3-glycan mAbs. Donor R-09 had the most neutralization resistant Env sequences; both R-09 PSVs (R-09_A and R-09_C2) showed resistance to the 3 Apex mAbs (PG9, PG16 and PGT145) and CD4bs mAb VRC01. Additionally, R-09_C2 was the only PSV that was resistant to neutralization by N6/PGD1400x10E8. Of the 16 mAbs tested, only 3BNC117 and 10e8 potentially neutralized all the PSVs.

Conclusion: Plasma-derived Envs from individuals with persistent viremia on ART exhibit reduced sensitivity to mAbs targeting CD4bs, Gp41, and Apex, compared to tier 1 and 2 Envs. 3BNC117 and 10e8, however, neutralized all PSVs assayed, indicating therapeutic potential for clearing persistent viremia in the individuals studied.

Modeling HIV Reservoir Decline After ART Initiation as a Function of NK Cell Features

Elena Vendrame1, Geoffrey T. Ivison1, Rosemary Vergara1, Nancy Q. Zhao1, Giovanni J. Martinez-Coleon1, R. Brad Jones2, Joshua C. Cytkowski, Hanna Mar1, Deborah McMahan3, Joseph J. Ern4, John W. Mellors5, Ronald Bosch1, Susan Holmes1, Rajesh T. Gandhi6, Catherine A. Blish7
1Stanford University, Stanford, CA, USA, 2George Washington University, Washington, DC, USA, 3University of Pittsburgh, Pittsburgh, PA, USA, 4Havard T.H. Chan School of Public Health, Boston, MA, USA, 5University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 6Massachusetts General Hospital, Boston, MA, USA

Background: A major challenge in the development of HIV curative strategies is the formation of viral reservoirs that are not eradicated with antiretroviral therapy (ART). Understanding mechanisms that determine HIV reservoir size may inform development of effective cure approaches. As natural killer (NK) cells may contribute to control of HIV infection, we hypothesized that NK cells may affect reservoir size.

Methods: To evaluate the association between NK cells and HIV reservoir, we used mass cytometry to profile NK cells from 50 people with HIV on suppressive ART in AIDS Clinical Trials Group study A5321. NK cell repertoire was assessed at time of study entry (median of 7.1 years after ART initiation) and 24 and 48 weeks later. Prior to ART initiation, one year following ART initiation, and at study entry, we assessed inflammatory markers and markers of HIV persistence (cell-associated DNA (CA-DNA), cell-associated RNA and HIV RNA by single copy assay). T cell responses to peptide pools were assessed at study entry.

Results: In participants on chronic ART, the NK cell repertoire was stable as assessed by expression patterns of NK cell activation and differentiation markers at study entry, week 24, and week 48. At study entry, there was no significant correlation between on-ART NK cell diversity and any of the on-ART HIV reservoir measures. We next evaluated whether NK cell features, inflammatory markers, or T cell responses can explain the reduction in log10-transformed HIV DNA levels between the pre-ART time point and one year post ART initiation (CA-DNA reduction). We performed a supervised multivariate regression using the least absolute shrinkage and selection operator (LASSO). This approach selected the expression of perforin, CD38, 2B4, TIGIT, and CD96 on NK cells as the best explanatory variables for the prediction of CA-DNA reduction (see Table).

Conclusion: Here we show that specific NK cell marker expression levels and T cell responses can be used as explanatory variables in the regression analysis of the decline in HIV DNA levels following ART initiation. These observations suggest that specific NK cell features may drive an enhanced response to infected cells in the context of treatment initiation. Harnessing this potential may lead to the development of novel therapeutic strategies aimed at a functional cure for HIV.
**385 HIV-1 RESERVOIR SIZE CORRELATES TO PD-1 EXPRESSION IN MEN, BUT NOT WOMEN, IN UGANDA**

Katherine Yu1, Jessica L. Progruber1, Eileen P. Scully2, Adam Capoferri3, Steven J. Reynolds3, Jinga Kasule1, Taddeo Kituyumwee1, Paul Buule4, David Serwadda5, Jun-Hee Chai6, Andrew D. Redd6, Thomas Quinn7

1Western University, London, ON, Canada; 2Johns Hopkins University School of Medicine, Baltimore, MD, USA; 3UNAIDS, Bethesda, MD, USA; 4Nakal Health Sciences Program, Kalojiga, Uganda; 5Makerere University, Kampala, Uganda; 6NIH, Bethesda, MD, USA

**Background:** There is evidence to suggest that HIV-1 latency varies by sex; women have been reported to have fewer CD4 T cells containing HIV-1 provirus, lower levels of residual viral activity in resting CD4 T cells (CD4T), and lower T cell activation. Immunologic characteristics that correlate with latent reservoir size have been used to inform cure strategies, but these studies have been performed in predominantly male cohorts. We sought to determine if immune correlates of reservoir size differed by biological sex.

**Methods:** Blood samples were collected from HIV-1+, ART-suppressed (<40 copies/ml for >1 year) adults living in Rakai, Uganda (n=42 females, n=20 males). The frequency of CD4 containing replication competent provirus was estimated by quantitative viral outgrowth assay (QVOA). 14 soluble immune biomarkers were measured in plasma using custom multiplexed immunosorbent assays (MesoScale Discovery) and T cell memory subsets, activation and exhaustion markers, and effector T cell function were quantified by flow cytometry. Regression analysis was used to identify immune characteristics associated with reservoir size according to biological sex.

**Results:** Women and men were similar in terms of age, HIV-1 subtype distribution (A, D and recombinants), nadir CD4, pre-Art viral load and duration of viral suppression on ART. Compared to men, women had significantly higher serum concentration of D-dimer (272.8 ± 130.1 ng/ml, p<0.01) and there was a trend (p<0.1) towards a lower proportion of IL2+ CD8 T cells (1.85 vs. 4.31%) and effector memory CD4 T cells (1.88 vs. 3.44%). Consistent with prior reports, among men reservoir size correlated positively with p24 expression on CD4 T cells (r = 0.4, p<0.05). However, this association was not observed in women. Among women, reservoir size correlated positively with CD8 and CD4 T cell effector function (IL2 and TNFα production, all p<0.05).

**Conclusion:** These data identify distinct immunologic correlates of the replicating competent HIV-1 reservoir in men and women. Whether these measures are biomarkers or imply differential immune control/response to the reservoir is unknown. This is important to consider as interventions target immune checkpoint molecules, such as PD-1, for latency reversal and immune stimulation. Globally, females make up more than half of all individuals infected with HIV-1, and cure studies must be adequately powered to examine efficacy in both sexes.

**386 EFFECT OF TIM-3 BLOCKADE ON T CD8+ AND NK CELLS IN ART- TREATED HIV-INFECTED PATIENTS**

Carolina Gutiérrez1, Marta Sanz1, Nadia Madrid-Elena1, Sergio Serrano-Villar2, María J Vivancos1, Alejandro Valdejo1, Francisco J. Hernández-Walias1, Santiago Moreno1

1Hospital Ramón y Cajal, Madrid, Spain

**Background:** TIM-3 is a large transmembrane inhibitory receptor that is expressed in multiple cells of the immune system, including T-CD8+ cells and NK cells. Galectin-9 that has been described as a potent mediator of HIV transcription and reactivation constitutes one of the most important ligands of TIM-3. The purpose of this study was to analyze the effect of TIM-3 blockade on the specific HIV-1 CTL response of T-CD8+ and NK cells from HIV-infected patients.

**Methods:** We included 10 ART-treated, HIV-1 infected donors from whom we obtained 200 ml of peripheral blood for the isolation of T-CD4+, T-CD8+ and NK cells. We cocultured the isolated T-CD4+ cells with T-CD8+ cells and NK cells in a 1:1 ratio. To evaluate the impact of TIM-3 blockade on the HIV-suppressive capacity of T-CD8+ cells we used a specific antibody against TIM-3. The impact of TIM-3 blockade was determined by measuring p24 levels in the supernatants of the cocultures at day 7 and day 10. To analyze the effect of Galectin-9 (natural ligand of TIM-3), p24 levels were compared in cocultures with or without the addition of exogenous Galectin-9.

**Results:** The 10 patients had plasma HIV RNA <50 copies/ml with a mean T-CD4 + 661 cells/mm³, and mean T-CD8+ 920 cells/mm³. We observed a poor HIV suppressive capacity of T-CD8+ cells with a mean p24 decrease of 0.9 log. However it was significantly improved after TIM-3 blockade (mean 2.4log), mean difference 1.5log (IQR, [0.4–2.20], p=0.007). No differences were observed with the presence of NK cells in the coculture (mean difference with and without blockade, 1.15log [0.49–1.69], p=0.011). The addition of Galectin-9 did not change the effect of TIM-3 blockade (mean difference, 1.25log [0.77–1.42], p=0.012).

**Conclusion:** We demonstrated that the blockade of TIM-3 improves the CTL response of the T-CD8+ cells of ART-treated HIV-infected patients. No negative effects were observed with the same blockage in NK cells. Galectin-9 does not have impact on the response. A combination of Galectin-9/TIM-3 could be evaluated as an effective shock and kill strategy in HIV-eradication.

**Table: Features predictive of decline in reservoir following treatment initiation.**

<table>
<thead>
<tr>
<th>Predictive Variable</th>
<th>Lasso coefficients in a model aimed at regression of the CA-DNA reduction following ART initiation</th>
<th>Pearson correlation coefficients with CA-DNA reduction following ART initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purinor</td>
<td>-2.6</td>
<td>0.35</td>
</tr>
<tr>
<td>CD3R</td>
<td>-1.2</td>
<td>-0.31</td>
</tr>
<tr>
<td>TCD4</td>
<td>0.85</td>
<td>0.33</td>
</tr>
<tr>
<td>TCD8</td>
<td>0.81</td>
<td>0.29</td>
</tr>
<tr>
<td>CD96</td>
<td>0.75</td>
<td>0.36</td>
</tr>
<tr>
<td>Net tat rev response</td>
<td>0.70</td>
<td>0.43</td>
</tr>
</tbody>
</table>

**387 REDUCED MEMORY, FUNCTIONAL CONNECTIVITY IN 41- TO 70-YEAR-OLD HIV+ APOE E4 CARRIERS**

Fan N. Yang1, Margarita Bronshteyn2, Sarah A. Flowers1, Matthew Dawson1, Monica M. Diaz2, Harvey R. Fernandez3, Princy N. Kumar1, G. W. Rebeck1, Raymond S. Turner1, David J. Moore1, Ronald J. Ellis4, Xiong Jiang5

1Georgetown University, Washington, DC, USA; 2University of California San Diego, La Jolla, CA, USA

**Background:** ApoE e4 is the strongest genetic risk factor for late onset Alzheimer’s disease. In people with HIV (PWH), the potential impact of ApoE e4 on brain structure and function remains to be determined. Older PWH ApoE e4 carriers may experience additional impairment in brain structure and function compared to age-matched PWH non-carriers; however, results are unclear for middle-aged PWH. Moreover, the interactions between ApoE e4 status and HIV disease severity are largely unknown.

**Methods:** Ninety-nine PWH participated in a cross-sectional study (56.2±6.5yrs, range 41-70yrs, 27 females). A comprehensive 7-domain neuropsychological (NP) test battery was administered and HIV-Associated Neurocognitive Disorders (HAND) diagnoses were assigned according to Frascati criteria. Structural MRI and resting-state functional MRI (functional connectivity, FC) were collected. All statistical analyses were performed after controlling for demographics, and additional MRI-specific confounding factors were accounted for in the MRI data analysis.

**Results:** Between ApoE e4 carriers (n=26) and non-carriers (n=73), there were no significant differences in age, education, sex, race, HIV disease, HAND diagnosis, and most individual NP test scores, except for memory performance measured by the Hopkins Verbal Learning Test–Revised (HVLT-R). Carriers had significantly lower delayed recall and retention score than non-carriers (p<0.05), but there was no interaction between age and ApoE e4 status. For MRI, there was no difference in gray matter volume or cortical thickness.
between carriers and non-carriers. In contrast, the FC between the right caudate and right hippocampus was significantly lower in carriers (p = 0.0002) and correlated with HIVLT-R retention (p = 0.015), along with a significant interaction between ApoE ε4 genotype and CD4 nadir (p = 0.026). A similar marginal, but non-significant, effect was found in the FC between the left caudate and left hippocampus.

**Conclusion:** In this sample of PWH (41-70 years old), ApoE ε4 was associated with reduced verbal memory performance and disrupted FC between the caudate and the hippocampus, suggesting that ApoE ε4 may be a genetic risk factor for memory impairment in PWH. In addition, the interaction between ApoE ε4 allele and CD4 nadir on FC suggests that the severity of HIV disease may exacerbate the effect of ApoE ε4 on brain health, resulting in an increased risk of dementia and Alzheimer’s disease later in life.

### Neurocognitive and Volumetric Changes after 24 Weeks of DTG/3TC/ABC Discontinuation

**Ignacio Pérez-Valera**, Alfonso Cabello, Pablo Ryan, Maria Luisa Montes, Sara De La Fuente Moral, María J. Vivancos-Gallego, Guillermo Cuevas, Alberto Iñigo García-Fraile, Mario Gil-Correa, Norberto Malpica, Guadalupe Rúa, María Yllésca, Alicia González, Hospital La Paz Institute for Health Research, Madrid, Spain, Fundación Jiménez Díaz, Madrid, Spain, Hospital Universitario Infanta Leonor, Madrid, Spain, Puerta de Hierro Research Institute and University Hospital, Madrid, Spain, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain, Hospital Universitario de La Princesa, Madrid, Spain, Universidad Rey Juan Carlos, Madrid, Spain, Universidad Rey Juan Carlos Alcorcón, Alcorcón, Spain, Fundación SEIMC-GesIDA, Madrid, Spain

**Background:** Dolutegravir/abacavir/efavirenz (DTG/3TC/ABC) fixed dose combination (FDC) discontinuation is associated with improvement of neuropsychiatric (NP) symptoms. However, limited data exist on the effect of DTG/3TC/ABC discontinuation on neurocognitive (NC) function and brain structure. We assessed NC function and neuroimaging in participants enrolled in the DREAM study, a multicenter clinical trial designed to evaluate the reversibility of NP symptoms in virologically controlled patients on DTG/3TC/ABC switching to Cabotegravir/abacavir/efavirenz (C/ABC/TAF). Clinical results from this trial have demonstrated significant improvements in NP symptoms when switching from DTG/3TC/ABC to E/C/F/TAF.

**Methods:** All participants performed a comprehensive NC assessment (7-domain) following Frascati criteria and a 3-Tesla brain MRI on day 1 and 24 weeks after switching therapy. Global NC performance was assessed using the global deficit score (GDS). Changes in NC function and brain volumes were determined using neuroradiometric atlas and analyzed using t-test. Multiple comparisons testing was corrected using the false discovery rate (FDR) adjustment.

**Results:** 38 participants, mostly Caucasian male of middle age with good immunological status, normal NC function that received DTG/3TC/ABC for a mean time of 1.45 years, were included. At week 24 after switching to E/C/F/TAF, we observed significant improvements in the global NC function (mean ± SD: ΔGDS change: 0.12 ± 0.32; p = 0.029) and in the speed of processing (Δ -0.26 ± 0.86; p < 0.001), delayed recall and motor domains. Brain volumes changes observed after FDR adjustment, only the changes in the right frontal pole (Δ = 0.53; p = 0.03). Significant changes in several brain volumes were observed (table). After FDR adjustment, only the changes in the right frontal pole, a cerebral region involved in information processing, emotion and motivated behaviors, remained significant (p < 0.03). We also observed a significant correlation between GDS changes and volume changes in the right superior occipital gyrus (r = 0.53).

**Conclusion:** Our study suggests that switching from DTG/3TC/ABC to E/C/F/TAF was associated with an improvement in NC functioning, especially in speed of processing, delayed recall and motor domains. Brain volumes changes observed in our study could be useful to delve into the pathological mechanisms of DTG/3TC/ABC-related NP toxicity.

### HIV is Independently Associated with Brain MRI White Matter Hypereosinophils


**Background:** Brain white matter hypereosinophilic (WMH) is nonspecific in etiology but occur commonly in the setting of HIV infection. Their relevance to disease remains uncertain as previous studies have used various methods of estimation in heterogenous groups of people with HIV (PWH). We evaluated the frequency, severity and clinical correlations of WMH in the setting of well controlled HIV infection, using the Fazekas visual rating scale.

**Methods:** Research protocol images from brain 3D fluid attenuated inversion recovery (FLAIR) on a 3T MRI were reviewed to determine the Fazekas score (total score of 0–6; 0-3 for periventricular hypereosinophilic and 0-3 for deep WMH) in people with HIV (PWH) with well controlled infection (antiretroviral therapy for at least one year and plasma viral load <200 copies/ml) and in controls. Simple linear regression was used for covariate selection, and forward stepwise regression was performed to evaluate the effect of HIV on Fazekas scores.

**Results:** Fazekas scores were determined in 203 PWH and 58 controls. The PWH group had a higher mean total Fazekas score compared to controls (2.2 ± 1.4 vs. 1.7 ± 1.3; p = 0.001). Multiple comparisons testing was corrected using the false discovery rate (FDR) adjustment.

**Conclusion:** HIV infection contributes to the extent of brain WMH, even in the setting of well controlled infection. Prior immunosuppression evidenced by lower nadir CD4 partially explains this association. The cohort is undergoing serial MRI scans and neuropsychological testing to evaluate the long-term clinical effects of WMH.

### Brain Age Based on Sleep Encephalography is Elevated in HIV+ Adults on ART

**Michael Leon**, Haoqi Sun, Christine Boutros, Robert Thomas, Gregory K. Robbins, Shibani S. Mukerji, Brandon Westover

**Background:** Co-morbidities and increased inflammation associated with HIV have raised concern for excess brain aging, yet diagnostic biomarkers for brain aging are lacking. Our lab developed a machine learning model that estimates...
Methods: Sleep EEGs from 43 HIV+ adults on ART were gathered and matched to controls (HIV-, n=28) by age, gender, race, alcoholism, smoking and substance use history. We compared BI among groups and used additional causal inference methods to ensure robustness. Individual EEG features that underlie BI prediction were also compared. Finally, we performed a sub-analysis of BI between HIV+ with or without a history of AIDS.

Results: After matching, mean CA of HIV+ vs HIV- adults were 49 and 48 years, respectively (n.s.). The mean HIV+ BI was 3.04 years higher than HIV- (4.4 vs 1.4 yr; p = 0.048). We found consistent and significant results with alternative causal inference methods. Several EEG features predictive of BI were different in the HIV+ and HIV- cohorts. Most notably, non-REM stage 2 sleep N2 delta power (1-4Hz) was decreased in HIV+ vs. HIV- adults, while theta (4-8Hz) and alpha (8-12Hz) power were increased. Those with AIDS (n=19, BI=4.40) did not have significantly different BI than HIV+ without AIDS (n=23, BI=5.22).

Conclusion: HIV+ individuals on ART have excess brain age compared to matched controls using a sleep EEG-based model of brain aging. This excess brain age is partially due to the relative reduction in delta power during N2, suggesting decreased sleep depth in HIV+ subjects. These results suggest sleep EEG could be a valuable brain aging biomarker for the HIV population.
ACTIVE LIFESTYLE IS ASSOCIATED WITH BETTER BRAIN FUNCTION IN PERSONS LIVING WITH HIV

Jeremy Strain1, Collin Killigore1, Dimitre Tomov1, Sarah A. Cooley1, Brittany Nelson2, Beau Ances1
1Washington University in St Louis, St Louis, MO, USA

Background: Mortality due to HIV has dramatically reduced due to the introduction of combination anti-retroviral therapy (cART). Despite virologically suppression many PLWH still develop cognitive impairment can occur. On average, PLWH have reduced physical exertion and a reduction in active lifestyles. A reduction in physical function may affect both brain function and structure in PLWH. We evaluated whether physical fitness (as measured by VO2 maximum) relates to metrics of brain structure (diffusion tensor imaging (DTI)) and function (arterial transit time (ATT)).

Methods: Forty-one sedentary elderly virologically well-controlled PLWH underwent neuroimaging (DTI and CBF). Each participant completed a graded exercise test on a cycle ergometer with 12-lead electrocardiography. Measurements of oxygen uptake, carbon dioxide production, heart rate, and blood pressure will be continuously monitored during testing to compute peak VO2. DTI fractional anisotropy (FA) was processed using tract-based spatial statistics FSL 5.0.9. CBF was processed with in-house scripts to calculate regional arterial transit time (ATT) that corresponds to how long the blood takes to perfuse into the brain tissue. ATT maps were registered to their corresponding T1 scan and regional volumes were extracted based on Freesurfer S.3 parcellations. Partial correlations were performed between VO2 max and imaging metrics for both structure and function. Each correlation was adjusted for age and gender with a statistical threshold set at p<0.05.

Results: A FA was positively associated with VO2 max in the Frontal Aslant Tract, frontal occupal fasciculus, inferior longitudinal fasciculus and superior longitudinal fasciculus (Figure 1B). ATT positively associated with VO2 max in several gray matter regions that correspond to the white matter projections (Figure 1A). The strongest correlations were seen in the paracentral, posterior cingulate, and dorsal lateral prefrontal regions.

Conclusion: We found that current fitness associated with both structure and function in an aviremic sedentary older PLWH. Higher VO2 max related to improved brain structure and function diversely throughout the cortex. Together, this bolsters the claim that physical fitness may improve brain integrity of virologically stable HIV participants.

EFFECTS OF PERINATAL HIV INFECTION ON THE CORTICAL THICKNESS IN YOUNG ADULTHOOD

Manuela Martin-Bejarano1, Beatriz Ruiz-Saez2, Ana Martinez De Aragon3, Carlos Velo4, Mario Gil-Correa5, Sara Guillen6, María Luisa Lorente5, Pablo Rojo Conejo5, Berta Zamora5, Talia Saiz6, José Tomás Ramos5, Juan Guzman5, María Luisa Navarro4, María Isabel González-Tomé6, for the NeuroCoRISpe

Background: Brain atrophy has been observed in perinatally HIV-infected patients (PHIV) despite initiation on combined antiretroviral treatment (cART), but studies measuring cortical thickness (CT) are limited. We aimed to evaluate the neurologic state and CT of immunovirologically stable PHIV youths with good daily functioning.

Methods: A total of 25 PHIV patients on cART and 25 healthy controls (HC) matched by age, sex, level of education and socioeconomic status underwent a Magnetic Resonance Imaging scan. CAT12 toolbox was used to extract cortical thickness values from T1w images using parcellations from to two atlases (Human Connectome Project multi-modal parcellation (HCP-MMP1) and Desikan–Killiany atlas (DK40)). Mean thickness values for all ROIs in both atlases were compared between HIV+ and HC with a two-independent-samples t-test with age and gender as covariates.

Results: Significant differences were found in the opposite contrast (HIV+ > HC).

Conclusion: Despite good control of HIV infection and no differences in neurocognitive evaluation, PHIV showed thinner cortices of the temporal, orbito-frontal and occipital lobes. Longitudinally studies are required to determine the impact of HIV on brain in PHIV patients during adulthood.
395 EFFECT OF ANTIChOLINERGIC MEDICATIONS ON BRAIN INTEGRITY IN OLDER HIV-POSITIVE ADULTS
Sarah A. Cooley1, Beau Ances1
1Washington University in St Louis, St Louis, MO, USA

Background: The aging population of people living with human immunodeficiency virus (HIV) (PLWH) has resulted in an increase in comorbidities requiring medications. While anticholinergic (AC) medications are sometimes prescribed to older adults for a limited period of time, they have been linked to a greater risk of cognitive impairment in the HIV-population. The effect of AC in older PLWH with regards to brain volumetrics has not yet been well-established. We compared AC burden between older (age ≥50 years) PLWH and HIV-controls (HC) and assessed the interaction of HIV status and AC burden on neurophysiological performance (NP) and brain volumes cross-sectionally and longitudinally at two-year follow-up.

Methods: The Anticholinergic Cognitive Burden Scale (ACB; Boustani et al., 2008) was used to categorize 105 HC and 215 PLWH with undetectable viral load (<50 copies/mL) aged ≥50 years as low (ACB score ≤3) or high AC burden (ACB score >3). NP (learning/memory, executive function (EF), psychomotor speed (PM)) and brain volumetrics were acquired. A chi-square test compared rates of high AC burden in HC and PLWH. General linear models examined main effects and interactions of HIV status and ACB group on NP and within the frontal, parietal, temporal, occipital lobes; cortical, subcortical, and total gray matter (GM); and total white matter volumes. Linear mixed models examined change in NP and volumes over two years for a subset of 30 HC and 94 PLWH who had no change in AC burden.

Results: PLWH (n=53; 25%) had a greater proportion of individuals with high AC compared to HC (n=13; 12%) (p=0.01). Overall, PLWH had significantly worse NP and greater reductions in brain volumes compared to HC (p <0.001). Individuals with a higher AC had worse NP and greater reductions in brain volumes compared to individuals who had a low AC. No significant interactions were observed between HIV status and ACB (p >0.05). Longitudinally, both HC and PLWH who had a higher AC displayed a greater decline in subcortical GM volume over time compared to individuals with low AC (Figure 1). The observed decline in brain volumetrics significantly correlated with worse PM over time.

Conclusion: The significant effect of higher AC on NP and GM volumes in older adults (regardless of HIV status) supports concerns over their continued use in older individuals. Although both HIV and high AC are associated with worse NP and reductions in brain volumetric, no interaction was observed.

Figure 1. Executive function (A) and subcortical volume Z-scores (B) by group (HIV– = HIV-negative controls; VS = virologic suppression (≤20 copies/mL); LL = low-level viremia (21-200 copies/mL); VF = virologic failure (>200 copies/mL)).

396 EFFECTS OF VIRAL LOAD ON NEUROIMAGING AND NEUROPSYCHOLOGICAL PERFORMANCE
Sarah A. Cooley1, Jaimie Navid1, Julie Wisco1, Jane A. O’Halloran1, Beau Ances1
1Washington University in St Louis, St Louis, MO, USA

Background: Previous studies have investigated the relationship between viral load (VL) and brain atrophy in people with HIV (PLWH). However, these studies often combine PLWH on and off antiretroviral therapy (ART) including those with and without detectable VL. Here we compare brain volumetrics and neuropsychological performance (NP) in HIV-controls (HIV–) and PWHL receiving ART who are further categorized into: 1) virologic suppression (VS, VL ≤ 20 copies/mL), low-level viremia (LL, 21 - 200 copies/mL) and virologic failure (VF > 200 copies/mL).

Methods: 128 HIV– (mean age 42.4, 50% male) and 239 PLWH (mean age 43.7, 62% male) on stable ART regimen completed NP testing (executive function, learning and memory, psychomotor speed, and language domains) and structural neuroimaging. Of the 239 PLWH, 175 (73.2%) demonstrated VS (≤ 20 copies/mL) and 64 had detectable VL (38 LL, 26 VF). NP scores, cortical volumes (frontal, occipital, parietal, and temporal) and subcortical volumes were converted into demographically-corrected z-scores. T-tests analyzed differences in NP domains, global cognition and volumetric z-scores between PLWH and HIV–. Analyses of variance with post-hoc Tukey’s tests were used to examine differences in NP scores and volumetrics between groups.

Results: In general, PLWH had significantly decreased NP z-scores in the executive function, language, and psychomotor speed domains as well as significantly smaller subcortical volumes compared to HIV– (p <0.05). When PLWH were sub grouped by VL, results indicated no significant differences between the VS, LL, and VF groups in any of the NP domains, global cognition or volumetric z-score (p >0.05). The VS group had significantly lower executive function and language z-scores compared to HIV–, and both the VS and LL groups had lower subcortical z-scores compared to HIV–. The VF group exhibited larger subcortical volume compared to the LL group, although this was non-significant (Figure 1).

Conclusion: Results suggest an HIV effect on subcortical volumes and NP scores but not a VL effect. Higher subcortical volumes in the VF group compared to the LL group may indicate inflammation, but increased group sizes are needed to determine if this effect is significant. The lack of a significant VL effect may signify that ART use is critical rather than viral suppression, but longitudinal studies are needed.

Figure 1. Executive function (A) and subcortical volume Z-scores (B) by group (HIV– = HIV- negative controls; VS = virologic suppression (≤20 copies/mL); LL = low-level viremia (21-200 copies/mL); VF = virologic failure (>200 copies/mL)).
Results: The sample includes 70 HIV+ and 69 HIV- adults who were matched on age (M=38.7, gender (70% male), and race (68% African-American). HIV+ participants had lower global neurocognitive functioning (p<.005), with differences in the domains of learning (p=.006), memory (p=.006), and executive function (p=.026). Figure 1 shows the independent joint component that significantly correlated with global neurocognitive functioning in all three modalities. Gray matter regions included thalamus and cerebellum. White matter regions included the cingulum tract of the cingulate and hippocampus, inferior and superior longitudinal fasciculus, and uncinate fasciculus. Functional regions included posterior parietal, lateral prefrontal, orbitofrontal, anterior cingulate, precuneus, and insular cortices. HIV+ status was associated with lower gray matter volume (p=.038) and lower fractional anisotropy (p=.028) in this component. Duration of HIV disease and nadir CD4 cell count were also associated with gray matter volume and functional connectivity in identified independent components.

Conclusion: These results suggest that linked structural and functional deficits in several brain networks are related to HIV-associated NCI. As MRI becomes more commonplace in HIV care, multimodal fusion may provide neural biomarkers to support diagnosis and treatment of NCI.

Method: PLWH and controls were recruited from an immunology clinic for a study of alcohol- and HIV-associated brain dysfunction. Participants were categorized as non-drinkers, moderate drinkers, or heavy drinkers per NIH guidelines. Diffusion tensor imaging was used to derive measures of fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD). Whole-brain voxelwise analyses were performed using tract-based spatial statistics (TBSS), corrected for multiple comparisons. Confirmatory region-of-interest (ROI) analyses were conducted to probe group differences.

Results: The sample of 108 participants (62 PLWH, 46 controls) averaged 45.2±11.1 years of age and was 42% female. Most PLWH were on antiretroviral therapy (94%) and were virally suppressed (69%). PLWH and controls were matched on rates of heavy drinking, smoking, and other drug use. In voxelwise analyses, heavier alcohol intake was significantly associated with lower FA, higher RD, and lower AD in widespread areas (p's<.05; Figure 1). ROI analyses confirmed that non-drinkers had higher FA than heavy drinkers in corpus callosum, cingulate gyrus, posterior thalamic radiation, and left external capsule (p's<.05). Non-drinkers had higher FA than moderate drinkers in genu and body of corpus callosum (p's<.05). Moderate drinkers had higher FA than heavy drinkers in body of corpus callosum, posterior thalamic radiation, and left external capsule (p's<.05). Older age extensively predicted lower FA (p<.05). Neither HIV status nor clinical characteristics were associated with FA, and the HIV by drinking group interaction was not significant (p's>.05).

Conclusion: Alcohol use significantly predicted white matter microstructural degradation in this sample of PLWH in care and seronegative controls. Results are consistent with a dose-dependent association of alcohol use with lower white matter microstructural coherence. The overlap between FA and RD maps points to dysmyelination as a possible mechanism. Findings underscore the need to address unhealthy alcohol use in HIV-positive and seronegative individuals.
400 MICROSTRUCTURAL MRI CHANGES ASSOCIATED WITH COGNITIVE IMPAIRMENT IN CONTROLLED HIV
Elizabeth F. Horne1, Gina Naroto1, Lillian Ham2, Joseph Snow2, Daniel S. Reich2, Bryan Smith1, Govind Nair1, Avindra Nath1
1National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, 2NIH, Bethesda, MD, USA

Background: Despite cART, cognitive impairment and brain MRI abnormalities are still prevalent in people with HIV (PWH). Diffusion tensor imaging (DTI) can be used to detect microstructural changes in both white matter (WM) and grey matter (GM), and it may be possible to detect subtle and early changes prior to neurocognitive decline. In this cross-sectional study, we investigated integrity of the brain parenchyma in virologically controlled PWH (HIV+) and socio-economically similar control subjects (HIV-). DTI parameters were also correlated with neuropsychological (NP) measures in both groups.

Methods: All participants underwent 3T MRI which included DTI at 2mm isotropic resolution and 30 diffusion directions, a comprehensive battery of NP testing, and clinical evaluation. Fractal anisotropy (FA) and mean diffusivity (MD) were determined from various regions of interest (ROIs). We analyzed group differences of FA and MD in various ROIs and conducted multivariate regressions with NP testing and DTI adjusted for age and sex.

Results: 134 HIV+ patients on long-term ART with viral load of <100c/mL and 47 HIV- controls were included in this study. In the HIV+ group, compared to HIV- controls, WM was higher (more abnormal) and FA lower (also more abnormal) in various WM ROIs including the cerebral WM (MD p=0.02, FA p=0.03). However, the white matter abnormalities were not associated with worse cognition in the HIV+ group (p=0.38 for overall T-score). Instead, it was the grey matter abnormalities that were associated with worse cognition including overall T-score (p=0.03), memory (p=0.02), and information processing (p=0.03).

Conclusion: DTI detected microstructural abnormalities in numerous brain parenchymal ROIs of HIV+ compared to HIV- participants. These changes are present even despite sustained virologic suppression with long-term ART. Both WM and GM were more abnormal in the HIV+ group, with the GM abnormalities more clearly associated with current NP outcomes in this cross-sectional study. Serial MRIs and NP testing with this cohort will evaluate whether the WM abnormalities are also associated with NP outcomes in the future.

401 COGNITIVE IMPAIRMENT AMONG HIV-INFECTED MEN WITH LONGITUDINAL FOLLOW-UP
Zheng Wang1, Yu Cheng1, Eric C. Seaberg2, James T. Becker1, for the Neuropsychology Working Group of the Multicenter AIDS Cohort Study
1University of Pittsburgh, Pittsburgh, PA, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: To control false discovery rate (FDR) in identifying cognitive impairment among individuals infected with HIV, the multivariate normative comparisons (MNC) method has been used to account for intercorrelations among cognitive domains. However, the existing MNC is for cross-sectional data and does not account for the intercorrelations among repeated visits. That is, the best predictor of future test performance is current test performance. This work developed a novel longitudinal MNC (LMNC) to classify cognitive status for individuals with multiple visits, yielding more accurate results than naïvely applying the cross-sectional MNC to each visit.

Methods: Data used in this work were collected before April 2017 among MSM from the Neuropsychological (NP) Substudy of the Multicenter AIDS Cohort Study. Six cognitive domains were evaluated bi-/semi-annually among these men: learning, memory, executive functioning, working memory & attention, motor speed & coordination, and speed of information processing. The final analysis included data from 22,900 visits by 3,701 men (mean age 34.9, 55.0% HIV+, mean 6.2 visits, mean follow-up 8.3 yrs) with complete data from all 6 domains. T-scores, at every domain, were adjusted for race, age, education and number of tests. HIV- men without comorbidities (n=922) were treated as healthy controls, and the LMNC was used to classify cognitive impairment among HIV- and HIV+ men. Also, the cross-sectional MNC was applied to each visit with and without Benjamini-Hochberg (BH) corrections.

Results: Among healthy controls the LMNC identified 5.5% with cognitive impairment. This suggests that the LMNC guarded FDR at the pre-determined 5% level. With the cross-sectional MNC applied with and without the BH correction, impairment rates were 19.8% and 9.5% in the healthy controls, respectively. In the HIV+ group, 7.3% men were identified as impaired with the LMNC, compared with 16.4% and 29.5% using the MNC method (with and without the BH correction). In the HIV- group, the rates are 9.3%, 11.7% and 24.1%, respectively. The rates of impairment and mean T-scores across visits did not differ between the HIV- and HIV+ men.

Conclusion: This newly developed LMNC successfully controlled the FDR at the pre-specified level across study visits. This means that the estimates of impairment over repeated testing is more accurate than simply applying cross-sectional criteria multiple times.

402 PLASMA CITRATE AND SUCCINATE PREDICT NEUROCOGNITIVE IMPAIRMENT IN OLDER PWH
Corrilyn O. Hileman1, Sausan Azzam1, Kunling Wu1, Katherine Tassiopoulos1, Roger Bedimo2, Ronald J. Ellis3, Kristine M. Erlandson4, Asha R. Kallipuran5, Susan L. Koletar1, Alan Landay1, Frank J. Palella6, Muralidhar Pallaki7, Babafemi Taiwo10, Charles L. Hoppel2, Robert Kalayan1
1MetroHealth Medical Center, Cleveland, OH, USA, 2Case Western Reserve University, Cleveland, OH, USA, 3Harvard T.H. Chan School of Public Health, Boston, MA, USA, 4VA North Texas Health Care Center, Dallas, TX, USA, 5University of California San Diego, San Diego, CA, USA, 6University of Colorado Denver, Denver, CO, USA, 7Cleveland Clinic, Cleveland, OH, USA, 8The Ohio State University, Columbus, OH, USA, 9Rush University, Chicago, IL, USA, 10Northwestern University, Chicago, IL, USA, 11Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA

Background: Neurocognitive impairment (NCI) is associated with monocyte activation, implicating a role for neuroinflammation. Activated macrophages increase glycolysis and accumulate the tricarboxylic acid (TCA) metabolites citrate and succinate, which may promote disease by engaging diverse cellular pro-inflammatory pathways or may be markers of mitochondrial dysfunction. We hypothesized that this metabolic shift contributes to NCI and frailty in people with HIV (PWH).

Methods: Fasting plasma citrate and succinate were quantified at entry by liquid chromatography/mass spectrometry in AIDS Clinical Trials Group HIV Infection, Aging, and Immune Function Long-Term Observational (HALO) study participants. Adjusting for clinically relevant variables, logistic regression and proportional hazard models examined associations of these TCA metabolites with prevalent and incident NCI, respectively; repeated measures analyses examined associations with neuropsychologic testing (NPZ-4) and 4-meter gait speed, a feature of frailty, over time.

Results: 376 participants were included (276 without NCI; 100 with NCI at entry). Participants with NCI were more likely to be Hispanic (35% vs 20%; p=0.01), have less education (p<0.001) and shorter antiretroviral therapy (ART) duration (p<0.01). Overall, median age was 51 (range 40-77) yrs; 81% were male; 60% were current or former smokers. Median entry and nadir CD4 counts were 613 (IQR 449-825) and 203 (68-317) cells/mm3, respectively; 93% had HIV RNA <50 copies/ml. Age modified citrate associations with: prevalent NCI (figure); NPZ-4 scores and gait speed over time (p<0.01, p=0.02 and p=0.04, respectively, for interaction with age). In the oldest age-quartile (ages 56-78; n=96) each 1 SD increase in citrate was associated with a 2.4 (95% CI 1.3, 4.2) increased odds of prevalent NCI; -0.17 SD (-0.28, -0.07) lower NPZ-4 scores over time; and 0.22 increase in citrate was associated with a 2.8 (95% CI 1.3, 4.2) increased odds of prevalent NCI. Each 1 SD increase in succinate was associated with a 1.9-fold (1.1, 3.9) increased hazard of incident NCI and -0.24 SD (-0.47, -0.02) lower NPZ-4 scores over time.

Conclusion: The identified associations suggest common pathways in the pathogenesis of NCI and gait speed, involving mitochondrial dysfunction or inflammation, to which older PWH appear more susceptible.
403 AGE-ASSOCIATED DEMENTIA AMONG OLDER PEOPLE WITH HIV IN THE US: A MODEL-BASED ANALYSIS

Emily P. Hyle1, Julia H. Foote2, Shibani S. Mukerji1, Keni N. Atthoff1, Paul E. Sax3, Krishna P. Reddy4, Liyang Yu5, Leah H. Rubin1, Kenneth Freedberg1, Milton C. Weinstein1, Anand Viswanathan1, Lee H. Schwamm1, Fatma Shebl1, Rochelle P. Walensky1
1Massachusetts General Hospital, Boston, MA, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3Bingham and Women’s Hospital, Boston, MA, USA, 4Johns Hopkins University School of Medicine, Baltimore, MD, USA, 5Harvard T.H. Chan School of Public Health, Boston, MA, USA

Background: Approximately 25-30% of people with HIV (PWH) in the US (~300,000) are ≥55y and at risk for age-associated dementias (AAD), including Alzheimer’s disease and vascular dementias. We project the lifetime cumulative incidence and mortality associated with AAD among PWH in the US.

Methods: We expanded the validated Cost-effectiveness of Preventing AIDS Complications (CEPAC) model to incorporate age- and sex-stratified risk of AAD with increased mortality among those who develop AAD. We first validated the model in the general population (age, mean±SD 62y±6). Next, we simulated a population of people at high risk for HIV acquisition given risk behaviors, so mortality is adjusted by a relative mortality rate (RMR) for MSM, IDU, and socio-economic status. We then simulated the 2015 US population of people ≥55y diagnosed with HIV (CD4, mean±SD [400] ±299) of whom 73% are in care and 63% are viremically suppressed. Loss to follow-up (LT FU) is 13%/year, and mortality is due to HIV, AAD, and RMR-adjusted other causes. We estimated AAD prevalence, AAD incidence, and AAD-associated mortality using published data from populations without HIV. Model outcomes included AAD cumulative lifetime incidence and life expectancy (LE). We performed sensitivity analysis on HIV-specific (e.g., LT FU) and AAD-specific (e.g., AAD incidence) parameters, as well as the impact of a 5y forward-shift in AAD incidence and non-HIV-associated mortality (i.e., premature aging).

Results: Among older males/females with HIV, we projected AAD cumulative incidence of 18%/17% and LE of 14.5y/14.6y, compared to higher cumulative incidence of 18%/17% and LE of 14.6y/14.7y, respectively. At baseline, median plasma NFL was 12.6 (IQR 8.8–21.1) pmol/L in the B-vitamin arm and 10.2 (IQR 8.02–14.9) in the control arm. The levels did not change significantly to month 12 in either arm, 13.8 (IQR 10.3–18.8) and 12.8 (IQR 8.4–14.7) pmol/L, respectively.

Conclusion: We found a significant correlation between p-homocysteine and p-NFL levels in neuroasymptomatic PLHIV on ART. B-vitamin substitution for 12 months had no effect on p-NFL. The mechanism behind the correlation between homocysteine and NFL at baseline, also seen in the earlier study, is unknown and needs to be further investigated. The study will continue until 24 months of follow-up.

405 CONSERVED CSF HIV ANTIBODY RESPONSE IN PATIENTS WITH DIVERSE NEUROLOGIC PHENOTYPES

Isobel A. Hawes1, Ryan Schubert1, Akshaya Ramesh1, Gavin Sowa1, Joanna Hellmuth2, Magnus Gisslén3, Richard W. Price1, Michael Wilson4
1University of California San Francisco, San Francisco, CA, USA, 2University of Gothenburg, Gothenburg, Sweden

Background: The CNS is exposed to HIV during primary infection and likely continuously during untreated chronic infection. ART that suppresses plasma HIV RNA also usually suppresses CSF HIV RNA with occasional asymptomatic episodes of detectable HIV RNA. A rare exception is development of neurocognitive symptoms, but the complex etiology of cognitive symptoms is not entirely understood. Here we screen for potential unidentified infections and HIV using next-generation sequencing.

Methods: We used a Cost-Effectiveness of Preventing AIDS Complications model to incorporate age- and sex-stratified risk of AAD with increased mortality among those who develop AAD. We project the lifetime cumulative incidence and life expectancy (LE) among older males/females with HIV, as well as the impact of a 5y forward-shift in AAD incidence and non-HIV-associated mortality (i.e., premature aging).

Results: Among older males/females with HIV, we projected AAD cumulative incidence of 18%/17% and LE of 14.5y/14.6y, compared to higher cumulative incidence of 18%/17% and LE of 14.6y/14.7y, respectively. At baseline, median plasma NFL was 12.6 (IQR 8.8–21.1) pmol/L in the B-vitamin arm and 10.2 (IQR 8.02–14.9) in the control arm. The levels did not change significantly to month 12 in either arm, 13.8 (IQR 10.3–18.8) and 12.8 (IQR 8.4–14.7) pmol/L, respectively.

Conclusion: We found a significant correlation between p-homocysteine and p-NFL levels in neuroasymptomatic PLHIV on ART. B-vitamin substitution for 12 months had no effect on p-NFL. The mechanism behind the correlation between homocysteine and NFL at baseline, also seen in the earlier study, is unknown and needs to be further investigated. The study will continue until 24 months of follow-up.
mapped to the V3 loop near the binding site for CCR5 and to the C-terminal heptad repeat domain.

**Conclusion:**
CSF mNGS did not identify additional infections in HIV NS escape. Preliminary VirScan data suggest that immunodominant epitopes in the CNS are highly conserved across patients, regardless of neurologic status. However, compared to similar epitopes described in sera, we identified CSF antibodies specific for the R306S mutation in the gp120 V3 region which has been associated with brain-derived env sequences and increased macrophage tropism.

<table>
<thead>
<tr>
<th>Neurologic Status</th>
<th>Treatment Status</th>
<th>Number of Patients</th>
<th>Time of CSF Samples</th>
<th>Neuronal Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varied</td>
<td>CSF ART (younger)</td>
<td>4</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Varied</td>
<td>CSF ART (sicker)</td>
<td>4</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Neurocysticlastic CSF exacer.</td>
<td>CSF ART (younger)</td>
<td>4</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Neurocysticlastic CSF exacer.</td>
<td>CSF ART (sicker)</td>
<td>4</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>CSF-opportunistic infection</td>
<td>CSF ART</td>
<td>4</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>HIV-associated neurocysticlastic disorder (HAND)</td>
<td>CSF ART</td>
<td>4</td>
<td>3</td>
<td>33</td>
</tr>
</tbody>
</table>

### 406 A RANDOMIZED TRIAL OF ADJUNCTIVE TELMISARTAN TO REDUCE CNS INFLAMMATION IN ACUTE HIV

**Michael J. Peluso,1 Eugene Kroon,2 Phillip Char,2 Somporn Tipsuk,3 Carlo Saccalani,1 Jennifer Chiarella,1 Magnus Gisslén,1 Henrik Zetterberg,1 Rob Gorelick1,2 Duanghathai Suttichom3,4 Napapon Salasuta3,4 Robert Paul5, Jintanat Ananworanich6,7 Robert Paul,7 Jintanat Ananworanich8,7 Serena S. Spudich9,10 for the RV408/SEARCH 018 Study Team**

1University of Gothenburg, Gothenburg, Sweden, 2Thai Red Cross AIDS Research Center, Bangkok, Thailand, 3Yale University, New Haven, CT, USA, 4University of Gothenburg, Gothenburg, Sweden, 5National Cancer Institute, Frederick, MD, USA, 6University of Hawaii, Honolulu, HI, USA, 7University of Missouri St Louis, St Louis, MO, USA, 8US Military HIV Research Program, Silver Spring, MD, USA, 9University of California San Francisco, San Francisco, CA, USA, 10Yale University, New Haven, CT, USA

**Background:** Telmisartan is an angiotensin II receptor antagonist that inhibits inflammatory cytokines and macrophage activity. We hypothesized that initiation of antiretroviral therapy (ART) with adjunctive telmisartan in acute HIV infection (AHI) would reduce inflammation and immune activation and alter the pathogenesis of HIV within the central nervous system (CNS).

**Methods:** In ART-naïve HIV+ participants with AHI, 2:1 randomization to telmisartan (n=14) or placebo (n=7) was conducted. At baseline, 48, and 72 weeks, we measured blood and cerebrospinal fluid (CSF) biomarkers of HIV infection, inflammation, and neural injury. Brain magnetic resonance spectroscopy (MRS) metabolites and neuropsychological (NP) performance assessed by a battery of 16 tests (summarized as NPZ) were evaluated at baseline and weeks 48 and 72. Wilcoxon rank sum and Mann Whitney tests examined differences within individuals and between groups at each time point.

**Results:** At baseline, there were no significant differences between ART groups in CSF biomarkers of inflammation or neurocognitive outcomes. At 48 weeks, there were no significant differences between ART and placebo groups in CSF biomarkers of inflammation or neurocognitive outcomes. At 72 weeks, there were no significant differences between ART and placebo groups in CSF biomarkers of inflammation or neurocognitive outcomes.

**Conclusion:** Telmisartan did not affect CNS biomarkers of inflammation or injury in ART-naïve HIV+ participants with AHI.

### 407 INFLAMMATORY MARKERS SHOW DYNAMIC CHANGES IN ACUTE HIV AND PREDICT COGNITIVE OUTCOMES

**August A. Longino,1 Javier R. Lama,2 Peter Brandes3,5, Eduardo Ruiz,2 Cecilia Corea,2 Serena S. Spudich,2 Christopher D. Pilcher,2 Kevin Robertson1, Rachel A. Bender Ignacio4, Ann Duey1**

1University of Washington, Seattle, WA, USA, 2Asociacion Civil Impacta Salud y Educacion, Lima, Peru, 3University of California San Francisco, San Francisco, CA, USA, 4University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 5Fred Hutchinson Cancer Research Center, Seattle, WA, USA

**Background:** In ART-naïve HIV+ participants, 39 inflammatory markers were measured in plasma (N = 87) and 37 in CSF (N = 29) at enrollment. Time from infection to enrolment (ITE) was estimated by an algorithm using testing history (type, date and result of test). NP was assessed with a 15-test battery, averaged as a total Z score derived from Peruvian normative data and administered every 24 weeks. Linear regression was used to evaluate associations between VL, biomarkers, and NP. In a subset analysis of 42 participants who started ART at enrollment, 13 of whom provided CSF samples, biomarker levels were used as predictors of change in standardized NP score from baseline (ΔNP). We adjusted for multiple comparisons with the Benjamini-Hochberg (BH) method.

**Methods:** MSM and transgender women in the Sabes study were followed with monthly testing (HIV Ab & RNA) and enrolled within 3 months of HIV acquisition. In ART-naive HIV+ participants, 39 inflammatory markers were measured in plasma (N = 87) and 37 in CSF (N = 29) at enrollment. Time from infection to enrollment (ITE) was estimated by an algorithm using testing history (type, date and result of test). NP was assessed with a 15-test battery, averaged as a total Z score derived from Peruvian normative data and administered every 24 weeks. Linear regression was used to evaluate associations between VL, biomarkers, and NP. In a subset analysis of 42 participants who started ART at enrollment, 13 of whom provided CSF samples, biomarker levels were used as predictors of change in standardized NP score from baseline (ΔNP). We adjusted for multiple comparisons with the Benjamini-Hochberg (BH) method.

**Results:** Longer ITE was associated with lower VL in CSF (β = -0.024 log 10 copies/mm 3 /day, p = 0.03) and plasma, (β = -0.037 log 10 copies/mm 3 /day, p < 0.0001). In univariate analysis, longer ITE was associated with lower levels of CSF and plasma, negatively associated with CSF CD-163 and positively associated with plasma CD-163. In the unadjusted subset analysis, higher levels of the following biomarkers predicted a negative ΔNP at a2 time points: plasma YKL-40; plasma and CSF IL-6, plasma IL-6, CSF TNF-α, CSF TNF-β, CSF IL-16, CSF TNF-α, and CSF IP-10.
Conclusion: Higher baseline values of key inflammatory biomarkers in plasma and CSF in early HIV were correlated with greater reductions in NP score over time after ART. There was also a novel pattern of CSF and plasma inflammatory marker dynamics observed in the first two months of untreated HIV infection. Additional investigation of inflammatory events during acute HIV infection could offer key information on longitudinal neurological outcomes.

Table 1: Baseline plasma and CSF biomarkers in ART-naive, recently HIV-infected participants with association to ascertain-time of infection (ETI)

<table>
<thead>
<tr>
<th>Name</th>
<th>Plasma b-1 copeps (ng/ml/day)</th>
<th>Plasma p-value</th>
<th>CSF b-1 copeps (ng/ml/day)</th>
<th>CSF p-value</th>
<th>CSF P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral load</td>
<td>-0.04</td>
<td>&lt;0.0001</td>
<td>-0.02</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>LCAM-1</td>
<td>-0.001</td>
<td>0.0013</td>
<td>-0.001</td>
<td>0.0007</td>
<td>0.015</td>
</tr>
<tr>
<td>IP-10</td>
<td>-0.01</td>
<td>0.0015</td>
<td>-0.015</td>
<td>0.0235</td>
<td></td>
</tr>
<tr>
<td>CD-149</td>
<td>0.001</td>
<td>0.0472</td>
<td>-0.005</td>
<td>0.0015</td>
<td></td>
</tr>
</tbody>
</table>

Note: * indicates a p-value < 0.05.

408 PROTEOMIC CHARACTERIZATION OF CSF EXTRACELLULAR VESICLES IN HIV PATIENTS

Debjani Guha1, David Lorenz2, Vikas Misra3, Sukrutha Chettimada4, Susan Margiello5, Dana H. Gabuzda6
1 Dana–Farber Cancer Institute, Boston, MA, USA, 2 Mt Sinai School of Medicine, New York, NY, USA

Background: Extracellular vesicles (EVs) are nano-sized particles present in most body fluids including cerebrospinal fluid (CSF). Little is known about CSF EV proteins in HIV+ individuals. In this cross-sectional study, we characterized the CSF EV proteome in HIV+ subjects and its relationship to neuroinflammation, stress responses, and HIV-associated neurocognitive disorders (HAND).

Methods: CSF EVs isolated from 20 age-matched HIV+ subjects with (n=10) or without (n=10) cognitive impairment were characterized by electron microscopy, nanoparticle tracking analysis, immunoblotting, and untargeted LC/MS/MS mass spectrometry. Functional annotation was performed by gene ontology (GO) mapping and expression annotation using Biobase Transfac and PANTHER software. Cultured astrocytic U87 cells were treated with hydrogen peroxide for 4 hours to induce oxidative stress and EVs isolated by ultracentrifugation. Selected markers of astrocytes (GFAP, GLUL), inflammation (CRP), and stress responses (PRDX2, PARK7, HSP70) were evaluated in EVs released by U87 cells following induction of oxidative stress, and in CSF EVs from HIV+ patients by immunoblotting.

Results: Mass spectrometry identified 2727 and 1626 proteins in EV fractions and EV-depleted CSF samples, respectively. CSF EV fractions were enriched with exosomal markers including Alix, synixin, tetraspanins, and heat-shock proteins, and a subset of neuronal (ENOD2, NFL, NPTN, NRXNS), astrocyte (GFAP, PEA15, S100B, SCL1A3), oligodendrocyte (MAG, MBP, MOG), and choroid plexus (ACO2, CLIC6, COMT, EZR, TTR) markers in comparison to EV-depleted CSF. Proteins related to synapses, immune/inflammatory responses, stress responses, metabolic processes, mitochondrial functions, and blood-brain barrier were also identified in CSF EV fractions by GO mapping. HAND subjects had higher abundance of CSF EVs (p<0.005) and proteins mapping to GO terms for synapses, gial cells, inflammation, and stress responses compared to those without HAND. GFAP, GLUL, CRP, PRDX2, PARK7, and HSP70 were confirmed by immunoblotting of CSF EVs of HAND subjects and were also detected in EVs released by U87 cells under oxidative stress.

Conclusion: CSF EVs derived from neurons, glial cells, and choroid plexus carry synaptic, immune/inflammation-related, and stress response proteins in HIV+ individuals with cognitive impairment, representing a valuable source for biomarker discovery.

409 EFFECT OF NON-HIV DRUGS ON NEUROCOGNITIVE DOMAINS IN A WELL-TREATED HIV POPULATION

Bernadette Jakeman1, Alexandra Scherrer2, Huldrych F. Günthard3, Matthias Cavassini4, Anna Hächfeld5, Alexandre Calmy6, Patrick Schmidt7, Enos Bernasconi8, Manuel Battegay9, Catia Marzolini10
1 University of Neuchatel, Neuchatel, Switzerland, 2 University Hospital Basel, Basel, Switzerland, 3 University Hospital Lausanne, Lausanne, Switzerland, 4 University of Geneva, Geneva, Switzerland, 5 University Hospital of Bern, Bern, Switzerland, 6 University Hospitals of Geneva, Geneva, Switzerland, 7 University Hospital of Berne, Berne, Switzerland, 8 University Hospitals of Geneva, Geneva, Switzerland, 9 Memory Clinic Felix Platter Spital, Basel, Switzerland, 10 University Hospital Basel, Basel, Switzerland.

Background: Neurocognitive impairment (NCI) remains a problem in people with HIV (PWH) despite advances in HIV management. Medications with anticholinergic (ACH) activity have been associated with NCI in aging, HIV-negative persons. Previously we described ACH use in PWH >65 years old in the Swiss HIV Cohort Study (SHCS) and the association with self-reported NCI using SHCS screening questions for memory, attention, and reasoning difficulties. The current study aimed to further assess the effect of ACH and sedative drugs on neurocognitive function in PWH who underwent detailed neuropsychological evaluation using a standardized testing battery.

Methods: A medication review was performed in PWH >45 years old enrolled in the prospective Neurocognitive Assessment in Metabolic and Aging Cohort (NAMACO), a sub-cohort of the SHCS. NAMACO participants were included regardless of self-reported NCI. Neurocognitive function was evaluated for 7 domains by trained neuropsychologists. Binary outcomes (presence/absence of impairment) were assessed for each individual domain and combined to determine overall neurocognitive function. The effect of ACH and sedative drugs on neurocognitive function was evaluated using multivariable logistic regression models adjusted for patient demographic characteristics, HIV history, comorbidities, illicit substance use, alcohol binge and delirium/delusional use.

Results: 963 PWH (88% male, 92% Caucasian, 96% virologically suppressed, median age 52 [IQR: 49-57]) were included. 16% of participants were prescribed ≥1 sedative drug and ≥1 ACH drug, with 82% of these drugs having an ACH activity score <3. 41% of participants had NCI, mainly related to impairment of motor domain. Sedative drugs were associated with impairment of verbal learning domains (OR 1.7; 95% CI 1.28-3.07; and OR 1.77; 95% CI 1.07-2.93), and ACH drugs with impairment of motor and sensory skills domains (OR 1.71; 95% CI 1.08-2.71; and OR 3.09; 95% CI 1.43-6.66). Increased risk of overall NCI was associated with sedative drugs (OR 1.55; 95% CI 1.00-2.40; p=0.048) and was borderline for ACH drugs (OR 1.58; 95% CI 0.98-2.55; p=0.06). Other significant associations with overall NCI were older age, lower education and being non-Caucasian.

Conclusion: Non-ACH drugs can contribute to NCI with sedative drugs altering attention and learning functions and ACH drugs impairing motor and sensory functions. HIV clinicians need to consider these drugs when assessing NCI.

410 ANTICHLINERGIC DRUG USE IN PATIENTS ≥ 65 YEARS OLD IN THE SWISS HIV COHORT STUDY

Bernadette Jakeman1, Alexandra Scherrer2, Huldrych F. Günthard3, Matthias Cavassini4, Anna Hächfeld5, Alexandre Calmy6, Patrick Schmidt7, Enos Bernasconi8, Manuel Battegay9, Catia Marzolini10, for the Swiss HIV Cohort Study
1 University of Neuchatel, Neuchatel, Switzerland, 2 University of Zurich, Zurich, Switzerland, 3 University Hospital Zurich, Zurich, Switzerland, 4 University of Lausanne, Lausanne, Switzerland, 5 University Hospital of Geneva, Geneva, Switzerland, 6 University Hospitals of Geneva, Geneva, Switzerland, 7 St. Gallen Cantonal Hospital, St. Gallen, Switzerland, 8 University Hospital Basel, Basel, Switzerland.

Background: Medications with anticholinergic (ACH) activity have been associated with neurocognitive impairment (NCI), particularly in elderly due to a reduced number of cholinergic receptors. People with HIV (PWH) are more likely to have NCI as they age. Additional risk factors include viral replication, chronic inflammation, antidepressive therapy (ATRT) toxicity, higher rates of depression, and previous central nervous (CNS) infections, making this population especially vulnerable to ACH effects. This study determined the prevalence of prescribed ACH drugs and their association with self-reported NCI in elderly PWH of the Swiss HIV Cohort Study (SHCS).

Methods: A literature review was performed to identify ACH drugs with documented ACH activity, supporting side effect profile, and CNS penetration. The degree of ACH activity was scored from 0 to 3, a higher score indicating more ACH activity. A medication review was performed in July 2019 for all SHCS participants ≥65 years old to assess the prevalence of prescribed medications with ACH properties. Association between ACH burden and neurocognitive complaints was evaluated using the SHCS self-reported NCI questions addressing memory loss, attention difficulties, and slowing of reasoning ability. Results: 1019 PWH (82% male) with a median age of 70 [IQR 67-74] years were included. Most patients were on ART (99%); 50.8% were integrase inhibitor regimens. The average number of non-ACH drugs was 3.1 ± 3.6, representing a
polypharmacy (i.e. >5 non-HIV drugs) prevalence of 50.2%. 200 participants (19.6%) were on >1 drug with ACH activity, with an average ACH score of 1.7. Overall, 131, 22 and 46 PWH had an ACH score of 1, 2 and >3, respectively. Antidepressants were the most prescribed ACH drugs (49.8%). Gender and age were not associated with ACH drug use however polypharmacy was (p<0.001). Self-reported NCI, adjusted for age, gender, and polypharmacy was associated with depression (OR=2.69; 95% CI 1.72-4.21) and a trend was observed with being on >1 ACH drug (OR=1.42; 95% CI 0.97-2.09; p=0.07). In a subgroup analysis of patients without depression (N=911), adjusted for age, gender, and polypharmacy, self-reported NCI was associated with the use of >1 ACH drug (OR=1.66; 95% CI 1.08-2.55; p=0.02).

Conclusion: ACH drug use is common in elderly PWH and may contribute to self-reported NCI. The effect of ACH drugs on NCI warrants further evaluation using neurocognitive tests.

BIMARKERS OF NUCLEIC ACID OXIDATION AND NEURODEGENERATION IN CSF IN PWH
Ronald J. Ellis1, David J. Moore1, Erin Sundermann1, Robert K. Heaton1, Todd Hulgan1, David C. Samuels2, Sanjay R. Mehta3, Scott L. Letendre1
1University of California San Diego, San Diego, CA, USA, 2University of California at Los Angeles, Los Angeles, CA, USA, 3Vanderbilt University, Nashville, TN, USA

Background: Oxidative stress is common in HIV, even among virologically suppressed individuals, and may contribute to or result from neurodegeneration. 7,8-dihydro-8-oxo-guanine (8-oxo-dG), representing oxidatively damaged guanine, is a marker of oxidative DNA damage. Important markers of age-related neurodegeneration include Aβ-42 reduction, reflecting amyloid deposition in brain, and CSF total Tau and neurofilament light (NFL), reflecting neuronal damage. We aimed to examine whether oxidative stress is associated with markers of AD-related neurodegeneration.

Methods: Participants were enrolled at six U.S. centers in the CNS HIV Antiretroviral Effects Research (CHARTER) study. Inclusion criteria included HIV RNA ≤50 copies/ml in plasma. Exclusions included significant CNS confounding conditions. Total Tau and Aβ-42 were measured in CSF and plasma by bead suspension array. NFL in CSF and 8-oxo-dG in CSF and plasma were measured using ELISA. Peripheral blood mitochondrial (mt) DNA copy number was obtained from genome-wide genotyping data as a ratio of mtDNA single-nucleotide polymorphism probe intensities relative to nuclear DNA single-nucleotide polymorphisms.

Results: Participants were 53 PWH, mean age 55 (+/-9.3), 19% women, 48% non-Hispanic white. Higher 8-oxo-dG correlated with markers of neurodegeneration including lower CSF Aβ-42 (r=-0.34; p=0.012), higher CSF NFL (r=0.39; p=0.0091) and higher total Tau (r=-0.6696; p<0.001). CSF 8-oxo-dG was not related to age, sex, or ethnicity. Aβ-42 was significantly lower in women and African Americans. Higher NFL levels were seen in men and older individuals. Higher total Tau was seen with increasing age. Relationships between 8-oxo and neurodegeneration markers remained after adjusting for demographic variables. 8-oxo-dG was higher among PWH exposed to dideoxynucleoside antiretrovirals. Levels of protein carbonyls, a marker of protein oxidation, were not related to neurodegeneration. Higher 8-oxo-dG, but not protein carbonyls, correlated with lower mtDNA copies per cell (r=-0.59; p=0.027 and r=-0.31; p=0.27, respectively).

Conclusion: Among virologically suppressed PWH, nucleic acid oxidation was associated with CSF biomarkers of neurodegeneration. Potential sources of oxidative stress in PWH include low-level HIV replication, inflammation, and specific ART drugs. Results suggest that the higher levels of oxidative stress among PWH may play a role in neurodegeneration.

PREDICTIVE VALIDATION OF AN UGANDAN INFANT EYE-TRACKING TEST OF MEMORY OF HUMAN FACES
Michael J. Boivin1, Tiazar Familiar-Lopez2, Alla Sikorski2, Ronak Chhaya1, Kwabena Nkansah-Amankra3, Aatirah Holmes4, Jonathan Weiss1, Victoria Seffren5, Ethan G. Arima5, Oujja J. Caes1, Noeline Nakasajja6
1Michigan State University, East Lansing, MI, USA, 2University of Michigan, Ann Arbor, MI, USA, 3Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, 4Makerere University College of Health Sciences, Kampala, Uganda

Background: Neurodevelopmental assessments in early childhood followed by neurocognitive assessments during the preschool–age years are sometimes used to monitor HIV-affected children in resource–constrained settings. Using an automated neurocognitive performance test at one-year of age, we evaluated its predictive validity with neuropsychological performance on validated preschool measures several years later.

Methods: 58 uninfected children (25 boys, 33 girls) of mothers with HIV were evaluated at one year of age with the Mullen Scales of Early Learning (MSEL) and the Fagan test of Infant Intelligence (FTII). FTII tests for recognition for pictures of local adult and children faces, using Tobii eye tracking instrumentation to measure gaze direction and duration during successive trials where familiar (previously presented) and novel faces were presented together. After familiarization trials, longer gaze to novel faces is expected. Total screen viewing duration (either face combined) was used as a measure of attention. Most of these children were then tested several years later with the Kaufman Assessment Battery for Children, 2nd Edition (KABC-2) and the visual computerized Tests of Variables of Attention (TOVA). Evaluation took place at the Tororo District Hospital in eastern Uganda.

Results: FTII proportion of time viewing novel (vs. familiar) faces was significantly related to overall KABC-2 performance (eta2=0.07), related especially to auditory working memory (KABC Number Recall; p<0.05). FTII proportional preference for novel faces was significantly related to TOVA percent omission errors (vigilance attention). FTII overall attention was related to KABC Hand Movements (eta2=0.11), Rebus (symbol coding learning; eta2=0.13) and TOVA D prime (signal detection; eta2=0.06). MSel and FTII performance were not significantly related to one another, suggesting they measure different things. MSEL cognitive ability did predict several TOVA performance measures.

Conclusion: An eye-tracking based measure of infant measure of attention and working memory (human faces) can predict aspects of neurocognitive performance several years later. Gathering test results automatically, eye tracking-based cognitive assessments in infants can be beneficial in evaluating neurocognitive risk in HIV-infected and affected children; gauging benefits from early treatment and supportive care. We thus provide an innovative performance-based window into the integrity of brain/behaviour development in infancy.

LOW NEUROSTEROIDS IDENTIFIES A BIOLOGICAL SUBTYPE OF DEPRESSION IN PEOPLE WITH HIV
Shibani S. Mukerji1, Vikas Misra1, David Lorenz2, Sukrutha Chettimada2, Kiana Keller2, Scott L. Letendre1, Ronald J. Ellis1, Susan Morgello2, Robert A. Parker1, Dana H. Gabuzda3
1Massachusetts General Hospital, Boston, MA, USA, 2Dana–Farber Cancer Institute, Boston, MA, USA, 3University of California San Diego, San Diego, CA, USA, 4Mt Sinai School of Medicine, New York, NY, USA

Background: The prevalence and mortality risk of depression in people with Human Immunodeficiency Virus infection (PWH) on antiretroviral therapy

LOW NEUROSTEROIDS IDENTIFIES A BIOLOGICAL SUBTYPE OF DEPRESSION IN PEOPLE WITH HIV
Shibani S. Mukerji1, Vikas Misra1, David Lorenz2, Sukrutha Chettimada2, Kiana Keller2, Scott L. Letendre1, Ronald J. Ellis1, Susan Morgello2, Robert A. Parker1, Dana H. Gabuzda3
1Massachusetts General Hospital, Boston, MA, USA, 2Dana–Farber Cancer Institute, Boston, MA, USA, 3University of California San Diego, San Diego, CA, USA, 4Mt Sinai School of Medicine, New York, NY, USA

Background: The prevalence and mortality risk of depression in people with Human Immunodeficiency Virus infection (PWH) on antiretroviral therapy

LOW NEUROSTEROIDS IDENTIFIES A BIOLOGICAL SUBTYPE OF DEPRESSION IN PEOPLE WITH HIV
Shibani S. Mukerji1, Vikas Misra1, David Lorenz2, Sukrutha Chettimada2, Kiana Keller2, Scott L. Letendre1, Ronald J. Ellis1, Susan Morgello2, Robert A. Parker1, Dana H. Gabuzda3
1Massachusetts General Hospital, Boston, MA, USA, 2Dana–Farber Cancer Institute, Boston, MA, USA, 3University of California San Diego, San Diego, CA, USA, 4Mt Sinai School of Medicine, New York, NY, USA

Background: The prevalence and mortality risk of depression in people with Human Immunodeficiency Virus infection (PWH) on antiretroviral therapy

LOW NEUROSTEROIDS IDENTIFIES A BIOLOGICAL SUBTYPE OF DEPRESSION IN PEOPLE WITH HIV
Shibani S. Mukerji1, Vikas Misra1, David Lorenz2, Sukrutha Chettimada2, Kiana Keller2, Scott L. Letendre1, Ronald J. Ellis1, Susan Morgello2, Robert A. Parker1, Dana H. Gabuzda3
1Massachusetts General Hospital, Boston, MA, USA, 2Dana–Farber Cancer Institute, Boston, MA, USA, 3University of California San Diego, San Diego, CA, USA, 4Mt Sinai School of Medicine, New York, NY, USA

Background: The prevalence and mortality risk of depression in people with Human Immunodeficiency Virus infection (PWH) on antiretroviral therapy
(ART) is higher than in the general population, yet biomarkers for therapeutic targeting are unknown. Here, we aimed to identify plasma metabolites associated with depressive symptoms in PWH on ART.

**Methods:** This is a prospective study of 99 ART-treated HIV-infected adults (94% with plasma VL < 200 copies/ml) with or without depressive symptoms assessed using the Beck Depression Inventory (BDI) from the NRTC and NWRC cohorts. Participants with BDI scores > 20 were classified as having high depressive symptoms. Plasma metabolite profiles from 55 participants comprised the discovery set; profiles from 44 additional participants were used to validate the accuracy of models. Metabolite profiling was performed using ultra high-performance liquid chromatography and tandem mass spectrometry (UHLC/MS/MS2) and gas chromatography/MS.

**Results:** Median age, CD4+ T-cell count, and nadir CD4+ T-cell count were 50y, 373 cells/µl, and 66 cells/µl in the discovery cohort and statistically similar to the validation set. Seventeen (31%; median BDI 32) and 18 (41%; median BDI 23) participants were classified as having high depressive symptoms in the discovery and validation cohort, respectively. Participants with depressive symptoms had lower neuroactive steroids (dehydroepiandrostosterone sulfates (DHEA-S), androstenediols, pregnenolon sulfates) compared to those without depressive symptoms. Cortisol/DHEA-S ratio, an indicator of hypothalamic-pituitary-adrenal axis imbalance, was associated with depressive symptoms due to low DHEA-S (Figure), and discriminated between participants with high vs. low depressive symptoms with AUC of 0.70 (p=0.03, discovery) and 0.80 (p<0.02, validation). When cortisol-DHEA-S was coupled with androstenediol and pregnenolon sulfates, discrimination improved with AUC of 0.81 (discovery) and 0.85 (validation). The odds of having high depressive symptoms increased with higher cortisol/DHEA-S ratios (odds 2.5 per z-score, 95% confidence interval 1.3-4.7), independent of age and gender. Kynurenine to tryptophan ratio showed no significant associations.

**Conclusion:** These findings suggest that altered neuroactive steroid metabolism may contribute to the pathophysiology of depression in ART-treated HIV-infected adults, representing a potential biological pathway for therapeutic targeting.

**Figure:** (A) lines and scatter plots illustrating the median and interquartile ranges for cortisol and dehydroepiandrosterone sulfate (DHEA-S) metabolites, and cortisol/DHEA-S ratios in participants with low versus high depressive symptoms in discovery (left) and validation (right) cohorts. (B) Receiver operating characteristic (ROC) curve from logistic regression models assessing low versus high depressive symptom participant classification using cortisol/DHEA-S ratio (z-score) or cortisol/DHEA-S ratio with androstenediol and pregnenolon sulfates in the discovery and validation cohorts. AUC denotes the area under the ROC curve. 

---

**414 ANTICHLONERGIC BURDEN IS ASSOCIATED WITH DEPRESSIVE SYMPTOMS IN PERSONS WITH HIV**

**Asante R. Kamkwala1, Qing Ma2, Maile Y. Karris3, Erin Sundermann1, Ronald J. Ellis1, David J. Moore1, Leah H. Rubin1, Scott L. Letendre1**

1. Johns Hopkins University, Baltimore, MD, USA, 2. University at Buffalo, Buffalo, NY, USA, 3. University of California San Diego, San Diego, CA, USA

**Background:** Persons with HIV (PWH) have a higher risk of depression and neurocognitive (NC) impairment than the general population. PWH are also at greater risk for polypharmacy, which increases the risk of adverse events. Many prescribed drugs have anticholinergic (AC) effects, which are risk factors for depression and NC in the general population and could contribute to the risk of these conditions in PWH.

**Methods:** To determine the relationships between AC effects and either depressive symptoms or cognitive performance, we analyzed data from 608 PWH on ART who had plasma HIV RNA ≤ 200 copies/mL. AC effects were quantified using the published AC burden (ACB) method. Depressive symptoms were quantified using the Beck Depression Inventory (BDI). Cognitive performance was assessed using a standardized, comprehensive neuropsychological test battery that assessed seven cognitive domains and was summarized by global and domain T scores. Analytical methods included correlation, analysis of variance, and multivariable regression that included demographic, HIV, and AC effects and other influential characteristics, including psychiatric diagnoses.

**Results:** Participants were mostly middle-aged (mean 44.6 years), European ancestry (55.4%) men (85.4%) who had taken ART for more than 4 years (53.0%) and whose current CD4+ T-cell count was >500/µL (54.2%). Median global T-score was 45.8 and median BDI was 12.7. Two hundred fifty-seven (42.3%) took at least one AC drug: The most common were codeine (9.0%), bupropion (8.9%), and trazodone (7.3%). Higher ACB was associated with worse BDI (p=0.22, p<0.0001) and global T score (p=0.19, p<0.0001). All seven cognitive domains were affected (p range 0.006 to <0.0001). In multivariable regression models, ACB remained associated with worse BDI (p=0.0001, model R2=0.41, p<0.0001) and trended toward association with global T score (p=0.07, model R2=0.21, p<0.0001). Addition of number of prescribed drugs to models weakened the association of ACB with Global T score below statistical significance (p=0.73) but not with BDI (p=0.003). The AC drugs most strongly associated with BDI were paroxetine, trazodone, atropine, olanzapine, and hydroxyzine.

**Conclusion:** AC drugs are associated with more depressive symptoms, even after accounting for other influential characteristics, including psychiatric diagnoses. This cross-sectional analysis cannot establish causality but eliminating AC drugs from medication regimens may improve depressive symptoms.

---

**415 ASSOCIATION BETWEEN LUNG AND COGNITIVE DISFUNCTION IN MEN WITH HIV INFECTION**

**Yoseob J. Hwang1, Seyed M. Nouraie2, James T. Becker3, Dong Chang3, Audrey French3, Ken M. Kunisaki4, Andrew Levine3, Eileen Martin5, Meredith C. McCormack6, Ned Sacktor2, Andrea M. Weinstein7, Alison Morris8**

1. University of Pittsburgh, Pittsburgh, PA, USA, 2. University of California Los Angeles, Los Angeles, CA, USA, 3. Rush University, Chicago, IL, USA, 4. University of Minnesota, Minneapolis, MN, USA, 5. Johns Hopkins University, Baltimore, MD, USA

**Background:** Lung dysfunction associated with chronic obstructive pulmonary disease (COPD) is common in HIV and a risk factor for developing cognitive dysfunction, a well-recognized comorbidity among persons with HIV infection. We evaluated the relationship between lung and cognitive function in men with and without HIV infection.

**Methods:** We performed a cross sectional analysis of participants in the Multicenter AIDS Cohort Study (MACS). Participants underwent pulmonary function testing including, diffusion capacity for carbon monoxide (DLCO; a measure of oxygen diffusion from the lungs to blood) and forced expiratory volume in one second/forced vital capacity ratio (FEV1/FVC; a measure of airway obstruction used to diagnose COPD). The neuropsychological test battery assessed Executive Function, Speed (of information processing), Attention and Working Memory; Learning, Memory, and Motor functional domains. A T score was derived for each functional domain. Multivariable linear regression models estimated the association between the measures of lung and cognitive function.

**Results:** Among 866 participants, 477 (55.1%) had HIV infection. The mean (standard deviation) of the participants was 52 (12) years. The majority were Caucasian (58.1%). Although a lower DLCO was associated with a lower Executive Function among men without HIV infection (β=0.10; p=0.01), this was not the case among the HIV-infected men (β=0.07; p=0.11). Lower levels of DLCO were associated with lower Speed scores among HIV-infected men (β=0.10; p=0.03), but not among the unaffected men (β=0.00; p=0.91). Among men without HIV infection, a lower FEV1/FVC was associated with reduced Learning (β=0.64; p=0.02) and Memory scores (β=0.13; p=0.01). However, among the HIV-infected men, the associations of FEV1/FVC with Learning (β=0.02; p=0.27) and Memory (β=0.47; p=0.05) did not reach statistical significance.

**Conclusion:** Reduced lung function was associated with poorer cognitive function in the domains of Executive Function, Speed, Learning, and Memory. However, these associations differed by HIV status. appear to be modified by HIV status. Future studies are needed to better elucidate the pathophysiology...
mechanisms by which airway obstruction and reduced oxygen diffusion in the lungs interact with HIV status to contribute to cognitive dysfunction.

Table 1. Relationship between lung and cognitive function in individuals with and without HIV

<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>Pulmonary Function Test</th>
<th>Individuals with HIV</th>
<th>Individuals without HIV</th>
<th>p</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive</td>
<td>FEV1/FVC</td>
<td>0.59 (0.48-0.62)</td>
<td>0.94 (0.82-1.03)</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>DLCO</td>
<td>0.07 (0.02-0.13)</td>
<td>0.09 (0.02-0.13)</td>
<td>0.10</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>DCO</td>
<td>0.39 (0.30-0.48)</td>
<td>0.40 (0.35-0.48)</td>
<td>0.45</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Atelectasis and</td>
<td>0.19 (0.12-0.23)</td>
<td>0.20 (0.12-0.23)</td>
<td>0.06</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Working capacity</td>
<td>0.04 (0.01-0.13)</td>
<td>0.04 (0.01-0.13)</td>
<td>0.00</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Learning</td>
<td>0.02 (0.00-0.03)</td>
<td>0.00 (0.00-0.03)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Memory</td>
<td>0.74 (0.65-0.82)</td>
<td>0.74 (0.65-0.82)</td>
<td>0.40</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Noise</td>
<td>0.02 (0.00-0.03)</td>
<td>0.00 (0.00-0.03)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

417 IMPACT OF WEB-BASED COGNITIVE TRAINING ON WORKING MEMORY IN COCAINE USERS WITH HIV

Sheri L. Tong†, Yunan Xu, Christina S. Meade

†Duke University, Durham, NC, USA

Background: Cocaine use is disproportionately prevalent among persons with HIV, and it is known to exacerbate HIV-associated neurocognitive impairments, specifically working memory, that contribute to impulsive decision making. This study tested the effectiveness of a web-based cognitive training intervention to improve working memory and reduce impulsivity in HIV-infected cocaine users.

Methods: In this randomized controlled trial, participants were assigned to one of two conditions of 48 cognitive training sessions, each lasting 20-30 minutes, over 10 weeks. Games in the active condition (ACT) targeted working memory, while games in the control condition (CON) targeted other domains. Each session included a random sampling of 4 out of possible 8 games repeated once back-to-back. Participants completed clinical interviews and comprehensive neuropsychological testing at baseline and post-intervention, as well as a process measure to provide feedback on the intervention.

Results: The sample of 58 participants was 48.6 years old on average, mostly male (71%) and African American (80%). Participants completed 37.3 of the 48 possible sessions on average, with no difference by condition, and 56 participants (97%) completed the post-intervention follow-up. We conducted repeated measures ANCOVAs on working memory (domain deficit score) and delay discounting (natural log k-value), controlling for age, education, and number of games improved (as proxy of intervention engagement). In the intent-to-treat sample, there was a significant group-by-time interaction for working memory with a medium effect size (F(1, 5) = 4.470, p = 0.039, eta squared = 0.081), such that ACT had greater improvements relative to CON. For delay discounting, there was a similar pattern, again with a medium effect, but the interaction effect was not significant (F(1, 48) = 3.546, p = 0.066, eta squared = 0.069). Overall, participants rated the sessions as helpful (M=4.09, on 5 point scale), but those in ACT perceived greater improvement on the games over time (M=4.39 (0.69) vs. 3.89 (0.92); t(54)= 2.31, p = .025).

Conclusion: Our findings support the acceptability and potential effectiveness of cognitive training to improve working memory in HIV-infected cocaine users. A larger trial with a longer duration of training targeting more domains is needed to test the durability of effects and improvement in daily living.

418 RETINAL THINNING CORRELATES WITH BRAIN ATROPHY IN WELL-CONTROLLED HIV INFECTION

Bryan Smith1, Katrina Geannopoulos1, Ramiro Maldonado2, Tianxia Wu1, Elizabeth E. Horne1, Lillian Ham2, Joseph Snow3, Govind Nair1, Daniel S. Reich1, Chuen-Yen Lau1, Emily Chew2, Avindra Nath1

1National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, 2NIH, Bethesda, MD, USA, 3NIAID, Bethesda, MD, USA

Background: Retinal measurements correlate well with neurologic disease in multiple sclerosis, however whether such measurements correlate with neurologic disease in well-treated persons living with HIV (PLWH) is unknown. We evaluated differences in retinal measures by spectral domain optical coherence tomography (SD-OCT) between PLWH and uninfected controls and correlations with the retinal measures and brain volumes, neuropsychological (NP) function, and markers of neuronal injury and neuroinflammation.

Methods: SD-OCT was performed on 69 PLWH and 28 uninfected controls. Participants also underwent brain MRI, neuropsychological testing, and an optional lumbar puncture. All procedures, including the SD-OCT, were completed for research only and there were no
clinical indications. Mean retinal nerve fiber layer (RNFL) and ganglion cell inner plexiform layer (GC-IPL) thicknesses were compared between groups using ANCOVA, and means were correlated with pre-selected MRI brain volumes, NP domain scores, and CSF cytokines and neurofilament light chain.

**Results:** There were no differences in age, race or visual acuity between the two groups; there were more women in the control group (p < 0.006). In the HIV+ group, the median time since diagnosis was 19 years and all had an HIV RNA level <100 copies/ml for at least one year prior to the SD-OCT. Multiple regression analyses indicated that the HIV+ group had thinner adjusted-mean RNFL (78.17µm, 95% CI 76.3, 80.0; control = 84.0µm, 95% CI 81.3, 86.5; p < 0.005) and GC-IPL (90.0µm, 95% CI 87.0, 92.6; control = 96.6µm, 95% CI 92.2, 101.0; p = 0.01). In the HIV+ group, retinal thicknesses were negatively associated with the fraction of CSF volume (i.e., brain atrophy) on MRI (p = 0.01 for RNFL and 0.006 for GC-IPL). There were few associations with NP domains and CSF measurements.

**Conclusion:** PLWH on ART had thinning of the RNFL and the GC layer of the retina. This retinal thinning was asymptomatic but was strongly associated with measures of brain atrophy. This suggests that there is widespread neurodegeneration including the retina despite adequate ART.

**Results:** Our results revealed higher levels of human hematopoietic cells in the brains of MuM-BLT (p = 0.0076) and HuM-BLT (p = 0.0534 [7.4x higher]) mice compared to GF BLT mice. Total human T cell, CD4+ T cell and CD8+ T cell numbers were significantly higher in the brains of HuM-BLT (p = 0.0034, p = 0.0034 and p = 0.0106 respectively) and MuM-BLT (p = 0.0041, p = 0.030, p = 0.0076 respectively) mice compared to GF BLT mice. Human B cell and myeloid cell levels were not significantly different.

**Conclusion:** Collectively, our results demonstrate that gut microbiota regulate immune cell homeostasis in the CNS and provide the first evidence that gut microbiota may have a direct role in HIV pathogenesis and the establishment and maintenance of the CNS HIV reservoir.

**420 CSF1R INHIBITION TARGETS CNS MACROPHAGES IN AN SIV/MACAQUE MODEL OF HIV CNS DISEASE**

**Methods:** Primary brain and spinal cord microglia were isolated from uninfected macaques. Cells were cultured for one week before treatment with 10µM PLX3397, a small molecule inhibitor of CSF1R, or vehicle. Calcine and ethidium staining was used to identify live and dead cells. Live cells were also quantified using interferon-beta qPCR. In vivo studies were conducted using daily oral treatment of 165mg/kg PLX3397 in ART-suppressed SIV-infected pigtailed macaques (N = 2). Two weeks after the start of PLX3397 treatment, ART was stopped while PLX3397 treatment continued. Plasma and CSF were collected every four days after release to measure viral loads. Animals were euthanized 16 days post-release from ART. Brain and spinal cord microglia were isolated after euthanasia to measure viral RNA, DNA, and replication competence.

**Results:** PLX3397 treatment in vitro significantly reduced the number of primary microglia over 72 hours (P < 0.0001). Two-Way ANOVA. In vivo, PLX3397 treatment was well tolerated; animals did not show side-effects or develop monocytopenia. PLX3397 did not significantly affect plasma viral rebound kinetics. However, treatment did prevent CSF rebound in one animal. In addition, neither SIV RNA nor DNA was detected in cultured primary microglia from this animal. In the second animal, viral RNA was isolated from CNS macrophages cultured from both brain and spinal cord.

**Conclusion:** PLX3397 reduced CNS macrophage viability in vitro, demonstrating that targeting CSF1R may reduce CNS macrophages, including those harboring HIV. PLX3397 treatment was associated with a lack of SIV rebound from the CNS and a decrease in INI+ CNS macrophages in one of two animals after stopping ART. These studies demonstrate the potential of targeting CSF1R to reduce the CNS latent reservoir.

**421 METAGENOMIC NEXT-GENERATION SEQUENCING FOR DIAGNOSIS OF CNS INFECTION IN PLWH**

**Methods:** Direct experimentation in humans to establish gut microbiota's role in CNS immune homeostasis is not possible. We established an in vivo platform to investigate gut microbiota’s role in human hematopoietic cell homeostasis in the brain. We generated germ-free (GF) bone marrow/liver/thymus (BLT) humanized mice and BLT mice colonized with human (HuM-BLT mice) or murine (MuM-BLT mice) gut microbiota. First, we rederived GF immunodeficient NSG mice. GF NSG mice were implanted with human thymus/liver tissue and transplanted with autologous stem cells in a GF surgical isolator. HuM-BLT and MuM-BLT mice were constructed by colonizing GF mice with human or mouse fecal microbiota. Using flow cytometry, we quantitated human T cells (CD4+ and CD8+), B cells and myeloid cells in the brains of BLT (n=10), HuM-BLT (n=14), and MuM-BLT (n=10) mice.
422 EXPRESSION OF HIV-1 INTRON-CONTAINING RNA IN MICROGLIA INDUCES INFLAMMATORY RESPONSES

Hisashi Akiyama1, Sallieu Jalloh1, Seonmi Park2, Gustavo Mostoslavsky3, Rahm Gummuluru3

1Boston University, Boston, MA, USA

Background: Chronic immune activation is observed in HIV-infected individuals on long-term combination antiretroviral therapy (cART) and is thought to lead to HIV-associated non-AIDS complications (HANA) such as neurocognitive impairment. We have recently reported that expression of HIV intron-containing RNA (icRNA) alone in productively infected monocyte-derived macrophages induces proinflammatory responses (PMID 30150664). Hence, in this study, we tested the hypothesis that persistent expression of HIV icRNA in microglia (MG), the brain-resident macrophage, contributes to neuroinflammation.

Methods: Monocyte-derived microglia (MDMGs) were derived from CD14+ cells purified from PBMCs. Human iPS-derived pluripotent stem cell (hiPS)-derived microglia (hiMG) were generated by co-culturing yolk-sac-derived primitive macrophages and iPSC-neurons. Expression of MG markers such as P2RY12, IBA-1 and TMEM119 was confirmed by qRT-PCR or flow cytometry. Microglia were infected with HIV-1, and extent of viral infection and induction of proinflammatory responses was determined by mRNA analysis (NanoString, qRT-PCR), flow cytometry and ELISA.

Results: HIV-1 infection in MDMGs up-regulated expression of iPSs and proinflammatory cytokines such as IP-10 and MCP-1. Treatment of infected MDMGs with raltegravir or a CRM1 inhibitor that blocks Rev–CRM1-dependent nuclear export of HIV-1 icRNA, or infection of MDMGs with Rev-mutant (M10) deficient for icRNA export did not induce IP-10 expression, suggesting that nuclear export of HIV-1 icRNA but not Rev or Tat expression is the trigger for proinflammatory responses in MDMGs. To better mimic the yolk-sac origin of MG, we generated hiMGs and found that hiMGs were robustly infected with replication competent CCR5-tropic HIV-1 (YU2). Importantly, establishment of productive infection led to secretion of proinflammatory cytokines IP-10 and MCP-1, which was inhibited upon pre-treatment with raltegravir or CRM1 inhibitor. Interestingly, HIV-infected hiMGs displayed poor phagocytic activity, suggesting that HIV infection negatively impacts homoeostatic functions of MG.

Conclusion: Collectively, our findings suggest that viral gene expression and nuclear export of HIV icRNA, even in the absence of viral spread, induces proinflammatory responses in microglia and suppresses their homoeostatic functions. Since none of the current cART regimens inhibit viral RNA expression, novel strategies are needed to suppress HIV icRNA expression-induced immune activation.

423 ACCELERATING CELLULAR SENESCENCE IN THE BRAIN OF SIV-INFECTED YOUNG RHESUS MACAQUES

Fei Wu1, Robert Blair1, Binhua Ling1

1Tulane National Primate Research Center, Covington, LA, USA

Background: HIV infection plays a role in accelerating aging. Limited studies have found cellular senescence can occur in some tissues in HIV-infected individuals. However, it is unclear whether HIV infection can accelerate senescence in the brain partially due to challenges of access to human brain tissues. Here we used the SIV infected rhesus macaque model to determine whether SIV contributes to aging of the brain.

Methods: Four groups of rhesus macaques were studied, which included SIVmac251-infected young (Mean 6.65 ± SD 0.94 years) and old aged animals (Mean 20.26 ± SD 3.91 years), and SIV-naive age-matched animals for comparison. Brain frontal lobes were collected and formalin-fixed paraffin-embedded. Lipofuscin, p16, p21, Cyclin D1 (CCND1), and Cavolin 1 (CAV1) were used as biomarkers of brain cellular senescence, and measured by RNAseq, RT-qPCR, and/or immunohistochemistry. Image data quantification analysis was performed by HALO and ImageJ software.

Results: As expected, in healthy SIV-naive groups, a significantly higher amount of lipofuscin was observed in old animals than young animals. However, interestingly, this age-dependent discrepancy disappeared between groups of young and old animals with SIV infection, although both groups had higher levels of lipofuscin than young uninfected group. Moreover, the increase of lipofuscin was significantly higher in SIV-infected young animals than those age-matched animals without SIV infection, this was not observed between the older groups of animals with or without SIV infection. CAV1 gene expression was significantly increased in the SIV-infected young animals. CCND1 was significantly higher in uninfected older animals than uninfected young animals, but SIV infection of young animals reduced this difference to insignificant. In the young groups, SIV infected animals had a higher expression levels of p21, CCND1, and CAV1 than uninfected cohorts.

Conclusion: Our results demonstrate that SIV infection contributes to accelerating brain cellular senescence in young rhesus macaques. Given that senescent cells in the brain contribute to the cognitive decline and neurodegeneration, our findings indicate that they play an important role in the acceleration of brain aging in young hosts and possibly towards to the development of HIV-associated neurocognitive disorders.
Background: One line of evidence that the CNS may be a source for HIV in the face of ART is cerebrospinal fluid (CSF) escape, where HIV is suppressed in the blood but detectable in the CSF. However, it is unclear if CSF HIV is CNS restricted or can transmit to other sites. For the latter, HIV requires high-level drug resistance and infection of a cell able to traffic out of the CNS. Here we investigated the cell of origin of HIV in the CSF of CSF escape study participants, as well as whether the ART concentrations found in the CSF could result in the evolution of high level resistance necessary for HIV replication outside the CNS compartment.

Methods: We collected blood and CSF from 122 South African participants clinically indicated for lumbar puncture. We performed a viral load assay and detected concentrations of antiretroviral drugs in the blood and CSF and chose participants on the first line regimen of efavirenz, emtricitabine, and tenofovir for further study to avoid confounding effects of regimen type. For CSF escape participants (22% of total), we used the COBAS 2018 host cell surface markers on the virion envelope to determine the cellular source of HIV using binding to anti-CD26 and CD36 antibody columns, followed by viral load assay of bound virus. The cell type specific signature of CD26 and CD36 was determined from in vitro infected macrophages and T cells and was unambiguous for these cell types. We also examined the effect of measured ART levels of CSF escape participants on HIV replication and evolution using in vitro infection.

Results: We observed that the CD26/CD36 signature on the viral surface of HIV from CSF escape was consistent with T cell origin of the CSF virus. This was also the case for CSF HIV from participants who were viremic in both compartments. ART levels of efavirenz, emtricitabine, and tenofovir were not significantly different between individuals with CSF escape and those who were fully suppressed. Furthermore, HIV replication at CSF ART levels was required in vivo for progression to high level, multidrug resistance and replication at ART levels found in the blood.

Conclusion: The combination of an infected cell type able to disseminate infection and ART levels conducive to stepwise evolution of resistance implicates the CNS as a source for the spread of drug resistant virus in the face of ART.

HIV-1 VIRAL DIVERSITY AND RESISTANCE IN CENTRAL NERVOUS SYSTEM BY DEEP SEQUENCING

Eleni Giatsou1, Basma Abdi1, Isabelle Plu1, Nathalie Desire1, Romain Palich1, Danielle Seilhean1, Vincent Calvez2, Anne-Genèvieve Marcellin1, Aude Jary1

1AP–HP, Hôpitaux Universitaires Pitié Salpêtrière, Paris, France

Background: The central nervous system (CNS) compartment is one of several sites in which compartmentalized HIV-1 replication has been observed. Most studies assessed viral compartmentalization in the CNS via cerebrospinal fluid, however, information about tissue compartmentalization of HIV-1 is still limited.

Methods: We used ultra-deep sequencing (UDS) to study viral diversity and resistance patterns in different brain areas by analyzing reverse transcriptase (RT) gene. Twelve samples from 3 patients (P1, P2 and P3) with possible or certain HIV-encephalopathy were studied and sequencing was performed on MiSeq (Illumina®). HIV proviral DNA reservoir quantification was performed with Generic HIV DNA Cell® kit and diversity by (i) phylogenetic analysis with approximately-maximum-likelihood phylogenetic trees with Fasttree 2.1, (ii) single-nucleotide polymorphism on GenoType Prime software and (iii) HIV-1 genotypic drug resistance identification with algorithms 2018 administered by ANRS.

Results: HIV-proviral DNA was undetectable in all P1 samples and in P2 cerebellum and thalamus sample. P2 temporal lobe and medulla oblongata sample as well as P3 specimens showed detectable proviral-DNA loads by increasing order: cerebellum (23 cp/10^6 cells), medulla oblongata (31 cp/10^6 cells), temporal lobe (91 cp/10^6 cells), substantia nigra (29 cp/10^6 cells), caudate nucleus (130 cp/10^6 cells) and frontal lobe (544 cp/10^6 cells). Overall, RT phylogenetic analysis revealed (i) a high diversity in each site analyzed, and (ii) HIV compartmentalization within different brain areas with a majority of them harboring a distinct HIV subpopulation. However, some cerebral sites also shared HIV variants; caudate nucleus and spinal cord in P1 or caudate nucleus, cerebellum and frontal lobe in P3 (Figure 1). On the other hand, brainstem (substantia nigra and oblongata specimen) area harbored a specific subpopulation in both P2 and P3. Some non-syzygous conferring resistance to Nucleoside and Non-Nucleoside Reverse Transcriptase Inhibitors were found, specifically M41L, Y90L and V106I. However, the presence or proportion of variants carrying these mutations varied within different brain areas of the same patient.

Conclusion: This work showed by UDS significant inter-regional and intra-regional viral diversity in CNS reflecting viral replication. It also confirmed HIV-compartmentalization in different brain areas suggesting that there is not a single but several reservoirs within CNS.

HIV DIVERSITY IN CSF AND PLASMA OF INDIVIDUALS WITH HIV AND CRYPTOCOCCAL MENINGITIS

Nametso Kelente1, Sikhulile Moyo1, Mampati L. Mogwe2, Kusa Lechile1, Kaelo Seatla1, Natasha O. Moraka1, Kwana Lechiile1, Joseph N. Jarvis1, Simani Gasetsewe1

1University of Botswana, Gaborone, Botswana, 2Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 3Stellenbosch University, Tygerberg, South Africa, 4Botswana–UPenn Partnership, Gaborone, Botswana, 5London School of Hygiene & Tropical Medicine, London, UK, 6St. George’s University of London, London, UK

Background: HIV-1 can compartmentalize in reservoir sites e.g. the central nervous system (CNS) and this is a barrier to complete HIV eradication. We compared cerebrospinal fluid (CSF) and plasma viral load (VL), drug resistance mutations (DRMs) and co-receptor usage in HIV-1 strains from individuals co-infected with HIV-1 and Cryptococcal meningitis (CM) in Botswana.

Methods: This was a cross-sectional study utilizing CSF and plasma paired samples from 60 participants enrolled in a clinical trial evaluating the early fungicidal activity of 3 short-course, high-dose liposomal amphotericin B regimens for CM between 2014–2016. HIV VL was measured in 38/60 (63%) paired samples. Viral escape was defined as HIV-1 RNA ≥0.5 log10copies/ml, respectively (p≤0.001). The prevalence of CSF viral escape was 1/34 (2.9%) [95% CI: 0.07-15.3]. HIV-1 VL discordance was observed in 7/34 (21%) pairs. Discordance was not associated with CD4 count, ART status, duration or regimen, abnormal mental status, or mortality. A total of 26/45 (58%) pairs were sequenced and 14% were on ART. Frequency of DRMs in the plasma and CSF was 9 and 11, respectively. The most predominant DRM in the plasma was K101E (n=2) whilst the other mutations occurred at equal frequency of 1 in plasma and CSF (table 1). HIV DRM discordance was present in 3/26 (12%) paired
samples. Of these, one had I84T and the other had M46I in CSF only, the third had K101E in plasma and V106M in CSF. V3 loop was sequenced from 18/45 (40%) pairs; 94% and 83% were CCR5- and CXCR4-using strains in the CSF and plasma, respectively (p=0.8).

**Conclusion:** Low rates of CSF viral escape were observed and co-receptor usage was similar in both compartments. PI-associated DRMs were found in the CSF but not in plasma. Studies investigating the clinical effectiveness of PIs are warranted.

### Table 1: Discordance and Reverse transcriptase-associated mutations in CSF and plasma

<table>
<thead>
<tr>
<th>PI</th>
<th>Plasma DRMs</th>
<th>CSF DRMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV</td>
<td>11/15</td>
<td>12/60</td>
</tr>
<tr>
<td>ATV</td>
<td>13/50</td>
<td>12/15</td>
</tr>
<tr>
<td>RTV</td>
<td>14/70</td>
<td>12/15</td>
</tr>
</tbody>
</table>

**427 HERPES ZOSTER IN HIV: THE ROLE OF PLEOCYTOSIS IN SECONDARY CSF ESCAPE AND DISCORDANCE**

Lars Hagberg1, Richard W. Price1, Magnus Gisslén1, Sahligherna Academy at the University of Gothenburg, Gothenburg, Sweden, 1University of California San Francisco, San Francisco, CA, USA

**Background:** HIV cerebrospinal fluid (CSF) escape is defined by higher HIV RNA levels in CSF than plasma in the presence of treatment-related plasma viral suppression, while CSF discordance is similarly defined by higher CSF than plasma HIV RNA in untreated individuals. Secondary escape or discordance implies that the disproportionate CSF HIV RNA relates to another infection in addition to HIV.

**Methods:** A retrospective review of people living with HIV enrolled in a cohort study or receiving clinical care at Sahlgrensa Infectious Diseases Clinic in Gothenburg, Sweden who developed uncomplicated herpes zoster (HZ) and underwent lumbar puncture (LP) within the ensuing 150 days. Based on treatment status and the relationship between CSF and plasma HIV RNA concentrations, they were divided into 4 groups: i) antiretroviral treated with HZ CSF escape (N=4), ii) treated without CSF escape (N=5), iii) untreated with HZ CSF discordance (N=8), and iv) untreated without CSF discordance (N=8).

We augmented these with two additional cases of secondary CSF HIV escape (N=4), i) treated without CSF escape (N=5), ii) untreated with HZ CSF discordance (N=8), and iii) untreated without CSF discordance (N=8).

**Results:** HIV CSF escape and discordance were correlated with higher CSF white blood cell (WBC) counts than their non-escape (P<0.01) and non-discordant (P<0.01) counterparts. The CSF WBC counts correlated with the CSF HIV RNA levels in both the treated (P<0.01) and untreated (P<0.01) group pairs. Moreover, the CSF WBC counts correlated strongly with the CSF-plasma HIV RNA ratios of the entire group of 27 subjects (P<0.0001) indicating a strong effect of the CSF WBC count on the relation of the CSF to plasma HIV RNA concentrations across the entire sample set.

The inflammatory response to HZ and its augmenting effect on CSF HIV RNA was found up to 5 months after the HZ outbreak in the cross-sectional sample, and continued for one year after HZ in one individually followed longitudinally.

**Conclusion:** HZ provides a useful model of secondary CSF escape and discordance. Likely, the inflammatory response to HZ pathology within the neurasis provokes or augments local HIV production by enhanced trafficking or activation of HIV-infected CD4+ T lymphocytes. Wherein treatment and other systemic factors determine the plasma HIV-1 RNA set-point, the CSF WBC count strongly influences the relation of the CSF HIV RNA level to that set-point.

**428 BRAIN HIV LATENCY BIOMARKERS**

Thomas Gates1, John Ng1, Tan-Nia Koh2, Selviana Dharmadi3, Sarah Palmer3, Vincent Mocilla3, Tony Johnson4, Avindra Nath5, Lucette A. Cysique6, Bruce J. Brew1, for the Chief Group

1St. Vincent’s Hospital, Sydney, NSW, Australia, 2University of New South Wales, Sydney, NSW, Australia, 3The Westmead Institute for Medical Research, Westmead, NSW, Australia, 4Johns Hopkins University School of Medicine, Baltimore, MD, USA, 5National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, 6Neuroscience Research Australia, Randwick, NSW, Australia

**Background:** The presence and quantification of HIV in the brain is important for eradication as neuropathological studies suggest that latent brain HIV varies considerably amongst individuals. HANDB, both past and stable in virally suppressed (VS) patients is associated with brain latency and may serve as a latency biomarker discovery approach. We hypothesized that putative brain latency biomarkers would differ in VS past/stable HANDB vs. non-HANDB.

**Methods:** 24 HIV+ men (age M=52.67±12.72; HIV infection duration: M=17.75±12.69 years) who were VS (in plasma <100cpml and CSF <100cpml) on cART underwent lumbar puncture and neuropsychological testing. Patients with past HANDB from which they had recovered and patients with stable HANDB (past/stable HANDB group) were compared to patients with no known past or current CNS involvement (non-HANDB group) for putative markers of HIV brain latency. CSF HIV RNA by single copy assay (SCA), HIV tat, BCL11b, neurofilament-light chain (NFL), neopterin, CCL2, and CSF:serum albumin ratio (Q-Alb). CSF markers were classified as normal/abnormal using normal references and a combined CSF latency biomarker risk score was created by summing the number of abnormal values. HANDB status was defined using Global Deficit Score (GDS≥0.5). Past HANDB was determined from medical record review.

**Results:** Low level HIV persistence (CSF HIV RNA SCA >1-12.4 cpml) was detected in CSF in both groups (17% of past/stable HANDB and 24% of non-HANDB; p=0.73) and HIV tat was also detected in both groups (17% of past/stable HANDB and 6% for non-HANDB; p=0.42) (SCA was <1cpml in each case). BCL11b levels were similar across the board. However, the past/stable HANDB group showed higher NFL levels (p=0.05) than the non-HANDB group. Neopterin was abnormal in many patients (57% of past/stable HANDB and 31% of non-HANDB; p=0.24). CCL2 and O-Alb levels were largely normal and similar in both groups. Consequently, the combined CSF latency biomarker risk score did not differ across groups (p=0.58).

**Conclusion:** Past/stable HANDB is not a useful model for identifying brain latency biomarkers using the latter markers. Past/stable HANDB remains an active virological immunological and degenerative process. The concept of a “legacy effect” from past HANDB is not supported.

### Table 1: Demographics and CSF biomarker levels

<table>
<thead>
<tr>
<th>Discrepancy</th>
<th>Past/stable HANDB</th>
<th>Non-HANDB</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain HIV RNA SCA</td>
<td>66 (8.37)</td>
<td>49 (6.35)</td>
<td>0.015</td>
</tr>
<tr>
<td>Education</td>
<td>15.50±5.64</td>
<td>15.16±5.17</td>
<td>0.67</td>
</tr>
<tr>
<td>HIV RNA CSF (%)</td>
<td>94±6</td>
<td>80±10</td>
<td>0.22</td>
</tr>
<tr>
<td>&lt;200 Nucleoside CSF (%)</td>
<td>95±6</td>
<td>94±9</td>
<td>0.32</td>
</tr>
<tr>
<td>Current Q-Alb (ng/ml)</td>
<td>674.9±43.1</td>
<td>178±150</td>
<td>0.19</td>
</tr>
<tr>
<td>HIVAcreos (copies/cell)</td>
<td>52.16±10.20</td>
<td>52.16±10.20</td>
<td>0.25</td>
</tr>
<tr>
<td>Plasma HIV RNA SCA</td>
<td>86±10</td>
<td>94±6</td>
<td>0.04</td>
</tr>
<tr>
<td>Plasma HIV RNA backbone</td>
<td>59±10</td>
<td>90±10</td>
<td>0.38</td>
</tr>
<tr>
<td>CSF HIV RNA SCA (%)</td>
<td>0±0</td>
<td>0±0</td>
<td>0.64</td>
</tr>
<tr>
<td>CSF HIV RNA backbone (%)</td>
<td>0±0</td>
<td>0±0</td>
<td>0.64</td>
</tr>
<tr>
<td>Log_2 SCR BCL11b (ng/ml)</td>
<td>2.05±0.95</td>
<td>1.95±0.80</td>
<td>0.66</td>
</tr>
<tr>
<td>Log_2 CSF CCL2 (ng/ml)</td>
<td>2.21±0.73</td>
<td>2.09±0.53</td>
<td>1.97</td>
</tr>
<tr>
<td>Log_2 CSF neopterin (ng/ml)</td>
<td>2.10±0.98</td>
<td>1.90±1.14</td>
<td>0.24</td>
</tr>
<tr>
<td>CSF CCL2 (ng/ml)</td>
<td>57±23</td>
<td>57±23</td>
<td>1.00</td>
</tr>
<tr>
<td>Log_2 CSF neopterin (%)</td>
<td>0.76±0.73</td>
<td>0.76±0.73</td>
<td>0.91</td>
</tr>
<tr>
<td>CSF CCL2 (ng/ml)</td>
<td>34±15</td>
<td>34±15</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**429LB HIGH LEVELS OF CELL-ASSOCIATED HIV-1 TRANSCRIPTION IN CSF DESPITE EFFECTIVE cART**

Kazuo Suzuki1, John Zaunders1, Angelique Levert1, Chin-Shiou Huang1, Takami Ishida2, Thomas Gates1, Caroline Rae1, Lauriane Juge1, Lucette A. Cysique1, John Ng1, Bruce J. Brew1

1St. Vincent’s Hospital, Sydney, NSW, Australia, 2PlexBio Co. Ltd, Taipei, Taiwan, 1Denka Co Ltd, Chiyoda-ku, Tokyo, Japan, 3Neuroscience Research Australia, Randwick, NSW, Australia
Background: CSF is a possible compartmentalized HIV reservoir though the cells involved and their level of HIV-1 transcriptional activity remain obscure. We used a novel highly sensitive assay of HIV-1 RNA/DNA and flow cytometry to study both CSF cells and PBMC.

Methods: We studied 10 HIV+ subjects (2 with current HAND) on cART with both plasma and CSF HIV RNA (Roche) <50 copies/mL.DNA and RNA were extracted from paired samples of CSF (13-20 ml) and PBMC. Cell-associated HIV-1 transcriptional activity and HIV-1 DNA levels were determined by a newly described quantitative piCode End-Point PCR assay, based on the extremely sensitive piCode MicroDiscs platform (>27-fold sensitivity of real-time PCR; Suzuki et al J AIDS HIV Treat. 2019; 1(2):69). It detects transcripts of HIV LTR, including unspliced RNA (gag/pol), incompletely spliced RNA (tat, vpr, vpu), and multiply spliced RNA (rev, nef), with a sensitivity of 3 infected cells/10^6 cells. Immunological profiles of CSF cells and PBMC were determined by 18-colour flow cytometry and compared with Wilcoxon signed rank test. MR spectroscopy (MRS) evaluated the frontal white matter (FWM), posterior circinate cortex (PCC), and caudate nucleus.

Results: 9/10 patients’ CSF had high levels of cell-associated HIV-1 RNA transcriptional activity (median 4711 copies per 10^6 cells, vs 270 in PBMC; p=0.004). 8/10 patients had HIV-1 DNA in CSF cells (median 1314 copies per 10^6 cells vs 752 in PBMC; p=0.09). Higher HIV-1 RNA in CSF cells was correlated with lower N-acetylated aspartate in FWM (r=-0.78; p=0.038) and PCC (r=-0.76; p=0.012). 95% of CSF cells were T cells, of which 95% were memory CD4 and CD8 T cells (median counts of 8,818 and 7,503 cells, respectively). 2.8% of CSF cells were CD14+CD16+ monocytes, 1.7% were NK cells and 0.4% were B cells. CSF CD4 T cells consisted of 75% CXCR3+CD49d+integrinβ7- cells (vs 15% in CD4 in PBMC); 48%CCR5+ (vs 16% in PBMC); and 18% expressing CD38 and/or HLA-DR activation markers (vs 7% in PBMC).

Conclusion: CSF cellular HIV-1 LTR transcriptional activity is compartmentalised and its biological significance is strongly indicated by the MRS correlations. The cellular origin is likely the dominant CXCR3+CD49d+integrinβ7- non-gut homing memory CD4+ T cells; monocytes may be less important. Transcriptional products eg tat (vs whole virus) are likely neuropathogenetically significant. These data support HIV-1 transcription inhibitor development.

PLASMA RAMS IN REVERSE TRANSCRIPTASE GENE ASSOCIATE WITH CSF HIV-1 ESCAPE

Mattia Trunfio1, Anna Celotti2, Francesca Bai3, Luigi Celani 4, Emanuele Focà 2, Mattia Trunfio1, Andrea Calcagno1

1University of Torino, Torino, Italy; 2University of Brescia, Brescia, Italy; 3University of Milan, Milan, Italy; 4Sapienza University of Rome, Rome, Italy

Background: Several risk factors for cerebrospinal fluid HIV-1 escape (CSFE) have been reported: length of HIV infection, cART interruptions, low CD4 nadir/CD8 score, persistent low-level viremia and the use of ABC+3TC, boosted PIs or unboosted ATV. We sought to assess whether the presence of previous plasma RAMs may be a determinant behind the reported risk association between CSFE and ARVs class composing cART.

Methods: Retrospective cross-sectional study on HIV+ adult patients on cART undergoing lumbar puncture (LP) for any reason (2007-2019) at 4 Italian hospitals (Brescia, Torino, Roma, Milano). Inclusion criteria: being on cART for at least 6 months, available coupled plasma and CSF HIV-1 RNA measurements, available historical cumulative plasma genotyping resistance testing (NGRT) for reverse transcriptase (RT), and protease (PI) genes. Exclusion criteria: secondary CSFE. CSF was defined as any measurable CSF HIV-1 RNA coupled with a plasma HIV-1 RNA <50 copies/mL and any difference ≥0.5 Log_{10} between CSF and plasma HIV-1 RNA when the latter was detectable.

Results: 197 patients were enrolled: 50 years (43-54), current and nadir CD4 count 312 (115-560) and 82 (24-200) cells/µL; median length of cART treatment 54 months (17-171). 126 patients (63.9%) had plasma HIV-1 RNA <50 cp/mL and 28 (14.2%) showed CSFE. The main reasons for LP were diagnostic assessment in diseases without eventually CNS involvement (25.4%), HIV-associated neurocognitive disorders (28.4%), CNS infections (19.8%) and research purposes (16.2%). CSFE was not associated with PIs use in the whole cohort (16.6% vs 8.6%, p=0.14) nor in any subgroup identified by cART type (3 different classes-, 3 drugs-NRTIs- and ≥4 drugs-based cART). Instead, PIs use was more common in patients with a positive HGR for RAMs in RT (44.9% vs 25.3%, OR 2.0 [1.1-3.8], p=0.04). Having a cumulative NGRT positive for RAMs in RT associated with a higher risk of CSFE (21.5% vs 9.3%, OR 2.7 [1.2-6.0], p=0.01), while no such an association was observed for RAMs in PI (17.4% vs 13.8%). Interestingly, at the CSFE diagnosis patients showed higher proportion of positive CSF RAMs in RT compared to patients without CSFE with available CSF RT (55.6% vs 19.0%, p=0.04). At multivariable analysis, only RAMs in RT and CD4 nadir were independent predictors of CSFE (tab.1)

Conclusion: In this cohort, CSFE prevalence was slightly higher than what reported in recent studies. Besides low CD4 nadir, the positivity of HGR for plasma RAMs in the RT gene and not the use of PIs per sé was an independent predictor of CSFE.
previous findings that CSF sCD30 rises after ART in chronic HIV and warrants further investigation to assess a possible distinct impact of very early ART.

**432 QUANTITATION OF CEREBROSPINAL FLUID PLEOCYTOSIS AND HIV-1 RNA DURING ACUTE INFECTION**

**Philipp Chan1, Camilla Muccini2, Carlo Sacdalan2, Eugène Kroon3, Donn J. Colby4, Nitiya Chomchey2, Peeriya Prueksakaew5, Nittaya Phanuphak2, Linda Jagodzinski3, Victor Valcour4, Sandhya Vasan5, Jintanat Ananworanich2, Serena S. Spudich1, for the RV254 Study Team**

_Disclosure of Interests_:

1. Yale University, New Haven, CT, USA, 2SEARCH, Bangkok, Thailand, 3San Raffaele Vita-Salute University, Milan, Italy, 4US Military HIV Research Program, Bethesda, MD, USA, 5University of California San Francisco, San Francisco, CA, USA

Background: HIV-1 RNA can be detected in cerebrospinal fluid (CSF) within days after viral transmission. CSF leukocyte level (clinically determined as white blood cell count, or WBC) is linked with levels of systemic and CSF HIV-1 RNA in untreated chronic HIV infection. We quantitated CSF WBC and investigated its associations with HIV-1 in blood and CSF during untreated acute HIV infection (AHI).

Methods: Individuals with AHI were enrolled in the RV254 cohort in Bangkok, Thailand. A subset underwent optional lumbar puncture (LP). We measured WBC, protein and glucose in whole CSF. HIV-1 RNA was tested in CSF supernatant by Roche COBAS TaqMan HIV-1 V2.0 with a lower limit of quantification (LLQ) of 80 copies/mL. A level of 79 copies/mL was assigned to samples with levels below LLQ. Logistic regression was used to determine factors predicting CSF pleocytosis (WBC>5 cells/mm³).

Results: From March 2016 to March 2019, 61/246 RV254 participants underwent LP. 60 (98%) were men, and median age was 26, CD4 count 335 (IQR 247-553) and CD8 count 540 (IQR 357-802) cells/μL. 22 (37%) presented at Fiebig stage I & II and 36 (59%) had acute retroviral syndrome but none had overt neurologic signs or symptoms. 7 had untreated syphilis and 2 had hepatitis C. 16 (26%) CSF samples had HIV-1 RNA below LLQ. Median HIV-1 RNA levels in plasma and CSF were 6.10 (IQR 5.15-6.78) and 3.15 (IQR 1.90-4.11) log₁₀ copies/mL respectively. The median CSF WBC was 2 (IQR 1-8; range 0-105) cells/μL. Median CSF protein and glucose were 27 (IQR 23.2-31.9) mg/dL and 62 (IQR 57-69) mmol/L respectively. 20 (33%) CSF samples had pleocytosis. Four extreme outliers had levels >40 cells/mm³ of whom 2 were later diagnosed with neurosyphilis. Paring plasma and CSF HIV-1 RNA with CSF WBC by Fiebig stages revealed that CSF pleocytosis lagged behind the rise in CSF HIV-1 (Figure). In the multivariate analysis, CSF pleocytosis was independently predicted by CSF HIV-1 levels (adjust odds ratio (aOR)=2.69 (95%CI 1.44 – 5.04); p=0.002) and CD8 T-cells (aOR=1.24 (95%CI 1.00 – 1.54); p=0.046).

Conclusion: CSF pleocytosis is present in one third of neuroasymptomatic individuals during AHI. It appears to emerge temporally after CSF viremia, suggesting that marked CSF lymphocytosis is not necessary to early CNS viral transmigration. Future studies should examine the functionality of the excessive T-cells among those with CSF pleocytosis and whether the presence of pleocytosis may impact central nervous system outcomes in long term follow up after ART.

**433 EVOLUTION OF IMMUNE ACTIVATION BIOMARKERS IN CSF IN FIEBIG I-V ACUTE HIV INFECTION**

**Julian Weiss1, Philipp Chan1, Carlo Sacdalan2, Eugène Kroon3, Siriwat Akapirat4, Jennifer Chiarella1, Victor Valcour1, Nittaya Phanuphak1, Ningbo Jian5, Sandhya Vasan5, Jintanat Ananworanich2, Bonnie Slike1, Shelly J. Krebs1, Serena S. Spudich1, for the RV254/SEARCH010 study**

_Disclosure of Interests_:

1Yale University, New Haven, CT, USA, 2SEARCH, Bangkok, Thailand, 3Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, 4University of California San Francisco, San Francisco, CA, USA, 5US Military HIV Research Program, Silver Spring, MD, USA

Background: The initial immune response in the central nervous system (CNS) during acute HIV infection (AHI) may set the trajectory for HIV-associated neurocognitive disorders (HAND). A better understanding of immune activation pathways and dynamics in the CNS during AHI could inform therapeutic modalities to lessen the neurological impacts of HIV.

Methods: We analyzed 41 biomarkers of immune activation in the cerebrospinal fluid (CSF) in the RV254/SEARCH010 Thai AHI cohort prior to antiretroviral initiation. We compared biomarker levels across Fiebig stages by univariate analysis and explored bivariate correlations with CSF HIV RNA levels. Temporal expression patterns were visualized by heatmap analysis (Figure 1), and pathway kinetics were identified through hierarchical clustering using Spearman’s correlation of biomarkers differentially expressed between Fiebig stages. To quantify the heatmap data, post-hoc Dunn’s test was performed for pairwise comparisons of biomarker levels between stages.

Results: CSF was collected for biomarker analysis from 78 enrollees (99% male, median age 28 (IQR 23-33) years, median duration of infection 18 (IQR 15-23) days, median CD4 T cells 400 (IQR 280-543) cells/μL, median log₁₀ plasma HIV RNA 5.69 (IQR 5.01-6.51) copies/mL). Analysis of median CSF biomarker levels across Fiebig stages revealed temporal patterns of immune activation. Univariate analysis showed a set of biomarkers with statistically significant increases at Fiebig II compared to Fiebig I, and continued to increase until peak CSF viremia, primarily at Fiebig IV. The diverse subset of markers exhibiting this pattern included IL-2, TNF-α and its receptors TNFR-1 and TNFR-2, and IL-6RA, among others. Most biomarkers that followed this induction pattern had strong positive associations with CNS HIV RNA level, such as IL-2 (R²=0.36, P<0.0001) and TNFR-2 (R²=0.20, P<0.0001). Others, such as IL-15 and MCP-1, were also induced following Fiebig I, but peaked prior to peak viremia with inconsistent correlations with CNS HIV RNA level.

Conclusion: This analysis revealed temporal pathways of multiple CSF biomarkers with differential dynamics of immune activation during AHI. The predominant pattern displayed significant increases at Fiebig II compared to Fiebig I, with peak biomarker concentration occurring at peak CSF HIV RNA level during Fiebig IV. The levels of these CSF biomarkers correlated with CSF HIV RNA levels, and may provide insight into early immunological mechanisms contributing to HAND.
434 ROLE FOR PLATELET ACTIVATION AND ENDOTHELIAL ASSOCIATION IN HIV ENTRY INTO THE BRAIN
Claire E. Lyons1, Hannah Schneider1, Elizabeth L. Engle1, Kevin M. Najarro1, Suzanne E. Queen1, Craig N. Morrell2, Joseph Mankowski3, Kelly A. Metcalf Pate1, 1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2University of Rochester, Rochester, NY, USA

Background: The brain is an important sanctuary site and barrier to cure in HIV. Platelet decline is associated with perivascular cuffs of infected cells in the brain in HIV infected humans and SIV infected macaques, but is considered subclinical and often untreated. Platelet activation and interactions with vascular endothelium can contribute to platelet decline, and impact the permeability of the blood brain barrier in the context of other diseases. We sought to determine if platelet-endothelial associations (PEAs) contribute to platelet decline and are associated with the presence of infiltrates of infected cells in the brain in the SIV-infected pigtailed macaque model of HIV infection, to confirm that PEAs exist in people living with HIV (PLWH) and in SIV-infected macaques. PEAs were more common compared with uninfected macaques (P=0.01), and that effect was abrogated if platelet-endothelial associations (PEAs) contribute to platelet decline and are affect the blood brain barrier.

Methods: The effect of platelets on microvascular endothelial integrity in the brain was determined using a transwell cell culture assay system. PEAs and perivascular macrophages in the brain were identified using immunohistochemistry on tissue from SIV-infected pigtailed macaques and uninfected controls and from PLWH, and associations between PEAs and macrophase subsets determined using unbiased stereology. Platelet activation was monitored throughout infection using flow cytometry of platelet p-selectin on peripheral blood.

Results: Permeability of brain microvascular endothelium (BMEC) decreased two-fold following incubation with platelets from SIV-infected macaques compared with uninfected macaques (P=0.01), and that effect was abrogated by preventing contact between the platelets and BMECs. PEAs were observed in the brains of PLWH and in SIV-infected macaques. PEAs were more common in SIV-infected than control macaques during acute (RR = 4.0, P = 0.03) and asymptomatic (RR = 3.6, P = 0.04) infection, and were more likely to be associated with blood vessels surrounded by SIV-infected non-resident macrophages (RR = 1.5, P = 0.007). Macaques that did not develop perivascular infiltrates of cells in their brains during terminal infection demonstrated higher platelet activation during acute (P = 0.04) and asymptomatic (P < 0.0001) infection compared to those that developed infiltrates.

Conclusion: Platelet activation and PEA formation may play a protective mechanism against entry of SIV-infected cells into the brain. Platelet decline in HIV infection may have clinical impacts and contribute to the development of latent viral reservoirs.

435 HIV SUPPRESSION AND CHANGES IN CSF MARKERS IN PATIENTS RANDOMLY SWITCHED TO DTG + 3TC
Juan M. Tiraboschi1, Jhon Rojas1, Henrik Zetterberg2, Jordi Niuibo3, Johanna Gostner4, Antonio Navarro-Alcaraz5, Camilla Piaatti6, Dietmar Fuchs7, Magnus Gisslén6, Esteban Martínez2, Daniel Podzamczer1

Background: A major concern of dual therapy is the potential lower efficacy in viral reservoirs, especially in the central nervous system (CNS). The aim of this study was to evaluate the maintenance of HIV viral suppression as well as changes in neurological and inflammatory markers in cerebrospinal fluid (CSF) in asymptomatic stable patients switching antiretroviral therapy within a clinical trial.

Methods: Prospective, single arm study. HIV+ virologically suppressed patients on triple therapy were randomly selected to switch to Lamivudine 300 mg + Dolutegravir 50 mg once daily throughout the DOLAM Study (EUDRA CT 2015-000274-35). A small group consented to participate in the Neuro-Substudy. All pts were on stable triple therapy and had no history of virological failure to regimens containing 3TC/FTC or INSTI as per inclusion/exclusion criteria. CSF and blood samples were taken at baseline and week 48. Plasma and CSF HIV-1 RNA were assessed by real-time PCR. CSF neurofilament light chain (NFL) as well as inflammatory markers (sTREM2, Neopterin, MCP-1, IL-6) were measured in CSF by sandwich ELISA method.

Results: 15 pts had baseline and week 48 plasma and CSF samples. 12 (80%) pts were male. Median (IQR) age was 46 (14) years, baseline and nadir CD4 count 746 (156) and 302 (165) cells/μl respectively. Most patients switched from a NNRTI based regimen (60%) followed by INSTI (26.7%). All subjects maintained plasma viral suppression at baseline, week12, 24, 36 and 48. HIV RNA in CSF was undetectable at baseline and week 48 in all participants (LOD 40 copies/ml). NFL median change from baseline to week 48 was not statistically significant [Median (Min-Max) NFL at baseline: 499 ng/L (268-734); Median (Min-Max) NFL at W48: 457 (226-886); p=0.3]. No significant changes were observed in the rest of inflammatory markers in CSF.

Conclusion: Treatment simplification from triple therapy to Dolutegravir+Lamivudine resulted in no changes in viral suppression in plasma and CSF. No evidence of neural damage or changes in inflammatory markers were found in CSF after 48 weeks of dual therapy. These data suggest that dual therapy with Dolutegravir+Lamivudine maintains viral control within the CNS reservoir, but larger studies are needed.

436 BILIRUBIN AS A SURROGATE MARKER OF DOLUTEGRAVIR-ASSOCIATED CNS ADVERSE EVENTS
Elena Alvarez-Barco1, Fergal Moran2, Ciara Levey2, Williard Tinago1, Patrick W. Mallon2
1University College Dublin, Dublin, Ireland, 2Mater Misericordiae University Hospital, Dublin, Ireland

Background: In Phase 3 trials, dolutegravir (DTG) was well tolerated, with only 2% prevalence of adverse events (AE) leading to discontinuation. However, in post-marketing data, use of DTG has been associated with central nervous system (CNS) events. Higher DTG plasma levels have previously been associated with CNS AE. Given that both DTG and bilirubin (BIL) are metabolised by the UGT1A1 enzyme, we aimed to assess if BIL levels, as a surrogate marker for DTG and UGT1A1 activity, could predict CNS effects with DTG.

Methods: Analysis of subjects treated with DTG within the UCD ID Cohort, a prospective cohort study, with BIL levels recorded pre and at weeks 4, 12, 48 and 96 after DTG initiation. Reported CNS AE were obtained at same time points. Subjects were divided into those who did or did not report CNS AE (CNS group vs no-CNS groups). Between group differences in BIL levels were assessed using Mann-Whitney tests and linear mixed effects model as appropriate. Contribution of BIL levels to development of CNS AE was assessed using logistic regression models.

Results: 372 subjects were included in the study, mean age (SD) 44.6 (9.3) years, 59% males, 61% Caucasian, 28% acquired HIV via intravenous drug use, median CD4-T cell count 515.3 (IQR 321, 720) cells/mm, 66% HIV RNA <40c/ml, 14% co-infected with HCV and 3% co-infected with HBV. A total of 102 (33%) subjects reported AE, of which 94% were CNS AE, with insomnia (40%), depression (15%) and headache (15%) most commonly reported. Subjects were divided into those who did or did not report CNS AE, of which 94% were CNS AE, with insomnia (40%), depression (15%) and headache (15%) most commonly reported. Median (IQR) time to develop CNS AE was 17 (5, 51) weeks. Although no between-group differences were observed in changes of BIL levels overtime (p=0.79), BIL levels at the time of reporting CNS AE were significantly higher in the CNS group compared to the same time point from non-CNS subjects matched by age and comorbidities.
437 ART INITIATED AT HIGH CD4 NADIR DOES NOT NORMALIZE CSF MARKERS OF IMMUNE ACTIVATION

Frida Ryberg1, Aylin Yilmaz2, Lars Hagberg3, Dietmar Fuchs3, Magnus Gisslén3, for the HIV Clinical Research Center, University of Gothenburg
Sahlgrenska University Hospital, Gothenburg, Sweden, 2Innsbruck Medical University, Innsbruck, Austria, 3Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Background: HIV infects cells in the central nervous system (CNS), mainly microglia and perivascular macrophages, and induces a chronic intrathecal immune activation. Similar to its effect outside the CNS, antiretroviral treatment (ART) substantially decreases CNS inflammation and CD4+ T-cell trafficking through the cerebrospinal fluid (CSF) is often reduced to near normal levels. Yet, CSF levels of neopterin, a byproduct marker of primary macrophage/microglia activation, have been found to be stably increased in the majority of persons living with HIV (PLWH) who begin treatment during the chronic phase of HIV infection when the immune function is impaired. By contrast, CSF neopterin is essentially normalized when ART is initiated early, during acute HIV infection (AHI). The aim of this study was to evaluate if CSF immune activation biomarkers normalize to a larger extent in PLWH who start ART at high, as compared to starting treatment at low CD4-cell counts.

Methods: 176 neuroasymptomatic patients who started ART during chronic HIV were retrospectively included from the longitudinal prospective Gothenburg CSF cohort study and followed for in median 5.0 years (mean 6.1 years). Lumbar punctures were performed at baseline before ART, after 1, and >3 years. Twenty-five participants had a CD4 nadir <50, 52 between 50 and 199, 61 between 200 and 349; 22 between 350 and 499; and 16 ≥500 cells/µL. Neopterin concentrations were measured using a commercially available immunoassay (NEOPT-SCR EIA 384 Det., Thermo Fisher Scientific – BRAHMS GmbH, Henningsdorf, Germany) with an upper normal reference value of 5.8 nmol/L in CSF.

Results: A significant inverse correlation between CD4 cell count and CSF neopterin was found at baseline (r = -0.57, F < 0.01) while no correlations between CD4 nadir and CSF neopterin were found after 1, or >3 years. ART. 15% of patients with the highest CD4 nadir (>500) had normal CSF neopterin (<5.8 nmol/L) compared to 0% of those with the lowest CD4 nadir (<50). After >3 years of ART, 57% and 50% respectively had normal CSF neopterin.

Conclusion: CSF Neopterin does not normalize in many patients initiating ART during chronic HIV.
This also applies to ART-initiation at high CD4 cell counts.

438 INTEGRASE INHIBITOR START OR SWITCH IMPACTS LEARNING IN WOMEN WITH HIV

1Washington University in St Louis, St Louis, MO, USA, 2Johns Hopkins University, Baltimore, MD, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4Georgetown University, Washington, DC, USA, 5Albert Einstein College of Medicine, Bronx, NY, USA, 6University of Illinois at Chicago, Chicago, IL, USA, 7SUNY Downstate Medical Center, Brooklyn, NY, USA, 8Cook County Health & Hospitals System, Chicago, IL, USA, 9University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 10University of Miami, Miami, FL, USA

Background: In recent years, the integrase strand transfer inhibitor (INSTI) class of antiretroviral therapy (ART) has become an integral component of HIV treatment. Despite concerns regarding neuropsychiatric adverse events there are limited data on cognitive side effects, particularly in women with HIV (WWH).

Methods: WWH enrolled in the Women’s Interagency HIV Study (WIHS), who started or switched to INSTI-based ART and had completed one comprehensive neuropsychological (NP) test battery before and after the start/switch, were included. The NP battery assessed learning, memory, fluency, attention/working memory, executive function, processing speed, and motor function. The primary NP outcomes were demographically-corrected T-scores (M=50, SD=10) for each cognitive domain. Linear mixed effects models adjusted for relevant covariates (e.g., age, race, education, income, substance use, body mass index, HIV RNA) were used to examine the effect of start/switch of any INSTI as well as each individual drug within the INSTI class on NP function.

Results: 628 WWH, median age 48 (interquartile range 36-68) years, 65% black non-Hispanic, had NP data before and after INSTI start/switch. While 14% started INSTI-based ART, the remainder switched primarily from protease inhibitor (PI)-based ART (51%) or a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART (27%). Raltegravir (RAL), elvitegravir (EVI), and dolutegravir (DTG) were included in 38%, 28% and 9% of WWH, respectively. Overall, any INSTI use was associated with poorer performance in learning after start/switch (p<0.001). Specifically, use of EVG (p=0.02) and DTG (p=0.002), but not RAL, was associated with poorer learning. In analyses restricted to INSTI switch, any INSTI use was associated with poorer performance in learning (p<0.009), as was use of DTG specifically (p=0.004). INSTIs and DTG remained associated with poorer learning among those switching from a PI-based regimen. DTG also remained associated with poorer learning among those switching from an NNRTI (p<0.05). Switching from an NNRTI to an INSTI was also associated with better processing speed.

Conclusion: Switching or starting an INSTI was primarily associated with poorer performance in learning among WWH. These changes were mainly observed in EVG and DTG users, and not with RAL, indicating that the impact of INSTI on cognition in WWH may not be a class effect.

439 HIV RNA IN CEREBROSPINAL FLUID OFF ART PREDICTS MORE DEPRESSIVE SYMPTOMS ON ART

Oluwakemi Okwuegbuna1, Albert Anderson2, Jennifer Ludicello3, Josue Perez-Santiago4, Florin Vaida5, Rachel Schrier6, Allen McClutchan7, Ronald J. Ellis1, Scott L. Letendre3
1University of California San Diego, San Diego, CA, USA, 2Emory University, Atlanta, GA, USA, 3University of Puerto Rico, San Juan, Puerto Rico

Background: HIV RNA in blood substantially differs between individuals without antiretroviral therapy (ART) due, in part, to differences in the immune response, such as endogenous interferons. Elite controllers suppress HIV RNA without ART but are at greater risk for vascular and central nervous system (CNS) complications than PWH on suppressive ART, possibly due to their robust immune response to HIV. HIV RNA in CSF also substantially differs between PWH on suppressive ART but relatively little is known about the effects of the antiviral immune response on CNS health trajectory.

Methods: The project aimed to determine a) the correlates of HIV RNA in CSF in 1,084 PWH without ART and b) the association between HIV RNA in CSF without ART and cognition or depression over time with ART (1,555 assessments in 300 PWH). All participants had plasma HIV RNA ≤ 200 copies/mL and were comprehensively assessed with neuropsychological (NP) testing, Beck depression inventory (BDI), and lumbar puncture. Statistical methods included univariable and stepwise multivariable regression using Bayesian Information Criterion and false discovery rate correction, recursive partitioning, and mixed models.

Results: Participants were mostly middle-aged (mean 39 years), European ancestry (50.4%) men (83.1%) with a mean duration of HIV of 7.5 years. Without ART, HIV RNA in CSF was ≤ 50 copies/mL in 161 (16.0%) and was less than HIV RNA in blood in 55% (median difference -1.4 log, copies/mL, range -4.8 to +1.3). Multivariable regression identified that higher HIV RNA in CSF was associated with higher HIV RNA in blood, higher CSF leukocyte count, fewer CD4+ T-cells, higher CD4+ and CD8+ percent, lower serum albumin, higher total protein in CSF and blood, and lower CSF glucose (model R2 = 0.27, p < 0.0001). Recursive partitioning identified that four variables explained 50% of the variance in HIV RNA in CSF (Figure). PWH who had lower HIV RNA in CSF without ART had worse BDI values (p=0.034) over time while on ART (but not worse NP performance), even after accounting for demographic, disease, and treatment covariates (model p<0.0001).

Conclusion: The relationship between HIV RNA in CSF and blood is highly variable with 1 in 6 having undetectable HIV RNA in CSF without ART and 1 in 20 having HIV RNA in CSF higher than HIV RNA in blood. PWH who better control HIV RNA in CSF without ART have more depressive symptoms on ART, which could reflect bystander injury from a more effective antiviral immune response.
440 CSF CXCL-10 IS ASSOCIATED WITH THE PRESENCE OF LOW-LEVEL CNS HIV DURING ART

Albert Anderson1, Bin Tang1, Florin Vaida1, Oluwakemi Owuabena1, Daniel McClernen1, Reena Deutsch1, Supratheek Kundus1, Mariana Cherners1, Debralee Cookson1, Melanie Crescinci1, Igor Grant1, Ronald J. Ellis1, Scott L. Letendre2, Emyr Center for AIDS Research, Atlanta, GA, USA, 1University of California San Diego, La Jolla, CA, USA, 2Emory University, Atlanta, GA, USA

Background: The central nervous system (CNS) is a reservoir of HIV persistence during antiretroviral therapy (ART). Our group and others have demonstrated that both HIV RNA by single copy assay (SCA) and HIV p24 antigen by digital ELISA can be detected in cerebrospinal fluid (CSF) during ART. However, these markers require specialized protocols and are not always quantifiable during ART. Therefore, surrogate markers of HIV CNS persistence are needed that are widely available and readily quantifiable.

Methods: We performed a cross-sectional analysis of persons with HIV (PWH) on combination ART with both plasma and CSF HIV RNA <50 copies/ml by conventional PCR. In addition to HIV RNA by SCA and p24 antigen by digital ELISA, we measured CSF CXCL10 and sCD30, immune activation markers that may reflect HIV persistence in the CNS. We also measured CSF neurofilament light chain (NFL) and neuron specific enolase (NSE), markers that reflect neuronal damage. Results are reported in pg/ml, with comparisons made with Wilcoxon rank sum. Logistic regression was performed with CSF HIV+ as outcome.

Results: 66 adult PWH with virologic suppression on ART were analyzed. 19 (29%) were CSF HIV+ (positive by either SCA or p24). CSF HIV+ participants did not differ from those without detectable CSF HIV (CSFHVneg) in terms of age, gender, race, current/nadir CD4+ T-cell count, CSF total protein, or duration of current ART regimen (all p = 0.2). CXCL10 was significantly higher in the CSF HIV+ group compared to the CSFHVneg group (median = 411 [IQR = 344-640] versus median = 313 [IQR = 205-469]), p = 0.008. In contrast, sCD30 was not significantly different (p = 0.43) between the two groups (median = 8.97 [IQR = 4.05-14.58] in CSF HIV+ versus median = 7.04 [IQR = 4.19-10.76] in CSFHVneg). There was no significant difference in NFL between the two groups (p = 0.85). However, there was a trend towards higher NSE values (p = 0.096) in the CSFHV+ group. In logistic regression accounting for the effect of detectable plasma HIV by SCA, there was a trend towards higher NSE values (p = 0.096) in the CSFHV+ group.

Conclusion: In this study of PWH on suppressive ART, there was a significant relationship between CSF CXCL10 and the presence of low-level HIV in CSF. CSF CXCL10 merits further study as a candidate marker of CNS persistence that may be useful in the evaluation of HIV eradication interventions.

441 USE OF D/C/F/TAF WITH NEUROLOGIC/PSYCHIATRIC COMORBIDITIES: AMBER SUBGROUP ANALYSIS

Keith J. Dunn1, Richard Simonsorn1, Donghan Luo1, Jiynn Cai1, David Anderson1, 1Janssen Scientific Affairs, LLC, Titusville, NJ, USA, 2Janssen Research & Development, LLC, Spring House, PA, USA

Background: Patients with human immunodeficiency virus (HIV)–1 and neurologic or psychiatric comorbidities (NPCs) may face challenges with HIV-1 care.

Methods: The phase 3 AMBER trial (ClinicalTrials.gov: NCT02431247) enrolled treatment-naïve, HIV-1–infected adults who were randomized 1:1 to receive once-daily darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10mg or control (D/C/F/tenofovir disoproxil fumarate). Here we report a subgroup analysis evaluating efficacy/safety in those with and without NPCs at baseline. NPCs were based on verbatim medical history; terms were coded and NPCs were defined as those within the MedDRA v22 system organ class Nervous System Disorders or Psychiatric Disorders. The primary objective was assessment of virologic response (HIV-1 RNA <50 copies/ml) at Week 48 by intent-to-treat FDA snapshot analysis in patients with or without NPCs in each treatment arm.

Results: Among 725 patients in AMBER, 88 (D/C/F/TAF) and 99 (control) had NPCs. Overall, psychiatric comorbidities (125/187 [67%]) were more common than neurologic comorbidities (81/187 [43%]). Patients with NPCs vs those without, were more likely to be black (17% vs 9%), from North America (37% vs 18%), use nicotine (52% vs 45%), and be drug users (26% vs 14%). Patients with NPCs had higher rates of early study discontinuation vs those without NPCs (D/C/F/TAF, 10% vs 5%; control, 10% vs 7%), which was largely driven by loss to follow-up. High virologic response rates (85-93%) were achieved at Week 48 regardless of NPCs (Table); while patients with NPCs had numerically lower response rates, no patients in either arm discontinued due to lack of efficacy or developed darunavir, primary protease inhibitor, or TAF resistance. Rates of discontinuation due to related adverse events (AES) were low regardless of NPCs (Table). Patients with NPCs did not experience a higher incidence of neurologic or psychiatric AES related to D/C/F/TAF. The most common (≥5%) neurologic AE, regardless of treatment arm or NPCs, was headache. For patients with NPCs, the most common (≥5%) psychiatric AES were anxiety and depression (D/C/F/TAF), and depression and insomnia (control); no psychiatric AES met this threshold among patients without NPCs.

Conclusion: In AMBER, the presence of NPCs did not preclude virologic response in either treatment arm. Patients with NPCs were not at added risk of discontinuing due to AES and did not experience a higher incidence of neurologic or psychiatric AES related to D/C/F/TAF.

Table: Virologic Response and Summary of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>D/C/F/TAF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic response</td>
<td>84 (46.0)</td>
<td>100 (57.8)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>24 (12.5)</td>
<td>25 (13.7)</td>
</tr>
<tr>
<td>Headache in total</td>
<td>5 (2.5)</td>
<td>10 (5.5)</td>
</tr>
<tr>
<td>Headache in NPC</td>
<td>7 (6.9)</td>
<td>10 (9.4)</td>
</tr>
<tr>
<td>Headache in control</td>
<td>3 (2.5)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Ankylosing spondylitis in NPC</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ankylosing spondylitis in control</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Depression in NPC</td>
<td>3 (3.0)</td>
<td>10 (9.4)</td>
</tr>
<tr>
<td>Depression in control</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Background: Dolutegravir is a safe and effective integrase strand transfer inhibitor used in combination in people living with HIV (PLWH). In several, but not all, cohorts a high rate of discontinuation for neuropsychological side effects (NPS) has been reported: age, female gender, older age and abacavir co-administration have been suggested as potential risk factors while pharmacological and genetic features are still under study. Aim of this analysis is to describe the clinical features and outcomes of patients stopping DTG for NEUROPSYCHIATRIC SYMPTOMS.

Andrea Calcagno1, Alberto Borghetti1, Maurizio Miledi1, Jessica Cusati1, Mariarainata Tettoni1, Antonio D’Avolfo1, Giovanni Di Perri2, Simona Di Giambenedetto2, Stefano Bonora3, 1University of Torino, Torino, Italy, 2Catholic University of the Sacred Heart, Rome, Italy

Background: Dolutegravir is a safe and effective integrase strand transfer inhibitor used in combination in people living with HIV (PLWH). In several, but not all, cohorts a high rate of discontinuation for neuropsychological side effects (NPS) has been reported: age, female gender, older age and abacavir co-administration have been suggested as potential risk factors while pharmacological and genetic features are still under study. Aim of this analysis is to describe the clinical features and outcomes of patients stopping DTG for NPS.

Methods: In a cohort study involving two Italian outpatient clinics we enrolled patients starting DTG and recorded clinical, therapeutic, pharmacokinetic and pharmacogenetic features. The study was approved by the two Ethics Committees and patients signed a written informed consent. In this analysis we focused on patients starting DTG for NPS in terms of pre-existing psychiatric comorbidities and outcomes after drug withdrawal. Symptoms were clinically assessed and no/partial/complete resolution was recorded. Results: 112 (out of 561) patients stopped DTG after a median follow up of 27 months (18-37); 66 for NPS. They were mostly sleep disorders (27.3%), anxiety (25.8%), depression (18.2%), psychosis (4.5%), vertigo (4.5%) and confusion (5%). Pre-existing psychiatric comorbidities were reported in 21
subjects (31.8%) mostly anxiety/depression in 24.2%; the latter was associated with the discontinuation for worsening depression (p=0.021, OR=4.4) but not other symptoms. Outcome was available in 57 participants: within 30 days a complete (61.4%) or partial (33.3%) improvement in symptoms was reported. Headache (p=0.039) and sleep disorders (p=0.083) were associated with complete resolution of symptoms. Patients were switched to raltegravir (30.3%), elvitegravir/cobicistat (28.8%), darunavir/cobicistat (25.8%) or rilpivirine (12.1%)-containing regimens. Partial/complete regression of NPS was observed in 66.7%/33.3% (DRV/c), 43.5%/55.2% (RA), 12.5%/62.5% (RPV) and 11.3%/72.2% (EVG/c) (Che² 1.99, p=0.158).

Conclusion: In our cohort study 11.7% of participants stopped DTG due to NPS: they were mostly sleep disorders and headache and a full regression of both was observed after switching to other drugs. In most cases a complete resolution of symptoms was observed; the incomplete resolution in almost one third of participants suggests alternative reasons.
Table 1. TFV-DP and FTC-TP concentrations across cell types

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>TFV-DP (pmol/µL)</th>
<th>FTC-TP (pmol/µL)</th>
<th>Neutrophil</th>
<th>Platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBMC</td>
<td>1.5 (1.0-2.0)</td>
<td>0.05 (0.01-0.1)</td>
<td>1.0</td>
<td>0.05</td>
</tr>
<tr>
<td>RBC</td>
<td>0.01 (0.005-0.02)</td>
<td>0.005 (0.0005-0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>1.0 (0.5-1.5)</td>
<td>0.05 (0.01-0.08)</td>
<td>0.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Platelet</td>
<td>0.01 (0.005-0.02)</td>
<td>0.005 (0.0005-0.001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All values are expressed as median (IQR).*

**Utility of Minimally Invasive Specimens to Inform ARV Adherence Test Development**


**Background:** Antiretroviral drug (ARV) efficacy in treatment and prevention of HIV infection is currently dependent on high levels of adherence to daily oral dosing regimens. Rapid point of care (POC) tests to measure ARV levels could be used to track and improve individual adherence. This study sought to define the utility of urine, dried blood spots, and buccal swabs as minimally invasive specimens amenable to development of POC tests for ARVs.

**Methods:** Urine, buccal swabs, and peripheral blood were collected from 35 HIV-negative men who have sex with men aged 18-49 years enrolled in a clinical trial examining the pharmacokinetics of a single dose of 4 ARVs with a pharmacologic booster. Specimens were collected up to 96 hours following a single oral dose of tenofovir alafenamide (TAF)/emtricitabine (FTC)/elvitegravir (EVG)/cobicistat (COBI) and darunavir (DRV). Drug concentrations were measured by high performance liquid chromatography-mass spectrometry with a lower limit of quantification of 10 ng/mL for plasma, urine, and whole blood and 2 ng/mL for buccal swabs.

**Results:** ARV was detectable in all urine specimens collected 48 hours following a single dose and TFV and DRV were detectable in all urine specimens collected 24 hours post dose. TFV, FTC and DRV remained detectable in most urine specimens collected at least 72 hours post dose. EVG was not detectable in urine, and COBI was only measurable up to 8 hours post dose. Urine ARV concentrations showed modest correlation with those in plasma for FTC (r=0.510, p<0.001), EVG (r=0.413, p<0.001), and COBI (r=0.431, p<0.001). FTC, EVG and DRV were detectable in all DBS collected up to 24 hours post dose, and FTC and DRV remained detectable in most DBS collected up to 48 hours post dose. COBI was only detectable in DBS up to 8 hours post dose. ARV concentrations in DBS correlated with plasma concentrations for FTC (r=0.914, p<0.001), EVG (r=0.867, p<0.001) and DRV (r=0.917, p<0.001), but not COBI.

**Conclusion:** Development of POC tests to detect ARV drugs from minimally invasive specimens may be attractive to assess adherence. Our results suggest that POC assays targeting TFV, DRV or THC in urine or FTC, EVG or DRV in whole blood may provide the most reliable indicators of ARV adherence.
Background: Protease inhibitors (PIs) cause drug-drug interactions (DDIs) with statins due to inhibition of drug metabolizing enzymes and/or the hepatic uptake transporter OATP1B1, which may alter the pharmacodynamic (PD) response to statins. There is a lack of data on real-life management of DDIs between antiretrovirals (ARVs) and statins.

Methods: Patients of the Swiss HIV Cohort Study followed-up in the centres of Lausanne and Basel were eligible if they received a statin concomitantly to ARVs. Low-density lipoprotein (LDL), total cholesterol (TC) and plasma concentration of the statin were measured during a follow-up visit. Individual LDL target values were set according to the Framingham score whereas TC target values were set according to the 2018 European AIDS Clinical Society recommendations. Statins concentrations were interpreted using published plasma concentration time curves. DDIs management was evaluated based on the statin dose adjustment considering coadministered ARVs and the PD response on the lipid profile.

Results: Data were collected for 99 rosuvastatin, 93 atorvastatin, 46 pravastatin and 21 pitavastatin. DDIs management and PD response varied according to the statin (figure 1). Statin underdosaging leading to suboptimal PD response was frequent with rosuvastatin and atorvastatin. However, the lipid target values were not always achieved in presence of PIs despite using the maximal recommended rosuvastatin dose. Similarly, suboptimal lipid control was observed with PIs despite high atorvastatin concentrations likely explained by inhibition of OATP1B1 resulting in less statin uptake in the liver, the site of action. Target lipid values were more often achieved with unboosted integrase inhibitors due to both their favourable DDIs profiles and neutral effect on lipids. Underdosaging was less frequent with pravastatin and pitavastatin, nevertheless suboptimal lipid control was common regardless of coadministered ARVs and despite using maximal recommended pravastatin and pitavastatin doses. This is likely due to their lower efficacy compared to rosuvastatin or atorvastatin.

Conclusion: Suboptimal management of DDIs with statins underdosaging was observed in overall 30% of cases. Management of dyslipidemia in patients on PIs is challenging due to this ARVs class negative impact on lipid profile and DDIs potentially impairing the effect of statins. Integrase inhibitors based regimens are recommended for aging people living with HIV (PLWH) because their increased prevalence of aging. Thus, in the absence of severe comorbidities, management of DDIs can be deferred in elderly compared to young PLWH.

Results:

- Underdosing was less frequent with pravastatin and pitavastatin, nevertheless suboptimal lipid control was common regardless of coadministered ARVs and despite using maximal recommended pravastatin and pitavastatin doses. This is likely due to their lower efficacy compared to rosuvastatin or atorvastatin.

- Underdosaging leading to suboptimal PD response was frequent with rosuvastatin and atorvastatin.

Conclusion:

- Suboptimal management of DDIs with statins underdosaging was observed in overall 30% of cases. Management of dyslipidemia in patients on PIs is challenging due to this ARVs class negative impact on lipid profile and DDIs potentially impairing the effect of statins. Integrase inhibitors based regimens are recommended for aging people living with HIV (PLWH) because their increased prevalence of aging. Thus, in the absence of severe comorbidities, management of DDIs can be deferred in elderly compared to young PLWH.

- Underdosing was less frequent with pravastatin and pitavastatin, nevertheless suboptimal lipid control was common regardless of coadministered ARVs and despite using maximal recommended pravastatin and pitavastatin doses. This is likely due to their lower efficacy compared to rosuvastatin or atorvastatin.

- Underdosaging leading to suboptimal PD response was frequent with rosuvastatin and atorvastatin.

Conclusion:

- Suboptimal management of DDIs with statins underdosaging was observed in overall 30% of cases. Management of dyslipidemia in patients on PIs is challenging due to this ARVs class negative impact on lipid profile and DDIs potentially impairing the effect of statins. Integrase inhibitors based regimens are recommended for aging people living with HIV (PLWH) because their increased prevalence of aging. Thus, in the absence of severe comorbidities, management of DDIs can be deferred in elderly compared to young PLWH.

- Underdosing was less frequent with pravastatin and pitavastatin, nevertheless suboptimal lipid control was common regardless of coadministered ARVs and despite using maximal recommended pravastatin and pitavastatin doses. This is likely due to their lower efficacy compared to rosuvastatin or atorvastatin.

- Underdosaging leading to suboptimal PD response was frequent with rosuvastatin and atorvastatin.

Conclusion:

- Suboptimal management of DDIs with statins underdosaging was observed in overall 30% of cases. Management of dyslipidemia in patients on PIs is challenging due to this ARVs class negative impact on lipid profile and DDIs potentially impairing the effect of statins. Integrase inhibitors based regimens are recommended for aging people living with HIV (PLWH) because their increased prevalence of aging. Thus, in the absence of severe comorbidities, management of DDIs can be deferred in elderly compared to young PLWH.
higher TAF doses. Unlike prior findings with TDF, adding LDV/SOF with TAF did not significantly increase plasma TFV or TFV-DP in PBMC. This is likely due to differences in hydrolysis pathways between TDF and TAF, and reassures on the safety of TAF + b/PI + LDV/SOF in HIV/HCV-coinfected patients.

### Table 1: Pharmacokinetic Summary of the Simulated Drug Interactions between Dolutegravir and Valproic Acid

<table>
<thead>
<tr>
<th>Dolutegravir Dose</th>
<th>Valproic Acid Dose</th>
<th>Cmin/PAIC50</th>
<th>Cmax/PAIC50</th>
<th>Cmin/PAIC50</th>
<th>Cmax/PAIC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG 50mg QD</td>
<td>VPA 300mg QD</td>
<td>0.70</td>
<td>0.69</td>
<td>0.70</td>
<td>0.69</td>
</tr>
<tr>
<td>DTG 50mg QD</td>
<td>VPA 600mg QD</td>
<td>0.85</td>
<td>0.80</td>
<td>0.85</td>
<td>0.80</td>
</tr>
<tr>
<td>DTG 100mg QD</td>
<td>VPA 300mg QD</td>
<td>0.85</td>
<td>0.80</td>
<td>0.85</td>
<td>0.80</td>
</tr>
<tr>
<td>DTG 100mg QD</td>
<td>VPA 600mg QD</td>
<td>0.85</td>
<td>0.80</td>
<td>0.85</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Where Cmin is the minimum plasma concentration and PAIC50 is the protein-adjusted IC50 of DTG. Bold values indicate greater than 2-fold difference from baseline.

**Figure 1:** A whole-body PBPK model was designed in Simbiology v. 9.4.0 (MATLAB R2018a) and used to simulate 100 adult individuals. The PBPK model predicted marked reductions in the Cmin of several DTG dosing regimens when co-administered with DTG 5mg QD and 10mg QD, respectively, while total DTG concentration in the controls remained comparable: 1.49, 1.74 and 1.51 mg/L on days 1, 7, and 14, respectively, while total DTG concentration in the controls remained comparable: 1.49, 1.74 and 1.51 mg/L on days 1, 7, and 14, respectively. The decrease can be explained, at least partly, by displacement of DTG by VPA via competitive protein binding. Since unbound DTG levels remained sufficient this DDI should not be a reason to withhold DTG treatment to people living with HIV-1 who are also receiving VPA.

**Conclusion:** This study shows that total DTG plasma concentrations decrease sharply after the addition of VPA, thus confirming the DDI. The decrease can be explained, at least partly, by displacement of DTG by VPA via competitive protein binding. Since unbound DTG levels remained sufficient this DDI should not be a reason to withhold DTG treatment to people living with HIV-1 who are also receiving VPA.
452 PHARMACOKINETICS OF RUXOLITINIB WITH ART IN HIV-SUPPRESSED INDIVIDUALS (ACTG # A5336)

Selwyn Hurwitz1, Siija Tao2, Yong Jiang3, Christina Gavegnano, Charles W. Flexner4, Randall Tressler1, Atie Tsibris5, Steven G. Deeks1, Carlos del Rio1, Edgar T. Overton1, Jeffrey J. Lenna2, Vincent C. Marconi1, Raymond F. Schinazi1
1Emory University, Atlanta, GA, USA, 2Johns Hopkins University, Baltimore, MD, USA, 3NIH, Bethesda, MD, USA, 4Harvard University, Cambridge, MA, USA, 5University of California San Francisco, San Francisco, CA, USA, 6University of Alabama at Birmingham, Birmingham, AL, USA

Background: Ruxolitinib is an FDA-approved Janus kinase (JAK 1/2) inhibitor (myelofibrosis, polyethylene) that blocks key cytokines involved in HIV persistence including IL-6, 7 and 15. In A5336, low dose ruxolitinib (10 mg bid) was administered to healthy people living with HIV (PLWH) on antiretroviral therapy (ART) for 5 wk to investigate safety and to reduce ongoing inflammation that persists even with virologic suppression. Because ruxolitinib is metabolized via the cytochrome P450 system. Analysis sought to model variability of ruxolitinib pharmacokinetics (PK) between participants (inter individual variability, IVIV) and assess PK interactions between ruxolitinib and ART.

Methods: Steady-state plasma concentrations of ruxolitinib and coadministered ART were drawn on wk 1 and 4/5 and assayed by liquid chromatography and tandem mass spectrometry (LC-MS/MS). Population PK models were fitted using NONMEM 7.4. Parameter distributions were assumed log-normal, and residuals having an additive and residual component. IVIV of Parameter and the variations in fraction of oral dose absorbed (between occasion variability of F) was estimated. Models converged to 3 decimals using the FOCE (first-order conditional estimation) with interaction method and were evaluated using statistical and graphical methods.

Results: No clinically relevant adverse events were observed across participants (33 male, 7 female), and HIV suppression was maintained. Ruxolitinib plasma concentrations versus time profiles from 39 and 38 participants on wk 1 and wk 4/5, respectively, were modeled. The PK profiles were adequately described using an open 2-compartment model with first-order absorption and elimination, and parameters were similar to reports in healthy volunteers and other indications: Distribution volumes V1/F = 61.83 L, 30.9% and V2/F = 2.36 L, 70.1% (normalized by body weight, mean 91.5 kg, IQ range 76.75-91.5 kg); Compartment clearance values were Cl/F = 14.47, 33.8% and Cl2/F = 4.84 L/hr; Absorption rate constant Ka = 4.96, 70.1%, and there was a 23% BOV in F. Area under the curve (AUC, dose/Cl2) distributions were similar on wk 1 and wk 4/5. Overall, concentrations of ART were consistent with those reported in population PK studies without ruxolitinib.

Conclusion: These data suggest that ruxolitinib can be safely administered to ART suppressed PLWH without adverse consequences regarding ruxolitinib or ART plasma levels, and variability of ruxolitinib plasma concentrations is similar to other populations.

453 INFILTRATION OF DNA-VR01 INTO THE CEREBROSPINAL FLUID IN HUMANS IN THE RV397 STUDY

Madhu Prabhakaran1, Sandeep Narpala1, Lucio Gama2, Donna J. Colby3, Phillip Chan4, Carlo Sacdalan4, Khunthalee Benjapornpong5, Jintanit Ananworanich6, Nitya Panupukund7, Suteeraporn Pinyakorn2, Trevor A. Crowell2, Serena S. Flexner2, Randall Tressler3, Athe Tsibris4, Steven G. Deeks5, Carlos del Rio1, Edgar T. Overton1, Jeffrey J. Lenna2, Vincent C. Marconi1, Raymond F. Schinazi1
1Emory University, Atlanta, GA, USA, 2Johns Hopkins University, Baltimore, MD, USA, 3NIH, Bethesda, MD, USA, 4Harvard University, Cambridge, MA, USA, 5University of California San Francisco, San Francisco, CA, USA, 6University of Alabama at Birmingham, Birmingham, AL, USA

Background: VR01 is a broadly neutralizing antibody (bNab) capable of potently neutralizing VZV meningoencephalitis (n=1). Backbone therapy co-administered to BIC since at least 1 month were enrolled between 2019 January and February. NeuroHIV Rehabilitation Care Unit, AP-HP, Bicêtre Hospital, France. Blood and CSF samples were collected simultaneously in the setting of routine care. Plasma and CSF HIV RNA were quantified by PCR (Abbott Realtime) with threshold of 40 copies/mL. Total plasma (Tot) and CSF BIC/TFC/tenofovir (TFV) concentrations and unbound plasma (U) BIC concentrations, separated by ultrafiltration (Centrifree devices, cutoff, 30 kDa; Millipore), were measured by quality controls validated assays (LC-MS/MS). The albumin quotient (QA), calculated as the ratio of CSF to plasma albumin, was used to evaluate the blood-brain barrier (BBB) function. All numerical variables were expressed as median (IQR). Results: Twelve pts (6 females) were enrolled. Age was 44 (12) years. HCI were: progressive multifocal leukoencephalopathy (PML, n=7), cerebral toxoplasmosis (CT) (n=3), CT combined with HIV encephalitis (n=1) and VZV meningoencephalitis (n=1). Backbone therapy co-administered to BIC was: TAF + FTC (n=10) or TAF + FTC + Maraviroc (n=2). Plasma HIV RNA was undetectable in 10 (83%) pts and <3 log copies/mL in others. Two (17%) pts had a detectable CSF viral load (1.7 and 1.9 log copies/mL). All concentrations and ratios are shown in table below. There are correlations between CSF and Tot concentrations for BIC and FTC (p=0.008 for BIC and p=0.002 for FTC) and between CSF and U concentrations for BIC (p=0.049). The median QA was 5.5 (1.8); 1 (8%) patient had a damaged BBB, but not related with a higher CSF BIC/TFC diffusion.

Conclusion: Total plasma concentrations remained as previously reported. Almost all CSF concentrations were above the in vitro 50% inhibitory concentration (IC50). BIC with FTC/TAF backbone should be effective to target
HIV replication in the CNS, which is a deep reservoir, even though BBB is undamaged.

<table>
<thead>
<tr>
<th></th>
<th>TFC</th>
<th>TFV</th>
<th>FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total plasma – ng/mL</td>
<td>2740 (2374)</td>
<td>17.6 (7.1)</td>
<td>231 (200)</td>
</tr>
<tr>
<td>Undetectable plasma – ng/mL</td>
<td>30.7 (13.2)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Total CSF – ng/mL</td>
<td>12.5 (4.8)</td>
<td>12.2 (4.6)</td>
<td>7.0 (5.4)</td>
</tr>
<tr>
<td>CSF TCDS – ng/mL</td>
<td>2.9</td>
<td>11.6</td>
<td>7.0</td>
</tr>
<tr>
<td>&gt; CSF TCDS/CSF ratio</td>
<td>11 (6.4)</td>
<td>12 (1.0)</td>
<td>8.6 (7.7)</td>
</tr>
</tbody>
</table>

Conclusion: The ART regimen IQ rank is a new approach to assess regimen vs individual drug activity. This tool provides a basis for continued work to expand regimen IQ data and investigate longitudinal relationships with biomarkers of HIV CSF persistence and inflammation.

Background: ACTG A5321 is a prospective cohort study of changes in HIV-1 reservoirs among participants with HIV on antiretroviral therapy (ART). We designed a single cross-sectional analysis of antiretroviral (ARV) pharmacokinetics (PK) in cerebrospinal fluid (CSF) and investigated relationships among a novel putative measure of ART regimen CSF activity and concurrent biomarkers of HIV persistence and inflammation.

Methods: Participants were on ART for ≥2 years with well-documented sustained plasma viral suppression at time of lumbar puncture (LP). CSF ARV concentrations, cell-associated HIV DNA and inflammatory biomarkers were measured at LP. ARV levels were quantified by LC/MS/MS. CSF inhibitory quotients (IQ) were calculated for each drug in ART regimen as ratio of measured CSF concentration to literature values for in vitro inhibitory concentration. Participants were ranked (low to high) by IQs for TFV, FTC, and third ARV, then drug ranks were averaged to give an overall rank for the ART regimen; a participant with highest IQ for all individual components would have the highest regimen IQ score. Rank-based analyses were used to evaluate associations among regimen IQ ranks and biomarkers.

Results: CSF ARV concentrations were available on 55 participants on TDF/FTC-based regimens: 52 males (95%); 40 (73%) white non-Hispanic, 15 (18%) black non-Hispanic; median age, 48 yrs; median yrs on ART, 8.1 yrs; median CD4 count, 651 cells/µL; 54 (98%) with plasma HIV-RNA <40 copies/mL. Third drugs in ART regimens included: EFV (n=17), ATV/r (8), ETV/c (8), RAL (8), DRV/r (4) and DTG (2). RPV and NVP (n=8) were not analyzed as CSF levels were unavailable. Figure shows CSF IQ values for ARVs drugs, which were consistent with CNS Penetration Effectiveness (CPE) scores. Associations among ART CSF IQ and HIV-1 persistence measures were restricted to participants treated with TFV, FTC, and third ARV, before breastfeeding started. Genomic DNA was extracted and genotyped by real-time PCR using TaqMan® nucleic assays for CYP2B6 516G>T and 983T>C single nucleotide polymorphisms (SNPs). Efavirenz was quantified using a validated LC/MS/MS method. Linear regression was used to explore association of genetic and non-genetic factors with newborn efavirenz concentrations.

Results: A total of 171 samples were available for this analysis (including 81 paired samples) from 86 women and 85 newborns. Mean (SD) maternal age at delivery was 30 (5.2) years, gestational age 40 (3.3) weeks, birth weight 2.9 (0.5) kg and APGAR score 7.6 (1.4). Samples were collected 18.5 (10.1) h after last maternal dose. A strong correlation was observed between maternal and newborn efavirenz concentrations (Figure A). Median (range) newborn efavirenz concentrations were 1180 (69.0-9230) ng/mL in unstratified newborns, 969 (15.9-2910), 1230 (69.2-9230) and 1790 (735-5230) ng/mL in fast (n = 28), intermediate (n = 37) and slow (19) metabolisers, respectively (Figure B).

Background: Understanding the influence of foetal and maternal genetics on prenatal drug exposure could play an important role in assessing observed risk-benefit differentials during pregnancy. In this sub-study of VADICT (NCT03284645), the influence of functional CYP2B6 polymorphisms on prenatal exposure to efavirenz was investigated.

Methods: VADICT is a cohort study that started recruiting in June 2017 in four Nigerian hospitals investigating viral and antiretroviral dynamics in fluids important for mother-to-child transmission. Women commencing efavirenz-based regimens before/early/late in pregnancy or postpartum are being recruited with followed-up until breastfeeding ends. For this sub-study, maternal and newborn samples were collected immediately after delivery before breastfeeding started. Genomic DNA was extracted and genotyped by real-time PCR using TaqMan® nucleic assays for CYP2B6 516G>T and 983T>C single nucleotide polymorphisms (SNPs). Efavirenz was quantified using a validated LC/MS/MS method. Linear regression was used to explore association of genetic and non-genetic factors with newborn efavirenz concentrations.
**ASSOCIATION BETWEEN INTEGRASE INHIBITOR HAIR CONCENTRATIONS AND WEIGHT GAIN IN WOMEN**

Cecile D. Lahiri,1 Cyra Christina Mehta,2 Christine D. Angert,3 Craig Sykes,3 Sheri Weiser,3 Deborah Gustafson,4 Audrey French,5 Adaora Adimora,6 John E. Celum,7 Robert J. Zembar,3 Deborah Konkle-Parker,3 Anjali Sharma,3 Hector Bolivar,3 Seble Kassaye,3 Igoho Ofotokun,3 Elizabeth T. Golub,8 Anandi N. Sheth,9

1 Emory University, Atlanta, GA, USA, 2University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 3University of California San Francisco, San Francisco, CA, USA, 4SUNY Downstate Medical Center, Brooklyn, NY, USA, 5Stroger Hospital of Cook County, Chicago, IL, USA, 6University of Mississippi Medical Center, Jackson, MS, USA, 7Albert Einstein College of Medicine, Bronx, NY, USA, 8University of Miami, Miami, FL, USA, 9Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** Integrase strand-transfer inhibitors (INSTIs) were associated with body weight gain among women living with HIV (WLH) in the Women's Intergroup HIV Study (WIHS). Hair drug concentrations measure cumulative exposure and are associated with toxicity in other antiretroviral therapy (ART) medications. For the first time, we report the relationship between INSTI hair concentrations and weight change in WLH.

**Methods:** Data from 2006-2017 were analyzed from virally-suppressed (<1000 cop/ml) WLH in WIHS who switched/added raltegravir (RAL) or dolutegravir (DTG) to ART with quantifiable hair concentrations. Body weights were measured 6-12 months pre- and 6-18 months post INSTI switch/FFD. Hair concentrations were measured with validated liquid chromatography/tandem mass spectrometry assays 6-18 months post INSTI switch/FFD and dichotomized at the median. Linear models assessed the association between dichotomized INSTI hair concentration and weight change from pre-switch/add. The association between clinically significant weight gain (≥7%) and INSTI hair concentrations was assessed through Wilcoxon Rank Sum Tests and chi-square tests.

**Results:** 136 WLH contributed 231 hair samples with mean 1.9 years (±0.12) follow up. Mean age was 49.6 (±9.2), 73 (54%) Black, baseline BMI 30.4 kg/m² (±9.5), 75 (55%) were on DTG, and 61 (45%) on RAL. Mean body weight change was +0.7 kg (±3.8) for RAL and +0.8 kg (±5.4) for DTG. No significant associations were seen between body weight change as a continuous variable with either RAL or DTG hair concentrations. Body weight change was +0.7 kg (±3.8) for RAL and +0.8 kg (±5.4) for DTG. No significant associations were seen between body weight change as a continuous variable with either RAL or DTG hair concentrations (p=0.2554 and p=0.2826, respectively). Median RAL and DTG hair concentrations were not significantly different in WLH with ≥7% weight gain compared to <7%: 0.71 ng/mg (Q1:0.55, Q3:1.10) vs 0.84 ng/mg (Q1:0.40, Q3:1.44), p=0.4735 and 793.0 pg/ml (Q1:198, Q3:714), p=0.1037 respectively (Figure). With combined INSTI groups, 14 of 24 (58%) WLH with ≥7% weight gain had hair concentrations above the median vs 51 of 109 (47%) with <7% weight gain, p=0.3057.

**Conclusion:** In virally-suppressed WLH, the effect of RAL and DTG cumulative drug exposure on body weight change over the short term appears to be limited. In addition to further pharmacologic assessments, other mechanisms to explain INSTI-associated weight gain should be explored.
ARP PENETRATION INTO FEMALE GENITAL TRACT DURING PREGNANCY: EFAVIRENZ AS A CASE STUDY

Oluwasegun I. Eniyewu1, Shakir A. Atoyebi1, Jacinta Nwogu1, Alieu Amara1, Oluseye Bolaji1, Damien Anweh1, Ebunoluwa Adejuyigbe1, Marco Siccardi3, Saye Khoo3, Andrew Owen3, Adeniyi Olagunju1

Methods: A novel assay to quantify efavirenz in cervicovaginal fluid from flocked swabs using LC-MS/MS was developed and validated as per FDA guidance. Efavirenz was quantified from cervicovaginal swabs (CVS) collected from HIV-infected pregnant women enrolled in the VADICT study (NCT03284645) receiving 600 mg daily. To further characterise efavirenz penetration into the female genital tract, we extended a previously described pregnancy PBPK model constructed and implemented in SimBiology® (MATLAB® version 2018b) to include a multi-compartmental cervicovaginal unit (vagina fluid, epithelium, stroma blood and tissues). Variables representing drug and system characteristics were obtained from the literature for model parameterization. Efavirenz movement within the cervicovaginal compartments was by passive diffusion. The model was qualified by comparing predictions with data from the VADICT study.

Results: Mean CVS efavirenz concentration with this method in the cohort (n = 39, mean gestational age 33.8 weeks) at 14.8 h post-dose was 1.237 µg/mL (95% CI: 1.038, 1.639), giving CVS:plasma concentration ratio of 0.64, more than previous reports. This was adequately predicted by the model, predicted CVS concentration being 1.190 µg/mL (0.542, 2.430) in a virtual cohort (n = 100, 29.5 weeks gestation). Trough (C_{trough}), maximum (C_{max}) efavirenz concentration and area under the concentration-time curve (AUC0-24h) were 0.62 µg/mL (0.29-1.33), 1.67 µg/mL (1.05-2.67), and 28.4 (µg/hr/mL) (16.89-41.41) respectively.

The corresponding parameters in vaginal epithelium, stroma blood and tissue were 7-22% higher. Importantly, both observed and predicted efavirenz C_{trough} were above reported protein-binding adjusted IC_{50} of 126 ng/mL for wild-type HIV-1 in all patients.

Conclusion: Our novel method indicates significantly higher penetration of efavirenz in the female genital tract than previously reported. This provided data for successful qualification of a PBPK model of efavirenz in pregnant women genitalia.

PK/PD STUDY OF RALTEGRAVIR ALONE OR COMBINED WITH LAMIVUDINE AS PRÉP: AN RCT

Julie Fox1, Carolina Herrera2, Laura Else1, Julianne Lwanga1, Ming Lee1, Alieu Amara1, Laura Dickinson1, Marta Boffito1, Robin J. Shattock1, Saye Khoo1, Carolina Herrera2, Laura Else1, Julianne Lwanga1, Ming Lee1, Alieu Amara1, Laura Dickinson1, Marta Boffito1, Robin J. Shattock1, Saye Khoo1

Methods: Open label trial of 36 HIV-females and males (1:1) randomised to 7d raltegravir 400mg bd followed by 7d raltegravir 400mg/lamivudine 150mg bd (after washout), in 6 sampling blocks to capture different times post-dose. Blood, saliva, rectal fluid (RF)/tissue (RT), vaginal fluid (VF)/tissue (VT) sampled at baseline, on PrEP (day2, 4 or 6) and off PrEP (day8, 10 or 12) for PK (RGV, 3TC, 3TC-triphosphate) and antiviral activity (ex vivo challenge RS-tropic HIV-1B; virus: p24 levels at 15d). Protection was defined as >50% reduction in p24 compared to baseline.

Results: RGV and 3TC were detectable in all tissue samples at day 2 PrEP. On day 6, GM RGV levels were 247.9 ng/mL in VT and 539.2 ng/mL in RT; GM tissue-to-plasma accumulation ratios 0.75 (VT) and 2.6 (RT). After PrEP cessation, 30% of VT and 66% of RT samples remained above RGV IC_{50} (15 ng/mL) day 10. Extensive 3TC VT (1397 ng/g) and RT (2662 ng/g) accumulation: GM Tissue-to-plasma accumulation ratios 7.3 (VT) and 17.1 (RT) day 6. Off PrEP, 3TC persisted in VT (182 ng/g) and RT (275 ng/g) until day 12. Plasma explained a greater variability in VT level (R² > 0.759; P < 0.001) compared with VF. Whereas RF explained more of the variability for 3TC RT levels (R² > 0.591; P < 0.001), than plasma. Raltegravir provided maximum ex vivo protection at day 2-8 (83% of rectal; 100% of vaginal samples) Raltegravir/Lamivudine provided 100% protection in rectal tissue from day 2-10, and in vaginal tissue from day 8-12.

Conclusion: Following discontinuation, high concentrations of RGV remained in RT (but rapid decline in plasma and VT concentrations) with persistent inhibitory activity in RT up to 4 days later. Addition of lamivudine increased inhibitory activity in RT and VT, with similar persistent inhibition associated with high 3TC RT concentrations 4 days after discontinuation.

MODELLING-SUPPORTED ISLATRAVIR DOSE SELECTION FOR PHASE III

Deanne J. Rudd1, Youfang Cao1, Pavan Vaddady2, Jay Grobler3, Ernest Asante-Apiah1, Tracy Diamond1, Stephanie O. Klopfer1, Anjana Grandhi1, Peter Sklar1, Carey Hwang1, Ryan Vargo3

1Merck & Co, Inc, West Point, PA, USA, 2Merck & Co, Inc, Upper Gwynedd, PA, USA, 3Merck Research Laboratories, Rahway, NJ, USA

Background: Islatravir (ISL) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1 infection. Single doses of ISL as low as 0.5 mg showed robust efficacy in a proof-of-concept (POC) clinical trial and established an IQ (ratio of drug exposure to potency) of 5 for ISL for wild-type HIV-1. In a Ph2 clinical trial (NCT03272347), participants who initiated ISL+doravirine (DOR) in combination with 3TC and switched to ISL+DOR no earlier than Week 24 had high efficacy at ISL 48 as measured by HIV-1 RNA <50 c/mL. Data through Week 48 showed that exposure-response was flat, indicating an achievement of maximal efficacy at the ISL doses examined (0.25, 0.75, and 2.25 mg). Modeling and simulation, along with in vitro potency data, were used to help select the dose for further clinical development of ISL most appropriate for HIV-1 treatment-naive, virologically suppressed, and highly-treatment experienced (HTE) populations.

Methods: A population pharmacokinetic model for ISL and its active moiety, ISL-triphosphate (ISL-TP), has been developed based on Ph1 and Ph2 data in healthy participants and people living with HIV-1 (PLWH) and used to examine the PH2 exposure-response relationship. The population pharmacokinetic
model was also used to predict the percentage of participants expected to have ISL-TP concentrations sufficient to have antiviral activity against common NRTI-resistant viruses (e.g., M184V, etc.).

Results: Based on an analysis of in vitro potency data, Ph1b POC efficacy, and Ph2a data, a dose of ISL 0.75 mg QD is expected to provide maximal efficacy in treatment-naive PLWH, and also be highly efficacious in virologically suppressed and HTE participants. Based on the in vitro potency and supported by the POC data for ISL, the expected concentrations of ISL-TP after a single 0.75 mg dose are sufficient to suppress both wild-type virus and HIV-RT resistant variants. ISL-TP accumulates after multiple dosing resulting in higher IQ at steady state. Simulations show that most patients would rapidly surpass the IQ threshold for all common HIV-RT resistant variants.

Conclusion: ISL 0.75 mg QD, in combination with DOR 100 mg QD, is appropriate for further evaluation in a development program consisting of treatment-naive, virologically-suppressed, and HTE PLWH.

463
FOSTEMSARV EXPOSURE-RESPONSE RELATIONSHIPS IN TREATMENT-EXPERIENCED HIV PATIENTS

Ridhi Parasrampuria1, Navin Goyal2, Katy Moore2, Peter Ackerman3, Cyril C. Llamosa4, Keith Barker4, Mindy Magee4
1GlaxoSmithKline, Collegeville, PA, USA, 2ViiV Healthcare, Research Triangle Park, NC, USA, 3ViiV Healthcare, Brantford, CT, USA, 4GlaxoSmithKline, Uxbridge, UK

Background: Fostemsavir (FTR) is an oral prodrug of its active moiety, temsavir (TMR), an investigational HIV-1 attachment inhibitor. Phase 3 efficacy-exposure-response (ER) relationships in heavily treatment-experienced (HTE; multi-drug resistant) HIV-1 patients with FTR 600 mg BID, and safety ER relationships from Phase 2b (TE) and P-3 (HTE) with FTR 400, 600, 800 mg BID and 600, 1200 mg QD were evaluated.

Methods: Individual PK parameters estimated from a population PK model were used to evaluate ER relationships. Efficacy endpoints: change in plasma HIV-1 RNA from Day 1 to 8 (functional monotherapy), >0.5 and >1.0 log10 decrease in HIV-1 RNA on Day 6 and at Week 24, proportion of subjects with HIV-1 RNA <40, <200 and <400 copies/mL. In addition, covariates of virologic (TMR IC50 and gp120 substitutions), immunologic (CD4+ T-cell count), and demographic factors as predictors of virologic response were investigated. Simulations were conducted to predict virologic responses on Day 8 under different extrinsic and intrinsic factors. Safety endpoints included: change from baseline in AST, ALT, CPK, SCr, QTcF up to Week 24, and occurrence of rash. Following graphical exploration, linear, inhibitory Emax and logistic regression models were explored.

Results: ER relationship was established between TMR Cmax and change in plasma HIV-1 RNA from Day 1 to 8, however, relationship was shallow and highly variable. Baseline HIV-1 RNA and CD4 + count were covariates; the higher the baseline value, the greater the reduction. Additional IC50 (as C tau /PBIC 50 ) did not improve the relationship. Model predicted probability of >0.5 and >1.0 log10 decrease in HIV-1 RNA on Day 6 was 80% and 58%, at plasma TMR Cmax of 300 ng/mL with median baseline HIV-1 RNA (4.65 log10 copies/mL) and CD4 >200 cells/μL. At Week 24, no relationship could be established between plasma TMR Cmax and HIV-1 RNA or CD4 + counts. Simulations showed no clinically relevant changes in Day 8 virologic response (Table 1). There was no clear correlation seen between TMR exposure and the safety endpoints explored.

Conclusion: Higher reduction in plasma HIV-1 RNA from Day 1 to 8 with increase in TMR Cmax in HTE HIV-1 patients on FTR 600 mg BID was observed. Simulations showed the impact of food, co-medications, and body weight were not clinically relevant.

464LB
BICTEGRAVIR DISTRIBUTION AND BICTEGRAVIR/FTC/TAF ACTIVITY IN GENITAL TRACT AND RECTUM

Arkaiz Imaz1, Juan M. Tiraboschi1, Jordi Niubo2, Javier Martinez-Picado2, Mackenzie L. Cottrell3, Pere Domingo4, Ivan Chivite5, Eugénia Negredo6, Sandra Morenilla7, Victor Ureña7, Sofia Secovla8, Benito García9, Angela Kashuba9, Daniel Podzamczer9
1Bellvitge University Hospital, Barcelona, Spain, 2IrCiiEa Institute for AIDS Research, Badalona, Spain, 3University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 4Hospital Sant Pau, Barcelona, Spain, 5Hospital de Sant Joan Despí Moisés Broggi, Sant Joan Despí, Spain, 6Fundació Iliana Contra la Sida, Badalona, Spain

Background: Antiretroviral distribution in the genital tract (GT) and rectum is required to suppress HIV replication within these compartments. Pharmacokinetics and HIV decay in the GT and rectum have not yet been described for the new integrase inhibitor bictegravir (BIC).

Methods: Prospective study of HIV-1–infected, ART–naïve males (n=15) and females (n=8) initiating BIC/FTC/TAF 50/200/25 mg. HIV-1 RNA was measured (Abbott RealTime HIV-1; quantification limit 40 c/mL) in blood plasma (BP) as well as in seminal plasma (SP) and rectal fluid (RF) in men, and cervicovaginal fluid (CVF) in women, at baseline (BL), days 3, 7, 14 and 28, and weeks 12 and 24. HIV-1 RNA decline between timepoints in SF and RF were compared to BP. Total BIC concentrations were quantified in BP, SP, RF, rectal tissue (RT) and CVF at 24 hours post dose (C24h) on day 28 and week 12 using a validated LC/MS/MS assay.

Results: Median (range) BL characteristics were: age 30 (20-57) yrs; CD4 419 (9-1165) cells/μL; BP HIV-1 RNA 4.89 (3.17-6.10) log10 c/mL. HIV-1 RNA was >40 c/mL at BL in SP, RF and CVF in 12/15, 13/14 and 4/8 individuals, with a median(range) of 3.74 (2.29-4.74), 4.29 (2.75-5.22) and 2.56 (1.61-3.56) log10 c/mL. HIV-1 RNA decrease was significantly lower in SP compared to BP up to day 14 with no statistically significant differences thereafter, whereas no differences were observed between RF and BP. Of those with HIV-1 RNA >40 c/mL in SP, RF and CVF at BL, 42%, 77% and 100% had undetectable HIV-1 RNA at day 14, and 92%, 92% and 100%, respectively, at day 28, whereas 47% of men and 37% of women had HIV-1 RNA >40 c/mL in BP at day 28. In men, median(range) BIC C24h in BP, SP, RF and RT were 2640 (424-10300) ng/mL; 65.5 (20.1-923) ng/mL; 2320 (834-5770) ng/mL and 61.6 (14.4-1760.2) ng/mL. On average BIC C24h in SP,CVF and RT (assuming tissue density=1g/ml) were 2.8% and 2.6% of BP C24h. Total BIC concentrations exceeded the EC50 for wild type HIV-1 (1.1 ng/mL) in all compartments.

Conclusion: BIC/FTC/TAF resulted in rapid HIV-1 RNA decay in GT and rectum. Total BIC concentrations in these compartments exceed the EC50 for wild-type HIV-1.

465LB
SAFETY AND PHARMACOKINETICS OF INTRAVENOUS VIRCOILS AND 10-1074 IN YOUNG CHILDREN

Edmund V. Capparelli1, Gbolahan Ajbola2, Kenneth Maswabi2, Kara Bennett3, Michael D. Hughes4, Molly Pretorius Holme5, Kelly Seaton5, Adrian Edmund V. Capparelli1, Gbolahan Ajbola2, Kenneth Maswabi2, Kara Bennett3, Michael D. Hughes4, Molly Pretorius Holme5, Kelly Seaton5, Adrian
1University of California San Diego, La Jolla, CA, USA, 2Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, 3Bennett Statistical Consulting, Inc.
468 MK-8504 AND MK-8583 (TENOFOVIR PRODRUGS) SINGLE-DOSE PK AND ANTVIRAL ACTIVITY IN HIV
Randolph P. Matthews1, Sarah J. Hsieh1, Jesse C. Nussbaum1, Guido H. Jajamovich1, Tian Zhao1, Diana Selverian1, Michaelanne Wasenius1, Liesbeth Haspeslagh2, Caroline Clissen1, Dirk Schuermann3, Sylvie Rottey4, Marta Boffito5, Deanne J. Rudd1, S. Aubrey Stoch1, Marian Iwamoto1

Background: Long-acting (LA) regimens of cabotegravir (CAB) + rilpivirine (RPV) given monthly and every 2–3 months are in development for maintenance of HIV suppression. Both products exhibit absorption–rate limited PK following intramuscular (IM) administration, with apparent half-life (t1/2) estimates of 5.6–11 weeks (CAB) and 26 weeks (RPV). Following LA treatment discontinuation, CAB and RPV may remain measurable in plasma for a year or longer. Available long-term follow up (LTFU) pharmacokinetic (PK) data from continued subjects in Phase 2b/3 studies (LATTE-2/ATLAS) are presented.

Methods: HIV-infected subjects who received CAB LA + RPV LA every 4 (Q4W, n=33) or every 8 weeks (Q8W, n=5) and withdrew for any reason were required to switch to alternative antiretroviral therapy (ART) and enter LTFU (1 year), with PK sampling at 1, 3, 6, 9 and 12 months after final injections. Plasma CAB and RPV concentrations were determined by validated LC-MS/MS assays. RPV concentrations in subjects receiving oral RPV in LTFU were excluded from the results (n=6).

Results: Figure 1 represents CAB and RPV plasma concentrations for subjects entering LTFU after having been on CAB LA + RPV LA from 4 to 72 weeks. Plasma CAB was > 0.166μg/mL (protein adjusted (PA)-IC90) in 30/30 subjects at the 1-month LTFU visit, and ranged between 0.034 to 0.152μg/mL (<PA-IC90) in 8 subjects and was nonquantifiable (<lower limit of quantification (LLOQ, 0.025μg/mL)) in 17 subjects at the 12-month LTFU visit. At the 1-month LTFU visit, plasma RPV was >12 ng/mL (PA-IC90) in all subjects (29/29); at 12-month LTFU visit, plasma RPV >LLOQ (1ng/mL in all subjects (23/23), ranging up to 63.8 ng/mL and >PA-IC90 in 11/23. Adverse events were uncommonly reported, and no patients met CVF criteria during LTFU on alternative ART, which included dolutegravir and elvitegravir integrase inhibit based regimens, darunavir protease inhibitor based regimens, and RPV non-nucleoside reverse transcriptase based regimens.

Conclusion: The CAB and RPV plasma concentrations observed during LTFU are consistent with the apparent absorption–rate limited t1/2, for each LA formulation. Both CAB and RPV have a low drug interaction potential as perpetrators. Alternative ART selection after discontinuing CAB LA + RPV LA may include CYP3A and/or UGT1A1 inducers or inhibitors, without efficacy or safety concerns despite potential for transient increases in CAB and RPV concentrations by inhibitors.
DOSE-RESPONSE RELATIONSHIP OF SUBCUTANEOUS LONG-ACTING HIV CAPSID INHIBITOR GS-6207

Eric Daar1, Cheryl McDonald1, Gordon Crofoot1, Peter Ruane1, Gary Sinclair2, Edwin DeJesus3, Mezgebe Berhe4, Henni Patel5, Ya-Pei Liu6, Rebecca Begley7, Diana Brainard7, Robert H. Hyland7, Martin Rhee8
1Harbor–UCLA Medical Center, Torrance, CA, USA, 2Tarrant County Infectious Disease Associates, Fort Worth, TX, USA, 3Creford Research Center, Houston, TX, USA, 4Peter J Ruane, MD Inc, Los Angeles, CA, USA, 5AIDS Arms, Inc, Dallas, TX, USA, 6Orlando Immunology Center, Orlando, FL, USA, 7North Texas Infectious Diseases Consultants, Dallas, TX, USA, 8Midway Immunology and Research Center, Fort Pierce, FL, USA

Background: GS-6207, a potent, selective, first-in-class, multi-stage inhibitor of HIV-1 capsid function is in development as a long-acting agent for treatment of HIV-1 infection. The safety, antiviral activity and pharmacokinetics (PK) of GS-6207 were evaluated in people living with HIV (PLWH) in this Phase 1b study.

Methods: This is an ongoing, Phase 1b, randomized, double-blinded, placebo-controlled dose-ranging study of GS-6207 in HIV capsid-inhibitor naïve PLWH who are not taking antiretroviral therapy. A single subcutaneous (SC) dose of GS-6207 (20, 50, 150, 450, or 750 mg; N=6/cohort) or placebo (N=2/cohort) was administered. The primary endpoint was maximum reduction of plasma HIV-1 RNA through post dose day 10 (D10). Safety was assessed using laboratory tests and adverse event (AE) reporting. We present antiviral activity, blinded safety, and dose-response relationship for the 20 to 450 mg dose cohorts; enrollment of the 750 mg cohort is ongoing.

Results: Demographics and baseline characteristics were similar across groups (N=32, n=8 per group). All PLWH who received active drug had significantly greater reductions in HIV-1 RNA by D10 than the placebo (all p<0.0001). The 50 to 450 mg groups had a numerically greater mean reductions in HIV-1 RNA through D10 (range: 1.8 to 2.2 log10 copies/mL) than the 20 mg group (1.4 log10 copies/mL). At these doses, the inhibitory quotients (mean GS-6207 concentrations for each group/protein adjusted 95% maximal effective concentration in MT-4 cells for wild type HIV-1) were as follows: 0.7 to 0.8 for HIV-1 RNA, 0.7 to 0.8 for HIV-1 RT, and 1.2 to 1.4 for HIV-1 IN.

Conclusions: GS-6207 oral tablets are well tolerated following single oral doses up to 1800 mg, and can be dosed without regards to food. These data support ongoing clinical development of oral GS-6207 for use in PWH.

Table 1. Preliminary PK data for GS-6207 oral tablets

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Tmax (h)</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-D8 (ng·h/mL)</th>
<th>KT1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>4-8</td>
<td>10.0 (9.9)</td>
<td>130 (114)</td>
<td>6.7 (3.9)</td>
</tr>
<tr>
<td>50</td>
<td>4-8</td>
<td>17.0 (16.3)</td>
<td>220 (198)</td>
<td>8.7 (4.9)</td>
</tr>
<tr>
<td>150</td>
<td>4-8</td>
<td>30.0 (28.3)</td>
<td>420 (378)</td>
<td>9.9 (6.0)</td>
</tr>
<tr>
<td>450</td>
<td>4-8</td>
<td>30.0 (28.3)</td>
<td>600 (515)</td>
<td>9.9 (6.0)</td>
</tr>
<tr>
<td>750</td>
<td>4-8</td>
<td>30.0 (28.3)</td>
<td>900 (740)</td>
<td>9.9 (6.0)</td>
</tr>
</tbody>
</table>

NA: not available; values represent mean (±SD).

471 ANTIRETROVIRAL & RIFAMPICIN TREATMENT AFFECTS DMPA EXPOSURE: DOSING IMPLICATIONS

Jose Francisco1, Paolo Denti1, Helen Mcllernon1, Michelle A. Kendall1, Xinyue Wu2, Kelly E. Dooley3, Cindy Finnhaber4, Catherine Godfrey5, Susan E. Cohn6, Rosie Mngobiza7
1University of Cape Town, Cape Town, South Africa, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4University of Colorado, Aurora, CO, USA, 5DAIDS, NIAID, Bethesda, MD, USA, 6Northwestern University, Chicago, IL, USA, 7Enhancing Care Foundation, Durban, South Africa

Background: For women in sub-Saharan Africa, the use of long-acting reversible contraception (LARC) is increasing to prevent pregnancy. While data are limited, the contraceptive efficacy and safety of long-acting reversible contraception (LARC) is needed to guide recommendations.

Methods: We conducted a randomized, double-blind, placebo-controlled clinical trial to assess the contraceptive efficacy and safety of DMPA 150 mg (0.63 mg pure ethinyl estradiol) and medroxyprogesterone acetate (MPA) 75 mg (75 mg MPA, 62.5 mg ethinyl estradiol) with/without rifampicin among HIV-infected women in South Africa. Participants were randomized to receive DMPA 150 mg alone or with 600 mg rifampicin daily for 28 days, followed by placebo for 28 days.

Results: A total of 562 women were included in the analysis: 56 completed dosing. GS-6207 oral tablets were generally well tolerated. No serious adverse events (AEs), Grade 3 or 4 AEs, or discontinuations due to AEs were reported. The most common AEs were back pain (n=2) and headache (n=3); all Grade 1.

Conclusions: The preliminary PK and safety data suggest GS-6207 oral tablets are well tolerated following single oral doses up to 1800 mg, and can be dosed without regards to food. These data support ongoing clinical development of oral GS-6207 for use in PWH.
Background: Depot medroxyprogesterone acetate (DMPA) is an intermediate-acting hormonal contraceptive, administered as 150-mg intramuscular injection every 3 months and is commonly used by women with HIV and TB. As MPA is a CYP3A4 substrate, drug-drug interactions (DDI) with drugs used for HIV or TB may lead to subtherapeutic MPA concentrations (<0.1 ng/mL) before the next injection, resulting in unwanted pregnancies.

Methods: Pharmacokinetic data from DMPA studies ACTG A5093 (DMPA alone, or with nelfinavir, efavirenz or nevirapine), A5283 (with lopinavir/ritonavir), and A5338 (with ritampicin+efavirenz), were pooled and interpreted with a population PK model. MPA concentrations were measured at week 2, 4, 6, 8, 10 and 12 after injection. Alomometric body weight was used to scale the clearance and volume of distribution parameters and the effect of DDI were investigated. Monte Carlo simulations were used to identify percentage of participants at risk of subtherapeutic MPA exposures and derive alternative dosing strategies.

Results: A total of 138 women with HIV, contributing 744 MPA concentration observations were included. Median (range) weight and age were 62.5 kg (41-125) and 34 years (15-47), respectively. A one-compartment model with first-order elimination characterized DMPA disposition, while the release of MPA from the micro-crystalline suspension was characterized using two-way absorption pathway. A fraction of the dose is readily available in the systemic circulation, while the rest is released more slowly. Rif-+EFV and EFV co-treatment increased clearance of MPA by 52.4% and 24.7%, respectively; whereas LPV/ and NFV decreased clearance by 28.7% and 15.8%, respectively. LPV/r co-treatment was also found to accelerate the rate of slow release of MPA into systemic circulation, thus shortening the terminal half-life. The model predicted that, at week 12, a typical 60-kg woman on RIF+EFV and EFV has a higher risk of having a subtherapeutic concentration (3.4% and 2.6%) compared to MPA-alone (1.6%). This risk increased with body weight. Simulations demonstrated that re-dosing every 8-10 weeks can overcome the risk of contraceptive failure associated with these DDI.

Conclusion: Co-treatment with Rif-+EFV, and to a lesser extent EFV alone, decreases systemic exposure of MPA, thus increasing the risk of subtherapeutic exposure and contraception failure. Dosing DMPA every 10 or even 8 weeks when prescribing Rif-+EFV should eliminate this risk.

Visual inspection of the final model (top graph) stratified by different study arms. The solid and shaded lines are the 95% SPV and 95% confidence intervals for the same parameters, respectively (as predicted by the model. An appropriate model is expected to have 0 observed data points within the simulated confidence interval).
474 CD4/CD8 RECOVERY AND FIRST-LINE ART: GREATEST IMPROVEMENT WITH INTEGRASE INHIBITORS

Sergio Serrano-Villar1, Javier Martinez-Sanz2, Raquel Ron1, Alba Talavera1, Borja Fernández2, Francisco Fanjul3, Joaquín Portilla4, Josefina Muñoz2, Concha Amador1, Miguel Alberto De Zarraga5, Matilde Sanchez-Conde1, Sabina Herrera1, Pilar Vizcarr1, Maria J. Vivancos-Gallego, Santiago Moreno2, Hospital Ramón y Cajal, Madrid, Spain, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain, Hospital Universitario de San Espíritu, Palma de Mallorca, Spain, Hospital General Universitario de Alicante, Alicante, Spain, Hospital de Basurto, Bilbao, Spain, Hospital Marina Baixa, Hospital Marina Baixa, Hospital San Agustín, Guadalupe, Mexico

Background: A low CD4/CD8 ratio during ART identifies subjects with heightened immuno-senescence and increased risk of mortality. We aimed to assess the effects of the INSTI, PI or NNRTI-based first-line ART on long-term CD4/CD8 ratio recovery in a large prospective cohort.

Methods: Prospective cohort study in 13,026 HIV-infected individuals registered in the Spanish HIV Research Network (COrIS) cohort. We included subjects who started triple ART and achieved HIV RNA suppression at 48 weeks.

We used multilevel mixed models with linear splines to compare longitudinal changes in the CD4/CD8 ratio and Cox proportional-hazard models to compare the times to CD4/CD8 normalization by treatment groups (NNRTI, PI, INSTI) at 0.4, 1 and 1.5 cut-offs.

Analyses were adjusted for sex, country of origin, mode of transmission, calendar year, educational level, baseline HIV RNA, presence of AIDS, pre-ART nadir CD4, acme CD8 count and backbone NRTI and censored at virologic failure.

Results: A total of 6,804 individuals contributing to 37,149 persons/years and 37,680 observations were analyzed. Median follow-up was 49 months (IQR 0-128). As compared to NNRTI and PI treatment, INSTI treatment was associated with greater CD4/CD8 gain. Differences were observed since the first year of therapy and were driven by changes in both CD4 and CD8 counts. At year 4, the adjusted mean CD4 count for INSTI, NNRTI and PI was 904, 718 and 696 cells/ul (p<0.0001) and the adjusted mean CD8 count was 832, 875 and 996 cells/ul, respectively (p<0.0001). Within INSTI, the greatest CD4/CD8 ratio gain was observed with elvitegravir, followed by dolutegravir, and was largely due to higher CD8 count declines. Compared to INSTI, the NNRTI and PI groups showed lower rates of CD4/CD8 ratio normalization ≥1 (INSTI, aHR 0.80 [0.72–0.89]; PI, aHR 0.81 [0.78–0.85]; NNRTI, aHR 0.82 [0.80–0.85]). Subanalyses adjusted for backbone NRTIs or allowing observations after virologic failure yielded similar results.

Conclusion: INSTI-based first line ART is associated with a greater CD4/CD8 ratio gain compared to NNRTI and PI-based ART. This study in real life indicates that ART initiation with INSTI improves immune recovery with respect to other ART classes, which could affect long-term mortality.

475 CLINICAL AND LABORATORY OUTCOMES 24 WEEKS AFTER STARTING DTG VERSUS EFV IN ACUTE HIV

Phillip Chan1, Orlando Goh1, Donn J. Colby1, Carlo Sacdalani1, Camilla Muccini2, Nittaya Phanuphak3, Sueteaporn Pinyakorn3, Praphan Phanuphak4, Nitya Chomche1, Robert Paul1, Sandhya Vasan3, Serena S. Spudich5, Jintanat Anawaroon1, Eugene Kroon6, for the RV254 Research Group

SEARCH, Bangkok, Thailand, 2San Raffaele Vita-Salute University, Milan, Italy, 3US Military HIV Research Program, Bethesda, MD, USA, 4Thai Red Cross AIDS Research Center, Bangkok, Thailand, 5University of Missouri St Louis, St Louis, MO, USA, 6Yale University, New Haven, CT, USA

Background: This study compared clinical and laboratory parameters before and after initiating Efavirenz(EFV)- and Dolutegravir(DTG)-based antiretroviral therapy (ART), the prior and current 1st line ART, during acute HIV infection (AHI).

Methods: Individuals with AHI (Fiebig I-V) enrolled in the RV254 cohort in Thailand initiated ART within days (median=0; IQR 0-9) after diagnosis (EFV+2 NRTI: 2009-Jan2017; DTG+2 NRTI: Feb2017 onwards). Plasma HIV-1 RNA, blood CD4 and CD8 T-cell counts, and mood parameters, measured by the 9-item Patient Health Questionnaire (PHQ-9, score 0-27) for depression symptoms and the Distress Thermometer (DT) for anxiety/stress (score 0-10) were measured before and 24 weeks after ART. Participants who received other ART regimens were excluded.

Results: From 2009-2019, 415 participants (98% male, median age 26 years) initiated ART at AHI (EFV-based=325; DTG-based=90). By week 24, 15% (5%) EFV users reduced their daily EFV dose from 600mg to 300mg due to side effects and super-therapeutic plasma EFV levels. Another 23% (7%) discontinued EFV due to EFV-associated adverse events (AEs) and/or resistance; 2 (2%) DTG users discontinued DTG, both for acute hepatitis C with liver enzyme elevations (p=0.130). At baseline, both groups (EFV=302; DTG=88) were similar in age, sex composition, CD4/CD8 ratio, plasma HIV-1 RNA, PHQ-9 and DT scores (p>0.05); 167 (43%) had moderate depression symptoms (PHQ-9=9). The DTG group had lower CD4 and CD8 T-cells and higher rates of Fiebig III and CRF01 AE/B recombinant subtype than the EFV group (p<0.05). HIV suppression (<50 copies/ml) rates were 98% and 93% in the DTG and EFV group respectively (p=0.124). Comparing the change of parameters (i.e. difference between week 24 and baseline) by ART regimen showed greater gain in CD4 and CD8 T-cells in DTG users (Table). DTG-based ART remained independently associated with greater CD4 recovery (mean diff +78.0, 95%CI [40.2 to 115.8], p<0.001) in multivariable analysis. At week 24, the rate of PHQ-9≥9 in the DTG and EFV groups were 15% vs 13% respectively (p=0.644). Both groups had lower PHQ-9 and DT scores than at baseline (p<0.001) but both scores were similar across the groups (p>0.05).

Conclusion: Compared to EFV, initiating DTG-based ART at AHI was associated with a greater gain in CD4 T-cells and a higher absolute CD4 count at week 24. There were no DTG related AEs leading to discontinuation. Self-reported depression symptoms observed at AHI improved with ART regardless of the regimen.
476 RAPID ART IN BLOOD DONORS WITH ACUTE AND RECENT HIV CLADE C INFECTION IN SOUTH AFRICA

Karina Van den Berg,* Marion Vermeulen,† Sonia Bakkour,‡ Mars Stone,§ Coreen Barker,§ Christopher McClure,¶ Darryl Creel,** Ute Jentsch,†† Genevieve Jacobs,‡ Brian Custer,† Michael P. Busch,‖ Edward Murphy‖ for the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)
South African National Blood Service, Johannesburg, South Africa; Vitalant Research Institute, San Francisco, CA, USA; Clinical HIV Research Unit, Johannesburg, South Africa; RIT International, Rockville, MD, USA; University of California San Francisco, San Francisco, CA, USA

Background: Blood donations in South Africa are tested in parallel for HIV antibody (Ab) and RNA using individual-donation nucleic acid testing (ID-NAT), allowing annual detection of ~60 Acute (RNA+/Ab-) vs. Fiebig stages I-III and >400 Recent (RNA+/Ab+); Fiebig stages IV to VI HIV infections. We hypothesized that initiation of antiretroviral therapy (ART) in earlier Fiebig stages would correlate with smaller HIV reservoir size.

Methods: A prospective cohort study enrolled Acute and Recent HIV clade C infected blood donors. HIV Ab (Abbott Prism) and RNA (Griifols ID-NAT) were measured on samples taken at index donation and enrolment. Recency (<195 days) was detected by limiting-antigen avidity assay (Sedia). Enrolled donors were referred rapidly for ART with RAL/TDF/FTC X 6 months followed by EFV/TDF/FTC. We measured plasma RNA using the Aptima HIV-1 Quant Assay (Hologic) with 5 replicates. Cell-associated (CA) HIV RNA and total DNA were measured by qRT-PCR and real-time nested PCR, respectively. After median treatment duration of 20 months, we compared HIV reservoir size between treatment initiated in Fiebig I-III vs. IV-VI using repeated measures analysis adjusting for baseline RNA or DNA.

Results: From 2015 to 2017 we enrolled 49 donors with Acute and 34 with Recent HIV. Cohort enrolment/ART initiation occurred at medians of 15/34 days after index donations. Longitudinal HIV reservoir DNA data were available for 18 Fiebig I-III and 42 Fiebig IV-VI subjects. Median plasma RNA was 5.4 log10 copies/mL at enrolment, declined to 0.23 log10 copies/mL did not differ by Fiebig stage (p=0.56) but was 0.31 log10 lower in females (p=0.02). Median CA RNA was 3.7 log10 copies/10^6 PBMC at enrolment, falling to 2.2 log10 copies/10^6 PBMC, and was 0.64 log10 higher in Fiebig IV-VI than Fiebig I-III treated-subjects (p=0.002). Median CA total DNA was 1.8 log10 copies/10^6 PBMC at enrolment, falling to 0.85 log10 copies/10^6 PBMC with no difference by Fiebig stage (p=0.95).

Conclusion: Among clade C HIV-infected donors initiated on ART within 195 days of infection, we observed lower CA HIV RNA in Fiebig I-III vs. Fiebig IV-VI groups, demonstrating a small impact of earlier treatment on long-term reservoir expression, and lower post-ART plasma HIV-1 (single copy assay) in women vs. men. This study demonstrated that a partnership between a national blood service and a treatment NGO can establish early treatment cohorts for female patients.

478 CD4:CD8 NORMALIZATION BY INTEGRASE INHIBITORS AMONG TREATMENT-NAIVE PATIENTS

Alice Zhabokritsky,† Leah Szadkowski,‡ Alison McClean,‖ Robert S. Hogg,¶ Curtis Cooper,¶ Marina Klein,‡ Zabrina Brumme,‖ Sharon Walmsley,¶ for the CANOC Collaboration
University of Toronto, Toronto, ON, Canada; British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada; Ottawa Hospital Research Institute, Ottawa, ON, Canada; McGill University, Montreal, QC, Canada

Background: HIV infection leads to selective depletion of CD4 + T cells and an increase in CD8 + T cells resulting in an inverted CD4:CD8 ratio which often persists despite antiretroviral therapy (ART). A low CD4:CD8 ratio is associated...
with AIDS and non-AIDS related morbidities. A positive association between CD4:CD8 ratio normalization and initiation of raltegravir containing regimens has been observed. We hypothesize that Integrase Strand Transfer Inhibitor (INSTI)-containing regimens are associated with shorter time to CD4:CD8 normalization relative to other ART regimens among treatment naive patients.

**Methods:** Retrospective analysis of the Canadian Observational Cohort (CANOC), a collaboration of HIV-infected individuals initiating combination ART between 2000 and 2014. Participants starting on 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)/1 INSTI or a non-INsti regimen on or after January 1, 2011 with a pre-treatment CD4:CD8 ratio <1.2 and ≥2 follow-up ratios within 6 months of treatment initiation were included. Kaplan Meier estimates were used to describe time to CD4:CD8 ratio normalization (CD4:CD8 ratio ≥1.2 on 2 consecutive measures ≥ 30 days apart). Multivariable proportional hazards models were used to estimate the association between ART class and time to CD4:CD8 normalization.

**Results:** 781 participants were included and followed for a median [IQR] 1.9 [1.0, 2.7] years. Median [IQR] age was 38 [31, 47] and 699 (90%) were men. 235 participants starting on INSTI-containing regimens were more likely to have a higher median [IQR] pre-treatment CD4 count (370 [225, 480] vs. 330 [210, 440], p=0.04) compared to those starting non-INsti regimens. 35 (15%) participants on INSTI-containing regimens normalized their CD4:CD8 ratio with a 0.21 (95%CI 0.13, 0.28) probability of achieving normalization within 2 years. 63 (12%) of those on non-INsti regimens normalized with a 0.11 (95%CI 0.08, 0.14) probability of achieving so within 2 years (p<0.01). After adjusting for pre-treatment CD4, viral load, risk factor, hepatitis B and C, those starting INSTI-containing regimens compared to other ART were more likely to achieve normalization (HR=1.75, 95%CI 1.10, 2.77).

**Conclusion:** Our results provide further evidence that initiation of INSTI-containing regimens results in a higher rate of normalization of the CD4:CD8 ratio in ART naive subjects. Whether this is associated with lower rates of comorbidity or improved survival requires further study.

---

**Background:** The aim of this study was to evaluate survival and treatment outcomes of AIDS presenters compared to the remaining portion of antiretroviral therapy (ART)-naïve patients (pts) in a large Italian cohort.

**Methods:** All consecutive ART-naive HIV+ pts, enrolled in Icona Foundation Study Cohort from January 2009 to December 2018, with HIV diagnosis within 3 months from enrolment, were included and divided into 3 groups: pts with an AIDS diagnosis at/within 3 months from HIV diagnosis (1: AIDS presenters), asymptomatic pts with CD4 count at the enrolment ≤200 cell/mL (2: asympt CD4≤200) or >200 cell/mL (3: asympt CD4>200). Survival probability was estimated by Kaplan Meier curves in both the overall period and separately, analyzing two 5-year periods (2009-2013; 2014-2018). Independent risk of survival and, in the subgroup of patients starting ART, virological failure (VF) (2 consecutive HIV-RNA >200 cp/ml after 6 months of ART) and treatment discontinuation (TD) for drug toxicity were identified by fitting a Cox regression model.

**Results:** Overall, 7001 pts included: 959 AIDS presenters, 1,565 asympt CD4≤200 and 4,477 asympt CD4>200. ART was started in 6440 pts of whom 95%, 97% and 90% in group 1, 2 and 3 respectively. From 2009 to 2013, pts with advanced HIV presentation were significantly more likely to start PI/b-based regimen compared to asympt CD4≤200 (63% and 68% vs 41%, p=0.001) whereas in the last five years INSTIs were the main third-drug started in all groups (60% for both group 1 and 2 and 52% for group 3). At survival analysis, AIDS presenters showed the lowest probability of survival among the treatment groups [Fig1a]. 4-year survival estimates remained substantially stable over the two time periods [Fig1b,c]. After adjusting for the main confounders, both the groups with advanced HIV presentation were associated to a higher risk of death compared to asympt CD4≥200. This data was confirmed also restricting the analysis to those who started ART [Fig1d]. By multivariable analysis, AIDS presenters were associated with a greater risk of VF and of TD for toxicity compared to asympt CD4>200 [Fig1d].

**Conclusion:** Over the last decade, pts presenting with advanced HIV disease, particularly AIDS presenters, remained at consistently higher risk of death and poor response to ART. Public health strategies for emerging unknown infections and early treatment access are urgent to constrain the mortality gap of this vulnerable population.
Background: Second generation INSTIs currently represent the most highly recommended option for first-line ART but superiority to boosted-PI regimens in people with advanced HIV disease (CD4 count <200 cells/mm³, or AIDS), generally underrepresented or excluded from RCTs, has not been demonstrated.

Methods: We included ART-naïve patients with CD4 count <200 cells/mm³, or AIDS diagnosis in the Icona Foundation Cohort between 2014-2018, who started a dolutegravir (DTG) or boosted-darunavir (DRV/b [tritonavir or cobicistat]) based ART. We estimated the effect of the difference in risk of a composite endpoint (death, AIDS, serious non-AIDS events - SNAE - viral failure >200 copies/mL, anchor drug discontinuation not followed by a restart of a drug in the same class) between the two strategies using a marginal structural model. We accounted for differences in prognostic factors measured at time of ART initiation. We also accounted for differences in censoring by these same prognostic factors, and time-varying CD4, HIV-RNA and ALT.

Results: Characteristics of the 685 ART-naïve patients were (DTG=416; DRV/b=269; 224 DRV/r and 45 DRV/cob): male 87%; heterosexual contacts 50%; MSM 37%; born outside Italy 48%; AIDS presenting 36%; median CD4 count 78 cells/mm³, (IQR 30-140); median HIV-RNA 5.25 log₁₀ copies/mL (IQR 4.64, 5.73). All these variables were comparable between the two groups, except for higher proportion of migrant in DTG (51% vs 43%; p <0.001) and higher HIV-RNA values (80% in DRV/b and 44% in DTG) compared to DRV/r (5.35 vs 5.18 log₁₀/mL; p=0.019). NTI backbone was TDF/FTC in 58% (80% in DRV/b and 44% in DTG), TAF/FTC in 11% (10% in DRV/b and 12% in DTG), and ABC/3TC in 30% (10% in DRV/b and 44% in DTG) (p <0.01). 116 patients receiving DTG and 145 receiving DRV/r experienced the composite endpoint. The 1-year weighted probability of the composite endpoint was 37% for DRV/b and 21% for DTG (Figure 1a). Patients who initiated DTG were at lower risk of experiencing the composite endpoint compared to those who started DRV/b [aHR 0.50 (95%CI 0.32, 0.79)] (Figure 1b). Calendar year of starting was a key factor but results were consistent across periods of ART initiation.

Conclusion: Under the assumptions of no unmeasured confounding and correct model specification, our analysis suggests that a RCT conducted in the target population of ART-naïve patients with CD4 count<200 or AIDS is likely to show a notable reduction in risk of treatment failure in people initiated with dolutegravir vs. boosted-darunavir based therapies.

481 FLOW CYTOMETRIC SCREENING OF HLA-B17 IN HIV+ PATIENTS UNDERGOING ABACAVIR THERAPY

Arianna Gatti¹, Cristina Ceriani¹, Bruno Brandò¹, Maurizio Mena¹, Paolo Viganò¹, Massimo De Pascale¹, Pierangelo Clerici¹
1ASTT Ovest Milanese, Legnano, Italy

Background: The Abacavir Hypersensitivity Syndrome (AHS) is a life-threatening side effect that can occur in HLA-B*5701+ HIV+ patients treated with Abacavir. Every HIV+ patient eligible for Abacavir therapy must be therefore screened for the presence of the HLA-B*5701 allele and treated only if negative. The B*5701 allele is a member of the HLA-B17 family. HLA-B*5701 typing is mostly based on molecular methods, that are expensive and require a median of 21 days for processing. In this study we have developed a rapid dual-color Flow Cytometric (FC) assay, including anti-B17 monoclonal antibody that provides a cheap and sensitive screening for putative HLA-B*5701+ patients.

Methods: 21 HIV+ patients already SSO-typed for HLA-B*5701 served as positive (6) or negative (15) controls, respectively. Other 437 HIV+ patients were prospectively evaluated for HLA-B17 by FC and their outcome during Abacavir treatment was monitored. Briefly, 50 mL of EDTA blood were stained with 10 mL of unconjugated IgM monoclonal anti-B17 antigen (One Lambda) in a stain-lyse-wash procedure. A secondary PE-anti-mouse IgM was used for indirect immunofluorescence, with anti-CD3 FITC counterstaining. Isotype cold IgM and secondary PE conjugate were used as negative controls. The staining intensity of anti-B17 PE expression on T cells was considered to calculate the reaction cutoff, which was used to discriminate positive and negative cases.

Results: The agreement between SSO typing and FC assay in the controls was 6/6 for double-positives; one false-positive FC case was due to the cross-reacting antigen B*5702; whereas 14/14 cases were double negatives. Of the prospective 437 cases, 43 (10%) resulted positive for anti-B17, as expected. In 28/43 cases a confirmatory molecular test for HLA-B*5701 allele was performed, which disclosed the B*5701 in 11 patients. In the other 17 cases different alleles of the B17 family were detected, that did not prevent Abacavir therapy. None of the 394 FC B17-negative patients developed AHS during Abacavir administration.

Conclusion: In conclusion, the rapid FC assay to evaluate the HLA-B17 phenotype in HIV+ subjects eligible to Abacavir therapy proved reliable to safely screen out HLAB*5701-negative subjects, that represent the majority of cases. Its prospective use allows significant saving of time and money, since it can restrict the confirmative molecular HLA B*5701 typing to the small group of FC positive individuals.

482LB LONG-ACTING CABOTEGRAVIR + RILPIVIRINE FOR HIV TREATMENT: FLAIR WEEK 96 RESULTS

Chloe Orkin¹, Shinichi Oka², Patrick Philibert¹, Cynthia Brinson¹, Ayesha Bassa¹, Denis Gussen³, Olaf Degen⁴, Juan González-García⁵, Ronald D’Amico⁶, David Dorey⁷, Sandy Griffith⁸, David A. Margolis⁹, Marty St Clair¹, Peter E. Williams¹, William Spreen¹
¹Queen Mary University, London, United Kingdom; ²National Center for Global Health and Medicine, Tokyo, Japan; ³Hôpital Européen, Marseille, France; ⁴Texas Clinical Research Institute, Austin, TX, United States; ⁵Mazzoni Ethical Research Centre, Meddelburg, South Africa;⁶State Medical Center for the Prevention and Control of AIDS and Infectious Diseases, St. Petersburg, Russia; ⁷University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; ⁸Hospital Universitario La Paz, Madrid, Spain; ⁹ViiV Healthcare, Research Triangle Park, NC, United States; ¹⁰GloXaSmithKline, Mississauga, Ontario, Canada; ¹¹Janssen Research & Development, Beerse, Belgium

Background: Chronic daily oral ART can be lifesaving but also inconvenient, increasing the risks of non-adherence and treatment failure. To address these issues, long-acting (LA) injectable regimens of the INSTI cabotegravir (CAB) and the NNRTI rilpiridine (RPV) are under evaluation. FLAIR (NCT02938520) is a randomized, Phase 3, open-label, multicenter study investigating whether switching to monthly CAB+RPV LA is non-inferior to daily dolutegravir/abacavir/lamivudine (DTG/ABC/3TC [CAR]) in virologically suppressed adults infected with HIV-1.

Methods: ART-naïve patients received induction therapy with oral CAR for 20 weeks. After 16 weeks, patients with HIV-1 RNA <50c/mL were eligible to enter the maintenance phase (MP) and were randomized (1:1) to either switch to LA or continue CAR. Those randomized to the LA arm received an oral lead-in of CAB 30mg + RPV 25mg once daily for 4 weeks before receiving monthly injectable CAB+RPV LA. Those randomized to the LA arm received an oral lead-in of CAB 30mg + RPV 25mg once daily for 4 weeks before receiving monthly injectable CAB+RPV LA.

Results: From 629 participants who initiated induction therapy, 566 were assessed at MP Week 96 (W96) and were randomized (1:1) to switch to LA or continue CAR. Those randomized to the LA arm received an oral lead-in of CAB 30mg + RPV 25mg once daily for 4 weeks before receiving monthly injectable CAB+RPV LA. The primary endpoint was viral load ≥50c/mL at MP Week 48 (W48) by FDA snapshot algorithm (N in margin 6%). Endpoints assessed at MP Week 96 (W96) included viral loads ≥50c/mL and <50c/mL, confirmed virologic failure (CVF; two consecutive viral loads ≥200c/mL), safety, tolerability, and patient satisfaction.

Results: Of 629 participants who initiated induction therapy, 566 were randomized to either the LA or CAR arm (283/arm). Median age was 34y (11% ≥50y); 22% were female and 74% were white. At W96, 9 (3.2%) participants in...
each arm had HIV-1 RNA ≥50c/mL, underscoring the non-inferiority established at W48 (Table). For the LA arm, the rate of CVF was unchanged from W48 at W96 (4 participants [1.4%]; 3 had mutations in the NRTI- INSTI domains and no mutations). The CAR arm had 4 CVFs through W96 (vs. 3 through W48); none had mutations. Across both treatment arms, AEIs leading to withdrawal were infrequent. Injection site reactions (ISRs) were the most common drug-related AE (88% of participants in the LA arm); their frequency decreased over time. Median ISR duration was 3 days and 99% were Grade 1 or 2. At W96, the LA regimen was associated with a greater treatment satisfaction vs. oral CAR as measured by HIVTSQs.

Conclusion: CAB+RPV LA maintained viral suppression with no further CVFs between W48 and W96 and was non-inferior to oral standard of care ART. Although ISRs were frequently reported with CAB+RPV LA, they seldom led to withdrawal, and overall treatment satisfaction was higher than with ART. These results attest to the durability of CAB+RPV LA.

483 DTG+3TC VS DTG+TDF/FTC (GEMINI 1&2): CONFIRMED VIROLOGIC WITHDRAWALS THROUGH WEEK 96

Mark Underwood1, Ruolan Wang1, Paul Benson1, Norma Porteiro3, Giuliano Rizzato3, José R. Santos5, Rickesh Patel6, Justin Koteff1, Rimgaile Urbaitye7, Joe Horton1, Jorg Sievers6, Choy Man1, Allan Raymond Tenorio1, Jean van Wyk5

1ViiV Healthcare, Research Triangle Park, NC, USA, 2Be Well Medical Center, Berkley, MI, USA, 3Fundación Ilda, Buenos Aires, Argentina, 4ViiV Healthcare, Research Triangle Park, NC, USA, 5St John of God Hospital, Badalona, Spain, 6ViiV Healthcare, Brentford, UK, 7ViiV SmithKline, Uxbridge, UK, 8PAREXEL International, Durham, NC, USA

Background: In GEMINI-1&2, the dualtegucerivir (DTG) + lamivudine (3TC)-2 drug regimen (2DR) is non-inferior to the DTG + tenofovir/emtricitabine (TDF/FTC) 3-drug regimen (3DR) in HIV-1 ART-naive participants at Weeks 48/96. Eleven participants on 2DR and seven on 3DR met protocol-defined Confirmed Virologic Withdrawal (CVW) criteria through Week 96. We present a detailed description of these CVWs.

Methods: Patients were stratified by viral load (VL) ≤/100,000c/mL and CD4+ ≤/200cells/mm3. Patients were not eligible if screening HIV-1 genotype showed major RT/PR resistance mutations. CVW was defined as two consecutive VLs meeting virologic non-response (VL ≥200c/mL after Week 24 or <1.0 log decline in VL by Week 12 unless HIV-1 RNA is <200c/mL) or virologic rebound criteria (≥200c/mL after prior suppression to <200c/mL). Monogram Bioscence performed integrated and RT/PR genotypic and phenotypic resistance testing on Day 1 and Virologic Withdrawal timepoint samples. We evaluated CVW patient baseline (BL) VL and CD4 characteristics, adherence, study drug interruption, and VL progression through the study course.

Results: In GEMINI-1&2, 3 participants screen failed due to M184I/V resistance. Overall, 11 participants on DTG+3TC and 7 on DTG+TDF/FTC met CVW criteria through Week 96. Of these, 5 vs 2 CVWs occurred after Week 48. All CVWs experienced virologic rebound; none had VL blips (VLs between 50c-<200c/mL with adjacent values ≥50c/mL) that preceded CVW. One DTG+3TC participant never suppressed to <50c/mL. Table 1 summarizes key information for CVWs in the DTG+3TC arm. Among the 11 and 7 participants on DTG+3TC vs DTG+TDF/ FTC respectively: 9 vs 7 were infected with HIV-1 subtype B; 3 vs 2 had Baseline CD4 ≥200cells/mm3; 5 vs 3 had Baseline HIV-1 VLs >100,000c/mL; and HIV-1 VL decreased from CVW time point to the withdrawal (WD) visit ≥2 fold for 7 of 9 vs 4 of 5 cases with WD visit VLs. Resistance data were available for all samples except 2 cases on DTG+TDF/FTC where testing failed with HIV-1 VL below the assay cut-off; no treatment-emergent genotypic or phenotypic resistance in IN or RT was observed in any CVWs.

Conclusion: In GEMINI1&2, there were low and comparable numbers of participants meeting CVW through 96 weeks in the DTG+3TC and DTG+TDF/FTC arms without apparent predisposition by BL VL or CD4; no emergent genotypic/phenotypic resistance to INSTI/NRTIs was observed. These data further support the potency and durability of DTG+3TC.

Table. DTG+3TC arm CVW: Baseline (BL) VL, Load and CD4 Values, GEMINI 1 & 2.

<table>
<thead>
<tr>
<th>BL VL</th>
<th>CD4</th>
<th>GEMINI 1 (n=9)</th>
<th>GEMINI 2 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL</td>
<td>CD4</td>
<td>VL</td>
<td>CD4</td>
</tr>
<tr>
<td>≤50c/mL</td>
<td>≥200 cells/mm³</td>
<td>≤50c/mL</td>
<td>≥200 cells/mm³</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

484 HIV-1 REPLICATION AT ≤50c/mL TO 148 WEEKS FOR SWORD-1/SWORD-2 STUDIES WITH DTG+RPV

Mark Underwood1, Kostas Angelis2, Ruolan Wang1, Joe Horton1, Veerle Van Eygen3, Jessica Matthews4, Lesley Kahl5, Jean van Wyk6, Brian Wynne6

1ViiV Healthcare, Research Triangle Park, NC, USA, 2ViiV Healthcare, Brentford, UK, 3ViiV Healthcare, Research Triangle Park, NC, USA, 4GlascoSmithKline, Uxbridge, UK, 5PAREXEL International, Durham, NC, USA, 6ViiV Healthcare, Brentford, UK

Background: The SWORD studies demonstrated non-inferiority on switch to dualtegucerivir (DTG) + rilpivirine (RPV) vs continuing a 3- to 4-drug Current Antiretroviral Regimen (CAR) for 48 weeks, and also showed long term suppression to HIV-1 RNA ≤50c/mL. The clinical significance of low-level viral load (VL) <50c/mL remains unclear. We present here low level qualitative VL data from the Phase 3 SWORD studies up to Week 148.

Methods: Adults with VL≤50c/mL for ≥6 months were randomized to switch to DTG+RPV (Early Switch (ES) group) for 148 weeks or continue CAR. CAR participants ≤50c/mL at Week 48 switched at Week 52 (Late Switch (LS) group) to receive DTG+RPV for 96 weeks. The Abbott Realtime assay measures VL quantitatively from 40c/mL to 10,000,000c/mL; when VL<40c/mL it returns qualitative Target Detected (TD) or Target Not Detected (TND) results. We explored participants’ TND and TD status over time, overall and by Baseline TD or TND status.

Results: 1024 participants were randomized and exposed (ES DTG+RPV 513; CAR 511) across both studies; 477 CAR participants switched to DTG+RPV at Week 52. The proportions of participants with TND at all visit weeks were similar and did not decline over time (Figure; TND ranges across visits were 75%–88% in the ES group, 79%–90% in the LS group and 79%–88% in the CAR group. Participant proportions with BL TD and TND at all visits through 48 Weeks exposure in comparator ES DTG+RPV, LS DTG+RPV, and CAR groups were respectively 47% (180/383), 52% (189/367), and 53% (215/408), and for participants with BL TD the proportions with TND at all visits were respectively 19% (18/94), 33% (25/75), and 19% (13/70). Among participants in the ES DTG+RPV group with pre-switch TD vs TD, the proportions with TND at all visits through Week 148 were respectively 23% (79/341) vs 10% (8/84), and among LS DTG+RPV group the proportions with TND through Week 148 (96 weeks of DTG+RPV) were respectively 40% (142/352) vs 20% (15/76). In the ES DTG+RPV group, 20% of the 433 participants who reached Week 148 had TND at all visits, and in the LS DTG+RPV group, 36% of the 434 participants who reached Week 148 (with 96 weeks of DTG+RPV exposure) had TND at all visits.

Conclusion: The frequency of participants with TND status under DTG+RPV remained high across all visits with no decline observed through 148 weeks. This is supportive evidence that long term treatment with DTG+RPV is efficacious in virologic suppression to <50c/mL.
**LONG-TERM DTG-3TC SWITCH EFFICACY IN PATIENTS WITH ARCHIVED 3TC RESISTANCE**

Rosa de Miguel1, David Rial1, Lourdes Domínguez-Domínguez2, Racío Montejano3, Andrés Esteban-Cantos4, Ottilia Bisbal5, Natalia Stella-Ascariz5, Paula Aranguren5, Mónica García-Álvarez5, BelenAlejos6, María Lagarde6, José I. Bernardino6, Federico Pulido6, Jose R. Arribas6, for the ART-PRO, PI16/00837-PI16/00678 Study Group

1Hospital La Paz Institute for Health Research, Madrid, Spain, 2Hospital Universitario 12 de Octubre, Madrid, Spain, 3Institute of Health Carlos III, Madrid, Spain

**Background:** ART-PRO pilot trial showed that at 48 weeks DTG+3TC was effective in maintaining virologic control despite history of lamivudine resistance and persistence of archived 3TC mutations detected by NGS. Here we present resistance analysis and virologic outcomes after 80 weeks of DTG+3TC treatment.

**Methods:** Open, single-arm, pilot trial including HIV-1 infected adults, INSTI-naive, CD4 count >350 cell/μL, VL <50 copies/mL for 1 year prior to study entry. Participants were excluded if baseline proviral DNA population genotyping detected M184V/I or K65R/E/N. Baseline proviral DNA NGS genotype was retrospectively performed to detect resistance minority variants. All participants were switched to DTG+3TC.

**Results:** 41 participants (78% male) switched to DTG+3TC. 21 participants had M184V/I or K65R/E/N in historical plasma genotyping and 20 had not. At baseline: median CD4 661, ART duration 18 years, duration of suppressed plasma HIV RNA 7.7 years, number of prior ART regimens 6. Participants with historical 3TC resistance were significantly less likely to receive a regimen including 3TC before the switch (p<0.001). NGS of baseline proviral DNA detected M184V/I at >5%/>20% thresholds in 67%/29% of participants with and 15%/5% of participants without history of 3TC resistance. K65R was detected in proviral DNA by NGS only in participants with historical resistance to 3TC (9.5%/5% at the >5%/>20% cut-off respectively). At week 80, 87.8% of participants (37/41) remained with VL <50 copies/mL (Table 1). There were no virologic failures through week 80. Of the 21 participants with historical 3TC resistance, 3 prematurely discontinued with suppressed viremia (2 protocol violations, one AE [insomnia, W8]). One participant without historical 3TC resistance declined to participate in the 144w study extension. There were 12 blips, 6 in the group with historical resistance. There were 30 related AE, 4/30 were severe and only 1 led to discontinuation.

**Conclusion:** In this pilot trial, DTG+3TC was effective in maintaining long-term virologic control after 80 weeks of follow up despite history of 3TC resistance and presence of archived 3TC mutations detected by NGS. 144-week study extension of our trial is ongoing.

---

**EFFECT OF PAST VIROLOGICAL FAILURE ON DOLUTEGRAVIR+LAMIVUDINE AS MAINTENANCE REGIMEN**

Roberta Galgatiardini1, Patrizia Lorenzini1, Alessandro Cozzi-Lepri2, Alessandro Tavelli3, Vanni Borghi4, Laura Galli4, Gianmarco Tagliaferri4, Franco Maggiolo5, Cristina Mussini6, Antonella Castagna7, Antonella D’Ammirino Monforte8, Andrea Antonini9, for the Icosa Foundation Study Group

1IRCCS Lazzaro Spallanzani, Rome, Italy, 2University College London, London, UK, 3Azienda Ospedaliera San Paolo, Milan, Italy, 4Azienda Ospedaliera Universitaria Policlinico di Modena, Modena, Italy, 5San Raffaele Vita-Salute University, Milan, Italy, 6Azienda Ospedaliera Papa Giovanni XXIII Bergamo, Italy

**Background:** Dolutegravir (DTG) + lamivudine (3TC) was shown to be as effective as triple therapy in RCT on patients (pts) switching during virological suppression, but limited data are available about the use of this regimen in pts with previous virological failures (VF), since RCT excluded these pts.

**Methods:** The analysis included data of HIV+ pts with HIV-RNA<50 c/ml enrolled in a retrospective multi-cohort study across Italian infectious disease clinics switching for the first time to DTG+3TC from any other regimen (baseline). Primary endpoint was viral rebound (VR, confirmed HIV-RNA>=50 c/mL). Kaplan-Meier curves were used to estimate probabilities of VR according to history of previous VF (single HIV-RNA>=1000 or confirmed HIV-RNA>=50 c/mL). Weighted Cox regression model was fitted to estimate causal HR of VR, after controlling for confounding variables (time of viral suppression and nadir CD4). A further analysis with a different definition (Def 2) of previous VF (only at NRTI or INSTI regimens) and of VR (that included also a single HIV-RNA>=50 c/ml followed by change of therapy) and a sensitivity analysis excluding pts with incomplete history of viral load data (>1 year gap in measurements) were performed.

**Results:** 966 pts included: 74% males, median age 51 (IQR 44-57), 50% CDC C stage, nadir CD4 246 (99-372), years of viral suppression 7 (3-12), 80% without previous VF, 12% with one previous VF, 8% with >=2 previous VFs. VR was detected in 11 pts over 1555 person-year-follow-up (PYFU): total incidence ratio (IR) was 0.7 x 100 PYFU (95% CI 0.4-1.3), 0.5 x 100 PYFU (0.2-1.1) in pts without previous failures and 1.4 x 100 PYFU (0.6-3.4) in pts with >=1 previous VF, with an estimated 1-year probability of 0.4% (0.1-1.4) and 1.3% (0.3-5.3) respectively (log-rank p=0.071). With Def 2, VR was detected in 18 pts, IR 1.2 x 100 PYFU (0.7-2.1), 1.9 x 100 PYFU (0.6-1.8) in pts without previous failures and 1.9 x 100 PYFU (0.8-4.2) in pts with >=1 previous VF. By multivariate analysis, pts with 1 previous VF had higher risk of VR but not statistically significant throughout all the analyses (table), while having >=1 previous VF resulted to be associated to VR in the two sensitivity analyses.

**Conclusion:** Despite the increased risk of VR in pts with previous VF, especially in those with >=1 VF, the 1-year VR was very low. Although longer follow-up is needed to confirm this observation, current data suggest that DTG+3TC should be cautiously used in pts with current viral suppression but a history of VF.
Table. Crude and adjusted hazard ratios (95%CI) of the risk of VF from fitting a weighted Cox regression model according to presence and number of previous virological failures and by standard and modified definitions (Ref 2) of VF. Sensitivity analyses excluded pts with incomplete data about past viral loads.

<table>
<thead>
<tr>
<th>Virologic Failure</th>
<th>HR (95%CI)</th>
<th>p-value</th>
<th>HR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>previous VF 1 vs 0</td>
<td>2.81 (0.90-8.15)</td>
<td>0.144</td>
<td>2.87 (0.84-9.97)</td>
<td>0.166</td>
</tr>
<tr>
<td>previous VF 1+ vs 0</td>
<td>2.50 (0.74-8.13)</td>
<td>0.125</td>
<td>3.39 (0.75-15.96)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

**Efficacy and Durability of 2-Drug vs 3-Drug INSTI-Based Regimens: Data from Real Life**

Massimiliano Fabbiani, Barbara Rossetti, Arturo Ciccolini, Maria Letizia Oreni, Filippo Lagi, Luigi Celeni, Manuela Colafaglì, Andrea De Vito, Maria Zazzetti, Alex Dusina, Stefano Rusconi, Amedeo Capetti, Gaetana Sarrantino, Gabriella d’Ettore, Simona Di Giambedettotto,

1 Siena University Hospital, Siena, Italy, 2 Catholic University of the Sacred Heart, Rome, Italy, 3 Luigi Sacco University Hospital, Milan, Italy, 4 University of Florence, Florence, Italy, 5 Sapienza University of Rome, Rome, Italy, 6 San Gallicano Dermatology Institute, Rome, Italy, 7 University of Sassiari, Sassari, Italy, 8 Magna Graecia University of Catanzaro, Catanzaro, Italy.

**Background:** Due to high efficacy and tolerability, the use of integrase strand transfer inhibitors (INSTI) is increasing not only in standard 3-drug regimens (3DR) but also in 2-drug regimens (2DR). However, few data are available about comparison of these strategies in a real-life setting.

**Methods:** Retrospective multicentre (8 clinical centers in Italy) observational study including HIV+ treatment-experienced patients with HIV-RNA (VL)<50copies/mL switching to INSTI-based 2DR or 3DR with at least one follow-up visit. Major outcomes were virological failure (VF, defined as 1 VL>1000copies/mL or 2 consecutive VL>50copies/mL) and regimen discontinuation due to any reason. Survival analyses were performed to estimate the probability of VF and discontinuation, and to evaluate their predictors.

**Results:** Overall, 1666 patients (73% males, median age 51 years, 26% previously exposed to INSTI, median time from last VL<50 copies/mL 55 months, current and nadir CD4+ 676 and 184 cells/mm3, respectively) were included, of which 1334(80%) treated with 3DR [n=265 elvitegravir(EVG), n=334 raltegravir(RAL), n=735 dolutegravir(DTG)] and 332(20%) with 2DR [n=263 lamivudine+DTG, n=69 rilpivirine+DTG]. Over a median follow-up of 100 weeks(IQR 52-150), 52(3.7%) patients experienced VF with an incidence of 1.5 per 100 PYFU; the estimated 48-week probability of VF was not different between 2DR and 3DR(1.4% vs 1.8%;p=0.53), but it was higher for EVG(3.5%) and RAL(3%) when compared to DTG(1.9%;p=0.04). By multivariate analysis, previous VF (aHR 2.7;p<0.001) and shorter time from last VL<50copies/mL (aHR 0.9;p=0.04) predicted VF. Four-hundred(24%) patients discontinued INSTI-based regimen with an incidence of 11.3 per 100 PYFU. Main reasons for discontinuation were toxicity(n=159 (40%) of which 51(13%) CNS toxicity) and simplification(n=119, 30%). The estimated 48-week probability of discontinuation for any reason was 20% for RAL, 10% for DTG and 16% for EVG(p<0.001), without differences comparing 2DR and 3DR DTG-based(9% vs 10%;p=0.21). By multivariate analysis, there was higher risk of discontinuation in 3DR vs 2DR (aHR = 2.1;95%CI 1.2, 3.7) and lower risk in MSM/MSI homosexual, aHR=0.75;95%CI 0.52,0.97) and regimens started for simplification(aHR 0.9;p<0.001).

**Conclusion:** In our real-life setting, both 2DR and 3DR INSTI-based regimens showed high efficacy and durability. Regimens including DTG were associated with a lower risk of VF and discontinuation.

**Assessing the Virologic Impact of Archived Resistance in an HIV-1 Switch Study, TANGO**

Ruanlon Wang, Jonathan Wright, Mounir Ait-Khaled, Allan Raymond Tenorio, Maria Claudia Nascimento, Thomas Lutz, Daniel Podzamczer, Richard Moore, Miguel Gorgolas Hernandez-Mora, Clifford KINDER, Jean van WYK, Mark Underwood

1 VIV HealthCare, Research Triangle Park, NC, USA, 2 GlassSmithKline, Unbridge, UK, 3 VIV HealthCare, Brentford, UK, 4 Infectiologieum, Frankfurt, Germany, 5 Hospital Universitario de Bellvitge, Barcelona, Spain, 6 Northside Clinic, Fitzroy, Australia, 7 Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain, 8 IAHF HealthCare Center, Miami, USA.

**Background:** TANGO study demonstrated that switching to DTG/3TC fixed dose combination (FDC) 2-Drug Regimen (2DR) was non inferior to continuing a TAF-based 3-drug regimen (TBR, 3DR) in maintaining virologic suppression in HIV-1 infected, ART-experienced adults through Week 48. The impact of pre-existing, HIV-1 drug resistance on virologic outcomes through Week 48 was assessed.

**Methods:** Participants with historical IAS major NNRTI or INSTI resistance associated mutations (RAMs) were excluded from the study. Pro-viral DNA genotyping was conducted retrospectively on baseline samples from randomized participants by Monogram Bioscience using GenoSure Archive assay. Virologic outcomes based on IAS major NNRTI, NNRTI, PI and INSTI RAMs.
Results: 322 (87%) of participants in the DTG/3TC arm and 321 (86%) in the TBR arm had both pro-viral genotype data and at least one on-treatment HIV-1 RNA result. Archived major NRTI, NNRTI, PI and INSTI RAMs were observed in 42 (7%), 90 (14%), 43 (7%) and 6 (1%) participants, respectively, across both arms (Table 1), and 474 (74%) participants were without any major RAMs at the baseline. The frequencies of NRTI RAMs M184V/I, K65E/N/R and thymidine analog mutations (TAMs) were low. Through Week 48, 322 (100%) of participants on DTG/3TC and 319 (99%) on TBR were virologically suppressed (last on-treatment HIV-1 RNA <50 c/mL). For participants with any major NRTI, NNRTI or PI RAMs, all were virologically suppressed. The results of a sensitivity analysis using the FDA Snapshot algorithm were consistent with those using last available on-treatment HIV-1 RNA. One participant in TBR arm without any archived RAMs met the protocol-defined, confirmed virologic withdrawal criterion (CVW) with no emergent resistance. None in the DTG/3TC arm met CVW criteria through Week 48.

Conclusion: In TANGRO, archived major NRTI (e.g., M184V/I, K65E/N/R and TAMs) and INSTI (e.g., Q148R, Y143C/H, R263K) RAMs were infrequent. High rates of virologic suppression were maintained in participants on both treatment arms through Week 48. The presence of pre-existing, archived RAMs did not appear to impact virologic outcomes through Week 48.

Table 1. Virologic Outcomes by Archived Resistance Mutations Through Week 48

<table>
<thead>
<tr>
<th>Resistance Mutations</th>
<th>DTG/3TC</th>
<th>TBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>M184V/I</td>
<td>90 (9%)</td>
<td>319 (99%)</td>
</tr>
<tr>
<td>K65E/N/R</td>
<td>50 (5%)</td>
<td>319 (99%)</td>
</tr>
<tr>
<td>TAMs</td>
<td>43 (4%)</td>
<td>319 (99%)</td>
</tr>
</tbody>
</table>

2.82, CI95% 1.04-7.6), while gender, age, duration of HIV RNA <50 c/mL prior to 2DR, nadir CD4, zenith HIV RNA and CDC stage C were not. No factor was associated with VF under DTG/xTC.

Conclusion: In this large real-life cohort, DTG-2DR maintained sustain HIV RNA virologic suppression, and were associated with a low rate of VF. DTG/xTC was associated with slightly lower VF rate than DTG/RPV and the absence of RAM emergence at VF. ARV history are prior VF are key issues to consider before offering 2DR maintenance.

### 490 VIROLOGIC FAILURE AND RESISTANCE IN Dolutegravir-BASED MAINTENANCE DUAL REGIMES

Colin Deschanvres, François Raffi, Jacques Reynes, Bruno Hoen, David Rey, Romain Palich, Olivier Robineau, Firozou Bani-Sadr, Claudine Duvivier, Laurent Hocqueloux, Lise Cuzin, Véronique Joly, André Cabié, Clotilde Allavena, for the Dat’AIDS Study Group

Background: Maintenance ART with dolutegravir (DTG)-based dual regimens (2DR) have proved their efficacy among HIV-1 infected subjects in large and randomized trials. Real-life data are scarce with limited population and follow-up. In a large cohort (Dat’AIDS), we evaluated virologic failure (VF) and resistance-associated mutations (RAMs) on DTG maintenance regimens in combination with rilpivirine (RPV) or 3TC/FTC (xTC), and we analyzed the factors associated with VF.

Methods: Between 2014 and 2018, all HIV-1 adults starting DTG/RPV or DTG/xTC as a maintenance 2DR (i.e. with HIV RNA <50 c/mL) were enrolled in a retrospective analysis within the Dat’AIDS cohort (NCT02899897). VF was defined as 2 consecutive HIV RNA >50 c/mL or a single value >400 c/mL. We compared cumulative genotypes prior to 2DR and at VF (ANRS algorithm V29; 2018). Cox models were used to analyze factors associated with VF.

Results: 1374 subjects were included (DTG/RPV: 799, DTG/xTC: 575) with a median follow-up of 587 days [IQR 334-934] and 562 days [IQR 126-938], respectively. Baseline characteristics are shown in Table. VF occurred in 3.8% (n=30) of DTG/RPV and 2.6% (n=15) of DTG/xTC subjects (p=NS), with a median delay to VF of 232 days [IQR 100-507] and 301 days [IQR 188-427], respectively. Among VF subjects, 91 (33%) had history of VF on NNRTI-based regimen in DTG/RPV group and 51 (30%) had history of VF on NNRTI-based regimen in DTG/xTC group. At DTG/RPV VF, 17/30 genotypes were available: 3 genotypes harbored NNRTI RAMs already detected on historical genotypes (E138A; E138D+A153T; E138A+K101E); 2 genotypes harbored new RAMs, 1 genotype with E138K on NNRTI and 1 genotype with E138K+K101E on NNRTI and xTC INSTI. At DTG/xTC VF, 6/15 genotypes were available: no new RAM was detected and 1 genotype harbored M184V already detected on historical genotypes. The only predictive factor of VF on DTG/RPV was history of VF on NNRTI-based ART (HR 2.82, CI95% 1.04-7.6), while gender, age, duration of HIV RNA <50 c/mL prior to 2DR, nadir CD4, zenith HIV RNA and CDC stage C were not. No factor was associated with VF under DTG/xTC.
492 SHALL WE DANCE? EXTENDING TANGO’S RESULTS TO CLINICAL PRACTICE
Gianmaria Baldin 1, Alberto Borghetti 1, Arturo Ciccullo 1, Stefano Rusconi 1, Amedeo Capetti 2, Gaetana Sterrantino 3, Manuela Colafigli 4, Gabriella d’Ettorre 5, Andrea Giacometti 6, Maria V. Cossu 2, William Gennari 7, Cristina Mussini 7, Vanni Rome, Italy, 6Azienda Ospedaliero Universitaria Ospedali Riuniti Ancona, Ancona, Italy, 5Medizinische Hochschule Hannover, Hannover, Germany, 1Kelvinkبحات Chicago, Munich, Germany, 2University of Bonn, Bonn, Germany, 3Muenchner Studienzentrum, Munich, Germany, 4Praxis Cordes, Berlin, Germany, 1Medizinische Hochschule Hannover, Hannover, Germany, 2Center for Infectious Disease Research, Berlin, Germany, 3Praxis am Ebertplatz, Cologne, Germany, 4Klinikum rechts der Isar, Munich, Germany

Background: Advances in potency and resistance barrier of antiretroviral drugs for HIV infection and evidence from recent randomized clinical trials (RCTs) support the use of dual therapy at least in specific patient populations. Both, Dolutegravir (DTG) and boosted darunavir (bDRV) are potent antiretroviral drugs with a high resistance barrier. Dualis, a phase IIb, open-label RCT demonstrated non-inferiority of a switch to DTG+ bDRV (2DR) versus continuous 2NRTI+bDRV (3DR) in virologically suppressed people living with HIV (PLWH) with week 48 virologic response rates of 86% (2DR) and 88% (3DR).

Methods: Post-hoc analysis of virologic outcomes in Dualis with respect to treatment history and HIV drug resistance. Among study inclusion criteria was an HIV-RNA level <50 cps/mL for ≥24 weeks (one blip accepted); any history/presence of drug resistance other than INSTI or bDRV was not exclusionary. Documentation of resistance-associated mutations (RAMs) was based on the Stanford HIVdb mutation list including specific additional RAMs. Virologic outcomes in subgroups include the primary endpoint (PE, i.e. % with HIV-RNA<50cps/mL at week 48) and % of patients with ≥50 cps/mL (i.e. data in window and ≥50 cps/mL or discontinuation for lack of efficacy or discontinuation for other reason and ≥50 cps/mL). Results: The ITTe set included 263 subjects (2DR n=131, 3DR n=132): 90.1% males, median age 48 years, CD4 stage C 29.7%, CD4 nadir<200/µl 47.0%; median time on ART 3.5 years, 27.4% with ≥2 ART changes, 8.4% with prior INSTI use; 20.9% and 11.0% had a history of ≥2 NRTI and ≥2 PI changes, respectively. NRTI, NRTI and (minor or major) PI RAMs were observed in 9.1, 12.9, and 26.6% (major PI RAMs 3.4%), respectively. Resistance categories and PE analyses within subgroups are shown in Table 1 with response rates ≥80% across groups. Response rates with major and/or minor RAMs were 88.9% on 2DR and 95.5% on 3DR versus 84.9% (2DR) and 84.1% (3DR) without documented RAMs. No patient with major/minor RAMs in either group had ≥50 HIV-RNA cps/mL at last follow-up. No emergence of RAMs during follow-up was observed. Conclusion: As shown in the Dualis study, dual therapy with DTG+bDRV tends to be an effective treatment option with no treatment-emergent resistance for PLWH on suppressive first- or further-line ART with or without evidence of pre-existing NRTI, NRTI or PI RAMs.

Table 1. Patients’ characteristics at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2DR (n=131)</th>
<th>3DR (n=132)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>49 (40-55)</td>
<td>52 (42-56)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>111 (86)</td>
<td>108 (82)</td>
<td>0.556</td>
</tr>
<tr>
<td>Risk factor for HIV, n (%)</td>
<td>56 (41)</td>
<td>66 (49)</td>
<td>0.001</td>
</tr>
<tr>
<td>- Baseline</td>
<td>37 (28)</td>
<td>40 (30)</td>
<td></td>
</tr>
<tr>
<td>- INSTI</td>
<td>18 (14)</td>
<td>16 (12)</td>
<td></td>
</tr>
<tr>
<td>- Other</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>- Exclusion</td>
<td>6 (5)</td>
<td>7 (5)</td>
<td></td>
</tr>
<tr>
<td>CDC stage C, n (%)</td>
<td>20 (15)</td>
<td>25 (19)</td>
<td>0.854</td>
</tr>
<tr>
<td>Anti-HIV-positive, n (%)</td>
<td>9 (7)</td>
<td>9 (7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Median CD4 cell count</td>
<td>775 (599, 979)</td>
<td>748 (596, 886)</td>
<td>0.307</td>
</tr>
<tr>
<td>% with HIV-RNA&lt;50cps/mL at week 48</td>
<td>80.2% (74.1-85.6)</td>
<td>83.8% (77.7-89.4)</td>
<td>0.189</td>
</tr>
<tr>
<td>% with ≥50 cps/mL</td>
<td>63 (47, 79)</td>
<td>67 (51, 83)</td>
<td></td>
</tr>
</tbody>
</table>

493 VIROLOGIC OUTCOMES BY RESISTANCE CATEGORY AND PRETREATMENT IN THE DUALIS STUDY
Eva Wolf 1, Christoph Boesecke 1, Annamaria Balogh 1, Helen Bildner 2, Christiane Cordes 1, Hans Heiken 1, Ivanka Krznaric 1, Tim Kümmerle 1, Jochen Schneider 1, Christian Bispe 1, for the DUALIS Study Group 1MUC Research, Munich, Germany, 2University of Bonn, Bonn, Germany, 3Muenchner Studienzentrum, Munich, Germany, 4Praxis Cordes, Berlin, Germany, 5Medizinische Hochschule Hannover, Hannover, Germany, 6Center for Infectious Disease Research, Berlin, Germany, 7Praxis am Ebertplatz, Cologne, Germany, 8Klinikum rechts der Isar, Munich, Germany

Background: Among ART-experienced, virologically suppressed PLWH initiating DTG/RPV as a 2-DR or standard 3-DR, there was no observed difference in the risk of virological failure in a real-world setting.

Conclusion: Among ART-experienced, virologically suppressed PLWH initiating DTG/RPV as a 2-DR or standard 3-DR, there was no observed difference in the risk of virological failure in a real-world setting.

Risk of VF between 3-DR, DTG/RPV initiators in adjusted Cox models were not significant (aHR 1.32, 95% CI 0.61, 2.89) (Fig. 1).

Andrea Giacometti 6, Maria V. Cossu 2, William Gennari 7, Cristina Mussini 7, Vanni Rome, Italy, 6Azienda Ospedaliero Universitaria Ospedali Riuniti Ancona, Ancona, Italy, 5Medizinische Hochschule Hannover, Hannover, Germany, 1Kelvinkبحات Chicago, Munich, Germany, 2University of Bonn, Bonn, Germany, 3Muenchner Studienzentrum, Munich, Germany, 4Praxis Cordes, Berlin, Germany, 1Medizinische Hochschule Hannover, Hannover, Germany, 2Center for Infectious Disease Research, Berlin, Germany, 3Praxis am Ebertplatz, Cologne, Germany, 4Klinikum rechts der Isar, Munich, Germany

Background: Advantages in potency and resistance barrier of antiretroviral drugs for HIV infection and evidence from recent randomized clinical trials (RCTs) support the use of dual therapy at least in specific patient populations. Both, Dolutegravir (DTG) and boosted darunavir (bDRV) are potent antiretroviral drugs with a high resistance barrier. DUALIS, a phase IIb, open-label RCT demonstrated non-inferiority of a switch to DTG+bDRV (2DR) versus continuous 2NRTI+bDRV (3DR) in virologically suppressed people living with HIV (PLWH) with week 48 virologic response rates of 86% (2DR) and 88% (3DR).

Methods: Post-hoc analysis of virologic outcomes in DUALIS with respect to treatment history and HIV drug resistance. Among study inclusion criteria was an HIV-RNA level <50 cps/mL for ≥24 weeks (one blip accepted); any history/presence of drug resistance other than INSTI or bDRV was not exclusionary. Documentation of resistance-associated mutations (RAMs) was based on the Stanford HIVdb mutation list including specific additional RAMs. Virologic outcomes in subgroups include the primary endpoint (PE, i.e. % with HIV-RNA<50cps/mL at week 48) and % of patients with ≥50 cps/mL (i.e. data in window and ≥50 cps/mL or discontinuation for lack of efficacy or discontinuation for other reason and ≥50 cps/mL).

Results: The ITTe set included 263 subjects (2DR n=131, 3DR n=132): 90.1% males, median age 48 years, CD4 stage C 29.7%, CD4 nadir<200/µl 47.0%; median time on ART 3.5 years, 27.4% with ≥2 ART changes, 8.4% with prior INSTI use; 20.9% and 11.0% had a history of ≥2 NRTI and ≥2 PI changes, respectively. NRTI, NRTI and (minor or major) PI RAMs were observed in 9.1, 12.9, and 26.6% (major PI RAMs 3.4%), respectively. Resistance categories and PE analyses within subgroups are shown in Table 1 with response rates ≥80% across groups. Response rates with major and/or minor RAMs were 88.9% on 2DR and 95.5% on 3DR versus 84.9% (2DR) and 84.1% (3DR) without documented RAMs. No patient with major/minor RAMs in either group had ≥50 HIV-RNA cps/mL at last follow-up. No emergence of RAMs during follow-up was observed.

Conclusion: As shown in the Dualis study, dual therapy with DTG+bDRV tends to be an effective treatment option with no treatment-emergent resistance for PLWH on suppressive first- or further-line ART with or without evidence of pre-existing NRTI, NRTI or PI RAMs.
494 ONCE-DAILY ETRAVIRINE/RALTEGRAVIR (400/800 MG) AS MAINTENANCE REGIMEN


Background: The ANRS163-ETRAL study showed 99.4% of virological success rate for etravirine/raltegravir (200/400 mg) twice-daily (ETR/RAL BID) dual therapy in suppressed HIV-infected patients older than 45 years [Katlama C, et al., J Antimicrob Chemother, 2019]. To simplify this regimen, we aimed to assess the efficacy of etravirine/raltegravir (400/800 mg) given once-daily (ETR/RAL QD).

Methods: Patients with viral load pVL (<50 copies/mL under ETR/ RAL BID) for at least 96 weeks were switched to ETR/RAL QD in this prospective, multicenter, open-label, single arm study. Primary outcome consisted in the rate of virological failure (VF, defined as 2 consecutive pVL >50 copies/mL 2-4 weeks apart or a single value >400 copies/mL) at W48, estimated with the Kaplan-Meier method. Secondary outcomes included tolerance, treatment strategy success rate (defined as absence of VF with no treatment discontinuation), plasma drugs concentrations and resistance profile in case of VF. The objective of the study was to show a VF rate <10%.

Results: A total of 111 patients were included with a median (IQR) age: 57 years (52-62), CD4: 710 cells/mm3 (501-919), CD4 nadir: 183 cells/mm3 (90-269) and hemoglobin A1C) and year of regimen initiation, and (4) employed propensity score matching using imputed baseline labs and demographics, allowing for squares and first order interactions between all included predictors. In addition to adherence, we assessed viral suppression (<200 copies/mL in a subset of 655 patients at 6 months (measured within 1 week prior and up to two months after).

Results: In observed (unadjusted) data, adherence was significantly greater at 6 months to BIC/FTC/TAF compared to any dolutegravir-regimen and to DTG/ABC/3TC in comparison to DTG+TDF/FTC or DTG+TAF/FTC at the 80% level [TABLE]. After controlling for non-treatment effects, adherence was only significantly different for BIC/FTC/TAF compared to DTG+TDF/FTC or DTG+TAF/FTC (p<0.01). Assessment of viral suppression at 6 months for patients with adherence benefits by adherence >80% (OR 2.27 [1.26-4.07] p<0.01) and ≥95% (OR 2.63 [1.55-4.48] p<0.01).

Conclusion: This study of bictegravir and dolutegravir-based regimens supports the notion that simplifying treatment to a single tablet aids in adherence, and that adherence improves virological outcomes in clinical settings.

Table 1. Observed (unadjusted) adherence between groups (Observed) and estimated Treatment Effect (Adjusted odds ratios [AOR] with 95% CI) on adherence within the first 6 months.

496 SOCIAL NORMS AND ART ADHERENCE: POPULATION-BASED STUDY OF PERSONS WITH HIV IN UGANDA

Jessica M. Perkins1, Bernard Kakuhikire2, Charles Baguma3, Justin D. Rasmussen4, Carolyn L. Audef5, Mark J. Siedner3, Jessica E. Haberer2, David R. Bangsberg6, Alexander C. Tsai7

1Vanderbilt University, Nashville, TN, USA, 2Mbarara University of Science and Technology, Mbarara, Uganda, 3Duke University, Durham, NC, USA, 4Massachusetts General Hospital, Boston, MA, USA, 5Oregon Health and Sciences University, Portland, OR, USA

Background: The extent to which certain health behaviors are perceived as normative is known to be an important determinant of one’s own propensity to
engage in such behaviors. It is unknown, however, whether people living with HIV (PLWH) accurately perceive norms around antiretroviral treatment (ART) adherence and whether these perceptions influence their own propensities to adhere to ART.

**Methods:** We recruited a population-based sample of PLWH on ART in Nyakabare Parish, a rural region of southwest Uganda. Self-reported ART non-adherence was defined as missing any ART doses in the past 7 days. We also elicited their perception about the extent to which most other adult PLWH in their community were non-adherent to ART. Actual ART non-adherence was calculated by aggregating responses across all PLWH. Non-adherence was classified as normative if reported non-adherence was present among more than 50% of PLWH in the village. We then compared individuals’ perception of the adherence norm to the actual adherence norm, and also assessed the relationship between perception and personal adherence.

**Results:** Adherence was normative among 158 adult PLWH (response rate 95%); only 15% of HIV+ men and 9% of HIV+ women reported missing any doses in the past 7 days. However, approximately one-half of study participants (45% of men and 54% of women) incorrectly believed that most PLWH in their communities were non-adherent to ART. In addition, approximately one-quarter (22% of men and 25% of women) did not know whether most people had missed any doses. Only about one-quarter of this population (33% of HIV+ men and 21% of HIV+ women) accurately perceived that ART adherence was normative among PLWH. Overestimating the pervasiveness of ART non-adherence was not associated with age, education, time since diagnosis, or serostatus status disclosure. Finally, there were almost three times as many non-adherents among the participants who misperceived the norm as compared to non-adherents among the participants who accurately perceived the norm (14% vs. 5%), though this difference was not statistically significant.

**Conclusion:** Many PLWH on ART believe that non-adherence to ART is present among most PLWH on ART in their community, despite adherence actually being normative among PLWH in this population-based study from rural Uganda. Because those who are non-adherent appear to also perceive poor adherence as a normative behavior, altering those misperceptions might represent an opportunity for novel ART adherence intervention development.

---

**497 RANDOMIZED STUDY OF AN ART ADHERENCE INTERVENTION USING A SMART-PILL BOTTLE SERVICE**

**Grant B. Ellsworth, Leah Burke, Martin T. Wells, Satish Mishra, Matthew Caffrey, David W. Liddle, Malika Madhava, Arsalan K. Muhammad, Curtis O’Neal, Peter L. Anderson, Lane R. Bushman, Lucas Ellison, Josh Stein, Roy M. Gulick**

1 Weill Cornell Medicine, New York, NY, USA, 2 Yale University, New Haven, CT, USA, 3 Cornell University, Ithaca, NY, USA, 4 Children’s Research Institute, Children’s National Health System, Washington, DC, USA, 5 Thomas Jefferson University, Philadelphia, PA, USA, 6 University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 7 AdhereTech, New York, NY, USA

**Background:** Adherence is critical to achieve the benefits of antiretroviral therapy (ART). Smart-pill bottles (AdhereTech) securely transmit real-time adherence information via cellular networks to a central service that sends prompts to non-adherent patients by phone call or text in addition to on-device visual and audio cues. The smart-pill bottle service may improve adherence to ART.

**Methods:** Adults with HIV taking a tenofovir disoproxil fumarate (TDF)-containing regimen with suboptimal adherence (2 detectable HIV RNA assays during the prior year) were randomized to receive adherence counseling with or without the smart-pill bottle service for 12 weeks. Tenofovir diprophosphate (TFV-DP) levels by dried blood spot, HIV RNA, CD4 levels, and self-reported adherence (using the AIDS Clinical Trials Group [ACTG] Adherence Questionnaire) were collected.

**Results:** 63 participants (22% women; 48% black, 25% Latino) were randomized (30 bottle, 33 control). At baseline, 49% of participants had HIV RNA <20 copies/mL and 61% reported 100% adherence with antiretroviral medications over the prior 4 days. From baseline to week 12, median TFV-DP levels increased from 1230 to 1887 fmol/punch in the smart-pill bottle group and 1108 to 1048 fmol/punch in controls (see figure; median change +252 versus -41 fmol/punch, respectively, P=0.01). Discontinuation rates were 5 of 30 (17%) in the smart-pill bottle group vs. 7 of 33 (22%) in the control group (P=0.89). The number of participants with HIV RNA >20 copies/mL at baseline who decreased to ≤20 copies/mL at 12 weeks was 3 of 24 in the smart-bottle group vs. 7 of 26 in the control group (OR for the intervention 0.4; 95% CI 0.1, 2.0). The median change in CD4 count from baseline to week 12 was +14 cells/µL in the smart-bottle group and -16 cells/µL in the control group (P=0.36). At week 12, 75% of the smart-bottle group and 77% of the control group reported 100% adherence taking their antiretroviral medications over the prior 4 days.

**Conclusion:** This pilot study demonstrates that in patients with HIV infection on ART, the smart-pill bottle service was associated with higher tenofovir diprophosphate levels (though this did not reach statistical significance); HIV RNA suppression rates, CD4 cell counts, and self-reported adherence rates (over the prior 4 days) were not different.

---

**498 PHARMACIST-DRIVEN RAPID ART REDUCES TIME TO VIROLOGIC SUPPRESSION IN RHODE ISLAND**

**Amy L. Brotherton, Rajeev B. Shah, Joseph Garland, Meghan L. McCarthy, Fizza S. Gillani, Martha C. Sanchez**

1 The Miriam Hospital, Providence, RI, USA, 2 Brown University, Providence, RI, USA

**Background:** Rapid start antiretroviral therapy (ART) protocols have emerged as an innovative care model for persons newly diagnosed with HIV (PNDW). Shifting to a model where clinical pharmacists are at the forefront of rapid ART initiation may provide a sustainable solution for the logistical challenges that limit widespread implementation.

**Methods:** We conducted a preliminary retrospective analysis at Rhode Island’s largest HIV clinic to compare clinical outcomes of PNDW before (1/2017 – 12/2017) and after (1/2019 – 8/2019) implementation of a Pharmacist Driven Rapid ART (PHARM-D RAPID) protocol. Prior to implementation of the protocol at this Ryan White clinic, patients attended an intake visit with a nurse upon HIV diagnosis, which preceded their first provider appointment and ART initiation by approximately 2 weeks. Following implementation of the PHARM-D RAPID protocol, PNDW are evaluated by a multidisciplinary team on intake and offered rapid ART initiation by clinical pharmacists prior to their first provider visit. During intake, clinical pharmacists provide education, assess readiness to initiate ART, evaluate drug-drug interactions, resolve medication access issues, and recommend patient-specific ART to the triage physician for initiation. Follow-up phone calls are conducted by pharmacists 2 weeks following ART initiation. Clinical and demographic data were extracted from the electronic medical record. The primary outcome was time from intake visit to viral suppression (HIV RNA <200 copies/mL).

**Results:** A total of 88 patients were included in the preliminary analysis; 55 and 33 in the pre-group and PHARM-D RAPID group, respectively. Baseline characteristics were similar between groups. Mean age was 37 with 85% male, 58% white, 25% black, 30% Hispanic, and 53% with MSM as their sole reported risk factor. 26% were uninsured, 25% presented with AIDS, and half had history of substance use (54%) and/or mental illness (50%). Pharmacists’ recommendations for ART regimens were accepted in all PHARM-D RAPID patients. Medication access issues were preemptively resolved in 61% of PHARM-D RAPID patients. Time from intake to viral suppression (81 vs. 34 days, P=0.001) and time from intake to ART (16 vs. 0 days, P<0.001) significantly decreased in the PHARM-D RAPID group.

**Conclusion:** Our PHARM-D RAPID protocol demonstrates a novel pathway for decreasing time to viral suppression and HIV transmission, which are key for achieving 90-90-90 efforts in a complex patient population.
DO PRESCRIBING DATA REFLECT ACTUAL TREATMENT IN PEOPLE LIVING WITH HIV (PLWH)?

Joseph J. Eron1, Dushyantha Jayaweera2, Gregory D. Huhn1, Kelsey Milligan1, Scott Milligan1, Paul E. Saxs Keith Spitz3, Richard A. Elion1
1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2University of Miami, Miami, FL, USA, 3Rush University Medical Center, Chicago, IL, USA, 4Trio Health, La Jolla, CA, USA, 5Harvard University, Cambridge, MA, USA, 6George Washington University, Washington DC, USA

Background: Data created during the care continuum are challenging to assemble and disparate sources may account for varied results in observational studies. To assess the limitation of one source, we contrasted adherence, duration, and regimen composition between prescription (RX) and pharmacy dispense (PD) data generated during care of PLWH.

Methods: Antiretroviral (ARV) RX and PD data were obtained for 1270 treatment-experienced PLWH from the TRIO network, consisting of 11 HIV treatment centers servicing 39 US states. Follow-up was ≥12 months (m) post index, defined as the first ARV regimen switch between 2014 to 2017 with final data collection Jun 2019. Adherence was based upon proportion of days (d) with all drugs. Regimen discontinuation was dated at exhaustion of all regimen components and/or upon addition of a new ARV drug. Time to discontinuation was assessed by Kaplan-Meier with log-rank. Univariate analyses were via chi-square, exact, or T-test.

Results: Discontinuation rates (46% RX v 43% PD, p=0.060) and median time to discontinuation (29 m RX v. 29 m PD, p=0.448) were not significantly different by data source, though time to discontinuation/censoring differed by >90 d (+/-) for 29% (374) of PLWH, with 20% (258) discontinuing therapy >90 d before the end of the RX-based regimen [FIGURE]. ≥80% adherence was assessed by Kaplan-Meier with log-rank. Univariate analyses were via chi-square, exact, or T-test.

Conclusion: These data suggest a lack of concordance between what is prescribed and dispensed for over a third of PLWH. As dispensing data are more likely to reflect actual treatment, observational studies should include this information whenever possible.
501  TREATMENT INTERRUPTION STRATEGIES FOR NNRTI-BASED ART: DOES THE NNRTI MATTER?

Alice K. Pau1, Jacqueline Neuhaus2, Edward M. Gardner3, Anna Maria Geretti4, Kimberly S. Scarl5, John D. Baxter6, Nakelu Eriobu7, Virginia L. Kan8, Vidar Ormaasen9, Sarah Pett10, H. Clifford Lane1, Andrew N. Phillips11, James Neaton12, for the INSIGHT SMART Study Group

1NIAID, Bethesda, MD, USA, 2University of Minnesota, Minneapolis, MN, USA, 3Denver Health Medical Center, Denver, CO, USA, 4University of Liverpool, Liverpool, UK, 5University of Nebraska, Omaha, NE, USA, 6Cooper University Hospital, Camden, NJ, USA, 7Institute of Human Virology Nigeria, Abuja, Nigeria, 8George Washington University, Washington, DC, USA, 9Oso University Hospital, Oslo, Norway, 10University College London, London, UK

Background: In the SMART trial, simultaneously stopping NNRTIs and NRTIs resulted in emergence of drug resistance mutations (DRMs) and lower HIV-RNA resuppression rates compared to either a PI-switch strategy or staggered resuppression. This finding was proposed to resuppression rates compared to either a PI-switch strategy or staggered resuppression. This finding was proposed to

Methods: A reanalysis of the SMART study was undertaken in participants who interrupted NNRTI-based ART and later restarted an NNRTI regimen. Participants were included who had HIV-RNA<400 c/ml at ART discontinuation and had an HIV-RNA level drawn 4-8 months after restart to assess resuppression. For individuals who had HIV RNA>1000 c/ml at 2 months after ART interruption and had standard HIV genotypic testing (TRUGENE), presence of NNRTI or NRTI DRMs was assessed. Results are given according to stopping approach, separately for each NNRTI vs. non-NNRTI use.

Results: Of the 513 participants who met the inclusion criteria, 319 (62.2%) received EFV, and 194 (37.8%) received NVP. Stopping was simultaneous in 100 (19.5%) participants, staggered in 302 (58.9%), and switched in 111 (21.6%). Overall, 124 (24.2%) received TDF and 389 (75.8%) received other NRTIs (AZT, D4T, or ddI); in both groups the most common second NRTI was 3TC and FTC. Irrespective of TDF use, resuppression was lowest with simultaneous stopping and highest with a switch strategy (Table). Among those who stopped simultaneously, there was no difference between TDF or non-TDF group for the changes from baseline of total HIV DNA, plasma seminal VL and plasma blood resiual viremia within and between the 2 groups over time.

Conclusion: Characteristics of sub-study population were similar to those of global trial population. Paired D0 and W48 HIV total DNA were obtained in 119 patients. 45% and 44% of patients showed a HIV DNA below the LOQ at D0 and W48 respectively. Median (IQR) HIV DNA was 1.7 log_{10} (1.0-10.2) PBMC (1.3-2.3) at D0 and 1.6 (1.3-2.4) at W48 in the 4D arm versus 1.9 (1.3-2.3) and 1.7 (<1.3-2.3) in the 7D arm. Plasma residual viremia was measured in 116 patients at D0 and W48 with a proportion of patients with USpVL detectable of 17.3 % and 26.9% respectively in the 4D arm and 21.9% and 29.7 % in the 7D arm. Semen HIV RNA was measured in 78 patients with a proportion of semen VL detectable in 2.3 % at D0 and 6.7 % at W48 in the 4D arm versus 6.1% and 9.1 % in the 7D arm. There is no significant evolution in HIV DNA, residual viremia and semen VL between D0 and W48 and no significant difference between arms.

Conclusion: No change was observed during the first year of 4/7 days maintenance therapy in plasma residual viremia level or in HIV cellular reservoir size, as in the 7/7 days. These findings are reassuring the potency of a 4/7 maintenance strategy on virological suppression at the level of residual viremia.

502  NO SIGNIFICANT CHANGE ON RESERVOIR IN QUATUOR: A 4/7 DAYS A WEEK MAINTENANCE STRATEGY

Sidonie Lambert-Nicolot1, Lambert Assoumou1, Pierre De Truchis1, Djeneka Bocar Fofana2, Karine Amat3, Jonathan Bellet4, François Raffi5, Philippe Morlat6, Christine Katlama7, Cécile Moins8, Dominique Costagliola9, Pierre-Marie Girard10, Roland Landman1, Laurence Morand-Joubert11, for the ANRS 170 QUATUOR Study Group


Background: ANRS 170 QUATUOR study demonstrated the non-inferiority of a 4/7 days maintenance strategy vs a 7/7 days regimen in patients with controlled viral load (VL) under triple therapy with either PI, NNRTI, or INSTI based regimen at week 48 (W48). The aims of these virological sub-studies were to assess HIV cellular reservoir size, HIV residual viremia and HIV RNA quantification in semen until W48.

Methods: HIV total DNA was measured using the real-time PCR kit GENERIC HVIDIA Cell® (Biocentric®, Bandol, France) with a limit of quantification (LOQ) of 10 copies/PCR. Ultra-sensitive plasma VL (USpVL) and semen HIV VL (1/5 dilution) were determined using COBAS® HIV-1, v2.0 (Roche Molecular Systems, Branchburg, NJ, USA). For USpVL, the limit of detection (LOD) was defined as an undetected PCR signal. Generalized estimating equation was used to compare the changes from baseline of total HIV DNA, plasma seminal VL and plasma blood residual viremia within and between the 2 groups over time.

Results: Characteristics of sub-study population were similar to those of global trial population. Paired D0 and W48 HIV total DNA were obtained in 119 patients. 45% and 44% of patients showed a HIV DNA below the LOQ at D0 and W48 respectively. Median (IQR) HIV DNA was 1.7 log_{10} (1.0-10.2) PBMC (1.3-2.3) at D0 and 1.6 (1.3-2.4) at W48 in the 4D arm versus 1.9 (1.3-2.3) and 1.7 (<1.3-2.3) in the 7D arm. Plasma residual viremia was measured in 116 patients at D0 and W48 with a proportion of patients with USpVL detectable of 17.3 % and 26.9% respectively in the 4D arm and 21.9% and 29.7 % in the 7D arm. Semen HIV RNA was measured in 78 patients with a proportion of semen VL detectable in 2.3 % at D0 and 6.7 % at W48 in the 4D arm versus 6.1% and 9.1 % in the 7D arm. There is no significant evolution in HIV DNA, residual viremia and semen VL between D0 and W48 and no significant difference between arms.

Conclusion: No change was observed during the first year of 4/7 days maintenance therapy in plasma residual viremia level or in HIV cellular reservoir size, as in the 7/7 days. These findings are reassuring the potency of a 4/7 maintenance strategy on virological suppression at the level of residual viremia.

503  CLINICAL SIGNIFICANCE OF gp120 POLYMORPHISMS, TMR IC1-FC AND HIV-1 SUBTYPE IN BRIGHTHE

Margaret Garland1, Peter Ackerman2, Frank Mannino3, Louise K. Garside4, Andrew Clark5, Amy Pierce1, Mark Krystal2, Cyril C. Llamoso2, Max Lataillade2

1VIV Healthcare, Research Triangle Park, NC, USA, 2VIV Healthcare, Branford, CT, USA, 3GlaxoSmithKline, Collegeville, PA, USA, 4GlaxoSmithKline, Oxbridge, UK, 5VIV Healthcare, London, UK
Background: The ongoing Ph3 BRIGHT study is evaluating Fostemsavir (FTR), an investigational produg of the first-in-class attachment inhibitor tamsavir (TMR), in heavily treatment-experienced (HTE) participants with multi-drug resistant HIV-1 infection who are unable to form a viable regimen from fully active ARV agents. We present the impact of key baseline (BL) factors on short-term virologic outcome and durability of response to FTR in the Randomized Cohort (RC).

Methods: RC participants, with 1-2 fully active ARVs were randomized (3:1) to blinded FTR 600 mg (n=203) or placebo (n=69) BID plus failing regimen for 8 days of functional monotherapy, followed by open-label FTR 600mg BID plus optimized background therapy (OBT; n=272). The impact of BL factors: gp120 polymorphisms, TMR IC50 fold-change (FC), and HIV-1 subtype, on change in HIV-1 RNA from Day 1 to Day 8, proportion of participants with a clinically relevant (>0.5 log10) decrease in HIV-1 RNA at Day 8, and HIV-1 RNA <40 c/mL at W96, was evaluated.

Results: Overall, 46% (122/263) of evaluable RC participants had a relevant gp120 polymorphism present at BL. Median change in HIV-1 RNA at Day 8 was lower among monotherapy participants with vs without BL gp120 polymorphisms of interest (-0.65 log10 vs -1.03 log10). However, 55% (48/88) of participants with BL gp120 polymorphisms achieved a viral load reduction >0.5 log10 at Day 8. BL TMR IC50FC from reference was observed over a broad range (0.05 to >5,000-fold; median 0.99-fold) with 74% (195/263) and 87% (229/263) of evaluable participants with TMR IC50FC >100-fold and >10-fold, respectively. While monotherapy participants with TMR IC50FC >100-fold at BL had a median change in HIV-1 RNA of <0.5 log10 at Day 8, this did not prevent a decline >0.5 log10. In fact, 38% (8/21) of participants with BL TMR IC50FC >100-fold achieved >0.5 log10 decline over this time. The majority of participants in the RC (79%, 216/272) had HIV-1 subtype B virus. Similar proportions of monotherapy participants with subtype B (66%, 108/163) vs non-B (65%, 108/163) were randomized to RC (79%, 216/272) had HIV-1 subtype B virus. Similar proportions of participants with non-B subtype, including AE, was small (n= 40 and 1, respectively).

Conclusion: In BRIGHT, BL gp120 polymorphisms of interest, TMR IC50FC, and HIV-1 subtype did not reliably predict virologic outcome at Day 8 of FTR functional monotherapy and did not impact durability of response (HIV-1 RNA <40 c/mL) to FTR + OBT through 96 weeks of therapy, among HTE participants as long-acting formulations.

504 A HIGHLY POTENT AND SAFE ALLOSTERIC HIV-1 INTEGRASE INHIBITOR, STP0404

Seohyun Ahn1, Uk-II Kim1, Won Young Seo1, Seongmi Choi1, Tatsuya Maehigashi2, Jared Lindenberger1, Mamuka Kvaratskhelia3, Baek Kim1, Kyungjin Kim1

1ST Pharm Co Ltd, Seoul, South Korea, 2Emory University, Atlanta, GA, USA, 3University of Colorado Anschutz Medical Campus, Aurora, CO, USA

STP0404 had a median change in HIV-1 RNA of <0.5 log10 at Day 8, this did not prevent a virus achieved >0.5 log10 decline in HIV-1 RNA at Day 8; although the monotherapy participants with subtype B (66%, 108/163) vs non-B (65%, 108/163) of evaluable participants with TMR IC50FC >100-fold achieved >0.5 log10 FC fold-change (FC), and HIV-1 subtype, on change in HIV-1 RNA from Day 1 to Day 8, proportion of participants with a clinically relevant (>0.5 log10) decrease in HIV-1 RNA at Day 8, and HIV-1 RNA <40 c/mL at W96, was evaluated.

Results: Overall, 46% (122/263) of evaluable RC participants had a relevant gp120 polymorphism present at BL. Median change in HIV-1 RNA at Day 8 was lower among monotherapy participants with vs without BL gp120 polymorphisms of interest (-0.65 log10 vs -1.03 log10). However, 55% (48/88) of participants with BL gp120 polymorphisms achieved a viral load reduction >0.5 log10 at Day 8. BL TMR IC50FC from reference was observed over a broad range (0.05 to >5,000-fold; median 0.99-fold) with 74% (195/263) and 87% (229/263) of evaluable participants with TMR IC50FC >100-fold and >10-fold, respectively. While monotherapy participants with TMR IC50FC >100-fold at BL had a median change in HIV-1 RNA of <0.5 log10 at Day 8, this did not prevent a decline >0.5 log10. In fact, 38% (8/21) of participants with BL TMR IC50FC >100-fold achieved >0.5 log10 decline over this time. The majority of participants in the RC (79%, 216/272) had HIV-1 subtype B virus. Similar proportions of monotherapy participants with subtype B (66%, 108/163) vs non-B (65%, 108/163) were randomized to RC (79%, 216/272) had HIV-1 subtype B virus. Similar proportions of participants with non-B subtype, including AE, was small (n= 40 and 1, respectively).

Conclusion: In BRIGHT, BL gp120 polymorphisms of interest, TMR IC50FC, and HIV-1 subtype did not reliably predict virologic outcome at Day 8 of FTR functional monotherapy and did not impact durability of response (HIV-1 RNA <40 c/mL) to FTR + OBT through 96 weeks of therapy, among HTE participants in the RC.

505 PRECLINICAL DEVELOPMENT OF SECOND GENERATION HIV-1 MATURATION INHIBITORS

Sherimay Ablan1, KC Yuvarj1, Dibya Ghimire2, T.J. Nitz3, David E. Martin3, Ritu Gaur1, Eric O. Freed1, Carl Wild1

1National Cancer Institute, Frederick, MD, USA, 2South Asian University, Chanakypuri, New Delhi, India, 3DH Pharma, Inc, Gaithersburg, MD, USA

Background: Maturation inhibitors (MIs) block HIV replication by disrupting conversion of CA-SP1 to mature CA, resulting in the formation of non-infectious viral particles. Mis bind inside a six-helix bundle that assembles at the cleft formed between two IN monomers and known to be the host LEDGF/p75 binding site, and EM study validated its activity to block HIV-1 maturation by mislocalizing HIV-1 RNA genomes outside of viral capsid. Two STP0404 resistant mutations (Y99H and A128T) were selected and co-crystal structure confirmed their locations near the STP0404 binding site.

Conclusion: STP0404 is a highly potent and safe ALLINIs with picomolar IC50 values in tissue culture as well as outstanding preclinical properties in animals, which will be soon pursued for its clinical evaluations for oral application as well as long-acting formulations.

Summary of GLP toxicology study

<table>
<thead>
<tr>
<th>Study*</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotoxic Toxicology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosome aberration</td>
<td>No-effects</td>
<td></td>
</tr>
<tr>
<td>Microsome test</td>
<td>No-effects</td>
<td></td>
</tr>
<tr>
<td>Safety Pharmacology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>No-effects</td>
<td></td>
</tr>
<tr>
<td>CV in-Drop</td>
<td>No-effects</td>
<td></td>
</tr>
<tr>
<td>4 wk GLP toxicity study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat 4 wk RML study</td>
<td>No-effects</td>
<td></td>
</tr>
<tr>
<td>Dog 4 wk + 24 week study</td>
<td>No-effects</td>
<td></td>
</tr>
</tbody>
</table>

505 PRECLINICAL DEVELOPMENT OF SECOND GENERATION HIV-1 MATURATION INHIBITORS
primary HIV-1 clinical isolates representing subtypes A-G and a set of viruses resistant to the approved classes of HIV-1 drugs. In vitro metabolic stability was characterized in human, rat, mouse, dog and monkey liver S9 fractions. Binding to human plasma proteins was determined using equilibrium dialysis and ii) in vitro activity assays employing human serum concentrations of 0-400%. In vivo pharmacokinetic studies were carried out in mice. Resistance selection experiments were carried out using both subtype B and C isolates.

**Results:** All compounds exhibit potent antiretroviral activity. Compound A exhibited an average IC50 value of 7.3nM against a panel of 12 primary isolates including those with the BVM-resistant SP1 V7A genotype (n=5). Compounds B and C inhibit HIV-1 with an average IC50 values against V7 virus of 7.9 and 14.9nM and against A7 isolates of 48.2 and 138.7, respectively. A, B and C inhibit drug resistant virus with average IC50 values of 3.1, 1.0 and 1.2nM, respectively (n=6). All compounds were metabolically stable in liver S9 fractions across species, demonstrated plasma protein binding of >99% and were orally bioavailable in the mouse. By using low concentrations of inhibitor, resistance-conferring mutations were identified.

**Conclusion:** As resistance to approved HIV therapies develops new drugs will be needed. Mls employ a novel mechanism to block HIV replication and could replace drugs that are no longer effective due to resistance. Compounds A-C exhibit pre-clinical development profiles similar or superior to MI drug candidates that have advanced to the clinic. Based on these results, we plan to continue development activities for each compound.

---

**506 PHASE II TRIAL OF VPU INHIBITOR BIT225 IN COMBINATION WITH ANTIRETROVIRAL THERAPY**

Anchalee Avihingsanon1, Carolyn A. Luscombe1, Gary D. Ewart1, Audrey S. Thomson1, Khuanchai Supparatpinyo2, Sivaporn Gatemicholom1, Win Min Han1, Michelle Miller1, Robert Murphy2

1HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand; 2Biotron Limited, North Ryde, Australia; 3Chiang Mai University, Chiang Mai, Thailand; 4Northwestern University, Chicago, IL, USA

**Background:** Vpu is a HIV-1 encoded membrane protein with multiple regulatory functions that enhance HIV-1 replication fitness and promote innate immune evasion in multiple cell types including monocytes. BIT225 inhibits HIV-1 replication in myeloid cells in vitro. BIT225 has been studied in patients with chronic HIV-1 infection receiving antiretroviral therapy (ART).

**Methods:** A randomized, placebo controlled, double-blind, Phase 2 study of BIT225 in individuals with HIV-1 commencing ART (males and females, aged 18 to 65 years, viral load >5,000 copies/ml; CD4+ count >100 cells/mm3, ART naive). HIV-1 infected individuals recruited from two sites in Thailand were treated with either BIT225 or placebo in addition to ART (Atripla) for 12 weeks. Individuals were randomized 2:1 (BIT225: placebo). Markers of viral replication and immune functions were investigated.

**Results:** Thirty-six patients were enrolled. Plasma HIV-1 RNA levels declined with similar viral decay kinetics in both cohorts over the 12 week study period. In contrast, significant changes were observed for multiple immune markers between the 2 cohorts. Levels of the monocyte activation marker CD163 showed significantly greater reduction from baseline (P<0.05) general linear model, two-way ANOVA) in the BIT225 treated cohort compared to ART alone over the 12 week treatment period. There was a statistically significant increase in activated CD8+, CD4+ cells, and NK cells in the BIT225 cohort. There was a transient statistically significant increase in plasma IL-21 production in the first 3 weeks of BIT225 therapy. There were no significant changes to plasma IL-6, TNF-alfa, and interferon-gamma in either cohort over the treatment period.

**Conclusion:** The addition of BIT225 to ART resulted in unique stimulation of multiple arms of the innate immune system. The increased numbers of CD8+, CD4+ and NK cells are consistent with enhanced recognition of HIV-1 infected cells. Vpu has been associated with reducing cell surface expression/function of numerous cellular proteins/receptors involved in viral antigen presentation to CD4+, CD8+ T cells and NK cells. The production of IL-21 by Tfh, Th17, and/or NK cells is a unique immunological consequence of addition of BIT225 to ART and offers the potential for treatment targeting different HIV-1 compartments during standard therapy.

---

**507 COMPARABLE EFFICACY OF IBALIZUMAB IN COMBINATION WITH 1 OR 2 FULLY ACTIVE AGENTS**

Edwin DeJesus1, Colleen S. McGary2, Pedro Mesquita3, Steven Weinheimer4, Zvi Cohen5

1Orlando Immunology Center, Orlando, FL, USA; 2Sunes Health, Somerset, NJ, USA; 3TalMed Biologies USA, Irvine, CA, USA; 4Therapeutics, Inc, Montreal, QC, Canada

**Background:** Current guidelines recommend a regimen containing at least two, preferably three, fully active agents to suppress viremia in HIV treatment-experienced patients. However, identifying three fully active agents presents a challenge for some multidrug resistant (MDR) HIV patients. Ibalizumab (IBA), a CD4-directed post-attachment HIV-1 inhibitor, is approved for MDR patients failing their ART regimen. We sought to determine if IBA had comparable and durable virologic efficacy in patients with one versus two other fully active agents.

**Methods:** Patients received IBA 2000mg loading dose followed by 800mg doses every 2 weeks up to Week 25 in TMB-301. An optimized background regimen (OB) with ≥1 additional fully active agent was added 7 days after starting IBA. Following completion of TMB-301, eligible patients continued to receive IBA every 2 weeks under study TMB-311.

**Results:** In TMB-301, 12 of the 40 patients had one fully active agent paired with IBA (OSS1) and 16 had two fully active agents with IBA (OSS2). Baseline median viral load (VL) and CD4 counts were 65,000 and 20,000 copies/ml and 57 and 89 cells/mm3 for the OSS1 and OSS2 patients, respectively. In OSS1 patients, fully active agents in addition to IBA were fostemsavir (n=6), DTG (n=4), TDF (n=1), and RPV (n=1). Of these, 11 (92%) had >0.5log10 VL decrease on IBA functional monotherapy after 7 days. At Week 25, 5 of the 7 OSSI completers (71%) achieved <50 copies/ml, of which three were on a fully active DTG. At Week 96, 5 of 7 OSS1 patients (71%) maintained viral suppression, which continued until they transitioned to commercial supply (some up to Week 124). In OSS2 patients, 13 of 18 (72%) reached a >0.5log10 VL decrease after IBA functional monotherapy. At Week 25, 9 patients (50%) with OSS2 achieved <50 copies/ml, 7 of which were on a fully active DTG regimen, demonstrating similar virologic efficacy when IBA is paired with one or two fully active agents. At Week 96, viral suppression was maintained in 9 patients and they continued on IBA until commercial was available (some up to Week 140).

**Conclusion:** Subgroup analyses of TMB-301/311 data show significant efficacy of IBA among patients with one or two other fully active agents, with durable responses regardless of the number of active agents. Patients who combined IBA with DTG showed impressive rates of suppression. Data support the long-term efficacy of IBA-based regimens that include two or three fully active agents.

---

**508 A PHASE I DOSE-ESCALATION TRIAL OF HUMAN MONOCLONAL ANTIBODY N6LS IN HEALTHY ADULTS**

Alicia T. Widge1, Katherine V. Houser1, Martin R. Gaudinski2, Grace Chen1, Cristina Carter1, Sophia P. Hickman1, Jamie Saunders1, Lasonji Holman1, Ingelise Gordon1, Sarah O’Connell1, Edmund V. Capparelli1, Mark Conners1, Richard A. Koup1, John R. Mascola1, for the VRC 609 study team

1Vaccine Research Center, NIAID, Bethesda, MD, USA; 2University of California San Diego, La Jolla, CA, USA; 3NIAID, Bethesda, MD, USA

**Background:** Developing monoclonal antibodies that broadly neutralize HIV-1 (bnMabs) through passive transfer is a key goal in the prevention and treatment of HIV-1 infection. N6LS is a bnMab isolated from a patient who was HIV infected for 21 years and was not on antiretroviral treatment. It was produced as an IgG1 with an LS mutation to the Fc region to increase half-life through increased binding affinity to the neonatal Fc receptor. N6LS targets the CD4-binding site (CD4bs) of the HIV-1 envelope glycoprotein and is a member of the VRC01 class of CD4bs antibodies. It is broader and more potent than VRC01, neutralizing up to 98% of viral strains. N6LS achieves this via two recognition characteristics. First, it is minimally insensitive to mutations in the variable gp120 V5 loop that typically diminish contacts and interrupt binding in other CD4bs antibodies. Second, it binds at a unique angle that avoids steric clashes with the highly glycosylated V5 region, which is a major mechanism of resistance for other bnMabs in this class.

**Methods:** We conducted a first-in-human dose-escalation open-label phase 1 clinical trial of N6LS in healthy HIV-1 negative adults aged 18-50 to determine its safety, tolerability, and pharmacokinetic (PK) profile. Three groups received a single IV dose of 5, 20, or 40 mg/kg, and one group received a single SC dose of 5 mg/kg. Two groups received three doses of either 5 mg/kg SC or 20 mg/kg IV at 12-week intervals.

**Results:** We enrolled 23 volunteers between June 18, 2018 and February 12, 2019, including 9 (39%) males and 14 (61%) females. 22 participants received all...
N6LS administrations for a total of 42 product administrations. N6LS was safe and well tolerated with no SAEs or dose-limiting toxicities. No infusion reactions were reported. The most common adverse events were headaches, nausea, vomiting, and fatigue. There were no differences in PK parameters following the initial N6LS administration compared to subsequent administrations.

**Conclusion:** N6LS was safe and well tolerated with no SAEs or dose-limiting toxicities. Given its high neutralization breadth and potency, N6LS is a promising candidate for inclusion in HIV-1 prevention and therapeutic strategies.

---

**Table 1. N6LS mean pharmacokinetic parameters by group**

<table>
<thead>
<tr>
<th>Group</th>
<th>N6LS peak (ng/mL)</th>
<th>Mean (ng/mL)</th>
<th>Area under the curve (ng/mL)</th>
<th>4 weeks post-infusion concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>100</td>
<td>500</td>
<td>5,000</td>
<td>250</td>
</tr>
<tr>
<td>IV 20 mg/kg (5x)</td>
<td>500</td>
<td>2,500</td>
<td>25,000</td>
<td>1,250</td>
</tr>
<tr>
<td>IV 40 mg/kg (10x)</td>
<td>1,000</td>
<td>5,000</td>
<td>50,000</td>
<td>2,500</td>
</tr>
</tbody>
</table>

---

**509 PREEXISTING RESISTANCE AND B/F/TAF SWITCH EFFICACY IN AFRICAN AMERICANS**

Kristen Andreatta1, Michelle L. D’Antoni2, Silvia Chang1, Ross Martin3, Christiana Blair4, Sean E. Collins1, Kirsten L. White1

1Gilead Sciences, Inc, Foster City, CA, USA

**Background:** The BRAAVE 2020 study is evaluating the safety and efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) among virologically suppressed adults with HIV in the US who identify as Black or African American. Here, we present resistance analyses and impact on virologic outcomes at Week 24.

**Methods:** Participants with prior treatment failure and documented resistance to NNRTIs, PIs, or non-tenofovir NRTIs were eligible for enrollment with the exception that patients with resistance to NNRTIs, PIs, or non-tenofovir NRTIs were not eligible. Participants started on B/F/TAF for a total of 42 product administrations. N6LS was safe and well tolerated with no SAEs or dose-limiting toxicities. No infusion reactions were reported. The most common adverse events were headaches, nausea, vomiting, and fatigue. There were no differences in PK parameters following the initial N6LS administration compared to subsequent administrations.

**Conclusion:** N6LS was safe and well tolerated with no SAEs or dose-limiting toxicities. Given its high neutralization breadth and potency, N6LS is a promising candidate for inclusion in HIV-1 prevention and therapeutic strategies.
Gomez-Sirvent,1 Joaquim Peraire,1 Joaquín Portilla,1 Estrella Caballero1, Mónica García-Álvarez1, José A. Iribarren,2 Mar Massá2, Federico García3 1Hospital Universitario San Cecilio, Granada, Spain, 2Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain, 3Hospital Universitario de San Espinosa, Palma de Mallorca, Spain, 4Hospital Universitari Mútua de Terrassa, Terrassa, Spain, 5Hospital Universitario de Bellvitge, Barcelona, Spain, 6Hospital Clínico Universitario de Murcia, Murcia, Spain, 7Hospital Universitario de Canarias, San Cristóbal de La Laguna, Spain, 8Hospital Universitario de Tarragona Joan XXIII, Tarragona, Spain, 9Hospital General Universitario de Alicante, Alicante, Spain, 10Hospital Universitario de la Vall d’Hebron, Barcelona, Spain, 11Hospital General Universitario de Elche, Elche, Spain

Background: Initial regimens currently recommended by treatment guidelines include high genetic barrier antiretrovirals (ARVs), thus it may be of interest to evaluate drug resistance mutations (DRMs) and, specifically, clinically relevant resistance. Here, we present data on trends in DRM and clinically relevant transmitted drug resistance to ARVs recommended for first-line treatment in Spain.

Methods: We analysed 6090 RT & Pro Fasta sequences from CoRIS (2007-2018). As integrase resistance is not part of routine testing in naïve patients in Spain, we ran a surveillance programme (2012-2018) and tested 1404 patients. We evaluated the prevalence of Transmitted DRM using the WHO 2009 list, and clinically relevant resistance with Stanford v8.8 Algorithm. First line regimens for each study period were those recommended by the Spanish treatment guidelines (GESIDA).

Results: Our results indicated a similar trend in NNRTIs and NRTIs TDR prevalence with values ranging from 2.4-5%. In regard to INsTIs TDR, we also described similar values with no significant changes over years. However, we observed a decrease in PIs TDR from 2016 (c.1% of prevalence). Clinically Relevant resistance to recommended first line regimens showed a slow decline from 2007-2012, and peaked in 2013-2014 due to the inclusion of Rilpivirine for 1st line in the Spanish recommendations. Detailed results for 2007-2018 are included in the enclosed table. Results for 2007-2018 are shown in the enclosed table.

Conclusion: While NNRTIs and NRTIs DRM prevalence remained stable in Spain through 2007-2018, we observed a slightly decrease in PIs and INsTIs DRM prevalence. Clinically relevant TDR to approved first line regimens showed a slow decline from 2007 to 2018. Resistance to INsTIs remains at very low levels. These findings, together with the very low prevalence of resistance to recommended first line NRTIs in 2015-2016 reinforce GESIDA recommendations on baseline resistance testing and test and treat strategies when starting PIs or INsTIs based regimens.

513 COUNTRY-LEVEL DRIVERS OF NNRTI RESISTANCE IN SOUTHERN AFRICA

Julien Riou1, Carole Dupont1, Silvia Bertagnolio2, Ravindra K. Gupta3, Leigh F. Johnson4, Roger Kouyos1, Matthias Egger1, Christian L. Althaus5
1University of Bern, Bern, Switzerland, 2WHO, Geneva, Switzerland, 3University College London, London, UK, 4Centre for Infectious Disease Epidemiology and Research, Cape Town, South Africa, 5University of Zurich, Zurich, Switzerland

Background: In 2015-2016, the prevalence of resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) in HIV-infected individuals initiating antiretroviral therapy (ART) is of critical importance for planning future ART programs. Understanding the dynamics and drivers of NNRTI resistance at the country level is of critical importance for planning future ART programs.

Methods: We first collected survey data on pretreatment drug resistance (PDR) to NNRTIs in nine countries of southern Africa from 2000 to 2018, including 66 studies and 14,639 individuals. We then fitted a mechanistic transmission model to key indicators of the local HIV epidemics (HIV prevalence, ART coverage and AIDS mortality) and the levels of PDR using a hierarchical Bayesian framework. For each country, we estimated the rate at which treatment failure with NNRTI resistance (TFNR) occurs during ART. We further explored the association between TFNR and socio-economic covariates.

Results: The model reliably described the local dynamics of HIV and the rise of NNRTI PDR, with the exception of Malawi and Zambia where data quality was insufficient. Predicted levels of NNRTI PDR in 2018 ranged between 4.7% (95% credible interval: 2.2, 9.8) in Mozambique and 32.8% (26.4, 38.7) in Namibia. The main driver of NNRTI resistance was the conjunction of ART coverage and the rate of TFNR. Estimates of the rate of TFNR were lowest in Botswana (0.002 per year; 0.006) and highest in the Republic of South Africa (0.14 per year; 0.11, 0.17). The regional average of this rate was 0.07 per year (0.04, 0.25) corresponding to a probability of 8% (4, 22) that patients initiating ART show treatment failure due to the acquisition of NNRTI resistance after one year. TFNR was associated with external health expenditure (Pearson correlation: -0.43; -0.59, -0.19) and out-of-pocket health expenditure (0.39; 0.01, 0.75).

Conclusion: Even with the introduction of dolutegravir, NNRTIs will remain a central component of first-line regimens in southern Africa. Between-country
Emergent integrase mutations were observed. 8 (80%) already had at least one NRTI or NNRTI RAM at baseline. No treatment-the 10 patients developing NRTI or NNRTI RAMS at VF in the TDF/FTC/EFV arm, more common for first-line treatment with TDF/FTC/EFV (10/14; 71%) compared to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) using Stanford drug resistance datasets (HIVDB 8.8 and SmartGene IDNS software. For ART-naive participants, World Health Organization surveillance drug resistance mutations (SDRMs) were noted. We calculated resistance scores for specific drugs and tallied major mutations present.

**515 PRETREATMENT AND ACQUIRED ANTIRETROVIRAL DRUG RESISTANCE IN 4 AFRICAN COUNTRIES**

**Background:** Standardized HIV management protocols that emphasize adherence counseling and forego genotypic testing for HIV drug resistance (HIVDR) have facilitated expanded access to antiretroviral therapy (ART) in resource-limited settings. However, emerging HIVDR could jeopardize the success of such approaches. We characterized HIVDR among ART-naive and experienced participants in the ongoing African Cohort Study (AFRICOS).

**Methods:** From January 2013 to July 2019, adults with HIV RNA ≥1000 copies/mL underwent HIVDR testing upon enrollment at 12 clinics in Uganda, Kenya, Tanzania, and Nigeria. ART history was obtained by medical record review. HIV pol subtype was assigned using five tools to achieve a consensus assignment. We calculated resistance scores for specific drugs and tallied major mutations to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) using Stanford HIVDB 8.8 and SmartGene IDNS software. For ART-naive participants, World Health Organization surveillance drug resistance mutations (SDRMs) were noted.

**Results:** Of 1024 eligible participants, 976 (95.3%) underwent HIVDR testing with median age 36 (interquartile range [IQR] 30-43) years and median CD4 295 (IQR 142-478) cells/mm$^3$. Among 710 ART-naive participants, SDRMs were seen in 75 (10.6%), with highest prevalence in Nigeria (15/90, 16.7%) and Uganda (38/275, 13.8%). Pre-treatment major NNRTI mutations were seen in 57 (8.0%) and NRTI mutations in 29 (4.1%), including 37 (5.2%) with K103N 10 (1.4%) and M184V/I (116, 43.6%). Variations by country were notable. In South Africa, 75% of ART-experienced participants had major NRTI and 79% had major NNRTI resistance mutations, again led by K103N (86/266, 32.3%) and M184V/I (116, 43.6%). Variations by country were noted. For genotype B (Figure Panel B), with 51 (19.2%) participants showing medium or high-level resistance to both tenofovir and lamivudine.**

**Conclusion:** There was a moderate prevalence of pre-treatment HIVDR. Participants on failing ART regimens had a high burden of HIVDR that potentially limits the efficacy of standard regimens containing tenofovir and lamivudine. Programmatic gaps need to be addressed to prevent HIVDR propagation, particularly with rollout of new first-line ART in Africa. Management strategies that emphasize adherence counseling while delaying ART switch may promote accumulation of drug resistance mutations and should be reconsidered.
516 HIV VIROLOGIC FAILURE AND DRUG RESISTANCE AMONG HOSPITAL INPATIENTS IN MALAWI
Ankur Gupta-Wright1, Katherine Fielding1, Elizabeth L. Corbett1, Joep J. van Oosterhout1, Melanie Alufandika-Moyo1, Doug K. Wilson1, Daniel Grill3, Elizabeth Chimbayo1, Judith Heaney1, Matthew Byott1, Eleni Nastouli1, Ravindra K. Gupta6
1London School of Hygiene & Tropical Medicine, London, UK, 2Dignitas International, Zomba, Malawi, 3Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi, 4Edendale Hospital, Pietermaritzburg, South Africa, 5University College London Hospitals NHS Trust, London, UK, 6University College London, London, UK

Background: Since antiretroviral therapy (ART) scale-up in high prevalence settings, most HIV+ hospital inpatients are taking ART at admission. However, few data exist on the prevalence of ART failure or HIV drug resistance (DR) in this population. We conducted a large cohort study, nested in a TB screening trial, to describe the proportion of adult inpatients established on ART with virological failure (viral load [VL] >1000 copies/ml), and HIVDR.

Methods: Patients were eligible if taking ART for ≥6 months at admission. Stored plasma samples from admission were tested for HIV-1 RNA by real-time qPCR. HIVDR mutations were detected by ultra deep sequencing on Illumina MiSeq platform for patients with VL >1000 copies/ml. Interpretation of HIVDR mutations used the Stanford HIVDR Algorithm. Drug resistance was defined as having intermediate or high-level resistance to specific drugs.

Results: Overall, 814/1316 (61.9%) patients recruited between Oct 2015 and Sept 2017 were on ART for ≥6 months. 28/814 patients had missing VL. 252/786 (32.1%) of patients had VL >1000 copies/ml. Of these, mean age was 38 years, 62% were female and median CD4 was 60 cells/µL, and 97.6% patients reported being treated with first-line ART (lamivudine [3TC], tenofovir [TDF] and efavirenz [EFV]). Successful sequencing and HIVDR results were available for 237/252 (94.0%). 195/237 (82.3%) of samples were resistant to 3TC, 128/237 (54.0%) to TDF and 219/237 (92.4%) to EFV. Protease and integrase inhibitor resistance was rare (1/233 and 2/225 had major mutations respectively). 84/237 (54.0%) to TDF and 219/237 (92.4%) to EFV. Protease and integrase inhibitor resistance was rare (1/233 and 2/225 had major mutations respectively). 84/237 (54.0%) to TDF and 219/237 (92.4%) to EFV. Protease and integrase inhibitor resistance was rare (1/233 and 2/225 had major mutations respectively). 84/237 (54.0%) to TDF and 219/237 (92.4%) to EFV. Protease and integrase inhibitor resistance was rare (1/233 and 2/225 had major mutations respectively). 84/237 (54.0%) to TDF and 219/237 (92.4%) to EFV. Protease and integrase inhibitor resistance was rare (1/233 and 2/225 had major mutations respectively).

Conclusion: These data demonstrate high prevalence of virological failure and HIVDR in hospitalised patients in Malawi. Critically, HIVDR was associated with increased mortality and therefore targeted interventions for virological failure are warranted. The high prevalence of resistance to first-line nucleotide-reverse transcriptase inhibitors is concerning, and has public health implications.

517 HIGH LEVELS OF DRUG RESISTANCE IN ART-NAIVE AND PLWHL FAILING FIRST-LINE ART IN HAITI
Samuel Pierre1, Santiago Avila-Rios3, John Wu3, Claudia García-Morales2, Vanessa A. Rouziier1, Gaetan R. Julmiere1, Patrice Severe3, Alexandra Apollon1, David Rice3, Gustavo Reyes-Terán2, Marie Marcelle Deschamps3, Bernard Liautauda, Serena Koening2, Jean William Page3
1GHESKIO, Port-au-Prince, Haiti, 2National Institute of Respiratory Diseases, Mexico City, Mexico, 3Analysis Group, Inc, Boston, MA, USA, 4Brigham and Women’s Hospital, Boston, MA, USA

Background: We assessed drug resistance in a sample of patients at GHESKIO in Port-au-Prince, Haiti (largest provider of HIV care in the Caribbean), to inform treatment guidelines.

Methods: From September 2018 to July 2019, we conducted HIV genotypes for patients who were ART-naive or with virologic failure on first-line ART; tenofovir (TDF)/lamivudine (3TC)/dolutegravir (DTG) (TLD) replaced efavirenz (EFV)/TDF/3TC as first-line ART in November 2018. Resistance was defined by the Stanford HIV Drug Resistance Database score: ≥15 at least low-level resistance; ≥30 at least intermediate resistance.

Results: HIV genotypes were conducted for 266 patients who were ART-naive and 91 on NNRTI-based first-line ART. Of those, 56.7% were female and median age was 35 (IQR: 26, 44). Among ART-naive patients, 24.8% had intermediate or higher resistance to EFV, with score ≥30 (27.5% among females). NRTI resistance (score ≥30) was detected in 8.6%, including 3.4% for both TDF and 3TC. M184V/I was detected in 7.5%, K65R/N in 2.3%, and both mutations in 1.9%. Among patients failing a first-line NNRTI-based regimen, 91.2% had EFV resistance score ≥30. NRTI resistance (score ≥30) was detected in 63.7%, including 35.2% for both TDF and 3TC. M184V/I was detected in 46.2%, K65R/N in 28.6%, and both mutations in 15.4%. Rates of PI resistance were low. Less than 1% of patients had intermediate or high-level resistance to any PI.

Conclusion: There are high levels of NNRTI and NRTI resistance among ART-naive and ART-experienced adults and children in Haiti. The use of EFV-based ART regimens for pregnant women as an alternative first line is of concern, as ART resistance testing is not conducted. DTG and PI based regimens should be prioritized. The high rate of abacavir resistance in children, and TDF cross-resistance, limits future treatment options in that age group. High levels of TDF and 3TC resistance in adults warrant caution in the implementation of new guidelines and roll out of TLD in patients failing NNRTI-based therapy.

518 PRETREATMENT HIV DRUG RESISTANCE AND 48-WEEK VIROLOGIC OUTCOMES IN THE ADVANCE TRIAL
Mark J. Siedner1, Michelle A. Moorman2, Andrew Hill3, Tulio de Oliveira3, Richard Lessels1, Bryony Simmons3, Godpower Akpomie1, Celicia M. Serenata2, Willem D. Verhe3, Ravindra K. Gupta6
1London School of Hygiene & Tropical Medicine, London, UK, 2Dignitas International, Zomba, Malawi, 3Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi, 4Edendale Hospital, Pietermaritzburg, South Africa, 5University College London Hospitals NHS Trust, London, UK, 6University College London, London, UK

Background: Since antiretroviral therapy (ART) scale-up in high prevalence settings, most HIV+ hospital inpatients are taking ART at admission. However, few data exist on the prevalence of ART failure or HIV drug resistance (DR) in this population. We conducted a large cohort study, nested in a TB screening trial, to describe the proportion of adult inpatients established on ART with virological failure (viral load [VL] >1000 copies/ml), and HIVDR.

Methods: Patients were eligible if taking ART for ≥6 months at admission. Stored plasma samples from admission were tested for HIV-1 RNA by real-time qPCR. HIVDR mutations were detected by ultra deep sequencing on Illumina MiSeq platform for patients with VL >1000 copies/ml. Interpretation of HIVDR mutations used the Stanford HIVDR Algorithm. Drug resistance was defined as having intermediate or high-level resistance to specific drugs.

Results: Overall, 814/1316 (61.9%) patients recruited between Oct 2015 and Sept 2017 were on ART for ≥6 months. 28/814 patients had missing VL. 252/786 (32.1%) of patients had VL >1000 copies/ml. Of these, mean age was 38 years, 62% were female and median CD4 was 60 cells/µL, and 97.6% patients reported being treated with first-line ART (lamivudine [3TC], tenofovir [TDF] and efavirenz [EFV]). Successful sequencing and HIVDR results were available for 237/252 (94.0%). 195/237 (82.3%) of samples were resistant to 3TC, 128/237 (54.0%) to TDF and 219/237 (92.4%) to EFV. Protease and integrase inhibitor resistance was rare (1/233 and 2/225 had major mutations respectively). 84/237 (54.0%) to TDF and 219/237 (92.4%) to EFV. Protease and integrase inhibitor resistance was rare (1/233 and 2/225 had major mutations respectively). 84/237 (54.0%) to TDF and 219/237 (92.4%) to EFV. Protease and integrase inhibitor resistance was rare (1/233 and 2/225 had major mutations respectively).
Background: Increasing prevalence of pretreatment HIV drug resistance (PDR) has motivated guideline changes to avoid non-nucleoside reverse transcriptase (NNRTI)-based first-line antiretroviral therapy (ART) regimens. Empiric data on the performance of ART regimens in the face of PDR are lacking in sub-Saharan Africa.

Methods: The ADVANCE study is a randomized controlled trial in South Africa that compares efavirenz (EFV) with delugetravir (DTG), both with two NNRTIs, as first-line ART. We performed pre-treatment genotypic drug resistance testing in 197 randomly selected participants with next generation sequencing using the Illumina platform at KRISP and set detection thresholds for resistant variants at >20%, 5-20%, 2-5%. For our primary outcome, we compared the proportion of individuals who achieved virologic suppression (<40 copies/mL) at 48-weeks with EFV versus DTG-based ART, by presence or absence of PDR at 20% threshold, defined with the WHO drug resistance mutation (DRM) list. In secondary analyses, we assessed the effect of resistance at 2 and 5% thresholds on outcomes and the effect of PDR on treatment failure, redefined as virologic failure, death or loss from observation.

Results: We successfully sequenced pre-treatment HIV RNA from 165 individuals, of whom 48 (29%) received EFV and 117 (71%) received DTG. Twenty of 165 (12%) had ≥1 DRMs, with no difference in PDR by study arm, sex (56% female), age (median 32 years) or pre-treatment CD4 count (median 284). The most common mutation was K103N (9%); K65R and M184V were both found in only 2 (1%) of individuals. The proportion achieving our primary outcome was similar in the EFV (36/40, 90%) and DTG groups (93/101, 91%), P=0.69. However, rates of confirmed virologic suppression among those with and without PDR was 25% (1/4) and 97% (35/36) in the EFV-arm, and 89% (8/9) and 92% (85/93) in the DTG arms, respectively (P<0.001 for interaction between PDR and treatment arm). These trends were similar when redefining PDR thresholds at 2.5% and 5-20%, and when redefining failure to include death and loss from observation.

Conclusion: PDR, primarily to NNRTIs, was associated with significantly diminished efficacy of EFV-based, but not DTG-based three drug ART in South Africa. These data support the use of integrase inhibitors as initial therapy in individuals with known drug resistance or in populations with a very high prevalence of circulating NNRTI PDR.

519 IMPACT OF PREEXISTING DRUG RESISTANCE ON RISK OF VIROLOGIC FAILURE IN SOUTH AFRICA


1Brigham and Women’s Hospital, Boston, MA, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3University of KwaZulu-Natal, Durban, South Africa, 4Iriscina Institute for AIDS Research, Badalona, Spain, 5University of Rochester, Rochester, NY, USA, 6Emory University, Atlanta, GA, USA

Background: There is conflicting evidence on the impact of pre-existing HIV drug resistance mutations (DRM) in patients infected with non-B subtype virus initiating first-line antiretroviral therapy (ART). Using next-generation sequencing, we assessed the impact of HIV DRMs on the risk of virologically failure (VF) in South African patients initiating an NNRTI-based ART regimen.

Methods: We performed a case-cohort substudy of the HIV Drug Resistance Surveillance Study (DRSS), which enrolled 1,000 peri-urban and rural patients initiating first-line efavirenz/tenofovir/emtricitabine in KwaZulu-Natal. Pre-ART DRMs were detected by multiplexed Illumina sequencing of HIV pol and sequence analysis performed using PAAseq software. Individual genotypic susceptibility scores at varying minority variant (MV) thresholds (0.5-20%) were calculated using the Stanford HIV database. DRMs present at ≥20% of the viral population were labeled as “majority” variants likely detectable by Sanger sequencing. Weighted Cox proportional hazards models estimated the association between pre-ART DRMs and risk of VF, defined as confirmed HIV-1 RNA ≥1,000 copies/mL after ≥5 months of ART.

Results: The evaluable case-cohort sample included 178 participants from the randomly selected subcohort (16 with VF, 162 without VF) and 83 additional participants with VF. In the random subcohort, 16% of participants harbored at least one majority DRM that conferred intermediate or greater ART resistance (Stanford score ≥30). The presence of any significant majority DRM was associated with a 3-fold risk of VF (p=0.002). In those with <2 active drugs due to majority DRMs, the risk of VF increased to 5.2-fold (p<0.001) compared to those with 3 active drugs. Thirteen percent of participants in the random subcohort harbored any MV DRMs in the absence of majority DRMs. The most commonly detected high-level majority DRMs (K103N, V106M, M184V) were rarely detected as MVs. Presence of MVs alone had no significant impact on the risk of VF. Inclusion of pre-ART MVs with majority DRMs improved the sensitivity, but reduced the specificity of predicting VF of first-line ART.

Conclusion: In a cohort of participants from KwaZulu-Natal, the presence of majority DRMs increased the risk of VF, an effect largely driven by the presence of dual-class resistance. The detection of drug-resistant minority variants alone did not significantly increase the risk of VF, but their inclusion with majority DRMs affected the sensitivity/specificity of predicting VF.
Vf with resistance and Vf without resistance (808 [503] vs. 589 [495] vs. 527 [555] fmol/punch; P<0.01; Table), respectively.

Conclusion: TVF-DP in DBS was associated with Vf and drug resistance in South African PLWH on TDF-based ART. Participants with Vf who developed drug resistance had TVF-DP concentrations in the mid-range of cumulative exposure, but higher than those who did not develop resistance. These results suggest that moderate cumulative drug exposure is required to develop ART resistance. Future research on the clinical utility of TVF-DP in DBS to prevent the development of VF and drug resistance is needed.

Table: Concentrations of TVF-DP in DBS in cases vs. controls among PLWH on TDF-based ART in South Africa.

<table>
<thead>
<tr>
<th>Category (n)</th>
<th>TVF-DP [fmol/punch] Mean (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vf with resistance (33)</td>
<td>589 (195)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vf with resistance (10)</td>
<td>527 (555)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

521 TRENDS AND CHARACTERISTICS OF HIV-1 DRUG RESISTANCE IN THE UNITED STATES (2012-2018)

Cassidy E. Henegar1, Mark Underwood1, Leigh Ragone2, Harmony Gargess, Vani Vannappagari1

VIV Healthcare, Research Triangle Park, NC, USA, VIV Healthcare, London, UK

Background: The prevalence of transmitted and acquired HIV-1 drug resistance impacts effectiveness of antiretroviral therapy in both treatment-naive and treatment-experienced people living with HIV. This analysis utilized data from a large, representative commercial patient testing database to assess trends in HIV-1 drug resistance prevalence in the modern treatment era.

Methods: Samples from HIV-1-infected individuals in the United States submitted for genotypic resistance testing to 4 antiretroviral (ARV) classes (protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and integrase strand transfer inhibitors (INSTI)) between July 1, 2012 and June 30, 2018 were analyzed. All samples were collected as part of routine clinical care and evaluated using Monogram Biosciences GenoSure PRIme assay.

Results: Of 84,611 samples evaluated, 27,911 (33.0%) demonstrated reduced susceptibility to at least one ARV. Between 2012 and 2018, resistance to NRTIs (54.8% to 40.8%) and PIs (14.7% to 8.3%) steadily declined. The proportion of samples with reduced susceptibility to at least one NRTI decreased from 2012 and 2015 (20.3% to 14.0%), stabilizing from 2015 to 2018. Multiclass (≥2 ARV classes) resistance declined between 2012 and 2018. The proportion of resistant samples increased to ≥ 1 NRTI, ≥ 1 PI, and ≥ 1 INSTI in the absence of NRTI, PI, and INSTI resistance (2012-2018: 36.2% to 52.6%). Among samples with multiclass resistance, 78.7% were still susceptible to at least 1 ARV in the NNRTI class, 93.4% to ≥ 1 NRTI, 97.9% to ≥ 1 PI, and 93.7% to ≥ 1 INSTI; of these, 29.1% were susceptible to a single INSTI. The proportion of resistant samples with reduced susceptibility to multiple ARV classes increased with older age (21-30 yrs: 21.9%; 31-40: 30.4%; 41-50: 38.1%; 51-60: 41.4%; >60: 42.4%). No associations between degree of resistance and gender or geographic region were observed.

Conclusion: Decreasing prevalence of multiclass ARV resistance was observed in testing data, in addition to declines in NRTI, PI, and INSTI resistance. These trends correspond with the availability of newer treatment options with favorable cross-resistance profiles, improved efficacy, and more convenient formulations leading to better adherence.

522 PREVALENCE OF RESISTANCE AND LIMITED THERAPEUTIC OPTIONS IN PATIENTS VIREMIC ON ART

Olivier Robinneau1, Elisabeth André-Garnier1, Lise Cuzin1, Solène Sécher1, Fécile Dewulf1, Fanny Taudière1, Laurence Bocket1, Raymond Césaire1, Virginie Ferre1, Clotilde Allavenna2, André Cabie1, François Rafig1

1Centre Hospitalier de Tourcoing, Tourcoing, France, 2CHU de Nantes, Nantes, France, 3CHU Fort de France, Fort de France, Martinique, 4CHU de Lille, Lille, France

Background: Although current ART has led to improved rates of prolonged virologic suppression, some patients remain viremic under ART. We evaluated the prevalence of resistance and therapeutic options among viremic subjects on ART in a large multicentric study.

Methods: All HIV infected adults on ART for ≥6 months on October 1, 2018 at 3 French sites from the Dat‘AIDS cohort (NCT02898887) were included. We compared the prevalence of resistance and potential therapeutic options among viremic subjects on ART among a large multicentric study.

Results: Of 5,429 individuals under follow-up, 215 (3.97%) had HIV RNA >50 c/mL. Excluding subjects with no available genotype, characteristics of the 208 viremic vs virologically suppressed subjects are shown in Table. Adherence issues and social problems were found in 64.9% and 49.5% of viremic individuals, respectively. On cumulative genotypic, 8.2% of viremic subjects had resistance to 3 or 4 ARV classes and 50.4% to none; susceptibility to TDF, ETR, DRV/r and DTG was 92.1%, 82%, 98.6% and 95.7%, respectively. Number of AD was ≥3 in 85.6% of viremic subjects, while last ART regimen had a GSS ≥3 in 68.2% and a GSS=2 in 24%. The proportion of subjects with limited TO was 4.33% (n=9) of viremic subjects and 0.17% of the total study population. Among these 9 subjects, all had an AIDS history, with mean nadir CD4 of 53/ mm³, and 5/9 zenith HIV RNA >6 log₁₀ c/mL. If we extrapolate our results to all patients under care in France (2016 estimation: 112,877; 95% CI: 111,635-114,053), we would obtain an estimate of 192 (95% CI: 190-194) HIV infected adults with limited TO.

Conclusion: Few individuals on ART ≥6 months had persistent viremia; they very rarely harbored multi-resistant viruses for which it is not possible to construct a suppressive ART regimen. In this context of poor adherence-related viremia without great loss of TO, interventions to improve compliance, rather than new ARV classes, are needed.

Table: Characteristics of patients with and without HIV RNA >50 c/mL.

<table>
<thead>
<tr>
<th></th>
<th>HIV RNA ≥50 c/mL</th>
<th>HIV RNA &lt;50 c/mL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: female</td>
<td>88.0%</td>
<td>32.1%</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean age years</td>
<td>57.2</td>
<td>48.0</td>
<td>0.06</td>
</tr>
<tr>
<td>MUM</td>
<td>25%</td>
<td>43.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-French</td>
<td>41.4%</td>
<td>29.0%</td>
<td>0.0004</td>
</tr>
<tr>
<td>CDC Stage</td>
<td>41.4%</td>
<td>20.2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Zenith HIV</td>
<td>73.1%</td>
<td>18.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nadir CD4</td>
<td>63.9%</td>
<td>43.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Last CD4</td>
<td>22.3%</td>
<td>8.9%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
FOUR-CLASS RESISTANCE IS RARE IN TREATMENT-EXPERIENCED PATIENTS ACROSS EUROPE

Jurgen Vercauteren, Anne-Mieke Vandamme, Barbara Rossetti, Massimiliano Fabiani, Francesca Incardona, Kristof Thys, Ana Abecasis, Carole Devaux, Rolf Kaiser, Anders Sönnerborg, Maurizio Zazzi, for the EuReisit Network Study Group

1Rega Institute for Medical Research, Leuven, Belgium, 2Hatholieke University Leuven, Leuven, Belgium, 3Siena University Hospital, Siena, Italy, 4EuReisit Network, Rome, Italy, 5Instituto de Higiene e Medicina Tropical Universidade NOVA de Lisboa, Lisbon, Portugal, 6Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg, 7University of Cologne, Cologne, Germany, 8Karolinska Institute, Stockholm, Sweden, 9University of Siena, Siena, Italy

Background: While most HIV-1 patients starting antiretroviral therapy (ART) in recent years achieve and maintain undetectable viral load, patients with a long ART history and failure of multiple therapy lines may have accumulated substantial drug resistance, challenging the possibility for virus control both at individual and population level. However, the prevalence of patients harboring virus with resistance to the four main drug classes (4CR) is largely unknown.

Methods: From the EuReisit database, we selected treated patients with protease, reverse transcriptase and integrase genotype information available at one or more time points. HIV-1 sequences were interpreted by the Stanford HIVdb 8.8 algorithm and cumulative scores were generated at each sequencing time point. 4CR was defined as high-level resistance to at least one drug in each of the four classes. The frequency of 4CR at each calendar year was estimated as the number of unique patients with 4CR divided by the number of unique patients with at least one sample, up to that year.

Results: Complete four classes HIV-1 genotype information was available from 2,643 distinct patients on ART contributing 3,544 genotype data from Italy (49%), Germany (24%), Portugal (8%), Luxembourg (7%), Sweden (7%) and Belgium (2%). 66% were male and risk groups included 45.3% MSM, 36% IDU, 49.9%, Germany (24.7%), Portugal (8.1%), Luxembourg (7.5%), Sweden (7.0%) and Belgium (2.7%). Overall, 65 patients (2.5%) had 4CR. The prevalence of 4CR declined from 2011 to 2012. Among 25 pts, 20 (80%) were male, median age 50 years (44-53), time since HIV-1 diagnosis 23 years (19-26), time on ART 20 years (16-23), 14 (56%) with a previous AIDS diagnosis, 17 (68%) with maraviroc (MVC) exposure, a median CD4+ count 207 cells/µl (73-326) and a median viral load 4.58 log10 copies/ml (4.02-5.11) with 2 pts with HIV RNA<40 copies/ml. 4CR-tropic virus was observed in 36%, 36% according to Sanger, NGS and the phenotypic assay; the overall concordance among the three methods was 65% while pairwise agreement ranged from 76% (NGS vs phenotypic assay) to 86% (Sanger vs phenotypic assay). All 9 viruses with 4CR-tropic phenotype were susceptible in vitro to PRO 140, with median IC50 0.4 (0.3-0.7) nM, comparable to the IC50 of the reference wild-type CCR5-tropic AD8 virus (mean IC50 0.7±0.4 nM). There was a variation between MVC naïve (n=3; median IC50=0.7, IQR=0.50-1.2 nM) and MVC-exposed (n=6; median IC50=0.35, IQR=0.30-0.40 nM) pts (p=0.087 [Wilcoxon rank-sum test]) (Table 1). Current exposure to MVC was not associated with different PRO 140 activity (p=0.376).

Conclusion: In this group of HTE pts with MDR virus, all 4CR-tropic strains were fully susceptible to PRO 140 and they were not significantly impacted by MVC exposure. PRO 140 can thus play a key role in subjects with very limited therapeutic options and CCR5-tropic virus.

524 PRO 140 IN VITRO ACTIVITY IN HTE SUBJECTS WITH A 4-CLASS DRUG-RESISTANT HIV-1 VIRUS

Stefano Rusconi, Francesco Saladini, Silvia Barbalsicca, Andrea Poli, Laura Galli, Roberta Gagliardini, Lidia Gazzola, Daniela Francisci, Francesca Vichi, Emanuele Focà, Maurizio Zazzi, Maria M. Santoro, Arianna Gabrieli, Antonella Castagna, for the PRESTIGIO Registry Study Group

1University of Milan, Milan, Italy, 2University of Siena, Siena, Italy, 3University of Rome Tor Vergata, Rome, Italy, 4San Raffaele Vita-Salute University, Milan, Italy, 5Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, 6Azienda Ospedaliera San Paolo, Milan, Italy, University of Perugia, Perugia, Italy, Santa Maria Annunziata Hospital, Florence, Italy, 7University of Brescia, Brescia, Italy

Background: PRO 140 is a novel humanized form of a mouse immunoglobulin G4 CCR5-directed monoclonal antibody with nanomolar potency in inhibiting HIV-1 cell entry through the CCR5 coreceptor. The aim of this study was to analyze HIV-1 tropism and in vitro susceptibility to PRO 140 according to MVC exposure in a cohort of heavily treatment-experienced (HTE) HIV-1-infected patients (pts) harboring a documented 4-class drug-resistance to NRTIs, NNRTIs, PIs, INSTIs, enrolled in the Italian PRESTIGIO Registry.

Methods: Plasma RNA (viremic pts) or PBMC DNA (non-viremic pts) was used for Sanger sequencing and Next Generation Sequencing (NGS, illumina platform) of the gpi120-V3 region followed by geno2pheno [coreceptor] interpretation. Viral tropism and susceptibility to PRO 140 were assessed through a home-made phenotypic assay based on pseudotyped viruses expressing patient derived Env protein and luciferase as reporter gene. Pts demographics and laboratory data are described as median (Q1-Q3), mean (±SD) or frequency (%).

Results: Among 25 pts, 20 (80%) were male, median age 50 years (44-53), time since HIV-1 diagnosis 23 years (19-26), time on ART 20 years (16-23), 14 (56%) with a previous AIDS diagnosis, 17 (68%) with maraviroc (MVC) exposure, a median CD4+ count 207 cells/µl (73-326) and a median viral load 4.58 log10 copies/ml (4.02-5.11), with 2 pts with HIV RNA<40 copies/ml. 4CR-tropic virus was observed in 36%, 36% according to Sanger, NGS and the phenotypic assay; the overall concordance among the three methods was 65% while pairwise agreement ranged from 76% (NGS vs phenotypic assay) to 86% (Sanger vs phenotypic assay). All 9 viruses with 4CR-tropic phenotype were susceptible in vitro to PRO 140, with median IC50 0.4 (0.3-0.7) nM, comparable to the IC50 of the reference wild-type CCR5-tropic AD8 virus (mean IC50 0.7±0.4 nM). There was a variation between MVC naïve (n=3; median IC50=0.7, IQR=0.50-1.2 nM) and MVC-exposed (n=6; median IC50=0.35, IQR=0.30-0.40 nM) pts (p=0.087 [Wilcoxon rank-sum test]) (Table 1). Current exposure to MVC was not associated with different PRO 140 activity (p=0.376).

Conclusion: In this group of HTE pts with MDR virus, all 4CR-tropic strains were fully susceptible to PRO 140 and they were not significantly impacted by MVC exposure. PRO 140 can thus play a key role in subjects with very limited therapeutic options and CCR5-tropic virus.

Table 1. Tropism analysis according to different clinical markers and IC50 PRO 140 in the Spanish from the PRESTIGIO Registry Study Group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median IC50 (nM)</th>
<th>IQR (nM)</th>
<th>P-value</th>
<th>Trends</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>0.4</td>
<td>0.3-0.7</td>
<td>0.002</td>
<td>Significant</td>
</tr>
<tr>
<td>MVC naïve</td>
<td>0.7</td>
<td>0.5-0.9</td>
<td>0.036</td>
<td>Significant</td>
</tr>
<tr>
<td>MVC-exposed</td>
<td>0.35</td>
<td>0.30-0.40</td>
<td>0.046</td>
<td>Significant</td>
</tr>
</tbody>
</table>

525 SUSCEPTIBILITY TO BNABS OF TRANSMITTED HIV VARIANTS AMONG RECENT INFECTIONS IN FRANCE

Karl Stefic, Melanie Bouvin-Pley, Asma Essat, Clara Visseloup, Alain Moreau, Cécile Goujard, Marie-Laure Chaux Baudier, Martine Brabant, Laurence Meyer, Francis Barin, for the ANRS PRIMO Cohort Study Group

1INSERM, Tours, France, 2Hôpital Bicêtre, Le Kremlin-Bicêtre, France, 3Hôpital Saint-Louis, Paris, France

Background: Pre-existing resistance to broadly neutralizing antibodies (bnAbs) restrains their use for prevention and treatment of HIV infection. In addition, an increasing resistance of HIV to neutralization over time has been observed arguing for a prospective monitoring of the sensitivity to bnAbs of all prevalent HIV subtypes. Here, we analyzed the susceptibility to bnAbs of HIV transmitted variants among recently infected individuals in France with a focus on evolution over time.

Methods: We assessed the sensitivity to seven bnAbs against a panel of 73 early-transmitted subtype B and CRF02_AG viruses (the most prevalent subtypes in Europe) over a 25-year period of the French epidemic (1987-2012). Samples were obtained during acute/recent infection from individuals
526 INVESTIGATION OF INTEGRASE-INHIBITOR RESISTANCE MUTATIONS IN gp41 IN CLINICAL SAMPLES
Hanwei Sudderuddin1, Anh Le1, Tetyana Kalyaynik1, Rob Hollebakken2, Kyle Cobarrubias1, Jinny Choi1, Weiyan Dong1, Winnie W. Dong1, Walter Scott1, Kate Laird1, Paul Sereda2, Eric O. Freed1, Zabrina Brumme1, Chanson J. Brumme1
1British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, 2Vaccine Research Center, NIAID, Bethesda, MD, USA

Background: In vitro studies have suggested that resistance to HIV Integrase strand transfer inhibitors (INSTI) can occur outside the integrase gene, including in env, but it remains unclear whether such mutations arise in vivo. Using a large database of clinically-derived HIV-1 sequences, we sought to identify mutations in env, but it remains unclear whether such mutations arise in vivo. Using a large database of clinically-derived HIV-1 sequences, we sought to identify mutations in env, but it remains unclear whether such mutations arise in vivo. Using a large database of clinically-derived HIV-1 sequences, we sought to identify mutations in env, but it remains unclear whether such mutations arise in vivo. Using a large database of clinically-derived HIV-1 sequences, we sought to identify mutations in env, but it remains unclear whether such mutations arise in vivo.

Methods: We identified 146 consenting participants of the BC-CFE Drug Treatment Program (DTP), infected with HIV-1 subtype B, whose physicians had ordered a genotypic INSTI resistance test following ≥3 months of INSTI exposure and whose genotype was susceptible to all INSTI (HIVdb v8.8 score <15). We ordered a genotypic INSTI resistance test following ≥3 months of INSTI exposure.

Results: Participants’ median CD4 count was 506 cells/mm³, median viral load was 5.1 log₁₀ copies/mL and the estimated time from infection was 41 days. bNAbs targeting the CD4 and 108E were the most potent and broadly neutralizing. VRC01 neutralized 92.5% of all variants at the target concentration of 10 µg/mL. 3BNC117 IC₅₀ were the lowest of all bNAbs (respectively 0.01 et 0.25 µg/mL for B and CRF02_AG variants; Mann-Whitney P<0.05). CRF02_AG were more resistant than B viruses regarding bNAbs targeting V3 (64-67% of the strains neutralized at 10 µg/mL vs 78-88%, respectively). This resistance was associated with the absence of the glycosylation site N332 (p<0.01). Both subtypes were more resistant to bNAbs targeting V2 (55-65% of the strains neutralized at 10 µg/mL). Finally, we observed an increased resistance to several bNAbs over the course of the epidemic – especially those targeting the CD4bs – which correlated with the continuous diversification of Env sequences over time (Spearman P<0.05).

Conclusion: Of the bNAbs in clinical development tested here, none neutralized 100% of T/F variants, indicating that combinations will be required to achieve a full coverage for prevention and treatment. As in other countries, we confirmed the natural drift of resistance to INSTIs for both subtypes spreading in France, arguing for a continuous surveillance of HIV transmitted variants around the globe.

527 MAPPING RESISTANCE OF POTENT HIV-1 ENTRY INHIBITORS TARGETING PREFUSION CONFORMATION
Yen-Ting Lai1, Megan Demouth2, Adam Dingens3, Amarendra Pegra1, Jesse Bloom2, John R. Mascola1, Peter D. Kwong3
1Vaccine Research Center, NIAID, Bethesda, MD, USA, 2Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: The entry of HIV-1 into target cells is a critical event in the viral life cycle and an attractive target for drug development. The HIV-1 envelope protein (Env), comprised of the gp120 subunits and three gp41 subunits, binds to cell-surface receptors before triggering the fusion of viral and host cell membranes. Entry inhibitors targeting the gp41 (Enfuvirtide) or co-receptor CCR5 (Maraviroc) have been approved by FDA for HIV-1 treatment. To date, no entry inhibitors targeting the gp120 have been FDA-approved although a promising small-molecule lead, fostemsavir (the produg of active compound BMS-626529), is currently in phase III clinical trials. We previously reported the crystal structure of BMS-626529 in complex with HIV-1 Env trimers, revealing its molecular basis of entry inhibition. This drug binds to a conserved pocket beneath the 620-621 hairpin between the inner and outer domains of gp120, suggesting that drug binding blocks the conformational changes required for viral fusion to occur. We also identified BMS-812851, a derivative of BMS-626529, which is >10-fold more potent in pseudovirus neutralization assays. Crystal structure of BMS-812851 revealed interactions between a tail functional group and the Env that likely contributed to the higher neutralization potency.

Methods: We characterized the viral suppression efficacy of BMS-812851 in ex vivo cell cultures that were derived from HIV+ patients. In addition, we used a site-saturated mutational library of BG505 Env to map the potential resistance mutations of BMS-812851 and BMS-626529.

Results: BMS-812851 exhibited superior viral suppression than BMS-626529 in HIV-1+ CD4-1-cell culture from two patients. The minimal inhibition concentration of BMS-812851 was >10-fold lower than BMS-626529, consistent with our previous observation in pseudovirus neutralization assays. In addition, we observed viral rebound in the cell culture of one patient treated with the highest concentration of BMS-626529 tested, suggesting selection of pre-existing resistance mutations. Viral rebound was not observed for BMS-812851 in the two samples tested. Mapping of resistance mutations by the BG505 mutational library revealed distinct resistance profiles by BMS-812851 and BMS-626529, suggesting different level of selection pressure between these two compounds.

Conclusion: Our data support further development of BMS-812851, which represents a novel class of HIV-1 drugs targeting gp120, as a next-generation entry inhibitor.

528 META-ANALYSIS OF UNUSUAL AND APOBEC MUTATIONS IN HIV-1 POL NEXT-GENERATION SEQUENCES
Philip L. Tzou1, Santiago Avila-Rios2, Susan Holmes1, Rami Kantor3, Sergei L. Kosakovsky Pond4
1Stanford University, Stanford, CA, USA, 2National Institute of Respiratory Diseases, Mexico City, Mexico, 3Brown University, Providence, RI, USA, 4Temple University, Philadelphia, PA, USA

Background: In the ANRS PRIMO cohort. Env pseudoviruses were constructed and neutralization assays on TZM-bl cells were performed using bNAbs targeting the CD4-binding site (CD4bs; VRC01, 3BNC117), the V1/V2 glycan region (PG9, PGT145), the V3-glycan region (PGT121, 10-1074), and the gp41 membrane proximal external region (MPER, 10E8).

Methods: Participants’ median CD4 count was 506 cells/mm³, median viral load was 5.1 log₁₀ copies/mL and the estimated time from infection was 41 days. bNAbs targeting the CD4bs and 108E were the most potent and broadly neutralizing. VRC01 neutralized 92.5% of all variants at the target concentration of 10 µg/mL. 3BNC117 IC₅₀ were the lowest of all bNAbs (respectively 0.01 et 0.25 µg/mL for B and CRF02_AG variants; Mann-Whitney P<0.05). CRF02_AG were more resistant than B viruses regarding bNAbs targeting V3 (64-67% of the strains neutralized at 10 µg/mL vs 78-88%, respectively). This resistance was associated with the absence of the glycosylation site N332 (p<0.01). Both subtypes were more resistant to bNAbs targeting V2 (55-65% of the strains neutralized at 10 µg/mL). Finally, we observed an increased resistance to several bNAbs over the course of the epidemic – especially those targeting the CD4bs – which correlated with the continuous diversification of Env sequences over time (Spearman P<0.05).

Conclusion: Of the bNAbs in clinical development tested here, none neutralized 100% of T/F variants, indicating that combinations will be required to achieve a full coverage for prevention and treatment. As in other countries, we confirmed the natural drift of resistance to INSTIs for both subtypes spreading in France, arguing for a continuous surveillance of HIV transmitted variants around the globe.
and strong antiviral effect, with a > 1.8 mean log10 decrease in HIV-1 RNA at
agent with dosing every 3 months or longer. In the clinic, a single SC injection
capsid function with the potential to be used as a subcutaneous (SC) long-acting
naïve or experienced PLWH were evaluated using a standard 5-day antiviral
by site-directed mutagenesis or by cloning of plasma samples. Infectious clones
Methods:
Results: Eight studies containing 855 samples from 821 persons in the NCBI
sequence read archive were analyzed. As the NGS threshold was lowered, there
was a progressive increase in the proportion of positions with both usual and
unusual mutations and a progressive increase in the proportion of mutations
that were unusual (Figure). The median proportion of positions with an unusual
mutation increased from 0% to 0.3% between the 20% and 1% thresholds and
then increased to 1.3% at the 0.5% threshold, 6.9% at the 0.2% threshold, and
23.2% at the 0.1% threshold. In 2 of 3 studies reporting plasma HIV-1 RNA levels,
the proportion of positions with unusual mutations was inversely associated
with virus levels. Although the complete set of signature APOBEC mutations
(n=296) was much smaller than the complete set of unusual mutations
(dubbed as having prevalence of <0.01% in HIV-1 group M population Sanger
sequences) or signature APOBEC mutations.
Conclusion: The marked increase in the proportion of unusual mutations at
thresholds below 1% and in samples with lower virus loads suggest that many
detected unusual mutations may derive from PCR error. However, in some
samples, APOBEC-mediated G-to-A hypermutation may be a greater contributor
to sequence artifacts than PCR error. Post hoc analyses of NGS data that quantify
the numbers of unusual and signature APOBEC mutations at different NGS
thresholds may be useful to avoid selecting a threshold that is too low and that
poses an unacceptable risk of identifying artifactual mutations.

529 ABSENCE OF GS-6207 PHENOTYPIC RESISTANCE IN HIV GAG CLEAVAGE SITE
AND OTHER MUTANTS
Nicolas A. Margot1, Renee R. Ram1, Martin Rhee1, Christian Callebaut1
1Gilead Sciences, Inc, Foster City, CA, USA
Background: GS-6207 is a potent, first in class, multistage inhibitor of HIV-1
capsid function with the potential to be used as a subcutaneous (SC) long-acting
agent with dosing every 3 months or longer. In the clinic, a single SC injection
of GS-6207 (50 mg to 450 mg) in people living with HIV (PLWH) showed a rapid
and strong antiviral effect, with a >1.8 mean log10 decrease in HIV-1 RNA at
day 10. Mutations in HIV-1 gag near protease (PR) cleavage sites have emerged
with the use of protease inhibitors (PIs), resulting in increased fitness and/or
PI-resistance. Here we have characterized the activity of GS-6207 in mutants
with HIV-1 gag cleavage site mutations, as well as mutants with resistance to
other drug classes.
Methods: HIV mutations were inserted into the pXXLAI infectious clone either
by site-directed mutagenesis or by cloning of plasma samples. Infectious clones
with HIV gag cleavage site mutations, or HIV gag-PR fragments from treatment-
naive or experienced PLWH were evaluated using a standard 5-day antiviral
assay (MT-2 cells). Isolates with resistance mutations against the 4 major drug
classes (NRTI, NNRTI, PI, INSTI) were tested phenotypically using a single-cycle
assay (Monogram Biosciences).
Results: In all, 19 HIV gag cleavage site mutants (single and double mutants
with L363F/M, A364V, Q430R, A431V, K436E, H374T/V, L44NF/Y/F, P435L, and/or
PR mutations V82A and I84V) as well as 55 patient derived clones were
analyzed phenotypically. GS-6207 EC50 fold-change compared to wild-type
(WT) ranged from 0.3 to 2.1 in these mutants, similar to the control drug. In
contrast, high levels of reduced susceptibility to PIs (>500 fold) and mutation
inhibitors (MIs) (>70 fold) were noted in some mutants. Testing of isolates with
resistance mutations against the 4 main classes of drugs (n=40) indicated WT
susceptibility to GS-6207 (fold-change ranging from 0.3 to 1.1), while highly
reduced susceptibility was observed for control drugs of each class.
Conclusion: HIV gag cleavage site mutations did not impact the activity of
GS-6207, while some conferred resistance to MIs and PIs. Similarly, GS-6207
activity was not affected by naturally occurring variations in HIV gag, in contrast
to the loss of activity observed for MIs in nearly half of the mutants. Finally,
the activity of GS-6207 was not affected by the presence of resistance mutations
to the 4 main ARV classes. These data support the evaluation of GS-6207 in PLWH
with multi-class resistance.
530 SUSCEPTIBILITY OF NRTI-RESISTANT HIV-2 ISOLATES TO A NEW NRTI,
GS-9131
Quentin Le Heritier1, Gilles Collin1, Samuel Lebougeois1, Benoit Vissers1,
Florencie Damond1, Jade Ghoss1, Antoine Bachelard1, Valentine Ferré1, Sophie
Matheron1, Charlotte Charpentier1, Diane Descamps1, for the ANRS CO5 HIV-2
Background: Management of HIV-2 infection is hampered by the limited
number of active ARV drugs and the rapid acquisition of drug resistance-
associated mutations (DRAMs). There is still a strong need for new ARV
effective on HIV-2, especially for patients infected by multi-drug resistant
viruses. GS-9131 is the prodrug of GS-9148, a new NRTI with low potential for
mitochondrial toxicity and renal accumulation that previously demonstrated its
in vitro efficacy against wild-type (WT) and NRTI-mutant HIV-1 isolates, except
those harbouring the Q151M complex. Here, we report GS-9131 antiviral activity
on HIV-2 clinical isolates.
Methods: Phenotypic susceptibility to GS-9131 was assessed for 13 HIV-2
isolates, and references strains of HIV-1 (BRU) and HIV-2 (ROD), using the
XRS assay. Briefly, viruses were cultured without GS-9131 and with 6 dilutions of
the drug, ranging from 6250 to 0.002 nM. At days 3 or 4, viral replication was
assessed by RT-PCR on the supernatant. All but one of the 13 HIV-2 isolates
were assayed for GS-9131 activity and the presence of drug resistance-
associated mutations (DRAMs). There is still a strong need for new ARV
effective on HIV-2, especially for patients infected by multi-drug resistant
viruses. GS-9131 is the prodrug of GS-9148, a new NRTI with low potential for
mitochondrial toxicity and renal accumulation that previously demonstrated its
in vitro efficacy against wild-type (WT) and NRTI-mutant HIV-1 isolates, except
those harbouring the Q151M complex. Here, we report GS-9131 antiviral activity
on HIV-2 clinical isolates.
Results: GS-9131 exhibited a potent activity against WT HIV-2 isolates (IC50 =
3.4 and 4.4 nM). The sole presence of K65R mutation or M184V mutation
increased the IC50 for GS-9131 (12.0 and 27.0 nM for K65R, and 16.6 nM for
M184V). GS-9131 had a lower activity on 2 isolates displaying a combination of 2
DRAMs (K65R+M184V and S215Y, IC50 = 108 and 134 nM, respectively). All
isolates harbouring a Q151M mutation were highly resistant to GS-9131 (with
IC50 ranging from 378 to >6250 nM), regardless of associated-NRTI mutations.
Conclusion: GS-9131 exhibits potent in vitro activity against WT HIV-2 isolates.
Regarding the 3 main resistance genotypic profiles described in HIV-2-infected
patients failing NRTI-based regimens (K65R, Q151M and M184V), our data
displays that isolates harbouring K65R or M184V mutations presented
moderate increases in IC50, while the presence of a Q151M mutation
rendered HIV-2 isolates highly resistant to GS-9131. These in vitro data suggest
that GS-9131 might offer an attractive, new therapeutic opportunity for persons
living with HIV-2, either at initiation of antiretroviral therapy or for second-line
regimens, as it retained potential for some activity against K65R and M184V
mutants.
531 PHENOTYPIC DORAVIRINE SUSCEPTIBILITY AFTER NNRTI EXPOSURE IN THE PRESTIGIO REGISTRY

Francesco Saladdini1, Federica Giammarino2, Franco Maggiolo3, Nicolò Ferrara4, Giovanni Cenderello5, Benedetto Maurizio Celesia6, Ferdinando Martellotta7, Vincenzo Spagnuolo8, Giulio Maria Corbelli9, Nicola Gianotti10, Maria M. Santoro11, Stefano Rusconi12, Maurizio Zazzi13, Antonella Castagna14, for the PRESTIGIO STUDY GROUP
1University of Siena, Siena, Italy, 2Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy, 3Amedeo di Savoia Hospital, Turin, Italy, 4Galliera Hospital, Genoa, Italy, 5Garthald Hospital, Catania, Italy, 6Centro di Riferimento Oncologico di Aviano, Aviano, Italy, 7San Raffaele Vita-Salute University, Milan, Italy, 8San Raffaele Scientific Institute, Milan, Italy, 9University of Rome Tor Vergata, Rome, Italy, 10Luigi Sacco University Hospital, Milan, Italy.

Background: Doravirine (DOR) is an NNRTI recently licensed for first-line ART showing superior genetic barrier to resistance and partial cross-resistance with older NNRTIs. We investigated susceptibility to DOR in patients with documented 4-class drug-resistance to NNRTI, NNRTI, PI INSTI (4CR), enrolled in the Italian PRESTIGIO Registry.

Methods: Recombinant HIV-1 expressing patient derived PR-RT were generated from plasma samples from 20-40 patients failing ART. In vitro susceptibility to DOR was assessed through a TZM-bl cell based phenotypic assay measuring fold-change (FC) values with respect to the NL4-3 virus. Patient demographics and laboratory data were described by median (Q1-Q3) or frequency (%). Statistical analysis included Mann-Whitney and Spearman correlation tests.

Results: Overall, 18 (90%) patients were male, median age 51 years (43-53), time since HIV-1 diagnosis 22 years (18-26), time on ART 19 years (16-22). 11 (55%) with a previous AIDS diagnosis, median viral load (VL) 4.42 log10 copies/ml (3.36-5.15) and median CD4+ cell count 195 cells/µL (75-278). 11 patients (55%) were receiving NNRTI (ER=10, RPV=1), while 7 (35%), 5 (25%), 8 (40%) patients had been exposed to 1, 2 and 3 NNRTI, respectively, with a median time of exposure to NNRTI of 1529 days (353-2169). Globally, median DOR FC was 9.8 (1.8-65.7), while FC were 17.9 (7.4-80.1) and 3.7 (0.7-53.5) in patients with and without current NNRTI pressure, respectively. According to Stanford HIVdb algorithm, intermediate to high-level resistance to DOR was predicted in 13/20 (65%) cases. DOR FC values correlated with the number of NNRTI mutations (r = 0.548; p = 0.010) and with the DOR resistance level by HIVdb algorithm (r = 0.754; p = 0.001) but not with the number of previously experienced NNRTI (r = -0.167; p = 0.483). VL (r = -0.121; p = 0.612) was a time of exposure to NNRTI.

Conclusion: DOR activity decreases with increasing number of NNRTI mutations and is inferred with fair accuracy by HIVdb and the IAS list, independently from the extent and time of NNRTI exposure.

532 HIV A1 OR B DO NOT DIFFERENTIALLY IMPACT CABOTEGRAVIR IN VITRO POTENCY OR DURABILITY

Jerry Jeffrey1, Marty St Clair1, Ping Wang2, Chunfu Wang3, Zhufang Li4, Jerry Jeffrey5, Peter W. Hunt5, Jeffrey Martin5, David R. Bangsberg6, Mark J. Siedner2, P. Richard Harrigan1, Jessica E. Haberer1
1Weill Cornell Medicine, New York, NY, USA, 2Massachusetts General Hospital, Boston, MA, USA, 3Mbarara University of Science and Technology, Mbarara, Uganda, 4Simon Fraser University, Burnaby, BC, Canada, 5University of California San Francisco, San Francisco, CA, USA, 6Oregon Health and Sciences University, Portland, OR, USA, 7University of British Columbia, Vancouver, BC, Canada

Background: The Phase 3 FLAIR study evaluates monthly i.m. Long Acting (LA) cabotegravir (CAB) and rilpivirine (RPV) as maintenance therapy in suppressed HIV infected adults over 48 weeks and demonstrated non-inferiority to 3 drug daily oral ART. A total of 3/283 (1%) participants (PTS) who received CAB+RPV had confirmed virologic failure (CVF). All 3 CVFs occurred among 8 B PTS in that study arm with subtype A1 virus and all 3 had baseline integrase (IN) substitution L74I, as did 2/3 PTS who maintained viral suppression. All 8 PTS with subtype A1 virus were sensitive to CAB at baseline. 174/283 (61%) PTS in the LA arm had subtype B, 7% with L74I without CVF. Given the apparent clustering of CVF among A1 and presence of L74I, we sought to determine the impact of L74I and subtype A1 compared to subtype B IN on CAB sensitivity.

Methods: In genotypes and phenotypic sensitivity to CAB were generated at Monogram Biosciences. Site directed mutants were generated in subtype B NL4-3 and a consensus A IN sequence derived from the 3 CVF baseline IN sequences. In vitro susceptibility to CAB was assayed and compared across virus subtypes. The in vitro durability of CAB was tested against bulk infected cultures at various CAB concentrations for 3 weeks.

Results: All baseline, A1 IN sequences (B/283 subjects) were sensitive to CAB with IC50 fold-change (FC) ranging from 0.7-1. The 3 CVF sequences at the failure timepoint had CAB IC50 values of 5.22 – 9.36 and substitutions at L74I and G140R or Q148R. The site-directed mutants L74I/G140R (FC 0.87 A1 vs 0.58 B) or L74I/Q148H (FC 4.1 A1 vs 4.4 B) in A1 background resulted in similar IC50 FC compared to subtype B background. Across both subtypes, time to viral breakthrough was similar at the lowest CAB concentration (1µM) and no viral breakthrough was detected at 3 weeks for CAB concentrations of 5nM or 40nM (1µM). The genotypes of the breakthrough viruses will be presented.

Conclusion: The FLAIR study demonstrated CAB + RPV LA was noninferior to oral ART at Week 48 with 3 CVFs harboring HIV subtype A1 with baseline L74I. In vitro virologic assessments do not indicate a differential sensitivity to CAB between subtypes A1 or B in viruses containing IN mutations observed in the CVFs. However, our evaluations cannot determine if HIV subtype A1 with L74I has greater likelihood of selection of additional INSTI mutations under selection pressure. Other factors may contribute to the risk of CVF and require further investigation.

533 HLA GENOTYPE IS ASSOCIATED WITH PRETHERAPY ACCESSORY INSTI RESISTANCE MUTATION L74I

Guinevere Q. Lee1, Suzanne McCluskey2, Nicholas Musinguzi3, Zabrina Brumm1, Yap Boum2, Bosco M. Bwana1, Conrad Muzoora3, Simone Kigozi1, Peter W. Hunt1, Jeffrey Martin2, David R. Bangsberg1, Mark J. Siedner2, P. Richard Harrigan1, Jessica E. Haberer1, Kenneth Bryant1, Robert S. DeGruttola1, Ronald L. DeGruttola1, Mark S. Lathrop1, David A. Margolis1, Kim Smith1, William Spreen1, Pierre P. Eger2,4,5,6,7,8,9,10,11,12,13, for the PRESTIGIO STUDY GROUP
1ViiV Healthcare, Research Triangle Park, NC, USA, 2ViiV Healthcare, Branford, CT, USA, 3ViiV Healthcare, London, UK

Background: The Phase 3 FLAIR study evaluates monthly i.m. Long Acting (LA) cabotegravir (CAB) and rilpivirine (RPV) as maintenance therapy in suppressed HIV infected adults over 48 weeks and demonstrated non-inferiority to 3 drug daily oral ART. A total of 3/283 (1%) participants (PTS) who received CAB+RPV LA had confirmed virologic failure (CVF). All 3 CVFs occurred among 8 B PTS in that study arm with subtype A1 virus and all 3 had baseline integrase (IN) substitution L74I, as did 2/3 PTS who maintained viral suppression. All 8 PTS with subtype A1 virus were sensitive to CAB at baseline. 174/283 (61%) PTS in the LA arm had subtype B, 7% with L74I without CVF. Given the apparent clustering of CVF among A1 and presence of L74I, we sought to determine the impact of L74I and subtype A1 compared to subtype B IN on CAB sensitivity.

Methods: In genotypes and phenotypic sensitivity to CAB were generated at Monogram Biosciences. Site directed mutants were generated in subtype B NL4-3 and a consensus A IN sequence derived from the 3 CVF baseline IN sequences. In vitro susceptibility to CAB was assayed and compared across virus subtypes. The in vitro durability of CAB was tested against bulk infected cultures at various CAB concentrations for 3 weeks.

Results: All baseline, A1 IN sequences (B/283 subjects) were sensitive to CAB with IC50 fold-change (FC) ranging from 0.7-1. The 3 CVF sequences at the failure timepoint had CAB IC50 values of 5.22 – 9.36 and substitutions at L74I and G140R or Q148R. The site-directed mutants L74I/G140R (FC 0.87 A1 vs 0.58 B) or L74I/Q148H (FC 4.1 A1 vs 4.4 B) in A1 background resulted in similar IC50 FC compared to subtype B background. Across both subtypes, time to viral breakthrough was similar at the lowest CAB concentration (1µM) and no viral breakthrough was detected at 3 weeks for CAB concentrations of 5nM or 40nM (1µM). The genotypes of the breakthrough viruses will be presented.

Conclusion: The FLAIR study demonstrated CAB + RPV LA was noninferior to oral ART at Week 48 with 3 CVFs harboring HIV subtype A1 with baseline L74I. In vitro virologic assessments do not indicate a differential sensitivity to CAB between subtypes A1 or B in viruses containing IN mutations observed in the CVFs. However, our evaluations cannot determine if HIV subtype A1 with L74I has greater likelihood of selection of additional INSTI mutations under selection pressure. Other factors may contribute to the risk of CVF and require further investigation.
of individuals. None of these polymorphisms, when present alone, were associated with reduced INSTI susceptibility according to Stanford HIVdb. Multivariate logistic regression analyses revealed associations between A*02, B*4415 and Cw*0407 with L74I (p=0.03, 0.01, 0.007, Fig 1) after adjusting for gender, age, subtype, and interactions between subtype and HLA-genotypes. Cohort prevalence of A*02, B*4415 and Cw*0407 were 37%, 10% and 9%, respectively. Sequences containing L74I did not cluster into a monophyletic group in phylogenetic analyses.

Conclusion: Our data suggest that certain polymorphisms associated with INSTI resistance in specific viral subtypes may be HLA-driven. L74I have not been previously associated with HLA-escape in any viral subtype, suggesting the epitope responsible is not immuno-dominant. Lack of phylogenetic clustering suggests results are not attributable to viral founder effects. Effects of L74I on INSTI-based therapy, its link to HLA-genotypes, and whether it lowers genetic barrier to INSTI require additional large-scale population-level validation.

Methods: Site directed mutagenesis generated pNL4-3 plasmid constructs harbouring Wild Type (WT), R263K, G118R, and G140S/Q148H integrase.

Background: In this study, we were interested in reproducing these observations on two newly developed integrase strand transfer inhibitors (INSTIs), Bictegravir (BIC) and Cabotegravir (CAB).

CABOTEGRAVIR WASHOUT

Overall, we observed an extended duration of viral suppression of wild-type (WT) and integrase-resistant HIV-1 by dolutegravir (DTG) as compared to Raltegravir (RAL) or Elvitegravir (EVG) following release of drug pressure. In this study, we were interested in reproducing these observations on two newly developed integrase strand transfer inhibitors (INSTIs), Bictegravir (BIC) and Cabotegravir (CAB).

Figure 1. HIV-1 integrase mutation L74I is associated with specific HLA-genotypes (subtype A1).

534 HIV-1 VIRAL REBOUND AFTER BICTEGRAVIR, DOLUTEGRAVIR, AND CABOTEGRAVIR WASHEROUT

Ernesto Cuadra Foy1, Nathan Osman2, Ruxandra-Liliana Ibanescu1, Maureen Oliveira2, Bluma G. Brenner1

1McGill University, Montreal, QC, Canada, 2Lady Davis Institute for Medical Research, Montreal, QC, Canada

Background: In past studies, we performed in vitro washout experiments to show a more durable suppression of wild-type (WT) and integrase-resistant HIV-1 by dolutegravir (DTG) as compared to Raltegravir (RAL) or Elvitegravir (EVG) following release of drug pressure. In this study, we were interested in reproducing these observations in two newly developed integrase strand transfer inhibitors (INSTIs), Bictegravir (BIC) and Cabotegravir (CAB).

Methods: Site directed mutagenesis generated pNL4-3 plasmid constructs harbouring Wild Type (WT), R263K, G118R, and G140S/Q148H integrase. MT-2 cells were infected with WT or resistant clones to establish IC50 and IC90 concentrations. MT-2 cells were then subjected to maximal drug pressure, using 20 times the IC50 for each drug. Three days post-exposure, drugs were washed out from the cells. Viral rebound was assessed at days 3, 7 and 11 post-infection.

Results: BIC showed a higher genetic barrier to resistance than DTG and CAB, based on IC50 values. The R263K G118R, G140S/Q148H clones showed 1-, 1.4-, and 3.5-fold resistance to BIC relative to WT, respectively. This compares to 3.5-, 1.7- and 6.6-fold resistance to DTG and 0.8-, 6.4-, and 6.8-fold resistance to CAB against R263K, G118R, and G140S/Q148H clones, respectively. In our washout experiments, WT and R263K were viral suppressed by all three drugs during selective pressure (20 x IC50) and following drug washout (day 11). With G118R infected cells, viral rebound occurred following DTG washout with minimal increase in replication following CAB washout and no rebound following BIC washout. The G140S/Q148H clones were not susceptible to BIC prior to and following drug washout. While DTG could suppress replication t of G140S/Q148H infected cells, viral rebound occurred following washout (day 7). In contrast, BIC successfully suppressed replication through the 11 days of infection, showing minimal rebound after drug removal.

Conclusion: Overall, we observed an extended duration of viral suppression of HIV-1 replication following release of drug pressure with BIC than either DTG or CAB. This included WT virus and viruses harboring mutations conferring low-, moderate and high-fold drug resistance. These findings show BIC may be pharmacologically more forgiving than DTG and CAB.
Background: HIV drug resistance can be an obstacle to successful antiretroviral therapy (ART), but the vast majority of studies on drug resistance have focused on studying blood. Here, we present evidence of drug resistance across multiple tissues in two persons with HIV.

Methods: Last Gift study participant 3 (LG03) was a 72-year-old man with HIV and metastatic pancreatic cancer with no previous history of drug resistance. LG03 was a 57-year-old man with HIV and amyotrophic lateral sclerosis with pre-existing resistance to nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI) identified by the GenoSure Archive NGS-based assay. Both had suppressed HIV RNA in blood plasma collected within 7 hours from death. Tissues were isolated via a rapid autopsy and HIV DNA was extracted from gut (ileum and duodenum), lymph nodes (axillary and aortic), kidney and spleen. 72.3-kb pol single genome amplicons were prepared in a single library and sequenced (Illumina MiSeq). Reads were mapped to HIV HXB2, and consensus sequences generated. Mutations at sites of drug resistance were determined (Stanford HIV Drug Resistance Database) and analyzed for each variant.

Results: Despite no previous diagnosis of ART failure with drug resistance, in tissues LG03 had mutations associated with NRTI resistance and a PI resistance mutation in 1 duodenum, 1 ileum, and 3 spleen SGA variants. Nonpolymorphic mutations associated with PI included M46I, E69K, V82T, I90V, and L90M. These mutations matched those identified in the GenoSure Archive assay.

Conclusion: This study found high rates of resistance associated mutations in proviruses across tissues in persons with HIV who were fully suppressed on ART. The pattern of HIV drug resistance associated mutations across PBMC and tissues was not consistent for either LG03 or LG05 (table 1). These discrepancies were pronounced between PBMC DNA (based on the GenoSure Archive assay) and non-circulating tissues. These findings highlight that HIV drug resistance might be present in various tissue reservoirs without prior diagnosis, and that just sampling in one compartment, like PBMC, is likely to miss the full repertoire of HIV drug resistance that is present.

Table 1: Summary of resistance mutations in tissues in viremic participants of the Last Gift Study

<table>
<thead>
<tr>
<th>Location</th>
<th>Total Clones</th>
<th>Any NRTI</th>
<th>Any NRTI</th>
<th>Any INSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>0</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Bowel</td>
<td>100</td>
<td>10.0%</td>
<td>10.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Kidney</td>
<td>100</td>
<td>10.0%</td>
<td>10.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Lung Node</td>
<td>6</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Lung Node Abry</td>
<td>6</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Duodenum</td>
<td>5</td>
<td>20.0%</td>
<td>20.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Bowel</td>
<td>5</td>
<td>20.0%</td>
<td>20.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Kidney</td>
<td>5</td>
<td>16.7%</td>
<td>16.7%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Lung Node</td>
<td>5</td>
<td>20.0%</td>
<td>20.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Lung Node Abry</td>
<td>5</td>
<td>16.7%</td>
<td>16.7%</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

Note: Frequencies are based on the number of NRTI or INSTI variants.

537 HIV DRUG RESISTANCE IN FEMALE SEX WORKERS FROM THE DOMINICAN REPUBLIC AND TANZANIA

Wendy Greenawalt¹, Jessica M. Fogel¹, William Clarke¹, Autumn Breaud², Jessie Mbambor³, Samuel Likindikoki⁴, Said Aboud⁵, Yeczy Donastorg⁶, Martha Perez⁷, Clare Barrington⁸, Wendy Davis⁹, Mark A. Marzinke¹⁰, Noya Galai¹¹, Deanna Kerrigan¹², Vanessa Cummings¹³, Ethan A. Wilson¹⁴, Christophe Fraser¹⁵, David Bonsall¹⁶, Theresa Gamble¹⁷, Carlos Del Rio¹⁸, D. Scott Batey¹⁹, Kenneth H. Mayer¹², Jason Farley²⁰, James Hughes²¹, Robert H. Remien²², Chris Beyerli²³, Susan H. Eshleman¹, for the HPTN 078 Study Team

¹Johns Hopkins University School of Medicine, Baltimore, MD, USA, ²Fred Hutchinson Cancer Research Center, Seattle, WA, USA, ³University of Oxford, Oxford, UK, ⁴FHI 360, Durham, NC, USA, ⁵Emory University, Atlanta, GA, USA, ⁶University of Alabama at Birmingham, Birmingham, AL, USA, ⁷Harvard Medical School, Boston, MA, USA, ⁸Johns Hopkins University School of Nursing, Baltimore, MD, USA, ⁹University of Washington, Seattle, WA, USA, ¹⁰Columbia University, New York, NY, USA, ¹¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: Female sex workers (FSW) are at high risk of HIV infection and sex work is known to play an important role in HIV transmission dynamics across settings. Low socioeconomic status, gender discrimination, and stigma associated with HIV and sex work may limit access to HIV care for FSW. We analyzed HIV drug resistance among HIV-infected FSW in the Dominican Republic (DR) and Tanzania who are enrolled in a longitudinal study of the social determinants of HIV outcomes.

Methods: Plasma samples were collected at study entry. Samples with viral loads >1,000 c/mL were retrospectively tested for HIV drug resistance and antiretroviral (ARV) drugs. HIV genotyping was performed using the ViroSeq HIV-1 Genotyping System. ARV drug testing was performed using a qualitative assay that detects 22 ARV drugs in five drug classes. Chi-square tests were used to evaluate factors associated with drug resistance.

Results: Among 410 enrolled FSW, 144 (35.5%) had a viral load >1,000 c/mL (50 from the DR, 94 from Tanzania). Genotyping results were obtained for 138 (95.8%) of 144 participants. Major drug resistance mutations were detected in 54 (39.1%) of the 138 samples (22 (15.9%) had non-nucleoside reverse transcriptase inhibitor resistance, 3 (2.2%) had nucleoside/nucleotide reverse transcriptase inhibitor resistance, 29 (21.0%) had multi-class resistance). ARV drugs were detected in 36 (25.0%) of the 144 cases; 19 (52.8%) of the 36 samples had only one or two drugs detected. The frequency of resistance was higher in the DR than Tanzania (27/50 [54.0%] vs. 27/86 [30.7%], p=0.011) and was higher among those with ≥1 ARV drug detected (27/35 [86.6%] vs. 27/103 [22.3%], p<0.0001). Seven participants with ≥1 ARV drug detected lacked corresponding resistance mutations; those individuals were at risk of acquiring additional drug resistance. K103N was the most common mutation detected among all 138 cases; M184V was the most common mutation detected among the 35 cases with ≥1 ARV drug detected.

Conclusion: In this cohort of FSW, nearly 40% of participants with viral loads >1,000 c/mL had HIV drug resistance and >20% had multi-class resistance. Drug resistance was associated with study site and ARV drug use. ARV drugs were detected in 25% of the participants who had a viral load >1,000 c/mL; in more than half of those cases, only one or two drugs were detected. These findings highlight the need for improved HIV care and treatment among FSW.

538 RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS AMONG MSM IN THE US: HPTN 078

Jessica M. Fogel¹, Vanessa Cummings¹, Ethan A. Wilson¹, Christophe Fraser¹⁵, David Bonsall¹⁶, Theresa Gamble¹⁷, Carlos Del Rio¹⁸, D. Scott Batey¹⁹, Kenneth H. Mayer¹², Jason Farley²⁰, James Hughes²¹, Robert H. Remien²², Chris Beyerli²³, Susan H. Eshleman¹, for the HPTN 078 Study Team

¹Johns Hopkins University School of Medicine, Baltimore, MD, USA, ²Fred Hutchinson Cancer Research Center, Seattle, WA, USA, ³University of Oxford, Oxford, UK, ⁴FHI 360, Durham, NC, USA, ⁵Emory University, Atlanta, GA, USA, ⁶University of Alabama at Birmingham, Birmingham, AL, USA, ⁷Harvard Medical School, Boston, MA, USA, ⁸Johns Hopkins University School of Nursing, Baltimore, MD, USA, ⁹University of Washington, Seattle, WA, USA, ¹⁰Columbia University, New York, NY, USA, ¹¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: Increasing viral suppression with antiretroviral therapy (ART) is a critical step in curbing the HIV epidemic. Integrase strand transfer inhibitor (INSTI)-based ART regimens are now recommended for first-line ART in the United States (US), but pre-treatment resistance testing does not routinely include testing for INSTI resistance. The HIV Prevention Trials Network (HPTN) 078 study evaluated an HIV prevention strategy in men who have sex with men (MSM) in four US cities. We analyzed INSTI resistance in MSM recruited for participation in HPTN 078.

Methods: HIV-infected MSM were recruited in Atlanta, GA; Baltimore, MD; Birmingham, AL; and Boston, MA (N=155 with a viral load >1,000 c/mL; screening/enrollment 2016-2017). 85% were Black, 76% reported a prior positive HIV test, and 65% reported prior or current ART. Population sequencing and next-generation sequencing (NGS) methods were performed using samples collected at study entry. HIV drug resistance was evaluated using the Stanford v8.7 algorithm. HIV-infected MSM were recruited in Atlanta, Georgia; Baltimore, Maryland; Birmingham, Alabama; and Boston, Massachusetts (N=155; screening/enrollment 2016-2017). Population sequencing and next-generation sequencing (NGS) methods were performed using samples collected at study entry (all available samples with a viral load >1,000 copies/mL). HIV drug resistance was evaluated using the Stanford v8.7 algorithm.

Results: High-level INSTI resistance was detected in 11 (8.0%) of 138 cases with integrase test results. All 11 cases had high-level resistance to elvitegravir; four also had high-level resistance to raltegravir and intermediate-level resistance to the second-generation INSTIs, bictegravir and dolutegravir. All cases with INSTI resistance also had resistance to additional drug classes (multi-class resistance); 11 had NRTI resistance, including five who also had NNRTI resistance, and one who also had PI resistance. NGS data for the integrase region was available for 114 (82.6%) of the 138 samples. NGS identified 10 additional cases with lower-level INSTI resistance (5%-45%); five of those 10 cases also had resistance to drugs in other drug classes. Potential transmitted resistance mutations were detected in three (37.5%) of eight MSM who reported no prior HIV diagnosis; two cases had INSTI resistance mutations (one had E92Q + M184V, one had T97A).

Conclusion: High prevalence of INSTI resistance and intermediate-level resistance to second generation INSTIs was observed among viroim MSM recruited for the HPTN 078 study. Many of those with INSTI resistance had
539 EXPANDED SPECTRUM OF ANTIRETROVIRAL-SELECTED HIV-2 MUTATIONS
Philip L. Touz1, Diane Descamps1, Soo-Yon Rhee1, Dana Raugi1, Charlotte Charpentier1, Florence Damond1, Nuno Taveira1, Robert A. Smith1, Vincent Soriano1, Carmen De Mendoza Fernández2, Susan Holmes1, Geoffrey S. Gottlieb1, Robert Shafer1
1Stanford University, Stanford, CA, USA, 2INSERM, Paris, France, 3University of Washington, Seattle, WA, USA, 4Universidade de Lisboa, Lisbon, Portugal, 5Puerta de Hierro Research Institute and University Hospital, Madrid, Spain

Background: There has been no systematic review of treatment-selected HIV-2 mutations.

Methods: We reviewed published HIV-2 sequences to identify previously unreported ARV-selected HIV-2 mutations. Prevalence of each ARV, RT, and IN mutation was determined by ARV status. Nonpolymorphic mutations (NPMs) were defined as occurring in <1% of ARV-naive persons. Nonpolymorphic treatment selected mutations (NP-TSMs) were defined as NPMs significantly associated with ARV therapy (Fishers Exact Test; p<0.05 after adjusting for multiple comparisons [Holm’s test]). Established drug-resistance mutations (DRMs) were determined by literature review. Correlated NP-TSMs were defined as mutation pairs with a Spearman coefficient >=0.2 and p<0.05.

Results: We analyzed PR sequences from 481 PI-naive and 222 PI-treated persons; RT sequences from 332 NRTI-naive and 252 NRTI-treated persons; and IN sequences from 236 INSTI-naive and 60 INSTI-treated persons. In PR, 12 NP-TSMs occurred in >10 persons: V33I, K40R, G48V, I54L, I82L, and I84L. In RT, 11 NP-TSMs occurred in >2 persons: Q91R, A73G, I82F, I84V, F85L, S215Y, A208T, and T97A. In IN, 10 NP-TSMs occurred in >2 persons: K45R, T56V, I54M, Q91R, and E92Q. Five NP-TSMs co-occurred with established HIV-1 IN-MDRs: K45R with I47A; T56V with I54M; and F85L with A73G. In RT, 9 NP-TSMs occurred in >2 persons: K40R, A62V, K70I, F115S, Q151M, M184V, and S215T. Additional RT NPMs at HIV-1 DRM positions M41I, D67N, N69T, K70N, I71V, and S215F occurred in 3-6 persons. The novel RT-TSM K40R correlated with S215T. In IN, 11 NP-TSMs occurred in >4 persons: Q91R, E92Q, T97A, G40S, Y134G, Q148R, A153G, N155H, H156R, and R213K amino acid insertions. Additional IN NPMs at HIV-1 DRM positions H51Y, E92G, G118R, K40R correlated with S215T. In PR, 12 additional NPMs at HIV-1 DRM positions occurred in 2-3 persons: G48V, I54L, I82L, and I84L. Among novel NP-TSMs, V33I correlated with E92A and N155H; H156R with E92Q and T97A. This systematic review of HIV-2 PR, RT, and IN sequences confirmed an ARV association of established HIV-2 DRMs and identified novel NP-TSMs. 32 NP-TSMs were significantly selected by ARVs in PR, RT, and IN. 20 additional NPMs at HIV-1 DRM positions were not statistically significant after multiple comparison adjustment. Most of the 9 novel NP-TSMs co-occurred with an established HIV-2 DRM. These results will improve approaches to predicting HIV-2 ARV susceptibility. Further clinical and phenotypic studies of HIV-2 drug resistance will be helpful in delineating it’s nuances and unique features.

540 HIV VIRAL BLIPS IN ADULTS TREATED WITH INSTI-BASED REGIMENS THROUGH 144 WEEKS
Rima K. Acosta1, Kristen Andreatta1, Michelle L. D’Antoni1, Sean E. Collins1, Hal Martin1, Kirsten L. White1
1Gilead Sciences, Inc, Foster City, CA, USA

Background: The clinical impact of viral blips on virologic failure and resistance development depends on the resistance barrier and forgiveness of the regimen. Here, we investigated the blip frequency and virologic outcomes of those experiencing blips among treatment-naïve persons with HIV (PWH) initiating antiretroviral therapy (ART) regimens. Methods: We reviewed published HIV-2 sequences to identify previously unreported ARV-selected HIV-2 mutations. Prevalence of each ARV, RT, and IN mutation was determined by ARV status. Nonpolymorphic mutations (NPMs) were defined as occurring in <1% of ARV-naive persons. Nonpolymorphic treatment selected mutations (NP-TSMs) were defined as NPMs significantly associated with ARV therapy (Fishers Exact Test; p<0.05 after adjusting for multiple comparisons [Holm’s test]). Established drug-resistance mutations (DRMs) were determined by literature review. Correlated NP-TSMs were defined as mutation pairs with a Spearman coefficient >=0.2 and p<0.05.

Results: We analyzed PR sequences from 481 PI-naive and 222 PI-treated persons; RT sequences from 332 NRTI-naive and 252 NRTI-treated persons; and IN sequences from 236 INSTI-naive and 60 INSTI-treated persons. In PR, 12 NP-TSMs occurred in >10 persons: V33I, K40R, G48V, I54L, I82L, and I84L. In RT, 11 NP-TSMs occurred in >2 persons: Q91R, A62V, K70I, F115S, Q151M, M184V, and S215T. Additional RT NPMs at HIV-1 DRM positions M41I, D67N, N69T, K70N, I71V, and S215F occurred in 3-6 persons. The novel RT-TSM K40R correlated with S215T. In IN, 11 NP-TSMs occurred in >4 persons: Q91R, E92Q, T97A, G40S, Y134G, Q148R, A153G, N155H, H156R, and R213K amino acid insertions. Additional IN NPMs at HIV-1 DRM positions H51Y, E92G, G118R, K40R correlated with S215T. In PR, 12 additional NPMs at HIV-1 DRM positions occurred in 2-3 persons: G48V, I54L, I82L, and I84L. Among novel NP-TSMs, V33I correlated with E92A and N155H; H156R with E92Q and T97A. This systematic review of HIV-2 PR, RT, and IN sequences confirmed an ARV association of established HIV-2 DRMs and identified novel NP-TSMs. 32 NP-TSMs were significantly selected by ARVs in PR, RT, and IN. 20 additional NPMs at HIV-1 DRM positions were not statistically significant after multiple comparison adjustment. Most of the 9 novel NP-TSMs co-occurred with an established HIV-2 DRM. These results will improve approaches to predicting HIV-2 ARV susceptibility. Further clinical and phenotypic studies of HIV-2 drug resistance will be helpful in delineating it’s nuances and unique features.

541 INVESTIGATION OF CLASSIC AND HIV-RELATED FACTORS FOR HEPATIC STEATOSIS AMONG PWID
Eve-Marie A. Benson1, Shruti H. Mehta1, Jacqui Astemborski1, David L. Thomas1, Gregory D. Kirk1
1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: Numerous studies show a link between visceral adiposity and metabolic disorders. Fatty liver is an established risk factor for cirrhosis and liver cancer and is increasing among aging persons living with HIV (PWH). We investigated the prevalence and correlates of hepatic steatosis, assessed non-invasively by elastography with controlled attenuation parameter (CAP), in a community cohort of HIV+ and HIV− people who inject drugs (PWID) and to determine if these associations varied by HIV infection or antiretroviral therapy (ART) regimen.

Methods: Adults from the AIDS Linked to the Intravenous Experience (ALIVE) study with validated liver elastography and CAP measurement from January 2017 to December 2018 were included. CAP >270 db/m was considered significant steatosis. Multivariable logistic regression estimated odds ratios (OR) for association of steatosis with demographic (age, gender, race), behavioral (at-risk alcohol use, current injection drug use), clinical (liver stiffness, HCV exposure, BMI, waist circumference, blood pressure, blood glucose, serum cholesterol), and HIV related factors (HIV RNA, CD4, ART regimen). Results: Of 1109 participants, 68% were male, 79% were black 40% reported recent drug use, 78% were anti-HCV+ and 35% were HIV infected (75% on ART; 65% had detectable HIV RNA). Median CAP score was 218 db/m (IQR, 190 – 258) and prevalence of hepatic steatosis was 25%. In multivariable analysis, steatosis was significantly associated with obesity/overweight, [OR= 8.2 (5.1 – 13)] and prevalence of hepatic steatosis was 25%. In multivariable analysis, steatosis was significantly associated with obesity/overweight, [OR= 8.2 (5.1 – 13)] and prevalence of hepatic steatosis was 25%. In multivariable analysis, steatosis was significantly associated with obesity/overweight, [OR= 8.2 (5.1 – 13)] and prevalence of hepatic steatosis was 25%. In multivariable analysis, steatosis was significantly associated with obesity/overweight, [OR= 8.2 (5.1 – 13)] and prevalence of hepatic steatosis was 25%. In multivariable analysis, steatosis was significantly associated with obesity/overweight, [OR= 8.2 (5.1 – 13)] and prevalence of hepatic steatosis was 25%. In multivariable analysis, steatosis was significantly associated with obesity/overweight, [OR= 8.2 (5.1 – 13)] and prevalence of hepatic steatosis was 25%.
Conclusion: Classic metabolic risk factors were strongly associated with hepatic steatosis in this community based PWID. While HIV did not independently increase risk, HIV-related factors of viral suppression and INSTI use were associated, contributing partly although not exclusively via adiposity. As HIV-infected PWID age on effective therapy, and with curative treatment for HCV, prevalence and morbidity of hepatic steatosis will likely increase.

542 RELATIONSHIPS BETWEEN HEPATIC STEATOSIS AND FRAILTY DIFFER BY HIV SEROSTATUS

Paula Debrovsky, Benjamin Barrett, Kristine M. Erlandson, Matthew Budoff, Todd T. Brown, Jennifer C. Price, Wendy Post, Valentina Stosor, Carling Lellop, Gypsambye D’Souza, Jordan E. Lake
University of Texas at Houston, Houston, TX, USA, 2Johns Hopkins University, Baltimore, MD, USA, 3University of Colorado, Aurora, CO, USA, 4Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA, 5University of California San Francisco, San Francisco, CA, USA, 6Northwestern University, Chicago, IL, USA, 7University of Pittsburgh, Pittsburgh, PA, USA

Background: Frailty and sarcopenia are associated with abdominal obesity and obesity-related comorbidities but their relationship with non-alcoholic fatty liver disease (NAFLD) in people living with HIV (PLWH) has not been described. We assessed the associations between NAFLD, sarcopenia, and components of a frailty-related phenotype (FRP) in Multicenter AIDS Cohort Study (MACS) participants.

Methods: MACS cardiovascular disease sub-study participants (40-70 years old) were included. NAFLD was defined as the ratio of liver/spleen in Hounsfield units (HU) < 1.0 on abdominal CT scans in men without chronic viral hepatitis or heavy alcohol use; FRP as having 3 of the following: weakness, slowness, weight loss, exhaustion, and low physical activity; sarcopenia as an appendicular skeletal muscle index [ASMI (kg)/height (m)²] ≤7.26 kg/m². Wilcoxon rank sum and Fisher’s exact tests compared between-group parameters. Multivariate regression assessed the relationship between NAFLD and a FRP controlling for HIV serostatus, study site, age, race, subcutaneous adipose tissue (SAT) density (HU), smoking status, alcohol use, liver fibrosis (FIB-4 >3.25), depression, and physical activity level (by international physical activity questionnaire). The final model included a NAFLD*HIV interaction.

Results: HIV- (n = 200) and HIV+ (n = 292) men had a median age of 55 and 52 years, BMI of 27 and 25 kg/m², and were 32% and 41% non-white, respectively. HIV+ men had a median CD4+ T lymphocyte count of 609 cells/ml, and 9.3 years on antiretroviral therapy. NAFLD prevalence was 21% in HIV- men vs 16% in HIV+ men; FRP 12% in HIV- vs 17% in HIV+. Among men with NAFLD, FRP was more prevalent in HIV- (21% vs 11% HIV+). In multivariate analysis, NAFLD, smoking, depression, and low physical activity were associated (p < 0.05) with a FRP. In stratified adjusted models, HIV- men with NAFLD had 2.6 times higher probability (95% CI: 1.2-5.7) of FRP. This association was not seen in HIV+ men. The probability of a FRP was higher among HIV-men with NAFLD (10% vs 27% in men with NAFLD) but lower among HIV+ men (18% vs 13% in men with NAFLD).

Sarcopenia was not associated with increased risk of NAFLD.

Conclusion: NAFLD was more prevalent in HIV- men, and independently associated with a FRP among HIV- men but not men living with HIV despite the latter’s increased prevalence of frailty. The mechanisms of the muscle-liver-adipose tissue axis underlying NAFLD might differ by HIV serostatus.

543 NAFLD AND LIVER FIBROSIS PREDICT HIGH CARDIOVASCULAR RISK IN HIV-MONINFECTED PATIENT

Giovanni Mazzola, Adriana Cervo, Giovanni Guaraldi, Thomas Kahn, Jovana Milic, Annamaria De Luca, Claudia Gioe, Benedetta Romanin, Marcello Trizzino, Sergio Mazzola, Pietro Colletti, Salvatore Petta, Giada Sebastiani, Antonio Cascio
1University of Palermo, Palermo, Italy, 2University of Modena and Reggio Emilia, Modena, Italy, 3McGill University Health Centre, Glen site, Montreal, QC, Canada, 4University of Palermo, Palermo, Italy

Background: Non-alcoholic fatty liver disease (NAFLD) is strongly associated to cardiovascular disease (CVD) in the general population. In people living with HIV (PLWH), this association has not been investigated yet. The aim of this study is to assess the impact of NAFLD and liver fibrosis on cardiovascular risk in PLWH.

Methods: 1410 HIV infected patients from three prospective cohorts (LHIVPA in Palermo, LIVEHIV in Montreal, MHHMC in Modena) were evaluated with Transient Elastography (TE). Exclusion criteria were: significant alcohol intake, coinfection with hepatitis B or C virus and failure of TE examinations defined as IQR value > 30%. NAFLD and significant liver fibrosis were defined as controlled attenuation parameter (CAP) ≥ 288 dB/m and as liver stiffness measurement (LSM) ≥ 7 kPa, respectively. Cardiovascular risk was assessed with Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator, according to American College of Cardiology, in patients aged 40 – 75 years, and categorized as: low if < 5%, borderline if 5 – 7.4%, intermediate if 7.5 – 19.9% and high if ≥ 20%. Patients with previous cardiovascular events were considered as high risk, regardless of age.

Results: 941 HIV mono-infected patients (mean age median 53, 74% males, 98% on ART) were included. 423 (45%), 128 (13.6%), 260 (27.3%) and 130 (13.8%) patients were categorized as low, borderline, intermediate and high ASCVD risk, respectively. Previous cardiovascular events were found in 8.5%. Prevalence of NAFLD and significant liver fibrosis was 20% and 17%, respectively. The probability of a FRP was higher among HIV-men with NAFLD (10% vs 27% in men with NAFLD). The distribution of ASCVD risk classes by NAFLD and fibrosis categories is shown in the Table. Overall, intermediate and high ASCVD risk were more frequent in patients with NAFLD (p < 0.001) and liver fibrosis (p < 0.05). In multivariate logistic regression, NAFLD (OR 2.16, 95% CI 1.44 – 3.26), liver fibrosis (OR 1.75, 95% CI 1.11 – 2.75) and time to HIV diagnosis (OR 1.04, 95% CI 1.02 – 1.06, p < 0.001) were independently associated with higher ASCVD risk.

Conclusion: Both NAFLD and liver fibrosis are predictors of cardiovascular disease in PLWH. Prevention of CVD, possibly with lifestyle modifications, should be strengthened in PLWH with NAFLD, in particular in those with longer HIV duration.

544 “FIB-4 FIRST” STRATEGY IN A PATHWAY ASSESSMENT FOR HIV MONINFECTED PATIENTS

Adriana Cervo, Thomas Kahn, Jovana Milic, Sahar Saeedi, Bertrand Lebouché, Marina Kleini, Philip Wong, Marc Deschenes, Peter Gahlai, Antonio Cascio, Giovanni Mazzola, Giovanni Guaraldi, Giada Sebastiani
1University of Palermo, Palermo, Italy, 2McGill University Health Centre, Glen site, Montreal, QC, Canada, 3University of Modena and Reggio Emilia, Modena, Italy

Background: Non-alcoholic fatty liver disease (NAFLD) is the main cause of liver disease in people living with HIV (PLWH). Even if transient elastography (TE) is a feasible and effective option to assess both NAFLD and fibrosis, it is not largely accessible. Fibrosis-4 (FIB-4) index at the threshold of 1.3 is used to exclude fibrosis in patients at risk for NAFLD from the general population. FIB-4 could be used to triage PLWH in need for further evaluation for NAFLD to exclude fibrosis in patients classified as at risk for NAFLD.

Methods: 1607 HIV mono-infected patients from three cohorts (LHIVPA in Palermo, LIVEHIV in Montreal, MHHMC in Modena) were included if they fulfilled the following criteria: available TE and FIB-4 within 3 months; absence of...
significant alcohol intake and of coinfected with hepatitis B or C. NAFLD was defined as a controlled attenuation parameter (CAP) ≥ 248 dB/m. Significant fibrosis and cirrhosis were defined as liver stiffness measurement ≥ 7.1 and ≥ 13 kPa, respectively. Failure of TE examination was defined as IQR value >30%.

Results: Prevalence of NAFLD and liver fibrosis was 37% and 15%, respectively. 1022 patients (64%) were stratified as low risk: 108 (11%) had significant liver fibrosis by TE (of whom 78 patients had NAFLD and 13 patients had cirrhosis) (see Figure). After adjusting for sex, CD4 nadir, viral load, time to HIV diagnosis and diabetes, BMI ≥ 25kg/cm² (Odds Ratio [OR] 3.66, 95% CI: 2.29-5.84) and low HDL cholesterol (OR 1.72, 95% CI: 1.06-2.78) were independently associated with discordance between TE and FIB-4 in patients with FIB-4 <1.3.

Conclusion: A FIB-4 first-stratification model could save more than 50% of TE examinations, helping resource optimization in HIV clinics. Patients stratified as low risk by FIB-4 should be considered for referral for TE examination in case of multiple risk factors for NAFLD, in particular overweight and low HDL cholesterol.

545 TRYPTOPHAN CATABOLISM IS ALTERED AMONG PERSONS WITH HIV WHO HAVE STEATOSIS

Andreas D. Knudsen1, Marco Gelpi1, Søren Bjørnskov1, Ditte M. Kirkegaard-Klitbo1, Anne-Mette Lebech1, Henrik Ullum1, Klaus F. Kofod1, Øivind Midttun1, Per M. Ueland1, Jens D. Lundgren1, Susanne D. Nielsen1

1Righospitalet, Copenhagen, Denmark, 2Hvidovre Hospital, Hvidovre, Denmark, 3University of Bergen, Bergen, Norway, 4CHIP, Department of Infectious Diseases, Copenhagen, Denmark

Background: Tryptophan catabolism as measured by the kynurenine-to-tryptophan ratio and concentrations of tryptophan metabolites are altered in persons with HIV (PWH). We aimed to explore if steatosis was associated with kynurenine-to-tryptophan ratio and quinolinic acid in PWH.

Methods: PWH were recruited from the Copenhagen comorbidity in HIV infection (COCOMO) study. We used an unenhanced CT liver scan to measure liver attenuation and defined steatosis as a liver attenuation ≤ 48 Hounsfield Units corresponding to moderate to severe steatosis. Concentrations of tryptophan metabolites in serum were measured using liquid chromatography-tandem mass spectrometry. Information on smoking and physical activity was collected through questionnaires, and anthropometry was performed by trained medical professionals. We performed multiple linear regression modelling of log-transformed biomarker levels adjusted for age, sex, smoking status, waist-to-hip ratio and physical activity. Furthermore, we explored if IFN-γ-mediated effects of steatosis on tryptophan catabolism.

Results: Among 799 PWH with both CT liver scan and measured kynurenines, steatosis was present in 61 (7.6%) (Table). KTR was 27.2 (95% Confidence Interval [CI]: 25.1, 29.4) (nmol/µmol) among those with steatosis and 25.3 (95%CI: 24.8, 25.8) in those without steatosis, p=0.046. Quinolinic acid concentrations were higher among those with steatosis compared to those without (466nm [95%CI: 425, 512] vs. 384nm [95%CI: 375, 394], p<0.001). In adjusted analyses, steatosis was independently associated with 14% (95%CI: 4; 25) higher concentration of quinolinic acid, p=0.005. After additional adjustment for IFN-γ, steatosis remained associated with 12% (95%CI: 3; 21) higher concentration of quinolinic acid. Kynurenine-to-tryptophan ratio was not associated with steatosis in adjusted analyses, p=0.82.

Conclusion: Serum levels of quinolinic acid were significantly higher among PWH with steatosis as defined by CT compared to PWH without steatosis, and this was not mediated by IFN-γ. There was no difference in kynurenine-to-tryptophan ratio. As quinolinic acid may impose oxidative stress, our findings suggest pro-inflammatory changes in the kynurenine pathway of tryptophan metabolism accompany steatosis in the context of HIV infection. However, the specific pathoetiological mechanisms underlying these changes should be explored in translational studies.

546 IL-18 IS ASSOCIATED WITH HEPATOSTEATOSIS AND HIGHER LIVER ENZYMES IN PEOPLE WITH HIV

Jae H. Sim1, Julia B. Sherman1, Kathileen V. Fitch3, Sara E. Looby1, Jake A. Robinson1, Michael Lu1, Steven K. Grinspoon2, Tricia H. Burdo1, Janet Lo1

1Massachusetts General Hospital, Boston, MA, USA, 2University of Massachusetts, Worcester, MA, USA, 3Temple University, Philadelphia, PA, USA

Background: People with HIV (PWH) are at increased risk of development of nonalcoholic fatty liver disease (NAFLD). In addition to insulin resistance and obesity, chronic inflammation is important in the pathogenesis of NAFLD. IL-18, a member of the pro-inflammatory IL-1 family, is regulated by inflammasomes in response to pathogens and danger signals. IL-18 is elevated in PWH and has been implicated in inflammation associated with obesity and NAFLD in people without HIV. We hypothesized that IL-18 may play a role in NAFLD progression in PWH.

Methods: IL-18 was measured by ELISA (R&D) in an observational cohort of PWH and matched uninfected controls in the Boston area. Participants with known hepatitis C and excessive alcohol use were excluded. Liver lipid content was assessed by liver/spleen CT attenuation ratio (an estimate of hepatosteatosis in which a lower ratio indicates higher lipid content). IL-18 was log transformed to approximate a normal distribution.

Results: A total of 134 PWH and 59 HIV-uninfected controls were included in the current analysis. PWH had higher log10 IL-18 (2.40 ±0.19 [mean ±SD] vs 2.29 ±0.22, p=0.002), AST (33.3 ±12.9 vs 26.6 ±14.0 U/dL, p=0.01), and ALT (33.4 ±25.8 vs 23.8 ±16.6 U/dL, p=0.002) compared to control group. In PWH, log10 IL-18 was associated with ALT (r=0.21, p=0.05), caspase-1 (r=0.31, p=0.0003), HIV plasma viral load (r=0.21, p=0.02), capase-1 (r=0.31, p=0.0003), IL-6 (r=0.19, p=0.047), and LPS (r=0.2, p=0.03), and inversely associated with liver/spleen ratio (r=0.23, p=0.02), HDL (r=-0.31, p=0.0001) and CD4+/CD8+ ratio (r=-0.2, p=0.02). The relationship between log10 IL-18 with ALT (β=0.35, p=0.0006) and ALT (β=0.37, p=0.001) remained significant after adjusting for age, gender, BMI, HIV RNA, and CD4+ count. In controls, log10 IL-18 was also associated with ALT (r=0.37, p=0.004) and inversely associated with HDL (r=-0.27, p=0.04).

Conclusion: We demonstrated significant relationships of IL-18 with liver transaminases and hepatosteatosis, suggesting the potential role of the inflammasome and IL-18 pathway in NAFLD progression in PWH. The relationship of IL-18 with LPS and MCP-1 may indicate IL-18’s actions via known causes of NAFLD including intestinal microbial translocation and MCP-1/CCL2 signaling. Further studies are necessary to elucidate precise mechanisms involving IL-18 and inflammatory pathways in NAFLD development in PWH.
547 EASL BIOMARKERS DIFFER IN PREDICTING NAFLD, NASH, AND FIBROSIS IN HIV +/– INDIVIDUALS

Ricky Hsu1, Laurence Brunet1, Jennifer S. Fusco2, Gregory Fusco2
1New York University Langone Medical Center, New York, NY, USA, 2Epividian, Durham, NC, USA

Background: Fatty liver is a major health concern for people living with HIV as well as for the general US population. This study sought to compare 2 EASL-recommended biomarker-based risk scores with high sensitivity and specificity for diagnosing each of the 3 stages of fatty liver disease; NAFLD, NASH, and fat-induced fibrosis over 3 calendar periods.

Methods: All HIV(+) and HIV(-) individuals in OPERA were included if all 6 scores could be calculated during one of the calendar periods of interest (2006-2008, 2011-2013, 2016-2018) and they had no diagnoses of viral hepatitis, celiac, sclerosing cholangitis, or alcohol abuse. To mitigate outliers, average scores were obtained over each period to identify NAFLD (HSI NAFLD score > 36 or NAFLD Liver Fat score > -1.455), NASH (HAIR score >= 2 or Campos NASH score >= 5) and fibrosis (Fib-4 index > 2.67 or NAFLD Liver Fat score > 0.675). Results were age and sex standardized using the HIV(-) population as the standard and risk differences were estimated.

Results: This study included 7,583 HIV(+) and 1,645 HIV(-) in 2006-2008; 25,347 HIV(+) and 65,903 HIV(-) in 2011-2013; and 46,229 HIV(+) and 100,699 HIV(-) persons in 2016-2018. Prevalence estimates varied substantially depending on the score used. HIV(-) persons were much more likely to have all biomarkers required for the 6 tests (>80%) than the HIV(+) persons (<25%). Among HIV(+) persons, after age/sex standardization, NAFLD prevalence increased over the years, ranging from 43-54% with HSI NAFLD score and 28-39% with NAFLD Liver Fat score; NASH prevalence remained stable, ranging from 16-17% with HAIR score and 3-6% with Campos NASH score; fibrosis prevalence remained stable, ranging from 3-4% with Fib-4 and 4-7% with NAFLD Liver Fat score (Fig). HIV(+) persons had a lower standardized prevalence of NAFLD and NASH than HIV(-) persons at most time points with either score (Fig).

Conclusion: Despite similar published predictive values among EASL-recommended biomarker risk scores, calculated prevalence of NAFLD, NASH and liver fibrosis based on these scores differed significantly in the OPERA cohort. The selection of a study population among whom all scores could be calculated likely disproportionately included individuals at higher risk of fatty liver disease, thus overestimating the true prevalence especially among those without HIV. Further clinical validation of these scores is required before broad utilization in the staging of fatty liver disease.

548 AN RCT OF RALTEGRAVIR-VERSUS EFAVIRENZ-BASED ART IN HIV-HCV COINFECTION

Thuy Le1, Chau V. Nguyen1, Thao P. Vu1, Ly T. Vo1, Thanh T. Nguyen1, Thu T. Nguyen1, Robert Paul5, Lishomwa C. Ndhlovu6, Dominic Chow6, Cecilia M. Shikuma6
1Duke University School of Medicine, Durham, NC, USA, 2Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam, 3Oxford University Clinical Research Unit in Vietnam, Ho Chi Minh, Vietnam, 4University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh, Vietnam, 5University of Missouri, Columbia, MO, USA, 6University of Hawaii at Manoa, Honolulu, HI, USA

Background: Drug induced liver injury following initiation of ART is more common in HIV/HCV coinfected patients; however comparative data on hepatotoxicity of ARVs used in this population are lacking as HIV/HCV coinfected patients are largely excluded from clinical trials. We compared hepatotoxicity, virological, and clinical outcomes between raltegravir (RAL)- and efavirenz (EFV)-based ART in HIV/HCV coinfected patients starting 1st-line ART in Vietnam.

Methods: This RCT allocated patients 1:1 to RAL/TDF/FTC or EFV/TDF/FTC between June 2014 and February 2017. Eligibility: HIV infection, ART-naive, age ≥18, met Vietnam guidelines for ART (CD4 <500 cells/µL or WHO stage 3 or 4 disease), HCV infection (positive HCV antibody and HCV RNA), AST and ALT ≤80 U/L, creatinine clearance ≥60 ml/min, negative HBsAg, no evidence of decompensated cirrhosis, and not on rifampicin. We tested AST, ALT, bilirubin every month and CD4, HIV RNA, HCV RNA, fibroscan, and lipids at w0, 24, 48, and 72. We compared the rates of ALT and AST toxicity > grade 2 (primary outcome) and time to AIDS or death by arm using Kaplan Meier curves and log rank test. We compared the proportions of HIV RNA suppression at w72 by Chi-square test.

Results: We screened 207 and enrolled 80 participants (39 on RAL, 41 on EFV; median age 32; 88% male, 75% with history of IDU). EFV was associated with higher incidence of ALT and AST elevation (73.0% vs. 62.2%, P=0.14 and 61.8% vs. 42.5%, P=0.10, respectively). The majority of liver events occurred during the first 12 weeks. 5 patients (6%) died (2 in RAL arm died of TB; 3 in EFV arm died of TB, CNS infection, and suicide). 18 developed AIDS events (9 each arm). There were no significant differences in time to AIDS or death (P=0.94) or proportions of HIV RNA <150 copies/mL at w72 (87.9% in RAL, 85.7% in EFV, P=1.00). EFV was associated with a lower CD4 cell gain (170 vs. 224 cells/
**549** HEPATIC STEATOSIS ASSOCIATED WITH EXPOSURE TO ELVITEGRAVIR AND RALTEGRAVIR

Thomas Benfield1, Jens D. Lundgren2, Flemming Bendtsen1, Susanne D. Nielsen1, Ditte M. Kirkegaard-Klitbo1

1University of Copenhagen, Copenhagen, Denmark, 2CHIP, Department of Infectious Diseases, Copenhagen, Denmark

**Background:** Treatment with integrase strand transfer inhibitors and nucleotide analogues may be associated with weight gain in people living with HIV (PLWH). Overweight is associated with fatty liver. Here we studied the association of antiretrovirals and moderate-severe hepatic steatosis.

**Methods:** PLWH without prior or current viral hepatitis or alcohol intake above 14 units/week were included in the study. Liver steatosis was assessed by unenhanced CT liver scan. Moderate-severe hepatic steatosis was defined by liver attenuation ≤ 48 Hounsfield units. Association with antiretrovirals exposure was presented as odds ratio with 95% CI after adjustment for age, sex, body mass index and duration of HIV infection.

**Results:** PLWH included in the study were predominantly male (86%), European (87%), MSM (73%) and with undetectable HIV RNA (97%). Of 516 PLWH, 37 (7.2%) had moderate-severe hepatic steatosis. The mean treatment duration was 11 years. Moderate-severe hepatic steatosis was associated with any (OR 3.67 [1.29;10.46] and cumulative (OR 1.19 [1.01;1.41] per year) exposure to elvitegravir (number exposed (Nexp) = 59) and with cumulative exposure to elvitegravir (OR 2.84 [1.56;5.10] per year) (Nexp = 63). The association with cumulative exposure to elvitegravir with emtricitabine/tenofovir disoproxil fumarate (OR 3.06 [1.63;5.75]) or with emtricitabine/tenofovir alafenamide (OR 3.62 [0.73;17.81]) were comparable. Further, moderate-severe hepatic steatosis was associated with body mass index and duration of HIV infection.

**Conclusion:** In patients co-infected with HIV / HCV receiving an ART based on RVP, a significant reduction in liver stiffness measured by TE was observed.

---

**550** BENEFITS OF RILPIVIRINE FOR LIVER FIBROSIS IN HIV/HCV COINFECTED SUBJECTS

María Luisa Montes1, Carmen Busca1, Antonio Oliveira1, Luz Martín-Carbonero1, Eulalia Valencia1, Victoria Moreno1, Jose I. Bernardino1, Ignacio Pérez-Velar1, Rocio Montejano1, Rafael Micán1, Rosa De Miguel1, Jose R. Arribas1, Juan González-García1

1Hospital La Paz Institute for Health Research, Madrid, Spain

**Background:** Recent studies have described that treatment with rilpivirine (RPV) induces antifibrotic effects in various models of chronic liver disease1. Our objective was to analyse whether HIV-infected patients with some degree of liver stiffness measured by transition elastography (TE) and treated with RPV-based regimens showed any improvement. Martí-Rodrigo A, Alegre F, Moragrega A, et al. Gut eubp ahead of print doi:10.1136/gutjnl-2019-318378

**Methods:** From a 4099 HIV-infected patients cohort in stable follow-up, patients who had some degree of liver stiffness measured by TE (≥ 5.2kPa) and at least 2 TE measurements were selected. A case–control study of exposed and non-exposed subjects to RPV was designed. In cases the exposure to RPV should have started in the period between the two TE measures (baseline and final).

Case and control groups were matched for chronic hepatitis (C,CHC), sustained virological response (SVR), years of HIV diagnosis (+3 years) and time elapsed between TE measures (+6 months).

A linear model of repeated measures (GLM-RM) of the TE was carried out, controlling for HCV coinfection, time of SVR, time of HIV-infection, time elapsed between TE and BMI measures.

**Results:** 120 case and 120 control subjects were selected without significant differences in gender (84% male), UDVP transmission (43%), CDC C stage (28%), and undetectable HIV viral load (85%). The median time between TE measurements was 51 (29–68) months. Main variables related to liver stiffness at baseline and final moments are shown in table. In the GLM-RM analysis a significant decrease was found in the measure of TE in case group. (mean difference of -1.9kPa [C95%: -3.0 - -0.8]; p <0.01) and not in control (mean difference of -0.3kPa [C95%: -1.6 - 0.6]; p = 0.4). This difference in the case group was found only in subjects who had CHC, mean difference of -2.9kPa ([C95%: -4.6 - -1.3]; p <0.01).

**Conclusion:** In patients co-infected with HIV / HCV receiving an ART based on RPV, a significant reduction in liver stiffness measured by TE was observed.

---

**551** ACCURACY OF FIBROSIS-4 FOR CIRRHOSIS IN HIV+ PATIENTS WITH HEPATOCELLULAR CARCINOMA

Jessie Torgersen1, Michael J. Kallan1, Dena M. Carbonari1, Lesley S. Park1, Rajni Mehta1, Kathryn D’Addio1, Janet Tate1, Joseph Lim1, Matthew B. Goetz1, Maria Rodriguez-Barradas1, Norbert Bru1, Sheldon T. Brown1, Tamar Taddei1, Amy C. Justice1, Vincent Lo Re1

1University of Pennsylvania, Philadelphia, PA, USA, 2Stanford University, Stanford, CA, USA, 3VA Connecticut Healthcare System, West Haven, CT, USA, 4Yale University, New Haven, CT, USA, 5VA Greater Los Angeles Health Care System, Los Angeles, CA, USA, 6Michael E. DeBakey VA Medical Center, Houston, TX, USA, 7James J. Peters VA Medical Center, Bronx, NY, USA

**Background:** Hepatocellular carcinoma (HCC) may develop in the absence of cirrhosis in HIV, and determining how often this occurs can provide insights into mechanisms of carcinogenesis. Studies evaluating the prevalence of cirrhosis in the setting of HCC among HIV+ patients often rely on non-invasive markers, such as the Fibrosis-4 Index for Hepatic Fibrosis (FIB-4). However, the accuracy of FIB-4 for cirrhosis in the setting of HCC has not been determined among HIV+ patients.

**Methods:** We conducted a cross-sectional study among HIV+ patients in the Veterans Aging Cohort Study with a HCC diagnosis from 1999-2015 and evaluated the accuracy of FIB-4 for medical record-confirmed cirrhosis. HCC diagnoses were identified in the VA cancer registry. FIB-4 was calculated using the age, alanine aminotransferase, aspartate aminotransferase, and platelet count obtained closest, but within one year prior, to the date of HCC diagnosis. Medical records were reviewed to abstract evidence of cirrhosis within one year prior to the date of HCC diagnosis. Cirrhosis was confirmed if: 1) liver histopathology report indicated cirrhosis (METAVIR stage F4 or Ishak fibrosis score ≥5); 2) abdominal imaging indicated cirrhosis (nodular contour of liver, splenomegaly with ascites, or esophageal varices); 3) endoscopy identified...
plasma MIR-99A and MIR-100 predict liver fibrosis progression in HIV/HCV subjects

Plasma MIR-99A and MIR-100 predict liver fibrosis progression in HIV/HCV subjects. 

Methods: Large-scale deep sequencing analysis of small RNA expression was performed on plasma samples from 46 HIV-1/HCV co-infected subjects that did not exhibit liver fibrosis at the time of sampling. After a mean of 10.3 years, 26 of the former subjects developed liver fibrosis (F2-4) and 20 remained without signs of liver fibrosis (F0-1). Twenty one healthy uninfected donors were also analyzed.

Results: At the time of sampling, there were not significant clinical differences between liver fibrosis progressing and non-progressing subjects (i.e. sex, age, AST, ALT, GGT, platelets, FIB-4, liver fibrosis). A total of 1355 different miRs were identified. When compared with healthy donors, HIV-1/HCV subjects showed significant (fold change > 2 and adjusted p < 0.05) dysregulated expression of 44 miRs, 38 of them upregulated (ranging from 13.8 to 2.0 fold increase). Previously described circulating miRs associated with NAFLD and NASH, with a non-invasive strategy is currently one of the main challenges that clinicians are facing. Recent evidence indicates that the plasma levels of specific microRNAs (miRs) may be significantly altered in subjects with liver injury, including HIV infected individuals.

Conclusion: The diagnostic accuracy of FIB-4 for cirrhosis in the setting of HIV and HCC is modest and may result in misclassification of cirrhosis in this population.

<table>
<thead>
<tr>
<th>miR Value</th>
<th>No cirrhosis by chart review (n=104)</th>
<th>Cirrhosis by chart review (n=55)</th>
<th>PPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.45</td>
<td>89</td>
<td>3</td>
<td>82.6%</td>
<td>25.4%</td>
<td>92.4%</td>
</tr>
<tr>
<td>&gt;0.50</td>
<td>76</td>
<td>12</td>
<td>79.2%</td>
<td>65.6%</td>
<td>84.5%</td>
</tr>
<tr>
<td>&gt;0.60</td>
<td>61</td>
<td>17</td>
<td>82.3%</td>
<td>45.5%</td>
<td>87.1%</td>
</tr>
<tr>
<td>&gt;0.75</td>
<td>51</td>
<td>9</td>
<td>80.4%</td>
<td>49.0%</td>
<td>85.6%</td>
</tr>
<tr>
<td>&gt;0.90</td>
<td>42</td>
<td>6</td>
<td>81.0%</td>
<td>33.0%</td>
<td>87.3%</td>
</tr>
</tbody>
</table>

Table 1: The positive predictive value, sensitivity, and specificity of FIB-4 values for patients with cirrhosis.

<table>
<thead>
<tr>
<th>miR Value</th>
<th>No cirrhosis by chart review (n=104)</th>
<th>Cirrhosis by chart review (n=55)</th>
<th>PPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.45</td>
<td>89</td>
<td>3</td>
<td>82.6%</td>
<td>25.4%</td>
<td>92.4%</td>
</tr>
<tr>
<td>&gt;0.50</td>
<td>76</td>
<td>12</td>
<td>79.2%</td>
<td>65.6%</td>
<td>84.5%</td>
</tr>
<tr>
<td>&gt;0.60</td>
<td>61</td>
<td>17</td>
<td>82.3%</td>
<td>45.5%</td>
<td>87.1%</td>
</tr>
<tr>
<td>&gt;0.75</td>
<td>51</td>
<td>9</td>
<td>80.4%</td>
<td>49.0%</td>
<td>85.6%</td>
</tr>
<tr>
<td>&gt;0.90</td>
<td>42</td>
<td>6</td>
<td>81.0%</td>
<td>33.0%</td>
<td>87.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>miR Value</th>
<th>No cirrhosis by chart review (n=104)</th>
<th>Cirrhosis by chart review (n=55)</th>
<th>PPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.45</td>
<td>89</td>
<td>3</td>
<td>82.6%</td>
<td>25.4%</td>
<td>92.4%</td>
</tr>
<tr>
<td>&gt;0.50</td>
<td>76</td>
<td>12</td>
<td>79.2%</td>
<td>65.6%</td>
<td>84.5%</td>
</tr>
<tr>
<td>&gt;0.60</td>
<td>61</td>
<td>17</td>
<td>82.3%</td>
<td>45.5%</td>
<td>87.1%</td>
</tr>
<tr>
<td>&gt;0.75</td>
<td>51</td>
<td>9</td>
<td>80.4%</td>
<td>49.0%</td>
<td>85.6%</td>
</tr>
<tr>
<td>&gt;0.90</td>
<td>42</td>
<td>6</td>
<td>81.0%</td>
<td>33.0%</td>
<td>87.3%</td>
</tr>
</tbody>
</table>

553 HEPATIC FIBROSIS DETERMINED WITH ARE SIGNIFICANTLY PREDICTS COGNITIVE IMPAIRMENT

Marianna K. Baum1, Javier Tamargo1, Richard L. Ehmni1, Christina S. Meade1, Kenneth E. Sherman1, Heidi L. Meeds1, Jun Chen1, Sabrina S. Martínez1, Gustavo G. Zarini1, Yongjun Huang1, Colby Teerman1, Jacqueline Hernandez2, Angelique Johnson1, Raul Mandel1, Adriana Campai1, for the MASH Team

1Florida International University, Miami, FL, USA, 2Mayo Clinic, Rochester, MN, USA, 3Duke University, Durham, NC, USA, 4University of Cincinnati, Cincinnati, OH, USA, 5National Institute on Drug Abuse, Rockville, MD, USA

Background: Liver disease is a leading cause of morbidity and mortality among people living with HIV (PLWH), and has been associated with neurocognitive impairments (NCI) in PLWH, even in the absence of viral hepatitis. Yet, co-infection with HCV is associated with greater NCI irrespective of cirrhosis or substance abuse. Associations have been reported between indirect measures of liver fibrosis and NCI in PLWH. However, studies using more sensitive markers of liver fibrosis are needed. Magnetic resonance elastography (MRE) is currently the most accurate non-invasive measure of liver fibrosis.

Methods: Cross-sectional analysis of 211 HIV mono-infected (HIV+), 74 HCV mono-infected (HCV+), 76 HIV/HCV coinfected and 265 HIV/HCV uninfected individuals from the Miami Adult Studies on HIV (MASH) cohort. NCI was determined with the Mini Mental State Examination (MMSE). Neurofilament light chain (NFL), a biomarker of neurodegeneration, was tested in plasma of 26 individuals. Substance use was assessed by questionnaire and urine drug screen. Liver fibrosis indicative of liver disease was determined as liver stiffness (LS) via MRE.

Results: LS was negatively correlated with MMSE scores (rho=-0.11, p=0.008) and directly correlated with NFL (rho=-0.46, p=0.017). LS >2.94 kPa (fibrosis) was more prevalent in HIV+ not virally suppressed than those virally suppressed (56.9% vs 29.2%, p=0.002). HIV infection was associated with 3.42 (1.97-5.94) and 1.72 (0.99-2.99) the odds for inflamed or fibrotic liver (LS >2.5 kPa) compared to HIV- and uninfected participants, respectively (p<0.0001). HIV infection was associated with decreased odds for LS >2.5 kPa (adjusted OR 0.71 [0.46-1.08], p=0.007) compared to HIV/HCV uninfected individuals. In PLWH, use of prescription opioids increased the odds for inflamed or fibrotic liver (adjusted OR: 1.62 [0.80-3.24], p=0.008) compared to opioid non-users. Hepatic fibrosis was associated with an adjusted odds ratio of 2.43 (1.28-4.59, p=0.006) for NCI (MMSE ≤24) compared to no fibrosis. In PLWH, cocaine use increased the odds for LS >2.94 kPa (adjusted OR 1.32 [0.67-2.61], p=0.036).

Conclusion: Hepatic fibrosis is associated with NCI irrespective of HIV and/or HCV infection. Substance abuse may contribute to liver disease and cognitive impairments in PLWH. Longitudinal studies with comprehensive neuropsychological testing are needed.
LIVER PATHOLOGY IN HIV-POSITIVE SUBJECTS UNDERGOING LIVER TRANSPLANTATION

Roberto Rossetti, Marco Merli, Chiara Mazzarelli, Stefano Di Sandro, Mario L. Camozzi, Giovanni Travi, Raffaella Viganò, Andrea Lauterio, Emanuela Bonoldi, Luca S. Belli, Luciano G. De Carlis, Massimo Puoti

1 ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Background: Liver transplantation (LT) represents the best therapeutic option for end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). Although LT in HIV+ subjects showed similar survival rates compared to HIV- recipients, HCV recurrence and HCC severity seem more harmful. Aim of this study is to compare pathologic features of livers explanted from HIV+ and HIV- patients.

Methods: All subjects with HCV/HBV infection who underwent LT for ESLD or HCC from 2001 to 2019 were retrospectively evaluated. Demographic and clinical features as well as macroscopic and histopathologic characteristics of explanted livers were collected. Descriptive statistics and non-parametric tests (Chi-square and Mann-Whitney U, as appropriate) were used.

Results: 278 individuals, mainly men (83.1%), with a median age of 57 (IQR 52-63) years were included; 30 (10.8%) were HIV+. The indication for LT was ESLD in 65.8% of cases. HIV+ recipients were younger (53 vs 58 years, p<0.0001), more commonly HCV+ after sustained virologic response achievement (43% vs 21%, p=0.0199) and less diabetic (10% vs 31%, p=0.0146). HIV+ subjects transplanted for ESLD showed a worse Child-Turcotte-Pugh score at the time of diagnosis (11 vs 10, p=0.0308) and a higher MELD score at the limit of significance (23 vs 17, p=0.0836), while no difference was observed for those transplanted for HCC. BCLC stage, alpha-fetoprotein level, portal vein thrombosis and previous bridging treatments were similar in the two groups. Table 1 shows features of included patients and explanted livers: HIV+ were comparable to HIV- individuals in terms of number and size of lesions, grading stage and vascular invasion. Histotype distribution resulted different, in particular for a higher presence of pseudoglandular pattern and cholangiocarcinoma in HIV- subjects. The presence of a capsule was more common in HIV- subjects, although they showed higher margin invasion. Of note, 30% of cases in both groups did not satisfy the so-called Milan criteria for LT eligibility.

Conclusion: Despite a lower presence of traditional risk factors for HCC (older age, viremic HCV, diabetes), HIV+ individuals showed several macroscopic and pathologic features similar to HIV- recipients. Although no histopathologic feature has been included in prognostic staging systems because of poor reproducibility, it is recognized that trabecular and pseudoglandular HCC are associated with different gene signature mutations, thus possible different mechanisms in tumor development in the two populations could be alleged.

Table 1. Demographic and clinical features of HIV+ and HIV- LT recipients and histopathologic characteristics of explanted livers.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIV+ (N=28)</th>
<th>HIV- (N=278)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 (49-58)</td>
<td>53 (52-63)</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>20/8</td>
<td>217/61</td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td>ESLD</td>
<td>19 (67.9)</td>
<td>150 (54.1)</td>
</tr>
<tr>
<td></td>
<td>HCC</td>
<td>10 (35.7)</td>
<td>128 (45.8)</td>
</tr>
<tr>
<td>HCV status</td>
<td>viremic</td>
<td>20 (71.4)</td>
<td>217 (77.7)</td>
</tr>
<tr>
<td></td>
<td>nonviremic</td>
<td>8 (28.6)</td>
<td>61 (22.3)</td>
</tr>
<tr>
<td>HIV status</td>
<td>viremic</td>
<td>12 (42.9)</td>
<td>84 (30.4)</td>
</tr>
<tr>
<td></td>
<td>nonviremic</td>
<td>16 (57.1)</td>
<td>194 (69.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 (20.5-31.8)</td>
<td>26.4 (20.5-31.8)</td>
<td>0.952</td>
</tr>
<tr>
<td>Blood AST (UI/L)</td>
<td>382 (139-1326)</td>
<td>295 (72-1386)</td>
<td>0.256</td>
</tr>
<tr>
<td>Blood ALT (UI/L)</td>
<td>241 (114-1392)</td>
<td>230 (87-1332)</td>
<td>0.33</td>
</tr>
<tr>
<td>Blood bilirubin (μmol/L)</td>
<td>20 (12-40)</td>
<td>16 (6-30)</td>
<td>0.252</td>
</tr>
<tr>
<td>Virologic status</td>
<td>sustained</td>
<td>20 (71.4)</td>
<td>217 (77.7)</td>
</tr>
<tr>
<td></td>
<td>non-sustained</td>
<td>8 (28.6)</td>
<td>61 (22.3)</td>
</tr>
<tr>
<td>BCLC stage</td>
<td>A</td>
<td>11 (39.3)</td>
<td>86 (30.4)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>11 (39.3)</td>
<td>86 (30.4)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>5 (17.9)</td>
<td>66 (24)</td>
</tr>
<tr>
<td>Serum AFP (ng/mL)</td>
<td>22 (1-730)</td>
<td>1 (1-12)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Serum CEA (ng/mL)</td>
<td>11 (1-182)</td>
<td>2 (1-15)</td>
<td>0.0072</td>
</tr>
<tr>
<td>Liver capsule</td>
<td>no capsule</td>
<td>22 (78.6)</td>
<td>217 (77.7)</td>
</tr>
<tr>
<td></td>
<td>capsule</td>
<td>6 (21.4)</td>
<td>61 (22.3)</td>
</tr>
<tr>
<td>Lesion size (cm)</td>
<td>4.5 (1.5-15)</td>
<td>4.5 (1.5-15)</td>
<td>0.977</td>
</tr>
<tr>
<td>Lesion number</td>
<td>3 (1-10)</td>
<td>3 (1-10)</td>
<td>0.977</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>no invasion</td>
<td>23 (82.1)</td>
<td>217 (77.7)</td>
</tr>
<tr>
<td></td>
<td>invasion</td>
<td>5 (17.9)</td>
<td>66 (24)</td>
</tr>
<tr>
<td>Histotype distribution</td>
<td>pseudoglandular</td>
<td>19 (67.9)</td>
<td>128 (45.8)</td>
</tr>
<tr>
<td></td>
<td>trabecular</td>
<td>10 (35.7)</td>
<td>128 (45.8)</td>
</tr>
<tr>
<td></td>
<td>mixed</td>
<td>10 (35.7)</td>
<td>128 (45.8)</td>
</tr>
<tr>
<td></td>
<td>cholangiocarcinoma</td>
<td>10 (35.7)</td>
<td>128 (45.8)</td>
</tr>
</tbody>
</table>

556 EPIDEMIOLOGICAL TREND OF CHRONIC HEPATITIS C IN SPAIN (2000-2015): NATIONWIDE STUDY

Irene Maté-Canó, Alejandro Alvaro-Meca, Paula Martínez-Román, Óscar Brochado Kith, Pablo Ryan, Salvador Resino, Verónica Bitiz

1 Institute of Health Carlos III, Madrid, Spain, 2 Universidad Rey Juan Carlos, Madrid, Spain, 3 Hospital Universitario Infanta Leonor, Madrid, Spain

Background: Chronically Hepatitis C infected patients are at risk of progression to liver disease, developing liver fibrosis, compensated cirrhosis (CC), end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), and finally dying, or need for liver transplantation (LT). The management of those patients generates a substantial economic cost on the National Health Services.

Objective: To analyze the epidemiological trends of hospital admissions, intra-hospital deaths, and costs related to chronic hepatitis C (CHC) taking into account four major clinical stages: CC, ESLD, HCC and LT during the 21st century in Spain.

Methods: Retrospective study in patients with CHC and a hospital admission in the Spanish Minimum Basic Data Set (2000-2015). The outcome variables were hospital admission, death, length of hospital stay (LOS) and costs. ICD-9-CM codes were used for CHC diagnosis and HCV chronical clinical stages: CC (070.44, 070.51, 070.54, 070.7x, or V02.62); compensated cirrhosis (571.2 or 571.5); end stage liver disease (ESLD), hepatocellular carcinoma (HCC), and finally dying, or need for liver transplantation (LT).

Results: 868,523 hospital admissions with CHC (25.3% CC, 25.3% ESLD, 8.6% HCC, and 2.5% LT) were identified. Overall rates of hospital admission and mortality increased from 2000-2004 to 2007-2008, but as of 2008, these rates stabilized and/or decreased. We found an upward trend for hospitalization percentage in CC (from 22.3% to 30%; p<0.001), ESLD (from 23.9% to 27.1%; p<0.001), HCC (from 7.4% to 11%; p<0.001), and LT (from 0.07% to 0.10%; p<0.001), HCC (from 7.4% to 11%; p<0.001), and LT (from 0.07% to 0.10%; p<0.001), HCC (from 7.4% to 11%; p<0.001), and LT (from 0.07% to 0.10%; p<0.001). We also found an upward trend for case fatality rate, except in ESLD (p=0.944). Gender and age influenced the evolution of hospitalization rates and mortality differently. LOS showed a significant downward trend in all strata analyzed (p<0.001) (Fig 1A). Cost per patient had a significant upward trend (p<0.001) except in LT, and a decrease from 2008-2011 to 2012-2015 in CC (p=0.025), HCC (p<0.001), and LT (p=0.050) was found (Fig 1B). Global expenditure amounted up to 1200x106 euros in 2008-2011, decreasing slightly in 2012-2015 (Fig 1C).

557 HEPATITIS C COINFECTION AND EXTRAHEPATIC CANCER INCIDENCE AMONG PEOPLE WITH HIV

Sarah J. Willis1, H. Nina Kim1, Chad J. Achenbach2, Edward R. Cachay3, Katerina A. Christopoulos1, Heidi M. Crane1, Ricardo A. Franco1, Christopher B. Hunt1, Mari M. Kizhaka1, Richard D. Moore4, Michael J. Silverberg1, Phyllis Tien1, Daniel Westreich1, Julia L. Marcus1

Background: Hepatitis C virus (HCV) coinfection may contribute to the elevated risk of cancers among people with HIV infection through increased inflammation or immune activation. Although HCV coinfection is a known risk factor for liver cancer, HCV may also be associated with an increased risk of extrahepatic cancers among people with HIV infection. However, few studies have explored the risk of extrahepatic cancers among people with HIV/HCV coinfection or the potential impact of HCV treatment using direct-acting antiviral agents (DAAs).

Methods: Our study population included adults in HIV care at a CINCS site in the U.S. during 1995-2018, excluding those with previous cancer diagnoses and those without HCV testing. We defined HCV infection by positive HCV antibody or detectable HCV RNA level up to baseline (i.e., 180 days after enrollment). Patients were followed from baseline until cancer diagnosis, death, or last HIV care visit. We used Cox regression to estimate hazard ratios (HRs) for age, sex, ethnicity, alcohol and injection substance use, social/material deprivation, and history of diabetes and hypertension were used to estimate subdistributional hazard ratios (HRs) and 95% confidence intervals (CIs) for incident ESRD. Further stratified analysis was performed accounting for diabetes.

Results: Of 524,186 individuals tested, we observed 3,762 incident ESRD events (0.7%) and 24,714 deaths (4.7%) during a median follow-up of 4.1 years. The highest ESRD incidence rate (per 1,000 person-years) was observed in persons with triple HBV/HCV/HIV infection (26.7) followed by HCV/HIV (10.2), HBV/HIV (10.0), HCV/HBV coinfection (5.8), and HIV (3.8), HCV (3.0) and HBV mono-infection (1.8) (Figure). In multivariable analysis, relative to those with no chronic infections, those with triple infection had the highest relative hazard for ESRD (HR 34, 95% CI: 29-41). When stratified by diabetes status, triple infection still had the highest relative hazard for ESRD (HRs 19, 95% CI: 15-24 and 30, 95% CI: 26-35) for both persons with diabetes and those without, respectively.

Conclusion: Extrahepatic cancers driven by immune dysfunction, specifically kidney cancer, may be prevented by HCV-curative DAA therapies among patients with HIV/HCV coinfection.
CAUSES OF DEATH AMONG THOSE DIAGNOSED WITH HEPATITIS C IN WASHINGTON, DC, 2009-2017

Jenevieve Opoku1, Adam Allston1
1District of Columbia Department of Health, Washington, DC, USA

Background: There was very limited research on mortality among people diagnosed with Hepatitis C (HCV) in the District of Columbia (DC). As the opioid use crisis continues to grow both nationally and locally, knowledge of how opiate use deaths has had an impact on residents, especially among those with HCV, may be useful in strategizing intervention programs. The purpose of this analysis is to describe the differentiating causes of death among those diagnosed with HCV in DC.

Methods: Data from DC Health HCV surveillance system and Vital Statistics records were matched to identify DC residents diagnosed with HCV who died between 2009 and 2017. Bivariate analysis was performed to identify differences between opiate overdose and non-opiate overdose deaths by demographics including gender identity, race/ethnicity age at death, HIV co-infection, year of death, HCV diagnosis class and last RNA results. Standardized mortality ratios for all causes of death were calculated and adjusted for age, sex, and death year.

Results: Between 2009 and 2017, there were 4,633 deaths among DC residents diagnosed with HCV. Majority of deaths were among those who were male (68.1%), Black (60.2%) and died between the ages of 50 and 69 (76.5%). Cardiovascular disease was the leading cause of death (30.6%) followed by non-AIDS defining cancers (12.6%), opiate overdose (9.8%) and liver diseases (8.9%). Over the 9-year period, there was a 561% increase in opiate overdose between the ages of 50-69 (84.1% vs 75.6%, p<.0001), and have a positive/detectable result at their year of death.

Discussion: The majority of deaths HCV+ persons. Self-harm is responsible for twice as many deaths in HCV+ vs. HCV-.

Conclusion: Liver disease, ASCVD and malignancy are responsible for the majority of deaths of HCV+ persons. Self-harm is responsible for twice as many deaths in HCV+ vs. HCV-.

Targeted strategies to reduce non-liver-related causes of death are needed to reduce mortality further in HCV+ persons.

Methods: HCV infected and uninfected participants in the ERCHIVES cohort between Jan 1, 2002 to December 31, 2016 were included. To determine cause of death, we linked deceased ERCHIVES participants to the National Death Index (NDI) data updated to end of 2016. NDI is a part of the National Center for Health Statistics and compiles cause of death data from the death certificates obtained from state vital statistics offices. Cause of death was retrieved from the underlying cause listed on the death certificate by using ICD-10 codes. Each cause of death was categorized according to the primary organ system listed in the cause of death form. Liver-related causes included viral hepatitis and HCC, but excluded alcohol-related liver disease. Malignancy included all malignant cancers but excluded benign neoplasms and HCC. Self-harm category included suicide, intentional self-harm, intentional and unintentional drug-overdose but excluded accidental death due to external causes, e.g. road traffic accidents, homicide and falls.

Results: Among 754,670 ERCHIVES participants, a total of 182,744 deaths were recorded during the study period (113,650 in HCV+ and 69,094 in HCV-). Among persons with HCV, the five most common causes of death were: Liver related (19.6%); malignancy (18.0%); ASCVD (16.8%); self-harm (6.2%); pulmonary disease (5.6%). Among those without HCV, the five most common causes were: Malignancy (25.2%); ASCVD (23.0%); pulmonary disease (7.8%); infections (5.4%); endocarditis including diabetes (5.1%).

Conclusion: Liver disease, ASCVD and malignancy are responsible for the majority of deaths of HCV+ persons. Self-harm is responsible for twice as many deaths in HCV+ vs. HCV-.

Targeted strategies to reduce non-liver-related causes of death are needed to reduce mortality further in HCV+ persons.

Methods: In order to reach WHO’s goal of HCV elimination it has been suggested to prioritize populations that are actively propagating infection, given e.g. several outbreaks of HCV among HIV-infected men who have sex with men in the last decade. Genotyping the infecting virus is part of routine care to guide antiviral treatment, but commercial assays have been shown to occasionally report inaccurate results. In this study, we use next-generation sequencing (NGS) to increase the discriminatory power and evaluate the accuracy of genotyping in routine HCV care.

Methods: From the University Hospitals of Leuven, Belgium, 64 samples from patients with HCV/HIV co-infection were selected and matched with 86 samples from HCV mono-infected patients to exhibit a similar genotype distribution based on determinations with the VERSANT HCV Genotype Assay. For the co-infected patients, 30.4%, 66.1%, and 46.4% reported intravenous drug use, same-sex practices, and being born outside of Belgium, respectively. HCV genomes were generated using the veSeq-HCV protocol and an in-house optimized bioinformatics pipeline. Concordance between geno- and subtypes designated by VERSANT and the Hepatitis C Virus Phylogenetic Typing Tool v2.4 using the generated consensus sequence was determined.

Results: When considering only the 87 samples with an associated VERSANT genotyping record and >90% of the coding region of HCV sequenced to a depth >100, the genotype distribution following NGS was: genotype 1a: 72% (42: 1b, 21: 1a), genotype 4: 15% (8: 4d, 2: 4k, 1 each: 4c, 4r), genotype 3: 9% (3: 3a).
and genotype 2: 3% (1 each: 2a, 2c, 2i). Despite not all samples passing quality control thresholds, 112 samples had both a genotype determined by VERSANT and the phylogenetic typing tool. Of these, 78% had identical subtypes using VERSANT and NGs, 20% had a genotype specified into one of its constituent subtypes, one sample had a different subtype (VERSANT: 1b, NGs: 1a) and one had a different genotype (VERSANT: 1a, NGs: 4d). Based on near full-genome coverage by contigs of different genotypes generated de novo, 5 samples showed signs of mixed infection not indicated by VERSANT.

Conclusion: While the applied sequencing strategy requires further optimisation to reliably classify all geno- and subtypes across a broad viral load range, a good overall concordance was found with the genotype determined by VERSANT. The higher resolution of NGs proves capable of resolving specific subtypes and detecting cases of potential mixed infections.

**562 VIROLOGIC PATTERNS OF HCV PATIENTS WITH FAILURE TO SECOND-GENERATION DAA**

**563 RESISTANCE-ASSOCIATED SUBSTITUTIONS (RAS) IN “UNUSUAL” HCV SUBTYPES**

**Table 1: Demographic, virological and clinical characteristics of the patients enrolled**

<table>
<thead>
<tr>
<th>No. patients</th>
<th>62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>67 (32-80)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>47 (75.8)</td>
</tr>
</tbody>
</table>

**Results:** Table 1 shows characteristics of patients enrolled and type of treatment. According to therapeutic outcome, 90.5% relapse, 4.7% breakthrough and 4.7% non-response. Among the 63 patients failed at three therapeutic regimens, 19 (30.1%) were treated with Sofosbuvir+Velpatasvir, 11 (17.4%) with Glapecaprevir/Pibrentasvir and 33 (52.4%) with Elbasvir/Grazoprevir. The duration of DAA in months, median (range) 12 (8-24), the timing of resistance test in months at the end of treatment, median (range) 5 (1-19). The NSSA-RASs were more frequent in Sofosbuvir+Velpatasvir (17/19, 89.5%) and in Grazoprevir/Elbasvir (32/33, 97%) failed patients than in Glapecaprevir/Pibrentasvir (4/11, 36.7%) failed patients (p=0.002 and 0.0000 respectively). According to Sofosbuvir/Velpatasvir regimen 36.4% pts showed at least 2 RAs at least two HCV region including NSSA and 70.3% pts showed at least 2 RAs only in NSSA region. Considering Grazoprevir/Elbasvir regimen 27.3% pts showed at least 2 RAs at least two HCV region including NSSA and 88% pts showed at least 2 RAs only in NSSA region.

**Conclusion:** Patients with failure to a second-line therapeutic regimen frequently present mutations above all in the NSSA region. At re-treatment all patients obtained SVR. According to our real-life experience, re-treatment with regimens observed at the laboratory of infectious diseases of University of Campania, Naples from January 2018 to February 2019 were enrolled. All the pts had been treated with DAA-regimens according HCV genotype, international guidelines and local availability. Sanger sequencing of NS3 (for genotypes 1 and 4), NSSA and NSSB (for all genotypes) was performed at failure by home-made protocols.

**Background:** Despite the excellent efficacy, direct-acting antivirals (DAA)-regimens are associated with failure in about 5% of cases. To characterize the virologic patterns and the resistant-associated substitutions (RASs) in the patients with failure to second-line DAA-regimen. It may help to identify the best approach of new line DAA-regimen.

**Methods:** All the consecutive 63 HCV patients (pts) with failure to IFN-free regimen observed at the laboratory of infectious diseases of University of Campania, Naples from January 2018 to February 2019 were enrolled. All the pts had been treated with DAA-regimens according HCV genotype, international guidelines and local availability. Sanger sequencing of NS3 (for genotypes 1 and 4), NSSA and NSSB (for all genotypes) was performed at failure by home-made protocols.

**Results:** Table 1 shows characteristics of patients enrolled and type of treatment. According to therapeutic outcome, 90.5% relapse, 4.7% breakthrough and 4.7% non-response. Among the 63 patients failed at three therapeutic regimens, 19 (30.1%) were treated with Sofosbuvir+Velpatasvir, 11 (17.4%) with Glapecaprevir/Pibrentasvir and 33 (52.4%) with Elbasvir/Grazoprevir. The duration of DAA in months, median (range) 12 (8-24), the timing of resistance test in months at the end of treatment, median (range) 5 (1-19). The NSSA-RASs were more frequent in Sofosbuvir+Velpatasvir (17/19, 89.5%) and in Grazoprevir/Elbasvir (32/33, 97%) failed patients than in Glapecaprevir/Pibrentasvir (4/11, 36.7%) failed patients (p=0.002 and 0.0000 respectively). According to Sofosbuvir/Velpatasvir regimen 36.4% pts showed at least 2 RAs at least two HCV region including NSSA and 70.3% pts showed at least 2 RAs only in NSSA region. Considering Grazoprevir/Elbasvir regimen 27.3% pts showed at least 2 RAs at least two HCV region including NSSA and 88% pts showed at least 2 RAs only in NSSA region.

**Conclusion:** Patients with failure to a second-line therapeutic regimen frequently present mutations above all in the NSSA region. At re-treatment all patients obtained SVR. According to our real-life experience, re-treatment with the new regimes is effective and safe.

**Background:** Despite the excellent efficacy, direct-acting antivirals (DAA)-regimens are associated with failure in about 5% of cases. To characterize the virologic patterns and the resistant-associated substitutions (RASs) in the patients with failure to second-line DAA-regimen. It may help to identify the best approach of new line DAA-regimen.

**Methods:** All the consecutive 63 HCV patients (pts) with failure to IFN-free regimen observed at the laboratory of infectious diseases of University of Campania, Naples from January 2018 to February 2019 were enrolled. All the pts had been treated with DAA-regimens according HCV genotype, international guidelines and local availability. Sanger sequencing of NS3 (for genotypes 1 and 4), NSSA and NSSB (for all genotypes) was performed at failure by home-made protocols.

**Results:** Table 1 shows characteristics of patients enrolled and type of treatment. According to therapeutic outcome, 90.5% relapse, 4.7% breakthrough and 4.7% non-response. Among the 63 patients failed at three therapeutic regimens, 19 (30.1%) were treated with Sofosbuvir+Velpatasvir, 11 (17.4%) with Glapecaprevir/Pibrentasvir and 33 (52.4%) with Elbasvir/Grazoprevir. The duration of DAA in months, median (range) 12 (8-24), the timing of resistance test in months at the end of treatment, median (range) 5 (1-19). The NSSA-RASs were more frequent in Sofosbuvir+Velpatasvir (17/19, 89.5%) and in Grazoprevir/Elbasvir (32/33, 97%) failed patients than in Glapecaprevir/Pibrentasvir (4/11, 36.7%) failed patients (p=0.002 and 0.0000 respectively). According to Sofosbuvir/Velpatasvir regimen 36.4% pts showed at least 2 RAs at least two HCV region including NSSA and 70.3% pts showed at least 2 RAs only in NSSA region. Considering Grazoprevir/Elbasvir regimen 27.3% pts showed at least 2 RAs at least two HCV region including NSSA and 88% pts showed at least 2 RAs only in NSSA region.

**Conclusion:** Patients with failure to a second-line therapeutic regimen frequently present mutations above all in the NSSA region. At re-treatment all patients obtained SVR. According to our real-life experience, re-treatment with the new regimes is effective and safe.
detected in specific subtypes (GT4q with R155Q +A156T/I-V+D168N, GT6q with A156F and type of treatment B and G, respectively). The S282T variant in NS5B occurred in 20% of GT4r patients (n=1).

Conclusion: Unusual subtypes (mainly but not only GT3b, 3h, and 4r) may be overrepresented among failures, suggesting lower SVR rates due to the presence of polymorphisms. In-depth characterization of these subtypes is crucial, in Africa and Asia where these subtypes are common as well as in countries of immigration from these regions. Our results emphasize the need for identification of RAS in these subtypes and their in vitro drug susceptibilities.

564 TRANSMISSION OF THE NSSA-RESISTANT VARIANT M28V AMONG ACUTE HIV/HCV COINFECTED MSM

Stephanie Popping1, Rosanne Verwij1, Lize Cuppers2, Mark Claassen3, Guido Van Den Berk4, Anja De Weggehele1, Joop E. Arends4, Anne Boerenkamps4, Richard Molenkamp4, Marion Koopmans5, Annelies Verbor1, Charles Boucher1, Bart Rijnders1, David Van De Vijver1
1Erasmus University Medical Center, Rotterdam, Netherlands, 2Katholieke Universiteit Leuven, Leuven, Belgium, 3Rijnstate Hospital, Arnhem, Netherlands, 4OLVG, Amsterdam, Netherlands, 5Institute of Tropical Medicine, Antwerp, Belgium, 6University Medical Center Utrecht, Utrecht, Netherlands

Background: The World Health Organization (WHO) has declared to eliminate hepatitic C virus (HCV) as a global health threat by 2030. To achieve this goal, WHO recommends expanding direct-acting antivirals (DAAs), which can achieve high cure rates and thereby prevent onward transmission. Widespread use of DAAs has drastically reduced new HCV infections in the Netherlands. Unfortunately, virological failure can still occur and is associated with emergence of resistance associated substitutions (RAS). Transmission of RAS can hamper HCV elimination efforts. In Western Europe, HCV is predominantly transmitted between HIV-positive men-who-have-sex-with-men (MSM). We investigated the transmission dynamics of HCV and its specific RAS among MSM, before and after the widespread use of DAAs.

Methods: We included 90 plasma samples from 101 acute HCV genotype 1a infected HIV-positive MSM that were diagnosed in one Belgian and ten Dutch HIV-treatment centres between 2013 and 2018. Samples were subjected to Sanger sequencing or illumina sequencing, using a 15% cut-off for variant calling. RAS were defined based on the EASL guidelines. Phylogenetic analysis was based on concatenated NSSA and NS5B sequences from the included plasma samples and from 425 publicly available sequences. Clusters were defined based on a bootstrap support of 100% and a genetic distance of <1.5% (maximum likelihood analysis GTR+G+I).

Results: We found strong clustering of HCV sequences and distinguished five major clusters including 84% of individuals. Four clusters included at least 10 individuals that were sampled in different treatment centres. One-third of all new HCV infections (28 individuals) clustered in one large cluster, of which 96% harboured the NSSA RAS M28V. The number of clusters and the proportion of individuals belonging to a cluster remained stable in the period before and after introduction of DAAs in 2015.

Conclusion: Large clusters of acute HCV infections were detected in the years preceding as well as after introduction of DAAs, suggesting active transmission of HCV among HIV-infected MSM. A stable transmission of the RAS M28V was found, which is known to influence susceptibility to some of the NSSA inhibitors. The continuing transmission of M28V illustrates the need for resistance surveillance in populations with ongoing HCV transmission. Despite elimination efforts, most clusters persisted, highlighting the need for targeted monitoring and risk reduction strategies to achieve HCV elimination.

565 RESISTANCE ANALYSIS IN HCV-3-INFECTED PATIENTS WITHIN THE ITALIAN NETWORK VIRONET-C

Velia Chiara Di Maio1, Silvia Barbaliccia1, Elisabetta Treti1, Caterina Pasqua2, Stefania Paolucci1, Teresa Pollicino1, Bianca Bruzzone1, Nicola Coppola2, Valeria Michel1, Fausto Baldanti2, Giustino Parruti10, Mario Angelico2, Massimo Andreoni2, Carlo Federico Perino3, Francesca Ceccherini Silberstein4, University of Rome Tor Vergata, Rome, Italy, 2Hospital of Rome Tor Vergata, Rome, Italy, 3Sapienza University of Rome, Rome, Italy, 4IRCSc Pollicino San Matteo Foundation, Pavia, Italy, 5University of Hong Kong, Hong Kong, China, 6University of Missouri, Columbia, MO, USA, 7University of Rome Tor Vergata, Rome, Italy, 8University of Rome Tor Vergata, Rome, Italy, 9University of Hong Kong, Hong Kong, China, 10University of Naples, Naples, Italy, 1IRCSc Pollicino San Matteo Foundation, Pavia, Italy, 2Pescara Hospital, Pescara, Italy, 3University of Milan, Milan, Italy

Background: This study aimed to investigate the presence and role of resistance-associated substitutions (RASs) in HCV genotype 3 (GT3).

Methods: Within the Italian VIRONET-C network, a total of 539 GT3 infected patients (pts, 417 DAA-naive and 135 DAA-failures, of them, 13 at both baseline [BL] and failure), were analysed. Sanger-sequencing of NS3/NS5A/NS5B was performed by home-made protocols.

Results: The majority of pts were male (79%) and cirrhotic (50%). 23 pts (14%) were HIV-coinfected. Phylogenetic analysis classified sequences as GT3a-3b, 3h (98%-0.4%-0.2%-1.2%), respectively. Notably, 39 pts were previously misclassified as infected with GT indeterminate, non-3, or mixed (N=10/22/7, respectively). Overall, 135 GT3 pts failed an interferon-free regimen: sofosbuvir/SOF (n=148/260), or voxilaprevir/VOX (n=9/15) and glecaprevir/G/plebirentavir (n=9/15). More than 14.8% of pts were treated with suboptimal regiments for GT3: 3b: RVR (n=2/260), 3h: RVR (n=55/260). A total of 1159 NS3 variants were observed in 228 pts (42%). In 212 pts, NS5A variants were observed in 84% of individuals. Four clusters included at least 10 patients, whereas 282 clusters were detected only in SOF/DCV failures (5% and 1%, respectively). Regarding DAA-naive pts with an available outcome, 228 were treated with the following regiments: SOF/DCV or VOX (N=150/475) and G/P (N=31). Overall, 94% achieved a SVR. In particular, for pts with BL Y93H and/or A30K the overall SVR rate was 72% vs 96% for pts without NSSA RASs (p=0.002).

Conclusion: In this large cohort of GT3 infected pts, the majority of failures harbored resistant HCV variants carrying one or two NSSA RASs, the most frequent being Y93H. The presence of natural NSSA RAS before treatment was associated with failure. Further analyses are needed to confirm this observation, particularly for the new current regimens.

566 BARRIERS TO DIRECTLY ACTING ANTIVIRALS THERAPY AMONG HIV/HCV-COINFECTED ADULTS

Gina M. Simiconci1, Qingjiang Hou2, Kate Buchacz3, Ellen Tedaldi1, Frank J. Palella4, Jack Fuhrer5, Richard M. Novak6, Cynthia Mayer1, David E. Korn1, Linda A. Battalora5, Stockton Mayer1, Stacey Purinton1, Jon Ll1, For the HIV Outpatient Study (HOPS) Investigators
1Temple University, Philadelphia, PA, USA, 2Cerner Corp, Kansas City, MO, USA, 3C/O, Atlanta, GA, USA, 4Northwestern University, Evanston, IL, USA, 5Stony Brook University, Stony Brook, NY, USA, 6University of Illinois at Chicago, Chicago, IL, USA, 7St. Joseph’s Comprehensive Research Institute, Tampa, FL, USA, 8Colorado School of Mines, Golden, CO, USA, 9University of Illinois College of Medicine, Peoria, IL, USA

Background: HIV and chronic hepatitis C virus (HCV) coinfection carries substantial risk for all-cause mortality and liver-related morbidity and mortality; yet many people co-infected with HIV/HCV remain untreated for HCV infection. We explored demographic, clinical variables and social determinants of health among coinfected participants in routine HIV care that may differentiate those treated versus untreated with directly-acting antivirals (DAA).

Methods: We analyzed medical record data as of December 31, 2018 of HIV Outpatient Study (HOPS) participants seen at 9 U.S. clinics who were diagnosed with HCV with at least one confirmatory HCV RNA viral load (VL) test or genotype test since June 30, 2010. DAA therapy was determined by medication prescription from the HOPS database. Participants treated with interferon/ribavirin along with DAA were excluded. Based on bivariate analyses, factors associated with the probability of receiving DAA therapy were further evaluated by multivariable logistic regression.

Results: Among 306 eligible participants, median age was 52 years, median duration of follow up was 3.96 years, 97 (32%) were female, and 202 (66%) were non-white, 131 (42.8%) were prescribed DAA therapy, 127 (96.9%) had at least one follow-up HCV VL and 13 (9.5%) participants remained HCV viremic 12 months after initiating DAA therapy, resulting in an overall cure rate of 90.1%. DAA treatment was not associated with patient’s race and ethnicity (p=0.17).
MEDICAID HCV TREATMENT RESTRICTIONS: SPILLOVER TO THE PRIVATE-PAYER HCV CARE CASCADE?

Rachel Epstein, Jianing Wang, Jack K. Morgan, Shashi Kapadia, Yuhua Bao, Laura F. White, Benjamin P. Lina
1Boston Medical Center, Boston, MA, USA, 2Boston University, Boston, MA, USA, 3Cornell University, Ithaca, NY, USA

Background: Medicaid HCV treatment restrictions limit access to HCV care. There is evidence that public insurance policies influence care more broadly, even among commercially insured patients. Further, if states limit HCV treatment access, screening may lag due to decreased provider motivation. This study investigates whether Medicaid HCV treatment restrictions ‘spillover’ to affect HCV testing among patients with commercial insurance.

Methods: We linked the MarketScan commercial claims database to the National Viral Hepatitis Roundtable state-by-state categorization of Medicaid HCV treatment policies. We considered any requirement for negative drug testing prior to HCV treatment to be a restrictive abstinence-based policy and any requirement that a patient have evidence of Metavir fibrosis stage F2 or greater to be a restrictive fibrosis-based policy. We categorized states into four groups: 1) maintained low fibrosis or abstinence restrictions over the study period (2014-2017), 2) relaxed both fibrosis and abstinence restrictions, 3) relaxed only one restriction type, and 4) maintained high restrictions in both domains. We analyzed HCV testing rates across these groups in 18-64-year-olds. We used negative binomial regression adjusted for calendar time and for sociodemographic factors over time, health insurance had a substantial positive effect on DAA initiation. Interventions to improve insurance coverage, such as Medicaid expansion or subsidies for private plans, should be prioritized in order to increase uptake of HCV curative therapy for persons with HIV.

These data suggest, however, that Medicaid HCV treatment restrictions may have spillover effects that hinder HCV elimination progress across all payers.

Conclusion: Only 42.8% of HIV/HCV-coinfected participants have been treated to increase uptake of HCV curative therapy for persons with HIV.
569 MOBILE HCV SCREENING IN AN AT-RISK URBAN POPULATION IDENTIFIES SIGNIFICANT FIBROSIS

Jennifer C. Price1, Rachel Kanner1, Emily Valadao1, Yesenia S. Laguardia1, Maria Duarte1, Norah A. Terrault1
1University of California San Francisco, San Francisco, CA, USA, 2University of Southern California, Los Angeles, CA, USA

Background: Most people living with hepatitis C virus (HCV) remain undiagnosed, impacting HCV elimination efforts. We designed a mobile unit to bring HCV screening and liver fibrosis staging to at-risk communities in San Francisco.

Methods: A university shuttle bus was furnished with a phlebotomy station, Fibroscan®430 Mini+ and clinical exam table. Screening with the OraQuick® HCV Rapid Antibody (Ab) test was performed at: 1) community events 2) street outreach and 3) outside methadone programs. HCV Ab+ clients were offered venipuncture for confirmatory HCV RNA, liver stiffness measurement (LSM) and linkage to care. Significant fibrosis and advanced fibrosis were defined as LSM ≥7.0 kPa and ≥9.5, respectively.

Results: From 1/17/2019-9/13/2019, 428 people underwent HCV Ab screening at community events (12%), street outreach (72%) and methadone programs (15%). Median age was 53 (IQR 43-62), 67% were male, 49% reported living outdoors or in a vehicle in the past year, and 5% were HIV-positive. Overall, 156 were HCV RNA+ (36%), and prevalence varied by screening location: 17% at community events, 34% at street outreach sites, and 66% outside methadone programs (p<0.001). HCV Ab+ individuals were more likely than HCV Ab- to be white (44% vs 32%, p=0.003), have Medi-Cal insurance (80% vs 61%, p<0.001), and report ever injection drug use (IDU) (86% vs 29%, p<0.001), ever smoking crack or speed (87% vs 64%, p<0.001), current IDU (54% vs 16%, p<0.001), current non-IDU (67% vs 50%, p=0.001), or history of incarceration (74% vs 53%, p<0.001). Among the HCV Ab+, 73% had HCV RNA testing and 36% were HCV RNA+. Fifty-nine of the HCV Ab+ underwent LSM: 27 (46%) and 16 (27%) had significant and advanced fibrosis, respectively. Fibrosis prevalence was similarly high regardless of HCV RNA status. The majority of the HCV RNA+ had health insurance (91%) and a primary care provider (PCP) (68%). Among the 44 HCV RNA+, 25 were referred to further HCV care, including 8 who were referred to an HCV provider on the van, 4 of whom have started HCV treatment on the van.

Conclusion: HCV screening on a mobile van in a large urban center demonstrated a high prevalence of HCV Ab+ (36%) among high-risk groups, with one-fourth having advanced fibrosis. Despite the majority having insurance and a PCP, 38% of the HCV Ab+ had active HCV viremia. This underscores the need for heightened efforts to improve HCV treatment access to high-risk groups and has motivated a program offering HCV treatment on the mobile unit.

570 PROGRESS AND REAL-LIFE CHALLENGES FOR HCV ELIMINATION IN PEOPLE LIVING WITH HIV

Edward R. Cachay1, Francesca Torriani1, Lucas Hill1, Craig Ballard2, Abigail Aquino1, Huifang Qin1, Sonia Jain1, Natasha Martin1, W. C. Mathews1
1University of California San Diego, La Jolla, CA, USA

Background: The state of California has provided unrestricted access to direct-acting antivirals (DAAs) since January 2018 for people living with HIV (PLWH). We aim to assess the impact of the hepatitis C virus (HCV) treatment uptake among PLWH on HCV population viremia and identify health-system areas for improvement to achieve HCV elimination.

Methods: Retrospective cohort of PLWH with active HCV infection (detectable HCV viral load) under care at UC San Diego between 2014 and June 2019. We describe the annual proportion of PLWH with active HCV who started DAA therapy and the resulting cumulative population level of HCV viremia. Our cohort was then divided into early DAA (2014-2017) and unrestricted DAA (2018-2019) era groups. We compared the difference of proportion in health system landmarks of HCV treatment referral, HCV care uptake, staged/retained/prescribed DAA therapy, DAA treatment initiation, and HCV care between the two groups.

Results: Following DAA approval, of 3,111 PLWH in care, 493 (15.9%) had HCV Ab positive and 263 (33.4%) of whom had active HCV viremia. The proportion of viremic patients starting DAA therapy increased from 13.5% in 2014 to 41% in 2017. After the first year of unrestricted DAA access, HCV treatment uptake increased to 54.9% and then dropped to 32% in 2019. The overall HCV population viremia among those with HCV Ab positive decreased from 53.4% in 2014 to 12.5% in 2019 (figure, panel A). In comparison to the early DAA era, following unrestricted DAA access, the proportion of patients who did not initiate therapy after establishing HCV care decreased from 22% to 14%.

During the early DAA era and after establishing HCV care, the main reason for not initiating DAA was lack of insurance approval. In contrast, all PLWH who did not start DAA in the DAA unrestricted era were due failure to pick up their approved DAA or lost to follow-up. Despite DAA unrestricted access in 2018, there was almost a 2-fold increase in the proportion of PLWH not linked to HCV care (figure, panel B). Among those patients with active viremia, the number of patients engaged in their HIV care decreased from 95% in 2014 to 63% after one year of unrestricted DAA access.

Conclusion: HCV linkage and HCV retention in care have emerged as main challenges among PLWH for HCV treatment uptake. As many of the remaining PLWH in need of DAA are not fully engaged in HIV care, DAA treatment outside conventional health system is needed to achieve HCV micro-elimination.

571 REAL-WORLD EFFECTIVENESS OF GLECAPREVIR/PIBRENTASVIR FOR HEPATITIS C VIRUS INFECTION

Lourdes Domínguez-Domínguez1, Juan Berenguer1, Ángela Gil-Martín1, Diego Rincón2, Antonio Olveira1, Inmaculada Fernández1, Beatriz Álvarez1, Laura Benitez1, Ignacio Santos2, José Barrio Antoranz3, Elvira Poves4, Juan E. Losa5, Inma Jarrin1, María J. Calvo3, Juan González-García1, for the RUA-VCH Study Group
1Hospital Universitario 12 de Octubre, Madrid, Spain, 2Hospital General Universitario Gregorio Marañón, Madrid, Spain, 3Subdirección General de
Background: Glecaprevir and pibrentasvir (GLE/PIB) are direct-acting antiviral agents (DAAs) with pan-genotypic activity and a high barrier to resistance. We evaluated the effectiveness and safety of GLE/PIB in a large prospective registry HCV-infected individuals with /without coinfection by HIV and receiving DAAs for HCV infection.

Methods: RUA-VHC (Madrid Registry of Use of DAA for HCV) is a prospective registry of HCV-monoinfected (MoP) and HIV/HCV-coinfected (CoP) individuals receiving all-oral DAAs in hospitals of the Madrid Regional Health Service. RUA-VHC was created in November 2014 (Hepatology 2017; 66:344). For this study, we selected patients with chronic hepatitis C who had received once-daily treatment with 3 tablets of the fixed-dose combination of GLE/PIB (total dose: 300 mg/120 mg) and were scheduled to finish treatment on or before 01/February/2019. Retreatment after all-oral DAA therapy was excluded. We assessed sustained virologic response at 12 wk by intention-to-treat (ITT) and by a modified intention-to-treat approach (m-ITT), in which non-virological failures for reasons other than discontinuation of treatment secondary to adverse events or death were not considered in the analysis.

Results: A total of 1,183 patients (1,078 MoP/105 CoP) met the inclusion criteria. Treatment duration was 8 weeks in 1,063 patients (964 MoP/99 CoP), 12 weeks in 115 patients (109 MoP/6 CoP), and 16 weeks in 5 MoP. Median age was 54 years, 51.7% were men, 9.4% had been treated previously with interferon-based anti-HCV therapies, and 7.0% had cirrhosis. Genotype distribution was as follows: G1, 70.7%; G3, 10.6%; G4, 10.2%; G2, 3.5%; Other/mixed/unknown genotypes accounted for 4.8%. Patient characteristics and treatment results overall and by treatment duration and the presence of HCV coinfection are shown in the Table. Sustained virologic response rates were 97.7% (95% CI, 96.7%-98.5%) by ITT and 99.0% (95% CI, 98.2%-99.5%) by m-ITT analysis. The presence of HIV or genotype distribution did not influence treatment response.

Conclusion: In this large prospective real-life cohort of patients with hepatitis C, treatment with GLE/PIB led to SVR rates of almost 98%. Treatment with GLE/PIB was highly efficacious across all genotypes and in the presence of HCV infection or liver cirrhosis.

572 REAL-WORLD EFFECTIVENESS OF SOFOSBUVIR/VELPATASVIR FOR HEPATITIS C VIRUS INFECTION

Teresa Aldán-Echevarría 1, Juan Berenguer 1, Ángel Gil-Martín 2, Javier García-Samaniego 3, Laura Marquez 1, José L. Calleja 4, Luz Martin-Carbonero 3, Ana Moreno 1, Benjamín A. Polo Lorduy 1, Pablo Ryan 1, Luisa Consuelo García Buey 5, María J. devesa 1, Inma Jarrín 1, María J. Calvo 1, Juan González-García 1
1Hospital General Universitario Gregorio Marañón, Madrid, Spain, 2Subdirección General de Farmacia, Madrid, Spain, 3La Paz University Hospital, Madrid, Spain, 4Hospital Puerta de Hierro, Madrid, Spain, 5Hospital Universitario Infanta Leonor, Madrid, Spain, 6Hospital Universitario Príncipe de Asturias, Madrid, Spain, 7Hospital Universitario Fundación Alcorcón, Alcorcón, Spain, 8Instituto de Salud Carlos III, Majadahonda, Spain

Background: Little is known about the real-world effectiveness of sofosbuvir and velpatasvir (SOF/VEL), a direct-acting antiviral agent (DAA) regimen with pan-genotypic activity. We evaluated the effectiveness and safety of SOF/VEL in a large prospective registry of individuals receiving DAAs for HCV.

Methods: RUA-VHC (Madrid Registry of Use of DAA for HCV) is a prospective registry of HCV-monoinfected (MoP) and HIV/HCV-coinfected (CoP) individuals receiving all-oral DAAs in the hospitals of the Madrid Regional Health Service.

Results: A total of 1,003 patients (888 MoP/115 CoP) met the inclusion criteria. Median age was 55 y, 61.1% were men, 10.3% were previously treated, 19.7% had compensated cirrhosis, and 3.9% had decompensated cirrhosis. Genotype distribution was as follows: G1, 40.0%; G2, 11.2%; G3, 36.9%; G4, 6.7%. Other/mixed/unknown genotypes accounted for 4.4%. Statistically significant differences were observed between MoP and CoP at baseline for age, gender, and genotype distribution. SVR rates overall were 95.4% by ITT and 97.9% by m-ITT. The presence of HIV or genotype distribution did not influence response to treatment. The SVR rate was lower in patients with decompensated cirrhosis than in patients without cirrhosis both by ITT (87.2% vs 96.1%, P=0.008) and by m-ITT (91.9% vs 98.3%, P=0.003).

Conclusion: In this large cohort of patients with hepatitis C, 12 wks of treatment with SOF/VEL led to SVR rates > 95%. Treatment with SOF/VEL was highly efficacious across all genotypes and in the presence of HIV. Response to treatment was significantly poorer in patients with decompensated cirrhosis than in patients without cirrhosis.

573 A MULTICENTER REGISTRY IN PATIENTS WITH HIV/HCV COINFECTION ON LEDIPASVIR/SOFOSBUVIR

Stefan Mauss 1, Cody A. Chastain 2, Nwora L. Okeke 3, Kristen M. Marks 4, Kimberly Workowski 1, Gregory K. Robbins 1, Kenneth E. Sherman 1, Chris Woods 1, Lawrence Park 1, Jürgen K. Rockstroh 3, Susanna Nagy 3, Hannah Robinson 1, 1Center for HIV and Hepatogastroenterology, Düsseldorf, Germany, 2Vanderbilt University, Nashville, TN, USA, 3University of Cincinnati, Cincinnati, OH, USA, 4Weill Cornell Medicine, New York, NY, USA, 5Emory University, Atlanta, GA, 6Massachusetts General Hospital, Boston, MA, USA, 7University of Cincinnati, Cincinnati, OH, USA, 8Durham VA Medical Center, Durham, NC, USA, 9Bonn University Hospital, Bonn, Germany, 10Institute of Clinical Research Institute, Durham, NC, USA

Background: Switches in antiretroviral therapy (ART) to simplify and/or update regimens are increasingly common, with safety supported by randomized clinical trials. Switches in ARTs to limit drug interactions prior to initiating direct-acting antivirals (DAAs) for HCV are also common, although there are limited data to guide this practice and the risk of loss of HIV control is unknown. Furthermore, there are reports that ART switches may increase HCV treatment failure.

Methods: This is the final analysis of a multicenter (N=9), observational clinical registry. The study population includes patients with HIV/HCV co-infection treated with ledipasvir/sofosbuvir. Cases (ART switch prior to HCV therapy) and controls (no ART switch prior to HCV therapy) were enrolled with a targeted 1:1 ratio and a planned total enrollment of 300 patients. The primary endpoint is HIV treatment failure defined by a combined endpoint of HIV virologic failure (confirmed HIV RNA >50 copies/mL >1 week apart), discontinuation of ART regimen, progression to AIDS, or death. Secondary endpoints include nephrotoxicity and sustained virologic response (SVR12), defined as an undetectable HCV RNA 12 weeks after DAA therapy. Analyses include use of Fischer’s exact for differences in proportions.
Results: Total enrollment was 287 and 281 had evaluable data for the primary endpoint. The cohort was predominantly male (83%), with a mean age of 55 years, and 43% Black race. Patients who switched ARTs were more commonly on protease inhibitors and/or boosted-TDF regimens (Table 1). Overall, a total of 17 patients, 6% in each group, met the primary composite outcome of HIV treatment failure. Nephrotoxicity events (change from baseline creatinine of ≥0.4 mg/dL, decrease in creatinine clearance <50 mL/min or new >3+ proteinuria) occurred in 26% of patients and was not associated with ART switch or boosted-TDF during DAA therapy. Nephrotoxicity was more common in patients with lower baseline creatinine clearance or baseline proteinuria. Overall, 242 patients (14% no HCV RNA available after DAA therapy) had evaluable SVR12, which was 99%.

Conclusion: In a real-world cohort of patients with HIV/HCV co-infection receiving ledipasvir/sofosbuvir, switches in ARTs were not associated with HIV treatment failure and did not prevent nephrotoxicity events. Nephrotoxicity was more common in patients with evidence of baseline renal dysfunction although it was not associated with discontinuation of therapy. HIV treatment success was independent of ART switch.

### 574 EFFECTIVENESS OF LDV/SOF FOR HIV-POSITIVE PATIENTS WITH HCV GENOTYPE 2 INFECTION


1 National Taiwan University Hospital, Taipei, Taiwan, 2 Far Eastern Memorial Hospital, Taoyuan, Taiwan, 3 Mackay Memorial Hospital, Hsinchu, Taiwan, 4 National Cheng Kung University Hospital, Tainan, Taiwan, 5 National Taiwan University Hospital, Yunlin County, Taiwan, 6 National Taiwan University Hospital, Taipei, Taiwan, 7 Chi Mei Medical Center, Tainan, Taiwan

**Background:** While the fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) (LDV/SOF) is not approved in the US for the treatment of hepatitis C virus infection genotype 2 (HCV-2), it is approved in Taiwan, Japan, and New Zealand. Data regarding its use for HIV-positive patients with HCV-2 are sparse, however.

**Methods:** From Jan-Jun 2019, HIV-positive patients with HCV-2 seeking care at 14 designated hospitals who received LDV/SOF were included for analysis. Laboratory investigations at baseline, end of treatment (EOT), and 12 weeks off therapy (SVR12), as required by the HCV treatment program of the Taiwan National Health Insurance.

**Results:** Of 264 patients (mean age, 50.7 years) initiating DAA therapy during the study period, 84.8% were men, 83.3% injecting drug users, 15.3% men who have sex with men, and 1.1% heterosexuals. Sofosbuvir-ledipasvir (SOF/LED) was used in 52.3% of the patients, glecaprevir-pibrentasvir (GP) in 45.8%, and sofosbuvir-velpatasvir (SOF/VEL) in 1.9%. At the time of DAA initiation, all had estimated glomerular filtration rate ≥30 ml/min/1.73m², and combination antiretroviral therapy included regimens containing TAF in 27.3% of the patients, TDF 32.2%, non-TDF/TAF 40.5%, NNRTI 29.9%, PI 3.4%, and InSTI 68.6% (dolutegravir 55.8%, elvitegravir 39.8%, and raltegravir 4.4%), with 95.5% of the patients having CD4 counts ≥200 cells/mm³ and 96.6% plasma HIV RNA load <50 copies/mL. 11.4% of the patients tested positive for HBsAg and 12.2% had liver cirrhosis and 0.8% hepatocellular carcinoma. 9.5% of the patients were HCV treatment-experienced. HIV seroconversion within one year was documented in 3.8%, while injection-related HCV infection was reported in 82.2% (217/264) and sexually transmitted infection in 13.6% (36/264). The mean plasma HCV RNA load was 6.2 log₁₀ IU/mL before DAA initiation. Overall, 98.3% achieved undetectable plasma HCV RNA load (<15 IU/mL) at EOT and 96.6% achieved SVR12 (97.2% in patients receiving SOF/LED, 96.0% in GP, and 100% in SOF/VEL).

**Conclusion:** Similar to the observation in HIV-negative patients, SVR12 with DAs is high in HIV-positive patients with HCV-6.

### 576 LB ADHERENCE AND 007-TP DBS LEVELS IN ACTIVE DRUG USERS WITH HCV: THE INCLUD TRIAL

Kristina M. Brooks1, Jose R. Castillo-Mancilla1, Mary Morrow1, Samantha MalWhinney1, Sarah E. Rowan2, David L. Wyles3, Joshua Blum4, Ryan T. Huntley1, Lana M. Salahi1, Arya Tehrani1, Laura Roon1, Lane R. Bushman1, Peter L. Anderson1, Jennifer J. Kiser1

1University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 2Colorado School of Public Health, Aurora, CO, USA, 3Denver Health and Hospital Authority, Denver, CO, USA

**Background:** Active drug users may be overlooked for HCV treatment due to adherence concerns. Here, we report treatment outcomes, objective adherence data, and predictors of adherence and 007-TP in dried blood spots (DBS) (a pharmacologic measure of sofosbuvir [SOF] adherence) in active drug and/or alcohol users receiving ledipasvir (LDV)/SOF.

**Methods:** INCLUD was a prospective, open-label study of LDV/SOF x 12 wks in active drug users ages 18-70 yrs. Participants were randomized to wireless (WOT) by Wisepill® or video-based directly observed therapy (DOT) with midDOT (Emocha®). DBS and drug use by urine toxic screen and self-report were collected every 2 wks. Two-wk adherence (adh2wk) was calculated as # doses taken/
days between visits by WOT or DOT. Generalized linear models examined risk factors for ≥1 missed dose between visits (i.e., adh2wk ≥100% vs. <100%) and mixed models identified predictors of ln-transformed 007-TP. Select covariates (n=17) were screened (p<0.25), followed by backward selection (p<0.1).

Results: 60 participants received ≥1 LDV/SOF dose (47 HIV/HCV, 13 HCV only; 78% male; 22% black; 25% cirrhotic). Drug use during treatment (286 person-visits) included: 20% IV drug use, 60% THC, 37% methamphetamine, 22% opioids (street or Rx), 10% cocaine, and 57% alcohol (21% binge, 20% heavy). The SVR rate by ITT was 83% (50/60). Two did not comply with study requirements and were withdrawn, 5 were LTFU, and 3 failed treatment (1 relapse, 1 reinfection, 1 unknown). As treated ≥1 LDV/SOF dose and SVR12 available, the SVR rate was 93% (50/53). Median (IQR [range]) total adherence was 96% (83-99% [1-101%]) and adh2wk was 90% (86-100% [0-107%]). As treated total adherence was 98% (87-100% [30-101%]) in cures vs. 90% [90-91%] [89-92%] in failures. HIV coinfection, black race, and meth and cocaine use were associated with lower odds of adh2wk ≥100%, whereas THC use and DOT were associated with higher odds (Table). Geometric mean 007-TP (Nlscv) in DBS were 218 (20.1%), 495 (9.7%), and 665 (6.3%) fmol/punch for 0-50%, 50-80%, and ≥80% adh2wk. Higher eGFR, black race, younger age, and higher BMI were associated with lower 007-TP levels after controlling for adh2wk (Table).

Conclusion: Active drug users with HCV had good but variable LDV/SOF adherence using technology-based methods, with improved adherence using video DOT. 007-TP in DBS increased with adherence, and SVR12 rates were high demonstrating substantial PK feasibility. These findings support efforts to expand HCV treatment to active drug users.

577 OVERALL SURVIVAL IN HIV-POSITIVE LIVER TRANSPLANT RECIPIENTS AND THE ROLE OF DAAs

Roberto Rossotti1, Marco Merli1, Chiara Mazzarelli1, Stefano Di Sandro1, Giovanna Travi1, Raffaella Viganò1, Andrea Lauterio1, Marco Cantone1, Maria Cristina Moioli1, Luca S. Belli1, Luciano G. De Carlis1, Massimo Puoti1

1AST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Background: Liver transplantation (LT) represents the best therapeutic option for end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). In recent years, LT in HIV+ recipients showed similar survival rates compared to HIV- even though the risks of rejection and infection seem higher. Direct-acting agents (DAAs) are widely available in Italy from 2015: few data are available on their impact on mortality.

Methods: Four HCV mono-infected participants from the ANRS CO22 HEPATHER cohort were matched on age and sex to each HIV/HCV co-infected participant from the ANRS CO13 HEPAVIH cohort. All participants were treated by DAA between March 2014 and December 2017. Cox proportional Hazards models adjusted on age, sex, duration since HCV diagnosis, HCV contamination routes, HCV genotype, cirrhosis status, tobacco and alcohol consumption were used.

Results: 592 HIV/HCV co-infected and 2049 HCV mono-infected were included. Median age was 52.9 years [IQR: 49.6 ; 56.7] and 53.3 years [IQR: 49.6 ; 56.9]; 436 (73.6%) and 1498 (73.1%) were men; median duration since HCV diagnosis was 18.0 years [IQR: 12.4 ; 22.2] and 14.5 years [6.4 ; 20.8], and 159 (28.8%) and 793 (41.2%) were cirrhotic, respectively. Participants were predominantly treated by Sofosbuvir and Ledipasvir (48.8% and 34.5%, respectively) or Sofosbuvir and Daclatasvir (32.6% and 31.2%, respectively) and SVR was observed in 92.9% and 94.6% overall, respectively. After a median follow-up of 2.8 years, incidence of liver-related events was 12.4 per 1000 PY (95%CI: 7.7 ; 19.1) in HIV/HCV co-infected and 4.9 per 1000 PY (95%CI: 3.4 ; 7.1) in HCV mono-infected (p<0.078). Incidence of liver-related mortality was 5.6 per 1000 PY (95%CI: 2.8 ; 11.1) in HIV/HCV co-infected and 4.9 per 1000 PY (95%CI: 3.4 ; 7.1) in HCV mono-infected (p=0.15). Incidence of non-liver-related mortality was 12.5 per 1000 PY (95%CI: 7.9 ; 19.8) in HIV/HCV co-infected and 4.9 per 1000 PY (95%CI: 3.4 ; 7.1) in HCV mono-infected (p<0.01). After adjustment, HIV co-infection was not associated with a higher risk of liver-related events (HR=0.67 95%CI: 0.27 ; 1.67) or liver-related mortality (HR=0.94 95%CI: 0.19 ; 4.67), but the risk of non-liver-related mortality (HR=2.67 95%CI: 0.97 ; 7.37) tended to be higher in HIV/HCV co-infected.

578 HIV CONNECTION AND RISK OF MORBIDITY AND MORTALITY IN HCV PATIENTS TREATED BY DAA

Mathieu Chalouni1, Stanislas Poil2, Philippe Sogni3, Hélène Fontaine3, Karine Lacombe3, Jean-Marc Lacombe3, Laure Esterle3, Camille Gilbert3, Céline Dorival5, Dominique Salmoni2, Caract Fracib3, Linda Wittkop1, for the ANRS CO22 HEPATHER cohort and ANRS CO13 HEPAVIH cohort Study Groups

1INSERM, Bordeaux, France; 2Assistance Publique – Hôpitaux de Paris, Paris, France; 3Paris Descartes University, Paris, France; 4Saint-Antoine Hospital, Paris, France; 5Institut Pierre Louis d’Épidémiologie et de Santé Publique, Paris, France; 6University of Bordeaux, Bordeaux, France

Background: HIV co-infection leads to increased mortality, liver disease progression and extra-hepatic manifestations in HCV-infected patients. DAA lead to high SVR rates and decrease the risk of disease progression. We compared risks of liver-related events, liver-related mortality and non-liver-related mortality in HIV/HCV co-infected and HCV mono-infected patients treated by DAA.

Methods: Four HCV mono-infected participants from the ANRS CO22 HEPATHER cohort were matched on age and sex to each HIV/HCV co-infected participant from the ANRS CO13 HEPAVIH cohort. All participants were treated by DAA between March 2014 and December 2017. Cox proportional Hazards models adjusted on age, sex, duration since HCV diagnosis, HCV contamination routes, HCV genotype, cirrhosis status, smoking and alcohol consumption were used.

Results: 952 HIV/HCV co-infected and 2049 HCV mono-infected were included. Median age was 52.9 years [IQR: 49.6 ; 56.7] and 53.3 years [IQR: 49.6 ; 56.9]; 436 (73.6%) and 1498 (73.1%) were men; median duration since HCV diagnosis was 18.0 years [IQR: 12.4 ; 22.2] and 14.5 years [6.4 ; 20.8], and 159 (28.8%) and 793 (41.2%) were cirrhotic, respectively. Participants were predominantly treated by Sofosbuvir and Ledipasvir (48.8% and 34.5%, respectively) or Sofosbuvir and Daclatasvir (32.6% and 31.2%, respectively) and SVR was observed in 92.9% and 94.6% overall, respectively. After a median follow-up of 2.8 years, incidence of liver-related events was 12.4 per 1000 PY (95%CI: 7.7 ; 19.1) in HIV/HCV co-infected and 4.9 per 1000 PY (95%CI: 3.4 ; 7.1) in HCV mono-infected (p<0.078). Incidence of liver-related mortality was 5.6 per 1000 PY (95%CI: 2.8 ; 11.1) in HIV/HCV co-infected and 4.9 per 1000 PY (95%CI: 3.4 ; 7.1) in HCV mono-infected (p=0.76). Incidence of non-liver-related mortality was 12.5 per 1000 PY (95%CI: 7.9 ; 19.8) in HIV/HCV co-infected and 4.9 per 1000 PY (95%CI: 3.4 ; 7.1) in HCV mono-infected (p<0.01). After adjustment, HIV co-infection was not associated with a higher risk of liver-related events (HR=0.67 95%CI: 0.27 ; 1.67) or liver-related mortality (HR=0.94 95%CI: 0.19 ; 4.67), but the risk of non-liver-related mortality (HR=2.67 95%CI: 0.97 ; 7.37) tended to be higher in HIV/HCV co-infected.
Conclusion: After DAA treatment, SVR rates were not impacted by HIV co-infection, the risk of liver-related events and liver-related mortality were similar between HIV/HCV co-infected and HCV mono-infected but HIV co-infection tended to increase the risk of non-liver-related mortality.

Conclusion: SVR with all-oral DAA regimens reduces the risk of death in HIV/HCV-coinfected patients with cirrhosis. The sum of this effect to the high uptake and SVR rates of this therapy has led to a decline in the incidence of liver-related mortality in our cohort.

579 EFFECT OF DAA REGIMENS ON MORTALITY IN HIV/HCV-COINFECTED PATIENTS WITH CIRRHOSIS

Nicolás Merchante1, Francisco Téllez2, Angela Camacho-Espejo3, Dolores Merino4, María J. Rios-Villagrasa5, Marina Villalobos6, Mohamed Omar Mohamed Balgahata7, Carolina Freyre-Carrillo2, Antonio Ríos7, Miguel Raffo6, María Paniagua-García1, Rosario Palacios5, Juan Macías1, Juan A. Pineda1, for the HEPAVIR-Cirrhosis Study Group

1Hospital Universitario de Valme, Seville, Spain, 2Hospital Universitario de Puerto Real, Cadiz, Spain, 3Hospital Universitario Reina Sofia, Cordoba, Spain, 4Complejo Hospitalario Universitario de Huelva, Huelva, Spain, 5Hospital Universitario Virgen Macarena, Sevilla, Spain, 6Hospital Virgen de la Victoria, Malaga, Spain, 7Complejo Hospitalario de Jaén, Jaén, Spain

Background: Our objective was to assess the impact of all-oral direct antiviral agents (DAA) regimens on mortality in HIV/HCV-coinfected patients with cirrhosis.

Methods: 637 HIV/HCV-coinfected patients with cirrhosis prospectively recruited in the HEPAVIR-cirrhosis cohort from 2006 were followed-up until death or December 2018. The primary end-point was death of any cause and secondary end-point was liver-related death. The incidence rate (IR) (95% CI) of death of any cause in different groups were computed. Time-to-event analyses were performed to identify predictors of death.

Results: After a median (Q1-Q3) follow-up of 72 (39-104) months, 131 (21%); 95% CI: 17-23) patients died, 59 (45%) from them due to liver-related complications. IR (95% CI) of death was 3.4 (2.8-4.1) per 100 person-years (PY), 480 (75%) patients achieved sustained virological response (SVR) during follow-up, 90 after interferon (IFN)-based regimens and 390 after all-oral DAA regimens. The median follow-up after all-oral DAA was 34 (23-41) months. 28 out of the 131 deaths and 8 out of the 59 liver-related deaths occurred after SVR. IR (95% CI) of death after SVR was 1.8 (1.2-2.7) per 100 PY versus 17.7 (14.6-21.5) per 100 PY in those not achieving SVR during follow-up (p<0.0001). When only patients with SVR were considered, the IR (95% CI) of death after SVR with all-oral DAA regimens was 2.1 (1.4-3.3) per 100 PY whereas it was 1.3 (0.5-2.8) per 100 PY in those achieving SVR with IFN-based regimens (p=0.27). The respective figures for liver-related death were 0.7 (0.3-1.5) and 0.2 (0.03-1.28) per 100 PY respectively (p=0.26). Figure 1 summarizes the trends in overall and liver-related mortality according to the changes of treatment strategies for hepatitis C in the cohort. Achieving SVR with an all-oral DAA regimen during follow-up was independently associated with a lower risk of death (adjusted hazard ratio 0.49; 95% CI: 0.26-0.93; p=0.027). The type of regimen leading to SVR (all-oral DAA vs IFN-based) had no impact on the risk of liver-related death in a competing risk model adjusted by propensity score (adjusted sub-hazard ratio 1.91; 95% CI: 0.21-17.09; p=0.56).

580 ALL-CAUSE MORTALITY AND CAUSES OF DEATH IN THE SWISS HEPATITIS C COHORT STUDY

Maroussia Roelens1, Barbara Bertisch2, Darius Moradpour3, Andreas Cerny4, Nasser Semmo4, Patrick Schindl5, Beat Muellhaupt6, Christoph Junker7, Francesco Negro8, Olivia Reiser9

1University of Geneva, Geneva, Switzerland, 2Lausanne University Hospital, Lausanne, Switzerland, 3Epatocentro Ticino Foundation, Lugano, Switzerland, 4University of Bern, Bern, Switzerland, 5St. Gallen Cantonal Hospital, St Gallen, Switzerland, 6University Hospital Zurich, Zurich, Switzerland, 7Swiss Federal Statistical Office, Neuchatel, Switzerland, 8University Hospitals of Geneva, Geneva, Switzerland

Background: Mortality rates and causes of death among persons with hepatitis C virus (HCV) infection are likely to change over time, with the introduction of direct-acting antiviral agents (DAA). However, the relatively slow progression of chronic hepatitis C may delay the emergence of such trends. To date, detailed analyses of cause-specific mortality among HCV-infected persons over time remain limited.

Methods: We evaluated changes in causes of death among the Swiss Hepatitis C Cohort Study (SCCS) participants, from 2008 to 2016. We analysed risk factors for all-cause and cause-specific mortality, accounting for changes in treatment, fibrosis stage and use of injectable drugs over time. Mortality ascertainment was completed by linking lost-to-follow-up participants to the Swiss Federal Statistical Office (SFSO) death registry.

Results: We included 4,700 SCCS participants, of whom 478 died between 2008 and 2016. Linkage to the SFSO death registry substantially improved the information on causes of death (from 42% of deaths with unknown cause before linkage to 10% after linkage). Leading causes of death were liver failure (crude death rate 4.4/1000 person-years), liver cancer (3.4/1000 p-yrs) and non-liver cancer (2.8/1000 p-yrs), with an increasing proportion of cancer-related deaths over time. Cause-specific analysis showed that persons with sustained virologic response (SVR) were less at risk for liver-related mortality.

Conclusion: Although the expected decrease in mortality is not yet observed, causes of death among HCV-infected persons evolved over time. With the progressive widening of guidelines for DAA use, liver-related mortality is expected to decline in the future. Continued monitoring of cause-specific mortality will remain important to assess the long-term effect of DAA and to design effective interventions.
581 KINETICS OF EMERGENCE OF LIVER COMPLICATIONS IN HCV-INFECTED PATIENTS AFTER SVR
Anaïs Corma-Gómez1, Juan Macías3, Francisco Téllez1, Luis Morano1, Antonio Rivero-Juárez1, Rafael Granados1, Marta Santos3, Maria Paniagua-García2, Francisco Vera3, Luis Miguel Real4, Jesús Santos5, Azucena Bautista5, Paloma Geijo10, Dolores Merino3, Juan A. Pineda4, for the RIS-HEP13 and GEHEP 011 Study Groups
1Hospital Universitario de Valme, Seville, Spain, 2Hospital Universitario de Puerto Real, Cadiz, Spain, 3Hospital Universitario Alvaro Cunqueiro, Vigo, Spain, 4Hospital Universitario Reina Sofia, Cordoba, Spain, 5Hospital Universitario de Gran Canaria Dr Negrín, Las Palmas, Gran Canaria, 6Hospital Universitario Jerez de la Frontera, Jerez de la Frontera, Spain, 7Hospital Universitario Virgen Macarena, Sevilla, Spain, 8Hospital General Universitario Santa Lucia, Cartagena, Spain, 9Hospital Virgen de la Victoria, Málaga, Spain, 10Hospital Virgen de la Luz, Cuenca, Spain, 11Hospital Juan Ramón Jiménez, Huelva, Spain

Background: Despite achieving SVR with DAA-based regimens, a few HCV-infected patients still develop liver complications. Consequently, life-long surveillance for hepatic events, including hepatocellular carcinoma (HCC), is recommended among individuals with pre-treatment cirrhosis. However, there is little available evidence on the distribution over time of these liver complications appearing after SVR. Thus, the aim of this study was to describe the kinetics of liver complications appearance in HCV-infected patients, with advanced fibrosis, who attain SVR after DAA based therapy.

Methods: Multicentric prospective cohort study, including HCV- and HIV/HCV-coinfected patients, who met: 1) Had achieved SVR with DAA-based therapy; 2) Liver stiffness prior to starting treatment ≥ 9.5 kPa; 3) Had an available LS measurement at the time of SVR. SVR was considered as the baseline time-point. Overall accumulated incidence of liver complications was estimated, as well as complication-specific incidences. The median time (Q1-Q3) to the emergence of a hepatic event was assessed.

Results: 1006 patients were included, 661 (61%) coinfected with HIV. 554 (55%) showed previous compensated cirrhosis. 598 (60%) patients showed cirrhosis prior to treatment and specifically 360 (36%) had LS values ≥ 21 kPa. The corresponding figures at SVR were: 413 (42%) individuals with LS ≥21 kPa and 227 (23%) with LS >21 kPa. After a median follow-up time (Q1-Q3) of 37 (24-42) months, 9 [0.9% (0.5%-1.7%)] patients developed a first PHGB episode. The cumulative incidences of PHGB in the group of patients with LS ≥21 kPa and in patients with LS >21 kPa, after SVR, were respectively 4.0% (2.1%-7.4%) and 2.2% (1.2%-4.1%). 133 (37%) individuals with LS ≥21 kPa prior to treatment had a value below this cut-off at the time of SVR. None out of the 764 patients who showed LS <21 kPa at SVR time-point presented a PHGB event. Hence, the negative predictive value of this LS cut-off for the emergence of a first PHGB episode after SVR was 100%.

Conclusion: The predictive ability of the LS ≥21 kPa cut-off for a first PHGB episode evidenced in patients with HCV-active infection remains among HCV-infected individuals who attain SVR with DAA-based therapy. These results suggest that stopping surveillance of esophagogastric varices in patients with LS <21 kPa at SVR is safe. At least 133 (37%) patients with LS ≥21 kPa in whom this parameter declines below to such a cut-off with SVR, may benefit from this decision.

582 LIVER STIFFNESS FOR PORTAL HYPERTENSIVE GASTROINTESTINAL BLEEDING AFTER HCV CURE
Anaïs Corma-Gómez1, Juan Macías3, Francisco Téllez1, Luis Morano1, Antonio Rivero-Juárez1, Rafael Granados1, Juan C. Alados2, Maria Paniagua-García2, Francisco Vera4, Nicolás Merchante1, Rosario Palacios1, Ignacio Santos16, Dolores Merino3, Juan A. Pineda4, for the RIS-HEP13 and GEHEP 011 Study Groups
1Hospital Universitario de Valme, Seville, Spain, 2Hospital Universitario Alvaro Cunqueiro, Vigo, Spain, 3Hospital Universitario Reina Sofia, Cordoba, Spain, 4Hospital Universitario de Gran Canaria Dr Negrín, Las Palmas, Gran Canaria, 5Hospital Universitario Jerez de la Frontera, Jerez de la Frontera, Spain, 7Hospital Universitario Virgen Macarena, Sevilla, Spain, 8Hospital General Universitario Santa Lucia, Cartagena, Spain, 9Hospital Virgen de la Victoria, Málaga, Spain, 10Hospital Virgen de la Luz, Cuenca, Spain, 11Hospital Juan Ramón Jiménez, Huelva, Spain

Background: Among patients with active HCV-infection, values of liver stiffness (LS)<21 kPa identify individuals without risk of developing portal hypertensive gastrointestinal bleeding (PHGB). Thus, this LS level has been incorporated to some management algorithm of HCV-infected patients, so that upper gastrointestinal endoscopy (UGE) is safely spared in those with LS<21 kPa. However, there is no information about its predictive value among HCV-infected patients after SVR. So, the aim of this study was to assess the predictive ability of LS for PHGB in HCV-infected patients with advanced fibrosis who attain SVR with DAA-based therapy.

Methods: Multicentric prospective cohort study where HCV-monoinfected patients and HIV/HCV-coinfected patients were included if they met the following inclusion criteria: 1) Had achieved SVR with a DAA-based regimen; 2) Had LS values ≥9.5 kPa prior to treatment; 3) Had an available LS measurement at SVR time-point. Patients with PHGB episodes prior to SVR were excluded. Absolute frequencies and accumulated incidences of PHGB after SVR were calculated.

Results: In this study, 991 individuals were included. 647 (65%) were coinfected with HIV. 598 (60%) patients showed cirrhosis prior to treatment and specifically 360 (36%) had LS values ≥21 kPa. The corresponding figures at SVR were: 413 (42%) individuals with LS ≥21 kPa and 227 (23%) with LS >21 kPa. After a median follow-up time (Q1-Q3) of 37 (24-42) months, 9 [0.9% (0.5%-1.7%)] patients developed a first PHGB episode. The cumulative incidences of PHGB in the group of patients with LS ≥21 kPa and in patients with LS >21 kPa, after SVR, were respectively 4.0% (2.1%-7.4%) and 2.2% (1.2%-4.1%). 133 (37%) individuals with LS ≥21 kPa prior to treatment had a value below this cut-off at the time of SVR. None out of the 764 patients who showed LS <21 kPa at SVR time-point presented a PHGB event. Hence, the negative predictive value of this LS cut-off for the emergence of a first PHGB episode after SVR was 100%.

Conclusion: The predictive ability of the LS ≥21 kPa cut-off for a first PHGB episode evidenced in patients with HCV-active infection remains among HCV-infected individuals who attain SVR with DAA-based therapy. These results suggest that stopping surveillance of esophagogastric varices in patients with LS<21 kPa at SVR is safe. At least 133 (37%) patients with LS ≥21 kPa, in whom this parameter declines below to such a cut-off with SVR, may benefit from this decision.
sustained virologic response (SVR) we used a segmented negative binomial mixed-effect models to evaluate the impact of SVR on HCSU. The model controlled for pre-treatment trends in HCSU, exposure time (offset) and time updated covariates: CD4 count cell, HIV RNA, active injection drug use, significant fibrosis (>=2) and fixed covariates: age and sex. We categorized HCSU as out-patient visits (walk-in, general GP) or GP practitioners, specialists; or in-patient visits (emergency room (ER) and hospitalizations). Observations were truncated 6-months before DAA initiation to account for changes in HCSU in preparation for initiating DAA.

**Results:** Between 2014-2018, 455 participants completed DAA therapy, of whom 424 achieved SVR. Median age at DAA initiation was 51 years (IQR 46, 56), 75% were male, 81% had HIV RNA <50 copies/mL; median CD4 was 520 cells/mL (IQR 331, 749) and 27% had liver fibrosis. A total of 2573 visits were divided as either pre-treatment (mean of 2.3 years (SD 1.2)) or post-SVR (mean 1.8 years (SD 0.9)). Overall, out-patient visits decreased from 12.6 visits/person-year (PY) before DAA initiation to 9.4 visits/PY post-SVR. Similarly, in-patient visits dropped from 2.8 visits/PY pre-treatment to 1.4 visits/PY post-SVR. Table 1 summarizes changes in HCSU by visit type. Before DAA initiation, annual rates of GP and specialist visits increased, hospitalizations and HIV visits were stable, while GP and walk-in clinic visits decreased over time. Reductions in ER, hospitalizations and specialist visits were seen immediately after SVR and this effect persisted over time with annual reductions of 13%, 6% and 18% respectively, controlling for pre-treatment trends.

**Conclusion:** We found evidence of immediate and sustained reductions of both in- and out-patient visits following SVR with DAA therapy in a real-world HIV-HCV co-infected population.

<table>
<thead>
<tr>
<th>Pre-GRAA trends, per year</th>
<th>Post-GRAA trends, per year</th>
<th>Annual decrease in HCSU per year</th>
<th>Post-SVR trends, per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.08 (95% CI 1.05, 1.11)</td>
<td>0.98 (95% CI 0.96, 1.00)</td>
<td>0.09 (95% CI 0.06, 0.11)</td>
<td>0.94 (95% CI 0.91, 0.97)</td>
</tr>
</tbody>
</table>

584 HCV CURE IN HIV INFECTION DAMPENS INFLAMMATION AND IMPROVES COGNITION

Lynn Pulliam1, Linda Abadji2, Alex Monto1, Bing Sun1
1University of California San Francisco, San Francisco, CA, USA, 2San Francisco VA Medical Center, San Francisco, CA, USA

**Background:** Chronic inflammation in HIV/HCV coinfection increases cognitive impairment. With new direct-acting antiviral therapies for HCV, sustained viral response (SVR) or cure is possible. Our objective was to determine if chronic inflammation and cognitive impairment in coinfection would be decreased after HCV SVR.

**Methods:** We studied 41 participants before and after treatment for HCV alone or with viral controlled HIV coinfection. We measured monocyte activation and gene expression, plasma inflammation and cognitive impairment. Monocyte-derived exosomal miRNAs were studied with RNA sequencing before treatment and followed by qRT-PCR after SVR.

**Results:** All HCV-coinfected subjects achieved SVR but one. Blood CD16+ monocytes were significantly decreased in coinfection after HCV treatment. Plasma sCD163 and neopterin were also decreased in HCV mono and coinfected persons. Overall cognition improved 25% in coinfection with visual learning/ memory the most improved. HCV SVR decreased monocyte interferon genes MX1, IFI17 and CD169 in coinfection and MX1, LGLS3BP and TINFAP5 in HCV monoinfection. CD83, IL6 and CXCL10 monocyte gene expression correlated with cognitive impairment before therapy; only CXCL10 continued to correlate with impairment and specifically worsening executive function and attention deficits despite DAA therapy. Monocyte exosomes from coinfected persons after treatment were significantly increased in miR-19a, miR-221 and marginally miR-223, all associated with decreasing inflammation and NF-kB activation.

**Conclusion:** HCV SVR in coinfection brings monocyte activation markers to levels seen with HIV alone. Cognitive impairment is significantly improved with HCV cure but not better than HIV infection alone strongly suggesting that cognitive impairment was driven by both HIV and HCV. Previous reports on the high percentage of cognitive impairment in HIV may have been greatly influenced by HCV coinfection.

585 TELOMERE LENGTH OF CIRRHOTIC HIV/HCV PATIENTS INCREASES AFTER HCV CLEARANCE WITH DAAs

Silvia S. Molina Carrión1, Óscar Brochado Kith1, Juan González-García1, Juan Berenguer1, Cristina Diez1, Juan Carlos López-Bernaldo1, Elba L. Herrera1, Victor Hontanon2, Luis Ibáñez-Samaniego3, Maria Luisa Montes1, Salvador Resino1, Amanda Fernández-Rodríguez1, María Á. Jiménez-Sousa1
1Instituto de Salud Carlos III, Madrid, Spain, 2La Paz University Hospital, Madrid, Spain, 3Hospital General Universitario Gregorio Marañón, Madrid, Spain, 4Puerta de Hierro Research Institute and University Hospital, Madrid, Spain, 5University Hospital Gregorio Marañon, Madrid, Spain

**Background:** Human immunodeficiency virus (HIV) infection and cirrhosis are associated with a senescent phenotype that decreases telomere length. We evaluated the impact of hepatitis C virus (HCV) elimination on telomere length in patients with advanced HCV-related cirrhosis after sustained virological response (SVR) with all-oral direct-acting antiviral agents (DAAs).

**Methods:** Prospective study of 60 HIV/HCV-coinfected and 30 HCV-monoinfected patients with advanced HCV-cirrhosis (liver decompensation or liver stiffness measurement [LSM] >= 5 kPa or hepatic liver pressure gradient [HLPG] >= 10 mmHg or Child-Pugh-Turcotte (CPT) >= 7). The relative telomere length (RTL) was quantified by real-time multiplex PCR (MMqPCR) on peripheral blood mononuclear cells at baseline and 48 weeks after completing successful DAA therapy. Generalized linear models (GLMs) adjusted for the most relevant clinical and epidemiological variables and mixed GLMs were used.

**Results:** In comparison with HCV-coinfected patients, HIV/HCV-coinfected patients were younger (p<0.001), had lower BMI (p=0.008), and had been exposed more frequently to interferon (p=0.011). Besides, they were more frequently men (p=0.011), smokers (p=0.005), prior IDUs (p<0.001), and alcohol abusers (p=0.005). RTL was significantly lower in HIV/HCV-coinfected patients than in HCV-coinfected patients both at baseline (p<0.001), and at the end of follow-up (p=0.032). A significant RTL increase over time was found only for HIV/HCV-coinfected patients (p<0.001), especially in those patients with compensated cirrhosis (p<0.001) (Figure).

**Conclusion:** Eradication of HCV with DAAs was associated with a statistically significant increase in telomere length in HIV/HCV-coinfected patients with advanced cirrhosis, particularly in compensated patients. This finding suggests that HCV clearance may have implications in age-related conditions in this population group.

586 T-CELL AND MONOCYTE ACTIVATION CORRELATE AND DECLINE DURING HCV THERAPY FOR HIV/HCV

Ann W. Auma1, Sofi N. Damjanovska1, Corinne N. Kowal1, Carey Shive1, Laura M. Smeaton1, Daniel E. Cohen1, Debika Bhattacharya2, Beverly Alston-Smith1, Ashwin Balagopal3, Mark Sulkowski4, David L. Wyles4, Donald D. Anthony1
1Case Western Reserve University, Cleveland, OH, USA, 2Harvard University, Cambridge, MA, USA, 3AbbVie, Inc, North Chicago, IL, USA, 4Los Angeles Biomedical Research Institute at Harbor—UCLA Medical Center, Torrance, CA, USA, 5NIH, Rockville, MD, USA, 6Johns Hopkins University, Baltimore, MD, USA, 7University of Colorado Denver, Denver, CO, USA

**Background:** Immune activation predicts morbidity in HCV, HIV and HCV-HIV co-infection despite antiretroviral therapy (ART). HCV DAA therapy is associated with partial/complete normalization of soluble markers of immune activation during HCV infection. How this extends to cellular immunity during HIV-HCV infection is less clear.

**Methods:** We analyzed plasma and PBMC from AIDS Clinical Trials Group (ACTG) A5329, where ART treated HCV-HIV co-infected participants were treated with paritaprevir/ritonavir/ombitasvir+dasabuvir+/-ribavirin for 24 (n=36) or 12 (n=9) weeks. In a subset of participants where viable samples were available (n=21 24 week therapy and n=7 12 week therapy) we performed flow cytometric analysis of T-cells, central memory (CM)/effector memory (EM)
subsets, monocyte subsets (CD14+CD16- classical, CD14+CD16+ inflammatory, and CD14-CD16+ patrolling), and cell activation (CD38 and HLA-DR expression) before (w0), during (w12) and after therapy (w36) to assess changes (Wilcoxon Signed Rank Test) pooled over the entire sample. Spearman’s correlations evaluated associations between soluble immune activation markers (plasma sCD14, sCD16, IL10 and IL6) and T cell and monocyte subset/activation.

**Results:** CD38/HLA-DR co-expression on CD4 and CD8 memory T-cells decreased 12 weeks after initiation of DAA therapy (p<0.05, Table 1), and for some parameters at w12 (CD4 CM p=0.02, and CD8EM p<0.001). HLA-DRhi expressing classical monocyte frequency tended to decrease at 12 weeks (p=0.06). Before therapy, HLA-DR expression on classical and inflammatory monocytes positively correlated with absolute counts of CD4 co-expressing CD38/HLA-DR (r=0.56, p=0.001), CD4CM (r=0.46, p=0.009), and CD4EM (r=0.43, p=0.02) T-cells, and CD8 CD38/HLA-DR co-expressing frequencies (CD8 r=0.38, p=0.04, CD8CM r=0.47, p=0.08 and CD8EM r=0.38, p=0.04) T-cells. Before DAA therapy, IL-6 levels negatively correlated with classical monocyte frequency (r=0.45, p=0.01), while 36 weeks after therapy initiation plasma sCD14 positively correlated with CD4s co-expressing CD38/HLA-DR (r=0.67, p=0.004) and CD4+CM (r=0.74, p=0.001) cells.

**Conclusion:** In this sample (n=28), memory T-cell activation associated with monocyte subset activation during HCV-HIV co-infection, consistent with related underlying mechanisms. 12 weeks following therapy initiation, monocyte, CD4 and CD8 activation was reduced. Residual memory CD4 CD38/HLA-DR+ cells correlated with fold change in US-RNA levels between12MPT and BSL (r=0.57, p=0.04). Also, 12MPT CD38 expression correlated with fold change in US-RNA levels between12MPT and BSL (r=0.5919, p=0.0462).

**Conclusion:** Downregulation of NK cell activation was observed immediately after HCV clearance although some markers rebounded one year later, in concomitance with increased transcriptional activity of HIV reservoir. This may reflect the priming of NK cells by the residual HIV transcription and might point out a role for NK cells in shaping HIV persistence.

**584 CHANGES IN IMMUNE-CELL SUBSETS IN HCV AND HCV/HIV PATIENTS UPON VIRALLY EFFECTIVE DAA**

**Elvira S. Cannizzo**, 1 Camilla Tincati, 1 Esther Merlini**, 2 Lorena Van Den Bogart**, 1 Roberta Curetti, Spinello Antonini, 1 Antonella D’Arminio Monforte, 1 Giulia Marchetti, 1 Laura Milazzo, 1
1University of Milan, Milan, Italy, 2Azienda Ospedaliera San Paolo, Milan, Italy, 3Fatebenefratelli Sacco Hospital, Milan, Italy

**Background:** Direct-Acting Antivirals (DAAs) eradicate HCV and reduce liver fibrosis by containing inflammation. Virologic response correlates with the restoration of NK and CD8, however, little is known on the effects of DAAs on γδ, Th17 and Treg which all play a role in liver fibrogenesis. Further, while B-cell activation has been linked to extrahepatic manifestations of HCV, literature is lacking on the role of these cells in liver damage.

**Methods:** We enrolled 97 virally infected (VI) subjects (15 HCV vART-suppressed, 35 HCV naive to HCV therapy; 47 HIV/HCV co-infected and naive to HCV therapy) and 10 age-matched healthy controls (HC). All HCV-infected individuals underwent DAA therapy. At baseline (T0) and 12 weeks after End of Treatment (SVR12) we measured: (i) γδ frequency (CD3+Pan γδ), activation (CD69/CD38), (ii) Th17-like (CD4+CD161+CCR6+); (iii) Treg (CD4+CD25+CD127-); (iv) B cell frequency (CD19-), activation (CD86/CD38); v) γ-globulin levels. vi) Fibrosis stage was determined by transient elastography (Fibroscan) Statistical analysis as appropriate

**Results:** At T0, VI presented lower Th17 and higher Treg versus HC (Fig1A). DAA led to a further contraction of Th17 and no changes in Treg frequency (Fig1B). While total γδ were comparable in VI and HC both prior to and following treatment (Fig1B), activated γδ subset decreased upon DAA (Fig1C). Compared to HC, VI also featured higher B- cell frequencies and activation which both decreased during DAA (Fig1C). Accordingly, γ-globulin concentrations also diminished in HCV mono and co-infection following DAA and correlated with B-cell activation (Fig1B). In VI, a low vδ2/Th17 ratio, known to predict liver damage, increased from baseline to SVR12, yet remained lower than HC (HIV vs HC: p=0.04). HIV vs HC (p=0.03) and negatively correlated with liver stiffness (Fig1E) and serum ALT and AST (Fig1F). Further, also γ-globulin levels were positively linked to liver fibrosis indexes following DAAs (r=0.6, p<0.001).

No differences in B and T cell phenotypes were registered (Fig1A).

**Conclusion:** Effective DAA in both HCV mono and HIV/HCV co-infected subjects resulted in decreased B- and γδ cell activation, with recovery of vδ2/Th17 ratio. These changes are linked to the reduction of hepatic necrosis and stiffness, suggesting that DAA-mediated lightening of the pro-inflammatory liver insult may limit organ damage.
589 LIVER FIBROSIS HINDERS NORMALIZATION OF SYSTEMIC INFLAMMATION AFTER HCV ERADICATION

Clara Restrepo1, Beatriz Álvarez2, Marcial García1, María Ángeles Navarrete2, Maria Ángeles Jiménez-Sousa1, Laura Prieto1, Alfonso Cabello2, Sara Nistal4, María Ángeles Navarrete1, Beatriz Álvarez2, Marcial García1, María Ángeles Jiménez-Sousa1.

1Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain, 2Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, 3Institute of Health Clara Restrepo1, Beatriz Álvarez2, Marcial García1, María Ángeles Navarrete1, A.

Background: HCV co-infection significantly impacts on inflammation, endothelial activation and coagulation function parameters leading to several comorbidities among people living with HIV (PLWH). The new direct-acting antivirals (DAAs) therapy achieves eradication of HCV in the majority of patients. However, the early effect of HCV eradication on these parameters on PLWH has been scarcely explored. We have analyzed the effect of HCV on systemic inflammation and endothelial/coagulation function in PLWH and its evolution after HCV eradication with DAAs.

Methods: Twenty-five HIV/HCV coinfected (HIV/HCV group), 25 HIV-infected (HIV group) and 20 healthy controls (HC) were included. All patients were on ART and HIV suppressed. Parameters of systemic inflammation, endothelial activation and coagulation were measured on plasma samples using Human Custom ProcartaPlex kit (Invitrogen, Thermo Fisher Scientific) and acquired on a Luminex analyzer (Bio-Plex 200 System by Biorad). Cross-sectional and longitudinal (comparing baseline vs 12 weeks after end of treatment in HIV/HCV group) analyses were performed. Non-parametric tests were used to establish inter and intra-group differences.

Results: No significant differences between HIV and HC groups were observed for any of the parameters analyzed. In contrast, at baseline HCV/HIV group showed increased levels of IL-18 (p=0.028), IP-10 (p<0.0001), VCAM-1 (p<0.0001) and ICAM-1 (p=0.045) compared to HC and HIV groups. Interestingly, the highest levels of these markers were observed in HCV/HIV patients with significant liver fibrosis (>F2, n=10), with significant differences between <F2 and >F2 HIV/HCV patients for IL18 and IP10 (p=0.007 and p=0.015, respectively). Of note, after HCV eradication, levels of VCAM-1 remained significantly increased compared to HIV and HC groups (p=0.006) with a similar profile in patients with >F2 and without (<F2) liver fibrosis (p=0.034 and p=0.033 respectively), whereas levels of IP-10 remained significantly increased only in patients with liver fibrosis (p=0.032).

Conclusion: Both HCV co-infection and presence of liver fibrosis significantly impacts on markers of systemic inflammation and endothelial activation in PLWH. Normalization of these parameters is not completely achieved after HCV eradication, especially in patients with liver fibrosis. These data prompts HCV treatment in all HIV/HCV coinfected patients at the earliest stages of liver damage to enhance normalization of systemic inflammation and endothelial activation.

590 HEPATITIS C TESTING OF INDIVIDUALS WITH HCV/HIV COINFECTION, MASSACHUSETTS 2013-2018

Quynh Vo1, Laura Kersanske1, Matthew Tumpney1, Betsey John1, Anthony Osniski1, Shauna Onofrey1, Daniel Church1, Monina Klevens1, 1Massachusetts Department of Public Health, Boston, MA, USA

Background: Current CDC guidelines recommend routine hepatitis C virus (HCV) screening for people living with HIV (PLWH) and that HCV testing should follow a testing cascade. Tests should be initiated with an anti-HCV antibody test and, if reactive (EIA+), should be followed with an HCV RNA test, and genotype tests to guide treatment decisions. Here we use state-level reports to model the HCV testing cascade to serve as a proxy for access to care for PLWH coinfected with HCV and those monoinfected with HCV.

Methods: The Massachusetts Department of Public Health receives electronic reports of laboratory tests for HIV and HCV in residents of the state. We analyzed demographic and laboratory data from all individuals diagnosed and reported as living with HIV in Massachusetts as of December 2016 and coinfected with HCV 2013-2018. PLWH were matched to HCV laboratory data reported 2013-2018 to characterize HCV testing after an HCV EIA+ test. We also analyzed HCV test results from those uninfected with HIV for the same period. Outcomes included type of (nucleic acid or genotype test) HCV tests received after HCV EIA+ test. The proportion of cases at each step in the cascade was calculated as a conditional proportion. Variables examined included sex, birth cohort, risk history, and race/ethnicity.

Results: As of December 2016, there were 642 PLWH who tested HCV EIA+ in Massachusetts. Among PLWH, the majority of HCV seroconversions occurred in males (71%), people who reported injection drug use (46%), and people diagnosed with HIV before 2013 (77%). Compared to HIV-uninfected HCV EIA+ persons, a greater proportion of PLWH received viral load testing (96% vs. 47%). A greater proportion of monoinfected HCV persons were reported to have a subsequent genotype test (56% vs. 38%).

Conclusion: While only 47% of HCV EIA+ cases reported to the state had a positive HCV RNA test reported, a majority (87%) of PLWH who tested HCV EIA+ were confirmed with HCV infection. This discrepancy may reflect that PLWH are more likely to be engaged in ongoing care, including HCV. Our findings on genotype testing require further investigation in the context of pan-genotypic direct acting antivirals. Effective surveillance is critical for success in evaluating and promoting HCV elimination among PLWH. Improved surveillance capture of demographic and behavioral information, such as injection drug use, is needed to help public health agencies ensure equity in HCV diagnosis and linkage to HCV care for PLWH and non-PLWH.

591 COST-SAVING OF POOLED HCV RNA TESTING TO DIAGNOSE ACUTE HCV IN HIGH-RISK POPULATIONS

Hsin-Yun Sun1, Yi-Ting Chen1, Wen-Chun Liu1, Li-Hsin Su1, Yu-Chung Chuang1, Yu-Shan Huang1, Lin-In Wu1, Kuan-Yin Lin1, Sui-Yuan Chang1, Chien-Ching Hung1, 1National Taiwan University Hospital, Taipei, Taiwan

Background: Acute HCV infection has emerged as a sexually transmitted disease (STD) in MSM. With highly effective direct acting antivirals (DAAs) against HCV, timely diagnosis and treatment of acute HCV infection can curb further transmission. Given the cost concerns about HCV RNA testing, we assessed the cost-saving strategy with the use of pooled sera for HCV RNA testing to diagnose acute HCV infection in high-risk populations.
Methods: We enrolled HIV-positive patients without HCV infection who presented with STDs or elevated aminotransferases within 6 months. HIV-positive patients with spontaneous HCV clearance or achievement of sustained virologic response (SVR) with HCV treatment, and PreP users without HCV infection. A total of 20 specimens were combined into a pooled specimen for HCV RNA testing. STD screening was performed for HIV-positive patients or PreP users with STDs. All of the 20 patients would be considered free of HCV if a pooled specimen was tested negative for HCV RNA. For any pooled specimen tested positive, every 5 specimens of the 20 specimens would be combined into a sub-pooled specimen for HCV RNA testing. For a sub-pooled specimen tested positive, each of the 5 specimens would be retested individually to identify the one with HCV.

Results: From Jun 25 to Sep 19, 2019, 322 individuals were enrolled, including 304 (94.4%) HIV-positive patients and 18 (5.6%) PreP users, with 99.1% being MSM. Patients were enrolled because of STDs in 228 (75.0%), follow-up of HCV status after SVR in 79 (26.0%) or spontaneous HCV clearance in 9 (3.0%), and elevated aminotransferases in 8 (2.6%). Chlamydia infection was identified in 23.4% (49/209) of HIV-positive patients and 44.4% (4/9) of PreP users, while gonorrhea was diagnosed in 11.5% (24/209) of HIV-positive patients and 22.2% (2/9) of PreP users. Acute HCV infection was diagnosed in 8 (2.5%) patients (3 with STD, 2 with SVR, 3, elevated aminotransferases) at the first determination and 1 at the second determination 3 months later, with negative anti-HCV antibody in 2. Instead of 340 tests, a total of 89 HCV RNA tests were needed to identify the 9 individuals with acute HCV infection by the pooled-serum approach, and we were able to save 73.8% of the total cost required if all the specimens had been tested individually.

Conclusion: Pooled HCV RNA testing is cost-saving to diagnose acute HCV infection in high-risk populations.

PERSISTENT HIV CONTROLLERS ARE MORE PREDISPOSED TO SPONTANEOUSLY CLEAR HCV

Beatriz Dominguez-Molina1, Laura Taranoan-Diez2, Yusnelks Milanes-Guisad2, Miguel Genestab, Salvador Resinob, Carmen Rodriguez2, Norma Rallon2, Cecilio Lopez-Galinde2, Jose Miguel Benitora, Felix Garcia, Jorge Romero, Pompeyo Viciana1, Luis Lopez-Cortes1, Manuel Leal, Ezequiel Ruiz-Mateos1
1Institute of Biomedicine of Seville, Seville, Spain, 2Institute of Salud Carlos III, Majadahonda, Spain, 3Centro Sandoval, Madrid, Spain, 4Fundacion Jimenez Diaz, Madrid, Spain, 5Hospital Clinic of Barcelona, Barcelona, Spain

Background: HIV-controllers have the ability to spontaneously maintain viremia at low or undetectable levels in absence of antiretroviral treatment. Furthermore, HIV controllers seem to have superior capacity to spontaneously clear hepatitis C virus (HCV) coinfection compared to non HIV-controllers. Some of these subjects eventually lose HIV-controller status (transient controllers), in contrast with HIV-controllers with persistent natural HIV control (persistent controllers). It is unknown whether persistent controllers have superior capacity to spontaneously clear HCV coinfection compared to transient controllers.

Methods: HIV-controllers with available data for antibodies to HCV (anti-HCV) were recruited (n=744). Factors associated with HIV spontaneous control in relation to HCV coinfection were analyzed in persistent and transient HIV-controllers with anti-HCV positive (n=202 and n=138, respectively) in comparison with HIV-negative. In addition, the factors related to the loss and time to lose HIV-controller status were explored (n=744).

Results: A higher frequency of HCV spontaneous clearance was found in persistent HIV-controllers (25.5%) compared to non-controllers (10.2%). After adjusting for potential confounders as sex, age, HCV transmission risk, CD4+ T-cell nadir and time of follow up, HCV clearance was independently associated with persistent HIV spontaneous control (p=0.002; OR (95% CI)= 2.573 (1.428-4.633), but not with transient spontaneous control (p=0.119; 1.589 (0.888-2.845). Furthermore, persistent HIV-controllers were more likely to spontaneously clear the HCV in comparison with transient controllers (p=0.027; 2.650 (1.119-6.276). Finally, no loss or a delayed time to lose HIV-controller status was independently associated with HCV spontaneous clearance (p=0.010; 1.990 (1.177-3.364).

Conclusion: This study shows an association between spontaneous persistent HIV-control and HCV spontaneous clearance. Our results support common mechanisms involved in spontaneous persistent HIV control and HCV clearance. These results suggest persistent but not transient HIV-controllers as a good model of functional HIV cure.

HPTN 078: HIGH INCIDENCE OF HEPATITIS C VIRUS INFECTIONS AMONG MSM

Risha Irvin1, Jowanna Malone2, Theresa Gamble1, James Hughes1, Jason Farley1, Kenneth H. Mayer4, Carlos del Rio5, D. Scott Batey6, Michael Murphy1, Oliver Laeyendecker2, Brian R. McVea3, Robert H. Remien4, Chris Beyrer5, Oliver Thio6
1Johns Hopkins University, Baltimore, MD, USA, 2FHI 360, Durham, NC, USA, 3University of Washington, Seattle, WA, USA, 4Harvard Medical School, Boston, MA, USA, 5Emory University, Atlanta, GA, USA, 6University of Alabama at Birmingham, Birmingham, AL, USA, 7Columbia University, New York, NY, USA

Background: Annual hepatitis C virus (HCV) testing is recommended for HIV-infected (HIV+) men who have sex with men (MSM) due to sexual transmission risk. While there is no HCV testing guideline for HIV-uninfected MSM, incident HCV infections have been noted. More data on incident HCV infection in MSM are needed.

Methods: HPTN 078 assessed the efficacy of an integrated strategy to achieve HIV viral suppression; MSM were screened using respondent driven sampling and direct recruitment to identify HIV+ MSM who were not in care in Atlanta, Birmingham, Baltimore and Boston. At screening, demographic and behavioral questionnaires were completed, along with HIV and HCV testing. To identify subjects with recent HCV infection, HCV antibody (Ab) and RNA+ samples were tested using a modified Green Cross antibody avidity assay. Incidence rate was calculated using the assay-Based Incidence Estimation Model. Phylogenetic analysis was used to assess clustering. Univariable logistic regression was used to evaluate associations with recent HCV infection.

Results: This study included 1041 HIV Ab- MSM and 96 HIV Ab+/HCV RNA- MSM who were tested for recent infection. Of the 96, 16 had a recent infection (12 HIV+), so further analyses were restricted to these 16 plus the 1041 HIV Ab- MSM. Of these 1057 men, median age 38 years, 70% Black, 83% insured, 38% employed, and 69% HIV+ (Table 1). The overall HCV incidence rate was 5.0/100 person-years (PYs) (95% confidence intervals [CI]: 2.0-8.0/100 PYs), with rates of 5.5/100 PYs (1.8-9.2/100 PYs) in HIV+ MSM and 4.0/100 PYs (0.4-8.5/100 PYs) in HIV-uninfected MSM (P=0.38). The median lifetime number of male sexual partners was 16 (interquartile range [IQR]: 6, 50) in HIV Ab- MSM and 100 (19, 150) in MSM with recent HCV (P<0.01). The proportion of men who had substance use counseling was significantly greater in those with recent HCV compared to those who were HIV Ab- (44% vs. 16%, P<0.01). These associations were similar in the HIV+ group. Recent infections were mainly genotype 1, 3, genotype 3; none clustered together.

Conclusion: Although recent HCV infection was more common in HIV+ than in HIV-uninfected MSM, it was higher in both groups than in other studies. This suggests that HCV risk counseling should be considered in both HIV+ and HIV-uninfected MSM, particularly in those with a high number of lifetime sexual partners and substance use. Integrating HCV prevention into substance use counseling should be explored.
594 SEX, NOT DRUG USE, IS DRIVING HCV REINFECTION AMONG HIV-INFECTED MSM IN NEW YORK CITY

Stephanie H. Factor1, Jesse R. Carollo2, Gabriela Rodriguez-Caprio1, Asa Radix1, Stephen M. Dillon1, Rona Vali1, Kitticjar J. Bunyag1, Robert Chavez2, José Larest-Guía3, Daniel S. Fierie3, for the New York Acute Hepatitis C Surveillance Network1, School of Medicine at Mt Sinai, New York, NY, USA, 2Callen–Lorde Community Health Center, New York, NY, USA, 3Gothenburg Medical Group, New York, NY, USA, 1AIDS Healthcare Foundation, New York, NY, USA, 2Office of José Lares-Guía, MD, New York, NY, USA

Background: HCV reinfection rates are high among HIV-infected MSM in Western European cities as well as in New York City (NYC). We have previously shown that the two behavioral risk factors for primary HCV infection in NYC were receipt of semen into the rectum with receptive anal intercourse (semen in rectum), and sex with use of crystal methamphetamine (sex on CM). Behavioral risk factors for HCV reinfection in this population, however, have not been studied.

Methods: We performed a prospective cohort study in NYC to determine the behavioral risk factors for reinfection after primary HCV among HIV-infected MSM. Reinfection was defined as new HCV viremia after successful therapy (SVR 12) or spontaneous clearance (SC). Clinical visits for surveillance for reinfection were performed between Jan 2006 and Dec 2018, starting at the end of therapy, or the first undetectable VL for SC. Participants were queried about engagement in the two previously demonstrated risk factors for primary HCV infection in NYC, semen in rectum and sex on CM, and, additionally, about injection use of CM. Cox proportional hazards models analyses with these three behaviors as time-dependent variables, adjusted for age, race, ethnicity, and year of HCV clearance, were used to identify the behavioral risk factors for 1st HCV reinfection.

Results: Among our full cohort of 305 men with cleared HCV, 37 had 1st reinfections (rate 4.4/100 PY). We had adequate behavioral data from 244 (80%) men, of whom 29 (78% of 37) had 1st reinfections (rate 4.5/100 PY). Median age was 44 years, 21% were black, 78% white, and 20% Latino, which mirrored the full cohort, as did HIV and HCV parameters. Over 647 PY (median 2.13 [IQR 0.78, 3.66]) there were 1,286 visits (median 4 [IQR 2, 6] per participant). While the full cohort, as did HIV and HCV parameters. Over 647 PY (median 2.13 [IQR 0.78, 3.66]) there were 1,286 visits (median 4 [IQR 2, 6] per participant).

Conclusion: Sex, with receipt of semen into the rectum, rather than drug (methamphetamine) use, was the behavior driving HCV reinfection in HIV-infected MSM. Taken together with previous research demonstrating HCV in semen, and as condom use has not been successful as an HCV prevention strategy, our results suggest the need for novel interventions to prevent seminal HCV from causing trans-rectal HCV infection.

595 HCV REINFECTION AMONG HIV PATIENTS AFTER DAA THERAPY IN THE COUNTRY OF GEORGIA

Nikoloz Chkhartishvili1, Pati Gabunia1, Akaki Abutidze1, Giorgi Korkotchavili1, Otar Chokoshvili1, Natia Dvali1, Lali Sharadze1, Tengiz Tsertsvadze1

1Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia

Background: In 2015, in partnership with US CDC and Gilead Sciences, Georgia launched national hepatitis C elimination program. All HCV patients, including HIV co-infected persons, have free access to direct acting antivirals (DAA). We report rates of HCV re-infection among HIV-infected persons in real-life settings.

Methods: Analysis included HIV patients treated with DAs during 2015-2017 and who achieved sustained virologic response (SVR), defined as undetectable HCV RNA after 12 weeks after completing treatment. Patients were followed until August 2019. Risk-based approach was used to screen for HCV re-infection, which included history of injection drug use (IDU), high risk sexual behavior, recent history of invasive procedures and elevated liver enzymes. Reinfection was defined as detectable HCV RNA after confirmed SVR.

Results: During the study period 420 patients achieved SVR and 274 (65%) were screened for HCV reinfection. Among 274 persons tested for HCV reinfection the median age was 46 (IQR: 40-51) years, 242 (88.3%) were men and 201 (73.4%) had history of IDU. HCV genotypes included: 103 (37.6%) genotype 1, 84 (30.7%) genotype 3, 83 (30.3%) genotype 2 and 4 (1.5%) genotype 4. With regard to DAA regimens, 142 (51.8%) were treated with ledipasvir/sofosbuvir ± ribavirin, 58 (21.2%) – with sofosbuvir/ribavirin and 74 (27.0%) – with sofosbuvir/ribavirin + peginterferon. Patients were followed for median 1.8 (IQR: 1.1-2.5) years contributing to 507 person-years (PY) of follow-up. In total, 12 (4.4%) persons had HCV re-infection with an overall incidence of 2.4 per 100 PY.

Conclusion: HIV positive IDUs are at high risk for HCV reinfection following successful DAA therapy. Greater engagement in OST programs are required to prevent reinfections and achieve elimination targets.

596 HCV REINFECTION AFTER DAA TREATMENT AMONG PEOPLE LIVING WITH HIV IN SAN DIEGO

Lucas Hill1, Natasha Martin1, Sonia Jain1, Francesca Torriani1, Xiaoying Sun1, Huifang Qin1, Craig Ballard1, W. C. Mathews1, Edward R. Cachay1, asa Radix2, Natasha Martin1, Sonia Jain1, Francesca Torriani1, Xiaoying Sun1, Huifang Qin1, Craig Ballard1, W. C. Mathews1, Edward R. Cachay1

1University of California San Diego, La Jolla, CA, USA

Background: Previously, we reported the HCV reinfection rate in San Diego from 2000 to 2014 among HIV-infected men who have sex with men (MSM) during the interferon era was 2.89/100 PYFU. Herein, we report the HCV re-infection rates in all groups of people living with HIV (PLWH) treated with interferon-free direct-acting antivirals (DAA) in San Diego, California.

Methods: Retrospective cohort analysis of adult PLWH treated with DAA at the University of California, San Diego between 2014 and April 2019. PLWH with documented sustained virologic response (SVR), and at least one subsequent HCV RNA measurement before September 2019 were included. HCV re-infection was defined as new HCV viremia after documented SVR. Follow up time was calculated from the date of SVR documentation until the first subsequent positive HCV RNA or the last negative HCV RNA. Clinical onset of re-infection was defined as the date of the first noted HCV RNA.

Results: There were 204 PLWH with documented SVR. Their median age was 52 years (95% CI: 50-53.4), 83.3% were male, and 21.6% were non-white. HCV genotypes were distributed 77 in 1 (68.1%), 1b in 20 (9.8%), 3 in 27 (13.2%) and other in 18 (8.8%). The median CD4 count in cells/µl was 503 (95% CI: 464-562) and 188 (92.2%) had undetectable HIV viral load. HCV risk factors were MSM in 54.9%, of which 40.2% also had a history of intravenous drug use (IVDU), and IVDU as the only risk factor in 39.2%. Sixteen men acquired a new HCV infection over 321.7 PYFU. The HCV reinfection rate overall was 1.87 and in MSM non-IVDU 3.54 per 100 PYFU.

Conclusion: The overall reinfection rate in San Diego among PLWH in the DAA era is low, and is highest among MSM but comparable to previously observed.
HCV reinfection rates based on HIV risk factor, race/ethnicity, age, and gender

<table>
<thead>
<tr>
<th>HIV/HCV Risk factor</th>
<th>Reinfection rate (per 100 PYFU) (95% CI)</th>
<th>Person-Years of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+ (436)</td>
<td>1.87 (1.69-2.06)</td>
<td>233.70</td>
</tr>
<tr>
<td>MSM-only (97)</td>
<td>3.54 (3.96-4.06)</td>
<td>15.13</td>
</tr>
<tr>
<td>MSM+HCV (45)</td>
<td>2.33 (2.06-2.98)</td>
<td>42.95</td>
</tr>
<tr>
<td>MSM+HIV only (80)</td>
<td>0.66 (0.32-1.67)</td>
<td>152.65</td>
</tr>
<tr>
<td>Intermittent only (5)</td>
<td>0.00</td>
<td>4.89</td>
</tr>
<tr>
<td>Other/Unknown (4)</td>
<td>0.00</td>
<td>8.88</td>
</tr>
</tbody>
</table>

Biologic sex/ethnicity

| Female (129)            | 0.00 | 44.07 |
| Male (172)              | 2.16 (0.79-2.71) | 277.62 |
| Race/Ethnicity [e]      |       |       |
| White (168)             | 2.03 (1.66-4.75) | 245.99 |
| Non-white (44)          | 1.32 (1.03-7.17) | 75.70 |

Age in years [p]

| <30 (10) | 0.00 | 10.71 |
| 30-39 (25) | 7.49 (9.91-27.07) | 26.70 |
| 40-49 (43) | 1.49 (1.04-4.29) | 67.24 |
| 50-59 (40) | 1.94 (1.40-6.65) | 155.16 |
| >60 (13) | 0.00 | 63.68 |

Results: A total of 15,692 HIV-positive MSM were included. Their median age was 45 years (interquartile range [IQR]: 35-52). The median number of HCV serology tests during follow-up for each individual was 3 (IQR: 2-4), with a median testing interval of 1.25 years (IQR: 0.85-1.93) between two tests. Overall, 330 incident HCV infections occurred over 45,866 person-years (PY) of follow-up. Incidence of first HCV infection decreased significantly (p-trend=0.04) over time during the study period: 0.98/100PY (2014), 0.82/100PY (2015), 0.67/100PY (2016) and 0.45/100PY (2017). The stronger decrease occurred in 2017 (33% reduction from 2016 to 2017). In sensitivity analyses, similar trends were observed when the date of first positive HCV was used as a proxy for the time of infection, or when follow-up was ceased at the date of last clinical visit or 12 months after for patients lost to follow-up.

Conclusion: The observed decrease in primary HCV infections among HIV-infected MSM may be related to a concomitant and continuous scaling-up in DAA use, which was especially marked in HIV-HCV coinfected individuals. The declining trend may also be considered in parallel with the rising incidence of HCV infection recently reported among HIV-negative MSM receiving preexposure prophylaxis (PrEP), suggesting a transfer of the epidemic from the former to the latter.
**SYNDROMIC OF HCV, PRESCRIPTION OPIOID USE, AND PSYCHIATRIC ILLNESS: A NOVEL FRAMEWORK**

**Adeel A. Butt**, for the ERICHVES Study Team

**Well Cornell Medicine, New York, NY, USA**

**Background:** The concept of “syndemic” or synergistic epidemic, was coined by medical anthropologists to describe the clustering of two or more diseases within a population, and their biologic, social, cultural, economic, and economic forces. We propose that the confluence of hepatitis C virus (HCV) infection, prescription opioid use (POU), and psychiatric illness (PI) constitutes a syndemic with critical individual and societal consequences. Our objective was to define the epidemiology of SHOPS as a first step towards understanding its impact on individual and population outcomes.

**Methods:** We used the ERICHVES cohort to identify persons with each component of SHOPS individually and in all combinations. ERICHVES includes all HCV diagnosed Veterans from 2001 onwards, who are identified based on a positive HCV antibody test and demographically matched HCV uninfected controls. HCV infection was defined based on a positive HCV antibody and at least one positive HCV RNA. POU was defined as prescription of any approved pharmacotherapeutic agent for the condition. PI was defined by the presence of > 1 inpatient or > 2 outpatient ICD-9/10 codes for any of the following conditions: major or minor depression; bipolar disorder; schizophrenia; post-traumatic stress disorder. Treatment for each condition was determined by prescription of any approved pharmacotherapeutic agent for the condition.

**Results:** Among 781,271 ERCHIVES participants between 2001-2018, 238,506 had chronic HCV only, 28,226 had POU only, and 99,681 had PI only. Other combinations of these conditions are listed in the figure. Overall, 205,473 had HCV and psychiatric illness (PI) and 51.7% of those with HCV, 23.9% with POU and 84.2% with PI received any treatment for those conditions, only 17.8% of persons with all three syndemic components received treatment for all three conditions. Further, 238,023 had chronic HCV and receive treatment for the condition, while 206,079 had POU and 385,356 had PI. While 51.7% of those with HCV, 23.9% with POU and 84.2% with PI received any treatment for those conditions, only 17.8% of persons with all three syndemic components received treatment for all three conditions.

**Conclusion:** Co-occurrence of HCV, POU, and PI is common, with treatment offered less frequently among those with multiple syndemic components. Next steps are to determine the clinical consequences of SHOPS and impact of treatment singly and in combination.

---

**Table 1. Characteristics of patients prescribed oral prescription opioids (OPOs) in NSR, January 1, 2001 – December 31, 2018**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OPD</th>
<th>HCV Ab+ (%)</th>
<th>ORadj (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean ± standard deviation</td>
<td>57.0 ± 17.7</td>
<td>58.8 ± 11.6</td>
<td>1.02 (1.01-1.03)</td>
</tr>
<tr>
<td>Ratio of female</td>
<td>67,294 (52.7%)</td>
<td>4,937 (10.2%)</td>
<td>0.77 (0.73-0.80)</td>
</tr>
<tr>
<td>Total</td>
<td>132,182 (10.2%)</td>
<td>7,061 (5.4%)</td>
<td>1.20 (1.18-1.22)</td>
</tr>
<tr>
<td>Race</td>
<td>76,099 (56.7%)</td>
<td>4,961 (12.6%)</td>
<td>1.21 (1.15-1.26)</td>
</tr>
<tr>
<td>Asian</td>
<td>15,478 (8.7%)</td>
<td>772 (10.8%)</td>
<td>0.87 (0.71-1.07)</td>
</tr>
<tr>
<td>White</td>
<td>107,684 (76.7%)</td>
<td>1,515 (8.2%)</td>
<td>1.00 (0.96-1.04)</td>
</tr>
<tr>
<td>Birth Cohort</td>
<td>35,744 (26.7%)</td>
<td>1,073 (20.3%)</td>
<td>1.05 (1.00-1.10)</td>
</tr>
</tbody>
</table>

**ORAL PRESCRIPTION OPIOID USE AS A HIGH-RISK INDICATOR FOR HCV INFECTION**

**Benjamin A. Hack**, Utsav Timalsina, Emily Paku, Brittany Wilkerson, Eshetu Tefera, Stephen Fernandez, Dawn Fishbein

**Georgetown University, Washington, DC, USA, MedStar Health Research Institute, Hyattville, MD, USA**

**Background:** The opioid epidemic across the U.S. poses an array of public health concerns, especially HCV transmission. HCV is now widely-curable, yet incident rates are increasing due to the opioid epidemic. Despite the established trajectory from oral prescription opioids (OPOs) to opioid use disorder (OUD), OUD to injection drug use (IDU), and IDU to HCV, we have found no studies or guidelines establishing OPOs as a defined risk factor (RF) for HCV infection. In this study we observed HCV testing and antibody reactivity (HCVAb+) in patients receiving OPOs, hypothesizing that they should be considered an HCV RF, critical in the global effort toward HCV elimination.

**Methods:** The study was conducted on all patients with any OPO reported in the EHR at a large regional US healthcare system between January 2017 and December 2018. Chi-square and Student t-tests were used for univariate comparisons; multivariate logistic regression was used for independent variable associations. Statistical significance was defined as p<0.05; Epi Info and SAS v9.4 were used for analyses. IRB approval was received.

**Results:** Among 218,030 persons receiving any OPO (Table 1); 8.6% (932) were HCVAb+. Among those, 70.6% (658) were black, 22.9% (210) were white, 1.7% (16) were Asian. There were 1,076 persons with OPOs and HCVAb+. Among all persons with OPOs, 8.6% (932) were HCVAb+. Among those, 70.6% (658) were black, 22.9% (210) were white, 1.7% (16) were Asian.

**Conclusion:** These results offer three applicable conclusions: 1) in a large population prescribed oral opioids, HCVAb+ was 8.6%, higher than our previously-published data (2.5%) and US rate (1.7%); thus, OPOs should be incorporated as a defined RF for HCV counseling and retesting; 2) although OUD may lead to known HCV RFs, only 20% of patients diagnosed with OUD were tested; thus, efforts should be increased to improve HCV RF awareness; and, 3) although the trajectory from OPOs to OUD to IDU to HCV would predict that a majority of HCVAb+ patients have OUD, only 25% of those HCVAb+ were classified with OUD; therefore, new strategies need consideration for reporting OUD, which will also increase HCV RF identification. These recommendations should be adopted as the natural next steps in global HCV elimination.
601 THE PERFECT ICE STORM: THE MIX OF METH AND HIV SPREADS HEPATITIS C IN THAI MSM

Donn J. Colby1, Sriporn Nonenoy2, Sataporn Waewklihong1, Jitsupa Peeralay1, Ratchadaporn Meksona1, Oranuch Nampaisarn3, Jipissut Ariyasirikul1, Piranun Honghoochkit1, Peeraporn Kaewon1, Pradit Chalit1, Sirichai Jarupitaya2, Nipat Teeratakulpisarn3, Reshmie Ramautarsing1, Praphan Phunaphak1, Nittaya Phunaphak1

1Thai Red Cross AIDS Research Center, Bangkok, Thailand

Background: Recent outbreaks of hepatitis C infection (HCV) have been reported among men who have sex with men (MSM) in multiple countries. We report on factors associated with baseline HCV prevalence in a study of the use of amphetamine-type stimulants (ATS) in Bangkok, Thailand.

Methods: MSM and transgender women (TW) who presented for routine HIV testing at the Thai Red Cross Anonymous Clinic (TRAC) were recruited into a longitudinal study of ATS use. Recruitment was stratified to over-sample for HIV infection and ATS use within the previous 6 months. Baseline assessment included HIV serology, anti-HCV antibody, sexually transmitted infection (STI) screen (syphilis, gonorrhea, chlamydia), and a computer-assisted self interview covering sexual and substance use risk behavior.

Results: Enrollment included 470 MSM (93.6%) and 32 TW (6.4%), of whom 161 (32%) were HIV-positive. Median age was 28 (IQR 24-35). Most (69%) had a bachelor degree or higher, and 95% were employed or in school. 94% reported ever having anal sex, 21% had group sex, and 54% of group sex events involved illicit drug use. Consistent condom use was only 38% for receptive and 41% for insertive anal sex. ATS use was reported by 131, most frequently crystal methamphetamine (METH) (n=122) followed by ecstasy (n=43) and oral amphetamines (n=18). HCV prevalence overall was 3.6%, and was associated with ATS use, HIV infection, or both (Figure, P<0.001). Over one-third (n=45) of METH users reported injecting the drug intravenously in the previous 6 months. However, only a minority (28%) of those with HCV reported injection drug use. STI were common: 16% had syphilis, 16% chlamydia, and 8% gonorrhea. On multivariable analysis, factors independently associated with HCV were HIV infection and ATS use within the previous 6 months. Baseline assessment included HIV serology, anti-HCV antibody, sexually transmitted infection (STI) screen (syphilis, gonorrhea, chlamydia), and a computer-assisted self interview covering sexual and substance use risk behavior.

Conclusion: HIV infection is spreading rapidly among MSM with HIV in Bangkok, and is closely associated with the use of METH. Injection use of METH is also increasing rapidly in Thai MSM. However, most cases of HCV appear to be transmitted by anal sex, possibly potentiated by the presence of STIs and/or prolonged sex in the context of illicit drug use. Harm reduction, and HCV treatment with direct-acting antivirals, are needed to address this newly emerging epidemic.

602 HEPATITIS C VIRUS INFECTION AND COINFECTION WITH HIV AMONG PWID IN 10 US CITIES

Johanna Chapin-Bardales1, Alice Asher1, Dita Broz2, Eyasu Teshale1, Tonya Hayden1, Carlos Blanco3, Senad Handanagic4, Cyprian Weinert5, for the NHHS HCV Study Group

1CDC, Atlanta, GA, USA, 2National Institute on Drug Abuse, Rockville, MD, USA

Background: Understanding the burden of acute and chronic hepatitis C virus (HCV) infection and HIV/HCV co-infection among persons who inject drugs (PWID) is important for informing HIV and HCV elimination efforts. We measured HCV infection and HIV/HCV co-infection among PWID in 10 U.S. cities.

Methods: In 2018 National HIV Behavioral Surveillance, PWID were recruited using respondent-driven sampling and offered a behavioral survey, HIV testing, and HCV antibody and RNA testing in Chicago, Dallas, Houston, Los Angeles, Miami, New York City, Philadelphia, San Francisco, San Juan, and Washington DC. We examined prevalence of acute (anti-HCV non-reactive/RNA detected) and chronic (anti-HCV reactive/RNA detected) HCV infection and HIV/HCV co-infection. We obtained adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) to assess characteristics associated with current HCV infection (RNA detected vs. not detected) and HIV/HCV co-infection (vs. no HIV/HCV co-infection).

Results: Overall, 62.4% (3239/5,190) had a reactive anti-HCV result, 44.2% (1678/3795) had HCV RNA detected, and 4.0% (153/3,779) had HIV/HCV co-infection. Of those with both antibody and RNA test results, 3.9% (149/3795) had acute and 40.3% (1529/3795) had chronic HCV infection. Acute infection was highest among PWID who were male (4.3%), ages 25-34 (4.2%), black (4.5%), HIV-positive (4.6%), injecting ≤5 years (4.3%), injected ≥1 time/day (4.2%), injected heroin most often (4.3%), and were from Miami (17.6%) or Philadelphia (5.3%). Current HCV infection was higher among PWID who male (aPR 1.2, 95% CI 1.1-1.3), white (aPR 1.3, 95% CI 1.1-1.5), injecting ≥5 years (aPR 1.5, 95% CI 1.2-1.8), injected ≥1 time/day (aPR 1.5, 95% CI 1.3-1.7), and shared syringes (aPR 1.2, 95% CI 1.1-1.3) or injection equipment (aPR 1.3, 95% CI 1.1-1.4) in the past year. HIV/HCV coinfection was highest among participants who were transgender (aPR 6.3, 95% CI 2.8-14.5), injecting >5 years (aPR 2.1, 95% CI 1.3-3.1), injected speedball (heroin and cocaine injected together) (aPR 2.1, 95% CI 1.4-3.0) or stimulants (aPR 1.8, 95% CI 1.1-2.9) most often (vs. heroin), and were from Miami (aPR 2.3, 95% CI 1.3-3.9).

Conclusion: Acute and chronic HCV prevalence was high among a sample of U.S. urban PWID. Nearly one in two PWID had current HCV infection and one in 25 had HIV/HCV co-infection in our sample. HIV and HCV elimination efforts should focus on providing treatment and reducing risk behaviors among PWID to prevent further transmission.

603 HEPATITIS B VIRUS VACCINATION IN A CURRENT-ERA HIV CLINIC

Meagan Deming1, Shyam Kotttil2

1University of Maryland, Baltimore, MD, USA

Background: Hepatitis B virus (HBV) infections remain a global health issue with complications including liver cirrhosis and hepatocellular carcinoma. Individuals co-infected with Human Immunodeficiency Virus (HIV) and HBV have increased liver-related morbidity and mortality compared to those with HBV mono-infection. Vaccination is a potent intervention to prevent HBV infection, but certain critical populations including people living with HIV are less likely to achieve seroprotection after vaccination. Seroprotection (antibody to hepatitis B surface antigen titer ≥ 10 IU/mL) is historically poor, with trial rates ranging from 34 to 88% and improving with immunologic reconstitution and viral suppression. We hypothesized that the seroprotection rates (SPR) in a clinic population of Veterans would reflect the improving immunologic status of the cohort.

Methods: We reviewed the HBV serologies and vaccination records of Veterans with HIV engaged in care at the Baltimore Veterans Affairs Infectious Disease Clinic over the past 20 years to assess the ultimate seroprotection status of the cohort.

Results: The overall seroprotection status is in line with previous data, with 79% of clinic patients showing serologic response to vaccination. Of the patients who remain nonimmune, 43% (89 of 207) have been vaccinated without seroprotection. Importantly, over half the clinic population is HBV core antibody positive, reinforcing the overlapping risk factors for HIV and HBV acquisition. In the two decades studied, the percentage of virally suppressed patients improved from 22.5% of 507 in 2000 to 50.7% of 554 in 2009 and to 86.6% of 261 in 2019. The median CD4 count improved from 394 (IQR 212-593) in 2000 to 532 (IQR 342-772) in 2010, and to 630 (IQR 417-833) in 2019. Despite the improved immunologic status of this cohort, the SPR after 2009 showed no significant improvement compared to the prior decade: 56.7% compared to 57.0%. The apparently static response rates may reflect the aging of the cohort, the SPR after 2009 showed no significant improvement compared to the prior decade: 56.7% compared to 57.0%. The apparently static response rates may reflect the aging of the cohort, but certain critical populations including people living with HIV are less likely to achieve seroprotection after vaccination. Seroprotection (antibody to hepatitis B surface antigen titer ≥ 10 IU/mL) was historically poor, with trial rates ranging from 34 to 88% and improving with immunologic reconstitution and viral suppression. We hypothesized that the seroprotection rates (SPR) in a clinic population of Veterans would reflect the improving immunologic status of the cohort.

Conclusion: Despite lower than anticipated SPR, consistent vaccination standards have contributed to seroprotection for a majority of the cohort, and revaccination of nonresponders with Gp4-adjuncted HBV vaccine is ongoing.
604 EFFECTIVENESS OF THE NOVEL ADJUVANTED HEPATITIS B VACCINE AMONG IMMUNIZATION RESPONSE IN INFANTS BORN TO HBsAg+ HBeAg+ MOTHERS RECEIVING TDF

Gonzague Jourdain1, Patriline Traisathit2, Nicolas Salvadori2, Nantawan Wangsaeng3, Woottchais Khhammadang2, Nicole Ngo-Giang-Huong1, for the iTAP Study Group
1French National Research Institute for Sustainable Development, Marseilles, France, 2Chiang Mai University, Chiang Mai, Thailand

Background: It is unknown whether maternal antiviral prophylaxis could affect the response to vaccine in infants receiving hepatitis B (HB) immune globulin (HBIG) born to mothers infected with HB virus (HBV). We analyzed the infant immunization response in a randomized clinical trial in Thailand (iTAP-1, NCT01745822).

Methods: iTAP-1 was an RCT assessing TDF prophylaxis (vs placebo) in HBsAg+ HBeAg+ women from 28 weeks’ pregnancy to 2 months postpartum. All infants received HBIG and HB vaccine (monovalent at birth and 1 month, as part of a multivalent vaccine at 2, 4 and 6 months). Antibody titers were measured using the Monolisa Anti-HBs Plus kit Blood at visits scheduled at 1, 2, 4, 6, 9 and 12 months. All infants were included in this analysis, except 3 (placebo group) confirmed HBV infected. Comparisons were made using the Wilcoxon rank sum test.

Results: 315 infants (162 TDF, 153 placebo) participated in the analysis: 166 male and 149 female. At birth, median (IQR) weight was 3.0 kg (2.8-3.4) and length 50.3 cm (49.0-52.0). Median (95% CI) anti-HBs geometric concentrations at 1, 2, 4, 6, 9 and 12 month visits were: 123 IU/L (115-132), 71 (66-77), 268 (228-315), 556 (477-648), 595 (512-691), 294 (253-342), respectively (see Figure: anti-HBs geometric concentrations according to actual age at assessment). All infants had anti-HBs titers > 10 IU/L at all visits, except 4 of 311 (1.3%) at 1 month, 3 of 303 (1.0%) at 2 months, and 1 of 274 at 12 months. At 6 months and thereafter, there were no significant differences in anti-HBs titers between treatment arm (TDF versus placebo), according to maternal bodyweight before delivery, gestational age at delivery, birth weight, sex, infant length, or durations from birth to vaccine birth dose or to HBIG administration.

Conclusion: Maternal antiviral prophylaxis had no effect on the infant response. HBIG masked the response until 2 months, then titers increased until the age at the first antibody titer, gender, or CMV serostatus. The absolute value of monthly decay was positively correlated with the initial antibody titer and the age at the first antibody titer, gender, or CMV serostatus. The absolute value of monthly decay was positively correlated with the initial antibody titer and the age at the first antibody titer, gender, or CMV serostatus. The absolute value of monthly decay was positively correlated with the initial antibody titer and the age at the first antibody titer, gender, or CMV serostatus.

Background: People living with HIV or chronic hepatitis C virus (HCV) have diminished immune responses to hepatitis B virus (HBV) vaccination. The current HBV vaccine has a positive response rate upwards of 85% in the general population, but that same vaccine series only provides immunity for 20-70% of people living with HIV and 40-60% for the HCV population, emphasizing the need for advancement. A novel, adjuvanted HBV vaccine, HepB-CpG, demonstrated improved immune response (>90%) in non-HIV and non-HCV cohorts. Yet, the effectiveness in HIV and HCV patients is unknown. This study evaluated the immune response to HepB-CpG among HIV and HCV patients at an outpatient virology clinic.

Methods: We evaluated HIV and HCV patients who received at least one dose of HepB-CpG beginning October 1, 2018. HBV vaccination and serology were performed in conjunction with routine clinical appointments. An HBV surface antibody ≥10 mIU/mL was considered a positive immune response. Population characteristics and overall effectiveness were evaluated using descriptive statistics and represented as n (%) or median(IQR) as appropriate.

Results: Among 130 individuals, 41 (32%) were living with HIV and 89 (68%) with HCV. Most were white (110, 85%) and non-diabetic (112, 86%). The median age was 53 (38-61). Viral load was <20 copies/mL in 26 (63%) HIV patients at the time of first vaccination, and the majority had CD4 counts greater than 500. Two-thirds of HIV patients had received at least one full HBV vaccine series previously, whereas the same was true for only one-third of HCV patients. Of the 11 HIV patients tested for immunity after series completion, 82% had a positive HBV antibody. Interestingly, an additional 6 patients became immune after just one dose, bringing the total positive response rate to 88%. HCV patients responded similarly, with 78% immune after completing the series and an additional 3 patients immune after one dose. No patients reported adverse events.

Conclusion: Our analysis shows an overall immune response to HepB-CpG of 84%, which is considerably higher than historical data using the non-adjuvanted vaccine. As part of a robust immunization program to protect HIV and HCV patients, HepB-CpG should be considered as an assured alternative to the traditional HBV vaccination series.
607 HIGH INCIDENCE OF HBV INFECTION IN HIV-COINFECTED PATIENTS: ACCESSING ART CARE

Noukuchanya Msomi1, Kugielem Naidoo2, Nonhlanhla Yende-Zuma, Keresha Govender3, Nesri Padayatchy2, Jerome Singh1, Salim S. Abdool Karim1, Quarraisha Abdoor Karim1, Koleka Milicana4

1University of KwaZulu-Natal, Durban, South Africa, 2CAPRISA, Durban, South Africa, 3University of Toronto, Toronto, ON, Canada, 4National Health Laboratory Service, Johannesburg, South Africa

Background: Hepatitis B virus (HBV), Human Immunodeficiency virus (HIV) and Tuberculosis (TB) are common infections in South Africa. HBV vaccination has been included in the country’s childhood immunization schedule since 1995; however, less is known of the current burden of HBV in adults. We utilized the opportunity of care provision or HIV-TB co-infected patients to determine the magnitude of, and the relationship between HIV and HBV, and identify risk factors for HBV infection in HIV infected patients with and without TB in urban and rural KwaZulu-Natal, South Africa.

Methods: This retrospective cohort analysis was undertaken in 2018. In-care HIV infected patients were included in the analysis. Results from clinical records were analysed to determine the prevalence, incidence, persistence and factors associated with HBV infection in HIV infected patients with or without TB co-infection.

Results: A total of 4292 HIV infected patients with a mean age of 35 (SD: 8.8 years) were included. The baseline prevalence of HBV was 8.5% (363/4292) [95% confidence interval (CI): 7.7 to 9.3] and 9.4% (95%CI: 8.6 to 10.3 %) at end of follow-up. The HIV incidence rate was 2.1/100 person-years (p-y). Being male was associated with a two-fold higher risk (HR 2.11; 95% CI: 1.14 - 3.92) of incident HBV infection while severe immunosuppression was associated with a two-fold higher risk of persistent infection (adjusted risk ratio 2.54; 95% CI 1.06-6.14; p=0.004). Active TB at enrolment was associated with a two-fold higher risk of persistent infection (adjusted risk ratio 2.54; 95% CI 1.06-6.14; p=0.004). Active TB at enrolment was associated with a two-fold higher risk of incident HBV infection (aHR 2.38; 95% CI: 0.77 to 7.35).

Conclusion: The provision of HIV care and treatment in high HBV burden settings provide a missed opportunity for HBV screening, immunization and care provision.

608 CHARACTERIZING HBV INFECTION AMONG PERSONS LIVING WITH HIV IN CARE IN URBAN SENEGAL

Adria Ramirez Mena1, Judicael M. Time1, Ousseyou Ndiaye1, Louise Fortes1, Ka Deye1, Ndeye Fatou Gnom1, Fall Fatou1, Moussa Sydi1, Gilles Wandelé4

1University of Bern, Bern, Switzerland, 2CHU de Fann, Dakar, Senegal, 3Hospital Principal de Dakar, Dakar, Senegal, 4University Hospital of Bern, Bern, Switzerland

Background: Chronic hepatitis B virus (HBV) infection affects 10% of the general population and is the leading cause of liver cirrhosis and cancer in West Africa. Despite current recommendations, HBV infection is generally not tested for in clinical routine in the region. We investigated the HBV infection status of HIV-infected individuals in care at an outpatient clinic in Dakar, Senegal, and determined the proportion of HIV/HBV-coinfected individuals with viral replication despite antiretroviral therapy (ART).

Methods: We tested all HIV-infected individuals presenting for routine clinical care between March and July 2019 for the presence of HBsAg using a one-step lateral flow assay rapid test (Novastest®). All individuals with a positive result underwent an HIV viral load (VL) and HBV VL (COBAS/TaqMan® HBV/HIV Test) measurement. Liver stiffness measurements (LSM) were conducted by a single investigator, using transient elastography. We compared the main characteristics between individuals previously tested for HBV and the others using Chi-square and Mann-Whitney tests. We determined the proportion of HBsAg-positive individuals who had current HBV replication (>20 IU/ml) on ART and/or who were on an inadequate ART regimen.

Results: Of 1,219 HIV-infected patients in active follow-up at Fann University Hospital, 973 had never been tested for HBsAg before our intervention. Their median time on ART was 9 years, and when compared with individuals previously tested, they were more likely to be female (67.7% vs. 55.5%; p<0.001) and to have a CD4 >350 cells/µL at enrollment (37.6% vs 29.5%, p=0.01). Of 449 patients tested during our intervention, 50 (11.1%) were HBsAg-positive, of whom 24 (50.0%) were female. Their median CD4 cell count at ART initiation was 153 cells/µL (interquartile range 57-234) and 2 (5.7%) had significant liver fibrosis (LSM >7 kPa). Seven (14.0%) individuals had a detectable HBV VL, of whom five were HIV suppressed. Four individuals were on ART including lamivudine and zidovudine as a backbone, and had to be switched to a TDF-containing regimen.

Conclusion: In our referral HIV clinic, the majority of patients on ART had never been tested for HBV. 15% of HIV/HBV-coinfected individuals had a positive HBV VL despite HIV suppression, and 10% were not receiving a TDF-containing regimen. Considering the high risk of liver-related complication in individuals with HBV replication, HBV testing should be performed routinely during HIV clinical care.

609 LIVER FIBROSIS CHANGES OVER 3 YEARS OF TENOFOVIR-BASED ART IN HIV-HBV COINFECTION

Michael J. Vinikoor1, Kalongo Hamusonde1, Shilpa Iyer2, Edforth Sinkala3, Lloyd Mulenga3, Michael Saag1, Mary-Ann Davies4, Matthias Egger5, Gilles Wandelé6

1University of Alabama at Birmingham, Birmingham, AL, USA, 2Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, 3University of Zambia, Lusaka, Zambia, 4Centre for Infectious Disease Epidemiology and Research, Cape Town, South Africa, 5University of Bern, Bern, Switzerland

Background: Although tenofovir-based therapy can potentially reduce HBV DNA and can reverse hepatic fibrosis in HBV mono-infection, its long-term impact on clinical outcomes in HIV-HBV coinfection is not well-established and some data suggest hepatic inflammation and fibrosis persist. In Zambian HIV-HBV coinfected adults treated with antiretroviral therapy (ART), we analyzed normalization of ALT and changes in liver fibrosis, based on transient elastography (TE).

Methods: We analyzed data from an active cohort of Zambian adults (19 years) who were HIV-positive, hepatitis B surface antigen-positive, and started tenofovir-based ART. At ART start and yearly during therapy, we measured CD4, HBV DNA, ALT, and liver stiffness (LSM; based on TE). LSM were categorized as no-minimal fibrosis (<7.9 kPa); F0-F1, significant fibrosis (7.9-9.5; F2-3), and cirrhosis (>9.5; F4). HBV viral suppression (VS) was defined as ≤20 IU/ml and ALT elevation was >30 U/L. We included in analysis any cohort participants with LSM at ART start and ≥1 follow-up measure. We described on-therapy HBV VS, normalization of ALT among those with baseline elevation, and regression and progression of fibrosis and cirrhosis.

Results: Among 358 HIV-HBV coinfected patients enrolled, 234 were analyzed (median age, 34 years; 60.8% men). At ART start, median CD4 count was 198 cells/mm3, median HBV DNA was 5400 IU/ml, 81 of 183 tested (44.3%) were HBsAg-positive, 102 (47.9%) had ALT elevation, 16 (6.6%) had significant hepatic fibrosis, and 23 (9.8%) had cirrhosis. Median follow-up was 2.6 years (interquartile range, 1.7-3.8). HBV DNA suppression at 1, 2, and 3-5 years was 62.7%, 80.3%, and 84.5%. Among the 102 with ALT elevation at ART start, 50 (49.5%) had persistent elevation at their last assessment. During ART, 13 of 16 (81.2%) with significant fibrosis and 18 of 23 (78.3%) with cirrhosis experienced regression to a lower category. Five patients progressed from no-minimal significant fibrosis (n=4) or cirrhosis (n=1) and 1 progressed from significant fibrosis to cirrhosis. The majority of patients with disease progression had evidence of both HIV and HBV VS.

Conclusion: Regression of liver fibrosis and cirrhosis was common during tenofovir-based ART. Persistent ALT elevation was seen in ~20% of HIV-HBV coinfected patients, likely due to non-HIV, non-HBV-related causes such as alcohol abuse.
LONG-ACTING TENOFOVIR AND NITAZOXANIDE FORMULATIONS SUPPRESS HBV REPLICATION

Denise A. Cobb1, Dhruv Kumar Soni2, Weimin Wang1, Murali Ganesan1, Raghubendra S. Dagur1, Edward Makarov1, Yimin Sun1, JoEllyn McMillan1, Howard E. Gendelman1, Natalia Osna1, Laila V. Polevko1, Benson Edagwa1

Abstract: We tested the potential of monthly NM1TAF and NM1NTZ dosing for treatment of HBV in humanized mice for a month after a single dose. These data sets support the hypothesis that long-acting prodrug formulations were taken up by MDM with sustained drug levels for 30 days; retention was determined in human monocyte-derived macrophages (MDM). Cellular drug uptake and release by (NM1TAF by 50%) and cccDNA pools (NM1NTZ by 88% and NM1TAF by 60%) were recorded. The combination long acting prodrug therapy reduced HBV DNA in plasma of humanized mice to undetectable levels in 2/4 animals by 60% or more, and the combination showed increased drug potency and improved distribution to liver cell viral compartments.

Methods: NTZ and TFV prodrugs (M1NTZ and M1TAF) were synthesized and nanoformulated creating NM1NTZ and NM1TAF. Cellular drug uptake and retention were determined in human monocyte-derived macrophages (MDM). The HBV-producing human hepatocellular carcinoma HepG2.2.15 cell and MDM were co-cultured with SUVs of NM1NTZ and NM1TAF at four weeks with readily detected human cells (Fig). The remaining two animals showed > log decrease in plasma viral load at equivalent times. The remaining two animals showed > log decrease in plasma viral load at equivalent times.

Results: NM1NTZ and NM1TAF had average particle sizes of 250-350 nm, polydispersity index of <0.2 and drug loading capacity of > 70%. Both formulations were taken up by MDM with sustained drug levels for 30 days; whereas native drugs were eliminated in one day. Suppression of HBV DNA release by (NM1TAF by 50%) and cccDNA pools (NM1NTZ by 88% and NM1TAF by 60%) were recorded. The combination long acting prodrug therapy reduced HBV DNA in plasma of humanized mice to undetectable levels in 2/4 animals tested for 4 weeks with readily detected human cells (Fig). The remaining two animals showed > log decrease in plasma viral load at equivalent times. Animals were monitored for 10 weeks to measure viral rebound.

Conclusion: Long-acting TFV and NTZ prodrugs sustained antiviral activity in humanized mice for a month after a single dose. These data sets support the potential of monthly NM1TAF and NM1NTZ dosing for treatment of HBV infections.

A RHEUSA MACAO MODE OF CHRONIC HBV INFECTION FOR CURE RESEARCH

Sreya Biswas1, Patrick Hashiguchi1, Jennifer Stanton1, Benjamin N. Bimber1, Ulrike Protzer2, Jonah Sacha2, Benjamin J. Burwitz3

Abstract: We treated three infant RM (<1-year-old) with an immunosuppression regimen consisting of daily tacrolimus and semi-monthly belatacept injections. Following initiation of this immunosuppression, we intravenously administered high-dose adenovirus expressing hNTCP. Seven days later we challenged all three RM intravenously with HBV (1 x 10^9 virions). We followed HBV infection in the blood and liver in these RM by qPCR, ELISA, and immunofluorescent microscopy over the course of 42 weeks.

Methods: We treated three infant RM (<1-year-old) with an immunosuppression regimen consisting of daily tacrolimus and semi-monthly belatacept injections. Following initiation of this immunosuppression, we intravenously administered high-dose adenovirus expressing hNTCP. Seven days later we challenged all three RM intravenously with HBV (1 x 10^9 virions). Immunosuppression was tapered after 18 weeks of HBV infection. We have followed HBV infection in the blood and liver in these RM by qPCR, ELISA, and immunofluorescent microscopy over the course of 42 weeks.

Results: We found persistently high levels of HBV plasma viremia (>1 x 10^5 copies/ml) accompanied by high levels of HBV surface (HBsAg) and envelope (HBeAg) antigens in blood for more than six months, the clinical definition of chronic HBV infection. In addition, high frequencies of HBV core antigen (HBcAg)- and HBsAg-positive hepatocytes were detected longitudinally in liver biopsies. Following immunosuppression tapering, two of the three animals maintained ongoing viral replication, indicating HBV immunotolerance. The set point HBV loads in these two animals correlated with the level of cccDNA expression in the liver by qPCR, indicating that hepatocyte target availability is the restricting factor in this model.

Conclusion: Our data indicate that RM can be chronically infected with HBV and represent a promising model for the testing of emerging HBV curative therapies.

CYTOKINE PROFILES IN ASYMPTOMATIC ACUTE HEPATITIS B

Kathleen E. Stevens1, Eric C. Seaberg1, Katherine Cascino1, Mallory Witt1, Claudia Hawkins3, Bernard J. Macatangay4, Chloe Thio1

Abstract: We found persistently high levels of HBV plasma viremia (>1 x 10^5 copies/ml) accompanied by high levels of HBV surface (HBsAg) and envelope (HBeAg) antigens in blood for more than six months, the clinical definition of chronic HBV infection. In addition, high frequencies of HBV core antigen (HBcAg)- and HBsAg-positive hepatocytes were detected longitudinally in liver biopsies. Following immunosuppression tapering, two of the three animals maintained ongoing viral replication, indicating HBV immunotolerance. The set point HBV loads in these two animals correlated with the level of cccDNA expression in the liver by qPCR, indicating that hepatocyte target availability is the restricting factor in this model.

Conclusion: Our data indicate that RM can be chronically infected with HBV and represent a promising model for the testing of emerging HBV curative therapies.
613 HIV-RELATED INFLAMMATION IS LINKED TO THE LEVEL OF GENETICALLY INTEGRATED HIV PROVIRUSES

Xiao Qian Wang1, Jennifer M. Zerbato2, Anchalee Avihingsanon3, Katie Fisher4, Bethany A. Horshburg, Timothy E. Schlub5, Ajantha Solomon1, Jennifer Audsley1, Kash A. Singh1, Wei Zhao1, Megan Crane5, Sharon R. Lewin2, Sarah Palmer1

1The Westmead Institute for Medical Research, Westmead, NSW, Australia, 2Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia, 3Kirby Institute, Sydney, NSW, Australia, 4Monash University, Melbourne, Victoria, Australia, 5Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Background: Hepatitis B virus (HBV) coinfection increases overall and liver-related mortality in people living with HIV, even with the availability of HIV-active ART. HIV can persist in individuals in both defective and intact forms and both can contribute to persistent inflammation. We assessed the relationship between HIV proviral genomes and markers of inflammation in people living with HIV-HBV coinfection.

Methods: HIV-HBV coinfection and HIV monoinfection participants, naïve to ART, were recruited in Bangkok, Thailand as part of a prospective observational cohort study. HIV subtype AE proviruses were sequenced from peripheral blood (PB) CD4+ T-cells using full-length individual proviral sequencing, covering 92% of the genome. Circulating markers of inflammation and microbial translocation were quantified by ELISA and bead arrays. Spearman rank correlations tests were performed to determine associations.

Results: 1008 and 222 HIV proviruses were sequenced from 18 HIV-HBV coinfected and 6 HIV monoinfected individuals respectively. The coinfected cohort had a significantly higher HIV viremia (p=0.03) and lower CD4+ T-cell count (p=0.007) than the monoinfected. A strong trend towards more intact proviruses (22-1000 copies/10^6 cells, p=0.055) was observed in the coinfected individuals. For the HIV-HBV cohort, the levels of soluble CD14 (sCD14), LPS and CXCL10 in the blood, markers of immune activation and/or inflammation, were significantly correlated with the frequency of intact HIV proviruses (p<0.01, p=0.04, p<0.01 respectively). sCD14 and CXCL10 were also correlated with the genetic diversity of the intact proviruses (p=0.03, for both). AST levels in blood, a marker of liver inflammation, and HIV DNA levels in the liver were also significantly correlated with the frequency of intact HIV proviruses in PB CD4+ T-cells (p=0.04, p=0.05 respectively). However, intact proviruses alone did not correlate with the number of PB CD4+ T-cells (p=0.2) but the inclusion of defective forms revealed a significant correlation with PB CD4+ T-cells (p=0.03).

Conclusion: During HIV-HBV coinfection, the levels of PB CD4+ T-cells may be influenced by the amount of intact and defective proviruses they contain. However, the frequency and genetic diversity of the intact proviruses within blood-derived cells from the HIV-HBV coinfected individuals appears to be linked to inflammation and liver damage.

614 LIVER DISEASE PROGRESSION IN HIV-HBV COINFECTION ON ART IS ASSOCIATED WITH HMGB1

Kasha P. Singh1, Jennifer M. Zerbato2, Wei Zhao1, Sabine Braat2, Surekha Tennakoon3, Ajantha Solomon1, Gail Matthews4, Christopher K. Fairley5, Joseph Lasadze6, Megan Crane7, Anchalee Avihingsanon3, Jennifer Audsley1, Sharon R. Lewin2

1Doherty Institute for Infection and Immunity, Melbourne, Australia, 2University of Melbourne, Melbourne, Australia, 3Kirby Institute, Sydney, NSW, Australia, 4Monash University, Melbourne, Victoria, Australia, 5Peter MacCallum Cancer Centre, Melbourne, Australia, 6HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand

Background: In HIV-HBV co-infection, liver disease progression is accelerated, and liver related mortality is increased, including in those on antiretroviral therapy (ART). Systemic inflammation and gut permeability are increased in HIV infection and may drive accelerated liver disease. We investigated liver disease progression in HIV-HBV co-infected individuals on ART, and its relationship with inflammatory cytokines and products of microbial translocation.

Methods: HIV–HBV co-infected adults on ART were recruited in Australia and Thailand and followed prospectively for 3 years with 6 monthly visits for clinical assessment and blood collection. Liver fibrosis was measured at baseline and yearly using transient elastography (Fibroscan®, Echosens) in kilopascals (kPa). Liver disease progression was defined as (1) an increase in Metavir grade (defined by kPa grade equivalent ranges defined in HIV-HBV infected individuals) or (2) at least 20% or a 2kPa increase in kPa with at least one value > 5.9kPa. Comparisons were made using Wilcoxon rank-sum test for continuous data and chi-square test or Fisher’s exact test for categorical data at baseline and later timepoints.

Results: 67 participants (57 male) were enrolled. The mean age was 51 years and median time since HIV diagnosis was 14.8 (interquartile range (IQR) 11.4-18.7) years. Median nadir CD4+ T-cell count was 25 (IQR 35-225) cells/mL. 21/69 were HBsAg+. 11 participants were classified as progressors by fibrosis grade and 7 by kPa. 6 were progressors by both definitions. Progressors had similar baseline characteristics to non-progressors but progressors had significantly higher levels of high mobility group box 1 protein (HMGB1), a marker of cell death, using either definition (1 (p=0.011) and 2 (p=0.041)). Nadir CD4 count was significantly lower in progressors than non-progressors when defined by kPa change (27 and 145 cells/mL respectively; p=0.018). No significant differences were seen between the two groups in other parameters including lipopolysaccharide, soluble CD14 or inflammatory markers including CXCL10, monocyte chemotactic protein-1 or tumour necrosis factor-a.

Conclusion: In the setting of ART, 20% of HIV-HBV co-infected individuals have progressive liver fibrosis. Liver disease progression was associated with higher HMGB1 and lower nadir CD4 count. Interventions to prevent liver disease progression on ART require further investigation.
HEPATOCELLULAR CARCINOMA SCREENING AMONG HIV/HBV-COINFECTED INDIVIDUALS IN ZAMBA

Carlotta Riebensahm1, Helen Chitundu, Belinda Variaizda Chihoita, Edford Sinkala1, Lloyd Mulenga1, Veronica Sunkutu, Adriá Ramirez Mena, Matthias Egger1, Carolyn Bolton Moore3, Michael J. Vinikoor3, Gilles Wandelé1
1University Hospital of Bern, Bern, Switzerland, 2University Teaching Hospital, Botswana, Gaborone, Botswana, 3Rutgers Robert Wood Johnson Medical School, Piscataway, NJ, USA, 4Hospital Universitario de Valme, Seville, Spain, 5Hospital Universitario San Antonio Rivero-Juárez

Background: Hepatitis B virus (HBV) infection is the single most important cause of hepatocellular carcinoma (HCC) in sub-Saharan Africa (SSA). Six-monthly abdominal ultrasound (AUS) screening allows the early diagnosis of HCC. Our aim was to identify HBV mutations associated with progression to HCC in HIV/HBV co-infected adults in Botswana.

Methods: This was a retrospective, cross-sectional study utilizing archived plasma samples from a study conducted at the Botswana Harvard AIDS Institute Partnership (2009–2012). A total of 100 samples from HIV/HBV infected adults were available of which 28 were hepatitis B surface antigen (HBsAg) positive, while 72 were HBsAg negative but HBV DNA positive (occult HBV infections). HBV regions were amplified using a semi-nested polymerase chain reaction. Sequences from Botswana were then compared to GenBank references to identify clinically relevant mutations.

Results: Of the 100 samples, 60 could be amplified and sequenced. Thirty-six (60%) samples belonged to genotype D, while 24 (40%) were genotype A. Fifteen samples (25%) had 29 mutations which have been previously associated with HCC. Eleven HCC-associated mutations were detected in genotype A, while 18 HCC mutations were detected in genotype D samples. W28* mutation was seen in more than one participant and also occurred as a dual mutation. E64D and L65V were the most common mutations, occurring in 3 participants each. Other common mutations were I127L which also was found in 3 participants followed by K130M and V131I which were seen found in 2 participants. K130M and V131I appeared as a dual mutation.

Conclusion: This is the first study to report on the presence of mutations linked to HCC in Botswana. As participants with these mutations might be more prone to rapid disease progression, they may require additional clinical monitoring. Other polymorphisms were also detected but have not been functionally characterized; thus, future in vitro studies on these mutations are warranted.

Table 4: HBV mutations associated with HCC in the precore and X regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precore</td>
<td>P164L, W28*</td>
</tr>
<tr>
<td>Precore</td>
<td>V131F, W28*</td>
</tr>
<tr>
<td>Core</td>
<td>P180L, L180M, L180F, L180V</td>
</tr>
<tr>
<td>Core</td>
<td>L180M</td>
</tr>
<tr>
<td>X</td>
<td>A120V, I127L, K130M, V131I</td>
</tr>
<tr>
<td>X</td>
<td>HBVST</td>
</tr>
</tbody>
</table>

616 HEPATITIS B VACCINATION AMONG HIV/HBV-COINFECTED INDIVIDUALS IN ZAMBA

Antonio Rivero-Juárez1, Maria Frías, Pedro Lopez-Lopez2, Juan Berengué, Federico García1, Juan Macías1, Begioha Alcaraz, Angeles Casro1, Javier Caballero-Gomez3, Antonio Rivero1, for the Spanish AIDS Research Network Hospital Universitario Reina Sofia, Cordoba, Spain, 2Hospital General Universitario Gregorio Marañon, Madrid, Spain, 3Hospital Universitario San Cecilio, Granada, Spain, 4Hospital Universitario de Valme, Seville, Spain

Background: Recent outbreaks of hepatitis A virus (HAV) infection among men who have sex with men (MSM) have occurred globally, nationally, and in New York City (NYC). An estimated critical immunity threshold against HAV is ≥ 70% to prevent outbreaks in MSM populations. National HIV Pre-exposure prophylaxis (PrEP) and post exposure prophylaxis (PEP) guidelines do not recommend HAV serology testing (ST) among MSM for PrEP/PEP initiation. At NYC sexual health clinics (SHC), all patients initiating PrEP or PEP receive HAVST. This analysis aims to determine the prevalence of HAV immunity among MSM initiating PrEP/PEP at SHC and determine subsequent HAV vaccine uptake.

Methods: Electronic medical record (EMR) data was extracted for HIV-negative MSM PrEP/PEP patients who had HAVST for the first time at SHC from September 2016 to March 2019, with a follow up through July 2019. We examined demographics, immunization history and EMR administered vaccines. Patients reactive for HAV IgG were considered immune. Patients were considered vaccinated against HAV if they received at least one dose of HAV vaccine (HAVrix™) or two doses of hepatitis A/B combination vaccine (Twinrix™) at SHC or (self-reported vaccination at other clinics).

Results: Of 306 HIV/HBV-coinfected patients included, 95.9% were male and the median age was 34 years (interquartile range 28-39). Their median CD4 count was 234 cells/µl (108-336), 36.8% had WHO clinical stage 3 or 4, and 140 (45.8%) reported hazardous alcohol consumption, defined as AUDIT-C > 3 for women and > 4 for men. HBV DNA >2000 IU/mL was observed in 54.7% of participants and 43.3% were HBeAg-positive. At ART initiation, significant fibrosis (>0.95 kPa; equivalent to Metavir score ≤ F3) was seen in 13.6% of patients and cirrhosis (>2.45 kPa; F4) in 8.0%. On ART, 84 (27.5%) participants had hepatomegaly, 7 (23.2%) peri-portal fibrosis, whereas 5 individuals (1.6%) had signs of cirrhosis, including surface nodularity, coarse and heterogeneous echotexture, atrophy or segmental hypertrophy, and 4 (1.3%) had liver steatosis. Of nine patients with a hypercholesterolaemic lesion, 7 (77.8%) were male, 8 (88.9%) showed elevated levels of ALT prior to ART initiation, 2 (22.2%) were HBeAg-positive and 1 had HBV DNA levels >2,000 IU/mL. Four patients with a lesion had significant fibrosis, of whom one had cirrhosis, according to TE.

Conclusion: We report results from one of the first HCC screening programs in SSA. At their first assessment, 9 of 306 HIV/HBV-coinfected individuals had a liver lesion, indicating the need for further diagnostic testing. Our data also suggest AIDS under-estimates cirrhosis.

617 SUBOPTIMAL IMMUNITY TO HEPATITIS A AMONG NYC MSM INITIATING PrEP OR PEP, 2016-2019

Tarek Mikati1, Addie Crafleley, Leah Stock, Susan Blank2
1New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, 2CDC, Atlanta, GA, USA

Background: Six-monthly abdominal ultrasound (AUS) screening allows the early diagnosis of hepatocellular carcinoma (HCC) and reduces related mortality. However, very few HCC screening programs exist in the region to date. We took advantage of a cohort of HIV/HBV-coinfected individuals in Zambia to pilot an AUS-based screening program in primary care clinics.

Methods: We enrolled HIV/HBV-coinfected adults on antiretroviral therapy (ART) at two outpatient clinics in Lusaka, Zambia. In line with international recommendations, we performed AUS imaging every 6 months in all participants and collected data using a standardized case-report form. All patients had yearly liver stiffness measurements using transient elastography (TE; Fibroscan 402®), HBV viral load, HBV serology, and alcohol consumption assessments using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C). We summarized the findings of the first AUS examination for the cohort.

Results: Of 306 HIV/HBV-coinfected patients included, 95.9% were male and the median age was 34 years (interquartile range 28-39). Their median CD4 count was 234 cells/µl (108-336), 36.8% had WHO clinical stage 3 or 4, and 140 (45.8%) reported hazardous alcohol consumption, defined as AUDIT-C > 3 for women and > 4 for men. HBV DNA >2000 IU/mL was observed in 54.7% of participants and 43.3% were HBeAg-positive. At ART initiation, significant fibrosis (>0.95 kPa; equivalent to Metavir score ≤ F3) was seen in 13.6% of patients and cirrhosis (>2.45 kPa; F4) in 8.0%. On ART, 84 (27.5%) participants had hepatomegaly, 7 (23.2%) peri-portal fibrosis, whereas 5 individuals (1.6%) had signs of cirrhosis, including surface nodularity, coarse and heterogeneous echotexture, atrophy or segmental hypertrophy, and 4 (1.3%) had liver steatosis. Of nine patients with a hypercholesterolaemic lesion, 7 (77.8%) were male, 8 (88.9%) showed elevated levels of ALT prior to ART initiation, 2 (22.2%) were HBeAg-positive and 1 had HBV DNA levels >2,000 IU/mL. Four patients with a lesion had significant fibrosis, of whom one had cirrhosis, according to TE.

Conclusion: We report results from one of the first HCC screening programs in SSA. At their first assessment, 9 of 306 HIV/HBV-coinfected individuals had a liver lesion, indicating the need for further diagnostic testing. Our data also suggest AIDS under-estimates cirrhosis.
population because of underlying immunosuppression. Our aim was to assess the prevalence and incidence of HEV in HIV-infected patients in a national cohort and describe the viral strains. 

**Methods:** We included HIV-infected patients recruited in the cohort of adult HIV-infected patients of the AIDS Research Network (CoRIS) in follow-up at 26 Spanish hospitals with available serum samples from the centralized BioBank in 2014 and 2015. All samples were tested for HEV IgG and IgM by ELISA (Pharmacy Enterprise奇 LTD, Beijing, China) and for RNA by qPCR. Samples with detectable HEV viral loads were genotyped following European HEVnet recommendations. Prevalence and incidence of HEV infection were calculated.

**Results:** A total of 845 individuals were included in the study. Seventy nine individuals and fifty-one (88.9%) were male and had a median age of 36.9 years (30.7-45.2 years). At baseline, 101 patients were positive for HEV IgG antibodies (11.9%), none had HEV IgM antibodies, and 2 presented detectable HEV RNA (0.2%). Of the 744 participants with negative HEV IgG antibody at baseline, 733 samples were available for testing during follow-up. Forty-two were seroconverted for IgG, supposing a cumulative incidence of 5.7%. One patient was positive for IgM (0.1%), and 2 showed detectable HEV RNA (0.2%). Viral strains were consistent with genotype 3f. Interestingly, in one patient, the isolated viral strain was consistent with genotype 3a (Figure 1).

**Conclusion:** Our study found a relatively high prevalence and incidence of HEV infection in HIV-infected individuals from Spain. We identified one case of infection with the HEV 3a genotype, the main host of which is rabbit, showing a potential zoonotic role of this emerging genotype in Spain.

619  **THE ROLE OF E6/E7 mRNA DETERMINATION FOR ANAL CANCER SCREENING IN HIV-POSITIVE MSM**

Ana C. Silva-Klug1, Maria Saumoy1, Montserrat Torres1, Loris Trenti1, Sonia Paytubi1, Laia Alemany2, Isabel Català2, Nuria Baixeras2, August Vidal4, Silvia De Sanjosé1, Daniel Podzamczer1

1Hospital Universitario de Bellvitge, Barcelona, Spain; 2Bellvitge University Hospital, Barcelona, Spain; 3Bellvitge Biomedical Research Institute, Barcelona, Spain

**Background:** To assess high-grade Squamous Intraepithelial Lesions (HSIL) screening strategies that include biomarkers as E6/E7 oncogenes by qPCR, Hybrid Capture®2 (HC2) (13 High-Risk HPV (HR-HPV) genotypes), and E6/7-mRNA test using Aptima® (14 HR-HPV genotypes). We evaluated two screening strategies that combined aLBC and biomarkers to triage candidates for HRA: 1) aLBC Atypical Squamous Cells of Undetermined Significance (ASCUS) or worse and/or positive biomarker; 2) aLBC HSIL and ASCUS that cannot rule out HSIL (ASC-H) and aLBC ASCUS and Low-grade SIL (LSIL) only if the biomarker results positive.

**Results:** 354 participants were included, mean age 45.3, mean CD4 count 802.3 cells/mm3, 87.3% undetectable viral load. aLBC results: 2.5% inadequate, 49.4% benign, 16.4% ASCUS, 15.8% LSIL, 13% ASC-H and 2.8% HSIL. HRA results: 54% benign, 24.9% LSIL and 21.2% HSIL (HSIL prevalence: 23.7%). Positive result of HPV DNA tests: 90.4% LA, 46.9% LA for the 14 HR-HPV genotypes included in the E6/7-mRNA test, 23.4% LA for HPV-16, 35.1% LA for HPV-18, 18% and 45.7% HC2. Positive result of E6/7-mRNA test: 51.7% for all 14 HR-HPV, 16.4% for HPV-16 and 20.3% for HPV-18, 18% and 45. aLBC with a threshold of ASCUS showed 80% sensitivity and 59.3% specificity for biopsy-proven HSIL (AUC=0.617). Sensitivity and specificity of biomarkers alone and in both combined strategies are shown in the table. Comparing the AUC of aLBC with the other AUC showed in the table, a p<0.05 was only found with E6/7-mRNA test in the second combined strategy.

**Conclusion:** E6/7-mRNA test could be considered for triage as an alternative to aLBC with the advantage of being a more objective and reproducible test. The second combined strategy using E6/7-mRNA test only if the aLBC result is ASCUS or LSIL seems to be the best strategy to triage candidates for HRA, with the highest AUC and the advantage of saving biomarker and HRA performance.

**Table:**

<table>
<thead>
<tr>
<th>Screening strategy</th>
<th>LA-HPV DNA test</th>
<th>LA-HPV DNA test for HR-HPV genotypes included in the E6/7-mRNA test</th>
<th>LA-HPV DNA test for HPV-16, 18 and 45</th>
<th>E6/7-mRNA test</th>
<th>E6/7-mRNA test for HPV-16, 18 and 45</th>
<th>biomarker only</th>
<th>Combined strategy biomarker for ASCUS/LSIL</th>
<th>Combined strategy biomarker for HSIL</th>
<th>aLBC with a threshold of ASCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA-HPV DNA test</td>
<td>14.7%</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
</tr>
<tr>
<td>LA-HPV DNA test for HR-HPV genotypes included in the E6/7-mRNA test</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
</tr>
<tr>
<td>LA-HPV DNA test for HPV-16, 18 and 45</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
</tr>
<tr>
<td>E6/7-mRNA test</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
<td>0.0465</td>
</tr>
</tbody>
</table>

**225**

620  **ANAL CANCER SCREENING: IS IT TIME FOR CYTOLOGY AND HIGH-RISK HPV TESTING?**

Michael Gaisa1, Yuxin Liu1, John Winters1, Ashish A. Deshmukh1, Keith M. Sigel1

1Icahn School of Medicine at Mt Sinai, New York, NY, USA, 2University of Texas at Houston, Houston, TX, USA

**Background:** Anal cancer screening targets cancer precursors, defined as high-grade squamous intraepithelial lesions (HSIL). Current guidelines suggest an anal cytology (AC) severity grade of atypical squamous cells of undetermined significance or greater (≥ASCUS) as referral threshold for high-resolution anoscopy (HRA). This study sought to determine whether co-testing AC for high-risk human papillomavirus (hrHPV) improves screening performance and to compare the efficiency of two novel HRA referral thresholds to current clinical practice. Novel algorithm A sets the threshold for HRA referral at any hrHPV or AC with low-grade squamous intraepithelial lesion or greater (≥LSIL); algorithm B was recently proposed by Sambursky et al.

**Methods:** Anal swabs were obtained simultaneously or within 3 months of HRA-guided biopsies and used for AC and Cobas® hrHPV DNA co-testing. Using biopsy-proven HSIL as an endpoint we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) as well as relative risk (RR) of HSIL for various AC/hrHPV co-testing combinations. Test characteristics were then compared between screening strategies using an efficiency frontier method.

**Results:** 1,947 paired AC and hrHPV results from 1,268 individual patients were analyzed (89% HIV-positive, 90% MSM and 9.5% women). Adding hrHPV testing to the current AC referral threshold of ≥ASCUS increased sensitivity from 80.4% to 95.9% (p<0.001). Requiring HPV16/18 positivity for referral markedly improved specificity but decreased sensitivity. For each AC category, the RR of HSIL was substantially greater when any hrHPV was detected. When comparing screening strategies, sensitivity for the current guideline approach, algorithm
A and B was 80.4%, 96.4%, and 86.9%, while specificity was 37.6%, 22.4%, and 35%, respectively (see Table). When calculating number of missed HSILs versus number of unnecessary HRAs for a hypothetical cohort of 10,000 persons with 30% HSIL prevalence, all strategies including co-testing were found to be more efficient than those without.

Conclusion: Co-testing AC for hrHPV improves the sensitivity to detect anal HSIL for all AC categories. Positivity for any hrHPV, especially types 16/18, implies a significant risk for anal HSIL. Algorithm A, combining ≥LSIL AC and reflex hrHPV testing for benign and ASCUS cytology results, may improve efficiency of anal cancer screening.

### 621 LOW ADHERENCE TO TREATMENT AND SURVEILLANCE OF HPV-RELATED ANAL PRECANCER


**1**cahn School of Medicine at Mt Sinai, New York, NY, USA, **2**University of Texas at Houston, Houston, TX, USA

**Background:** Persons living with HIV (PLWH) have nearly 20-fold elevated risk of anal cancer compared to the general population. Several guidelines recommend annual anal cancer screening using anal cytology, high-resolution anoscopy (HRA) guided biopsies, and treatment of high grade intraepithelial lesions (HSIL) for anal cancer. Untreated HSIL can progress to invasive cancer and frequently recurs after treatment (>50%) necessitating longitudinal surveillance. Using data from our large screening cohort, we evaluated rates and predictors of adherence to surveillance HRAs following a diagnosis of anal HSIL.

**Methods:** The Mount Sinai Anal Dysplasia Program is an HRA referral site for a large urban population of PLWH and HIV-uninfected MSM. We collected data on demographics, HIV clinical variables, and HRA attendance and outcomes from 2009-2019. We identified patients who were diagnosed with HSIL on first HRA and measured the following outcomes: (1) adherence to any follow-up, including repeat HRA or ablation, at any time after initial HSIL diagnosis; (2) follow-up examination within 18 months of HSIL diagnosis; (3) return for HSIL ablation within 6 months; (4) surveillance HRA following ablation. We also evaluated the predictors of these outcomes.

**Results:** 3,646 unique patients underwent at least one HRA during the study. 387 patients (11%) had HSIL or cancer on initial HRA. Of this group, median age was 45, 92% were PLWH, 90% were male, 88% MSM, with diverse race/ethnicity: 30% White, 23% Black, and 30% Hispanic. 202 patients (52%) of the HSIL cohort; see Figure) underwent ablation. Median time to ablation from HRA diagnosis was 49 days (10% were ablated > 180 days). Of those who received ablation, 71% followed up at any time. Among those not receiving ablation, 27% followed up at any time. Among HSIL patients the only significant predictor of adherence to surveillance was Hispanic ethnicity (p = .02). 35% of patients diagnosed with HSIL never returned. Compared to Whites (69%), Hispanics were more likely to return (73%, p = .04), while Blacks (54%, p = .02) and PLWH with viremia (57%; p = .05) were less likely to return after HSIL diagnosis.

**Conclusion:** Adherence to treatment and surveillance following an initial diagnosis of anal HSIL was poor in a large, urban anal cancer screening cohort. Future research to understand barriers and facilitators could inform interventions to improve adherence to anal cancer screening.

### 622 ANAL PRECANCER SCREENING AMONG MSM: WHAT IS THE BEST STRATEGY?

**Jing Sun**, Dorothy J. Wiley, Teresa Darragh, Hilary K. Hou, Nancy Joste, Stephen Young, W. David Hardy, Sushele Reddy, Jeremy J. Martinson, Gypsyamber D’Souza, for the Multicenter AIDS Cohort Study (MACS)

**1**ohns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, **2**University of California Los Angeles, Los Angeles, CA, USA, **3**University of California San Francisco, San Francisco, CA, USA, **4**University of New Mexico, Albuquerque, NM, USA, **5**Ticore Reference Laboratories, Albuquerque, NM, USA, **6**ohns Hopkins University School of Medicine, Division of Infectious Diseases, Washington, DC, USA, **7**Northwestern University, Chicago, IL, USA, **8**University of Pittsburgh, Pittsburgh, PA, USA

**Background:** Risks of non-AIDS defining cancers has increased among people living with HIV since the advent of potent ART. Anal cancer is rare in the general population, but men who have sex with men (MSM) have elevated risk. We evaluated three screening strategies (single anal cytology [aCyt], sequential aCyt, and co-testing [aCyt plus oncogenic HPV]) and their ability to predict anal precancer (anal histological high-grade squamous intraepithelial grade 2+ [hHSIL/AIN2+]) among MSM.

**Methods:** 1027 MSM from the Multicenter AIDS Cohort Study (MACS) had repeated aCyt and HPV testing. Men with abnormal aCyt and a subset with normal aCyt were referred for high-resolution anoscopy (HRA). All men had HRA (N=430) within 5 years of their aCyt, 72% of HRAs performed in Pittsburg and LA study sites. Multivariable logistic regression models evaluated risk of AIN2+ within 5 years of screening using the three screening strategies adjusted for age, race, HIV status, number of anal sex partners, and study site. Sensitivity and specificity were calculated among participants who had HRA and results were corrected for potential verification bias (in all participants who had screening tests) using Begg and Greenees method.

**Results:** Among those who had HRA tests, the median age at time of HRA was 48 years, 70 % were HIV+, 81% non-Hispanic white, and 9% had CD4 cell count<350 (cells/mm3). Prevalence of AIN2+ was similar among HIV+ vs MSM than HIV- MSM (31% vs 24%, p=0.13), but was higher among the subgroup with CD4<350 (41%, p=0.04). Odds of AIN2+ was significantly higher in those with abnormal screening results with an 83% increase (95% CI: 1.1-3.04) in those with a single aCyt+, a 3-fold increase (95% CI: 1.33-7.11) following two aCyt+, and more than a 4-fold increase (95% CI: 1.93-10.29) in those with oncHPV+/aCyt+ co-testing.

Specificity was low in single aCyt (44%) but increased with sequential aCyt testing (79%) or oncHPV co-testing (62%). Sensitivity was moderate in single aCyt+ (67%) or dual positive cotests (61%), and high in cotests where positivity on either marker was considered as positive (93%). Sensitivity was only 36% among those with sequential aCyt+ results. After correcting for potential verification bias, specificity increased but sensitivity reduced in all strategies.

**Conclusion:** Anal cytology screening had moderate specificity and sensitivity among HIV+ and HIV- MSM. Sequential aCyt testing or adding an HPV co-test to aCyt improved test performance.
Background: The detection rate of histologically confirmed high grade anal intraepithelial neoplasia (HGAIN) and anal carcinoma by screening with anal cytological (cyto.) smears and/or human papilloma virus (HPV) typing in HPV-positive individuals (HPV+) has been examined in the TECAIN Study.

Methods: The prospective, randomized, national, multicenter TECAIN study compared the efficacy of local treatment with 85% trichloroacetic acid to no treatment in cases of intracellular neoplasia (AIN) and anal carcinoma by screening with anal cyto. and virological smears. Intraepithelial neoplasia (HGAIN) and anal carcinoma were confirmed by histology.

Results: Of 227 patients (median age 48 years, 98% of HIV+ took antiretroviral therapy and 81% were MSM), 98% of HIV+ took antiretroviral therapy and 81% were MSM. The median age was 48 years, 98% of HIV+ took antiretroviral therapy and 81% were MSM. Histologically, 108 exa. (37%) showed AIN I as the highest grade HPV-associated lesion, 84 (29%) AIN II and 100 (34%) AIN III. Thus in 215 cases (63%) HGAIN were histologically confirmed.

Conclusion: Simultaneous screening with anal cyto. and virological smears detect HGAIN much more reliably than cytology alone (fig. 1). Comparable results in gynecology have led to an extension of routine diagnostics by the addition of HPV typing to cervical cancer screening guidelines in Germany.

624 CERVICAL CANCER KNOWLEDGE AND ATTITUDES AMONG HIV-POSITIVE MEN IN MALAWI

Corrina Moucheraud1, Samuel W. Lewis1, Misheck Mphande1, Ben Allan Banda1, Hitler Sigaue1, Paul Kawale1, Aubrey Dkangoma2, Kathryn Doval1, Alemayehu Amberbir3, Agnes Moses3, Sundeepe Gupta3, Rita M. Hoffman1 1University of California Los Angeles, Los Angeles, CA, USA, 2Partners in Hope, Lilongwe, Malawi, 3African Institute for Development Policy (AFIDEP), Lilongwe, Malawi

Background: Malawi has the greatest cervical cancer burden globally (72.9 cases and 54.5 deaths per 100,000 women), with an elevated risk among HIV-positive women. Malawian women have reported being reluctant to screen without obtaining spousal permission. This study is the first to examine Malawian HIV-positive men’s knowledge and opinions of cervical cancer disease and decision-making around screening, and evaluate associations with women’s screening. The goal is to develop strategies to increase women’s uptake of screening.

Methods: A survey was administered at a large, free ART clinic in Lilongwe, Malawi. Male clients (≥18 years) were eligible if they were married and had ever heard of cervical cancer. The survey asked about cervical cancer awareness and perceptions, knowledge of cervical cancer screening and treatment services, and women’s experiences with screening (primary wife if polygamous). Gender attitudes were measured with the Gender Equitable Men (GEM) scale. Logistic regression was used to identify factors associated with partner screening status.

Results: A total of 125 respondents with median age of 44 years (IQR: 39–50 years) were surveyed. Just over half (58%) reported that their wife had ever received cervical cancer screening. Cervical cancer was perceived to be more dangerous than HIV by 78% of men, and 21% reported knowing someone who had died from cervical cancer. When asked who should make decisions about cervical cancer screening, 6% responded their wife only, 55% responded both partners jointly, and 39% responded himself only. Respondents correctly answered an average of 4/8 risk factor questions and 6/8 screening and treatment questions, but knowledge was not associated with whether a respondent’s wife had been screened (aOR 0.97, 95% CI: 0.77, 1.22) (Table 1). Men with more progressive gender views about sexual behaviors (higher GEM scores) were more likely to have a partner who had been screened (aOR 1.46, 95% CI: 1.00, 2.13) (Table 1).

Conclusion: Men in this study recognized the high burden and threat of cervical cancer. However, important gaps in knowledge and a strong role in decision-making may limit access to potentially life-saving services for their wives. Our findings suggest that cancer control programs should engage male partners, given their critical role in women’s decisions about use of cervical cancer prevention.
followed from index date until LC diagnosis, death or 12/31/2016. LC cases and histologic types were identified using the VA Corporate Data Warehouse and medical record review of individuals with LC ICD-9/10 codes. We identified 46604 HIV+ and 88783 HIV- veterans who met eligibility criteria. We calculated cumulative LC incidence rates by histologic types and used Joinpoint software for modeling trends. Cox regression analyses were used to identify risk factors for specific LC histologic types and subtypes among PWH. Models were adjusted for age, race, gender, year of index HIV, smoking, baseline CD4 count, and percent undetectable viral load.

**Results:** A total of 931 incident cases of LC were ascertained among HIV+ and 1206 among HIV-. The overall incidence rate (IR) of SCLC was 20.43/100,000 among HIV+ veterans and 21.37/100,000 among HIV-, and the incidence rate ratio (IRR) was 0.96 (0.84 – 1.09). Among the NSCLC subtypes, the IRs for AC was the highest for both HIV+ and HIV- (93.52/100,000 vs 49.82/100,000, IRR was 1.88 CI: 1.75 – 2.01), and the IRs for SC were lower for both HIV+ and HIV- (67.7/100,000 vs 38.3/100,000, with an IRR of 1.77 CI: 1.63 – 1.92). Fig. 1 shows the joinpoint analysis of IRs per 3-year intervals for AC and SC for HIV+/+ veterans. In multivariable analysis of PWH by LC histology, we found that baseline CD4 count >200 was not significantly protective for AC (HR 1.05 CI: 0.67 – 1.63, p=0.83) and was marginally protective for SC (HR 0.61 CI:0.35 – 1.05, p=0.08).

**Conclusion:** The IRRs of SC and AC NSCLCs but not SCC are higher among PWH. The IRRs of AC and SC have remained stable over time for both HIV+/+ veterans.

## IMPACT OF UNIVERSAL ART ACCESS ON KAPOSI SARCOMA: RESULTS FROM THE ICONA COHORT


1University of Milan, Milan, Italy, 2MRC Clinical Trials Unit at UCL, London, UK, 3Ministry of Health, Maputo, Mozambique, 4University Hospitals of Geneva, Geneva, Switzerland, 5University of Toronto, Toronto, Canada, 6Luigi Sacco University Hospital, Milan, Italy, 7Azienda Ospedaliera San Paolo, Milan, Italy, 8IRCCS Lazzaro Spallanzani, Rome, Italy

**Background:** The widespread introduction of effective ART reduced the burden of AIDS-related Kaposi Sarcoma (KS), even if KS does still occur also in individuals with well-controlled HIV infection.

**Methods:** We included naive HIV-infected individuals (PLHIV) enrolled in the ICONA cohort over 1997-2019. Prevalent cases were PLHIV with a diagnosis of KS prior and up to 30 days after enrolment. Incident cases were defined as new KS diagnoses occurring after ART initiation. Patients’ characteristics at the date of enrolment were compared by prevalent KS status and associations identified by logistic regression modelling. In the subset of people KS-free at enrolment, standard Kaplan-Meier curves were used to model time from ART initiation to development of KS and a Cox regression model to identify factors associated with this outcome. A similar analysis was performed in PLHIV with prevalent KS to identify factors associated with their risk of KS relapse or death after ART (clinical failure).

**Results:** Among 17,742 PLHIV enrolled in the ICONA cohort over 1997-2019, 248 prevalent KS cases and 36 incident KS cases were identified. Prevalent cases were mostly male (93%), with median age of 45 years (IQR 37-53) and median CD4+ count of 76/mm^3 (IQR 24-193). No significant differences in prevalence (by year of enrolment) and incidence (by year of ART initiation) of KS were observed (Figure). At multivariable logistic regression, the only factor independently associated with prevalent KS was mode of HIV transmission (MSM versus PWID, adjusted odds ratio (aOR): 5.24 (1.35, 20.39)). In contrast, factors independently associated with the risk of incident KS were pre-ART CD4+ count (adjusted relative hazard (aHR): 0.57 (0.42, 0.77) for 100 cells/mm^3 higher)т and mode of HIV transmission (MSM versus HS, aHR: 3.82 (1.62, 9.02)). Over 1,316 PYFU, clinical failure after ART introduction was observed in 52 prevalent cases (29 deaths and 23 relapses) with an incidence rate of 3.9% (95% CI: 2.9–5.1). However, none of the considered factors showed an association with the risk of clinical failure.

**Conclusion:** Despite universal ART access, we did not observe a reduction of KS prevalence and incidence in recent years. The strong association of pre-ART CD4+ count with incidence of KS in ART-treated PLHIV strengthens the role of immune competence in KS. Further KSHV and HIV immune-virological characterization is warranted to better identify factors associated with KS occurrence in PLHIV.
and multiple social problems. 92 participants achieved complete or partial remission at any point during follow-up (overall response 80%), including 15 (13%) who achieved complete remission. Of those achieving CR or PR, 26 (28%) eventually restarted PLD because of recurrent disease or worsening symptoms. The most common AEs were due to neutropenia and anemia. Quality of life improved significantly after 6 months.

Conclusion: PLD was safe, well-tolerated and effective for the treatment of KS in Mozambique. The high mortality rate is likely due to advanced immunosuppression at baseline and underscores the need to provide earlier screening and referral for treatment of KS. Efforts should be made to increase access to PLD in Mozambique.

628 BREAST CANCER RISK AMONG WOMEN WITH HIV IN NORTH AMERICA (2000-2015)

Sally B. Coburn1, Michael J. Silverberg2, Richard D. Moore3, W. C. Mathews3, Julia L. Marcus4, Jessica L. Castilho5, Mari M. Kitahata6, Heidi M. Crane7, Marina Klein8, Sonia Napravnik8, Todd T. Brown1, Kala Visvanathan1, Bryan Lau1, Keri N. Althoff1, for the NA-ACCORD of IeDEA

We used Fine & Gray regression to quantify breast cancer risk by time-varying linkages with cancer registries and/or record review of cancer site/pathology. Administrative censoring. Standardized case validation included abstraction, death, loss to follow-up (≥2-year gap after CD4/HIV RNA measurement), or enrollment. Study exit was the earliest date of: invasive breast cancer diagnosis, entry was the latest date of: 1/1/2000, age 35, ART initiation, or NA-ACCORD 12/31/2015, had no cancer history, and had ≥6 months of follow-up. Study inclusion was the earliest date of: invasive breast cancer diagnosis, death, loss to follow-up (≥2-year gap after CD4/HIV RNA measurement), or administrative censoring. Standardized case validation included abstraction, linkages with cancer registries and/or record review of cancer site/pathology.

Methods: We included women ≥35 years old who were prescribed antiretroviral therapy (ART), observed in the NA-ACCORD from 1/1/2000-12/31/2015, had no cancer history, and had ≥6 months of follow-up. Study entry was the latest date of: 1/1/2000, age 35, ART initiation, or NA-ACCORD enrollment. Study exit was the earliest date of: invasive breast cancer diagnosis, death, loss to follow-up (≥2-year gap after CD4/HIV RNA measurement), or administrative censoring. Standardized case validation included abstraction, linkages with cancer registries and/or record review of cancer site/pathology.

With age as the time metric, we used non-parametric estimators accounting for the competing risk of death to assess breast cancer cumulative incidence. We used Fine & Gray regression to quantify breast cancer risk by time-varying HIV viral load, obesity (body mass index (BMI) ≥30 kg/m²), race, smoking status, and CD4 count at ART initiation. We calculated adjusted subdistribution hazard ratios (aSDHR) with 95% confidence intervals (95% CI). Age and sex were included in the regression model stratified by province of first HIV test to obtain hazard ratios of association with first reported CD4 cell count, age, sex, and calendar period.

Results: Between 2004 and 2014, over 8,586,130 person-years of follow-up, 4,083 incident BC cases were diagnosed in the NA-ACCORD cohort of 3,137,992 WLHIV. BC incidence was 47.6 cases per 100,000 person-years (95% CI 46.1-49.0). The median age of WLHIV at baseline was 32 years (interquartile range IQR: 26-40), and the median age at diagnosis was 44.9 years (IQR: 38-52.1). The median baseline CD4 cell count was 310 cells/μL (IQR: 177-477). There was a general increase in CD4 cell count through calendar years. Only age was strongly associated with BC risk (Table 1).

Conclusion: We found no evidence of association between immunosuppression and BC risk in WLHIV in RSA. BC incidence in WLHIV was high and increased with age, closely similar to what is observed in the NCR SA data for the general female population. Additional analyses of trends in the stage at BC diagnosis and BC mortality are needed to inform the public health response to BC in WLHIV in RSA.

Table 1. Risk factors for breast cancer among women in the NA-ACCORD 2000-2015

<table>
<thead>
<tr>
<th>Covariate</th>
<th>aSDHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>REF</td>
</tr>
<tr>
<td>Black</td>
<td>1.04 (0.995, 1.09)</td>
</tr>
<tr>
<td>Other</td>
<td>0.89 (0.82, 1.00)</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²)</td>
<td>1.76 (0.88, 3.51)</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>REF</td>
</tr>
<tr>
<td>Current</td>
<td>2.07 (1.96, 2.19)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.08 (0.82, 0.57)</td>
</tr>
<tr>
<td>CD4 count at ART initiation (&lt;350 vs ≥350 cells/μL)</td>
<td>1.17 (1.01, 1.22)</td>
</tr>
<tr>
<td>Per log, mmol/L increase</td>
<td>0.61 (0.61, 3.53)</td>
</tr>
</tbody>
</table>

Abbreviations: aSDHR, adjusted subdistribution hazard ratio; aSDHR confidence interval; BMI, body mass index; ART, antiretroviral therapy.
HIV-ASSOCIATED HEMATOLOGIC MALIGNANCIES IN PEOPLE LIVING WITH HIV IN SWEDEN

Oscar Kieri1, Piotr Nowak1, Anders Sönnerborg1, Gaetano Marrone1
1Karolinska Institute, Stockholm, Sweden

**Background:** People living with HIV (PLHIV) have an increased risk of developing hematologic malignancies (HM) and in particularly non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Despite a decline observed since the introduction of effective combined antiretroviral therapy (ART) the risk is still increased. There is no published data regarding HMs in PLHIV in the era of ART in Sweden.

**Methods:** A retrospective study was conducted of PLHIV receiving care at the Department of Infectious Diseases, Karolinska University Hospital, between 01/2004 and 12/2018. PLHIV diagnosed with HMs were identified and data was collected linking the InfCareHIV cohort with medical records. For incidence assessment of lymphoma, cases occurring within 30 days after cohort enrollment were excluded.

**Results:** During the study period, 3,484 patients received HIV care for a total of 22,903 person-years (py). HMs were identified in 43 patients (Figure 1) (31 males, 12 females). The incidence rate of lymphoma was 127.6/100 000 py, compared to 21.2/100 000 py in the general population in Sweden (Socialstyrelsen). In the early period, 2004–2010, the incidence rate was significantly higher compared to the late period, 2011–2018 (232.4 vs 73.4 per 100 000 py; p=0.003). Median follow up time was 7.6 years (IQR 3.1–9.3). Median time from HIV diagnosis was significantly shorter in patients developing NHL compared to HL (1.2 vs 8.9 years; p=0.01). Fourteen patients with HMs (33%) were diagnosed within 6 months of HIV diagnosis. Treatment with effective ART (>800 d prior to malignancy) with undetectable viral load was significantly more common in the HL group compared to NHL (89% vs 30%; p=0.005). Median CD4+ cell count at malignancy diagnosis was 190 cells/ml and a majority (86%) had a nadir CD4+ cell count <200 cells/ml. A majority of the patients (79%) received chemotherapy. Autologous hematopoietic stem-cell transplantation was conducted in three cases. Eighteen deaths occurred during the study period with a median time from malignancy to death of 0.4 years (IQR 0.1–2.3). The five-year survival rate for lymphoma was 55% (16/29), as compared to 74% (p=0.03) five-year survival rate for lymphoma in the general population in Sweden (Socialstyrelsen).

**Conclusion:** The incidence rate of lymphoma was more than 6 times higher in PLHIV and the five-year survival rate was significantly poorer when compared to general population in Sweden. The incidence declined in recent years. HL occurred significantly later and were more frequent in PLHIV on effective ART.

**Methods:** The ANRS C024 ONCOVHIC (NCT03354936) is an ongoing prospective cohort study in France enrolling PLHIV with cancer treated by ICPi. HIV RNA viral load (VL), CD4 and CD8 were collected at baseline (date of first ICPi injection) and during follow-up, as were adverse events (AEs).

**Results:** From January 17th, 2018 to September 21st, 2019, 43 patients were enrolled across 20 sites. Among them, 31 enrolled at least 6 months ago were included in this analysis. Median age was 59 years (IQR: 53–66) and 25 (58.6%) were males. HIV has been diagnosed in 1990 (1987–1997) and CD4 nadir was 98/µL (42–240) with 22.6% prior AIDS events. At baseline, 20 received nivolumab, 10 pembrolizumab and 1 atezolizumab for the following cancers: lung (n=15), melanoma (4), head/neck (4), bladder (3), Hodgkin (3), Kaposi sarcoma (1), anal (1), tongue (1), squamous cell carcinoma (1). All patients were under CART with a median CD4 count of 314/µL (148–642) and CD4/CD8 ratio of 0.46 (0.37–0.94) and 5 had HIV RNA >50 copies/µl with a median of 4.6 log10 (4.3–5.1).

During a mean follow-up of 8.1 months (21.0 person-years), 101 AEs occurred in 25 pts with 28 grade 3/4 AEs in 15 pts and only 2 Immune-mediated AEs in 2 pts (neuropathy and thyroiditis). No drug-related fatal AE occurred. Overall, 6 pts (21%, 95%CI: 8–50) discontinued ICPi: 4 for progression and 2 for SAE (epilepsy and meningoradiculitis) and 12 died (6 with lung cancer). The 8-month survival rate was 56.8% (27.5–78.1) for lung cancer and 81.3% (52.5–93.5) for the other cancers.

During the follow-up, 118 HIV RNA VL/CD4/CD8 were measured with a median of 2 per patient (IQR: 1–6). All patients with HIV VL<50 copies/µl at baseline maintained VL<50 copies/µl throughout the follow-up, while those with HIV VL≥50 copies/µl reached a VL<50 copies/µl. CD4 and CD8 T cell count significantly increased over time, respectively, +8.9/µL per month, P=0.007 and +19.4/µL, P=0.028, while CD4/CD8 ratio remained stable (-0.001, P=0.739).

**Conclusion:** In this ongoing French cohort of PLHIV with cancer receiving ICPi, no HIV VL rebound occurred during an 8-month follow up. An increase of CD4 and CD8 cells was observed, associated with a low frequency of serious events relative to that expected in this population.

T-CELL SUBPOPULATION PROFILES AND CANCER RISK FOR HIV+ AND HIV– VETERANS

Keith M. Sigel1, Suman Kundu2, Lesley S. Park1, Kaku So-Armah1, Margaret F. Doyle1, Russell Tracy1, Janet Tate1, Amy C. Justice1, Matthew Freiberg1
1Icahn School of Medicine at Mt Sinai, New York, NY, USA, 2Vanderbilt University, Nashville, TN, USA, 3Stanford University, Stanford, CA, USA, 4Boston University, Boston, MA, USA, 5University of Vermont, Burlington, VT, USA, 6VA Connecticut Healthcare System, West Haven, CT, USA

**Background:** Alterations in cell-mediated immunity have been associated with cancer risk for people living with HIV (PLWH). Circulating levels of T regulatory cells (Tregs), and activated and senescent T cells have been linked to cancer risk and outcomes in HIV uninfected persons but there has been limited study of T cell subset alterations and cancer development unique to PLWH. We therefore aimed to determine whether the proportions of these T cell phenotypes predicted the incidence of non-AIDS cancers that have been associated with responses to immunotherapy (lung, anus, kidney).

**Methods:** We used longitudinal data from 1,429 PLWH and 765 uninfected persons from the Veterans Aging Cohort Study Biomarker Cohort linked to VA cancer registry data to identify 75 incident lung, anus, and kidney cancers (the most common cancers arising in the cohort with known immunotherapy link). Subjects were followed from enrollment (2005–2006) until cancer incidence, death or were censored on 9/31/2017 (10 years of median follow-up). We measured the proportion of seven subpopulations of T cells, including Tregs (CD4+CD25+FOXp3+), activated (CD4+CD38+ and CD8+CD38+) and senescent (CD4+CD28−, CD4+CD57+, and CD8+CD28−, CD8+CD57+) CD4 and CD8 phenotypes. We used Cox proportional hazard regression to model associations between these immune cells and the risk of cancer while adjusting for age, sex, race/ethnicity and smoking status.

**Results:** The cohort was mostly male (95%) of median age 52 years. PLWH accounted for the majority (75%) of the cancer cases. Among PLWH, lower overall CD4 count was associated with greater proportions of Tregs, senescent CD4 and activated CD8 phenotypes. Of the included T cell subpopulations, greater proportions of circulating Tregs were significantly associated with increased incidence of the combined group of lung, anus and kidney cancers for the overall combined cohort and for PLWH only (see Table). Alterations in the
proportion of subsets of CD4 and CD8 cells expressing markers of senescence or activation were not significantly associated with cancer risk during follow-up.

**Conclusion:** Among PWH increased circulating Tregs as a proportion of CD4 cells were associated with increased risk of lung, anus and kidney cancers. Correlation of these findings with the precancerous tumor microenvironment may provide greater insight into the role of HIV infection as an increased risk for some cancers.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Adjusted Hazard Ratios—Profile Cancer (vs. Healthy Controls)**</th>
<th>Unadjusted Hazard Ratios**</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>1.34 (0.64-2.75)</td>
<td>1.34 (0.64-2.75)</td>
</tr>
<tr>
<td>CD4 (low CD8)</td>
<td>1.48 (0.72-3.02)</td>
<td>1.48 (0.72-3.02)</td>
</tr>
<tr>
<td>CD8</td>
<td>1.20 (0.88-1.59)</td>
<td>1.20 (0.88-1.59)</td>
</tr>
<tr>
<td>CD8 (low CD4)</td>
<td>0.64 (0.38-1.06)</td>
<td>0.64 (0.38-1.06)</td>
</tr>
<tr>
<td>TET2-VL</td>
<td>1.03 (0.70-1.51)</td>
<td>1.03 (0.70-1.51)</td>
</tr>
<tr>
<td>TET2-VL (low CD4)</td>
<td>1.51 (0.89-2.56)</td>
<td>1.51 (0.89-2.56)</td>
</tr>
<tr>
<td>TET2-ESPRIT</td>
<td>2.17 (1.32-3.57)</td>
<td>2.17 (1.32-3.57)</td>
</tr>
<tr>
<td>TET2-ESPRIT (low CD4)</td>
<td>0.83 (0.49-1.41)</td>
<td>0.83 (0.49-1.41)</td>
</tr>
</tbody>
</table>

633 TET2 SNPS AND RISK OF CANCER IN THE START, SMART, AND ESPRIT COHORTS

**Daniel D. Murray**, 1 Cameron MacPherson, 1 Birgit Grund, 2 Christina Ekenberg, 3 Adrian G. Zucco, 1 Dahleene Fusco, 1 Julien Gras, 1 Jan Gerstoft, 1 Marie Helleberg, 1 Álvaro H. Borges, 1 Mark Polizzotto, 1 Jens D. Lundgren, 1 for the INSIGHT START, SMART and ESPRIT Study Groups

1Centre of Excellence for Health, Immunity and Infections, Copenhagen, Denmark, University of Minnesota, Minneapolis, MN, USA, Tulane University, Metairie, LA, USA, AP–HP, Paris, France, Rigshospitalet, Copenhagen, Denmark, Kirby Institute, Sydney, NSW, Australia

**Background:** Previously we have identified two groups of SNPs in the TET2 gene associated with either higher or lower HIV Viral Load (VL). These results indicated that TET2 is involved in HIV replication and the identified SNPs alter TET2 in a way that impacts that function. As TET2 also plays a role in cancer development, as a tumor suppressor gene, we hypothesized that these SNPs would also impact that function. To test this, we performed a targeted association analysis between VL-associated SNPs and risk of cancer across INSIGHT network cohorts.

**Methods:** We assessed associations between the 36 previously identified TET2 VL-associated SNPs with incidence of cancer (any type) in the START (NCT00667048), SMART (NCT00273532) and ESPRIT (NCT00004978) cohorts, using Cox regression models adjusting for age, gender, study arm and race (using the first 4 eigenvectors). Only SNPs with minor allele frequency (MAF) > 1% were included in the analyses. P-values are shown unadjusted and adjusted using the max(T) permutation test (10,000 permutations), which accounts for correlations amongst the SNPs.

**Results:** In SMART, 60 (2.6%) pts were diagnosed with cancer during follow-up. Two SNPs, rs6811468 (HR=2.79, CI=1.41-5.53, p=0.003, adjusted p (Ap)=0.03) and rs27955158 (HR=3.24, CI=1.29-8.11, p=0.012, Ap=0.09) were associated with risk of cancer; the number of cancer events in pts with 0, 1 and 2 risk alleles of rs6811468 was 52/2141 (2.4%), 6/125 (4.8%) and 2/4 (50%), respectively. In ESPRIT, a total of 110 pts had cancer. No SNPs were formalin-fixed and paraffin-embedded.

**Conclusion:** FoundationOne CDx could give relevant information on treatment strategies in subjects with cancer and HIV infection, so becoming an important tool in personalized medicine. Indeed, the study of genomic signatures and gene alterations could indicate also in HIV+ patients with cancer (and not only on the basis of tumor type) the possible use of check-point inhibitors or eventually of other anticancer drugs that are registered for that specific cancer or for other cancer types.

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Genetic signatures</th>
<th>Therapy for this type of cancer (vs. matched)</th>
<th>Gene alterations</th>
<th>Therapy for this type of cancer (vs. matched)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck squamous cell carcinoma</td>
<td>Microsatellite stable</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Head and neck squamous cell carcinoma</td>
<td>Microsatellite unstable</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Pancreas cancer</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ovary cancer</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

634 NEXT-GENERATION SEQUENCING TO PROFILE CANCER-RELATED GENES IN HIV+ PATIENTS

**Margherita Diagaeto**, 1 Antonio Maiorana, 1 Roberto Sabbatini, 1 Carlotta Rogati, 1 Andrea Cossarizza, 1 Cristina Mussini

1University of Modena and Reggio Emilia, Modena, Italy

**Background:** Check-point inhibitors and other antitumor drugs have become a cornerstone in cancer treatment. Now it is very important to profile cancer-related genes to understand which could be the most active drug in a specific tumor. Recently, a novel test based on massively parallel DNA sequencing to characterize base substitutions, short insertions and deletion, copy number alterations and selected fusions became available. Aim of our study was to evaluate, for the first time in HIV positive patients with cancer, the use of FoundationOne CDx, a new next-generation sequencing based assay (NGS) that identifies genomic findings within hundreds of cancer-related genes.

**Methods:** FoundationOne CDx, that analyzes genomic changes in 324 genes of relevance for tumor cells, was used on stored clinical samples that were formalin-fixed and paraffin-embedded.

**Results:** We analyzed 10 samples: type of cancer, genomic signatures, gene alterations and possible treatments are described in Table 1. Only one patient showed a high microsatellite instability, that suggests the possible use of check-point inhibitors. Among the 4 patients with kidney renal papillary carcinoma, gene alteration profile was markedly different, so potentially the treatment has to be individualized, and not given on the basis of this cancer type only. Other gene alterations were present in the rest of the patients, that could thus become a possible target for check-point inhibitors or for other anti-tumor drugs, such as mTOR or tyrosine kinase inhibitors, even if these drugs are not registered or studied in these specific cancers. During the follow-up, however, none of the patients received any of these potentially active drugs.

**Conclusion:** FoundationOne CDx could give relevant information on treatment strategies in subjects with cancer and HIV infection, so becoming an important tool in personalized medicine. Indeed, the study of genomic signatures and gene alterations could indicate also in HIV+ patients with cancer (and not only on the basis of tumor type) the possible use of check-point inhibitors or eventually of other anticancer drugs that are registered for that specific cancer or for other cancer types.
HOST GLYCOMIC DETERMINANTS OF CORONARY Atherosclerosis DURING TREATED HIV INFECTION

Leila B. Giron1, Susan Langan1, David B. Hanna1, Juan Lin1, Mohammad Damra1, Qin Liu1, Ian Frank2, Mallory Witt3, Lawrence Kingsley4, Frank J. Palella7, Wendy Post1, Alan Landay5, Todd T. Brown1, Mohamed Abdel-Mohsen6

1Wistar Institute, Philadelphia, PA, USA, 2Johns Hopkins University, Baltimore, MD, USA, 3Albert Einstein College of Medicine, Bronx, NY, USA, 4University of Pennsylvania, Philadelphia, PA, USA, 5Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA, 6University of Pittsburgh, Pittsburgh, PA, USA, 7Northwestern University, Chicago, IL, USA, 8Rush University, Chicago, IL, USA

Background: HIV-induced inflammation is associated with accelerated atherosclerosis, even after virally suppressive antiretroviral therapy (ART). In the general population, host glycemic alterations, in particular, loss of galactose and sialic acid on circulating glycoproteins (including IgG) drive inflammation and are associated with premature aging. Whether glycomic alterations contribute to the development of coronary atherosclerosis during HIV infection remains unknown.

Methods: We designed a case-control study within the Multicenter AIDS Cohort Study (MACS); cases had coronary stenosis ≥50% in one or more coronary segments and controls had no coronary plaque (by CT angiography). We used a 1:1 nearest neighbor matching algorithm to select 34 HIV+ART+ men cases / 34 HIV+ART+ controls, and 22 HIV- men cases / 22 HIV- controls. Median Framingham Risk Score (FRS) was similar between HIV+ cases and controls (7 vs 6, p=0.8), but different between HIV- cases and controls (11 vs 7, p=0.01).

Capillary electrophoresis was used to profile plasma and IgG glycomes. Kruskal-Wallis, Mann-Whitney, and Spearman’s rank tests were used for statistical analyses. False discovery rates (FDR) were calculated to account for multiple comparisons.

Results: Levels of the anti-inflammatory galactosylated glycans were lower in the IgG of HIV+ cases compared to HIV+ controls (FDR=0.005; Fig. 1A). Consistently, levels of the pre- premature-aging agalactosylated glycans were higher in HIV+ cases compared to HIV+ controls (FDR<0.02). These differences were not observed between HIV+ cases and HIV- controls. We also found that levels of the pro-inflammatory hypo-sialylated and agalactosylated glycans were higher in the plasma of HIV- cases compared to HIV+ cases (FDR<0.01; Fig. 1B). Examining the links between galactosylation and risk/degree of cardiovascular disease (CVD), we found that levels of several IgG and plasma galactosylated glycans associated with lower CVD scores, including FRS, segment stenosis, and plaque severity; whereas levels of agalactosylated glycans associated with higher scores (FDR<0.05; Fig. 1C).

Conclusion: Premature-aging-associated glycemic dysregulation, in particular, agalactosylation and hyposialylation, are more evident among HIV+ART+ individuals (compared to all other groups) and are associated with the prevalence and degree of subclinical atherosclerosis. Potential HIV-promoted glycemic pathways fostering CVD warrant further investigation to examine their prognostic and functional significance.

ADVANCED GLYcation END PRODUCTS ASSOCIATED WITH CARDiometabolic RISK ON ART

Vanessa El Kamari1, Katherine Rodriguez2, Carlee Moser1, Judith S. Currier1, Theodoros Kelesidis1, James H. Stein1, Scott K. Howell5, Paul J. Beisswenger5, Todd T. Brown1, Grace A. McComsey1

1University Hospitals Cleveland Medical Center, Cleveland, OH, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3University of California Los Angeles, Los Angeles, CA, USA, 4University of Wisconsin-Madison, Madison, WI, 5Dartmouth College, Hanover, NH, USA, 6Johns Hopkins University, Baltimore, MD, USA

Background: Advanced glycation end products (AGEs) are products of normal aging and are involved in the progression of different conditions such as diabetes and atherosclerosis. AGEs were recently found to be higher in people with HIV compared to uninfected controls. The effect of antiretroviral therapy (ART) on AGEs and its role in cardiometabolic complications in this population remains unknown.

Methods: In ACTG A5260s, a substudy of A5257, we compared changes in serum levels of different AGEs (methylglyoxal hydroimidazolone (MG-H1), carboxymethyl and carboxyethyl lysine (CML and CEL), 3-deoxyglucosone hydroimidazolone (3DGH), and glyoxal hydroimidazolone (GH-1)) in ART-naive participants with HIV randomized to tenofvir disoproxil fumarate- emtricitabine (TDF/FTC) plus atazanavir-ritonavir (ATV/r), darunavir-ritonavir (DRV/r), or raltegravir (RAL) for 96 weeks. Linear regression models were used to study the associations between serum AGEs, and cardiometabolic outcomes of carotid intima media thickness (cIMT), visceral and subcutaneous adipose tissue (VAT and SAT), total fat, lean mass, BMI, homeostatic modal assessment – insulin resistance (HOMA-IR), leptin, and adiponectin, while adjusting for potential baseline confounders (age, sex, race, HIV-1 RNA, CD4+ T cell count, smoking, illicit drug use, alcohol use, and physical activity).

Results: 248 participants were included; 90% male, 48% white, non-Hispanic, with median age of 36 yrs, HIV-1 RNA 4.58 log, copies/mL, and CD4 count 338 cells/μL. Most AGEs increased following 96 weeks of ART initiation, but only MG-H1 levels were significantly higher at week 96 (mean fold change of 1.15, 95% CI [1.02, 1.30]), with no differences between arms At baseline, AGEs were positively associated with HOMA-IR, even after confounder adjustment. At week 96, additional associations emerged between various AGEs and cIMT, VAT, SAT, total fat, leptin and adiponectin, even after adjusting for confounders. A two-fold increase in MG-H1 over 96 weeks was independently associated with 0.1 log increase in HOMA-IR (95% CI [0.05, 0.12]), 0.5% increase in cIMT (95% CI [0, 0.9]), and 0.7% increase in lean mass (95% CI [0.1, 1.2]).

Conclusion: Initiation of ART seems to increase levels of AGEs in ART-naive participants with HIV, regardless of regimen used. Accumulation of AGEs is independently associated with subsequent cardiometabolic risk while on ART.

SINGLE-CELL TRANSCRIPTOMICS OF HIV HEART TISSUE IDENTIFIES UNIQUE NK CELL POPULATION

Thomas C. Martin1, Neil C. Chi1, Sara Gianella1, Sebastian Preissl1, Justin Buchanan1, Davey M. Smith1, Priscilla Huse2

1University of California San Diego, La Jolla, CA, USA, 2University of California San Francisco, San Francisco, CA, USA

Background: Cardiovascular disease, in particular heart failure, is elevated among people living with HIV (PLWH) though the etiology of this disease process remains unclear. Using single cell RNA-seq approaches, we interrogated the spectrum of cell types and their gene expression in heart tissue from PLWH to further elucidate the underlying pathogenesis of HIV-associated heart disease.

Methods: Left ventricular tissue samples were obtained from 3 participants: 1) HIV uninfected without heart failure (CTRL); 2) HIV infected without heart failure (HIV_CTRL); 3) HIV infected with non-ischemic heart failure (HIV_NICM). Both PLWH donors were virally suppressed on therapy at the time of biopsy. Samples were immediately flash frozen in liquid nitrogen at collection. Nuclei were subsequently isolated from frozen tissue and processed for single-nuclear RNA-sequencing using the 10X Chromium platform. Clustering was performed using Seurat 3.0.

Results: Single nuclear transcriptomic data were obtained from 9008, 8746 and 8176 nuclei for CTRL, HIV_CTRL and HIV_NICM samples respectively. Cluster analysis was performed and clusters expressing high fold change were selected for further analysis. CD45+ cells were re-clustered and natural killer (NK) cells were identified using markers NCAM1 (CD56), Granulysin (GNLY), TBX21 and NKG7. NK cells expressed additional markers including Killer Cell Lectin Like Receptor C1 (KLRC1) and Killer Cell Lectin Like Receptor D2 (KLRD2) compared to T-lymphocytes (p-adj <10-17 and <10-7 respectively). Figure 1 shows cluster allocation for CD45+ cells from the 3 samples (panel A – CTRL, panel B – HIV_CTRL, panel C – HIV_NICM). As a proportion of all CD45+ cells, NK cells comprised 0.7%, 8.4% and 3.0% for samples CTRL, HIV_CTRL and HIV_NICM respectively (p<0.001).
Conclusion: This study found a unique NK cell population in cardiac tissue from two PLWH compared to a person without HIV. Dysregulation of the immune system, including NK cells, has been associated with cardiac fibrosis, myocarditis and cardiac transplant rejection in the HIV uninfected population. This is the first study to our knowledge to apply single cell transcriptomics to evaluate the underlying mechanisms of HIV-associated cardiovascular disease. The direct impact of HIV, immune activation and NK cells on cardiomyocytes and heart failure merits additional investigation in larger studies.

Methods: We studied 125 HIV+; 85% male, 58% Caucasian, with a median age of 51, median CD4 count was 477 cells/μL (Q1: 323; Q3: 612), 86% undetectable HIV viral load. MCPT correlated with non-classical monocyte (r=.451, p=.046), MCP-1 (r=.487, p=.016), TNFα (r=.474, p=.019), sVCAM1 (r=.472, p=.020), ApoB6 (r=-.473, p=.019) and IL-6 (r=.455, p=.025). In a multivariable regression model, MCP-1, TNFα, and sVCAM1 remained significant even after adjustment for age. Longitudinal analysis of 15 HIV+ participants with two MCPT assessments revealed no correlation with types of ART; lipid lowering, hypertensive and antiplatelet medications; or illicit drug use.

Conclusion: Worsening carotid plaque burden is associated with increased non-classical monocytes and inflammatory markers. Changes in MCPT were not associated with anti-lipid therapy.

INCREASED LEUKOCYTE/PLATELET INTERPLAY WITH ENDOTHELIUM IN ABC-TREATED HIV PATIENTS

Maria Amparo Blanch-Ruiz1, Ainhoa Sanchez-Lopez2, Raquel Ortega-Luna1, Patricia Garcia-Martinez2, Samuel Orden1, Maria Angeles Martinez-Cuesta1, Ramon Fernando-Vilata1, Maria J. Galindo2, Angeles Alvarez2, Juan V. Esplugues2

University of Valencia, Valencia, Spain, 1Hospital Clinic of Valencia, Valencia, Spain

Background: Abacavir (ABC) has been associated with a risk of myocardial infarction. We have demonstrated experimentally that clinical concentrations of ABC added in vitro, but not of tenofovir disoproxil fumarate (TDF), have pro-inflammatory (it induces leukocyte-endothelium interactions) and pro-thrombotic (it causes the interplay of platelets with endothelial cells or leukocytes) actions. Furthermore, ABC promoted thrombus formation in a well-established in vivo model. The aim of the present study was to test the pro-inflammatory and pro-thrombotic status of HIV patients undergoing ABC versus TDF treatment by analysing leukocyte- and/or platelet-endothelium interactions in cells isolated from blood of these two groups of HIV patients.

Methods: This is a non-aleatorized prospective observational study in which we used blood cells from HIV-patients at Hospital Clínico Universitario de Valencia who had been receiving treatment, for at least 6 months, with a ART regime that included either ABC or TDF. Interactions of isolated leukocytes (peripheral blood mononuclear cells, PBMC) – rolling and adhesion - and platelets were evaluated by means of a parallel-plate flow chamber system. Platelets were labelled with an anti-CD41 (specific platelet marker) antibody linked to Alexa-Fluor®488 in order to visualize them by Epi-fluorescence microscopy.

Results: 39 patients were included in the study, 18 of whom were receiving ABC and 21 of whom were receiving TDF. There were no significant differences in demographic and cardiovascular risk parameters between the two groups. PBMC rolling (Figure 1A) and adhesion (Figure 1B) along the endothelium were significantly higher in the ABC group than in the TDF group. Moreover, the number of platelets adhering to endothelial cells was higher in the ABC versus TDF group (Figure 1C).

Conclusion: Treatment with ABC enhances PBMC-endothelium interactions, thus promoting the initial phases of the inflammatory process. Furthermore, it induces platelet adhesion to endothelial cells, which is an important step in thrombus formation. Our results give support to the increased risk of myocardial infarction observed in ABC-treated HIV patients.
640 FIBROBLAST GROWTH FACTOR 21: EFFECT OF HIV THERAPY AND ASSOCIATION WITH CVD RISK

Corriylln O. Hileman1, Sarah E. Scott2, Beth A. Zavoda-Smith1, Grace A. McConney3
1MetroHealth Medical Center, Cleveland, OH, USA, 2University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Background: Fibroblast growth factor 21 (FGF21) is a pleiotropic signal protein molecule for several metabolically active organs. The liver releases FGF21 in response to a broad range of stress conditions resulting in beneficial effects on glucose, lipid and energy homeostasis. FGF21 may be part of a compensatory response to offset atherosclerosis in certain disease states. People with HIV (PWH) are at heightened risk for cardiovascular disease (CVD). Whether FGF21 is modified by antiretroviral therapy (ART) or could serve as a marker for subclinical atherosclerosis in PWH is not known.

Methods: Fasting plasma FGF21 concentrations were quantified by ELISA from ART-naïve HIV+ adults enrolled in a longitudinal study of carotid intima media thickness (IMT) progression and in ART-treated HIV+ adults matched by sex, race and body mass index (BMI) at entry (all participants), and weeks 48 and 96 (those who initiated ART at entry). Multivariable linear regression and mixed effects linear modeling were used to explore associations between ART status, FGF21 and common carotid artery (CCA) IMT at entry and over time.

Results: 162 participants (81 ART-naïve; 81 ART-treated) were included. Groups were similar except ART-treated were older (median 48 vs 41; p<0.01) had higher FGF21 and common carotid artery (CCA) IMT at entry and over time. Among WHIV, aPWV related to heightened monocyte activation as well as to extracellular matrix – a measure of myocardial fibrosis (whole group: R=0.54, P=0.001; WHIV: R=0.47, P=0.04). Both HIV status and sCD163 levels independently predicted aPWV, even after controlling for age, BMI, cigarette smoking burden, and SBP (R2=0.63, P=0.0002; HIV status: P=0.02; sCD163: P=0.01). Among WHIV, sCD163 levels independently predicted aPWV after controlling for duration of HIV, CD4 count, and HIV viral load (R2=0.62, P=0.007; sCD163: P=0.0005).

Conclusion: Asymptomatic ART-treated WHIV demonstrated increased aPWV. Among WHIV, aPWV related to heightened monocyte activation as well as to downstream CVD pathology. Additional studies are needed to identify targeted immune-modulatory therapies which slow the progression from vascular dysfunction to incident CVD in this at-risk population.

657 MONOCYTE ACTIVATION AND CARDIAC-MR1–DERIVED VASCULAR DYSFUNCTION AMONG WOMEN WITH HIV

MabelToribio1, MagidAwadalla1, EvelyneSFulda1, AdamRokicki1, TakaraL. Stanley1, LidiaSzczepaniak2, MichaelD. Nelson1, MichaelJerosch-Herold1, Tricia H. Burdo2, TomasG. Neilan3, MarkellaV. Zanni1
1Massachusetts General Hospital, Boston, MA, USA, 2UMass Medical School, Worcester, MA, USA, 3University of Texas, Arlington, TX, USA

Background: Women with HIV (WHIV) on ART face an increased risk of cardiovascular disease by TTh use status among MWH in the Multicenter AIDS Cohort Study (MACS).

Methods: WHIV in the MACS CVD sub-study in 4 U.S. cities from 2010–17 were included, each of whom underwent two coronary CT angiography (CCTA) measurements 4.5±0.7 years apart. Inclusion criteria were age 40–70 without coronary intervention or kidney dysfunction. TTh use was self-reported semi-annually, and classified as never, prior to baseline CCTA (former), after baseline CCTA (new), or both (consistent). We evaluated associations between TTh and progression of subclinical atherosclerosis, specifically 1) coronary artery calcium (CAC), 2) total plaque volume, and 3) noncalcified plaque volume. CAC

664 TESTOSTERONE THERAPY AND SUBCLINICAL ATHEROSCLEROSIS PROGRESSION AMONG MEN WITH HIV

Sabina A. Haberlen1, Wendy Post2, Matthew Budoff2, Jordan E. Lake3, Adrian Dobs1, Frank J. Palella5, Evelynne S. Fulda1, Adam Rokicki1, Takara L. Toribio3, Anne K. Monroe6, Lawrence Kingsley7, Todd T. Brown2
1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA, 3Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA, 4University of Texas at Houston, Houston, TX, USA, 5Northwestern University, Chicago, IL, USA, 6Georgetown University, Washington, DC, USA, 7George Washington University, Washington, DC, USA

Background: Testosterone therapy (TTh) use is highly prevalent among middle-aged and older men with HIV (MWH) in the United States, but its cardiovascular safety is unclear. We assessed progression of subclinical coronary artery disease by TTh use status among MWH in the Multicenter AIDS Cohort Study (MACS).

Methods: MWH in the MACS CVD sub-study in 4 U.S. cities from 2010–17 were included, each of whom underwent two coronary CT angiography (CCTA) measurements 4.5±0.7 years apart. Inclusion criteria were age 40–70 without coronary intervention or kidney dysfunction. TTh use was self-reported semi-annually, and classified as never, prior to baseline CCTA (former), after baseline CCTA (new), or both (consistent). We evaluated associations between TTh and progression of subclinical atherosclerosis, specifically 1) coronary artery calcium (CAC), 2) total plaque volume, and 3) noncalcified plaque volume. CAC
progression was defined by incident CAC if baseline CAC=0, ≥10 Agatston units/yr increase if baseline CAC=1-100, and ≥10%/yr increase if baseline CAC>100, and analyzed by robust Poisson regression. Progression was defined by the upper tertile of annualized change in total and noncalcified plaque volume, using multinomial logistic regression. Regression models adjusted for demographic, cardiovascular risk, and HIV-related clinical factors, and baseline serum testosterone.

Results: Median age among the 300 MWH was 51 years, 48% were white, 41% were in the ASCVD high risk category, 91% were on antiretroviral therapy, and 81% had undetectable HIV viral load (<20 copies/mL). TTh trajectories were: 70% never, 8% former, 7% new, and 15% consistent use. Median total testosterone was 606 ng/dL (IQR = 445.808). Adjusting for age, race, testosterone<300 ng/dL, and cardiovascular and HIV co-factors, the risk of significant CAC progression was 2.0 times greater among continuous users (p=0.03) and 2.4 times greater among new users (p=0.01) relative to former users. We observed a similar trend for total and noncalcified plaque volume progression, but these estimates were not statistically significant (Table). Conclusion: MWH who continued or started TTh were twice as likely for former users to experience significant CAC progression over 4 years. To our knowledge, this is the first contemporary study of cardiovascular outcomes associated with TTh use among MWH; additional observational data should be leveraged to further elucidate the potential health implications of TTh use among MWH.

Estimated and observed means of association for coronary artery calcium score, total plaque volume, and noncalcified plaque volume across TTh users. By history of testosterone therapy among men with HIV

Conclusion: Following treatment for ACS, HIV-infected individuals are less likely to be taking guideline-recommended medical therapy and have worsened clinical outcomes compared to uninfected individuals. Optimizing use of medical therapy and longitudinal care of this high risk group is greatly needed.

INSOMNIA AND RISK OF INCIDENT MYOCARDIAL INFARCTION AMONG PEOPLE LIVING WITH HIV

Background: Current research suggests that people living with HIV (PLWH) suffer from a substantially higher burden of sleep disturbances, including insomnia, compared to the general population. Insomnia is associated with increased risk of cardiovascular disease (CVD) and may play a role in the increased incidence of myocardial infarctions (MIs) seen among PLWH. Type 1 MIs (T1MI) are due to atherothrombotic coronary plaque rupture, whereas type 2 MIs (T2MI) are from supply-demand mismatch, such as with sepsis or cocaine use; T2MIs are more common in PLWH than in the general population. The disproportionate risk of MI by type due to insomnia in PLWH is unknown.

Methods: The multisite Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort includes clinical data, patient-reported outcomes and measures (PROs), and centrally adjudicated MIs with distinction between T1MIs and T2MIs. Using data from PLWH in care at 5 CNICS sites between 2005-2019 we evaluated the relationship between insomnia and first MIs (n=241) among 11,189 PLWH. We used separate Cox models adjusted for age, sex, race/ethnicity, CD4 count, viral suppression (VL<400), and traditional CVD risk factors, including treated hypertension, treated dyslipidemia, kidney function (eGFR<30), and smoking.

Results: Among 11,189 PLWH there were 241 incident MIs (n=141 T1MIs and n=100 T2MIs) over an average of 4.3 years of follow-up. Sleep disturbance was common, with 6,405 (57%) PLWH reporting some difficulty falling or staying asleep and 5,415 (48%) PLWH reporting their insomnia symptoms were bothersome. In adjusted analyses, PLWH experiencing insomnia were 53% more likely to have an incident T2MI compared to PLWH without insomnia (Hazard Ratio (HR) = 0.47, 95% CI: 0.37-0.59; p<0.001). PLWH with insomnia had higher rates of mortality following discharge, and receive sub-optimal medical management compared with uninfected individuals. Conclusion: Approximately half of PLWH reported insomnia, an estimate consistent with the 50-70% prevalence reported in the literature. We found that PLWH with insomnia had a substantially increased risk of T2MI, but not T1MI, highlighting the importance of distinguishing MI types. Further investigation into the relationship between insomnia and T2MIs by T2MI cause may elucidate mechanisms underlying this association.
HORMONE USE AND HIV ALTER CARDIOVASCULAR BIOMARKER PROFILES IN TRANSWOMEN WOMEN

Jordan E. Lake1, Rubina Wang1, Benjamin Barrett1, Nicholas Funderburk1, Emily Bowman1, Paula Debro1, Jury Candelario1, Linda Teplin1, Jessica McGuinness1, Robert Bolan2, Heather McKay3, Michael Plankey3, Todd T. Brown3, Judith S. Currier4

1University of Texas at Houston, Houston, TX, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3The Ohio State University, Columbus, OH, USA, 4Asian Pacific AIDS Intervention Team, Los Angeles, CA, USA, 5Northwestern University, Chicago, IL, USA, 6University of Pittsburgh, Pittsburgh, PA, USA, 7Los Angeles LGBT Center, Los Angeles, CA, USA, 8Georgetown University, Washington, DC, USA, 9Johns Hopkins University School of Medicine, Baltimore, MD, USA, 10University of California Los Angeles, Los Angeles, CA, USA

Background: Feminizing hormonal therapy (FHT) and HIV potentially alter cardiovascular disease (CVD) risk in transgender women (TW). We assessed serum biomarkers of CVD risk and inflammation among TW by HIV serostatus and FHT use, compared to cis-gender male (CM) controls.

Methods: TW were enrolled from community-based organizations and clinics in Los Angeles, CA and Houston, TX and frequency-matched to Multicenter AIDS Cohort Study CM on age, race, substance use and ART type. Serum biomarker concentrations were assessed via ELISA. Wilcoxon rank sum and Fisher’s exact tests compared groups. Multivariable linear regression analyses assessed factors associated with log2-transformed biomarker concentrations.

Results: TW (HIV+ n=75, HIV- n=47) and CM (HIV+ n=40, HIV- n=40) had mean age of 43 and 45 years; 90%/91% were non-Hispanic black, Hispanic, or multi-racial, 26%/53% obese, and 34%/29% current smokers, respectively. Persons with HIV (PWH) had current median CD4+ T lymphocyte count 689 cells/μL; 67% of TW were on FHT (68% HIV+, 66% HIV-). ART use included 29% NNRTIs, 30% PIs, and 37% INSTIs. Among PWH, TW had higher median extracellular newly-identified receptor for advanced glycation end-products (EN-RAGE), lipoprotein-associated phospholipase A2 (LpPLA2), oxidized LDL (oxLDL), soluble TNF receptor type 1 (sTNFR I/II), interleukin (IL)-8 and plasminogen activator inhibitor (PAI)-1, but lower soluble CD14, von Willebrand factor (vWF) and endothelin (ET)-1 levels than CM, with similar findings for participants without HIV (all p<0.05). In PWH, ENRAGE, oxLDL, and sTNFR I/II concentrations were higher, and vWF and ET-1 were lower, moving from CM to TW not on FHT (n=24) to TW on FHT (n=51). For persons without HIV, ENRAGE, oxLDL and PAI-1 were higher moving from CM to TW not on FHT (n=16) to TW on FHT (n=31).

In multivariate analysis restricted to persons with undetectable HIV-1 RNA and adjusted for HIV serostatus, gender, age, race/ethnicity, BMI, and smoking, being a TW but not HIV status was associated with higher EN-RAGE, IL-6, IL-8, P selectin, PAI-1, oxLDL and sTNFR I/II concentrations, and lower vWF. Both being a TW and a PWH were associated with lower ET-1.

Conclusion: Compared to matched CM, TW have altered profiles of biomarkers associated with systemic inflammation and CVD that seem to be influenced by both FHT and HIV, even after adjusting for key risk factors. Clinical data are needed to understand the contributions of FHT and HIV to CVD risk among TW.

HIV SEVERITY AND INCIDENT HEART FAILURE AMONG PATIENTS IN A LARGE HEALTH CARE SYSTEM

Jennifer O. Lam1, Wendy Leyden1, Kristi J. Reynolds1, Michael A. Horberg2, William J. Towne1, Rulin Hechter2, Suma Vupputuri3, Thomas K. Leong3, Harshith Avula4, Teresa J. Harrison4, Keane K. Lee5, Sue Hee Sung5, Romain Neugebauer6, Alan S. Go7, Michael J. Silverberg8

1Kaiser Permanente, Oakland, CA, USA, 2Kaiser Permanente Southern California, Pasadena, CA, USA, 3Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA

Background: Persons with HIV (PWH) are at increased risk for heart failure (HF) compared with uninfected persons but few studies have evaluated whether this risk varies by severity of HIV infection.

Methods: We conducted an observational cohort study of adults (age ≥21 years) with and without HIV, frequency-matched 1:10 by age, sex, race/ethnicity, primary medical facility and calendar year, who were members of Kaiser Permanente in Northern California, Southern California, Maryland, D.C. or Virginia between 2000 and 2016. Patients’ electronic health records were reviewed to determine incident HF (either preserved or reduced left ventricular systolic function). Using Poisson regression, we estimated relative risk (RR) of incident HF by HIV status overall, and by HIV status with PWH stratified by recent CD4 count, nadir CD4 count, or HIV RNA level, with laboratory measures lagged by 6 months (i.e., at least 6 months prior to HF assessment). We adjusted for sociodemographic characteristics (sex, current age, race/ethnicity, socioeconomic status) and risk factors for HF, including BMI>25, antecedent acute myocardial infarction, hypertension, diabetes mellitus, dyslipidemia, even documented history of smoking, alcohol use disorder and drug use disorder.

Results: The study included 38,868 PWH and 386,569 matched uninfected persons (average age 41 years at start of follow-up; 88% male; 38% White, 20% Hispanic, 21% Black). There were 414 HF cases among PWH and 3,298 HF cases among uninfected comparators (0.23 and 0.15 cases of HF per 100 person-years, respectively). Risk of HF was higher overall in PWH (vs. uninfected persons, adjusted RR 1.34, 95% CI: 1.21-1.49). However, when evaluating HF by HIV severity, heightened HF risk was observed only among PWH with lower recent CD4, lower nadir CD4 and higher HIV RNA level (Table). PWH with recent CD4≥500, nadir CD4≥200 and HIV RNA level ≤200 did not have significantly higher risk of HF compared with uninfected persons.

Conclusion: Higher HIV viremia and lower CD4 cell count (both recent and nadir) are associated with elevated HF risk. Our data suggest that, in addition to addressing cardiovascular risk factors, earlier HIV diagnosis and treatment, and adherence to antiretroviral therapy, are strategies to prevent HF in PWH.

PLASMA INFLAMMATORY BIOMARKER SIGNATURE ASSOCIATED WITH CVD IN HIV INFECTION

Mohamed El-Far1, Madeleine Durand1, Carl Chartand-Lefebvre1, Rémi Bunet1, Hardik Ramani1, Jean-Guy Baril1, Benoit Trotter1, Samer Mansour2, Ali Filali3, Petronela Ancuta1, Nicolas Chomont1, Robert C. Kaplan3, Alan Landay4, Cécile Tremblay4, for the Canadian HIV and Aging Cohort Study (CHACS)

Table: Relative risk of incident heart failure in HIV-infected (n=38,868) compared with HIV-uninfected (n=386,569) patients, overall and stratified by HIV severity as defined by recent CD4 count, nadir CD4 count or HIV RNA level

<table>
<thead>
<tr>
<th>HIV Status</th>
<th>Incident HF Rate</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>0.23/0.15</td>
<td></td>
</tr>
<tr>
<td>HIV+ low CD4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-</td>
<td>0.23/0.15</td>
<td></td>
</tr>
<tr>
<td>HIV- low CD4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Reference for socio-demographic characteristics, time-varying variables.

2Reference for incident heart failure (HR) and myocardial infarction (MI).

3Reference for HIV severity.
Background: We have recently shown that a specific isoform of the human proinflammatory cytokine IL-32 (IL-32D) is selectively upregulated in HIV+ individuals with cardiovascular disease (CVD). Here we extend our studies to screen for other inflammatory markers that could be combined with IL-32D to enhance the prediction of CVD in HIV infection.

Methods: Using the MesoScale Technology, we measured 84 inflammatory and anti-inflammatory factors in plasma from n=79 HIV+ aviremic males participating in the Canadian HIV and Aging Cohort Study (n=49 CVD+ with coronary artery atherosclerosis measured by cardiac computed tomography and n=30 CVD-) and HIVneg controls (n=25 CVD+ and n=24 CVD-). We used a generalized linear regression algorithm (glmnet) with Lasso regularization and Leave-One-Out cross validation to predict the presence of coronary artery atherosclerosis in the study participants.

Results: Alongside with the upregulation of IL-32D, we observed an HIV-specific signature characterized by higher plasma levels of IL-18, VEGF-A, FGF23, FLT3L and FSH in HIV+ individuals with CVD (univariate analysis, p=0.0016, 0.0053, 0.0386, 0.0075 and 0.049, respectively) combined with lower levels of TNF-related apoptosis inducing ligand (TRAIL), IFNβ and IL-3 (p=0.0149, 0.0093 and 0.0288, respectively). By integrating IL-32D expression with these modulated factors in a multivariate analysis, CVD was predicted as a binary outcome (presence/absence) with a misclassification error of 34%. The prediction model was independent of age, statin treatment and smoking. Given the growing evidence for the atheroprotective role of TRAIL-expressing monocytes, we tested the functional link between IL-32D and TRAIL. We show here that primary human monocytes treated with IL-32 down-regulate TRAIL expression, acquire an M1 activated phenotype (CD206negCD163negCD80+TRAILneg) and produce inflammatory cytokines such as IL-6 and TNFα.

Conclusion: Here we report a specific plasma inflammatory signature that holds promise to predict CVD in HIV+ individuals independently of traditional risk factors. Moreover, the functional link between IL-32D and TRAIL and their opposite effects on monocyte functions further highlight the key role of IL-32D in CVD and its potential as a therapeutic target in HIV infection.

468 ASSOCIATION OF INFLAMMATORY MARKERS WITH CARDIAC INDICES IN THE MACS
Bethel Woldu1, Henrique Doria De Vasconcellos1, Joseph B. Margolick2, Heather McKay1, Jared Magnani3, Matthew J. Feinstein4, Roger Detels5, Todd T. Brown1, Matthew J. Liao1, Henrique Doria De Vasconcellos1, Joseph B. Margolick 2, Heather McKay1, Jared Magnani3, Matthew J. Feinstein4, Roger Detels5, Todd T. Brown6, Leah H. Rubin1, 2,796 participants had non-invasive B-mode ultrasound of the right carotid artery in 2004-2006, and 528 (30% women) were identified with plaque (focal IMT >1.5 mm). We used random forests and hierarchical clustering on 76 demographic, behavioral and clinical markers assessed near the time of the scan to classify individuals into phenotypically similar clusters among those with plaque. Over 13 years of follow-up, we assessed the association of each cluster with all-cause mortality, and in women, hospitalization rates and cognitive decline.

Results: Our approach identified 4 distinct clusters that differed by age and hypertension history (Figure). Clusters C and D (mean age 56-57) were on average 14 years older than A and B, and D and C were much more likely to be hypertensive than A and C (p<0.001). Even though C and D were of similar age, C had less carotid disease (fewer plaques, less stiffness) than D (p<0.001), but similar levels as B. Compared with D, C also was significantly less likely to smoke (34% vs 43%) or be diabetic (12% vs 21%), more likely to be treated for hypertension (among hypertensives, 92% vs 52%), and had lower BMI (mean 25 vs 27 kg/m²) and higher bilirubin (mean 0.85 vs 0.69 mg/dL). Among PWH, C was more likely to be on ART (73% vs 65%) than D and more likely to have history of AIDS (36% vs 25%) and lower CD4+ count (mean 478 vs 523 cells/μL). Over time, C had better survival (HR 0.56, 95% CI 0.36-0.88), fewer hospitalizations and association with highest IL-6 quintile, independent of HIV serostatus. There were no significant associations between inflammatory markers and echodetected parameters of diastolic function including transmural Flow velocity (E), mitral annular velocity (e') and E/e' ratio. Conclusion: In this analysis of HIV+ and HIV- men, larger LA size was associated with markers of heightened systemic inflammation, regardless of HIV serostatus. As left atrial dilatation predicts future risk of atrial fibrillation and stroke, further investigation is needed to evaluate whether systemic inflammation mediates increased atrial arrhythmic risk among both HIV+ and HIV- people.

Table 1: Correlation of inflammatory markers with echocardiographic indices

<table>
<thead>
<tr>
<th>HIV status</th>
<th>Ejection fraction (%)</th>
<th>LV mass index (g/m²)</th>
<th>LA volume index (cm³/m²)</th>
<th>Mitral valve E/E' ratio</th>
<th>Mitral valve E/A ratio</th>
<th>Mitral valve reserve E/A ratio</th>
<th>Mitral valve reserve E' velocity (cm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIVseronegative</td>
<td>0.43 (0.66)</td>
<td>2.52 (2.25)</td>
<td>4.92 (2.01)</td>
<td>0.88 (0.63)</td>
<td>0.80 (0.65)</td>
<td>0.92 (0.66)</td>
<td>0.91 (0.57)</td>
</tr>
<tr>
<td>HIVnegative</td>
<td>0.40 (0.62)</td>
<td>2.48 (2.22)</td>
<td>4.89 (2.03)</td>
<td>0.86 (0.61)</td>
<td>0.85 (0.65)</td>
<td>0.91 (0.64)</td>
<td>0.90 (0.56)</td>
</tr>
<tr>
<td>HIV+</td>
<td>0.41 (0.63)</td>
<td>2.51 (2.23)</td>
<td>4.95 (2.02)</td>
<td>0.88 (0.63)</td>
<td>0.80 (0.65)</td>
<td>0.92 (0.66)</td>
<td>0.91 (0.57)</td>
</tr>
</tbody>
</table>

469 PHENOTYPIC CLUSTERING OF HIV-ASSOCIATED ATHEROSCLEROSIS AND AGE-RELATED OUTCOMES
David B. Hanna1, Jee-Young Moon1, Bryan Lau2, Kathryn Anastos3, Russell Tracy1, Sabina A. Haberlein1, Caitlin A. Moran1, Todd T. Brown1, Leah H. Rubin1, 1 Albert Einstein College of Medicine, Bronx, NY, USA, 2 Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3 Montefiore Medical Center, Bronx, NY, USA, 4 University of Vermont, Burlington, VT, USA, 5 Emory University, Atlanta, GA, USA, 6 Johns Hopkins University School of Medicine, Baltimore, MD, USA, 7 University of Pittsburgh, Pittsburgh, PA, USA, 8 University of Southern California, Los Angeles, CA, USA

Background: People with HIV (PWH) have increased cardiovascular disease risk, but the underlying mechanisms are not fully elucidated. We used machine learning to develop phenotypic profiles of individuals with subclinical atherosclerosis that incorporate multiple risk factor interactions, and determined whether these profiles differentially associate with age-related disease.

Methods: The MACS/WHI CCS prospectively follows people with and without HIV at 14 sites. 2,796 participants had non-invasive B-mode ultrasound of the right carotid artery in 2004-2006, and 528 (30% women) were identified with plaque (focal IMT >1.5 mm). We used random forests and hierarchical clustering on 76 demographic, behavioral and clinical markers assessed near the time of the scan to classify individuals into phenotypically similar clusters among those with plaque. Over 13 years of follow-up, we assessed the association of each cluster with all-cause mortality, and in women, hospitalization rates and cognitive decline.

Results: Our approach identified 4 distinct clusters that differed by age and hypertension history (Figure). Clusters C and D (mean age 56-57) were on average 14 years older than A and B, and B and D were much more likely to be hypertensive than A and C (p<0.001). Even though C and D were of similar age, C had less carotid disease (fewer plaques, less stiffness) than D (p<0.001), but similar levels as B. Compared with D, C also was significantly less likely to smoke (34% vs 43%) or be diabetic (12% vs 21%), more likely to be treated for hypertension (among hypertensives, 92% vs 52%), and had lower BMI (mean 25 vs 27 kg/m²) and higher bilirubin (mean 0.85 vs 0.69 mg/dL). Among PWH, C was more likely to be on ART (73% vs 65%) than D and more likely to have history of AIDS (36% vs 25%) and lower CD4+ count (mean 478 vs 523 cells/μL). Over time, C had better survival (HR 0.56, 95% CI 0.36-0.88), fewer hospitalizations...
(RR 0.79, 95% CI 0.48–1.29), and less decline in processing speed (difference in Z-score for Trail Making Test A 0.03, 95% CI 0.001-0.05) than D. Outcomes for C were similar to A and B despite older age.

**Conclusion:** Our current analysis identified a profile of individuals with subclinical atherosclerosis who, as they entered their 6th decade, seemed to represent more of a “healthy aging” phenotype than others of the same age. Future work should further characterize this group and identify mechanisms underlying their apparent resiliency.

---

**Figure:** Unrelated demographically showing clustering of AACS/MS1hS1h patients with concerning atherosclerotic plaque (stain: 520).

---

**Methods:** PWH from NA-ACCORD cohorts that validated type 1 MIs (induced by plaque rupture with thrombus) were included. Study entry began as the latest of NA-ACCORD enrollment, age 40, ART initiation date, 1 Jan 2000, or the cohort start date of MI observation. Study entry date was defined as the earliest of MI date, death date, loss to follow up (2 years with no HIV RNA or CD4 measures), age 80, 31 Dec 2015, or the cohort start date of MI observation. Study exit was defined as the earliest of death, loss to follow up, NA-ACCORD enrollment, age 40, ART initiation date, 1 Jan 2000, or the cohort start date of MI observation.

---

**Background:** Physicians who care for people with HIV (PWH) need to know the person’s risk for myocardial infarction (MI) to initiate discussions with these patients under their care, provide appropriate prophylaxis, and immediately, including smoking cessation, lipid control, and blood sugar control.

---

**Figure 1:** Cumulative incidence of myocardial infarction (MI) and MI incidence rates (and 95% confidence intervals) by AHA/ACC ASCVD risk score at study entry among 20,675 adults under observation for MI (of whom, 282 had an MI)

---

**Results:** We included 333 cases (median age at CAD event, 54 years; 14% women; 83% with HIV RNA<50) and 745 controls. Median (IQR) time of TL measurement was 9.4 (5.9-13.8) years prior to CAD event. Participants in the 5th (longest) TL quintile, compared to the 1st (shortest) TL quintile had univariable and multivariable (OR) for a first MI event from conditional logistic regression analyses, including as variables TL, age, gender, smoking, family history, hypertension, diabetes, hypercholesterolemia, and HIV-related factors (recent exposure to abacavir, exposure >1 year to abacavir, lopinavir/ritonavir, darunavir; ART discontinuation; or ART but HIV RNA<50 copies/ml).

**Conclusion:** HIV-positive persons with the longest telomeres (measured >9 years prior to CAD event) had approx. half the odds of developing CAD of those with the shortest telomeres. TL measurement may, in addition to traditional and HIV-related risk factors, provide prognostic information with respect to CAD risk.

---

**Figure 1A:** Contribution of telomere length and clinical risk factors to coronary artery disease risk.
652 PREVALENCE OF SUBCLINICAL MYOCARDIAL ABNORMALITIES IN HIV: SMASH STUDY RESULTS
Katherine Wu1, Sabina A. Haberlen1, Michael Plankey1, Frank J. Palella5, Damani A. Piggott1, Gregory D. Kirk2, Joseph B. Margolick3, Wendy Post1
1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3Georgetown University, Washington, DC, USA, 4Northwestern University, Chicago, IL, USA
Background: It is unknown whether HIV infection remains an independent risk factor for subclinical myocardial disease in the era of combination antiretroviral therapy (cART). We assessed differences in cardiac structure and function by cardiac magnetic resonance (CMR) imaging among people with (HIV+) and without HIV (HIV-) after controlling for potential confounders.
Methods: 432 participants (71% men, 63% HIV+) in the Multicenter AIDS Cohort Study, AIDS Linked to the Intravenous Experience study, and Women's Intergender HIV Study, aged 40-70 years, underwent CMR for biventricular volumes and mass, left atrial (LA) volumes, and left ventricular (LV) and LA strain. CMR with contrast and T1 mapping comprehensively assessed scar patterns and burden.
Results: Median participant age was 55 years, 47% smokers, 53% hypertensive, 13% diabetic, and 59% dyslipidemic. Prevalence of stimulant, opioid and marijuana use was 39%, 32%, and 44%. Among HIV+ persons, 89% were on cART, 74% had viral suppression (HIV RNA<50 copies/ml), and most recent median CD4 count was 610/µl (IQR 398-826). For most characteristics, HIV- and HIV+ participants were similar. Median LV ejection fraction (EF) was normal and similar by HIV serostatus (73% for HIV- vs. 72% for HIV+, p=0.53, n=2 with LVEF<40%) as were right ventricular EF, biventricular volumes and masses. Focal myocardial scar prevalence was also similar (32% vs. 37%, p=0.38) with similarly low median scar extents (4.1 vs. 5.0 grams, p=0.46). The pattern of myocardial scar was predominantly non-ischemic. An ischemic scar pattern was found among only 3% of HIV- vs. 5% of HIV+ (p=0.05). Indices of nonischemic diffuse fibrosis did not differ by HIV serostatus. After adjusting for demographics, parent cohort, education, cardiac risk factors, and drug use, LA volumes (maximal, maximal and pre-atrial) were the only CMR parameters that differed significantly by HIV serostatus and were ~10% larger for HIV+ (Table). Among HIV+ people, LA volumes did not differ by viral suppression status.
Conclusion: Among a comparable group of HIV- and HIV+ people with similar characteristics and patterns of recreational substance use, prevalent ventricular disease was rare and ventricular indices did not differ by HIV serostatus. However, HIV+ serostatus was independently associated with larger LA phasic volumes, possibly reflecting diastolic dysfunction and predisposal to atrial arrhythmias.

Background: In the antiretroviral era, cardiovascular disorders have become more prevalent in people living with HIV. However, it is unclear whether HIV affects the extracardiac vascular system. Ascending aortic aneurysms are associated with increased risk for dissection and rupture. It is possible that increased inflammation resulting from HIV may increase the risk for dilatation. To date, no large studies have been conducted evaluating dilatation of the aortic root and ascending aorta in people with HIV. The aim of this study is to compare the prevalence and features of ascending aortic dilatation in men with HIV (HIV+) and without HIV (HIV-) in the Multicenter AIDS Cohort Study (MACS).
Methods: 1179 MACS participants underwent complete echocardiograms. Linear regression was performed to assess the association between HIV serostatus and aortic diameters indexed for body surface area (BSA) at the aortic root and supravalvular levels, after adjusting for potential confounders. The multivariable model adjusted for age, race/ethnicity, MACS site, enrollment period (pre/post 2001), atherosclerotic risk factors (systolic blood pressure, medications to treat hypertension, smoking history, diabetes, total cholesterol level, high density lipoprotein level) and statin use.
Results: We included 653 HIV+ men (mean age 54.6 years, 47.8% white, 32.6% black, 16.8% diabetic, 13.0 pack-year smoking history) and 526 HIV- men (mean age 60.4 years, 69.0% white, 21.7% black, 11.8% diabetic, 12.5 pack-year smoking history). After adjusting for the aforementioned covariates and indexing for BSA, aortic root (p<0.01), sinotubular junction (p<0.01), and ascending aorta (p<0.001) were all significantly larger in HIV+ compared to HIV- men. There was no significant difference in aortic root annulus size (>500 cells/mm compared to men with CD4 counts <500 cells/mm, compared to men with CD4 counts <200 cells/mm, prior to initiating antiretroviral therapy (p=0.05).
Conclusion: To our knowledge this is the first study to demonstrate an independent association between HIV serostatus and ascending aortic dilatation, even after controlling for traditional cardiovascular risk factors, which may have implications for ongoing surveillance and management.

Table 1. Mean adjusted differences* in indexed aortic diameters in men with compared to those without HIV

<table>
<thead>
<tr>
<th>Difference Measure</th>
<th>Mean Difference in aortic diameter (cm²/m²)</th>
<th>Mean difference in aortic root (cm³/m²)</th>
<th>Mean difference in sinotubular junction (cm²/m²)</th>
<th>Mean difference in ascending aorta (cm³/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>0.02 [-0.01, 0.05]</td>
<td>0.04 [0.01, 0.06]</td>
<td>0.04 [0.01, 0.06]</td>
<td>0.05 [-0.02, 0.07]</td>
</tr>
<tr>
<td>Constant (mean)</td>
<td>-1.48</td>
<td>1.62</td>
<td>1.38</td>
<td>1.41</td>
</tr>
</tbody>
</table>

* Adjusted for age, race/ethnicity, MACS site, enrollment period (pre/post 2001), atherosclerotic risk factors (systolic blood pressure, medications to treat hypertension, smoking history, diabetes, total cholesterol level, and high density lipoprotein level) and statin use.

654 PREVALENCE OF PULMONARY HYPERTENSION IN HIV-INFECTED PATIENTS AND REDUCED OUTCOME
Nico Reinsch1, Hendrik Streeck2, Meinhard Mende2, Till Neumann2, Norbert H. Brockmeyer1, Jan Kehrmann3, Dirk Schadendorf3, Stefan Esser2
1Alfred Krupp Hospital, Essen, Germany, 2University of Duisburg-Essen, Essen, Germany, 3University Hospital of Duisburg-Essen, Essen, Germany, 4Ruhr-University Bochum, Bochum, Germany
Background: The epidemiology and prognostic impact of increased pulmonary pressure among HIV-infected individuals in the antiretroviral therapy era is not well described. We therefore examined the prevalence and outcomes of increased echocardiographic pulmonary pressure in HIV-infected individuals.
Methods: This study evaluated subjects from the HIV-HEART study. The HIV HEART study (HIVH) is an ongoing prospective observational cohort study in the German Ruhr Area starting in 2004 to assess the rate of cardiovascular disease (CVD). This longitudinal analysis included HIV+ patients with up to 12 years of follow-up. Echocardiography with reported pulmonary artery systolic pressure (PASP) and tricuspid annular plane systolic excursion (TAPSE) as sign of right heart dysfunction was obtained in almost all patients.
Results: PASP was documented in 1064 subjects. The mean follow-up was 8.9 ±4.1 years. Pulmonary hypertension (PH) > 35mmHg was detected in 157/1064 patients (14.8%). Of these, 81 (5%) were asymptomatic and 76 (49%) patients presented with dyspnoe. TAPSE < 20mm as a sign of right heart dysfunction. PASP was lower in patients without PH compared to patients with PASP > 35mmHg but without symptoms and patients withand PASP > 35mmHg and

653 AORTIC DILATATION IS PRESENT AMONG MEN WITH HIV
Anum S. Minhas1, Bin Liu1, Henrique Doria De Vasconcellos, Sabina A. Haberlen1, Matthew J. Feinstein1, Valentina Stosor1, Matthew Budoff1, Kara W. Chew1, Jared Magnani1, Todd T. Brown1, Sean Altekruse1, Wendy Post1, Joao Lima1, Katherine Wu1
1Johns Hopkins University, Baltimore, MD, USA, 2Northwestern University, Chicago, IL, USA, 3University of California Los Angeles, Los Angeles, CA, USA, 4University of Pittsburgh, Pittsburgh, PA, USA, 5National Heart, Lung, and Blood Institute, Bethesda, MD, USA
Background: It is unknown whether HIV infection remains an independent risk factor for subclinical myocardial disease in the era of combination antiretroviral therapy (cART). We assessed differences in cardiac structure and function by cardiac magnetic resonance (CMR) imaging among people with (HIV+) and without HIV (HIV-) after controlling for potential confounders.
Methods: 432 participants (71% men, 63% HIV+) in the Multicenter AIDS Cohort Study, AIDS Linked to the Intravenous Experience study, and Women's Intergender HIV Study, aged 40-70 years, underwent CMR for biventricular volumes and mass, left atrial (LA) volumes, and left ventricular (LV) and LA strain. CMR with contrast and T1 mapping comprehensively assessed scar patterns and burden.
Results: Median participant age was 55 years, 47% smokers, 53% hypertensive, 13% diabetic, and 59% dyslipidemic. Prevalence of stimulant, opioid and marijuana use was 39%, 32%, and 44%. Among HIV+ persons, 89% were on cART, 74% had viral suppression (HIV RNA<50 copies/ml), and most recent median CD4 count was 610/µl (IQR 398-826). For most characteristics, HIV- and HIV+ participants were similar. Median LV ejection fraction (EF) was normal and similar by HIV serostatus (73% for HIV- vs. 72% for HIV+, p=0.53, n=2 with LVEF<40%) as were right ventricular EF, biventricular volumes and masses. Focal myocardial scar prevalence was also similar (32% vs. 37%, p=0.38) with similarly low median scar extents (4.1 vs. 5.0 grams, p=0.46). The pattern of myocardial scar was predominantly non-ischemic. An ischemic scar pattern was found among only 3% of HIV- vs. 5% of HIV+ (p=0.05). Indices of nonischemic diffuse fibrosis did not differ by HIV serostatus. After adjusting for demographics, parent cohort, education, cardiac risk factors, and drug use, LA volumes (maximal, maximal and pre-atrial) were the only CMR parameters that differed significantly by HIV serostatus and were ~10% larger for HIV+ (Table). Among HIV+ people, LA volumes did not differ by viral suppression status.
Conclusion: Among a comparable group of HIV- and HIV+ people with similar characteristics and patterns of recreational substance use, prevalent ventricular disease was rare and ventricular indices did not differ by HIV serostatus. However, HIV+ serostatus was independently associated with larger LA phasic volumes, possibly reflecting diastolic dysfunction and predisposal to atrial arrhythmias.
655 CARDIAC EVENTS IN HIV-INFECTED PATIENTS WHO USE TENOFOVIR ALAFENAMIDE (TAF)
Brent Appelman1, Guido Van Den Berk1, Marijke De Regt1, Narda Van Der Meche1, Daoud Ait Moha2, Pieter Oosterhof2, Joost Vanhommerig1, Kees Brinkman1, OLVG, Amsterdam, Netherlands

Background: Although cardiac events (CEs) were not reported as side effects of TAF in registration trials, we observed some new CEs in HIV positive patients who started TAF. We retrospectively studied all CEs in our HIV cohort, with special focus on the use of TAF compared to tenofovir disoproxil fumarate (TDF).

Methods: All OLVG patients receiving cART between January 1st, 2016 and May 31st, 2018 were selected and allocated to 3 mutually exclusive groups according to cART component prior May 31st, 2018. Patients that used TAF (TAF), patients that used TDF but never used TAF (TDF) and patients without ever using a tenofovir cART (NT). The start date was registered as the first day of treatment with the group defining component of tenofovir; for the NT group this was the date of initial cART start. CEs were defined as myocardial infarction, cardiomyopathy, arrhythmia or angina pectoris. CEs-free survival was estimated using Kaplan-Meier analysis. Hazard ratios (HR) for CEs were adjusted for previous cardiac history, BMI, gender, age per quartile and smoking using Cox regression analysis.

Results: We included 2985 patients: 1170 in TDF, 1537 in TAF and 278 in NT. Median follow-up was 2.2 years (IQR: 1.4-2.6) for TAF, 7.0 years (IQR: 4.0-9.9) for TDF and 9.0 years (IQR: 3.5-17.0) for NT. In TDF (8.5%); CEs were reported, in TAF (32.8%) and in NT (11.0%). Cardiac history was more frequent in TAF vs. TDF, odds ratio: 1.9 (95% CI: 1.3-2.9; P<0.001) and in TAF vs. NT, HR: 2.8 (95% CI: 1.6-5.0; P<0.001). After adjusting for covariates, the HR of CEs in TAF vs. NT decreased to 3.9 (95% CI: 1.5-9.8; P=0.005) and in TAF vs. TDF to 1.9 (95% CI: 1.0-3.6; P=0.034).

Conclusion: The occurrence of CEs in TDF and in NT were significantly different compared to TAF. In contrast to registration trials, an older population with more cardiac history might explain our unexpected observation in this real-life cohort. Since follow-up of TAF was short and the rate of CEs low, confirmation of our observation in larger cohorts is necessary, to better advise about TAF use in elderly patients with a history of CEs.

656 INPATIENT OUTCOMES FOR HIV-INFECTED PATIENTS HOSPITALIZED FOR ACUTE CORONARY SYNDROME
Monica Parks1, Eric A. Secemsky2, Robert W. Yeh2, Changyu Shen2, Eunhee Choi1, Dhruv Kazi1, Priscilla Hseue1
1University of California San Francisco, San Francisco, CA, USA, 2Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: HIV-infected adults have excess morbidity and mortality from cardiovascular disease. Differences in the presentation and management of acute coronary syndromes (ACS) in this population may drive these findings. We hypothesized that HIV-infected adults admitted with ACS are less likely to receive percutaneous coronary intervention and have greater adverse outcomes compared with uninfected patients.

Methods: This was a retrospective cohort study using inpatient claims data from Symphony Health, a nationwide data warehouse. All adults admitted between January 1st, 2014 and December 31st, 2016 with ACS were included. Patient characteristics and outcomes were defined by ICD-9 or ICD-10 billing codes. Logistic regression adjusted for clinical characteristics was used to evaluate outcomes.

Results: A total of 1,125,126 patients were included, of whom 6,612 (0.59%) had HIV. The HIV-infected group was younger (57 vs 67 years old, p<0.0001) and had a higher burden of medical comorbidities such as diabetes and substance abuse (p<0.0001). Rates of ST-elevation myocardial infarction were similar between groups. In adjusted analysis, HIV-infected individuals were less likely to receive coronary angiography (31.6% vs 33.4%, OR 0.85, 95% CI 0.80-0.90, p<0.0001) or drug eluting stents (16.5% vs 18.2%, OR 0.88, 95% CI 0.82-0.94, p=0.0001). They also had significantly higher inpatient mortality (5.5% vs 5.3%, OR 1.28, 95% CI 1.15-1.43, p<0.0001) despite having fewer complications such as acute heart failure (19.9% vs 23.2%, OR 0.82, 95% CI 0.76-0.88, p<0.0001) or major bleeding (2.8% vs 3.5%, OR 0.82, 95% CI 0.70-0.95, p=0.0074).

Conclusion: Among contemporary HIV-infected patients hospitalized with acute coronary syndrome, disparities in treatment persist, with less use of percutaneous coronary interventions. Further attention is needed in order to improve the use of guideline-based therapies with the goal of optimizing the care and outcomes among persons living with HIV.

Table 1: Inpatient Procedures and outcomes

<table>
<thead>
<tr>
<th>Procedure</th>
<th>HIV (n=6,612)</th>
<th>HIV+ (n=1,218,338)</th>
<th>Adjusted*</th>
<th>v value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedures</strong></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Balloon angioplasty</td>
<td>177 (2.7%)</td>
<td>17,730 (1.68%)</td>
<td>1.96 (1.07-3.6)</td>
<td>0.0333</td>
</tr>
<tr>
<td>Bare metal stent</td>
<td>327 (4.8%)</td>
<td>31,595 (3.0%)</td>
<td>1.16 (1.01-1.31)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Drug eluting stent</td>
<td>593 (9.3%)</td>
<td>59,514 (5.7%)</td>
<td>1.09 (0.83-1.4)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Left heart catheterization</td>
<td>2,092 (32.6%)</td>
<td>217,327 (21.8%)</td>
<td>0.86 (0.70-1.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Transcatheter catheter angioplasty</td>
<td>204 (0.3%)</td>
<td>2,077 (0.2%)</td>
<td>3.64 (2.19-6.15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient mortality</td>
<td>509 (5.2%)</td>
<td>50,197 (5.0%)</td>
<td>1.28 (1.15-1.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>58 (0.9%)</td>
<td>5,919 (0.6%)</td>
<td>0.83 (0.68-1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>1,078 (16.2%)</td>
<td>103,915 (10.0%)</td>
<td>1.09 (1.07-1.11)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Major bleed</td>
<td>144 (2.2%)</td>
<td>14,409 (1.4%)</td>
<td>0.02 (0.00-0.49)</td>
<td>0.0074</td>
</tr>
<tr>
<td>Stroke</td>
<td>155 (2.4%)</td>
<td>15,533 (1.5%)</td>
<td>0.08 (0.01-0.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, substance use, medical comorbidities.
Background: The risk of atherosclerotic cardiovascular disease (CVD) is increased amongst people living with HIV in the global north. However, there is scant data on the contributions of HIV infection and its treatment on atherosclerosis in sub-Saharan Africa.

Methods: We conducted an analysis of baseline data from the Ugandan Noncommunicable Diseases and Aging Cohort Study, which is a longitudinal cohort consisting of PLWH older than 40 years of age on antiretroviral therapy (ART) for at least 3 years, and a population-based control group of HIV-uninfected persons matched by age and sex. We conducted carotid ultrasonography and collected CVD risk factor data. Our outcome of interest was carotid plaque at enrollment, defined as a thickness of >1.5 mm measured from the intima-lumen interface to the media- adventitia interface. We fit multivariable logistic regression models to estimate adjusted correlates of plaque, including HIV infection and traditional cardiovascular risk factors.

Results: Carotid ultrasounds were completed among 150 (49%) PLWH and 155 (51%) HIV-uninfected individuals. Among PLWH, median CD4 count was 433 (IQR, 336-559) at enrollment and the median duration of ART was 10 years. The crude prevalence of carotid plaque was 8.4% (13/155) in PLWH and 3.3% (5/150) in HIV-uninfected controls. HIV infection (aOR 1.99; 95% CI, 1.39-3.30), active smoking (aOR 2.11; 95% CI, 1.01-4.38) and untreated hypertension (aOR 4.16; 95% CI, 1.65-10.48) were associated with an increased odds of carotid plaque. Physical activities of moderate intensity (aOR 0.10; 95% CI, 0.01-0.87) and vigorous intensity (aOR 0.21; 95% CI, 0.08-0.52) were associated with lower odds of carotid plaque.

Conclusion: The prevalence of carotid plaque was greater among PLWH compared with age- and sex-matched HIV-uninfected comparators in southwestern Uganda. Other correlates of plaque included smoking and untreated hypertension. These data suggest that treated HIV infection might predispose PLWH in rural Africa to increased risk of atherosclerosis. Future work should explore the mechanisms underlying this observation, and whether improved treatment of hypertension and lifestyle modifications might reduce atherosclerotic burden among PLWH in the region.

MAJOR VASCULAR EVENTS IN ADULTS ON ART IN A SOUTH AFRICAN HIV MANAGEMENT PROGRAMME

Johannes P. Mouton, Renee De Waal, Morna Cornell, Gary Maartens, Karen Cohen

University of Cape Town, Cape Town, South Africa; Centre for Infectious Disease Epidemiology and Research, Cape Town, South Africa

Background: Studies from high-income settings found increased risk of major vascular events (MVEs) in people living with HIV (PLWH). Data on MVE incidence in PLWH in Africa are limited. We aimed to describe incidence of MVEs and factors associated with MVEs in PLWH on antiretroviral therapy (ART) in the Aid for AIDS (AfA) private sector cohort.

Methods: This was a cohort analysis of adults (≥18 years) starting ART through AfA from 1 January 2011 to 30 September 2018. We defined MVE as hospitalisation claims for stroke, acute coronary syndrome, or coronary revascularisation procedure. We excluded hospitalisations with evidence for concomitant infectious or neoplastic diseases that may mimic stroke presentations. We calculated MVE incidence. We explored associations with MVE using Cox regression. We identified hypertension, diabetes, and dyslipidaemia from hospitalisation claims, drug claims, and laboratory results, and included these as time-updated variables.

Results: We included 125,978 patients, of whom 75,485 (60%) were women, with total follow-up 320,176 person-years. At entry, median (IQR) age was 38 [33-45] years, CD4 count 276 [140-446] cells/µL, and viral load 4.4 [2.6-5.1] log$_10$ copies/mL. 5,344 patients (4.2%) died. Hypertension was present in 18%, diabetes in 8%, and dyslipidaemia in 9%. Efavirenz/nevirapine with two nucleoside reverse transcriptase inhibitors (NRTIs) was in use for 89% of person-time.

There were 788 first MVEs: 457 (58%) stroke, and 331 (42%) acute coronary syndromes and revascularisation procedures. Incidence of MVE was 2.5 per 1,000 person-years follow-up. In the Cox regression model, adjusted for other variables, MVE was associated with older age, male sex, longstanding HIV infection, lower CD4 count at first ART at ART claim, unsuppressed viral load at first ART claim, hypertension, diabetes, and dyslipidaemia. In addition, ART regimens consisting of two NRTIs with a protease inhibitor, or two NRTIs with ritonavir/efavirenz were associated with increased risk of MVE, versus a regimen of two NRTIs with efavirenz/nevirapine.

Conclusion: In this young, mostly female, African cohort, MVE incidence was 2.5 per 1,000 person-years. Background incidence data from this setting is lacking. Stroke predominated, in contrast to high-income settings, where
coronary disease is more common. The MVE associations with specific ART regimens we identified deserve further study.

### 660 ASSOCIATION OF HYPERTENSION AND ART USE IN A POPULATION-BASED COHORT, RAKAI, UGANDA

Grace Monge-Bua1, Victor Ssempijja2, Anthony Ndyabanob1, Doreen Nabakulub3, Jesca Basimur4, Edward Kankada2, Fred Naluigod2, Gertrude Nakigudj, Joseph Kagayji3, Larry W. Chang1, Ronald H. Gray4, Maria Wawer4, Godfrey Kigozi4, Steven J. Reynolds1, 4

1Rakai Health Sciences Program, Kalisizo, Uganda, 2Leidos Biomedical Research, Inc, Frederick, MD, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 4University of Pittsburgh, Pittsburgh, PA, USA, *University of California Los Angeles, Los Angeles, CA, USA, 4National Heart, Lung, and Blood Institute, Bethesda, MD, USA

**Background:** People with HIV (PWH) have higher risks for myocardial scar, heart failure, and sudden cardiac death compared with HIV-uninfected (HIV-) persons. However, little is known regarding the relative burden and characteristics of ventricular ectopy and ventricular tachycardia (VE/VT) among PWH.

**Methods:** We evaluated ventricular arrhythmias among men with HIV (MWH) and HIV- men in the Multicenter AIDS Cohort Study (MACS). We included 666 MWH (mean age 54 ± 11 years, 51.3% white, 31.6% black, 46.2% current smokers, 15.6% diabetic, last CD4 count mean 720 ± 308, and 80.7% with last HIV RNA (viral load) undetectable) and 586 HIV- men (mean age 60.5 ± 11.7 years, 72.3% white, 19.2% black, 54.4% current smokers, 14.3% diabetic) who underwent continuous ambulatory electrocardiographic monitoring (ZioPatch® by iRhythm) for a median of 12.7 days (interquartile range 5.7-13.8 days). The primary endpoint was the occurrence of any VE/VT, comparing PWH vs. HIV-.

**Results:** One participant had sustained VT and 43 participants had VT lasting ≥4 beats per 24 hours. Additional analyses of primary and secondary endpoints were performed among PWH by CD4 count and viral load.

**Conclusion:** People with HIV have higher risks for myocardial scar, heart failure, and sudden cardiac death compared with HIV-uninfected (HIV-) persons. However, little is known regarding the relative burden and characteristics of ventricular ectopy and ventricular tachycardia (VE/VT) among PWH. Further studies are needed to elucidate the mechanism for prolonged ART use and hypertension are needed.

### 661 VENTRICULAR ARRHYTHMIA PREVALENCE AND FREQUENCY: THE MULTICENTER AIDS COHORT STUDY

Matthew J. Feinstein1, Alexander Meyer1, Frank J. Palella1, Hiroshi Ashikaga1, Sabina A. Haberlin1, Jared Magnani1, Matthew Budoff1, Kathryn Berlacher1, Sean Altekruse1, Gypsyamber D’Souza1, Todd T. Brown1, Katherine Wu1, Wendy Post1

1Northwestern University, Chicago, IL, USA, 2The Ohio State University, Columbus, OH, USA, 3Johns Hopkins University, Baltimore, MD, USA, 4University of Pittsburgh, Pittsburgh, PA, USA, 5University of California Los Angeles, Los Angeles, CA, USA, 6National Heart, Lung, and Blood Institute, Bethesda, MD, USA

**Background:** Ventricular arrhythmia (VA) prevalence and frequency have been well studied in HIV-infected persons (PWH) in clinical settings; however, VA are poorly understood in the community setting.

**Methods:** We conducted a cross-sectional study among HIV infected adults (35–49 years old on ART in the Rakai Community Cohort Study (RCCS) using 18th survey data conducted from August 2016 to May 2018. Systolic and diastolic blood pressure was measured twice, averaged, and classified as: hypertension (stage 1): Systolic blood pressure (BP) ≥ 140mmHg and/or diastolic BP ≥ 90mmHg; Severe hypertension (stage 2): Systolic BP> 160mmHg and/or diastolic BP > 100mmHg; Hypertension significantly increased beyond 5 years of ART treatment (Stage 1 aORs=1.55 (95%CI=1.07-2.26); stage 2 aOR=1.70 (95% CI 0.97- 3.01) and stage 3 at aOR=2.32 (95% CI 1.05-5.16).

**Conclusion:** The risk of developing hypertension significantly increases after 5 consecutive years of ART treatment. Routine screening for hypertension should be incorporated into clinical care of PLHIV. Further studies to elucidate the mechanism for prolonged ART use and hypertension are needed.
662 ASSOCIATION BETWEEN HIV AND THE PREVALENCE OF ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Ngozi C. Osuji, Sabina A. Haberlen, Hiroshi Ashikaga, Todd T. Brown, Matthew J. Feinstein, Mallory Witt, Lawrence Kingsley, Sean Altekruse, Katherine Wu, Wendy Post

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, Johns Hopkins University School of Medicine, Baltimore, MD, USA, Northwestern University, Chicago, IL, USA, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA, University of Pittsburgh, Pittsburgh, PA, USA, National Health, Lung, and Blood Institute, Bethesda, MD, USA

Background: People living with HIV are at increased risk for cardiovascular disease (CVD). The association between HIV serostatus and atrial arrhythmias is incompletely understood. This study was conducted to study the relationship between HIV and atrial fibrillation/flutter (AF/AFL).

Methods: HIV infected (HIV+) and uninfected (HIV-) participants in the 4-city Multicenter AIDS Cohort Study (MACS) were assessed for AF/AFL by standard resting 12 lead electrocardiograms (EKG) and/or ambulatory EKG monitoring using Zio patch (iRhythm) in 2016-17. Multivariable logistic regression was used to evaluate the association between the composite outcome of AF/AFL and the primary exposure of HIV infection. Associations were adjusted sequentially, first for demographic variables (age, race, and study center), and second for both demographic and CVD risk factors (body mass index, cumulative pack year of smoking, cocaine use since last visit, use of medications to treat hypertension or diabetes, heavy alcohol use (>13 drinks/week), fasting glucose level and systolic BP).

Results: The sample included 1669 men; HIV+ men were younger than HIV- men (median 55.5 vs 61.7 years, p<0.001) and were more likely to be African-American (30.6% vs 17.9%, p<0.001). Most HIV+ men (80.0%) had detectable plasma viral load (<20 copies/mL). A positive Zio patch was worn by 2 men for a median of 13.0 days (IQR 5.9-14.0). AF/AFL was present in 12 (1.3%) HIV+ men and 25 (3.2%) HIV- men. There was only 1 case of AF/AFL in African-Americans, and 36 cases in Caucasians (2.7% vs 97.3%, p<0.001). Although there was a lower odds of AF/AFL among HIV+ compared to HIV- men in unadjusted analyses (odds ratio, 0.41; 95% confidence interval [CI], 0.03-0.82; p=0.012), there was no association between the odds of AF/AFL and HIV serostatus after adjusting for age, race, and study center (odds ratio, 0.79; 95% CI, 0.38-1.63; p=0.53) and after further adjustment for CVD risk factors (odds ratio, 0.88; 95% CI, 0.34-2.24; p=0.79). There was a 6% increase in the odds of AF/AFL for each yearly increase in age after adjusting for demographics and CVD risk factors (odds ratio, 1.06; 95% CI 1.00-1.03, p<0.001), regardless of HIV serostatus.

Conclusion: HIV serostatus was not associated with prevalent AF/AFL in this cohort of HIV+ men with suppressed viral replication. The prevalence of AF/AFL was low, strongly associated with aging, and rare in African-American men.

663 MitoQ ATTENUATES EX Vivo PROATHEROGENIC EFFECTS OF HIV PLASMA IN CHRONIC TREATED HIV

Eleni Ritou, Rachel Heymans, Theodoros Kelesidis

University of California Los Angeles, Los Angeles, CA, USA

Background: The mechanisms that drive atherosclerotic cardiovascular disease (CVD) in treated HIV remain unclear. (Pre)clinical studies have shown that the antioxidant MitoQ improves vascular endothelial function by reducing reactive oxygen species production by mitochondria, but its effects in HIV-CVD are unknown. We used an established model of arterial wall to assess ex vivo the impact of MitoQ on early mechanisms of atherogenesis in the presence of plasma from HIV+ individuals on potent antiretroviral therapy (ART).

Methods: Human umbilical vein endothelial cells (HUVECs) were pretreated with MitoQ or vehicle control at 200 nM for 24 hours. Peripheral blood mononuclear cells from healthy donors (n=10) were added to HUVEC for 24 hours on type I collagen gels to undergo transendothelial migration (TEM) and form foam cells (monocyte-derived foam cell formation (MDFCF)) in the presence of pooled plasma (PMID: 28926407). Pooled plasma was isolated from healthy (18-40 years old) and HIV+ (>40 years old) males with no known inflammatory comorbidities other than HIV or risk factors for CVD and on stable potent ART. Flow cytometry assessed MDFCF (BDODIPY signal) and TEM. (Un)paired t-tests were used for statistical comparison between and within compared groups.

Results: When media containing HIV+ compared to HIV- plasma was added to HUVECs pretreated with vehicle, a significantly increased proportion of monocytes underwent TEM (mean 1.6 fold increase) and CD33+ macrophages inside the collagen gel had increased lipid content per cell (mean 2.4 fold increase in ∆MFI BODIPY) (p<0.05). When media containing HIV+ compared to HIV- plasma was added to HUVECs pretreated with MitoQ, a significantly increased proportion of monocytes underwent TEM (mean 1.2 fold increase) and CD33+ macrophages inside the collagen gel had a mean 1.3 fold increase in ∆MFI BODIPY (p<0.05). In collagen gels treated with HIV+ plasma, pretreatment of HUVEC with MitoQ attenuated both TEM and MDFCF compared to vehicle control (p<0.05 for all comparisons).

Conclusion: MitoQ attenuated proatherogenic effects of HIV-plasma from patients on potent ART with no clinical CVD in ex vivo model of arterial wall. The role of MitoQ in CVD in chronic treated HIV needs to be further studied in vivo.

664 HIV AND AGEING: PRIMARY AND SECONDARY PREVENTION OF CAD AMONG PLHIV

Gaetano Marrone, Olof Elvstrand, Anders Sönnerborg

Karolinska University Hospital, Stockholm, Sweden, Lund University, Lund, Sweden

Background: With the introduction of combined antiretroviral therapy for HIV patients, the clinical focus has shifted from AIDS-related opportunistic infections to age-related co-morbidities, specifically cardiovascular disease (CVD). As of 2019, there are approximately 7,760 People living with HIV (PLHIV) in Sweden. This study aims to assess the incidence of MI and stroke among PLHIV in Sweden, as well as their the socio-demographic and biological risk factors. Furthermore, this study aims to compare patients with any CVD with and without HIV with regard to baseline and presentation characteristics and mortality.
For this retrospective cohort study, a total of 6,987 PLHIV were included from the Swedish National HIV Registry database and linked to the National patient register and the cause of death register to gather information on the incidence of MI or stroke. To determine whether HIV was a risk factor for mortality following a CVD event, data from an existing national quality registry for coronary care was merged with the Swedish National HIV Registry. As many as 751,889 patients were included for analysis.

Results: The incidence of MI and stroke among PLHIV in Sweden was 5.2%. The multivariable Cox regression model revealed that the hazard of MI or stroke among PLHIV increased, compared to patients aged <30 years old, by 90% (95% CI: 1.3-2.8, p=0.001) among patients 31-40 years old, 2.9 times (95% CI: 2.0-4.3, p<0.001) among patients 41-50 years old, and almost 9-fold (95% CI: 6.1-12.5, p<0.001) among patients >50 years old. Patients who injected drugs had a double hazard (95% CI: 1.4-2.8, p<0.001) compared to patients infected through heterosexual intercourse, while patients infected in Sweden had a 40% higher hazard (95% CI: 1.0-1.8, p=0.020). A multivariable Cox regression model assessing risk factors for mortality following a CVD event showed that HIV positive patients had a 67% (95% CI: 0.93-3.02, p=0.008) higher risk of mortality than HIV negative patients.

Conclusion: The increased incidence of MI in PLHIV compared to the general population of Sweden calls for an increased focus on prevention of CVD in PLHIV. Given that older age is a risk factor for MI among PLHIV, CVD prevention efforts targeting older PLHIV should be scaled up. Moreover, the increased risk of mortality among HIV patients following a CVD event highlights the need for secondary prevention following a CVD event.

Results:

- The incidence of MI and stroke among PLHIV in Sweden was 5.2%.
- The multivariable Cox regression model revealed that the hazard of MI or stroke among PLHIV increased, compared to patients aged <30 years old, by 90% (95% CI: 1.3-2.8, p=0.001) among patients 31-40 years old, 2.9 times (95% CI: 2.0-4.3, p<0.001) among patients 41-50 years old, and almost 9-fold (95% CI: 6.1-12.5, p<0.001) among patients >50 years old. Patients who injected drugs had a double hazard (95% CI: 1.4-2.8, p<0.001) compared to patients infected through heterosexual intercourse, while patients infected in Sweden had a 40% higher hazard (95% CI: 1.0-1.8, p=0.020).
- A multivariable Cox regression model assessing risk factors for mortality following a CVD event showed that HIV positive patients had a 67% (95% CI: 0.93-3.02, p=0.008) higher risk of mortality than HIV negative patients.

Conclusion:

- The increased incidence of MI in PLHIV compared to the general population of Sweden calls for an increased focus on prevention of CVD in PLHIV.
- Given that older age is a risk factor for MI among PLHIV, CVD prevention efforts targeting older PLHIV should be scaled up.
- Moreover, the increased risk of mortality among HIV patients following a CVD event highlights the need for secondary prevention following a CVD event.

Table 1: Incremental cost-effectiveness of statins for primary prevention of CVD among PLHIV over a 20-year horizon

<table>
<thead>
<tr>
<th>Strategy</th>
<th>IMR per 1000 person-years</th>
<th>ICER per 1000 person-years</th>
<th>CVD, per 1000 person-years</th>
<th>Total QALYs</th>
<th>Incremental QALYs</th>
<th>ICER per QALY gained ($)</th>
<th>IRR per QALY gained ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No statins</td>
<td>5.6</td>
<td>0.35</td>
<td>2.7</td>
<td>107,710</td>
<td>0.028</td>
<td>79,000</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>5.6</td>
<td>6.2</td>
<td>2.2</td>
<td>107,710</td>
<td>0.028</td>
<td>79,000</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>5.6</td>
<td>0.35</td>
<td>2.7</td>
<td>107,710</td>
<td>0.028</td>
<td>79,000</td>
<td></td>
</tr>
<tr>
<td>Pravastatin vs. No statins</td>
<td>0.028</td>
<td>79,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitavastatin vs. No statins</td>
<td>0.028</td>
<td>79,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: At a cost-effectiveness threshold of $100,000/QALY gained, pravastatin was projected to be cost-effective compared with no statin. However, pitavastatin was not cost-effective compared with pravastatin as the incremental benefit was modest.

665 COST-EFFECTIVENESS OF STATIN USE IN HIV-POSITIVE PERSONS IN THE USA: THE D:A:D STUDY

David C. Boettiger1, Anthony Newall2, Andrew N. Phillips3, Lene Ryom4, Peter Reiss1, Eran Bendavid6, Fabrice Bonnet7, Rainer Weber8, Wafaa M. El-Sadr9, David C. Boettiger1, Anthony Newall2, Andrew N. Phillips3, Lene Ryom4, Peter Reiss1, Eran Bendavid6, Fabrice Bonnet7, Rainer Weber8, Wafaa M. El-Sadr9, for the D:A:D Study Group

1Kirby Institute, Sydney, NSW, Australia, 2University of New South Wales, Sydney, NSW, Australia, 3University College London, London, UK, 4CHIP, Department of Infectious Diseases, Copenhagen, Denmark, 5Academic Medical Center, Amsterdam, Netherlands, 6Stanford University, Stanford, CA, USA, 7University of Bordeaux, Bordeaux, France, 8University Hospital Zurich, Zurich, Switzerland, 9ICAP at Columbia University, New York, NY, USA, 10University of California San Francisco, San Francisco, CA, USA, 11Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: People living with HIV (PLHIV) have an elevated risk of atherosclerotic cardiovascular disease (CVD) compared to people without HIV. Expanding statin use for the primary prevention of CVD may help alleviate this burden. However, the choice of statin in the context of antiretroviral therapy is challenging. Pravastatin and pitavastatin are preferred agents because they improve cholesterol levels in PLHIV without interacting substantially with antiretroviral therapy. They are also more expensive than most statins. We evaluated the cost-effectiveness of using pravastatin and pitavastatin regardless of cholesterol level for the primary prevention of CVD among PLHIV aged 40-75 years and not currently using lipid-lowering therapy.

Methods: We developed a model that randomly selected (with replacement) individuals from the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. The model simulated each individual’s probability of experiencing CVD over 20 years. We evaluated: 1) treating no one with statins; 2) treating everyone with pravastatin 40mg/day (drug cost $236/year); and 3) treating everyone with pitavastatin 4mg/day (drug cost $2,828/year). Direct medical costs (in 2019 US dollars) and quality-adjusted life-years (QALYs) were assigned in annual cycles and discounted at 3% per year. We assumed the US healthcare sector perspective. Comprehensive sensitivity and scenario analyses were undertaken.

Results: PLHIV receiving pravastatin accrued 0.028 additional QALYs compared with PLHIV not receiving a statin, at an incremental cost of $2,195, giving an incremental cost-effectiveness ratio (ICER) of $79,000/QALY gained. PLHIV receiving pitavastatin accumulated 0.008 additional QALYs compared with PLHIV using pravastatin, at an additional cost of $26,864, giving an ICER of $3,160,000/QALY gained. These findings were most sensitive to the quality-of-life decrement associated with taking an additional daily pill, statin costs and statin efficacy. In scenario analyses, whereby the treatment strategies were only administered to PLHIV at higher risk of CVD, our ICERs improved but did not alter the main conclusions (Table).

Conclusion: At a cost-effectiveness threshold of $100,000/QALY gained, pravastatin was projected to be cost-effective compared with no statin. However, pitavastatin was not cost-effective compared with pravastatin as the incremental benefit was modest.

666 DEPRESSION COGNITIVE BEHAVIORAL THERAPY TO IMPROVE HIV-CVD RISK: A PILOT RCT

Samir K. Gupta1, Ziyue Liu1, James E. Slaven1, Brittany Polanka1, Matthew Freiberg1, Jesse C. Stewart1

1Indiana University, Indianapolis, IN, USA, 2Vanderbilt University, Nashville, TN, USA

Background: Depression is associated with an increased risk of cardiovascular disease in the HIV+ population. We hypothesized that reducing depressive symptoms would improve cardiovascular risk in HIV.

Methods: We conducted a single-center, randomized (1:1), controlled, parallel-group, assessor-blinded trial comparing Beat the Blues (BtB) — an evidence-based, 8-session, internet cognitive behavioral therapy for depression — with usual care (UC) in HIV+ patients receiving virologically-suppressive ART (VL <75c/mL) and with Patient Health Questionnaire (PHQ)-9 scores ≥10. The primary endpoint was change in brachial artery flow-mediated dilation (FMD) at 12 weeks. Secondary endpoints were FMD change at 24 weeks and inflammation, coagulation and metabolic biomarker changes at 12 and 24 weeks. Changes in endpoint comparisons were performed using Student t-tests with a p-value <0.05 considered statistically significant. Pre-specified comparisons were also performed for those completing at least 6 sessions in the BtB arm (BtB6-8). FMD comparisons were further adjusted for baseline depression symptoms using ANOVA.

Results: 34 patients were randomized (17% women, 67% Black, mean age 43.1 yrs, PHQ-9 15.6, Symptom Checklist Depression Scale (SCL)-20 2.2, 69% on antidepressants); 15 in the BtB arm completed at least 6 sessions. Table 1 shows the study results. Mean reductions in PHQ-9 were significantly greater at 12 and 24 weeks with BtB vs. UC; reductions in SCL-20 were significantly greater with BtB vs. UC at 24 weeks. Changes in FMD between arms were no different at 12 or 24 weeks. ANOVA models adjusting for Entry FMD, ART regimen, SCL-20, or antidepressant use or for changes in VL over the study period did not affect FMD comparisons, though significantly worse FMD at 12 weeks (but not 24 weeks) was now found in the BtB6-8 arm compared to UC. Significant reductions in sCD14 and sCD163 were found with BTB at 12 and 24 weeks. Changes in FMD between arms were no different at 12 or 24 weeks.
those who completed a majority of treatment sessions. Monocyte activation may also be reduced by depression treatment. These data support performing larger studies to determine the short and long term effects of depression treatment on HIV-CVD risk.

### 667 FAT GAINS OCCUR AFTER ART WITHOUT CHANGES IN METABOLIC RATE OR CALORIC INTAKE

Allison Ross Eckard1, Abdus Sattar2, Yao Yu1, Heather Y. Hughes1, Danielle Labbate1, Theresa D. Rodgers1, Julie C. Kosco2, Grace A. McComsey3

1 Medical University of South Carolina, Charleston, SC, USA, 2 Case Western Reserve University, Cleveland, OH, USA, 3 University Hospitals Cleveland Medical Center, Cleveland, OH, USA

**Background:** Increases in weight and fat gains with antiretroviral treatment (ART) are serious problems in people with HIV (PWH), but the pathogenesis is poorly understood. Some have suggested changes in resting metabolic rate (RMR) and/or caloric intake are responsible, but no data exists. We examined changes in RMR, oxygen consumption (VO2), and dietary intake and associations with changes in weight and body composition after ART initiation.

**Methods:** ART-naive PWH were prospectively enrolled and underwent a comprehensive clinical and laboratory assessment at baseline and at 6 and 12 months after ART initiation. Fasting RMR/VO2 and body composition were measured by indirect calorimetry and whole-body DXA, respectively. Nutrient intake was assessed by a registered dietician via 24-hour dietary recalls at each time point and analyzed using dietary analysis software. Changes in variables and associations were assessed using linear mixed effects models.

**Results:** 30 PWH were enrolled (mean age: 31 yrs, 77% male, 74% black; mean baseline CD4 444 cells/mm3; HIV RNA 267,148 copies/mL, BMI 28.6 kg/m2, RMR associations were assessed using linear mixed effects models. Changes in variables and slopes estimated pre- and post-switch weight over time, adjusting for age, sex, race, cohort site, HIV acquisition mode, calendar year, pre-switch ART class (NNRTI vs. PI), and CD4+ T cell count and BMI at the time of switch. We included interaction terms for sex, race, and age (<50 vs. >50) with regimen and time. **Results:** A total of 2,255 participants switched to an INSTI and had the required follow-up time; of these, 677 met viral suppression criteria and were included. At switch, median age was 50 years, BMI 26 kg/m2, and CD4+ count 916 cells/mm3; 33% were men, and 59% were white. Overall, the annualized weight slope among PI users was: -0.80 (95% CI: -0.57 to 1.04) kg/year before switch, which decreased by -0.46 (-0.67 to -0.26) after switch to an INSTI (absolute slope +0.34 kg/year after switch). For NNRTI users, the slope before switch was 0.63 (0.34 to 0.91) kg/year, increasing by +0.50 (0.23 to 0.77) after switch to an INSTI (absolute slope +1.13 kg/year after switch). This difference was primarily driven by an increase in the weight slope among women, non-whites, and older PWH in the INSTI group (table). Among individual INSTI drugs, the slope change after switch from NNRTI was highest for dolutegravir (DTG) at +0.93 (0.39 to 1.46) kg/year vs. +0.44 (-0.04 to 0.92) kg/year for elvitegravir and +0.23 (-0.13 to 0.58) kg/year for raltegravir.

**Conclusion:** Women, non-whites and older PWH with viral suppression had greater annualized weight gain after switch from NNRTI- to INSTI-based ART, which was greatest for dolutegravir, whereas those switched from a PI had slowing of weight gain. These findings may reflect a heterogeneous effect of ART class and agent on body weight regulation.

### 669 BODY COMPOSITION CHANGES OVER THE MENOPAUSAL TRANSITION IN HIV+ AND HIV− WOMEN

Thuy Trang J. Nguyen1, Yifei Ma1, Rebecca Sherzer2, Anjali Sharma3, Mark H. Kuniholm1, Audrey French1, Margaret Fischl2, Howard Minkoff2, Michael Planken2, Adaoa Adimora3, Carl Grunfeld1, Phyllis Tien1

1 University of California San Francisco, San Francisco, CA, USA, 2 Albert Einstein College of Medicine, Bronx, NY, USA, 3 University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

**Background:** Over 40% of HIV+ women are menopausal, and they may also be reduced by depression treatment. These data support performing larger studies to determine the short and long term effects of depression treatment on HIV-CVD risk.

**Methods:** Between 2000 and 2013, 632 HIV+ and 218 HIV− Women’s Interagency HIV Study participants underwent serial measures of BMI, WC, and Anto-Mullerian Hormone (AMH), a biomarker of ovarian reserve. The menopausal transition was categorized as: premenopausal (>5 years before onset).
before AMH became undetectable, early perimenopause(-1-5yrs before), late perimenopause(first visit with undetectable AMH and up to 5yrs after), menopause(>5-10yrs after), and late menopause(>10yrs after). We used multivariable linear mixed regression models which adjusted for demographic, behavioral, viral hepatitis, and CD4 count to estimate percentage(% in BMI and WC relative to premenopause.

Results: Women were mostly African-American (58%); mean age at onset of late perimenopause was ~45yrs in both HIV+ and HIV- women. HIV+ had lower BMI and WC than HIV- (mean:29 vs. 32kg/m^2 , p=0.0001 and 94 vs 98cm;p=0.004, respectively). Figure shows the % BMI and WC change after adjustment. In HIV- women, we found the expected increase in BMI across the menopausal transition (from 5.2 to 10% higher when than in premenopause) whereas in HIV+, the increase was much lower (1.2-1.8% higher) and blunted across the entire menopausal transition (difference in BMI change by HIV status at every stage,p<0.01). By contrast, WC progressively increased over the menopausal transition in HIV+ but the increase was blunted (difference in WC change by HIV status,p<0.01 except early perimenopause,p=0.41 and late menopause,p=0.14).

Conclusion: Our findings suggest that HIV infection blunts the expected trajectory of increase in BMI over the menopausal transition, whereas the expected trajectory of increase in WC is preserved but also blunted. Studies are needed to examine whether women with HIV in the menopausal transition are at greater risk for perturbations associated with visceral obesity (e.g. insulin resistance, fatty liver disease) and to determine optimal timing of interventions to reduce visceral obesity.

Background: Adipose tissue has a central role in the regulation of metabolism. Exposure to early antiretroviral therapy (ART) regimens, including thymidine analogues, was associated with increased adipose tissue inflammation and risk of diabetes in persons with HIV (PWH). Few studies have assessed the relationship of adipose tissue inflammation and insulin resistance in PWH on newer ART regimens.

Methods: 73 PWH with > 12 months sustained viral suppression, principally on integrase inhibitor-based ART and < 10% with historic thymidine analogue exposure, were classified as insulin sensitive (n = 46; hemoglobin A1c < 5.7% and fasting blood sugar < 100 mg/dL) vs. diabetic (n = 27; on anti-diabetic medications) and underwent subcutaneous abdominal adipose tissue liposuction. Tissue was immediately flash frozen for subsequent total RNA extraction, and mRNA was quantified using the Nanostring nCounter® human inflammation panel containing 250 genes, and a separate panel containing 77 genes modified from the KEGG adipocyte pathway. mRNA expression was compared by diabetes status adjusting for age, sex, and body mass index (BMI).

Results: 78% of study participants were male. The median age was 45 years and 55 years, and median BMI 31 kg/m^2 and 34 kg/m^2 , for non-diabetic and diabetic participants, respectively. Analysis of adipocyte-related genes revealed that diabetic individuals had lower expression of genes involved in the AMPK signaling (FASN, PPAR, PKC2) and fatty acid biosynthesis (FASN, ACSL6) pathways, and increased expression of genes involved in fatty acid degradation (ACOX1, ACSL3) (FDR-adjusted p value < 0.05; Figure 1). Inflammatory gene analysis showed that diabetics had lower expression of genes related to inflammation than non-diabetics, including NF-kappa B signaling and cytokine-cytokine interaction pathways (FDR-adjusted p value < 0.05; Figure 1).

Conclusion: In one of the largest and broadest assessments of adipose tissue gene expression in non-diabetic vs. diabetic PWH on modern ART, we found pronounced differences in adipocyte-related genes, consistent with dysregulation of metabolic pathways in diabetes, but less evidence of increased adipose tissue inflammation in contrast to studies of PWH on older ART. Single-cell studies are planned to investigate whether adaptive immune cells or other mechanisms that may not be captured in whole tissue contribute to adipocyte dysfunction and diabetes.
**672 INCREASED INFLAMMATORY CX3CR1+GPR56+CD57+CD4+ T CELLS IN FAT FROM HIV+ DIABETICS**

Celestine Wanjalja1, Wyatt J. McDonnell1, Ramesh Ram1, Abha Chopra1, Rama Gangula1, Shay Leary2, Beverly O. Woodward1, Mark Pilkinton1, Mark Pilkinton1, Mona Woodward1, Samuel Baillie1, Curtis Gabriel1, Alyssa Hasty1, Simon Mallal1, Spyros Kalams1, John Koethe1

1Vanderbilt University, Nashville, TN, USA, 2Murdoch University, Murdoch, Australia

**Background:** Persons with HIV are at higher risk of diabetes mellitus compared to the general population, which may be due, in part, to altered lipid metabolism and storage. Compared to HIV+ non-diabetics, adipose tissue from HIV+ diabetics is enriched for CX3CR1+GPR56+CD57+ (i.e., C-G-C) CD4+ T cells and a separate population of CD69+ CD4+ T cells. CX3CR1 and GPR56 are associated with anti-viral responses, including against cytomegalovirus (CMV). To assess if these cells are also common in HIV-negative diabetics, we compared C-G-C and CD69+ T cells in the adipose tissue of HIV+ vs. HIV-negative diabetics of similar age and body mass index.

**Methods:** We performed subcutaneous abdominal liposuction and T cell isolation on 11 diabetic persons (6 HIV+ and 5 HIV-negative, all subjects CMV-), followed by flow cytometry phenotyping and single-cell sorting of memory T cells. Single-cell RNA libraries were created using well-specific barcodes followed by 3' and 5' amplification and sequencing. Pooled data were demultiplexed and the transcriptome was linked to the indexed flow cytometry phenotype. We compared the proportion of C-G-C and CD69+ T cells by HIV status using Mann-Whitney tests. Differential expression and pathway analyses were performed for immune genes in C-G-C and CD69+ T cells in the adipose tissue of HIV+ vs. HIV-negative diabetics.

**Results:** A larger fraction of the adipose tissue memory CD4+ T cells from HIV+ diabetics expressed the C-G-C combination (23% versus 3% in HIV-negative, p < 0.01; Fig. A), CD69+ cells trended higher in the HIV-negative (54% versus 28% in HIV-positive, p = 0.18). The proportion of adipose tissue C-G-C cells was positively correlated with the percent of T effector memory RA+ cells (p < 0.01), a subset expanded in CMV infection. Compared to adipose tissue C-G-C cells, pathway analysis of the top 100 immune genes expressed by C-G-C T cells in the HIV+ diabetics indicated TH1, interferon-gamma response (Fig. B) and IL-27 signaling pathways (a promoter of TH1 polarization).

**Conclusion:** Adipose tissue of HIV+ diabetics is enriched for CX3CR1+GPR56+CD57+ (i.e., ‘C-G-C’) CD4+ T cells as a proportion of all memory CD4+ T cells in adipose tissue of HIV+ diabetics, while C-G-C T cells are more common in HIV-negative diabetics. Within the diabetic HIV+ participants, single-cell RNA sequences of C-G-C and C-G-C+ T cells show enrichment for pro-inflammatory TH1 cell polarization and response pathways.

---

**673 TELMISARTAN DECREASES MONOCYTE CX3CR1 EXPRESSION IN TREATED HIV INFECTION**

Jordi E. Lake1, Eunice Ye1, Douglas W. Kitch1, Anoma Somasunderam2, Michael M. Lederman3, Judith S. Currier1, Netanya S. Ulay1, for the A5317 Team

1University of Texas at Houston, Houston, TX, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3Case Western Reserve University, Cleveland, OH, USA

**Background:** Telmisartan is an angiotensin receptor blocker and PPAR-γ agonist that is active in adipose tissue (AT) and has anti-inflammatory properties.

**Methods:** AIDS Clinical Trials Group study A5317 randomized (2:1) PWH >/=18 years old on ART and with HIV-1 RNA <50 copies/mL for >/=48 weeks to receive telmisartan or no drug (controls) for 48 weeks. In a secondary analysis of persons remaining on study drug (if applicable) and ART, maintaining HIV-1 RNA < 200 copies/mL and having subcutaneous AT biopsy samples at weeks 0 and 48, AT immune cell profiling was performed via flow cytometry and IL-6, adiponectin and insulin gene expression determined by PCR array. 48-week changes were compared used two-sided rank-sum, signed-rank tests, and Spearman correlations (a = 0.05).

**Results:** Thirty-five participants (22 telmisartan, 13 control) met inclusion criteria; 94% were male and 49% white non-Hispanic. Median age was 49 years and CD4+ T cell count 572 cells/mm³. Over 48 weeks, median CD14+16-CX3CR1+monocyte numbers decreased -10.4% in telmisartan-treated PWH, and increased 13.1% in controls (between-group p = 0.029). Similar trends were observed for CD14+16-CX3CR1+T cells, CD16+CX3CR1+ and CD163+CX3CR1+monocytes (Table). CD14+16-TLR4+monocytes decreased -4.2% in telmisartan-treated PWH vs 0.0% change in controls (between-group p = 0.036). Trends were seen for correlations between decreases in CD14+16-CX3CR1+monocytes/increases in insulin gene expression (r = -0.50, p = 0.07, n=14), and decreases in CD14+16-TLR4+monocytes/inscreases in adiponectin gene expression (r = -0.50, p = 0.08, n=13).

**Conclusion:** In PWH on suppressive ART, telmisartan reduced CX3CR1 and TLR4 expression on monocytes, changes that correlated with improved markers of AT function. Given the role of CX3CR1 in AT inflammation, obesity and CVD, telmisartan has the potential to modulate CVD risk in PWH.
675 CONTRIBUTION OF INSTI, BMI, PHYSICAL ACTIVITY, CALORIC INTAKE TO WEIGHT GAIN IN PWH

Giovanni Guraldi1, Jovana Milic1, Andrea Malagoli2, Federica Carli1, Marianna Menozzi1, Alessandro Raimondi1, Giacomo Ciusa1, Valentina Masi1, Michela Belli1, Francisco Erlandson3, Carla Menozzi1, Alessandro Raimondi1, Giacomo Ciusa1, Valentina Masi1, Michela Belli1, Stefano Guaraldi1, Cristina Mussini1, Todd T. Brown4, Jordan E. Lake2, Kristine M. Bowman5, Peter W. Hunt6, Nicholas Funderburg5, Grace A. McComsey7

1University of Modena and Reggio Emilia, Modena, Italy, 2University of Texas at Houston, Houston, TX, USA, 3University of Colorado, Aurora, CO, USA, 4Johns Hopkins University School of Medicine, Baltimore, MD, USA, 5Medical University of South Carolina, Charleston, SC, USA, 6University of California San Francisco, San Francisco, CA, USA, 7Chesire and Westminster Hospital, London, UK

Background: Fat accumulation after ART initiation remains a serious problem in people with HIV (PWH), but little is known about its pathogenesis. Gut barrier dysfunction may play a role, but data are inconsistent and lack adequate control groups. We compared gut integrity markers in PWH before and after ART to an uninfected control group and assessed associations between gut integrity markers and body composition.

Methods: Data from uninfected controls (matched by age, sex, and race) were prospectively collected and compared to data from participants prospectively enrolled in a treatment initiation study. ACTG A5265, at 2 timepoints: pre-ART and 96 weeks after suppressive ART. Plasma levels of gut integrity markers, zonulin, intestinal fatty-acid binding protein (I-FABP), lipopolysaccharide binding protein (LBP) and beta-D-glucan (BDG), were measured by ELISA.

Body composition was assessed by whole-body DXA. Groups were compared using logistic or linear regression with adjustment for matching factors, and associations were assessed using linear regression models.

Results: 234 PWH and 116 controls were included. Groups were similar in age and race (PWH: mean 38 yrs, 65% white, non-Hispanic), but PWH included more men (90% vs 80%, P<0.01). PWH pre- and post-ART had significantly higher levels of I-FABP and zonulin (mean difference: 0.37 to 0.59 log₂ pg/ml, and 0.54 to 0.65 log₂ ng/ml, resp), but lower levels of LBP (mean difference: 2.65 to 2.66 log₂ ng/ml vs controls (all P<0.001). PWH had similar levels of BDG pre-ART, but higher levels post-ART vs controls (mean difference: 0.14 log₂ pg/ml, P=0.004). In all models for controls, LBP, I-FABP and BDG showed associations with body composition measures (Table); however, associations with SAT were slightly attenuated when adjusted for sex. In PWH post-ART, I-FABP was significantly associated with outcomes in both unadjusted and adjusted models with effect sizes larger than magnitude in controls (Table); limited associations were observed with I-FABP at the pre-ART time point.

Conclusion: Levels of gut integrity markers, I-FABP and zonulin, were higher in PWH both pre- and post-ART, and BDG was higher in PWH post-ART. Gut integrity markers showed significant associations with several body composition measures in uninfected controls, but the strongest associations were seen with I-FABP among PWH on suppressive ART. I-FABP levels may help predict deleterious fat changes after ART initiation.

676 UNDERSTANDING WHO DOES AND DOES NOT GAIN WEIGHT WITH INTEGRASE INHIBITORS (InSTI)

Grace A. McComsey1, Kent N. Althoff2, Todd T. Brown3, Joseph J. Eron4, Gregory D. Huhn5, Anthony Mills6, Graeme Myelle7, Soodi Navadeh8, Janna Radtchenko9, Paul E. Sax10, Richard A. Elson11

1Case Western Reserve University, Cleveland, OH, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 5Roththein Center, Chicago, IL, USA, 6Men’s Health Foundation, Los Angeles, CA, USA, 7Chesire and Westminster Hospital, London, UK, 8Gilead Sciences, Inc, Foster City, CA, USA, 9Trio Health Analytics, 10Brigham and Women’s Hospital, Boston, MA, USA, 11George Washington University, Washington, DC, USA

Background: Randomized clinical trials have shown greater weight gain with INSTI regimens vs other classes of antiretrovirals. Why do some patients gain weight on INSTI and others do not? Are there synergies with other ART agents and INSTI? We examine HIV patients (pts) in US clinical care switching to INSTIs and compare those with gain ≥5% body weight vs loss or gain <5% after 12 months (mo) on INSTIs.

Methods: A retrospective evaluation of 38000 HIV pts with EMR records selected 2384 viral suppressed pts per protocol. Subgroup analysis was conducted in 387 subjects: pts ≥ 18 years, switched to INSTI regimens in Jan 2015-Jun 2018 for ≥12 mo, with ≥6 mo history, viral suppression and weights at baseline (BLS) and 12 mo (±2 mo). Univariate analyses (UV) were conducted via chi-square for ≥ 12 mo, with ≥6 mo history, viral suppression and weights at baseline (BLS) and 12 mo (±2 mo). Multivariate analysis (MV) with a binary outcome of gain ≥5% at 12 mo compared those with gain ≥5% body weight vs loss or gain <5% after 12 months (mo) on INSTIs.

Results: Of 387 pts switched to INSTIs, 103 (27%) gained ≥5% weight, 140 (36%) lost weight or had 0% change, 144 (37%) gained <5%. In comparison...
to other study pts, those who gained ≥5% had significantly lower BSL weight, BMI, AST (but not ALT; alcohol abuse by ICD-10 observed in <4%), lower use of prior PI, and higher use of prior NNRTI. There were no statistically significant differences by NRTI backbone and specific INSTIs between those who gained ≥5% vs those who did not. In MV, pts were less likely to gain ≥5% if they had BSL AST ≥30 (relative risk [RR] = 0.31 [0.18-0.54], p = 0.001) or higher BSL weight (RR = 0.72 [0.50-1.05], p = 0.09). Conclusion: Of 387 pts switching to INSTIs, over 1/3 lost or maintained weight, over 1/3 experienced weight gain <5%, while remaining 27% experienced gain ≥5% after 12 mo on therapy. UV indicated ≥5% gain was associated with prior regimen components and BSL factors of which only BSL weight and AST remained significant in MV. Future research questions include clinical significance of weight gain thresholds that have implications for morbidity, as well as heterogeneity of responses to ARV agents.

677 DRUG CONCENTRATIONS AND BODY WEIGHT GAIN IN PLWH SWITCHED TO 3TC & Dolutegravir (DTG)

Charles Burdet1, Gilles Peytavin2, Minh Le3, Roland Landmann4, Delphine Bachelet5, Christine Kaltama6, François Raffi7, André Cabré8, Charlotte Charpentier9, Aïda Benalycherif10, Diane Descamps11, Yazdan Yazdani12, Véronique Joly13, for the Lamidol Study Group

Background: Weight gain after initiation of DTG-containing ART has recently been reported in clinical trials and cohorts, but pathophysiology remains unclear. In most switch studies, DTG was associated with a 2-NRTIs backbone. We evaluated changes in body weight in virologically suppressed PLWH switched to 3TC plus DTG dual therapy (ANRS 167 Lamidol trial).

Methods: Virologically suppressed patients included in the ANRS 167 Lamidol [Joly et al. Antimicrob. Agents Chemother. 2019], a single arm study, received 8 weeks DTG (50 mg qd) combined with 2 NRTIs backbone (phase 1, from W-8 to D0) before switching to DTG/3TC for 48 weeks (phase 2, from D0 to W48, 104 patients). All patients entering phase 2 were evaluated, except for 8 subjects exposed to DTG prior to study entry. Body weight was recorded at each visit i.e. W-8, W-4, D0, W8, W16, W24, W36 and W48. The evolution of weight over time was analyzed using a linear mixed effects model. Total DTG and 3TC plasma concentrations (Cmax) were measured at D0, W24 and W48 using UPLC MS/MS. The relationships between weight variation between W-8 and W48 and the geometric means of DTG and 3TC concentrations were studied using the Spearman correlation coefficient.

Results: 96 patients were evaluated (median age 45.2 years, range 23.9-70.6). 82 (85.4%) were male. Before inclusion in the trial, ART regimen included a PI in 24 patients, a NNRTI in 58 patients and an INSTI other than DTG in 14 patients. Median baseline weight was 73.5 kg (IQR 65-80). Weight gain was 1.15 kg (IC 95% 0.45-1.85, p = 0.002) during phase 1 and 1.22 kg (IC 95% 1.04-1.40, p < 0.0001) during phase 2. Weight gain was significantly more rapid during phase 1 (p = 0.0001). There was no relationship between weight variation and geometric means of DTG and 3TC Cmax.

Conclusion: In this population of virologically controlled patients, administration of DTG was associated with significant weight increase. This effect was more important at initial phase of DTG administration when DTG was associated to a 2 NRTIs backbone, but persisted when DTG was combined with 3TC only, and was not related to trough plasma DTG concentrations. These results suggest that other factors than intensity of drug exposure are involved in weight increase under DTG.

678 RACE IMPACT ON Dolutegravir-ASSOCIATED WEIGHT GAIN AMONG PREVIOUSLY ART-NAIVE PLWH

Stephanie A. Ruderman1, Robin M. Nance1, Bridget M. Whitney1, Kenneth H. Mayer2, Richard D. Moore3, Joseph I. Eron4, W. C. Mathews5, Michael Saag6, Greer Burkholder7, Mari M. Kitahata8, Sara Lindström9, Brian Wood10, Ann Collier11, Joseph Delaney12, Heidi M. Crane13

1University of Washington, Seattle, WA, USA, 2Harvard Medical School, Boston, MA, USA, 3Johns Hopkins University, Baltimore, MD, USA, 4University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 5University of California San Diego, San Diego, CA, USA, 6University of Alabama at Birmingham, Birmingham, AL, USA, 7University of Manitoba, Winnipeg, MB, Canada

Background: Initiation of dolutegravir (DTG)-based antiretroviral therapy (ART) has been associated with weight gain in some people living with HIV (PLWH), and race has been proposed as a risk factor. Prior studies have mixed naive and treated PLWH or used historic regimen comparisons complicating interpretation. Therefore, we examined the role of race in substantial weight gain among previously ART-naive PLWH initiating DTG vs other currently used non-integrase inhibitor-based regimens in a US cohort.

Methods: We included ART-naive PLWH who initiated ART between 2012-2018 across 8 Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites. ART regimens included efavirenz, rilpivirine, atazanavir, darunavir, and DTG-based ≥3 drug regimens. We compared DTG to regimens without integrase inhibitors to assess the association between DTG and substantial weight gain, defined as ≥15 kg, an empirically-based cut-off, 1 year following ART initiation. We restricted race to white vs black and baseline BMI ≥18.5 kg/m². Data were modeled using logistic regression with the rare disease assumption and adjusted for age, sex, hepatitis B and/or C virus coinfection, smoking, diabetes, and baseline BMI, with an interaction between race and DTG use. We conducted sensitivity analyses including baseline HIV disease severity as measured by lowest CD4 count (cells/mm³) and limitations to tenofovir (TDF) with emtricitabine/lamivudine backbones.

Results: Among 922 PLWH (n=302 with DTG; n=520 without DTG), DTG users were more likely to gain ≥15 kg compared to non-DTG users (RR:1.79 [95%CI:0.9-3.0]). Overall, 52 (6%) PLWH gained ≥15 kg, with 26 (59%) taking DTG, and of those, 19 (73%) were black. Within DTG users, black PLWH gained an average of 5.1 kg while their white counterparts gained an average of 3.3 kg. Black DTG users had a 3.2 times greater risk of gaining ≥15 kg compared to white DTG users in their first year after ART initiation (95%CI:1.3-8.0). The risk was attenuated after accounting for HIV disease severity (RR:2.49 [95%CI:0.9-6.3]) and limiting regimens to those with TDF (RR:2.3 [95%CI:0.7-7.3]), and no longer significant after smaller size but remained suggestive. Differences in risk of weight gain between black and white participants was not observed for non-DTG based regimens.

Conclusion: Black PLWH had an increased risk of substantial weight gain compared to white PLWH in their first year after DTG initiation. Additional studies are needed to clarify reasons for racial disparities.

Table. Logistic regression for the risk of gaining at least 15 kg, including an interaction term for race and DTG use (n=822)

<table>
<thead>
<tr>
<th>Group</th>
<th>RR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White not on DTG</td>
<td>1.00</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>White on DTG</td>
<td>3.01</td>
<td>1.03-9.05</td>
<td>0.036</td>
</tr>
<tr>
<td>Black not on DTG</td>
<td>3.00</td>
<td>1.33-6.65</td>
<td>0.003</td>
</tr>
<tr>
<td>Black on DTG</td>
<td>3.30</td>
<td>1.56-7.03</td>
<td>0.0001</td>
</tr>
<tr>
<td>Race x DTG interaction</td>
<td>2.29</td>
<td>0.64-8.00</td>
<td>0.31</td>
</tr>
</tbody>
</table>

679 DTG PRESCRIBING PATTERNS IN PLWH ≥65 YEARS: THE IMPACT OF 2DR AND WEIGHT GAIN

Giovanni Guaraldi1, Stefano Calza2, Andrea Calcagno3, Jovana Milic4, Emanuele Foca5, Matteo Rota5, Anna Celotti1, Benedetto Maurizio Celesia1, Stefania Picioni4, Annamaria Cattelan6, Giuseppe V. De Socio7, Giancarlo Orofino3, Agostino Riva5, Silvia Nozza8, Giovanni Di Perri9

1University of Modena and Reggio Emilia, Modena, Italy, 2University of Brescia, Brescia, Italy, 3University of Torino, Torino, Italy, 4Garibaldi Hospital, Catania, Italy, 5University of Pavia, Pavia, Italy, 6University of Verona, Verona, Italy, 7University of Turin, Turin, Italy, 8University of Modena and Reggio Emilia, Modena, Italy, 9University of Brescia, Brescia, Italy

Background: Due to advancing age, PLWH ≥65 years with ART may be at risk of weight loss, and the impact of ≥3 drug regimens on weight change is unclear. Among 822 PLWH (n=302 with DTG; n=520 without DTG), DTG users were more likely to gain ≥15 kg compared to non-DTG users (RR:1.79 [95%CI:0.9-3.0]). Overall, 52 (6%) PLWH gained ≥15 kg, with 26 (59%) taking DTG, and of those, 19 (73%) were black. Within DTG users, black PLWH gained an average of 5.1 kg while their white counterparts gained an average of 3.3 kg. Black DTG users had a 3.2 times greater risk of gaining ≥15 kg compared to white DTG users in their first year after ART initiation (95%CI:1.3-8.0). The risk was attenuated after accounting for HIV disease severity (RR:2.49 [95%CI:0.9-6.3]) and limiting regimens to those with TDF (RR:2.3 [95%CI:0.7-7.3]), and no longer significant after smaller size but remained suggestive. Differences in risk of weight gain between black and white participants was not observed for non-DTG based regimens.

Conclusion: Black PLWH had an increased risk of substantial weight gain compared to white PLWH in their first year after DTG initiation. Additional studies are needed to clarify reasons for racial disparities.
Background: No randomised clinical studies assessed antiretroviral (ART) prescription in geriatric HIV patients. Data can be obtained from observational studies or geriatric HIV cohorts. The aim of this study was to characterize ART prescription patterns of INSTI naïve virally suppressed ART-experienced people living with HIV (PLWH) ≥65 years who switch to a DTG based regimen (DTG-s) vs remaining INSTI-naive (INSTI-n) on stable ART.

Methods: People were prospectively recruited in the Geriatric Patients Living with HIV/AIDS (GEPPo) cohort, a prospective observational multicentre study in PLWH ≥65 years with a special focus on ART prescription and anthropometric changes. Body weight was assessed at 1st study visit and at last evaluation. In the DTG-s group, the 1st visit was prior to switch.

Results: Out of 591 PLWH (16.2% females),164 were in the DTG and 427 in the INSTI-n group. At study entry, median age was 70.8 (±4.6) years, CD4 cell count was 661 (±243) c/mL and HIV RNA was undetectable in 96% of PLWH. Mean weight at 1st visit was 74.4 (±13.9) kg in INSTI-n and 70.9 (±12.4) kg in DTG-s (p = 0.053). A significantly higher proportion of patients in DTG-s received dual therapy (2DR) compared to INSTI-n (60.7% DTG vs. 44.6% INSTI-n, p < 0.001). Table describes top five 2DR and 3DR regimens. No difference in demographic, immunovirological, multimorbidity and polypharmacy prevalence were observed between the two groups (all p > 0.05). After an average follow up of 2.8 (±0.76) years we still observed no significant difference in CD4 (669±663, p = 0.57) or virologic suppression (96.3% vs. 96.2%, p = 0.59). At follow-up, no change in body weight was present in the two groups: mean absolute weight change was -0.1 (±7.4) in INSTI-n and -0.3 (± 4.8) in DTG-s (p = 0.7). Weight gain (≥5%) was not significant in study arms.

Conclusion: This report analyzed real-life data of geriatric PLWH switching to DTG as first INSTI regimen. DTG initiation was not associated with important immune-virological changes, but led to double proportion of PLWH undergoing a 2DR. This option may be considered as a deprescribing recommendation in elderly. Over a follow-up, no change in absolute body weight nor significant weight gain was observed, indicating that this phenomenon is not present in geriatric PLWH.

Methods: We included treatment-naive adults (≥18 years) initiating INSTI-, protease inhibitor (PI)-, or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART from 01/2007-12/2016 with 12-month (±6 months) weights in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). We followed individuals until incident DM (HgA1c >6.5%, initiation of diabetes-specific medication, or DM diagnosis along with diabetes-related medication, precluding prevalent DM or pre-diabetes), virologic failure (<400 copies/mL), regimen core switch, administrative close, death, or loss to follow-up (>12 months without a visit or lab before cohort close). We excluded those with incident DM before 12-month weight measure, and we multiplied imputed missing baseline data. Cox regression stratified by clinic site and adjusting for age, sex, race, HIV transmission risk, year of ART initiation, and baseline weight, CD4+ cell count, and HIV-1 RNA yielded adjusted hazard ratios (HR) and 95% confidence intervals (CI) for incident DM by ART class. We conducted mediation analysis including 12-month weights along with all covariates from the primary analysis.

Results: Among 16,305 eligible ART initiators, 8,082 (50%) started NNRTIs, 5,152 (32%) PIs, and 3,071 (19%) INSTIs, with median follow-up of 3.3, 2.8, and 2.1 years, respectively. Among INSTI initiators, 18% started delutegravir (DTG), 30% raltegravir (RAL), and 52% elvitegravir (EVI). Overall, 333 (2%) developed DM. Tenofovir alafenamide (TAF) was part of <1% of regimens. Those starting INSTIs vs. NNRTIs had elevated incident DM risk (HR=1.30; CI: 0.89-1.90), greater than PI- vs. NNRTI-initiators (HR=1.07; CI: 0.83-1.38). Mediation analysis revealed an INSTI-DM association attenuated 5% (HR=1.24; CI: 0.85-1.81) by including 12-month weight in the full model (Figure).

Conclusion: Initiating ART with INSTI- vs. NNRTI-based regimens may confer greater risk of incident DM, and this risk is likely only partially due to 12-month weight gain. Research to elucidate metabolic changes after INSTI initiation and identify interventions to mitigate them continues.
July 2019 were included in the analysis. We analyzed weight and BMI changes at 18m from 12m and from baseline, using generalized estimated equations adjusted for facility clustering.

**Results:** 271 patients were enrolled in the original study, of these, 151 patients were ART experienced and had weight and BMI data at baseline and 18m; 35% were female, mean age 46, 61% had a normal baseline BMI and mean weight of 60kg, 81% switched from TLE and 95% were virally suppressed time of switch (n=130). For patients with a normal baseline BMI there was a statistically significant weight increase of 3kg (p<0.01) at 18m, an average 9% increase (p<0.01). There was a 1.8kg increase (p<0.01) from 12m weight. Patients of all BMI categories gained 7% (p<0.01) from their baseline weight. At 18m, 36% of normal baseline BMI patients had a weight gain of 10% or greater, and 29% had increased BMI category to overweight. There was no interaction of gender and weight gain at 18m. Patients with overweight or obese baseline BMI were not found to gain weight at 18m (p=0.95).

**Conclusion:** Supplementing previous findings of a weight increase in the DTG cohort at 6 and 12 months, there was continued weight increase at 18m. Patients with above normal baseline BMI did not show a weight increase at 18m nor a gender association. While the original study was not designed to measure weight changes and has not been compared to a control group, the real world findings show that weight gain may be expected in ART experienced patients that were predominantly virally suppressed at time of switch in African patients.

682 **RISK FOR INCIDENT DIABETES IS GREATER IN PREDIABETIC MEN WITH HIV THAN WITHOUT HIV**

Laurence Slama1, Benjamin Barrett1, Alison Abraham1, Frank J. Palella1, Lawrence Kingsley2, Jean-Paul Viard3, Jordan E. Lake1, Todd T. Brown4, for the MACS

1Assistance Publique – Hôpitaux de Paris, Paris, France, 2Johns Hopkins University, Baltimore, MD, USA, 3Northwestern University, Chicago, IL, USA, 4University of Pittsburgh, Pittsburgh, PA, USA, 5University of Texas at Houston, Houston, TX, USA

**Background:** Abnormalities in glucose metabolism contribute to the pathogenesis of aging-related comorbidities in people with HIV (PWH). Hyperglycemia below the diabetic range has been termed pre-diabetes mellitus (pre-DM) and may be more common in PWH compared to those without HIV. It is unclear whether the progression from pre-DM to DM differs by HIV serostatus.

**Methods:** Fasting glucose (FG) was measured at each semi-annual visit among men in the Multicenter AIDS Cohort Study (MACS) since April 1999. Men who had confirmed pre-DM, defined as a FG 100-125 mg/dL (baseline visit), were included. Men with prevalent DM at the baseline visit were excluded. Incident DM was defined as a FG ≥126 mg/dL, confirmed at a subsequent visit with anti-DM medication use or a second FG ≥126 mg/dL; self-reported DM, confirmed at a subsequent visit with anti-DM medication use or two FG ≥126 mg/dL; or report of anti-DM medication use at a visit. We used binomial transition models to determine whether the progression from pre-DM to DM differs by HIV serostatus.

**Results:** Between 1999 and 2018, 1546 men (772 with HIV [MWH], 776 men without HIV) had pre-DM. Men with pre-DM were included. At baseline, MWH were younger (median 46 vs 51 years, p<0.01), had lower BMI (median 25 vs 27 kg/m², p<0.01), and were more likely to be non-white (44% vs 28%, p<0.01), and were more likely to be HCV-infected (8% vs 5%, p<0.01) than men without HIV. Over a median of 12 years of follow-up (Q1, Q3 8, 14), 22% (166/772) of pre-DM MWH had greater gait speed decline (-0.015 m/s [-0.028, -0.001], p<0.03) and those with uncontrolled diabetes had greater gait decline (-0.877 kg [1.623, -0.130], p<0.02) regardless of serostatus. In multivariate models restricted to PWH, neither IFG nor DM had significant effects on gait speed, but uncontrolled DM was associated with significantly greater decline in gait speed (-1.818 kg [-2.868, -0.767], p<0.001), with a larger effect among men with HIV vs all participants (-1.818 vs -0.877 kg).

**Conclusion:** Abnormal glucose metabolism was associated with declines in gait speed and grip strength regardless of HIV serostatus, with uncontrolled DM exerting a greater effect on grip strength decline among PWH. These data suggest that improved glucose control, independent of virologic suppression, is an intervenable target to prevent progression of physical function limitations among PWH.

684 **GREATER INCIDENCE OF DIABETES OVER 10 YEARS AMONG DEPRESSED US VETERANS WITH HIV**

Kassem Bourgi1, Suman Kundu1, Jesse C. Stewart1, Matthew Freiberg2, Samir K. Gupta1

1Indiana University, Indianapolis, IN, USA, 2Vanderbilt University, Nashville, TN, USA

**Background:** Persons living with HIV (PLWH) have an increased prevalence of depression and incidence of cardiovascular disease (CVD) and diabetes mellitus (DM). We previously found that depressed US veterans with HIV have a greater incidence of CVD, possibly due to biological (increased systemic inflammation/coagulation) and/or behavioral (smoking, sedentary lifestyle, insomnia, poor medication adherence) mechanisms. As these mechanisms may also predispose to DM, we evaluated whether baseline depressive symptom severity predicts incident DM in US veterans living with HIV.

**Methods:** We used the Veterans Aging Cohort Study (VACS)-Survey Cohort and included patients without DM at baseline. Baseline DM was identified by a validated measure consisting of ICD-9 codes, laboratory tests, and DM medications. Baseline depressive symptom severity was assessed using the Patient Health Questionnaire-9 (PHQ-9), with prevalent depression defined by a score ≥10. Participants were followed until incident DM, death, or last follow-up date (12/31/14). Incident DM cases were identified by ICD-9 codes. Multivariate Cox regression models were run to examine the associations between baseline PHQ-9 variables (continuous and categorical) and incident DM.

**Results:** 2,936 PLWH were included, 628 (21%) of whom had prevalent depression. The median follow-up time was 9.6 years, and a total of 466 (15.8%) incident diabetes cases were identified. The unadjusted incidence rate of DM per 100 person-year was 21.4 (95% CI: 17.5-25.8) in depressed veterans vs 18.9 (95% CI: 17.0-20.9) in nondepressed veterans. Cox models revealed that each 1-point increase in PHQ-9 score (5.6 points of a 0-27 scale) was associated with a 12% (HR=1.12, 95% CI: 1.02-1.22, p=0.015) and 10% (HR=1.10, 95% CI: 1.00-1.20, p=0.048) increase in the risk of incident diabetes after adjustment for demographics alone and demographics plus traditional DM risk factors, respectively. Similarly, compared to nondepressed veterans, depressed veterans (PHQ-9 score ≥10) had a 24% (HR=1.24, 95% CI: 1.01-1.55, p=0.050) and 18% (HR=1.18, 95% CI: 0.94-1.47, p=0.148) greater risk of incident diabetes after
adjustment for demographics alone and demographics plus traditional DM risk factors, respectively.

**Conclusion:** Among US veterans with HIV, depression is associated with a significant increase in the incidence of DM. Future research should examine whether depression treatment lowers diabetes risk in PLWH.

### 685 TRICARBOXYLIC ACID METABOLITES PREDICT METABOLIC COMORBIDITIES AND DEATH IN AGING PWH

**Background:** Monocyte activation is implicated in the pathogenesis of age-associated comorbidities in people with HIV (PWH). Upon activation, macrophages switch or remodel their metabolism from predominantly oxidative phosphorylation to glycolysis resulting in accumulation of the tricarboxylic acid (TCA) metabolites, succinate, and citrate. These metabolites engage diverse cellular pro-inflammatory pathways that may contribute to comorbidity.

**Methods:** Associations between entry fasting plasma succinate and citrate concentrations, quantified by liquid chromatography mass spectrometry, and incident comorbidities were analyzed by proportional hazard models from a random sample of participants in the prospective, multicenter AIDS Clinical Trials Group HIV Infection, Aging, and Immune Function Long-Term Observational (HAILO) study. Clinically relevant variables, age, sex, race/ethnicity, and smoking, were evaluated as confounders by adding them one at a time to univariable models.

**Results:** Among 212 participants (92.6% male, 76.0% white, mean age 31 years) received study therapy and were included in the analyses. At baseline, the mean CD4 + T-cell count was 492 cells/mm³, and 22% of participants had HIV-1 RNA >100,000 copies/ml. Changes in metabolic endpoints from baseline to Week 48 are shown below (see table).

**Conclusion:** The ISL regimen, regardless of dose, demonstrated minimal impact on BMD and similar changes in fat distribution, weight, and BMI compared to the DOR/3TC/TDF group, through 48 weeks of treatment.

### 684 ISLATRAVIR METABOLIC OUTCOMES IN PHASE IIb TRIAL OF TREATMENT-NAIVE ADULTS WITH HIV-1

**Background:** Islatravir (ISL) is a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment of HIV-1 infection. Decreases in bone mineral density (BMD) and changes in body fat have been reported in people taking antiretroviral therapy for HIV-1.

**Methods:** In this randomized, double-blind, dose-ranging trial, participants were initially assigned to receive once-daily ISL (0.25 mg, 0.75 mg, or 2.25 mg) with doravirine (DOR, 100 mg) and lamivudine (3TC, 300 mg) or a fixed-dose combination of DOR, 3TC, and tenofovir disoproxil fumarate (DOR/3TC/TDF). Participants receiving ISL who achieved HIV-1 RNA <50 copies/ml at Week 24 or later stopped taking ISL at their next study visit and continued DOR+ISL at the initial dosage (most participants stopped ISL at Week 24). BMD, spine BMD, peripheral fat, and trunk fat were assessed by dual-energy x-ray absorptiometry (DEXA) performed in all randomized participants at Weeks 0 and 48 and evaluated by a central imaging reader. Change (with 95% confidence interval) from baseline to Week 48 was calculated for each of the DEXA endpoints, weight, BMI, and fasting plasma levels of glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides.

**Results:** A total of 121 participants (92.6% male, 76.0% white, mean age 31 years) received study therapy and were included in the analyses. At baseline, the mean CD4 + T-cell count was 492 cells/mm³, and 22% of participants had HIV-1 RNA >100,000 copies/ml. Changes in metabolic endpoints from baseline to Week 48 are shown below (see table).

**Conclusion:** The ISL regimen, regardless of dose, demonstrated minimal impact on BMD and similar changes in fat distribution, weight, and BMI compared to the DOR/3TC/TDF group, through 48 weeks of treatment.

### 687 NONCOMMUNICABLE DISEASES AND RISK FACTORS AMONG PEOPLE LIVING WITH HIV IN CAMBODIA

**Background:** HIV and antiretroviral therapy (ART) had been linked with increased risk of non-communicable diseases (NCDs) such as diabetes and hypertension alongside other well-established traditional risk factors. Empirical evidence from low- and middle-income countries (LMICs) on this relationship is scarce. Therefore, we examined the prevalence of NCDs in people living with HIV (PLWH) and the general population in Cambodia to assess the contribution of HIV and ART on NCDs and identify if locally adapted policies and/or interventions are needed.

**Methods:** In a cross-sectional study, we collected data on 78 PLWH and 320 non-HIV controls from the general population. Data were collected from medical records and a standardized questionnaire.

**Results:** The prevalence of diabetes, hypertension, and obesity was higher in PLWH compared to the general population. The prevalence of NCDs was higher in PLWH who were on ART compared to those who were not.

**Conclusion:** Our findings highlight the importance of implementing policies and interventions to address the increased risk of NCDs among people living with HIV in Cambodia.
IAS–USA

Topics in Antiviral Medicine

Methods: We merged data from two surveys conducted among PLWH (n=510)
and the general population (n=2747) by KHANA Center for Population Health
Research (nongovernmental organization) in 2015 and by the University of Health
Sciences in 2016, respectively. Both employed a standardized questionnaire and
physical/biochemical measurement protocols developed by the World Health
Organization (STEPwise Approach to Surveillance or STEP survey or STEPS)
and were conducted across selected provinces in Cambodia. We computed
NCD prevalence and performed logistic regression to examine the relationship
between NCDs and HIV while adjusting for age, sex, residence types, behavioral
risk factors (such as smoking, heavy alcohol consumption, less than 5 servings of
fruits and vegetables and low physical activity) and body mass index (BMI).
Results: The prevalence was 9% (n=46) for diabetes, 13% (n=67) for
hypertension and 3% (n=16) for high cholesterolemia among PLWH, all of
which (except diabetes) were lower than that of the general population. Half of
PLWH had prediabetes compared with only 16% of the general population. In
logistic regression, PLWH were more likely to present prediabetes, aOR=6.94
(95% CI: 5.41, 8.90) and diabetes, aOR=1.41 (95% CI: 0.95, 2.09), and less likely
to present hypertension and high cholesterolemia, aOR=0.59 (95% CI: 0.42,
0.81) and aOR=0.13 (95% CI: 0.08, 0.23), respectively.
Conclusion: In Cambodia, compared to the general population, PLWH had an
alarmingly high prevalence of prediabetes and, to a lesser extent, diabetes,
while hypertension, prehypertension, high and borderline-high cholesterolemia
appeared to be significantly lower. Differences in the host factors, the ART
regimen and the traditional risk factor distribution could explain these
contrasting findings in certain conditions in most Western studies. Our findings
underscore the need to put in place proper measures to address prediabetes and
diabetes among this vulnerable population.

688

Results: In 15,528 participants (71% % female, median age : 38 years;
median nadir CD4 : 186 cells/mm3) followed for a median duration of 6 years
(interquartile range : 3 to 9), 692 (4.5%) progressed to CKD, with an incidence
(95% CI) of 7.6 (7.9;10.7) per 1,000 person-years (PY). The D:A:D score ranged
from -7 to 17 with a median of -2. Incidence increased markedly across the risk
score groups : 2.4 (2.0;2.8); 8.3 (7.0;9.8) and, 30.1 (27.3;33.2) per 1,000 PY in the
low, medium and high risk groups, respectively (Table). In the high risk group,
14.6 % (95% CI: 13.1;16.2) had progressed to CKD at 5 years. Discrimination was
acceptable with a C-statistics of 0.81 (95% CI: 0.79-0.82). In predicting CKD,
score ≥ 0 and ≥ 5 performed at sensitivities of 78% and 59% and specificities of
67% and 85%, respectively.
Conclusion: The performance of the D:A:D score in predicting CKD was
acceptable. PLHIV with a score ≥0 could benefit from a closer monitoring of
renal function to prevent progression to end-stage renal disease. Introduction
of additional predictors such as hepatitis C, hypertension or diabetes should
improve the performance of the D:A:D score

689

VALIDATION OF THE D:A:D CHRONIC KIDNEY DISEASE RISK SCORE IN A
LARGE AFRICAN COHORT
Firmin N. Kabore1, Armel Poda2, Karen Malateste3, Akouda Patassi4, Henri
Chenal5, Eugène Messou6, François Dabis3, Didier K. Ekouevi3, Antoine Jaquet3,
Amandine Cournil7, for the IeDEA West Africa Collaboration
1
IRD, Montpellier, France, 2Centre MURAZ, Bobo-Doulasso, Burkina Faso, 3INSERM,
Bordeaux, France, 4CHU de Sylvanus Olympio, Lome, Togo, 5CIRBA, Abidjan, Côte
d’Ivoire, 6CePReF, Abidjan, Côte d’Ivoire, 7Université de Montpellier, Montpellier,
France
Background: A prognostic risk score for chronic kidney disease (CKD) in persons
living with HIV (PLHIV) has been developed using data from the D:A:D cohort
(PLoS Med. 2015;12(3):e1001809) but this score has not been validated in subSaharan Africa. We assessed performance of the D:A:D risk score in a large cohort
of PLHIV in West Africa.
Methods: We used longitudinal data from 15,528 PLHIV initiating antiretroviral
treatment between 1996 and 2018 in 4 clinics in Burkina Faso (n=1), Côte d’Ivoire
(n=2), Togo (n=1) participating in the International epidemiology Databases to
Evaluate AIDS (IeDEA) West Africa collaboration. Estimated glomerular filtration
rate (eGFR) was calculated using the CKD-EPI equation. Participants included had
≥3 creatinine measurements, a follow-up in the cohort ≥3 months and a baseline
eGFR >60 ml/min/1.73m². CKD was defined as a confirmed (>3 months apart)
eGFR ≤ 60 ml/min/1.73m². The risk score (short version) was calculated based on
age, gender, nadir CD4 and baseline eGFR and categorized as low (<0), medium
(0-4) and high (≥5) risk groups. Discrimination was assessed by the C-statistics and
calibration parameters were expressed as ratio of observed / expected events.

253

eGFR RECOVERY 96 WKS AFTER A TDF TO TAF OR ABC SWITCH FOR TDFASSOCIATED eGFR DECLINE
Rosanne Verwijs1, Ingeborg Wijting1, Marjo Van Kasteren2, Jan G. Hollander3,
Inge Derdelinckx4, Guido Van Den Berk5, Saskia Vrouenraets6, Mark Claassen7,
Wouter Bierman8, Casper Rokx1, Bart Rijnders1
1
Erasmus University Medical Center, Rotterdam, Netherlands, 2Elisabeth–TweeSteden
Ziekenhuis, Tilburg, Netherlands, 3Maasstad Hospital, Rotterdam, Netherlands,
4
University Hospitals Leuven, Leuven, Belgium, 5OLVG, Amsterdam, Netherlands,
6
Slotervaart MC, Amsterdam, Netherlands, 7Rijnstate Hospital, Arnhem, Netherlands,
8
University Medical Center Groningen, Groningen, Netherlands
Background: Use of tenofovir-disoproxil fumarate (TDF) containing ART can
result in an accelerated decline of the estimated glomerular filtration rate (eGFR).
Limited data are available on the reversibility of this decline and if a switch to
T-alafenamide (TAF) is non-inferior to abacavir (ABC) regarding eGFR recovery.
Methods: The BACTAF-studies are 2 multicenter studies; a prospective
randomized (NCT02957864) and a retrospective study with similar goals;
Evaluate the reversibility of the TDF-associated eGFR decline and compare eGFR
recovery between pts switching to TAF or ABC. Pts switched from TDF to TAF or
ABC for a significant eGFR-decline, defined as >3mL/min/yr during ≥5yrs of TDF
or decline of >25% or eGFR<70mL/min with eGFR>90mL/min at TDF initiation.
We excluded pts with ABC resistance, HBV/HCV coinfection and detectable
HIV-RNA at switch. To increase the likelihood of TDF-relatedness of the eGFR
decline, pts with diabetes, cardiovascular disease, uncontrolled hypertension,
use of >1 antihypertensive drug, use of nephrotoxic medication, or with another
kidney disease that may explain the eGFR-decline were excluded as well. The
prim. endpoint was an eGFR recovery of >50% 48 wks after the switch with the
96 wks results as a sec. endpoint.
Results: Of 250 pts included, 130 switched to TAF and 120 to ABC. During 7.5
and 5.5yrs of TDF use, eGFR had declined by 4.4mL/min/yr and 5.9 mL/min/
yr, respectively. eGFR was 73mL/min at TAF and 68mL/min at ABC initiation,
and 20% and 28% had an eGFR<60mL/min. W48 results were available
for 213 while data were not available for 37 (discontinuation of TAF or ABC
before w48 in 17, LTFU in 4, other reasons in 16). Significant eGFR increases
were observed by 5.0mL/min with TAF and 6.0mL/min with ABC (p<0.001
compared to baseline for both, p>0.1 for TAF versus ABC). A >50% recovery was
observed in 23/121(19%) and 18/99(18%) respectively (p>0.1). Of the 52 pts
with an eGFR<60 at TDF discontinuation, 33 (57%) showed an eGFR recovery
to >60ml/min at w48. At w96 a >50% recovery was observed in 18/101(18%)
and 24/88(27%), respectively(p>0.1). Of the 44 pts with an eGFR<60ml/min
at TDF discontinuation, 30(68%) recovered to >60ml/min at w96. More pts
discontinued ABC than TAF(15% vs 2%, p<0.001), mainly for drug-related AE
(13% vs 2%, p<0.01). HIV-RNA remained suppressed in all but 3 pts.


690  CHRONIC KIDNEY DISEASE IN PEOPLE WITH HIV OF AFRICAN ANCESTRY IN THE UK

Lisa Hamzah1, Rachel Hung1, John Booth1, Rachel Hilton1, Mark Harber1, Catherine Cosgrove2, Sarah Petti3, Fiona M. Burns3, Amanda Clarke4, Andrew Ustianowski5, Beatriz Santana-Suarez5, Elizabeth Binns-Roemer6, Caroline Sabin7, Frank Post8, for the GEN-AFRICA Study Team

1King’s College Hospital, London, UK, 2Barts Health NHS Trust, London, UK, 3Guy’s and St Thomas’ NHS Foundation Trust, London, UK, 4Royal Free Hospital, London, UK, 5St. George’s University of London, London, UK, 6Mortimer Market Centre, London, UK, 7Brighton & Sussex University Hospitals NHS Trust, Brighton, UK, 8Manchester Royal Infirmary, Manchester, UK, 9Frederick National Laboratory for Cancer Research, Frederick, MD, USA, 10University College London, London, UK

Background: Black ethnicity is a risk factor for chronic kidney disease (CKD) due to HIV-associated nephropathy (HIVAN) and hypertensive kidney disease through carriage of apolipoprotein L1 risk alleles. Among Africans, substantial regional variability in CKD prevalence has been reported. We prospectively evaluated kidney function and CKD risk factors in black-African and black-Caribbean people with HIV (PWH) in the UK.

Methods: Participants were recruited from HIV and dialysis/transplantation clinics. Renal risk factors including hypertension, diabetes mellitus and smoking status, current kidney function (estimated glomerular filtration rate, eGFR mL/min/1.73m2; CKD-EPI) and urine protein/creatinine ratio (uPCR) were obtained. Multivariable logistic regression was used to analyze factors associated with CKD (eGFR <60), end-stage kidney disease (ESKD; eGFR <15 or renal replacement therapy) and proteinuria (uPCR >35 mg/mmol in those without ESKD). These cross-sectional analyses were restricted to those with both parents born in the same region (East/Southern/West Africa or the Caribbean).

Results: While demographic and HIV characteristics differed by region, the prevalence of hypertension, diabetes mellitus and cardiovascular disease was similar (Table). The prevalence of CKD and ESKD, but not proteinuria, differed by region. In unadjusted analyses, with East African ancestry as reference, West-African ancestry was associated with CKD (HR 1.86 [95%CI 1.17, 2.97] p=0.008) and ESKD (2.02 [1.06, 3.82] p=0.027) but not proteinuria (0.92 [0.67, 1.25] p=0.598). After adjustment for demographic, HIV-associated and renal risk factors, West African ancestry remained associated with CKD (aOR 1.87 [1.09, 3.22] p=0.023) and ESKD (aOR 2.45 [1.21, 4.97] p=0.013). Caribbean ancestry was significantly associated with CKD (aOR 2.23 [1.09, 3.22] p=0.016) but not ESKD (aOR 2.33 [0.98, 5.31] p=0.054) while Southern African ancestry was associated with neither CKD nor ESKD. Among West Africans, the odds of ESKD was greatest among those of Nigerian ancestry (aOR 3.37 [1.57, 7.26] p=0.002).

Conclusion: The prevalence of CKD and ESKD, but not proteinuria, varied significantly among black PWH who have universal access to healthcare in the UK, and was not explained by traditional CKD risk factors. The highest rate of ESKD was observed among those of West African, and particularly Nigerian ancestry, highlighting the need for increased renal vigilance in this cohort.

692  CHANGE IN TRABECULAR BONE SCORE (TBS) AFTER ZOLEDRONIC ACID INFUSION OR TDF SWITCH

Jennifer Hoy1, Stephen J. Kerr1, Didier Hans2, Nicholas Pockoo3, Andrew Carr4, for the ZeST Study Group

1Alfred Hospital, Melbourne, VIC, Australia, 2HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, 3University of Lausanne, Lausanne, Switzerland, 4St. Vincent’s Hospital, Sydney, NSW, Australia

Background: Significantly greater increase in bone mineral density (BMD) occurred in osteoporotic adults on suppressive Tenofovir Disoproxil Fumarate (TDF)-based ART randomized to receive 2 annual infusions of zoledronic acid versus switching off TDF. The aim of this study was to determine the impact of TDF switch versus zoledronic acid on TBS (an indirect measurement of bone microarchitecture and independent predictor of fracture risk in the general population).

Methods: TBS scores were derived from annual lumbar spine dual-energy x-ray absorptiometry (DXA) images following extraction of the raw data using TBS insight software (Medimaps SA, France). TBS was calculated as the mean value of the L1-L4 vertebral images, corrected for weight. Change between TBS insight scores after TDF switch versus zoledronic acid on TBS (an indirect measurement of bone microarchitecture) and 17.5% had a TBS <1.2 (degraded bone microarchitecture). The mean (SD) baseline TBS was 1.3 (0.11) for the zoledronic acid group and 1.31 (0.13) for the TDF switch group. The mean (SD) percent change from baseline were significantly different between zoledronic acid and TDF switch groups (p<0.001). In contrast, the mean (SD) increase in BMD in 37 individuals on zoledronic acid was 6.3 (2.9)% at month (M)12 and 7.4 (3.5)% at M24 while in 38 individuals who switched off TDF it was 3.1 (1.2%). The mean (SD) percent increase in BMD in 37 individuals on zoledronic acid was 6.3 (2.9)% at month (M)12 and 7.4 (3.5)% at M24 while in 38 individuals who switched off TDF it was 3.1 (1.2%). The mean (SD) percent increase in TBS insight scores after TDF switch versus zoledronic acid on TBS (an indirect measurement of bone microarchitecture) and 17.5% had a TBS <1.2 (degraded bone microarchitecture).

Results: At baseline, 41.3% of participants had a TBS >1.35 (normal bone microarchitecture) and 17.5% had a TBS <1.2 (degraded bone microarchitecture). The mean (SD) baseline TBS was 1.3 (0.11) for the zoledronic acid group and 1.31 (0.13) for the TDF switch group. The mean (SD) percent increase in BMD in 37 individuals on zoledronic acid was 6.3 (2.9)% at month (M)12 and 7.4 (3.5)% at M24 while in 38 individuals who switched off TDF it was 3.1 (3.9)% at M12, and 2.9 (4.2)% at M24. The absolute and percent changes in BMD from baseline were significantly different between zoledronic and TDF switch groups (p<0.001). In contrast, the mean (SD) increase in TBS was 1.08 (6.1)% at M12 and 0.99 (6.7)% at M24 for the zoledronic acid group compared with 0.68 (0.01)% at M12 and 1.04 (0.47)% at M24 for the TDF-switch group (Figure 1). There was no significant mean (95%CI) difference between groups in percent change in TBS at 24 months (-0.05 [-2.9 to 2.8]).

691  FERRITIN AND TRANSFERRIN INDEPENDENTLY REFLECT RENAL FUNCTION IN PEOPLE WITH HIV

Harpreet Kaur1, Ronald J. Ellis1, Donald Franklin1, Scott L. Letendre1, Asha R. Kallianpur1

1Cleveland Clinic, Cleveland, OH, USA, 2University of California San Diego, San Diego, CA, USA, 3Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA

Background: Chronic kidney disease (CKD) remains a serious complication in people with HIV (PWH), despite effective antiretroviral therapy (ART), and early markers of renal injury are needed. Iron homeostasis, involving the iron-storage and delivery proteins ferritin and transferrin, has an emerging role in renoprotection and is dysregulated by HIV and inflammation. Since PWH have persistent inflammation on suppressive ART, we hypothesized that these iron-regulatory proteins are markers of renal injury and/or renal function in PWH.

Methods: Ferritin, transferrin, beta-2-microglobulin, and neopterin were quantified by ELISA in serum or plasma in 94 PWH with available markers of renal function (blood urea nitrogen (BUN), creatinine) and renal outcome (serum albumin) from a large, observational HIV study. Glomerular filtration rate was estimated using the CKD–EPI equation (eGFR). Ferritin and transferrin associations with renal function, injury, and outcome markers were evaluated using Pearson’s correlations and multivariable regression models, adjusting for potential confounders.

Results: Study participants included in this analysis were 19% women, 30% black, 9.6% diabetic, and all virologically suppressed (mean age 48±9 years, median nadir CD4 158 cells/µL (interquartile range, IQR 30-263, mean hgb 14.4±2 g/dL; 63% were on tenofovir. Median ferritin levels were 135 ng/mL (IQR 73-250) and transferrin 314 mg/dl (IQR 286-364). Ferritin was correlated to serum creatinine (r=0.73, p<0.0001), BUN (r=0.58, p<0.0001), the eGFR (r=0.20, p<0.05), immune activation, renal injury and outcome markers (r=0.74 for neopterin, p<0.001; beta-2-microglobulin, r=0.75, p<0.0001; serum albumin, r=-0.23, p=0.02), but not to transferrin. Ferritin was weakly correlated to creatinine, eGFR, and serum albumin (r=-0.23, 0.30, and 0.21, respectively, all p<0.05). Higher serum ferritin and transferrin were each associated with higher (better) eGFR, adjusting for age, black race, hemoglobin, tenofovir use, hypertension, beta-2-microglobulin, and each other (p=0.037 for ferritin; p=0.001 for transferrin). Adjustment for diabetes had minimal effect on results.

Conclusion: Higher levels of transferrin and ferritin are associated with better renal function in virologically suppressed PWH, independent of inflammation, immune activation, and other factors; these proteins may actively contribute to renal iron homeostasis during ART, dysregulation of which can promote renal injury and CKD.
Conclusion: In this osteopenic population with relatively preserved bone microarchitecture, both TDF cessation and zoledronic acid were associated with small increases in TBS that were not significantly different by randomised arm, unlike the significant increase in BMD. The results are consistent with an increase in BMD due primarily to mineral accretion by both interventions rather than an improvement in bone micro-architecture.

Results: 247 individuals (median age 57 [IQR 53, 65] years, 47% female, 87% white, time on ART 10 [6, 16] years, CD4 643 [473, 811] cells/mm³, and 98% with HIV RNA <200c/ml) contributed to the analysis. Prevalence of low BMD (T-score <-1) at LS and FN was 55% and 60%, respectively. RRBP/Cr, FEPO4, OC, P1NP, CTX-1 and PTH differed significantly by ART group, with higher values in the TDF groups. In unadjusted analysis, OC and CTX-1 negatively correlated with BMD-LS at both TDF and BMD-FN, and RRBP/Cr and BMD-FN. In adjusted analyses, compared to the noTDF/noPI group, those on TDF/PI were 4 times more likely to have low BMD-FN and those on TDF and/or PI 3 times more likely to have low BMD-LS (Table, model 1). Further adjustment for the OC, CTX-1 and RRBP/Cr had minimal impact on the observed associations (models 2-3).

Conclusion: Exposure to ART rather than levels of bone turnover or renal tubular markers best predicts low BMD in older PWH. Treatment with TDF/PI combined predicted low BMD-FN while TDF with or without PI predicted low BMD-LS. These data do not support routine measurement of biomarkers to predict low BMD in older PWH.

Table. Adjusted Odds Ratios and 95% Confidence Intervals derived from logistic regression models exploring the contributions of ART to low BMD.

<table>
<thead>
<tr>
<th>Effect on BMD-LS</th>
<th>Effect on BMD-FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>NoTDF/noPI</td>
<td>1.00 (0.62-1.62)</td>
</tr>
<tr>
<td>TDF/noPI</td>
<td>1.75 (0.92-3.35)</td>
</tr>
<tr>
<td>TDF/PI</td>
<td>3.08 (1.66-5.75)</td>
</tr>
<tr>
<td>TDF/FTC/NNRTI</td>
<td>3.41 (1.96-5.90)</td>
</tr>
<tr>
<td>TDF/FTC/NNRTI</td>
<td>3.41 (1.96-5.90)</td>
</tr>
</tbody>
</table>

Methods: We conducted a randomized controlled trial (Bone Evaluation in women who Switch from TDF/FTC/NNRTI to ABC/3TC/DTG) in which 181 women (91% black ethnicity, mean ± SD age 44.2 ± 5.9 years, CD4 range 425-725 cells/μl) were randomized in a 1:2 ratio to either ABC/3TC/DTG or TDF/FTC/NNRTI. The primary endpoint was change in total hip BMD at 12 months. Secondary endpoints included changes in lumbar spine BMD, bone turnover function, and renal bone and renal tubular function.

Results: Ninety-one women (68.9% black ethnicity, mean ± SD age 40.5 ± 5.4 years, CD4 range 425-725 cells/μl) were randomized. The primary endpoint was met, with a significant increase in total hip BMD at 12 months in the ABC/3TC/DTG group compared to the TDF/FTC/NNRTI group (3.2 mg/cm² vs. 0.8 mg/cm², p < 0.001). The secondary endpoint of bone turnover function also showed a significant improvement in the ABC/3TC/DTG group, with lower levels of markers of bone turnover (OC and CTX) and improved renal bone and renal tubular function.}

694 BONE MINERAL DENSITY IMPROVES IN WOMEN WHO SWITCH FROM TDF/FTC/NNRTI TO ABC/3TC/DTG

Fowzia Ibrahim1, Amanda Samaraevickrama1, Yvonne Gillleece1, Julie Fox1, Nargis Hemat1, Stephen Keggi2, Chloe Orik3, Lisa Hamzah4, Jonathan Ainsworth5, Birgit Barbini6, Lucy Campbell1, Frank Post6, for the BESTT Trial Team


Background: Tenofovir disoproxil fumarate (TDF) is associated with decreased bone mineral density (BMD) which is of particular concern to peri/post-menopausal women. We hypothesized that BMD and renal tubular function would improve in women who switch from a TDF- and NNRTI-containing regimen to abacavir/lamivudine/dolutegravir (ABC/3TC/DTG).

Methods: We conducted a randomized controlled trial (Bone Evaluation in women who Switch from TDF/FTC/NNRTI to Triomex [BESTT, EudraCT 2015-005297-37]) in which 181 women aged ≥40 years with HIV RNA <50 copies/ml on TDF/FTC/NNRTI for ≥12 months were randomized 1:2 to continue TDF/FTC/NNRTI or switch to ABC/3TC/DTG for 96 weeks. Primary endpoint was change from baseline in total hip BMD at week 48. Secondary endpoints included changes in lumbar spine BMD, bone turnover function, and renal bone and renal tubular function. Linear regression was used to estimate the mean difference from baseline to week 48 between the two study arms, using multiple imputation with chained equations for missing BMD data.

Results: Ninety-one women (86% black ethnicity, mean ± SD age 50.4 ± 7.0 years, BMI 30.3 ± 6.5 kg/m²) were randomized; 29/32 (91%) in the TDF/FTC/NNRTI vs. 51/59 (86%) in the ABC/3TC/DTG arm continued through week 48. Women who switched to ABC/3TC/DTG maintained viral suppression and experienced improvements in total hip and lumbar spine BMD and proteinuria (Table). No change in vitamin D, parathyroid hormone, bone turnover markers (CTX and P1NP), estimated glomerular filtration rate (eGFR-cystatin C) or fractional excretion of phosphate was observed. Switching to ABC/3TC/DTG was associated with an improved CD4 cell count (adjusted mean difference 74.0 [6.9, 141.2] cells/mm³, p = 0.032) and 1.8kg weight gain vs. no change in those who continued TDF/FTC/NNRTI (adjusted mean difference 1.81 [0.03, 3.59] kg, p = 0.046); weight increased >5% from baseline in 37% vs. 0% (p < 0.001). Nine participants (15%) discontinued ABC/3TC/DTG for drug-associated adverse events (hypersensitivity, N=2; neuropsychiatric, N=5; other, N=2).

Conclusion: Switching from TDF/FTC/NNRTI to ABC/3TC/DTG resulted in improvements in BMD, proteinuria and CD4 cell count. However, the possible
695 BONE DENSITY IN ART TREATED HIV+ AND HIV– SUBJECTS IN FOLLOW UP; HIV UPBEAT RESULTS
Tara McGinty1, Willard Tinago1, Alan Landay1, Aoife G. Cotter1, Caroline Sabin1, Alan Macken1, Eoin Kavanagh1, Gerard Sheehan1, John Lambert1, Patrick W. Mallon1, for the HIV UPBEAT Study Group
1University College Dublin, Dublin, Ireland; 2Rush University Medical Center, Chicago, IL, USA; 3University College London, London, UK; 4Mater Misericordiae University Hospital, Dublin, Ireland

Background: Decreases in bone mineral density (BMD) in people with HIV (PWH) have been associated with initiation of antiretroviral therapy (ART) containing tenofovir disoproxil fumarate (TDF). With recent introduction of new ART strategies we aimed to explore the effect of switching to non-TDF regimes on BMD.

Methods: HIV UPBEAT, a single site, prospective cohort study recruited PWH and a comparable HIV- group from 2011 to 2017. Demographic, clinical, medication history and BMD measured by DXA at lumbar spine (LS) and femoral neck (FN) were recorded at 4 visits over at least 5 years. Subjects with at least 2 DXA were included in the analysis. We used linear mixed models to determine predictors of rate of absolute change in BMD adjusting for HIV status, age, gender, ethnicity, BMI and smoking status for the whole cohort and discontinuous change mixed models to assess effect of switching-off TDF in the PWH subgroup, excluding those who switched back to TDF. Data are median[IQR] unless specified.

Results: Of 409 subjects, 191(47%) were PWH (62% male, 61% Caucasian, age 40 [34-47] yrs) and 218 were HIV– (45% male, 77% Caucasian, age 42 [35-50] yrs). The PWH group were 32% MSM, 18% IVDU and 50% heterosexual, with 11[8,14] yrs since HIV diagnosis and 7.9 [6,10.3] yrs cumulative ART. 76% were on TDF at visit 1 with 48 (28%) subjects switching off TDF over 7.3 [3.7, 9.5] yrs. The PWH group had a net (although not statistically significant) gain in LS BMD suggesting reversal of prior reduction in BMD; LS 0.15 [-3.48, 3.52] vs -0.62 [-3.99, 3.09], P=0.49 and FN 0.63 [-3.69, 4.69] vs -0.55 [-4.26, 3.97], P=0.31, respectively. PWH had a net (although not statistically significant) gain in LS BMD suggesting reversal of prior reduction in BMD; LS 0.15 [-3.48, 3.52] vs -0.62 [-3.99, 3.09], P=0.49 and FN 0.63 [-3.69, 4.69] vs -0.55 [-4.26, 3.97], P=0.31, respectively. PWH had a net (although not statistically significant) gain in LS BMD suggesting reversal of prior reduction in BMD; LS 0.15 [-3.48, 3.52] vs -0.62 [-3.99, 3.09], P=0.49 and FN 0.63 [-3.69, 4.69] vs -0.55 [-4.26, 3.97], P=0.31, respectively. PWH had a net (although not statistically significant) gain in LS BMD suggesting reversal of prior reduction in BMD; LS 0.15 [-3.48, 3.52] vs -0.62 [-3.99, 3.09], P=0.49 and FN 0.63 [-3.69, 4.69] vs -0.55 [-4.26, 3.97], P=0.31, respectively. PWH had a net (although not statistically significant) gain in LS BMD suggesting reversal of prior reduction in BMD; LS 0.15 [-3.48, 3.52] vs -0.62 [-3.99, 3.09], P=0.49 and FN 0.63 [-3.69, 4.69] vs -0.55 [-4.26, 3.97], P=0.31, respectively. PWH had a net (although not statistically significant) gain in LS BMD suggesting reversal of prior reduction in BMD; LS 0.15 [-3.48, 3.52] vs -0.62 [-3.99, 3.09], P=0.49 and FN 0.63 [-3.69, 4.69] vs -0.55 [-4.26, 3.97], P=0.31, respectively.

Conclusions: In a contemporary cohort of ART treated PWH change in BMD was similar over time regardless of HIV status, with no between-group difference in BMD at last study follow up. Switching away from TDF was independently associated with increases in LS BMD suggesting reversal of prior reduction in BMD in PWH to levels comparable to the HIV- population.

696 INTERSTITIAL LUNG ABNORMALITIES IN PEOPLE LIVING WITH HIV AND UNINFECTED CONTROLS
Andreas Ronit1, Thomas Benfield1, Jens D. Lundgren2, Jørgen Vestbo1, Shoaib Afzal4, Børge Nordestgaard4, Klaus F. Kofoed5, Susanne D. Nielsen1, Thomas Kristensen1
1Department of Infectious Diseases 8632, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; 2Department of Infectious Diseases 144, Amager Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark; 3CHP, Dept of Infectious Diseases 8632, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; 4Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, UK; 5The Copenhagen General Population Study, Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark

Background: Chest computed tomography (CT) findings in people living with HIV (PLWH) remain poorly characterized. We aimed to visually characterize interstitial lung abnormalities (ILAs) in PLWH and uninfected controls and assessed whether these abnormalities are associated with reduced pulmonary function and symptoms.

Methods: ILAs that included focal ground-glass opacity (GGO), reticulation, patchy GGO (<5% of the lung), non-dependent GGO and non-dependent reticulation (>5% of the lung), diffuse centrilobular abnormality with GGO, honeycombing, traction bronchiectasis, non-empysematous cysts, and architectural distortion were assessed by chest CT scans in PLWH from the Copenhagen Comorbidity in HIV-infection (COCOMO) Study and in uninfected controls from the Copenhagen General Population Study (CGPS) who were >40 years. Based on these CT findings we defined four outcome variables as: i) any ILA (any of the above findings), ii) equivocal for interstitial lung disease (ILD), iii) suspicious for ILD, and iv) definite ILD. Multivariate logistic regression was used to determine associations between HIV status, any ILA, equivocal and suspicious for ILD.

Results: Of 754 PLWH (95.4% with full viral suppression), 82 (10.9%) had any ILA, 59 (7.8%) were classified equivocal, 22 (2.9%) as suspicious and only one (0.1%) as definite ILD. Of 470 uninfected controls, these numbers were 36 (7.7%, p=0.079), 33 (7%, p=0.684), 4 (0.9%, p=0.025) and 0 (0%, p=1). In multivariate analysis adjusting for age, sex, ethnicity and pack-years of smoking, HIV infection was associated with aORs of 1.82 (95%CI: 1.18-2.88), 1.35 (95%CI: 0.85-2.21) and 5.15 (95%CI: 1.72-22.2) for any ILA, equivocal and suspicious ILD, respectively. PLWH with suspicious ILD only seemed to have slightly lower forced vital capacity (FVC%) predicted (86.3% vs. 92.5%, p=0.052) and increased respiratory symptoms (cough 25% vs 12.5%, p=0.163; dyspnea 9.1% vs 8.3%, p=1), although not reaching statistical significance. We found no associations between current and nadir CD4+ T cells counts and any of the outcomes considered.

Conclusion: HIV infection was independently associated with ILAs. Moreover, the proportion of individuals with radiographic findings suspicious of ILD was higher in PLWH. Whether these ILAs may develop into more recognizable disease states over time is unknown but warrants ongoing investigation.
IMPLEMENTATION OF A LUNG CANCER SCREENING INITIATIVE IN HIV-INFECTED SUBJECTS

Patricia Roiz1, Javier Díaz1, Javier Martínez-Sanz1, José L. Casado1, María Jesús Perez-Elías1, Santiago Moreno2, Ana Moreno3, Sabina Herrera4, María J. Vivancos-Gallego1, Pilar Vizcarra3, Ana M. Ayala-Carbonero4, Sergio Perez-Pinto1, Luis Gorospe1, Sergio Serrano-Villar4
1Hospital Ramón y Cajal, Madrid, Spain

Background: Low-Dose Computed Tomography (LDCT) screening has shown to decrease mortality in at-risk individuals. While HIV-infected individuals exhibit approximately a two-fold higher risk of lung cancer compared to the general population, the role of LDCT in this population remains controversial. We report the results of a lung screening program with LDCT in HIV-infected individuals.

Methods: HIV-infected individuals on follow-up in a tertiary hospital were offered LDCT for lung cancer screening. Inclusion criteria were: 45 years or years older, 30 pack-year history of smoking, quit smoking in the previous 15 years, and absence of previous lung cancer diagnosis. We registered the following radiological data: presence of lung nodules, pathological lymph nodes, coronary atherosclerosis, aortic dilation, bone marrow attenuation, lung emphysema, and non-nodular lung opacities.

Results: A total of 141 patients underwent LDCT of whom 86% were men and 14% were women. The median age was 57 years (54-60), 87 (62 %) had positive HCV antibodies, median nadir CD4 count was 179 (75-305), current CD4 count was 666 (403-911), HIV RNA count <20 copies/mL in 138 (97.1%) subjects. The median pack-year was 34 (25-41), 122 (82%) were active smokers. Radiological abnormalities were common, including pulmonary emphysema in 90 patients (64%), lung non-nodular opacities in 29 (21%), lymph nodes >1cm in 10 (7%), aortic dilation in 4 (2.8%), and radiological bone marrow attenuation in 21 (15%). Lung nodules were found in 52 subjects (37%); <4mm in 21 (15%), 4-8mm in 18 (13%) and >8mm in 13 (9%).

Lung cancer was diagnosed in 5 cases, yielding a prevalence of 3.6%. Histological examination revealed 4 cases of squamous cell carcinoma and 1 adenocarcinoma. Compared to the rest of our cohort, patients with lung cancer were of similar age (56.5 [53.5-59.5] years), had a lower CD4 nadir count (71 [4-105] cells/μL), lower current CD4 counts (352 [242-517] cells/μL), and higher median pack-year (71 [50-91]).

Conclusion: In this program of lung cancer screening in HIV-infected individuals we registered a high prevalence of lung cancer (3.6%). These results indicate that people living with HIV with additional risk factors for lung cancer are a target population for screening programs.

HIV IS ASSOCIATED WITH WORSE PULMONARY DIFFUSING CAPACITY INDEPENDENT OF EMPHYSEMA

Sarah Raju1, Meredith C. McCormack1, Jacqueline Astemborski1, M. Brad Drummond1, Jing Sun2, Robert H. Brown2, Gregory D. Kirk2
1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: HIV is associated with accelerated decline in lung function and increased risk for Chronic Obstructive Pulmonary Disease (COPD). Recently there has been more focus on the Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO), a marker of gas transfer. Studies note that HIV is associated with lower DLCO. While increased emphysema and COPD likely contribute to the DLCO impairment observed, there may be other factors that drive this association. We aimed to 1) Describe the association between HIV and DLCO independent of emphysema severity and 2) Identify the joint influence of HIV and COPD on DLCO impairment.

Methods: We utilized data from the Study of HIV in the Etiology of Lung Disease (SHIELD) in Baltimore, MD. SHIELD characterized COPD, and early lung disease, among 229 HIV+ (67%) and 110 HIV- participants, with lung function testing and Chest CT imaging. COPD was defined as post-bronchodilator FEV1/FVC<0.70. Emphysema severity was defined by % emphysema on CT. To examine the contribution of HIV to DLCO impairment, linear and logistic regression models were generated with % predicted DLCO(corrected for hemoglobin, age, sex) and odds of moderate-severe DLCO impairment(<60% predicted) as primary outcomes. Models were adjusted for race, emphysema, FEV1 predicted (to account for differences in COPD sampling across group), smoking status, pack-years, and injection drug use. Models were also stratified by COPD status.

Results: Participants had a median age of 50.9 (+/- 4.84), 235(69%) were male, 131(39%) had COPD. Of those with HIV 86(38%) had detectable viremia. After adjusting for confounders, including emphysema, HIV was associated with lower DLCO(β -3.69%; P=0.02) and higher odds of significant DLCO impairment(Odds Ratio 1.93; P=0.01). Among HIV+ participants, we did not see effect modification by CD4 count or viremia. When analyzed by COPD status (figure), a higher percentage of those with HIV and COPD(69.3%) had significant DLCO impairment versus COPD alone(54.2%)(P<0.01). Even among those without COPD, HIV was independently associated with lower DLCO(β -4.81%; P=0.04) and significant impairment(OR 2.68; P=0.01).

Conclusion: HIV was associated with DLCO impairment independent of emphysema severity or COPD. Our data also suggest a potentially additive influence between HIV and COPD on DLCO impairment. Future studies are needed to further understand the mechanisms driving these findings.
HIV is a risk factor for incident pulmonary hypertension

Meredithe S. Duncan, Suman Kundu, Charles Alcorn, Emily Epstein, Grace Wallace, Kaku So-Armah, Amy C. Justice, Kristina Crothers, Matthew Freiberg, Evan L. Brittain

Vanderbilt University, Nashville, TN, USA, 2University of Pittsburgh, Pittsburgh, PA, USA, 3Boston University, Boston, MA, USA, 4VA Connecticut Healthcare System, West Haven, CT, USA, 5University of Washington, Seattle, WA, USA

Background: HIV is associated with prevalent pulmonary hypertension (PH). However, PH incidence based on echocardiographic measures of pulmonary artery systolic pressure (PASP) in both HIV-infected and uninfected persons remains unstudied. We hypothesized that HIV-infected individuals have higher PH incidence rates and risk versus uninfected individuals and that markers of poor HIV viral suppression would further elevate PH risk.

Methods: This analysis used data from the Veterans Aging Cohort Study (VACS), an electronic health record cohort of HIV-infected veterans matched to a cohort of uninfected veterans. Eligible patients were enrolled at the time of their first echocardiogram (baseline). We then performed Cox proportional hazards regression to estimate risk of incident PH in HIV-infected individuals as a whole, by CD4 cell count, and by HIV viral load versus uninfected. Adjusted models included age, sex, race/ethnicity, prevalent heart failure, chronic obstructive pulmonary disease, body mass index, and eGFR as covariates. PH incidence was defined as the presence of at least one subsequent echocardiogram with PASP above 35 mmHg. Individuals with a single echocardiogram or follow-up PASP measures at/below 35 mmHg were censored at date of death or end of follow-up (9/30/2015).

Results: We estimated PH incidence rates by HIV status using Poisson regression; PH incidence rates and risk versus uninfected individuals and that markers of poor viral suppression would further elevate PH risk.

Conclusion: PH incidence and risk in HIV-infected individuals was 50% higher in HIV-infected individuals compared to uninfected; highest risk was observed in individuals with low CD4 cell counts and/or unsuppressed HIV viral load. Adjusted models included age, sex, race/ethnicity, prevalent heart failure, chronic obstructive pulmonary disease, body mass index, and estimated glomerular filtration rate as covariates. PH incidence rates and risk versus uninfected individuals and that markers of poor viral suppression would further elevate PH risk.

702 PTSD SYMPTOMS AND HYPERAROUSAL INFLUENCED BY CHILDHOOD TRAUMA IN WOMEN WITH HIV


Washington University in St Louis, St Louis, MO, USA, 2Johns Hopkins University, Baltimore, MD, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4Georgetown University, Washington, DC, USA, 5Albert Einstein College of Medicine, Bronx, NY, USA, 6SUNY Downstate Medical Center, Brooklyn, NY, USA, 7University of Illinois at Chicago, Chicago, IL, USA, 8Cook County Health & Hospitals System, Chicago, IL, USA, 9University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 10University of Miami, Miami, FL, USA

Background: Depressive symptoms are associated with use of some antiretroviral therapy (ART) agents. Recently, concerns regarding neuropsychiatric symptoms with integrase strand transfer inhibitor (INSTI) use have been raised. We examined INSTI-associated changes on the profile of depressive symptoms in women with HIV (WWH).

Methods: Women’s Interagency HIV Study (WIHS) participants who started or switched to INSTI-based ART and had two consecutive records (one before and one after the start/switch) with a completed Center for Epidemiologic Studies Depression Scale (CES-D) were included in the present analysis. We examined the adverse effects of INSTI start or first switch as a drug class on subscale-level (interpersonal, somatic, negative and positive affect) CES-D symptoms using linear mixed effects models adjusting for relevant covariates (e.g., age, race, substance use, body mass index, HIV RNA). Subsequent models examined each of the INSTIs separately.

Results: 1036 WWH, median age 48 (interquartile range 36, 60) years, 697 (67%) black, non-Hispanic were included in the analysis. Twenty-one percent were INSTI starters (30% raltegravir [RAL]; 29% elvitegravir [EVI]; 41% dolutegravir [DTG]) and the remainder of observations were switches to INSTI-based regimens (35% RAL; 27% EVI; 38% DTG). The majority of switches were from a protease inhibitor (PI) (56%) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (34%) based regimen. Overall, INSTI use was not associated with subscale changes in depressive symptoms after start/switch. Similarly, start/switch to individual INSTIs did not affect depressive symptoms. When analysis was restricted to those who switched to INSTIs from any ART, again no effects on depressive symptoms were observed. Similarly, switch from a NNRTI-based or PI-based regimen to any INSTI or individual INSTIs did not impact depressive symptoms. Starting any INSTI on the other hand improved positive affect symptoms and this was predominantly driven by EVI use.

Conclusion: Among WWH, switching to INSTI-based therapy did not have an impact of depressive symptoms. Initiation of INSTIs did result in improvement in positive affect symptoms and this was predominantly driven by EVI use.
Methods: African American women (18-65 yrs) recruited from Women's Interagency HIV Study (WHIS) in Atlanta, GA (n=91, 30 without HIV, 61 with HIV (WWH)), provided informed consent, and underwent interviews to capture trauma exposure and PTSD symptoms for DSM-5. Psychophysiological hyperarousal was assessed by skin conductance (SC) at baseline and during CAPS-5 using mobile eSense SC Level App. ANOVAs controlled for income and HIV viral load.

Results: Rates of adult and childhood trauma did not differ by HIV serostatus (p>0.05). Sociodemographic variables were similar among groups: age (p=0.19); education (p=0.24); employment (p=0.84). Income level was greater in WWH (p=0.02). Within WWH, the median CD4 count was 652 and 82% had undetectable viral loads. PTSD symptom severity was influenced by interaction of HIV serostatus and childhood trauma (p=0.018; eta2=0.07; Fig 1). HIV was associated with greater PTSD symptoms only with low childhood trauma (p=0.016; eta2=0.07). There was no impact of HIV status on PTSD symptoms in women with high childhood trauma (p=0.46). HIV serostatus interacted with childhood trauma to impact baseline arousal (p=0.05; eta2=0.17) and reactivity to trauma reminders (p=0.015; eta2=0.25). Higher childhood trauma in uninfected women associated with greater baseline SC compared to uninfected women with low childhood trauma (p=0.05; eta2=0.15). Childhood trauma did not impact baseline SC in WWH (p=0.69). HIV associated with lower baseline SC in women with high childhood trauma (p=0.08; eta2=0.14). In women with low levels of childhood trauma, psychophysiological response to trauma reminders was lower in WWH compared to uninfected women (p=0.06; eta2=0.15). In women exposed to high childhood trauma, HIV associated with augmented reactivity to trauma reminders (p=0.06; eta2=0.15).

Conclusion: Taken together, these findings suggest HIV impacts PTSD symptoms and hyperarousal in women dependent on childhood trauma. Given that HIV status impacts PTSD symptoms as well as baseline and trauma reminder-evoked SC response, the current data have high clinical relevance for treating PTSD in WWH.

DYSREGULATED SYNTHESIS OF NEUROTRANSMITTERS IN METHAMPHETAMINE USERS LIVING WITH HIV

Antonio Chahine1, Tulay Koru-Sengul1, Daniel J. Feaster1, Nichole Klatt1, Margaret Roach1, Suresh Pallikkuth1, Mark Sharkey1, Jessica Salinas1, Mario Stevenson1, Savita Pahwa1, Dietmar Fuchs1, Adam W. Carrico1
1University of Miami, Miami, FL, USA, 2Innsbruck Medical University, Innsbruck, Austria

Background: Elevations in the kynurenine/tryptophan (K/T) ratio are only partially reversed by effective treatment, linked to neuropsychiatric disorders, and predict faster clinical HIV progression. However, relatively less is known about the mechanisms of HIV-associated increases in the phenylalanine/tyrosine (P/T) ratio, which disrupts catecholamine synthesis (e.g., dopamine). This 15-month longitudinal study examined whether co-occurring stimulant use and HIV-associated pathophysiological processes predict greater K/T and P/T ratios even after adjusting for detectable HIV viral load.

Methods: In total, 110 sexual minority men (i.e., gay, bisexual, and other men who have sex with men) living with HIV were enrolled in a randomized controlled trial. All participants had biologically confirmed, recent methamphetamine use via urine or hair toxicology screening. Peripheral venous blood samples were collected at baseline, 6, 12, and 15 months. Marginal, generalized linear mixed models were constructed to identify predictors of the time-varying K/T and P/T ratios. Generalized Estimating Equations were used to test the predictors of screening positive for clinical depression using the Centers the Epidemiologic Study of Depression scale (scores > 16).

Results: The majority of participants were racial/ethnic minorities (57%) and middle-aged (mean = 43.2 years; SD = 8.9). At baseline, the median baseline CD4+ T-cell count was 646 cells/mm3 (Interquartile Range = 428 – 816) and 26% had a detectable HIV viral load (> 40 copies/mL). As shown in the Table, greater time-varying sCD14 and detectable viral load were independent predictors of a higher K/T ratio in adjusted analyses. On the other hand, greater proviral HIV DNA at baseline and time-varying sCD14 as well as time-varying reactive urine toxicology results for stimulants (i.e., methamphetamine or cocaine) independently predicted an increased P/T ratio. Time-varying reactive urine toxicology results for stimulants (Adjusted Odds Ratio = 2.26, 95% CI: 1.06-4.80, p = 0.043) but not the time-varying K/T or P/T ratios were significantly associated with screening positive for clinical depression.

Conclusion: HIV persistence and stimulant use are independent risk factors for dysregulated catecholamine synthesis. Findings support the need for targeted pharmacologic treatments to mitigate dysregulated catecholamine synthesis in those who co-occurring HIV and stimulant use.

EXERCISE-INDUCED EPIGENETIC CHANGES IN MUSCLE DIFFER BY HIV SEROSTATUS

Kristine M. Erlandson1, Colleen Julian1, Iain Konigsberg2, Jing Sun3, Todd T. Brown1, Catherine M. Jankowski2
1University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3Johns Hopkins Hospital, Baltimore, MD, USA

Background: Exercise is an effective intervention for improving physical function among aging persons. Whether persons with HIV (PWH) experience the same benefits of exercise, and whether mechanisms underlying exercise effects are unique to HIV is not well understood.

Methods: Sedentary PWH (16 baseline; 14 paired) and controls (18 baseline; 15 paired), all men, aged 50 to 75 underwent biopsy of the vastus lateralis prior to and following 24 weeks of supervised cardiovascular and resistance exercise training. Skeletal muscle DNA methylation was quantified on MethylationEPIC BeadChip 850K array (Illumina), normalized and adjusted for batch effects. Linear models were fit for methylation values to test for the association of HIV status or exercise, adjusted for age and race/ethnicity to generate differentially methylated positions (DMPs). DMPs were then used to identify differentially methylated regions (DMRs) between pre- and post-exercise intervention for PWH and controls using Comb-p and adjusted for multiple comparisons. Pathway analysis was performed using Ingenuity.

Results: Pre-exercise, 983 DMPs differed between PWH and controls. Top canonical pathways included gas signaling (p=3.5E-3), IL-1 signaling (p=6.9E-3) and androgen signaling (p=3.4E-3). Post-exercise, 237 DMPs differed between PWH and controls, enriching neuroinflammation signaling (p=5.0E-3) and interferon pathways (p=1.6E-2). Exercise induced 209 genome-wide significant DMRs in PWH; top enriched canonical pathways included amytrophic lateral sclerosis signaling (p=1.3E-6), glutamate receptor signaling (p=1.1E-3), phosphatase and tensin homolog deleted on chromosome 10 (PTEN) signaling (p=3.7E-3), giall-cell-line-derived neurotrophic factor family ligand-receptor interactions (p=3.6E-3), and fibroblast growth factor signaling (p=5.1E-3). In controls, exercise training induced 75 genome-wide significant DMRs, enriching pathways associated with cyclins and cell cycle regulation (p=1.6E-3), telomerase signaling (p=3.4E-3), aldehyde degradation/biosynthesis (p=5.7E-3), and hippo signaling (p=1.8E-3).

Conclusion: Epigenetic responses to exercise differ by serostatus: PWH experienced changes in DNA methylation status of genes involved in oxidative damage, mitochondrial function, angiogenesis, and metabolism while controls experienced changes in cell cycle, proliferation, protein synthesis and immune senescence.
705  

**EFFECTS OF HIV, AGE, AND SEX ON SKELETAL MUSCLE MASS AND DENSITY**  
Stephen J. Gange, Phyllis Tien, Michael T. Yin, Todd T. Brown  
Johns Hopkins University, Baltimore, MD, USA, University of California San Francisco, San Francisco, CA, USA,  
Columbia University Medical Center, New York, NY, USA  

**Background:** Lower muscle density due to ectopic fat in skeletal muscle is associated with worse physical function. Muscle density declines with antiretroviral therapy (ART) initiation; both density and area decline with increasing age in persons with HIV, though few women have been studied.

**Methods:** Men and women with and without HIV in the musculoskeletal substudies of the Multicenter AIDS Cohort Study (BOS) and Women's Interagency HIV Study (MSK) were included. Participants underwent L4-L5 computed tomography scans to quantify total density (Hounsfield Units, HU) and area (centimeters²) of four trunk muscle groups. We identified factors associated with muscle density and area using generalized linear regression models.

**Results:** Among 650 participants (198 HIV and 452 non-HIV) with available CT scans. Among men, mean age was 64, 20% were black, 13% current smokers, and 44% were obese. All with HIV were on ART. Older age, female sex, and obesity were associated with lower muscle density in all 4 muscle groups; HIV serostatus was associated only with lower psoas density (table). Black race was associated with greater muscle density of nearly all muscle groups. No interaction between sex and HIV serostatus was observed. In sex-stratified models, HIV infection was significantly associated with lower psoas density in men (-1.8 [SE 0.54] HU, p = 0.01) but not women (-1.0 [0.8] HU, p = 0.19). Muscle area was lower with older age (effect range: -0.22 to -0.6 cm) and female sex (-0.6 to -3.1), but greater with obesity (range 1.5 to 5.4), all p ≤ 0.02; no race effect was detected. HIV serostatus was associated with greater muscle area in men (-0.09 [0.02] and 0.03) but lower psoas area (-0.6/0.2, p < 0.01) area. Similar to density, in sex-stratified models, the association between HIV serostatus and area was only in men.

**Conclusion:** Older age and being a woman was associated with smaller and fatty muscle, while obesity was associated with larger and fatty muscle. Detrimental effects of HIV on the psoas density and area, particularly among men, may have important implications on balance, trunk stability, and mobility.

---

706  

**CONSISTENT STATIN USE DOES NOT AFFECT AGE-GAIDED GAIT SPEED AND STRENGTH DECLINES**  
Kristine M. Erlandson, Susan Langan, Jing Sun, Jordan E. Lake, Frank J. Palella, Lawrence Kingsley, Todd T. Brown  
University of Colorado Anschutz Medical Campus, Aurora, CO, USA, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, University of Texas at Houston, Houston, TX, USA, Albert Einstein College of Medicine, Bronx, NY, USA, Northwestern University, Chicago, IL, USA, University of Pittsburgh, Pittsburgh, PA, USA, Johns Hopkins University, Baltimore, MD, USA, University of California San Francisco, San Francisco, CA, USA, University of Colorado Denver, Denver, CO, USA  

**Background:** People with HIV (PWH) are at risk for accelerated development of physical function impairment and frailty with increasing age; both of which are associated with increased risk of falls, hospitalizations and mortality. We evaluated the prevalence of physical function impairment and frailty, and their association with demographics, clinical characteristics and risk factors among middle-aged PWH with low to moderate cardiovascular risk.

**Methods:** At enrollment, REPRIEVE (A5332) participants were 40-75 years of age, on stable antiretroviral therapy (ART) with CD4+ count >100 cells/mm³, cardiovascular risk score ≤15%, excluding diabetes if LDL cholesterol ≥70 mg/dL; those concurrently enrolled into the physical function substudy A5361S (PREPARE) between 2017-2018 at US sites were evaluated at baseline. The evaluations included Short Physical Performance Battery (SPPB, 10x repeated chair stand, balance, 4-m walk), frailty phenotype, Duke Activity Status Index (DASI) and Rapid Eating and Activity Assessment for Patients (REAP). Physical function impairment was defined as a composite SPPB score ≤10. Associations between covariates and physical function impairment were evaluated using logistic regression.

**Results:** Among the 266 participants, the median age was 51 (Q1: 43; Q3: 46) years; 81% were male; 47% white, 45% Black; 18% Hispanic. The median CD4+ count was 610 (437, 840) cells/mm³; 93% had HIV-1 RNA <50 copies/mL, 28% by handheld dynamometer. Generalized estimating equations included an interaction term for statin group and age; models were further adjusted for demographics, HIV status, and CV risk factors.

**Results:** Among 2021 men, median age was 52 (IQR 46, 58) years; 68% were white, 27% black non-Hispanic, and 60% were overweight/obese. 636 were consistent (51% with HIV), 396 intermittent (61% HIV), and 987 never statin users (49% HIV). Duration of follow-up was 8.5 years (IQR 4.4, 10.4). Baseline gait speed was 1.12 m/sec (IQR 0.59, 1.25) and grip strength 39 kg (IQR 32, 44). Unadjusted changes in gait and grip are shown in the Figure. After adjusting for baseline, demographics, and CV risk factors, gait speed declined at: -0.0028 m/sec per year of age among all men, with no significant difference in gait speed decline among consistent vs never users (-0.0002 [-0.002, 0.0016], p = 0.87). Intermittent users had a steeper gait speed decline over time vs never users (-0.0028 [-0.0048, -0.0007], p = 0.007). Similar effects were seen with statin group and grip strength, with similar strength changes over time among consistent vs never users (-0.062 [-0.17, 0.041], p = 0.24), but tended to decline more among intermittent users (-0.109 [-0.22, 0.007], p = 0.07). HIV serostatus was not associated with gait speed (-0.002 [-0.0162, 0.0123] or grip strength (-0.212 [-0.997, 0.574], p = 0.60). Although pain was strongly associated with gait and grip decline, severe baseline pain did not confound the association between statin use and physical function.

**Conclusion:** Consistent statin use had no apparent effect on declines in gait and grip strength, suggesting no statin-associated impairments in physical function in this population.
CAUSE-SPECIFIC HOSPITALIZATION TRENDS AMONG NORTH AMERICAN HIV/AIDS, Vancouver, BC, Canada, 9McGill University, Montreal, QC, Canada, 1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2Johns Hopkins of IeDEA North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) San Diego, San Diego, CA, USA, 6University of California San Francisco, San Francisco, CA, USA, 7CDC, Atlanta, GA, USA, 8British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, 9McGill University, Montreal, QC, Canada

Methods: Among patients ≥18 in care (≥1 CD4 or HIV RNA in a year) in 6 dynamic cohorts in NA-ACCORD 2005–2015, we categorized primary hospital discharge diagnoses with modified Clinical Classifications Software. We calculated all-cause and cause-specific annual hospitalization rates and used Poisson regression with GEE to estimate rate ratios for linear calendar time trends, unadjusted and adjusted for sex, age, race/ethnicity, HIV risk factor, and time-updated age, CD4, and HIV RNA.

Results: Of 27,347 patients, 8% were male, 33% Black, 52% MSM, and 13% with IDU history. From 2005 to 2015, median (IQR) age increased from 43 (38, 50) to 49 years (39, 57), CD4 count from 389 (243, 568) to 579 cells/µL (385, 786), and proportion with HIV RNA <400 copies/mL from 54% to 86%. Over 126,468 person-years (PY) of follow-up, 21,946 hospitalizations occurred. From 2005 to 2015, the annual all-cause hospitalization rate per 100 PY decreased from 22.8 (21.1, 24.6) to 13.5 (12.6, 14.5), with a mean annual change of -4% (-4%, -2) and ADI (-8%; CI -11, -6) and were stable for other categories, including renal (-1%; CI -4, +2) and pulmonary (-2%; CI -5, +1).

Conclusion: Crude hospitalization rates decreased during 2005–2015 for most diagnostic categories. Preventing and treating non-AIDS infection, the most common hospitalization cause, remains important in HIV patient management. Adjusted decreases in CVD and ADI hospitalizations may be due to improvements in viral suppression, immunologic status, and outpatient care. Adjusted rates did not increase for organ systems potentially susceptible to cumulative damage from long-term HIV infection or ARV toxicity.

Modified risk factors and incident CKD and CVD among HIV+ and HIV− patients

Michael A. Horberg1, Wendy Leyden1, Rulin Hechtcer2, Jennifer O. Lam2, Haihong Hu3, Alexandra N. Anderson3, Julia L. Marcus3, Qing Yuan4, Alan S. Go5, William J. Towner6, Michael J. Silverberg7

1Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, 2Kaiser Permanente Division of Research, Oakland, CA, USA, 3Kaiser Permanente Southern California, Pasadena, CA, USA, 4Harvard Pilgrim Health Care Institute, Boston, MA, USA

Background: HIV increases the risk of chronic kidney disease (CKD) and cardiovascular disease (CVD), but whether the association of preventable or treatable (“modifiable”) risk factors with incident CKD or CVD is similar in people with HIV (PWHA) and uninfected people is unknown.

Methods: We evaluated the association of modifiable risk factors with incident CKD (sustained eGFR ≤60 ml/min/1.73m2) and CVD (hospitalized CHD, unstable angina or stroke) among adult (≥21 years) PWHA and HIV-uninfected patients (“uninfected”, age, sex, race/ethnicity, medical center, and calendar year matched 1:10) from Kaiser Permanente (KP) California (Northern and Southern) and Mid-Atlantic States (DC, MD, VA) healthcare systems during 2000-2016. We excluded patients with prior known CKD or CVD. Modifiable risk factors included diabetes mellitus, hypertension, dyslipidemia, smoking (ever documented history) and alcohol use disorder. We compared adjusted rate ratios (RRa) separately for each risk factor and outcome by HIV status using Poisson regression with terms for HIV status, risk factor of interest, and HIV×risk factor interaction. Models additionally adjusted for sociodemographic characteristics (time-updated age, sex, race/ethnicity, socioeconomic status, insurance type, KP region), years of KP membership, obesity (BMI>25), drug use disorder, CKD (for CVD), CVD (for CKD).

Results: Among 38,545 PWHA and 384,658 uninfected without prior CKD, there were 1,084 and 10,257 incident CKD events, with rates of 1.7 and 0.5 per 100 person-years, respectively. Among 38,757 PWHA and 384,404 uninfected without prior CVD, there were 1,227 and 10,039 incident CVD events, with rates of 0.6 and 0.4 per 100 patient-years, respectively. All modifiable risk factors had a stronger association with CKD among uninfected compared with PWHA in adjusted models (all p<0.001, Table). Alcohol use disorder and dyslipidemia appeared protective for CKD among PWHA. For CVD, dyslipidemia (p<0.001) and smoking (p=0.06) were stronger risk factors among uninfected compared with PWHA.

Conclusion: All modifiable risk factors evaluated had a stronger association with CKD, and dyslipidemia and smoking a stronger association with CVD.
BASELINE AND ACQUIRED COMORBIDITIES IN PATIENTS INITIATING ART IN THE HOPS, 2008-2018

Ellen Tedaldi,1 Carl Armon,2 Jun Li,1 Gina M. Simencini,3 Frank J. Palella,4 Stacey Purinton,3 Kate Buchacz1
1Temple University, Philadelphia, PA, USA, 2Cerner Corp, Kansas City, MO, USA, 3CDC, Atlanta, GA, USA, 4Northwestern University, Chicago, IL, USA

Background: Among persons living with HIV (PLWH), the presence of physical and psychiatric comorbidities at baseline and the rate at which they develop may be related to aging, metabolic changes, medication, or socioeconomic factors.

Methods: We analyzed antiretroviral therapy (ART)-naïve participants in the HIV Outpatient Study (HOPS) initiating ART from 2008-2018 with ≥2 tests of CD4 counts from ART initiation by demographic factors, HIV risk activity, ART type and comorbid conditions: lipid disorders, diabetes, cardiovascular disease (CVD), cancer and mental health diagnoses at ART-start until last HOPS encounter. Yates-corrected chi-square analyses were used to test for changes in burden of comorbidity by sex during observation. Poisson regression was used to compare outcomes by sex, adjusted by age, race, payor, and individual person-time observation.

Results: There were 1236 participants, with 982 (79%) males and 254 (21%) females, median age 36 years, 66% non-white, 44% publicly insured, 53% with Medicaid and 47% with Medicare. There were 3129 women (2239 HIV+, 890 HIV-) with 36,589 person-years (PY) of follow-up. At enrollment, median age was 37 years, 65% were black, 47% currently smoked, and median body mass index was 28 kg/m². At last visit, women had a median CD4 count of 484 cells/mm³, 69% were on ART and 45% viremically suppressed. Of 10 NACM evaluated, mean NACM count at enrollment was higher among WWH vs HIV- women (1.4 vs 1.2, p=0.006), though only prevalent liver disease (26% vs 16%, p<0.001) and psychiatric illness (26% vs 21%, p=0.003) differed significantly by HIV serostatus.

Conclusion: Certain medical and psychiatric comorbidities are already present in persons initiating ART therapy in the past 10 years. There is a predominance of acquired metabolic comorbidities such as dyslipidemia, as well as psychiatric conditions that will complicate the long term management of persons living with HIV. With aging, PLWH who start ART experience a significant increase in the burden of physical and psychiatric non-HIV comorbidities over time that warrants continued surveillance, prevention, and treatment.
### 712 PERSISTENT LOW-LEVEL VIREMIA IS ASSOCIATED WITH NONINFECTIOUS COMORBIDITIES

Allahna L. Esber1, Julie Ake1, Emmanuel Bahema2, Francis Kiweeka3, Jonathjon Maswai4, John Owuoth4, Michael Iroezindu5, Christina Polyak1, Trevor A. Crowell6, for the AFRICOS Study Group

1US Military HIV Research Program, Silver Spring, MD, USA, 2HJF Medical Research Institute, Aptos, CA, USA, 3Kampala, Uganda, 4Kenya Medical Research Institute, Nairobi, Kenya, 5Henry Jackson Foundation, Abuja, Nigeria

**Background:** Despite improved life expectancy with antiretroviral therapy (ART), persons living with HIV (PLWH) have higher rates of noninfectious comorbid diseases (NCDs) than do uninfected individuals. Chronic inflammation and immune activation due to persistent low-level viral replication may contribute to the heightened risk of NCDs among some PLWH. We characterized the risk of several NCDs among PLWH with undetectable plasma viral load, persistent low-level viremia (PLLV), and viral failure in the African Cohort Study (AFRICOS).

**Methods:** AFRICOS is an ongoing cohort enrolling participants in 12 clinics in Uganda, Kenya, Tanzania, and Nigeria. Clinical assessments, including HIV viral load testing, are completed every six months. Participants without an NCD at baseline were included in these time-to-event analyses. PLLV was defined as at least two consecutive visits with a detectable viral load <100 copies/mL. We examined four different NCDs: elevated blood pressure (any single systolic pressure >139, diastolic >89 mmHg, or use of anti-hypertensive medications), hypercholesterolemia (total cholesterol >199 mg/dL or lipid-lowering medications), dysglycemia (any non-fasting glucose >199 mg/dL or fasting glucose >99 mg/dL), and renal insufficiency (estimated glomerular filtration rate <60). We also evaluated the presence of any one or more of these NCDs as a dichotomized outcome variable. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard modeling. Models were adjusted for study site, education, ART regimen, and age.

**Results:** As of June 1, 2019, 2,872 PLWH were enrolled of which 1,773 did not have an NCD at baseline and were included in these analyses. The majority of participants were female (58%) and between 18-39 years (61%) with 12% >50 years at enrollment. Over the course of follow-up, 623 (35%) participants developed any NCD, including 261 (15%) who developed elevated blood pressure, 359 (20%) hypercholesterolemia, 359 (20%) hypercholesterolemia, 176 (10%) dysglycemia, and 28 (2%) renal insufficiency. Participants with PLLV developed any NCD sooner than their viremically-suppressed counterparts (HR 1.49 [95% CI 1.24-1.80]). Similar associations were observed for most of the individual NCDs evaluated (Table).

**Conclusion:** PLLV was significantly associated with NCDs in this population. Targeting viral suppression below the limit of detection on clinical HIV viral load assays may reduce the risk of non-infectious complications of HIV.
**In Vitro Impact of TAF on Mitochondrial Function in Immune Cells**

Eleni Ritou, Rachel Heymans, Theodoros Kelesidis

**University of California Los Angeles, Los Angeles, CA, USA**

Mitochondrial dysfunction has been involved in toxicity of antiretrovirals such as zidovudine (ddC). Markedly lower plasma levels of tenofovir (TFV) are thought to lead to the more favorable bone and renal safety profile of tenofovir alafenamide (TAF) compared to tenofovir disoproxil fumarate (TDF). It is unknown whether an increase in intracellular levels of the active metabolite, tenofovir-diphosphate (TFV-DP) with TAF (compared to TDF) may alter mitochondria. This study was designed to address whether TAF affects in vitro mitochondrial membrane potential (MMP), a direct measure of the state of energization of the mitochondria, in peripheral blood mononuclear cells (PBMCs).

**Methods:** PBMCs were isolated from healthy 18-40 years old participants (n=10). PBMCs were incubated for 2-hour with TDF and/or TAF at concentrations of 0.12-3.3 µM TAF, TDF and ddC. 3.3 µM ddC and 0.12, 3.3 µM TDF did not affect the median fluorescence intensity (MFI) of TMRE in CD3+ T cells and CD14+ cells compared to DMSO control (p<0.05). 3.3 µM TAF increased the MFI of TMRE in CD3+ T cells and in CD4+ monocytes compared to DMSO control (p<0.05). 3.3 µM TAF increased the MFI of TMRE in CD6+ T cells compared to ddC (p<0.05).

**Results:** After 2 hours of in vitro exposure of PBMCs to 0.12-3.3 µM TAF, TDF and ddC, 3.3 µM ddC and 0.12, 3.3 µM TDF did not affect the median fluorescence intensity (MFI) of TMRE in CD3+ T cells and CD14+ cells compared to DMSO control. 3.3 µM TAF increased the MFI of TMRE in CD3+ T cells and in CD4+ monocytes compared to DMSO control (p<0.05). 3.3 µM TAF increased the MFI of TMRE in CD6+ T cells compared to ddC (p<0.05). 2 hours of in vitro exposure of primary PBMCs to 0.12-3.3 µM TAF did not affect the MFI of TMRE in CD4+ T cells and increased the MFI of TMRE compared to TDF in CD3+ T cells and CD4+ monocytes (Figure).

**Conclusion:** We did not find any evidence of in vitro mitochondrial toxicity (reduction in MMP) with TAF. TAF may increase in vitro the MMP in resting PBMC as early as 2 hours. This concentration dependent effect was more prominent in monocytes compared to T cells. The clinical relevance of these in vitro findings is unknown. The effect of TAF on mitochondrial function in chronic treated HIV should be further explored in patients switching from TDF to TAF regimens.

**Table:**

<table>
<thead>
<tr>
<th>Cell type</th>
<th>EA (p&lt;0.05)</th>
<th>TL (p&lt;0.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ T cell</td>
<td>-0.340 (0.007)</td>
<td>0.297 (0.001)</td>
</tr>
<tr>
<td>CD4+ naive T cell</td>
<td>-0.154 (0.002)</td>
<td>0.426 (0.001)</td>
</tr>
<tr>
<td>CD8+ T cell</td>
<td>0.023 (0.01)</td>
<td>0.216 (0.003)</td>
</tr>
<tr>
<td>CD14+ monocyte</td>
<td>-0.162 (0.003)</td>
<td>0.402 (0.001)</td>
</tr>
<tr>
<td>CD14CD28CD45RA</td>
<td>0.350 (0.001)</td>
<td>-0.377 (0.001)</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>-0.240 (0.013)</td>
<td>0.233 (0.001)</td>
</tr>
<tr>
<td>B cell</td>
<td>0.057 (0.079)</td>
<td>0.070 (0.747)</td>
</tr>
<tr>
<td>Plasma cell</td>
<td>0.031 (0.076)</td>
<td>0.312 (0.236)</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>0.325 (0.001)</td>
<td>-0.46 (0.001)</td>
</tr>
<tr>
<td>Macrophage</td>
<td>0.139 (0.001)</td>
<td>0.613 (0.596)</td>
</tr>
<tr>
<td>Granulocyte</td>
<td>-0.203 (0.282)</td>
<td>0.563 (0.061)</td>
</tr>
</tbody>
</table>

715 IN VITRO IMPACT OF TAF ON MITOCONDRIAL FUNCTION IN IMMUNE CELLS

716 INFLAMMATION AND MITOCHONDRIAL DYSFUNCTION NOT NRTIs DRIVE EVENTS IN ACTG A5241

Carl J. Fichtenbaum, Timothy M. Stone, Gregory S. Gojanovich, Roman Jandarov, Joseph J. Eron, Rajesh T. Gandhi, Karen T. Tashima, Mariana Gerschenson, for the AIDS Clinical Trials Group

**University of Cincinnati, Cincinnati, OH, USA, 2University of Hawaii at Manoa, Honolulu, HI, USA, 3University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 4Massachusetts General Hospital, Boston, MA, USA, 5Brown University, Providence, RI, USA**

**Background:** ACTG A5241 (OPTIONS Study) randomized individuals experiencing treatment failure to omit or add nucleoside reverse transcriptase inhibitors (NRTIs) to a regimen that had a cumulative activity of 2 or more active antiretroviral agents. There were more deaths and clinical events observed in those randomized to add NRTIs. We hypothesized that clinical events were associated with markers of inflammation and mitochondrial dysfunction.

**Methods:** Cohort study of 174 participants enrolled in OPTIONS (N=413) selected randomly and enriched to include those with clinical events (death, AIDS defining opportunistic infections and non-AIDS clinical events). Protein levels relating to inflammation (IL-6, TNFα, FGF21, cTnI, CRP, Insulin) or mitochondrial dysfunction (NADH dehydrogenase [C1], FGF21 and GDF15) were measured by LumineX and ELISA, respectively at baseline, weeks 24 and 48 and evaluated for their association with the composite endpoint of clinical events. At baseline sampling, all participants were taking a failing regimen of NRTIs plus protease inhibitors. The statistical analysis included univariate parametric (t-tests) and non-parametric tests (Wilcoxon test) with selected variables analyzed using linear and generalized linear models.

**Results:** 174 participants were evaluated with a median age of 47 years, 40% women; 43% Black, 20% Hispanic, 36% white. There were 58 participants with clinical events and 116 participants without clinical events of whom 35% vs. 36% were randomized to omit NRTIs, respectively. At baseline, cTnI (555, 263 vs 448, 584 pg/ml, P=0.03); CD4 count (148 vs 209 cells/mm , P=0.03); CD4/CD8 ratio (0.16 vs 0.22, P=0.02; VACS Index (46 vs. 33, P=0.02) were significantly different in those who subsequently experienced a clinical event. At baseline, there were no significant differences in the two groups NADH
dehydrogenase activity, GFO-21, GOF-15, IL-6, TNFRI, TNFRII, insulin or HIV RNA levels. Censoring for those with clinical events before weeks 24 or 48, GFO-21, sCD4, CD4:CD8 ratio and VACS index were significantly different at weeks 24 and 48 (Table). Analyses were similar when adjusted for randomization to omit or add NRTIs. Only sCD4 remained significant on multivariate analyses at baseline, week 24 or week 48 (Odds ratio, 1.0).

Conclusion: Severity of illness, biomarkers of inflammation and mitochondrial dysfunction were associated with clinical events. Randomization to omit or add NRTIs was not associated with clinical events. sCD4 identifies a group at higher risk of developing clinical events.

717 IMPACT OF TREAT-ALL GUIDELINES ON TB INCIDENCE AMONG PLWH IN RIO DE JANEIRO, BRAZIL

Leila H. Chaisson¹, Valeria Saraceni², Juliana Domenico², Richard D. Moore³, Richard E. Chaisson¹, Jonathan Golub¹, Betina Durovni⁴
¹Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, ²Secretaria Municipal de Saúde do Rio de Janeiro, Rio de Janeiro, Brazil, ³Johns Hopkins University School of Medicine, Baltimore, MD, USA, ⁴Osvaldo Cruz Foundation – Fiocruz, Rio de Janeiro, Brazil

Background: Antiretroviral therapy (ART) substantially lowers tuberculosis (TB) risk, and implementation of universal ART ("treat all") guidelines therefore has the potential to reduce TB burden among people living with HIV (PLWH). We evaluated the impact of treat all guidelines on TB incidence and mortality in Rio de Janeiro, Brazil.

Methods: Brazilian guidelines recommended ART for patients with CD4≤500 from 2010-2013 and treatment for all starting in 2014. We included all PLWH entering public sector care in Rio from 2010-2016 with follow-up through 2017, excluding those with prevalent TB. We used national electronic registries to obtain data on CD4s, viral loads, TB diagnoses, ART prescriptions, and deaths; and joined databases using probabilistic linkage. We followed patients from entry into care until TB diagnosis, death, or administrative censoring at 2 years. We calculated incidence rates (IR) per 100 person-years (pys) and the 2-year cumulative hazard (CH) of 1) TB and 2) TB death prior to and following implementation of treat all guidelines, stratified by baseline CD4 and ART status.

Results: 16,552 PLWH entered public sector care in Rio from 2010-2016 with follow-up through 2017, excluding those with prevalent TB. We included all PLWH from 2010-2013 and treatment for all starting in 2014. We included all PLWH entering public sector care in Rio from 2010-2016 with follow-up through 2017, excluding those with prevalent TB. We used national electronic registries to obtain data on CD4s, viral loads, TB diagnoses, ART prescriptions, and deaths; and joined databases using probabilistic linkage. We followed patients from entry into care until TB diagnosis, death, or administrative censoring at 2 years. We calculated incidence rates (IR) per 100 person-years (pys) and the 2-year cumulative hazard (CH) of 1) TB and 2) TB death prior to and following implementation of treat all guidelines, stratified by baseline CD4 and ART status.

Conclusion: There was a 22% reduced rate of TB (IR ratio 0.78, 95% CI 0.61-0.99) and TB death (IR ratio 0.78, 95% CI 0.69-0.88) post treat all compared with pre treat all. The 2-year CH of TB and TB death declined between periods for those with unknown baseline CD4 (TB: 2.2% vs 1.7%, p=0.14; TB death: 7.2% vs 5.4%, p=0.01) but did not decline for those with CD4≥500 (TB: 1.8% vs 1.9%, p=0.82; TB death: 10.8% vs 10.1%, p=0.49) or CD4<500 (TB: 6.0% vs 7.0%, p=0.78; TB death: 2.4% vs 2.1%, p=0.50). ART was associated with a 66% reduced rate of TB (IR ratio 0.34, 95% CI 0.22-0.52) and TB death (IR ratio 0.34, 95% CI 0.28-0.42) in the pre treat all period; in the post treat all period, ART was associated with a 17% reduced rate of TB (IR ratio 0.83, 95% CI 0.59-1.17) and a 44% reduced rate of TB death (IR ratio 0.56, 95% CI 0.47-0.67).

Conclusion: Risk of TB and death fell in the treat all era in Rio but remains high. ART coverage must increase, and additional interventions, including TB preventive therapy, should be scaled-up to reduce TB morbidity and mortality.

718 ESTIMATING TB TRANSMISSION IN PRIMARY CARE CLINICS IN TB/HIV HIGH-BURDEN SETTINGS

Kathrin Zürcher¹, Carl Morrow², Julien Riou³, Simon Bertschinger¹, Marie Ballif¹, Keren Middelkoop², Robin Wood³, Matthias Egger¹, Lukas Fenner¹, for the IeDEA Consortium
¹Institute of Social and Preventive Medicine, Bern, Switzerland, ²Desmond Tutu HIV Foundation, Cape Town, South Africa, ³Bern University of Applied Sciences, Bern, Switzerland

Background: Tuberculosis (TB) transmission is difficult to measure and its drivers are not well understood. We piloted a novel approach using clinical, environmental and position-tracking data to study the risk of TB transmission in a primary care clinic in Cape Town, South Africa.

Methods: We collected risk factors for airborne transmission during 4 weeks on workdays in August 2019. Patient data included characteristics and number of patients, waiting times and anonymous patient movements using video sensors. Environmental data included indoor carbon dioxide levels (CO2 in parts per million [ppm]), relative humidity (RH, associated with Mycobacterium tuberculosis [MtB] survival in the air), frequency and intensity of patients’ coughing using sound recording (analyses ongoing), and number of MtB particles in the air using bio-aerosol sampling devices (molecular detection; analyses ongoing). We calculated rebreathed air volume (RAV) based on people density and CO2 levels (indicating airborne transmission). We defined three areas in the clinic: registration desk (1, see figure), waiting room (2), and TB treatment room (3).

Results: 14,795 people visited the clinic. The median number visiting per day was 706 (interquartile range [IQR] 622-803), with a median time of 12.4 min (IQR 12.3-12.7) spent in the waiting room. Density of people was highest in the waiting room (see figure). Overall, the median CO2 level was 623 ppm (IQR 501-751); higher in the morning, compared to midday and afternoon (715 vs. 668 vs. 485; p<0.001). The median RAV was 40 L/day (IQR 18-77): higher in the waiting room compared to the registration area and TB room (69 vs. 26 vs 12 L/day; p<0.001). The ventilation rate (air change) was relatively high with 11.2 l/h per person (typical value for bedrooms: 5.0 l/h per person). The proportion of patients’ time spent above 1,000 ppm CO2 indicating poor ventilation was 10% (typical outdoor value: around 400 ppm). The median RH was above 65% in 32% of time. We are in the process of combining these data with clinical data, cough recordings and the number of MtB particles in the air to construct a mathematical TB transmission model.

Conclusion: This pilot study documents the feasibility of a novel approach to the control of TB in a high-risk transmission setting. Mathematical modelling will allow us to identify factors driving the risk of TB transmission and to evaluate interventions such as separating patient flows or improving ventilation.
719 ALARMING TUBERCULOSIS RATE AMONG PWID IN VIETNAM
Nicolas Naget1, Vu H. Vinh2, Khuat T. Qanh3, Delphine Rapoud4, Hoang T. Giang4, Catherine Quillet1, Pham M. Khue4, Roselyne Vallo2, Thanh T. Nhâm1, Jean-Pierre Molès1, Don Des Jarlais5, Duong T. Huong4, Phuong N. Lan6, Thuy T. Dong2, Didier Laureillard1 1INSERM, Montpellier, France, 2Viet Tiep Hospital, Hai Phong, Vietnam, 3Center for Supporting Community Development Initiatives, Hanoi, Vietnam, 4Hai Phong Medical University, Hai Phong, Vietnam, 5New York University, New York City, NY, USA, 6Friends for International Tuberculosis Relief, Gräfelfing, Germany, 7Friends for International Tuberculosis Relief, Haiphong, Vietnam, 8CHU de Nimes, Nimes, France

Background: Vietnam belongs to the 30 high TB burden countries according to WHO, with an annual TB incidence of 129/100,000. A few reports suggested that PWID had increased TB rate, most likely due to high TB prevalence in this key population (eg. 27% in Haiphong, 2 million inhabitant city, Vietnam). The record of a high numbers of deaths due to TB during the implementation of large project aiming at ending HIV transmission among PWID in Vietnam, prompted the evaluation of the TB rate in this population.

Methods: We implemented a cross-sectional assessment of active TB during a follow-up visit of 2 open cohorts of HIV-negative and HIV-positive PWID in Hai Phong. Cohort participants were recruited through 2 community-based Respondent-Driven-Sampling surveys carried out at 1 year interval (N=1383 and 1451, respectively). Adult PWID with heroin detected in urine and recent injection skin marks were available. During a cohort follow-up visit, community-based organization (CBO) members systematically assessed TB symptoms using a standardized questionnaire. If any symptom was recorded, then a Chest X-Ray (CXR) was done at the local TB hospital, followed by a Xpert MTB/RIF test on sputum if the CXR was abnormal.

Results: Among the 581 HIV positive and 672 HIV-negative participants expected, 484 and 457 PWID completed their cohort visit. Overall, 93% were males, their median age was 42 years; 75% and 51% were using methadone, respectively. Among PWID with HIV, 90% were on ART and 82% had a viral load < 1000 copies/mL, with a median CD4 count of 472 cells/µL. Among the 451 HIV-positive PWID screened for TB, 293 (65%) had at least one symptom, 84/253 (33%) had an abnormal CXR, and among the 38 who had a Xpert MTB/RIF result available, 8 were positive. Assuming all PWID who dropped from the screening cascade had no TB, the conservative TB prevalence was 1.8% (0.6; 3.0). Very similar figures were found among HIV-negative PWID, with 7 active TB cases for a TB prevalence of 1.6% (0.4; 2.8).

Conclusion: In this high TB burden setting, the active TB prevalence among PWID is more than 10 times higher than the annual TB incidence in the general population, with no increased risk due to HIV. This very high TB rate suggests transmission of M. tuberculosis within PWID. Urgent interventions targeting PWID are required to reach the objective of ending the TB epidemic.

720 PREVALENCE OF TB SYMPTOMS, DIAGNOSIS, AND TREATMENT AMONG HIV PATIENTS NOT ON ART
Alana T. Brennan1, Mihaili Maskew2, Bruce Larson2, Isaac Tsikhurstu3, Margaret Bir1, Lungisile Vez1, Matthew P. Fox1, William D. Venter2, Peter Ehrenkranz2, Sydney Rosen1 1Boston University, Boston, MA, USA, 2Health Economics and Epidemiology Research Office, Johannesburg, South Africa, 3Henry M Jackson Foundation, Bethesda, MD, USA, 4Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 5Bill and Melinda Gates Foundation, Seattle, WA, USA

Background: Current WHO guidelines recommend that HIV-positive patients who report >1 symptom of tuberculosis (TB) require further investigation for TB disease prior to antiretroviral treatment (ART) initiation. This requirement for ruling out active TB before initiating ART may preclude same-day treatment initiation for many patients who do ultimately not have TB, and, by requiring extra clinic visits, contributes to loss-to-follow-up. We compared the prevalence of TB symptoms, which can delay ART initiation, to the prevalence of TB diagnosis and treatment in intervention arm patients enrolled in the Simplified Algorithm for Treatment Eligibility clinical trials (SLATE I and II) in South Africa and Kenya.

Methods: We used intervention arm screening data to describe prevalence of TB symptoms (cough, weight loss, fever, night sweats), diagnosis, and treatment in patients presenting for HIV care not currently on ART in South Africa (n=594) and Kenya (n=240). Data for SLATE I and II in South Africa were combined.

Results: 38%/95%(CI:32-44%) of patients in Kenya and 41%(37-45%) in South Africa had >1 symptom of TB when presenting for HIV care. 70% of patients in both countries who presented with >1 TB symptom were tested for TB disease. 13%(7-22%) tested positive for TB in Kenya and 6%(4-10%) tested positive in South Africa. All 27 patients who tested positive for TB disease in both countries reported having >3 symptoms. In both countries, patients with TB symptoms had lower CD4 counts at study enrollment than did those with no symptoms of TB (Kenya: median 152 cells/mm³, IQR(64-329) vs. 357(191-632); South Africa: 205(104-391) vs. 351(172-513)). The lowest median CD4 counts were recorded among those with active TB disease (Kenya 124(12-150); South Africa 193(50-223)). Among the 493 asymptomatic patients in SLATE I and II, 43% of patients in Kenya and 151(44%) of patients in South Africa were tested for TB. One patient tested positive for TB in South Africa and commenced TB treatment; no adverse events (eg. immune reconstitution inflammatory syndrome) were reported.

Conclusion: Among 234 patients with WHO-defined TB symptoms, 88% did not have TB but experienced an unnecessary delay in ART initiation. Requiring TB test results for all symptomatic patients prior to ART initiation, without consideration of symptom number or severity, should be reconsidered.

721 HOUSEHOLD AIR POLLUTION INCREASES RISK FOR PULMONARY TB IN HIV-INFECTED ADULTS
Patrick Katoto1, Bihehe Masemo2, Amanda S. Brand3, Aline Kusinza4, Brian Allwood5, Richard Van Zyl-Smit6, Nadia A. Sam-Agudu7, David Dowdy8, John Z. Metcalfe9, Grant Theron10, Kevin Mortimer9, Jeroen Vanoirbeek11, Tim Nawrot10, Benoît Nemery1, Jean B. Nachega1
1Katholieke Universiteit Leuven, Leuven, Belgium, 2Université Évangélique en Afrique, Bukavu, Congo, 3Stellenbosch University, Cape Town, South Africa, 4Université Evangélique en Afrique, Bukavu, Congo, 5University of Cape Town, Cape Town, South Africa, 6University of Maryland, Baltimore, MD, USA, 7Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 8University of California San Francisco, San Francisco, CA, USA, 9Vanderbilt School of Tropical Medicine, Liverpool, UK, 10University of Hasselt, Hasselt, Belgium, 11University of Pittsburgh, Pittsburgh, PA, USA

Background: Millions of deaths related to household air pollution (HAP), pulmonary tuberculosis (PTB), and HIV occur annually in low income countries. However, little is known about the influence of HAP on PTB risk among people living with HIV (PHLV).

Methods: We conducted a case-control study among PLHIV with pulmonary tuberculosis (PTB), and HIV occur annually in low income countries. However, little is known about the influence of HAP on PTB risk among people living with HIV (PHLV).

Methods: We conducted a case-control study among PLHIV at four clinics in eastern Democratic Republic of Congo (DRC) from March 2018 to February 2019. Cases were ≥ 18 years old, with recent (<5 years) or current PTB. Controls were age- and sex-matched PLHIV with neither recent nor current PTB. During home visits, HAP exposure was assessed using a validated International Multidisciplinary Programme to Address Lung Health and TB in Africa (IMPAALA) questionnaire. Personal carbon monoxide (CO) exposure was assessed using the
Alcohol use was assessed using the Alcohol Use Disorders Test-C (AUDIT-C). Induration from 0mm to >5mm if HIV+ or >10mm if HIV- at reassessment. Our primary outcome, incident TB infection, was defined as a change in TST induration from 0mm to >5mm if HIV+ or >10mm if HIV- at reassessment. The World Health Organization estimates nearly 500,000 cases of tuberculosis (TB) among people living with HIV (PLHIV) go unreported each year. Among PLHIV, four-symptom TB screening (cough, fever, weight loss, and night sweats) is recommended at every clinical encounter, followed by sputum testing with Xpert MTB/RIF for positive screens. We assessed TB screening programs in countries supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).

**Methods:** We analyzed TB screening and diagnostic testing data collected at PEPFAR-supported sites during October 2017–March 2019. Countries reporting TB screening data with ≥90% completeness were included. Using pooled and country-specific data, we determined the proportion of patients screened for TB symptoms and those who screened positive among PLHIV newly initiating ART vs those already receiving ART at the time of screening. We also determined the proportion of patients with a positive TB screen who had TB diagnostic testing, including Xpert MTB/RIF.

**Results:** Of 30 countries reporting TB screening data, we included 20. Of the 8,337,799 PLHIV already receiving ART, 7,273,266 (87%) were screened at least once for TB symptoms in the most recent biannual reporting period. In the same period, the pooled rate of positive TB symptom screens was 2.6% (7.0% among ART-naïve PLHIV vs 2.3% among those already receiving ART). Median country-specific rates of positive TB screening results were 2.5% (interquartile range [IQR], 1.7%–5.8%) overall (ART-naïve PLHIV, 7.4% [IQR: 5.8%–13.8%]; PLHIV already receiving ART, 2.1% [IQR: 1.5%–5.3%]). Since 2017, the rate of positive TB screens globally has increased from 3.9% to 6.9% among ART-naïve PLHIV and has decreased to 2.8% from 3.4% among those already receiving ART. Among all PLHIV with a positive TB screen result, 85% had spu ta sent for diagnostic testing (58% for Xpert MTB/RIF testing); trends in specimen testing decreased over the analysis period.

**Conclusion:** The proportion of ART-naïve PLHIV with a positive TB screen result is increasing but remains lower than expected for high-burden settings. We identified gaps in TB diagnostic services; roughly 1 in 6 PLHIV with TB symptoms does not receive diagnostic testing. Our findings suggest that improved TB screening and GeneXpert-based TB testing will be crucial in improving progress.

**Tuberculosis Prevention Treatment in New vs Existing Antiretroviral Therapy Patients**

Meaghan L. Peterson1, Rena Fukunaga1, Joseph S. Cavanaugh1, Patricia Hall1, Erin Rottinghaus1, N. Sarita Shal1, Adam MacNeil1, CDC, Atlanta, GA, USA

**Background:** The World Health Organization estimates nearly 500,000 cases of tuberculosis (TB) among people living with HIV (PLHIV) go unreported each year. Among PLHIV, four-symptom TB screening (cough, fever, weight loss, and night sweats) is recommended at every clinical encounter, followed by sputum testing with Xpert MTB/RIF for positive screens. We assessed TB screening programs in countries supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).

**Methods:** We analyzed TB screening and diagnostic testing data collected at PEPFAR-supported sites during October 2017–March 2019. Countries reporting TB screening data with ≥90% completeness were included. Using pooled and country-specific data, we determined the proportion of patients screened for TB symptoms and those who screened positive among PLHIV newly initiating ART vs those already receiving ART at the time of screening. We also determined the proportion of patients with a positive TB screen who had TB diagnostic testing, including Xpert MTB/RIF.

**Results:** Of 30 countries reporting TB screening data, we included 20. Of the 8,337,799 PLHIV already receiving ART, 7,273,266 (87%) were screened at least once for TB symptoms in the most recent biannual reporting period. In the same period, the pooled rate of positive TB symptom screens was 2.6% (7.0% among ART-naïve PLHIV vs 2.3% among those already receiving ART). Median country-specific rates of positive TB screening results were 2.5% (interquartile range [IQR], 1.7%–5.8%) overall (ART-naïve PLHIV, 7.4% [IQR: 5.8%–13.8%]; PLHIV already receiving ART, 2.1% [IQR: 1.5%–5.3%]). Since 2017, the rate of positive TB screens globally has increased from 3.9% to 6.9% among ART-naïve PLHIV and has decreased to 2.8% from 3.4% among those already receiving ART. Among all PLHIV with a positive TB screen result, 85% had spu ta sent for diagnostic testing (58% for Xpert MTB/RIF testing); trends in specimen testing decreased over the analysis period.

**Conclusion:** The proportion of ART-naïve PLHIV with a positive TB screen result is increasing but remains lower than expected for high-burden settings. We identified gaps in TB diagnostic services; roughly 1 in 6 PLHIV with TB symptoms does not receive diagnostic testing. Our findings suggest that improved TB screening and GeneXpert-based TB testing will be crucial in improving progress.

**Tuberculosis Evaluation Among HIV-Positive Patients on Antiretroviral Therapy**

Meaghan L. Peterson1, Catherine Nichol2, Rena Fukunaga1, Joseph S. Cavanaugh1, Patricia Hall1, Erin Rottinghaus1, N. Sarita Shal1, Adam MacNeil1, CDC, Atlanta, GA, USA

**Background:** The World Health Organization estimates nearly 500,000 cases of tuberculosis (TB) among people living with HIV (PLHIV) go unreported each year. Among PLHIV, four-symptom TB screening (cough, fever, weight loss, and night sweats) is recommended at every clinical encounter, followed by sputum testing with Xpert MTB/RIF for positive screens. We assessed TB screening programs in countries supported by the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR).

**Methods:** We analyzed TB screening and diagnostic testing data collected at PEPFAR-supported sites during October 2017–March 2019. Countries reporting TB screening data with ≥90% completeness were included. Using pooled and country-specific data, we determined the proportion of patients screened for TB symptoms and those who screened positive among PLHIV newly initiating ART vs those already receiving ART at the time of screening. We also determined the proportion of patients with a positive TB screen who had TB diagnostic testing, including Xpert MTB/RIF.

**Results:** Of 30 countries reporting TB screening data, we included 20. Of the 8,337,799 PLHIV already receiving ART, 7,273,266 (87%) were screened at least once for TB symptoms in the most recent biannual reporting period. In the same period, the pooled rate of positive TB symptom screens was 2.6% (7.0% among ART-naïve PLHIV vs 2.3% among those already receiving ART). Median country-specific rates of positive TB screening results were 2.5% (interquartile range [IQR], 1.7%–5.8%) overall (ART-naïve PLHIV, 7.4% [IQR: 5.8%–13.8%]; PLHIV already receiving ART, 2.1% [IQR: 1.5%–5.3%]). Since 2017, the rate of positive TB screens globally has increased from 3.9% to 6.9% among ART-naïve PLHIV and has decreased to 2.8% from 3.4% among those already receiving ART. Among all PLHIV with a positive TB screen result, 85% had spu ta sent for diagnostic testing (58% for Xpert MTB/RIF testing); trends in specimen testing decreased over the analysis period.

**Conclusion:** The proportion of ART-naïve PLHIV with a positive TB screen result is increasing but remains lower than expected for high-burden settings. We identified gaps in TB diagnostic services; roughly 1 in 6 PLHIV with TB symptoms does not receive diagnostic testing. Our findings suggest that improved TB screening and GeneXpert-based TB testing will be crucial in improving progress.

**Tuberculosis Evaluation Among HIV-Positive Patients on Antiretroviral Therapy**

Meaghan L. Peterson1, Catherine Nichol2, Rena Fukunaga1, Joseph S. Cavanaugh1, Patricia Hall1, Erin Rottinghaus1, N. Sarita Shal1, Adam MacNeil1, CDC, Atlanta, GA, USA

**Background:** The World Health Organization estimates nearly 500,000 cases of tuberculosis (TB) among people living with HIV (PLHIV) go unreported each year. Among PLHIV, four-symptom TB screening (cough, fever, weight loss, and night sweats) is recommended at every clinical encounter, followed by sputum testing with Xpert MTB/RIF for positive screens. We assessed TB screening programs in countries supported by the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR).

**Methods:** We analyzed TB screening and diagnostic testing data collected at PEPFAR-supported sites during October 2017–March 2019. Countries reporting TB screening data with ≥90% completeness were included. Using pooled and country-specific data, we determined the proportion of patients screened for TB symptoms and those who screened positive among PLHIV newly initiating ART vs those already receiving ART at the time of screening. We also determined the proportion of patients with a positive TB screen who had TB diagnostic testing, including Xpert MTB/RIF.

**Results:** Of 30 countries reporting TB screening data, we included 20. Of the 8,337,799 PLHIV already receiving ART, 7,273,266 (87%) were screened at least once for TB symptoms in the most recent biannual reporting period. In the same period, the pooled rate of positive TB symptom screens was 2.6% (7.0% among ART-naïve PLHIV vs 2.3% among those already receiving ART). Median country-specific rates of positive TB screening results were 2.5% (interquartile range [IQR], 1.7%–5.8%) overall (ART-naïve PLHIV, 7.4% [IQR: 5.8%–13.8%]; PLHIV already receiving ART, 2.1% [IQR: 1.5%–5.3%]). Since 2017, the rate of positive TB screens globally has increased from 3.9% to 6.9% among ART-naïve PLHIV and has decreased to 2.8% from 3.4% among those already receiving ART. Among all PLHIV with a positive TB screen result, 85% had spu ta sent for diagnostic testing (58% for Xpert MTB/RIF testing); trends in specimen testing decreased over the analysis period.

**Conclusion:** The proportion of ART-naïve PLHIV with a positive TB screen result is increasing but remains lower than expected for high-burden settings. We identified gaps in TB diagnostic services; roughly 1 in 6 PLHIV with TB symptoms does not receive diagnostic testing. Our findings suggest that improved TB screening and GeneXpert-based TB testing will be crucial in improving progress.
725 POTENTIAL IMPACT OF LATENT TUBERCULOSIS IN PEOPLE LIVING WITH HIV

Katharina Kusejko1, Huldrych F. Günthard1, Kyra Zens1, Katharine Darling1, Nina Khamda1, Hansjöakob Furrer1, Pauline Vetter1, Enos Bemasoni2, Pietro L. Vernazza1, Roger Kouyos1, Johannes Nemeth1, for the Swiss HIV Cohort Study 1University Hospital Zurich, Zurich, Switzerland, University of Zurich, Zurich, Switzerland, 1Lausanne University Hospital, Lausanne, Switzerland, 1University Hospital Basel, Basel, Switzerland, 1University Hospital of Bern, Bern, Switzerland, 1University Hospitals of Geneva, Geneva, Switzerland, 1Ospedale Regionale di Lugano, Lugano, Switzerland, 1St. Gallen Cantonal Hospital, St Gallen, Switzerland

Background: Tuberculosis (TB) preventive treatment (TPT) has been shown to drastically reduce mortality among people living with HIV (PLHIV). The World Health Organization recommends TPT for all PLHIV without contraindications or active TB disease. Accordingly, the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) is committed to providing TPT to the eligible 14 million PLHIV currently supported by this program. In 2017, PEPFAR-supported programs began biannual reporting on TPT among all new and existing antiretroviral (ART) patients.

Methods: We conducted a descriptive analysis of TPT completions and expected completions (i.e., those initiated on TPT in the previous six-month reporting period) in PEPFAR-supported sites during 2017–2019. Countries with >90% TPT data completion were included for analysis. We calculated the proportion of PLHIV who completed TPT of those that initiated in the previous reporting period. We then determined the proportion that initiated TPT in the previous reporting period and the proportion that completed TPT among all eligible PLHIV on ART (based on negative TB symptom screen), disaggregated by those newly initiating ART versus already receiving ART in the reporting period.

Results: Nineteen of twenty-nine countries were retained for analysis. In the most recent reporting period (October 2018—March 2019), number of PLHIV eligible for TPT based on negative TB symptom screen ranged from 555—981,037 per country. Among eligible patients newly initiating ART, only 33% were initiated on TPT, and only 17% completed TPT. Among eligible patients already receiving ART, only 8% were initiated on TPT and only 6% completed a course. Since October 2017, overall TPT completion among all PLHIV that initiated in the previous reporting period increased from 59% to 69%. During the same time, among those already receiving ART, completion increased from 73% to 76%; completion was consistently lower (35–53%) in those newly initiating ART (Figure 1).

Conclusion: Programmatic data suggests TPT implementation remains low. Only one in six eligible patients who were newly initiated on ART completed a course of TPT in the most recent data. A marginal increase in completion rates was observed among those newly initiating ART; however, overall, completion rates remained consistently higher among those already receiving ART. Accelerated efforts will be necessary to provide TPT to all eligible PLHIV by reducing barriers to TPT initiation and completion among both new and existing patients.
and time-dependent receipt of antiretroviral therapy (ART). We performed a multivariate Cox proportional hazards analyses of factors associated with experiencing a primary endpoint and tested two-way interactions between each factor and treatment.

**Results:** Rates of TB or death from TB on an unknown cause varied by country, with incidence rates per 100 person years of 0 (Brazil and US), 0.48 in South Africa, 0.50 in Botswana, 0.54 in Kenya, 0.57 in Peru, 0.58 in Thailand, 0.89 in Zimbabwe, 1.33 in Malawi and 1.4 in Haiti. Half of participants were on ART at baseline, 75% 1 year post-entry, 89% post-entry, and 93% by end of study. Primary endpoint rates were higher in individuals with lower CD4 counts, who were not on ART, and who had a positive TST or IGRA at baseline. In the Cox proportional hazards analysis (Table), reaching an endpoint was significantly associated with baseline CD4 count, TST/IGRA positivity, and BMI, but not with time-dependent ART status, age, sex, or treatment assignment. There remained unexplained heterogeneity between countries when added to the model (not shown), but estimates of other covariates were similar in both models.

**Conclusion:** TB risk was greater for those with lower CD4 counts, lower BMI, and a positive TST/IGRA test at baseline. There was considerable heterogeneity by country of residence, indicating that local TB transmission patterns likely affect TB risk. IHP represents an exciting new strategy for preventing TB in people living with HIV.

### Table 1: Summary of adverse pregnancy outcomes by country of residence

<table>
<thead>
<tr>
<th>Country</th>
<th>Rate of fetal demise</th>
<th>Rate of PTD</th>
<th>Rate of LBW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>0</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>US</td>
<td>0</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>South Africa</td>
<td>0.5</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Argentina</td>
<td>1.0</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Brazil</td>
<td>0.5</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>US</td>
<td>0</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>South Africa</td>
<td>0.5</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Argentina</td>
<td>1.0</td>
<td>1.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

**272 ADJUSTED ANALYSIS OF EFFECT OF IPT ON ADVERSE PREGNANCY OUTCOMES IN WOMEN WITH HIV**

Gerhard B. Theron 1, Nahida Chakhtoura 2, Grace Montepiedra 3, Lisa Aaron 4, Patrick Jean-Philippe 4, Adriana Weinberg 5, Katie McCarthy 6, Teacler AIDS Institute Partnership, Gabarone, Botswana, 7Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, 8Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 9Stellenbosch University, Tygerberg, South Africa, 1NIH, Bethesda, MD, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3NIAD, Bethesda, MD, USA, 4University of Colorado Denver, Denver, CO, USA, 5FHI 360, Durham, NC, USA, 6University of Zimbabwe, Harare, Zimbabwe, 7Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 8Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, 9Stellenbosch University School of Medicine, Cape Town, South Africa

**Background:** IMPAACT P1078 is a randomized non-inferiority study designed to compare safety of starting isoniazid preventive therapy (IPT) in pregnant women with HIV during pregnancy or after delivery. Previous unadjusted analyses compare safety of starting isoniazid preventive therapy (IPT) in pregnant women with HIV on ARTs living in high TB burden settings.

**Methods:** Randomized controlled trial of economic incentives to reduce heavy alcohol use and improve isoniazid preventive therapy (IPT) completion in HIV+ TB+ drinkers in rural Uganda. Adults had TSTs placed if they were HIV+ on ART ≥6 months, reported no history of TB or IPT, endorsed hazardous drinking and had a positive urine ethyl glucuronide test (alcohol biomarker). Alcohol use was measured by the Alcohol Use Disorders Identification Test-C (AUDIT-C). Hazardous use was a score ≥3 if female and ≥4 if male and was stratified into medium (AUDIT-C 3-5 men/3-5 women), high (6-7) and very high (8-12) levels. Positive TST was defined as induration ≥5mm 48-72 hours after placement; TST results outside the testing window were excluded. We conducted logistic regression with robust standard errors to evaluate associations between drinking levels and TST. **Results:** Among 729 HIV+ hazardous drinkers who underwent TST placement, 617 (85%) returned for TST reading on time. Among those with TST results, 217 (35%) were TST-positive, 452 (73%) were male, median age was 40 years (IQR 32-48) and median AUDIT-C score was 6 (IQR 5-8). Drinking levels were: 42% medium, 31% high and 28% very high. TST positivity by drinking level was: 31% medium, 33% high, very high 45%. In the multivariate model, very-high level use was significantly associated with TST positivity compared to medium level drinking (aOR 1.61, 95%CI: 1.03-2.50, P=0.04). Very high level drinking had a non-significant association with TST-positivity compared to medium level use (aOR 1.05, 95%CI: 0.69-1.69, P=0.83).

**Conclusion:** Very high-level alcohol use was associated with increased TST-positivity among a cohort of PLWH. Potential mechanisms of increased TB infection are unclear but may include more time spent in high transmission environments.
729 PRAGMATIC DOSING RECOMMENDATIONS OF RIFAPENTINE-CONTAINING REGIMENS FOR LATENT TB

Kendra K. Radtke1, Jennifer E. Hibma1, Radojka M. Savic1, University of California San Francisco, San Francisco, CA, USA

Background: Two short-course regimens containing rifapentine (P) and isoniazid (H) have demonstrated efficacy in preventing tuberculosis (TB) disease: 1 month of daily H and P (1HP) and 3 months of weekly H and P (3HP). Weight-based dosing of both drugs is recommended in adults and children; however, dosing algorithms (weight band or mg/kg) are not aligned for the two drugs nor with available formulations (P=150 mg; H=100 mg), over-complicating implementation. Further, pharmacokinetic (PK) rationale for dosing by weight is lacking in adults. Here, we provide PK evidence supporting flat (non-weight-based) P dosing in adults and simplified weight band dosing in children, easily implementable with current formulations.

Methods: A population PK model of P was established based on PK data from 9 clinical studies (n=863 adults). The impact of weight, HIV, age and other factors on PK were examined using nonlinear mixed effect approaches. For H in adults and P and H in children, previously published models were used. Dosing simulations were performed with current and proposed regimens for 1HP (adults only) and 3HP using established PK models. PK metrics (eg, time above MIC, AUC) were compared by regimen and relevant patient factors (eg, HIV status, weight).

Results: Weight-based dosing of P in adults is not justified by population PK and results in lower P exposures in low weight individuals who receive smaller doses. Flat P dosing (600 mg in 1HP or 900 mg in 3HP) would ensure equal exposures as 900 mg P weekly in HIV–. In children, aligning H and P weight bands delivered equal exposures to the current guidelines and utilized available formulations (Table 1). Future coformulation of 300/300 HP in a child-friendly tablet could further simplify therapy. For H, dosing stratification by NAT2 genotype is justified, when possible, as it is the main driver of drug exposure discrepancies, not weight.

Conclusion: 3HP dosing recommendations can be simplified to improve implementation without compromising clinical efficacy. Further, flat dosing of P in adults should be recommended to avoid underexposure in low weight people and HIV+ adults need 30% higher P doses to match exposures in HIV– adults.

Table 1: Proposed dosing chart for 3HP.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of tablets</th>
<th>Dose (mg)</th>
<th>Number of tablets</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1HP</td>
<td>4</td>
<td>300 mg</td>
<td>1</td>
<td>150 mg</td>
</tr>
<tr>
<td>3HP</td>
<td>6</td>
<td>900 mg</td>
<td>1</td>
<td>450 mg</td>
</tr>
</tbody>
</table>

730 INCREASED HLA-DR EXPRESSION IN MONOcyTES WITH HIV AND LATENT TB INFECTION

Moises A. Huaman1, Steven Juchnowski2, David A. Zidar2, Cissy Kityo3, Sophie Naluwango1, Rashidah Nazzinda1, Carl J. Fichtenbaum1, Chris T. Longenecker2, University of Cincinnati, Cincinnati, OH, USA, University of Pittsburgh, Pittsburgh, PA, USA

Background: Persistent monocyte activation contributes to the increased risk of end-organ complications in persons with HIV (PWH). Whether Mycobacterium tuberculosis (MtB) coinfection has an effect on monocyte activation in PWH is unknown. We hypothesized that there would be greater monocyte activation phenotypes in PWH with MtB coinfection.

Methods: Cross-sectional study within a cohort of HIV-infected and -uninfected participants enrolled at the Joint Clinical Research Centre in Kampala, Uganda. Participants were ≥45 years with at least one traditional cardiovascular disease risk factor. PWH had to be on stable antiretroviral therapy with HIV viral load ≤1,000 copies/mL within the 6 months prior to study entry. Participants completed a TB questionnaire and had a QuantiFERON TB (QFT) test. Latent TB infection (LTBI) was defined by a positive QFT and no TB symptoms. Prior active TB was defined by self-report and/or medical records review. Participants without evidence of MtB infection had a negative QFT, no TB symptoms, and denied prior TB. Fresh blood samples were stained with monocyte subset markers (CD14, CD16), CD62p, CD69, CX3CR1, HLA-DR, and tissue factor, and examined with flow cytometry.

Results: We included 125 participants (83 PWH and 42 without HIV) with flow cytometry data and defined TB status in this analysis. Median CD4 count was 556 cells/μL in PWH. PWH had a higher frequency of total monocytes (4.3% vs 3.2%; p<0.001) and inflammatory monocyte subset (15.5% vs 11.7%; p=0.016) compared to those without HIV. Among PWH, prior TB was associated with increased frequency of total monocytes compared to LTBI (5.1% vs 3.7%; p=0.013), but not when compared to PWH without MtB infection. HLA-DR density on all monocyte subsets was higher in PWH with LTBI or prior TB compared to PWH without MtB infection (Table). In multivariable regression, a higher frequency of inflammatory monocytes remained associated with HIV infection after adjusting for TB status, age, sex, cholesterol, and diabetes mellitus (log-β, b=0.37; p=0.019). Among PWH, a higher density of HLA-DR on monocytes remained associated with LTBI or prior TB in adjusted modeling (log-β, b=0.17; p<0.001).

Conclusion: Inflammatory monocytes are expanded in HIV infection. LTBI and prior active TB were associated with increased HLA-DR expression on all monocyte subsets in PWH, which indicates increased immune activation in the setting of MtB and HIV coinfection.

Table 1. Density of HLA-DR on circulating monocytes among PWH by TB status (n=83). *

<table>
<thead>
<tr>
<th>HLA-DR MFI</th>
<th>No MtB infection</th>
<th>LTBI</th>
<th>Prior active TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=67)</td>
<td>(n=10)</td>
<td>(n=17)</td>
<td>(n=25)</td>
</tr>
<tr>
<td>Total Monocytes</td>
<td>1.5 (1.0–2.1)</td>
<td>1.5 (1.0–2.1)</td>
<td>1.8 (1.2–2.5)</td>
</tr>
<tr>
<td>Inflammatory subset</td>
<td>1.5 (1.0–2.1)</td>
<td>1.5 (1.0–2.1)</td>
<td>2.1 (1.5–2.9)</td>
</tr>
<tr>
<td>Preceding subject</td>
<td>0.8 (0.4–1.2)</td>
<td>0.8 (0.4–1.2)</td>
<td>1.4 (1.0–2.1)</td>
</tr>
</tbody>
</table>

* Data presented as median and interquartile range in parentheses.

731 INTRAVENOUS BCG VACCINATION IN SIV+ MACAQUES CONFRONTS HIGH-LEVEL PROTECTION AGAINST TB

Erica C. Larson1, Mark A. Rodgers1, Amy Ellis1, Cassandrea A. Ameel1, Janelle Gleim1, Abigail K. Gubernat2, Alexis Balgeman3, Ryan Moriarty1, Pauline Maieillo1, Patricia A. Darrah5, Johnne L. Flynn5, Mario Roederer1, Robert A. Seder1, Shelby O’Connor1, Charles A. Scanga2

1University of Pittsburgh, Pittsburgh, PA, USA, 2University of Wisconsin–Madison, Madison, WI, USA, 3Vaccine Research Center, NIAID, Bethesda, MD, USA

Background: The only licensed vaccine to prevent tuberculosis (TB) is BCG, a live attenuated M. bovis strain, given intradermally (ID) to infants at birth. While BCG-ID confers protection against disseminated TB infection, it has more limited protection against pulmonary TB in adolescents and adults. Vaccination with BCG has been limited in HIV+ persons due to safety concerns related to BCG dissemination, even though TB is the major cause of morbidity and mortality in this population. BCG vaccine safety and efficacy can be assessed in macaques in the setting of SIV and M. tuberculosis (MtB) infection. Recently, intravenous (IV) BCG was shown to prevent MtB infection and disease in rhesus macaques and was associated with a sustained increase in lung T cells. Here, we used our established model of SIV/MtB coinfection of Mauritian cynomolgus macaques (MCM) to determine whether IV BCG would be safe and effective at protecting chronic SIV+ macaques from TB.

Methods: We infected MCM intracereally with SIVmac239. Five months later, they were vaccinated IV with 8x107 CFU BCG. Beginning 4 weeks later, vaccinated animals were treated with an 8-week regimen of isoniazid/rifampin/ethambutol (HRE) to prevent potential disseminated BCG as well as to determine whether this BCG exposure period was sufficient to confer protection. Four weeks after stopping HRE treatment and 12 weeks after BCG IV, animals were challenged with low-dose (~10 CFU) MtB Erdman via bronchoscope. Control animals consisted of SIV+ unvaccinated and SIV- vaccinated MCM that were all challenged with MtB.

Results: Administration of BCG IV in SIV+ MCM resulted in a notable spike in plasma SIV followed by natural reestablishment of viral control. Even prior to HRE treatment, SIV+ MCM exhibited no signs of disseminated BCG. Flow
cytometry of BAL revealed a rapid and sustained increase in mycobacteria-specific, cytokine-producing T cells in airways following BCG vaccination in both SIV+ and SIV- animals. Following TB challenge, 18F-FDG PET/CT imaging showed rapid TB progression in unvaccinated, SIV- animals, but complete absence of inflammation in 6 of 7 BCG IV-vaccinated SIV+ MCM. Remarkably, necropsy at 12 weeks after Mtb challenge showed the protected animals to be free of TB and without culturable bacilli in their tissues.

Conclusion: These data show that IV BCG is safe, immunogenic, and extraordinarily protective in SIV+ macaques.

732 EARLY BACTERICIDAL ACTIVITY OF MEROPENEM (+ AMOX/CLAV) WITH & WITHOUT RIFAMPICIN FOR TB

Veronique De Jager1, Ahmed A. Abufathi2, Hannelise Feyt1, Nikhil Gupte3, Naadira Vanker1, Grace Barnes4, Elana Van Brakel1, Eric Nuermberger1, Susan E. Dorman5, Elin M. Svensson6, Andreas H. Diacon1, Kelly E. Dooley4, for the COMRADE Study Team

1TASK Applied Science, Cape Town, South Africa, 2Stellenbosch University, Cape Town, South Africa, 3BIGMC Clinical Trials Unit, Pune, India, 4Johns Hopkins University School of Medicine, Baltimore, MD, USA, 5Medical University of South Carolina, Charleston, SC, USA, 6Radboud University Medical Center, Nijmegen, Netherlands

Background: A dose finding study was conducted to measure the early bactericidal activity (EBA) of meropenem and amoxicillin/clavulanate, with or without rifampicin, in patients with pulmonary tuberculosis.

Methods: In this Phase 2A RCT, patients with sputum smear-positive pulmonary TB were randomized to receive 14 days of: Meropenem 2g TID plus Rifampicin 20 mg/kg (Arm C); Meropenem 2g TID (Arm D); Meropenem 1g TID (Arm E) or Meropenem 3g QD (Arm F). All received Amoxicillin/Clavulanate. Overnight sputum was collected on days 0, 1, 2, 3, 4, 6, 8, 10, 12, 14. The mean daily fall in log colony forming units (CFU) of M. tuberculosis per mL of sputum over 14 days of treatment (EBA0-14CFU) was calculated. Intensive PK sampling over 8h was performed on Day 13. PK data were analyzed in R and WinNonLin. EBA0-14 CFU were calculated as (baseline log CFU/mL – log CFU/mL at day 14)/14.

Results: Sixty patients were recruited in Cape Town, South Africa. Mean (range) age was 36.8 years (19.9-62.7), 75% were male, and 23.3% were HIV-positive. Mean AUC0-24 for regimens C, D, E, and F were 573, 595, 289, and 315 h•mg/L, respectively; C max were 134, 134, 68.1, and 179 mg/L, respectively. Over 14 days, mean (95% CI) EBA0-14CFU were 0.11 (0.03-0.18), 0.11 (0.06-0.17), 0.05 (0.01, 0.09), and 0.03 (-0.01, 0.08), in Arms C, D, E, and F, respectively (Figure). Over the first 2 days of treatment, mean EBA0-2CFU were 0.39; 0.11; 0.14; and 0.02, in regimens C, D, E, and F, respectively.

Conclusion: Meropenem exhibits linear dose–dependent PK, and rifampicin does not impact its exposures. Addition of Rifampicin to Meropenem and Amoxicillin/Clavulanate increased early EBA (EBA0-2) but did not significantly increase 14-day EBA. 14-day EBA was significantly higher with Meropenem doses of 2g thrice–daily (total daily dose of 6g) than with total daily doses of 3g. With total daily doses of 3g, given once–daily or in divided doses, 14-day EBA was negligible, and similar. The activity of Meropenem against drug-resistant strains remains to be explored.

734 EFFECT OF RIFAMYCINS ON PRETOMANID EXPOSURE IN PATIENTS WITH PULMONARY TB

Mahmoud T. Abdelwahab1, Elisa Ignatius2, Paolo Denti1, Kelly E. Dooley3, Nikhil Gupte4, Rodney Dawson5, Grace Barnes6, Kim Narunskey7, Bronwyn Hendricks8, for the APT Study Team

1University of Cape Town, Cape Town, South Africa, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA, 3Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: Pretomanid is a novel anti-TB nitroimidazole that was granted FDA approval for treatment of XDR TB this year. It may be a useful drug for treatment shortening for drug-sensitive TB, if delivered with other potent sterilizing drugs. Pretomanid is 20% metabolized by CYP3A4 isoenzyme. In healthy volunteers, rifampicin reduced pretomanid AUC by 66% (from 13.7 vs. 42.5 mg•h/L) but there are no data in patients to guide pretomanid and rifamycin co-administration.

Methods: APT (Assessing Pretomanid For Tuberculosis) is a phase IIb RCT assessing the safety and efficacy of pretomanid added to first-line drugs over 12 weeks among patients with TB. Arm 1 received pretomanid 200 mg (Pa) plus isoniazid (H), rifampin (R), pyrazinamide (Z) for 8 weeks, followed by PaHR (weeks 9-12); Arm 2 received PaHRbZ for 8 weeks, followed by PaHbR (weeks 9-12); Arm 3 received standard therapy. This interim PK analysis includes 57 patients from Arms 1 and 2. PK samples were collected prior to and 1, 2, 5, 8, and 24 hr post-dose on day 14 and a standard meal was provided.

Results: A one-compartment model with first-order elimination and transit compartment absorption fitted the data well. Allometric scaling using body weight was applied to clearance (CL) and volume of distribution. Patients taking rifampin had a 44% reduction in AUC compared to rifabutin. The individual median estimates of Cmax were 2.15 and 3.40 mg/L for rifampin and rifabutin, respectively. For the AUC-24, the values were 29.9 and 58.9 mg•h/L. CL was 20% higher in men than women.

Conclusion: As part of a multidrug regimen, co-administration of pretomanid with rifampin increases the CL substantially compared to rifabutin. However, exposures in the rifampin arm in our study were similar to those seen in patients taking 200mg of pretomanid alone, without food (AUC of 36 mg•h/L). Though pretomanid co-administered with rifabutin is more likely to maintain exposure levels equal to or exceeding regimens that do not contain rifamycins, the reduced exposure with rifampicin is less pronounced when given with food and may still permit co-administration.

735 CLINICAL PHARMACOKINETICS AND TOXICODYNAMICS OF LINEZOLID IN THE NIX-TB TRIAL

Marjorie Imperial1, Jerry Nedelman2, Radojka M. Savic3

1University of California San Francisco, San Francisco, CA, USA, 2Global Alliance for TB Drug Development, New York, NY, USA

Background: FDA recently approved a high dose linezolid (LZD) containing regimen in combination with pretomanid and bedaquiline (BPAL) for treatment of extremely drug resistant-tuberculosis (XDR-TB). WHO also prioritized LZD for the treatment of DR-TB. Use of LZD is associated with significant toxicities, but limited data is available on optimal dosing and best clinical practices for LZD. We performed population pharmacokinetic (PK)-toxicodynamic modeling and simulation to quantify PK/toxicity relationships of LZD as part of a 6-month BPAL regimen from the NiX-TB study.

Methods: Data was available for 88 patients; all initially administered 1200 mg LZD daily (BID or QD schedules). Dose adjustments of LZD were allowed per discretion of the investigator to manage LZD toxicity. LZD PK profiles that accounted for individual dosing histories were predicted from the PK model and linked to safety profiles. Delayed PK/toxicity response models described suppression of platelets (PLT) and hemoglobin (HB). A proportional odds model described graded peripheral neuropathy (PN) rates over time. Final models were used to simulate and compare PK and safety outcomes following daily doses of 1200 mg LZD as well as alternative dosing regimens.
Results: LZD PK was described by a two-compartment model with nonlinear clearance. At 1200 mg QD and 600 mg BID nonlinearity was mild with steady-state average concentrations of 11 and 9.8 mg/L. HB and PLT suppression and PN were each significantly (p<0.001) related to LZD PK. HB production was largely suppressed for LZD concentrations above 7.7 mg/L, consistent with anemia reported for ~40% of subjects. Simulations indicated that the median time to onset of severe anemia was 9 weeks and HB values at baseline and week 4 might predict severe anemia (ROC AUC=0.91) better than LZD PK troughs (0.56). A greater than 10% decrease in HB levels at week 4 had maximum sensitivity and specificity to predict severe anemia and a dose reduction to 600 mg QD for these patients prevented 65% of severe anemia cases. For PN, simulations showed reversal by 3 months for most patients following dose reductions or termination, with the more aggressive adjustments better minimizing longer durations. The significant PK/PLT effect was small, consistent with thrombocytopenia reported in only 6% of subjects.

Conclusion: QD and BID dosing had comparable toxicity. PN is reversible and week 4 HB levels can be used to guide early dose adjustments to prevent anemia.

Management strategy to predict and prevent severe anemia cases.
A. Decision tree algorithm for the proposed management strategy to predict severe anemia cases, defined as Division of Microbiology and Infectious Disease Grade 3 or greater anemia toxicity (HB levels < 9 g/dL). B. Simulated hemoglobin profiles following 1200 mg QD dose of linezolid for full 6-months of treatment (left panel) and following implementation of anemia toxicity management strategies for initial 1200 mg QD dose (right panel). Solid black lines represent the typical patient (median of 1000 simulations) and the shaded areas the 90% prediction interval. Red dashed line represents Grade 2 toxicity threshold (hemoglobin levels < 9.5 mg/dL) and red solid line represents Grade 3 toxicity threshold (hemoglobin levels < 8 mg/dL).

736 DRUG-RESISTANCE MUTATIONS AND TUBERCULOSIS MORTALITY IN HIGH-BURDEN COUNTRIES
Veronika Skrivankova1, Matthias Egger2, for the IeDEA TB Genomics Group 1Institute of Social and Preventive Medicine, Bern, Switzerland, 2University of Bern, Bern, Switzerland

Background: Strategies to control Mycobacterium tuberculosis (Mtb) drug resistance include universal access to quality-controlled drug resistance (DR) testing coupled with aligned treatment regimens and patient centred treatment support. We examined the impact of drug resistance mutations (DRM) on mortality in HIV+ and HIV- patients with TB in eight high-burden countries.

Methods: We included 247 HIV+ and 335 HIV- adult patients diagnosed with TB in Kenya, South Africa, Democratic Republic of the Congo, Nigeria, Côte d’Ivoire, Peru and Thailand; 60 patients died during treatment. Sampling was stratified by HIV status and on-site DR diagnosis, as determined by locally available tests (Xpert/LPA and/or culture). Whole genome sequences (WGS) were scanned for high-confidence DRM. We compared the DR profiles diagnosed at sites with the DRM from WGS to identify the most common mutations and the DR missed locally. We used logistic regression to examine their association with mortality during TB treatment, adjusted for sex, age and HIV status. We ran a separate model for each DRM with frequency >20 and for combined groups of rare DRM.

Results: The most common mutations in our sample were S315T, S450L, L79S, C217W, M20G (details in Table 1). While DR to rifampicin (RIF) was missed only in 2% of cases, DR to isoniazid (INH) was missed in 25% of cases and for all other drugs in >70% cases. The DRM individually associated with the largest increase in mortality were S315T with OR 3.7 (95%CI: 2.2-6.5), D453V with OR 4.13 (95%CI: 2-8.5), S450L with OR 3.8 (95%CI: 2.2-6.5), RIF to aminoglycoside (Gm) was missed in 96% of cases and for all other drugs in >70% cases. The DRM individually associated with the largest increase in mortality were S315T with OR 3.7 (95%CI: 2.2-6.5), D453V with OR 4.13 (95%CI: 2-8.5), RIF to aminoglycoside (Gm) was missed in 96% of cases and for all other drugs in >70% cases. The DRM individually associated with the largest increase in mortality were S315T with OR 3.7 (95%CI: 2.2-6.5), D453V with OR 4.13 (95%CI: 2-8.5), S450L with OR 3.8 (95%CI: 2-8.5), E453K with OR 4.3 (95%CI: 2-8.5), the OR for groups of rare DRM conferring resistance to RIF, ethambutol (EMB) and all second-line drugs were also statistically significant, ranging from 2.9 to 4.5. Results were similar in HIV+ and HIV- patients.

Conclusion: We identified several DRM associated with increased mortality in patients infected with Mtb in eight high-burden countries. Many of the conferred DR were missed by local DR testing, potentially leading to an inadequate treatment. Our results highlight the critical need of rapid molecular point-of-care DR tests that cover a broader range of DR and thus could contribute to more effective treatment and reduced mortality among patients with MDR TB.

Table 1:

<table>
<thead>
<tr>
<th>DRM</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>2.2</td>
<td>(1.2-4.1)</td>
</tr>
<tr>
<td>Gm</td>
<td>4.3</td>
<td>(2.8-6.5)</td>
</tr>
<tr>
<td>RIF</td>
<td>3.7</td>
<td>(2.2-6.5)</td>
</tr>
<tr>
<td>D453V</td>
<td>4.13</td>
<td>(2-8.5)</td>
</tr>
<tr>
<td>S450L</td>
<td>3.8</td>
<td>(2-8.5)</td>
</tr>
<tr>
<td>S315T</td>
<td>3.7</td>
<td>(2.2-6.5)</td>
</tr>
</tbody>
</table>
737 CSF TB BACILLARY LOAD PREDICTS 2-WEEK MORTALITY IN HIV-ASSOCIATED TB MENINGITIS

Emily Martyn1, Ananta Bangdiwala2, Enock Kagimu1, Morris K. Rutakingirwa1, John Kasibante1, Michael Okirwoth1, Gavin Stead1, Vincent Wadda3, and Matthew Pullen2

University of Pennsylvania, Philadelphia, PA, USA, 2McGill University, Montreal, QC, Canada, 3Mulago National Referral Hospital, Kampala, Uganda, University of Kansas, Lawrence, KS, USA, 4London School of Hygiene & Tropical Medicine, London, UK

**Background:** Tuberculous meningitis (TBM) carries a ~40% in-hospital mortality in HIV-positive persons and neurologic sequelae are frequent among survivors. WHO has recommended GeneXpert MTB/RIF Ultra (Ultra), a fully automated PCR assay, as the initial TBM diagnostic test. TB bacillary load can be estimated by PCR Cycle threshold (Ct) values, which represent the number of PCR cycles required for probe signal to reach a detection threshold (low Ct value = high bacillary load). Based on PCR Ct values and configuration of probe positivity, Ultra reports 5 semi-quantitative categories of: trace, very low, low, medium and high. We aimed to explore whether CSF TB bacillary load (by Ct value or semi-quant category) is associated with mortality.

**Methods:** We prospectively enrolled 107 HIV+ Ugandans with TBM from April 2015 to August 2019. Ultra semi-quant category and Ct tertiles were separately analysed as predictors of 2-week mortality. We investigated associations between Ct and baseline clinical and CSF parameters.

**Results:** Subjects in the lowest Ct tertile (i.e. highest bacillary load) had 60% 2-week mortality; significantly worse than the intermediate (18%) and highest (26%) Ct tertiles and Ultra-negative (31%) probable TBM cases (Figure, p=0.03). Using the reported Ultra semi-quant category, subjects with medium-low semi-quant category also trended toward worse 2-week survival (50%) compared to very low (22%), trace (27%) and negative (31%) categories but was not statistically significant (p=0.25). Participants with negative Ultra results (probable TBM) had evidence of CSF inflammation and a high mortality (31%), suggesting a bacillary load undetectable by Ultra is not associated with improved survival. TB bacillary load was not associated with focal neurological deficit but a high bacillary load was associated with higher CSF lactate levels (p=0.04).

**Conclusion:** High CSF TB bacillary load, as measured by Ultra Ct, is associated with over 2-fold higher 2-week mortality in HIV-associated TBM, being a better predictor than the reported Ultra semi-quant category. This is the first study to investigate Ultra Ct values and TBM outcomes and raises the possibility of Ultra Ct values being used to identify patients at greatest risk of death and who may benefit from enhanced supportive care or intensified TBM treatment.

---

**Table 1:** Description of most common DRMs and groups of rare DR in number (% of mixed DR and odds ratios for death during the TB treatment.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Gene</th>
<th>DR resistance</th>
<th>No. (%)</th>
<th>Mortality OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA/IR</td>
<td>rpsl</td>
<td>IR</td>
<td>64 (2.5%)</td>
<td>0.36 (0.18, 0.73)</td>
</tr>
<tr>
<td>D554/IV</td>
<td>rpsl</td>
<td>IR</td>
<td>62 (1.0%)</td>
<td>3.75 (1.20, 6.44)</td>
</tr>
<tr>
<td>any other RIF</td>
<td>rpsl</td>
<td>IR</td>
<td>74 (3.1%)</td>
<td>3.85 (1.06, 13.15)</td>
</tr>
<tr>
<td>SL1</td>
<td>katG</td>
<td>INH, ETH</td>
<td>152 (23.2%)</td>
<td>3.74 (2.31, 5.69)</td>
</tr>
<tr>
<td>C-LS</td>
<td>rpsl</td>
<td>INH, ETH</td>
<td>43 (13.9%)</td>
<td>2.02 (0.87, 4.66)</td>
</tr>
<tr>
<td>any other RIF</td>
<td>katG</td>
<td>INH, ETH</td>
<td>43 (15.5%)</td>
<td>1.57 (0.63, 3.94)</td>
</tr>
<tr>
<td>MO95</td>
<td>rpsl</td>
<td>EMB, EMB</td>
<td>63 (3.3%)</td>
<td>2.33 (0.85, 6.36)</td>
</tr>
<tr>
<td>MDR3</td>
<td>rpsl</td>
<td>EMB, EMB, EMB</td>
<td>39 (31.0%)</td>
<td>1.71 (0.87, 4.98)</td>
</tr>
<tr>
<td>any other EMB</td>
<td>rpsl</td>
<td>EMB, EMB</td>
<td>40 (38.5%)</td>
<td>4.43 (2.09, 9.43)</td>
</tr>
<tr>
<td>L749</td>
<td>gdhB</td>
<td>SM</td>
<td>49 (50.0%)</td>
<td>4.12 (2.01, 8.49)</td>
</tr>
<tr>
<td>L274</td>
<td>gdhB</td>
<td>SM</td>
<td>39 (9.4%)</td>
<td>1.76 (0.80, 3.81)</td>
</tr>
<tr>
<td>any other SM</td>
<td>rpsl</td>
<td>SM, emB, emB</td>
<td>41 (3.82%)</td>
<td>3.15 (1.72, 7.21)</td>
</tr>
<tr>
<td>any other ET</td>
<td>rpsl</td>
<td>EMB, EMB, EMB</td>
<td>45 (300%)</td>
<td>2.92 (1.43, 6.37)</td>
</tr>
<tr>
<td>any gq</td>
<td>rpsl</td>
<td>EMB</td>
<td>25 (77.1%)</td>
<td>4.50 (1.62, 12.47)</td>
</tr>
<tr>
<td>any gq</td>
<td>rpsl</td>
<td>EMB</td>
<td>35 (9.0%)</td>
<td>0.29 (0.14, 0.60)</td>
</tr>
</tbody>
</table>

* CI adjusted for age, sex, HIV status, INH, rifampin, RIF, ethambutol, EMB, streptomycin, INH, ethambutol, EMB, ciprofloxacin.

**738 MORTALITY IN ADULT HIV/MDR-TB BY ART USE: INDIVIDUAL PATIENT DATA META-ANALYSIS**

Gregory P. Bisson1, Mayara Bastos2, Jonathan Campbell3, Didi Bang4, James C. Brust5, Petro Isakidios5, Christopher Lange6, Giovanni Battista Migliori7, Jean William Pape8, Domingo Palmero3, Staci C. Vibulb9, Petros Isaakidis5, Christoph Lange6, Giovanni Battista Migliori7, Jean William Pape8, Suzanne Marks9, William Pape8, Domingo Palmero3, Staci C. Vibulb9, Petros Isaakidis5, Christoph Lange6, Giovanni Battista Migliori7, Jean William Pape8, Suzanne Marks9, William Pape8, Domingo Palmero3, Staci C. Vibulb9, Petros Isaakidis5, Christoph Lange6, Giovanni Battista Migliori7, Jean William Pape8, Suzanne Marks9

1Infectious Disease Institute, Kampala, Uganda, 2University of Minnesota, Minneapolis, MN, USA, 3Mulago National Referral Hospital, Kampala, Uganda, 4University of Kansas, Lawrence, KS, USA, 5London School of Hygiene & Tropical Medicine, London, UK

**Background:** Tuberculosis and HIV infection is associated with increased adjusted odds of death during treatment for multidrug-resistant tuberculosis (MDR-TB), but factors affecting this risk have been difficult to identify because of low MDR-TB incidence in any one setting. We examined how the use of HIV anti-retroviral therapy (ART) and effective antitubercular medications modify mortality among adults with MDR-TB and HIV using a large, multi-country database.

**Methods:** We conducted a individual patient data meta-analysis (IPD) from studies published between 2009 and 2018 of adults from 40 countries/regions with MDR-TB, systematic drug susceptibility testing for fluoroquinolones (FQ) and second-line injectables (SLI), and known HIV status who were not lost to follow-up. Data included clinical and demographic characteristics, use of ART, and ever-use of antitubercular medications (grouped according to World Health Organization (WHO) categorizations). The primary outcome was death, compared to treatment success, treatment failure, and relapse. Patients without HIV were compared to HIV+ (all), HIV+/on ART, and HIV+ /no or unknown ART using logistic regression after exact matching on country-level income, SLI and FQ resistance and after propensity score matching on age, sex, site, year of treatment initiation, previous TB treatment, directly observed therapy, and acid-fast-bacilli-smear positivity to obtain adjusted odds ratios (aORs) and 95% confidence intervals (CI).

**Results:** Of 10,044 patients, 3,215 (32%) were HIV-infected, 2,504 (25%) were HIV+/on ART, 6,066 (60%) were males, 9,615 (96%) had only pulmonary TB, and 1,611 (16%) had extensively drug-resistant TB. The aOR of death for those with HIV (all) vs HIV-negative patients was 2.4 (2.1-2.8), and varied according to ART use (1.8 [1.5-2.2] for HIV+/on ART vs 4.6 [3.0-7.1] for HIV+/no or unknown ART) (Table). Among persons with HIV, aORs for death were lowest for HIV+/on ART, HIV+ patients receiving at least 5 effective drugs, and HIV+ patients on WHO Group A drugs (later generation FQs, rifampicin, EMB, streptomycin, INH, ethambutol, EMB, ciprofloxacin).

**Conclusion:** In a large, diverse population of HIV-infected adults with MDR-TB, HIV-infection is associated with an increased adjusted odds of death during MDR-TB treatment, but use of ART and more effective antitubercular drugs
739 CD4 COUNT AND VIRAL LOAD DYNAMICS UNDER DIFFERENT ART REGIMENS IN HIV/TB COINFECTION

Rosana Elisa G. Pinho1, Ana R. Patai Pascom2, Kleydson Alves, Patricia B. Oliveira1, Ana Isabel Menezes1, Filipe Barros Perini1, Ronaldo De Almeida Coelho1, Gerson F. Pereira1, Vivian I. Avelino-Silva2

1Ministry of Health, Brasília (DF), Brazil, 2Universidade de São Paulo, São Paulo, Brazil

Background: Tuberculosis (TB) is still a leading cause of morbidity and mortality among people living with HIV (PLHIV). Although it is widely accepted that the use of antiretroviral treatment (ART) reduces the risk of death among HIV-TB coinfected patients, studies comparing the efficacy of different ART regimens in this population are scarce.

Methods: Retrospective cohort using real life data collected by the Brazilian Ministry of Health HIV program. We included all HIV-TB coinfected patients aged ≥18 years-old who had a first ART delivery up to 6 months after TB notification, with regimens containing lamivudine + tenofovir combined with either Elvitegravir (EFV), Raltegravir (RAL) or Dolutegravir (DOL) between Jan 2017-Dec 2018. We analyzed the percentage of undetectable (<200 copies/ml) HIV viral load (VL) and mean change in CD4+T cell counts at 90-180 days after ART initiation in each treatment group adjusted for sex, age, social vulnerability index and baseline values of CD4+T cell counts and HIV VL.

Results: 1427 HIV-TB coinfected patients were included. Patients were mostly young (84% <50 years old), males (79%), of black/mixed color (48%). Baseline HIV VL was >10,000 for most patients (79%), and CD4+ T cell counts were <200/mm3 for 71% of the sample. Overall, 78.1% of HIV-TB coinfected patients had HIV VL<200/ml at 90-180 days after ART initiation (95% CI 75.8-80.3); CD4+ T cell increment at 90-180 days after first ART prescription was 148 cells/mm3 (SD 156), with mean increment of 156, 139 and 154 cells/mm3 among patients receiving RAL, EFV and DOL, respectively.

We found no statistically significant differences in the percentage of undetectable HIV VL or CD4+T cell count increment at 90-180 days after ART initiation according to ART regimen in univariable models or after adjustment for potential confounders.

Conclusion: Although studies comparing different ART regimens in PLHIV without TB suggest that VL suppression is achieved more frequently and faster with regimens containing integrase inhibitors when compared to those with EFV, we failed to find similar results among patients with TB. Our findings are relevant in reassuring that RAL and DOL can replace EFV for HIV-TB coinfected patients. This is of greater importance for HIV-TB coinfected patients with EFV resistance mutations or significant intolerance.

740 SUBOPTIMAL TUBERCULOSIS TREATMENT COMPLETION: A MULTICENTER OBSERVATIONAL STUDY

Felipe Ridiolfi1, Lauren Saag Peetluk1, Gustavo Amorim1, Megan M. Turner2, Marina Cunville1, Marcelo Cordeiro-Santos3, Solange Cavalcante1, Afrânio Kritski1, Betina Durovni1, Bruno Andrade1, Timothy R. Sterling1, Valéria C. Rolla1,1 Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, 2Vanderbilt University, Nashville, TN, USA, 3Fundação de Medicina Tropical Doutor Heitor Vieira Dourado, Manaus, Brazil, 4Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, 5Osvaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil, 6Instituto Gonçalo Moniz, Salvador, Brazil

Background: Standard anti-tuberculosis (TB) treatment includes two months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by four months of isoniazid and rifampicin. To meet the WHO target for reduction in TB deaths by 2025, programs must strive for 90% TB treatment completion. Treatment discontinuation due to treatment toxicity or other reasons may interrupt the course of treatment and decrease effectiveness.

Methods: This 4-year (2015-2019), multicenter, prospective cohort study in Brazil included culture-confirmed, drug-susceptible, pulmonary TB patients who started standard TB treatment. All participants were followed for >9 months from enrollment and were categorized into three groups: (I) treatment discontinuation – treatment interruption before 6 months, default, or loss to follow-up prior to treatment completion, (II) treatment completion within 9 months, and (III) treatment completed, but duration >9 months.

Results: Among 797 patients included, 592 (74%) completed their first-line treatment regimen, 161 (20%) had early treatment discontinuation, and 44 (6%) were on first-line treatment longer than 9 months. Compared to patients who completed treated, those who discontinued were more likely PLWH (32% vs 14%, p<0.01), younger (median age 34 vs 36, p=0.06), and male (80% vs 64%, p<0.01). Overall, the reasons for treatment discontinuation were death (28%, p<0.01), treatment abandonment/loss to follow up (92, 57%), treatment toxicity (9, 6%), resistance detection (7, 4%), or other/unknown reasons (18, 11%). Compared to those without HIV, PLWH were more likely to discontinue due to toxicity (15% vs 1%) and death (33% vs 10%), but less likely to discontinue due to abandonment/loss to follow up (46% vs 62%) and resistance (0% vs 6%). PLWH who discontinued treatment were less likely to be on ART at baseline than PLWH who completed treatment within 9 months (29% vs 50%, p=0.01). CD4 count and viral load were similar among PLWH in all three groups. Patients who received treatment for >9 months, were similar to those who completed treatment within 9 months regarding sex, but were older (median age 43 vs 36, p<0.01) and more likely PLWH (27% vs 14%, p=0.02) – rates of ART at baseline were similar between the treatment completion groups.

Conclusion: This study highlights suboptimal TB treatment completion rates, due primarily to death and loss to follow-up. This reinforces the need for early ART initiation and better-tolerated TB treatment regimens, particularly in PLWH.

741 N-ACETYLCYSTEINE FOR ANTI-TB DRUG-INDUCED LIVER INJURY: A RANDOMISED CONTROLLED TRIAL

Muhammed S. Moosa1, Gary Maartens2, Hannah Gunter1, Shaazia Allie2, Masikhlo Sethshedi2, Mahamed F. Chuqylay2, Nicole Kramer1, Annemie Stewart1, Wendy Spearman1, Mark Sonderup1, Karen Cohen1

1University of Cape Town, Cape Town, South Africa

Background: First-line anti-tuberculosis (TB) therapy can cause liver injury. N-Acetylcysteine (NAC) is widely used in patients with paracetamol toxicity and there is limited evidence of benefit in liver injury due to other causes.

Methods: We conducted a randomised, double-blind, placebo-controlled trial to assess whether intravenous NAC improves liver recovery in adult patients admitted to hospital with first-line anti-TB drug induced liver injury (AT-DILI), diagnosed by alanine transaminase (ALT) ≥3 times upper limit of normal (ULN) with hepatitis symptoms or ALT ≥5 times ULN if asymptomatic. NAC was dosed as paracetamol toxicity guidelines. The primary endpoint was the...
time for ALT to fall below 100 U/L. Secondary endpoints included duration of hospitalization, in-hospital mortality and adverse events. We compared time to ALT<100 U/L and time to discharge from hospital using Kaplan–Meier analyses and log-rank tests. We included all participants who commenced NAC/placebo infusion in the analysis.

**Results:** Fifty-three participants received NAC and 49 placebo. Mean age was 38 years (SD±10), 38 (57%) were female and 89 (87%) were HIV positive, 40 (45%) of whom were on antiretroviral therapy. Median serum ALT and total bilirubin at presentation were 462 U/L (IQR 266-790) and 56 mmol/L (IQR 25-100) respectively. There was no difference in the time to ALT<100 U/L (figure 1A), with a median of 7.5 days (IQR 5.5-11) and 8 days (IQR 5-13) in the NAC and placebo arms respectively. Hospital stay was shorter in participants who received NAC (figure 1B), log rank p=0.0093; median hospital stay was 9 days (IQR 6-15) in the NAC arm and 18 days (IQR 10-25) in the placebo arm. Mortality was 14% and did not differ by study arm. The infusion was stopped early due to an adverse reaction in 5 participants, all of whom were receiving NAC (nausea and vomiting in 3, anaphylactoid reaction in 1, drip site pain in 1).

**Conclusion:** NAC did not shorten time to ALT<100 U/L in participants with AT-DILI. However, NAC significantly reduced duration of hospital stay. NAC may contribute to the development of CLD and also remain at risk for pulmonary opportunistic infections including tuberculosis (TB) that may contribute to the development of CLD. We hypothesized that prior active TB would independently increase the risk for CLD and sought to determine whether HIV modifies the relationship between TB and CLD.

**Methods:** This is a cross-sectional, interim analysis of a cohort of PLWH with well controlled HIV and uninfected adults in Kisumu, Kenya, enrolled from 12/2018 through 10/2019. All participants underwent standardized spirometry and a validated respiratory specific questionnaire. Prior active TB and pneumonia were based on self-report. Multivariable logistic regression was used to evaluate cofactors of CLD as defined by spirometry: obstructive, restrictive, and impaired (a composite of obstructive and/or restrictive patterns). Effect modification was evaluated by an interaction term between HIV and impaired lung function.

**Results:** We have enrolled 474 participants (79% of target sample size), 246 PLWH and 228 uninfected. PLWH are more likely to report prior active TB (28% vs 4%, p<0.0001) and pneumonia (28% vs 19%, p=0.008). Impaired lung function is more common in PLWH compared to uninfected participants (21% vs 14%, p=0.07). Of those reporting prior TB, a similar proportion of PLWH and uninfected adults had impaired lung function (36% vs 30%, respectively; p=0.05). In multivariable analyses, prior TB was associated with impaired lung function among all participants (aOR 3.1, 95% CI 1.75-5.7, p=0.004) (Table). In separate multivariable analyses, prior TB was also associated with obstructive spirometry (aOR 2.7, 95% CI 1.35-5.8, p=0.009). An interaction between HIV and impaired spirometry was not statistically significant.

**Conclusion:** In adjusted models, impaired lung function was not significantly associated with HIV but was strongly associated with prior active TB, which was more common in PLWH. Prior TB was also more likely to be associated with an obstructive as opposed to restrictive pattern. TB may potentially account for a greater prevalence of CLD in PLWH, but we did not find evidence for an interaction between HIV and TB in the risk for impaired spirometry in this ongoing cohort. Future work should investigate mechanisms and potential management strategies that could mitigate the risk of impaired lung function in those with prior TB.

**Table. Multivariable analysis of cofactors of impaired lung function**, and all or either obstruction or restriction.

<table>
<thead>
<tr>
<th>Impaired lung function</th>
<th>p-value</th>
<th>Obstruction</th>
<th>p-value</th>
<th>Restriction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>0.197</td>
<td>0.11</td>
<td>0.91</td>
<td>0.17</td>
<td>0.71</td>
</tr>
<tr>
<td>Prior TB</td>
<td>0.004</td>
<td>0.03</td>
<td>0.009</td>
<td>0.009</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.14</td>
<td>0.03</td>
<td>0.15</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>0.90</td>
<td>0.13</td>
<td>0.83</td>
<td>0.014</td>
<td>0.014</td>
</tr>
<tr>
<td>Age</td>
<td>0.12</td>
<td>0.019</td>
<td>0.08</td>
<td>0.01</td>
<td>0.014</td>
</tr>
<tr>
<td>BMI</td>
<td>0.36</td>
<td>0.005</td>
<td>0.96</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Kreatinose size</td>
<td>0.64</td>
<td>0.005</td>
<td>0.96</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Wood use</td>
<td>0.68</td>
<td>0.005</td>
<td>0.93</td>
<td>0.005</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Figure 1.** Correlative analysis of time to ALT<100 U/L and time to hospital discharge in participants with AT-DILI treated to NAC/placebo.
744 EARLY FUNGICIDAL ACTIVITY AS SURROGATE ENDPOINT FOR CRYPTOCOCCAL MENINGITIS SURVIVAL

David R. Boulware1, Matt Pullen1, Katherine Huppier Hullsiek1, Joshua Rhein1, Lillian Tugume1, Edwin Nuwagira2, Kenneth Siebambulidize1, Mahsa Abassi2, Radha Rajasingham1, Katelyn Pastick1, Caleb P. Skipper1, Abu Musubire1, Conrad Muzorra2, David Meyla2, for the ASTRO-CM Team

1University of Minnesota, Minneapolis, MN, USA, 2Infectious Disease Institute, Kampala, Uganda, 3Mbarara University of Science and Technology, Mbarara, Uganda

Background: In cryptococcal meningitis phase 2 clinical trials, early fungicidal activity (EFA) of Cryptococcus yeast clearance from cerebrospinal fluid (CSF) is used as a surrogate endpoint. The US FDA allows for surrogate endpoints for accelerated regulatory approval, but there are no accepted surrogate endpoints for this neglected disease. For tuberculosis, the FDA recognizes an official surrogate endpoint as “time to sputum culture conversion to negative.” We examined the relationship between the rate of CSF Cryptococcus clearance (i.e. EFA) and mortality through 18 weeks.

Methods: We pooled individual-level CSF data from 3 sequential cryptococcal meningitis clinical trials conducted in Uganda during 2010-2013 (COAT trial, n=162; also in South Africa), 2013-2014 (ASTRO-CM pilot, n=179), and 2015-2019 (ASTRO-CM trial, n=397). All subjects received amphotericin B deoxycholate + fluconazole induction therapy and had serial quantitative CSF cultures performed. The log10 transformed colony forming units (CFU) per mL CSF were analyzed by general linear regression vs day of CSF culture over the first 10 days. The slope of the fit line is the EFA or the rate of CSF fungal clearance in units of log10 CFU/mL/day. We grouped subjects by EFA and compared mortality by Kaplan-Meier.

Results: 738 subjects had non-sterile initial cultures with a calculable EFA (median 0.38; IQR, 0.20-0.57 log10 CFU/mL). Risk of death through 18-weeks was higher with EFA <0.20 log10 CFU/mL/day (37% mortality; Hazard Ratio 1.60; 95%CI, 1.25 to 2.04; P=0.002). Mortality through 18-weeks was 37% for EFA ≥0.60 (n=170), 36% for EFA 0.40-0.59 (n=182), 39% for EFA 0.30-0.39 (n=112), and 35% for EFA 0.2-0.29 (n=87). When adjusting for baseline Glasgow coma scale, hemoglobin, CSF quantitative culture, CSF WBC, biological sex, and cohort, EFA remained significant (adjusted Hazard Ratio 1.83, 95%CI, 1.40 to 2.40; P<0.001).

Conclusion: EFA was associated with all-cause mortality using individual level data from 738 subjects receiving amphotericin-combination induction therapy. An EFA better than 0.20 log10 CFU/mL/day was associated with similar survival, and this threshold may be considered a target for a surrogate endpoint. Yet, 25% of patients receiving amphotericin had EFAs worse than 0.20 log10 CFU/mL/day, with 50% mortality. This builds upon prior systematic reviews of smaller pooled studies from different sites to validate EFA as a surrogate endpoint.

745 EVALUATING THE IMMY SEMI-QUANTITATIVE CrAg LFA IN HIV-POSITIVE PATIENTS IN BOTSWANA

Kwane Lechile1,2, Mark W. Tenforde1, Thandi Milton1, Amber Booze1, Tshepo B. Leeme1, Leabaneng Tawe3, Charles Muthoga3, Fredah Mulenga1, Radhika Rulaganangy1, Julia Ngidi1, Desira Mine1, Joseph N. Jarvis1

1Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 2University of Washington, Seattle, WA, USA, 3Botswana–UPenn Partnership, Gaborone, Botswana, 4National Health Laboratory, Gaborone, Botswana, 5London School of Hygiene & Tropical Medicine, London, UK

Background: Cryptococcal antigen (CrAg) titers are an important prognostic indicator in HIV-positive patients with cryptococcal infection and could potentially be used to stratify treatment. Current titration methods are expensive and labor intensive. A novel semi-quantitative (SQ) CrAg test has been developed that can provide an indication of CrAg titer using a simple dipstick lateral flow assay (LFA). We performed a study to evaluate the performance of the SQ-CrAg assay against the standard CrAg LFA in patients with HIV-associated cryptococcal infection in Gaborone.

Methods: Residual EDTA blood samples from sequential HIV-positive patients undergoing routine CrAg testing with CD4 counts of ≥200 cells/mL were screened through the reflex CrAg-screening program in Botswana using both the IMMY CrAg LFA and the novel SQ-CrAg LFA. The sensitivity and specificity of the SQ-CrAg in the reflex CrAg screening cohort were determined relative to the standard CrAg LFA. To further validate the SQ assay known CrAg+ EDTA blood samples from a prior CrAg-screening study and a CM treatment trial were also tested with both assays. Serial dilutions were performed for all CrAg+ samples and re-tested with the standard LFA to determine titres. SQ titers and conventional titers were compared. All testing was performed by two independent blinded investigators and inter-rater reliability assessed using the Kappa coefficient.

Results: 692 sequential samples were screened using both assays; 43 (6.2%) were IMMY CrAg LFA-positive. Using this standard CrAg LFA as a reference, the overall sensitivity and specificity of the novel SQ-CrAg LFA were 93.0% (95%CI 89.0 – 95.9%) and 93.8% (95%CI 91.7-95.6%) respectively. A further 180 known CrAg+ samples were tested and the combined results used to evaluate the SQ-CrAg quantification. Median (IQR) CrAg titers for SQ-CrAg 1+, 2+, 3+, and 4+ bands were 1.00 (1.00 – 2.00), 1.00 (1.00 – 2.00), 2.00 (1.00 – 4.00), and 3.00 (2.00 – 8.00) respectively (Figure 1). Inter-rater agreement in titer assessment was excellent at 98.2%, with a kappa coefficient of 0.96, p<0.001.

Conclusion: Overall sensitivity and specificity of the novel IMMY SQ-CrAg assay were high in a cohort of HIV-positive individuals with CD4 counts ≥200 cells/mL undergoing reflex CrAg screening. An SQ titre of 3+ or greater corresponded to a titer of ≥1:160 which has previously been shown to be associated with increased mortality.
HIGH RATES OF MENINGITIS OR MORTALITY AMONG CrAg+ PLHIV WITH CD4 100-200 CELLS/MM³

James H. Wykowski1, Paul K. Drain1, Sean Galagan1, Sabina M. Goveree2, Connie L. Celum1, Mahomed-Yunus Moosa1, Carole Wallis3

1University of Washington, Seattle, WA, USA, 2AIDS Healthcare Foundation, Durban, South Africa, 3University of KwaZulu-Natal, Durban, South Africa

Background: Cryptococcal antigen (CrAg) screening with fluconazole prophylaxis has been shown to prevent cryptococcal meningitis and mortality for people living with HIV (PLHIV) with CD4 <100 cells/mm³. While cryptococcal meningitis occurs in individuals with CD4 100-200 cells/mm³, there is limited evidence that CrAg screening predicts cryptococcal meningitis or mortality among this group with moderate immunosuppression. Current IDSA and WHO clinical guidelines recommend restricting CrAg screening to PLHIV with CD4 <100 cells/mm³.

Methods: We conducted a prospective cohort study of PLHIV >=18 years who had not initiated ART in South Africa. We followed participants for 14 months to determine onset of cryptococcal meningitis or all-cause mortality. At study completion, we retrospectively tested stored serum samples for CrAg using an enzyme immunoassay (EIA). We calculated CD4-stratified incidence rates of CrAg positivity and outcomes.

Results: We enrolled 2,383 PLHIV, and 1,309 participants and had serum samples tested by CrAg EIA. The median CD4 was 317 cells/mm³ (interquartile range: 173-491 cells/mm³). By CD4 count at baseline, there were 209 individuals with a CD4 count of 100-200 cells/mm³, with available CD4 test results and four (1.9%) tested positive. Among this group, two of four (IR: 58.8 per 100 person-years) CrAg+ participants and 11 of 205 (IR: 5.6 per 100 person-years) CrAg- participants developed cryptococcal meningitis or died for an overall rate of death or cryptococcal meningitis that was 10.0 times higher for those who were CrAg+ (CI: 2.2-45.3) (figure). Among those with CD4 <100 cells/mm³, CrAg EIA test results (n=179), ten (5.6%) participants tested CrAg+. Among this group, seven of ten (IR: 137.6 per 100 person-years) CrAg+ participants and 26 of 169 (IR: 17.8 per 100 person-years) CrAg- participants developed cryptococcal meningitis or died for a rate of death or cryptococcal meningitis that was 6.3-times higher for those who were CrAg+ (CI: 2.7-14.6).

Conclusion: Although few PLHIV with moderate immunosuppression screened CrAg positive, a positive CrAg test was predictive of increased risk of cryptococcal meningitis or death. Systematic CrAg screening may reduce morbidity and mortality in PLHIV with CD4 100-200 cells/mm³.

CSF CYTOKINES AND CHEMOKINES ASSOCIATED WITH MORTALITY IN CRYPTOCOCCAL MENINGITIS

Elizabeth C. Okaror1, Liliane Mukaremera1, Nicole Wyman Engeri2, Katherine Huppler Hullsie1, Lillian Tugume2, Kenneth Ssebambulidde3, Abdul Musubire3, Edwin Nuwagira1, Edward Mpoza2, Darlisha A. Williams1, Conrad Musoro4, David Meya2, Joshua Rhein1, David R. Boulware1, for the ASTRO-CM Team

1University of Minnesota, Minneapolis, MN, USA, 2Infectious Disease Institute Kampala, Uganda, 3Mbarara University of Science and Technology, Mbarara, Uganda

Background: Cryptococcal meningitis causes substantial mortality globally. Our understanding of the role of the host immune system in patient outcomes is limited. We investigated the cytokine and chemokine environment at the site of infection, the CNS, to better understand the impact of immune cell activation and tissue inflammation on mortality.

Methods: We prospectively enrolled Ugandans presenting with first episode cryptococcal meningitis from March 2015 to May 2017, as part of a larger study focused on drug treatment with amphotericin + fluconazole +/- sertraline to improve neurological outcomes. We analyzed the CSF of 321 subjects at diagnosis for soluble biomarkers of immune cell activation utilizing a luminex assay. Statistical analysis grouped each biomarker into quartiles (Q1, Q2+Q3, Q4) and compared each group for 14-day mortality via logistic regression, adjusted for Glasgow Coma Scale and CSF quantitative culture. We compared Q1 (low) and Q4 (high) to the reference Q2+Q3 group.

Results: Participants with Q1 (low) levels of markers indicative of cytotoxic cell function such as TRAIL (p=0.004), Granzyme-B (p=0.03), and IP-10 (p=0.007) had significantly increased risk of 14-day mortality compared to middle two quartiles (Q2+Q3) reference group levels. Participants with Q1 (low) levels of markers associated with naive T cell activation and recruitment such as CXCL2 (p=0.003), PDL1 (p=0.013), and CCL19 (p=0.013) had increased risk of 14-day mortality while those with Q4 (high) levels of CCL19 (p=0.009) had decreased mortality, when compared to the Q2+Q3 reference group. Inflammatory mediators such as TNF-alpha, IFN-gamma, IL-6, and IL-1beta were not associated with 14-day mortality in either Q1 or Q4, but participants with Q1 (low) levels of cytokines involved in Th2 cell function IL-13 (p=0.004) and IL-33 (p=0.039) had increased risks of 14-day mortality.

Conclusion: These findings demonstrate a crucial role for cytotoxic cell populations and naive T-cell stimulation in human cryptococcal outcomes. Further research efforts should include characterizing the role and activating
studies of cytotoxic cells in the clearance of Cryptococcus as well as T-cell function in activation of the adaptive immune response in humans with cryptococcosis.

748 TUBERCULOSIS IN HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS AND ITS IMPACT ON MORTALITY

Morris K. Rutakingirwa1, Fiona V. Cresswell2, Enoch Kayagaba1, Edwin Nwagiga3, Kenneth Siebambulide1, Lillian Tugume3, Edward Mpazoz3, Joanna Dobbin4, David B. Meya4, David R. Boulware4, Katherine Huppler Hullsiek5, Joshua Rhein4,1 

1Infectious Disease Institute, Kampala, Uganda, 2London School of Hygiene & Tropical Medicine, London, UK, 3Mbarara University of Science and Technology, Mbarara, Uganda, 4University of Minnesota, Minneapolis, MN, USA

Background: Tuberculosis (TB) and cryptococcal meningitis are leading causes of morbidity and mortality in advanced HIV. Data on TB co-infection amongst people with cryptococcosis is scarce. We described the occurrence of TB in Ugandan adults with cryptococcal meningitis and determined the impact of co-infection on survival.

Methods: We performed a retrospective analysis of patients diagnosed with cryptococcal meningitis during 2010-2017. Baseline TB status was classified as: 1) 'prevalent TB' if TB diagnosed >14 days prior to cryptococcal diagnosis, 2) 'concurrent TB' if diagnosed with TB +/− 14 days from cryptococcal diagnosis, or 3) 'no baseline TB'. Baseline demographics were compared. Among those with no baseline TB, 'TB incident' was defined as occurrence of TB >14 days after cryptococcal diagnosis. Time-updated proportional hazards regression models were used to assess TB diagnosis as a risk factor for death. Models were adjusted for age, antiretroviral therapy status, Glasgow Coma Scale <15, and initial CSF quantitative cryptococcal culture.

Results: Of 870 with cryptococcosis, 50 (6%) had prevalent TB, 67 (8%) had concurrent TB, and 753 (86%) had no baseline TB. Baseline demographics were similar between groups with exception of weight, duration on ART and CSF opening pressure. The 18-week mortality was 50% in prevalent TB, 46% in concurrent TB, and 45% in the no TB group. Among 753 participants without baseline TB, 67 (9%) were diagnosed with incident TB, with a median time to TB incidence of 41 (IQR, 22-69) days. TB diagnosis was associated with an increased risk of death (Hazard Ratio (HR)=1.62; 95%CI, 1.23, 2.14; p<0.01), which increased in models adjusted for age, ART use, GCS <15 and CSF quantitative culture (HR=1.75; 95%CI, 1.33, 2.23; p<0.001). Table

Conclusion: Nearly a quarter of adults with cryptococcosis received treatment for TB, giving rise to potential drug-drug interactions and overlapping toxicities. There is an increased risk of death in patients who begin TB treatment after cryptococcal diagnosis. Further studies are needed to better characterize the increased risk of mortality with Cryptococcus and TB co-infection, and to determine the benefit of systematic TB screening in patients with cryptococcal meningitis.

749 THE GLOBAL DISTRIBUTION, DRIVERS, AND BURDEN OF TALAROMYCOSIS, 1964-2017

Chuanyi Ning1, Wudi Wei1, Bo Xu1, Thanh T. Nguyen1, 2, Nguyen Le Nhu Tung3, Jasper F. Chan1, 2, Patrick C. Woo5, Chau V. Nguyen4, Nga N. Cao1, Kwok-Yung Yuen5, Thuy Le1, 2, 3

1University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam, 2Duke University School of Medicine, Durham, NC, USA, 3Oxford University Clinical Research Unit in Vietnam, Ho Chi Minh, Vietnam, 4Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam, 5University of Hong Kong, Pok Fu Lam, Hong Kong

Background: Talaromyces marneffei infection (Tm) is a leading cause of HIV-associated morbidity and mortality in Southeast Asia. Diagnostic delays due to protracted culture methods is the most challenging clinical problem. We have demonstrated that the Mp1p antigen enzyme immunoassay (EIA) is more sensitive than blood culture in detecting Tm in a retrospective cohort. Here we reported the accuracy and predictive values of the Mp1p EIA in a prospective study.

Methods: We consecutively recruited HIV patients aged ≥18 who were hospitalized at the Hospital for Tropical Diseases in Ho Chi Minh city with any
751 IN VITRO ANTIFUNGAL SUSCEPTIBILITY AND ANTIFUNGAL TREATMENT OUTCOME IN TALAROMYCOSIS

Thu T. Nguyen1, Hannah Shepard1, Ly T. Vo1, Thanh T. Nguyen1, Thuy Le1
1Duke University School of Medicine, Durham, NC, USA; 2Duke University, Durham, NC, USA; Ho Chi Minh City Medicine and Pharmacy University, Hô Chi Minh, Vietnam; 3Oxford University Clinical Research Unit in Vietnam, Ho Chi Minh, Vietnam

Background: The dimorphic fungus Talaromyces marneffei (Tm) causes an invasive mycosis which ranks 3rd as the most common HIV-associated infections in Southeast Asia with a mortality as high as 30%. We recently demonstrated in a randomized control trial (N=440 patients) that induction therapy with itraconazole was associated with higher mortality, persistent fungemia, incidence of relapse and IRIS when compared to amphotericin B over six months. We hypothesize that disease relapse and other complications in patients who received itraconazole are associated with a reduced susceptibility to itraconazole. Currently methods for antifungal susceptibility testing (AFST) and clinical breakpoints to define antifungal resistance have not been established for Tm. Methods: To test our hypothesis, we developed a new AFST testing method for Tm. We followed the CLSI guidelines for broth microdilution of itraconazole and preparation of a standardized yeast inoculum of 10^6 cells/ml. We utilized alamarBlue, a dye which fluoresces as a result of cellular metabolic activity, allowing percent reduction in fluorescence intensity to be precisely calculated. We generated MIC_{50} and MIC_{90} values for 136 unique Tm strains isolated from patients treated with itraconazole, and we compared the MIC geometric means in patients who had a good treatment outcome and multiple groups of patients who had poor treatment outcomes. Results: The assay performed consistently with intra-assay MICs of 0.008-0.01 μg/mL for 6 sample replicates, and inter-assay MICs testing 6 runs on separate days were within the CLSI acceptable range of 2-1 fold dilution. Among 136 isolates, 79% had MIC_{50}=0.008 μg/mL, 16% had MIC_{50}=0.016 μg/mL, and 4% had MIC_{50}=0.03 μg/mL. In multiple pairwise comparisons, the differences in MIC_{50} geometric means between patients who responded well to itraconazole (N=59) and patients who had any bad outcome (N=77), including death (N=23), relapse (N=9), prolonged fungemia (N=55), and IRIS (N=14) were not statistically significant, all P values from Wilcoxon rank sum tests were >0.05. Conclusion: We developed a highly reliable and reproducible method for in-vitro AFST for Tm in the yeast form. The use of alamarBlue enables precise quantification of MIC without relying on visual perception and can be standardized across laboratories. The MICs against itraconazole in all isolates were low (<0.03 μg/mL), and the MIC distribution did not correlate with the outcome of itraconazole therapy in HIV-associated talaromycosis.

Table 1. Comparison of MIC distribution between patients who had a good outcome and patients with poor outcomes

<table>
<thead>
<tr>
<th>Comparison</th>
<th>N</th>
<th>Good outcome</th>
<th>P value(*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean of MIC_{50} (μg/mL) (95% CI)</td>
<td></td>
<td>0.0074</td>
<td></td>
</tr>
<tr>
<td>Good outcome</td>
<td>59</td>
<td>0.0073</td>
<td>0.0073</td>
</tr>
<tr>
<td>Poor outcome</td>
<td>77</td>
<td>0.0160</td>
<td>0.0160</td>
</tr>
<tr>
<td>Death</td>
<td>23</td>
<td>0.0189</td>
<td>0.0189</td>
</tr>
<tr>
<td>Relapse</td>
<td>9</td>
<td>0.0080</td>
<td>0.0080</td>
</tr>
<tr>
<td>Protracted fungemia</td>
<td>55</td>
<td>0.0079</td>
<td>0.0079</td>
</tr>
<tr>
<td>IRIS</td>
<td>14</td>
<td>0.0187</td>
<td>0.0187</td>
</tr>
</tbody>
</table>

(*) By Wilcoxon rank sum test, P values from pairwise comparison to the reference group

752 PREVALENCE OF CMV VIREMIA AND ASSOCIATED RISK IN HIV-INFECTED PERSONS STARTING ART

Shweta Sharma1, Mark R. Schleiss1, Hansjakob Furrer2, Daniel Nixon1, Mark Blackstad1, Nelmary Hernandez-Avila1, Dominic Dwyer1, Álvaro H. Borges3, H. Clifford Lane1, Jean-Michel Molina7, Jens D. Lundgren5, James Neaton1, for the INSIGHT and ANRS groups.
1University of Minnesota, Minneapolis, MN, USA; 2University Hospital of Bern, Bern, Switzerland; 3Virginia Commonwealth University, Richmond, VA, USA; 4Westmead Hospital, Westmead, Australia; 5CHIP, Department of Infectious Diseases, Copenhagen, Denmark; 6NIAID, Bethesda, MD, USA; 7Hôpital Saint-Louis, Paris, France

Background: Morbidity and mortality in advanced HIV-infection is still high despite ART use and prophylaxis for opportunistic infections. Data on prevalence of CMV viremia pre- and post- ART initiation at varying CD4 thresholds are limited. The impact of CMV viremia on morbidity and mortality is unclear. Methods: Using plasma samples from participants initiating ART at study entry in 4 clinical trials (INSIGHT: FIRST, SMART, START, and ANRS: REFLATE), we measured CMV-specific IgG and CMV viremia at baseline and in year 1 visits. CMV DNA was measured centrally. Detectable (lower limit 88.5 IU/mL) CMV DNA was used for CMV+ vs CMV- classification. CMV+ during follow-up was defined as CMV DNA at any visit. Analyses for the association of CMV+/CMV- with clinical risk were limited to FIRST (longer follow-up and number of outcomes). Using all follow-up in FIRST, we estimated the hazard ratio (HR) for baseline CMV+ vs CMV- for a composite outcome of AIDS, serious non-AIDS (SNA), or death. HRs were also computed for outcomes after 8 months of ART across 4 subgroups defined by baseline and follow-up CMV+ vs CMV- through month 8. Models were adjusted for CD4 counts and HIV RNA.

Results: There were 1169 participants from FIRST, 137 from REFLATE, 54 from SMART, and 1815 from START with median baseline CD4 counts of 153, 140, 429, and 648 cells/µL, respectively. CMV infection by IgG was ≥90% across trials. Baseline CMV+ prevalence was 17%, 26%, 1%, and 0% in FIRST, REFLATE, START, and SMART, respectively. Pooled across trials, baseline CMV+ prevalence by CD4 was limited. The impact of CMV viremia on morbidity and mortality is unclear.
CMV VIREMIA IN PATIENTS WITH ADVANCED HIV INFECTION: A 48-WEEK FOLLOW-UP STUDY

Paula Suárez1, Adria Albascas2, Juliana Esperalba2, Candela Fernández2, Júlia Sellarés3, Aina Torrella Domingo4, Bibiana Planas4, Antonio Segura3, Mario Falcó1

1Hospital Universitario de la Vall d’Hebron, Barcelona, Spain, 2Hospital Universitario de Bellvitge, Barcelona, Spain, 3Hospital Universitario de la Vall d’Hebron, Barcelona, Spain, 4Vall d’Hebron Research Institute, Barcelona, Spain

Background: Nowadays, the incidence of CMV end-organ disease (EOD) is very low even though the prevalence of CMV viremia is around 30% in patients with HIV infection and ≤100 CD4 lymphocytes. CMV viremia is high but the incidence of CMV-EOD is low nonetheless. CMV viremia gets suppressed after starting ART without specific anti-CMV treatment.

Methods: A prospective observational study including patients with HIV infection and ≤100 CD4 T-lymphocytes (TL) was performed between September 2015 and July 2018. We determined HIV viral load (VL), CD4-count at baseline, 4, 12, 24 and 48 weeks. We determined specific immune response against CMV (QuantiFERON-CMV®) at baseline and at 48 weeks. We aimed to assess the dynamics of CMV viral replication and the recovery of specific immune response against CMV after the initiation of ART.

Results: Fifty-two patients were included, 19 (36.5%) were women, median age (IQR) was 43.8 (36.5-53.3) years. At baseline median (IQR) CD4-TL count was 30.0 (20.0-60.0) and median (IQR) HIV VL was 45,150,500 copies/mL (7,750-1,285,000). Sixteen (30.8%) patients had detectable CMV viremia at baseline, 7 (13.4%) died, none of them related to CMV infection. Thirty-seven (71.2%) patients had specific CMV immune response at baseline compared to 27 (69.2%) at 48 weeks. The specific CMV IFN-γ response increased from baseline (median: 1,285,000) to 48 weeks (median: 2.5, IQR: 0.1-7.425) in the 39 patients who completed the follow-up (p=0.07).

Conclusion: The prevalence of CMV viremia in patients with advanced HIV infection is high but the incidence of CMV-EOD is low nonetheless. CMV viremia gets suppressed after starting ART without specific anti-CMV treatment.

Table 1: CMV viremia in patients with advanced HIV infection: a 48-week follow-up study

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N in Baseline</th>
<th>N in Week 48</th>
<th>Median (IQR)</th>
<th>CD4 (absolute, median [IQR])</th>
<th>HIV VL (copies/mL, median [IQR])</th>
<th>QuantiFERON-CMV® (median IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>52</td>
<td>39</td>
<td>30.0 (20.0-60.0)</td>
<td>45,150,500 (7,750-1,285,000)</td>
<td>1,285,000 (20-300,000)</td>
<td>1,25 (0.1-5.5)</td>
</tr>
<tr>
<td>CMV+</td>
<td>16</td>
<td>13</td>
<td>30.0 (20.0-60.0)</td>
<td>45,150,500 (7,750-1,285,000)</td>
<td>1,285,000 (20-300,000)</td>
<td>1,25 (0.1-5.5)</td>
</tr>
<tr>
<td>CMV-</td>
<td>36</td>
<td>26</td>
<td>30.0 (20.0-60.0)</td>
<td>45,150,500 (7,750-1,285,000)</td>
<td>1,285,000 (20-300,000)</td>
<td>1,25 (0.1-5.5)</td>
</tr>
</tbody>
</table>

RISKS OF OPPORTUNISTIC INFECTIONS FOR HIV+/VETERANS UNDERGOING CANCER CHEMOTHERAPY

Alain Makinson1, Lesley S. Park2, Kimberly Stone1, Maria Rodriguez-Barradas3, Sheldon T. Brown1, Roxanne Wadia1, Kristina Crothers1, Cynthia L. Gibert1, Roger Bedimo1, Matthew B. Goetz1, Fatima Shebil1, Jacques Reyes1, Vincent Le Moing1, Keith M. Sigel1

1University Hospital Montpellier, Montpellier, France, 2Stanford University, Stanford, CA, USA, 3'Inich School of Medicine at Mt Sinai, New York, NY, USA, 4Baylor College of Medicine, Houston, TX, USA, 5James J. Peters VA Medical Center, Bronx, NY, USA, 6VA Connecticut Healthcare System, West Haven, CT, USA, 7University of Washington, Seattle, WA, USA, 8Washington DC VA Medical Center, Washington, DC, USA, 9VA North Texas Health Care Center, Dallas, TX, USA, 10VA Greater Los Angeles Health Care System, Los Angeles, CA, USA, 11Massachusetts General Hospital, Boston, MA, USA

Background: Persons living with HIV (PLWH) treated for cancer may be at increased risk of opportunistic infections (OIs) compared with uninfected patients.

Methods: Using the Veterans Aging Cohort Study we evaluated OI incidence in 5,289 patients with malignancies diagnosed 1996-2018, and treated with chemotherapy. We identified zoster, cytomegalovirus (CMV), tuberculosis, Candida esophagitis, pneumocystis pneumonia (PCP), toxoplasmosis, Cryptococcus, atypical Mycobacterium, Salmonella bacteriaemia, histoplasmosis, coccidiomycosis or Progressive Multifocal leukoapthy using ICD diagnosis codes, chart review confirmed, within 6 months of chemotherapy initiation. We fitted Poisson models to evaluate the association between HIV and OI risk overall, stratified by hematological and non-hematological cancers. We used inverse probability weighting (IPW) of HIV status to control for differences between comparison groups and adjusted for prophylaxis use. Models including only PLWH were fitted to evaluate risk factors for OI incidence.

Results: Amongst 2,237 PLWH, a greater proportion of malignancies were hematologic (29%) than in uninfected Veterans (16%). Median age was 58 years, 98% were males, 81% were current/ever smokers, 49% were African-American. PCP prophylaxis was used more frequently in PLWH (42% vs. 5%; p<0.001). We confirmed 107 OIs in 101 subjects: Candida esophagitis (n=43), zoster (n=31),Cryptococcus (n=3), atypical Mycobacterium (n=6), Salmonella bacteriaemia (n=1), histoplasmosis (n=1). HIV was an independent risk factor for OIs (incidence rate ratio [IRR] 4.3; 95% CI: 2.3-8.1) after accounting for IPW and prophylaxis use. 83% of OIs in PLWH occurred in the setting of a viral load >500 copies/mL and/or CD4 count <200/mm3. There were no definitive cases of PCP in non-hematologic tumors among PLWH with CD4 >200/mm3. In multivariable analyses of PLWH only, HIV viremia (IRR 9.9; 95% CI: 5.9-16.5) and comorbidity burden (IRR 1.1; 95% CI: 1.05-1.3 for 1 point Charlson increase) were independently associated with OI risk.

Conclusion: OIs were significantly increased in PLWH with malignancies undergoing chemotherapy. However, our study does not support systematic PCP prophylaxis in PLWH with non-hematologic malignancies and controlled HIV-disease.

Table 1: Opportunistic infection incidence after cancer chemotherapy by HIV status.

<table>
<thead>
<tr>
<th>Number of events (person-years at risk)</th>
<th>Non-OIs</th>
<th>OIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-negative (n=1,023)</td>
<td>11,652</td>
<td>98</td>
</tr>
<tr>
<td>HIV-positive (n=1,256)</td>
<td>12,481</td>
<td>142</td>
</tr>
<tr>
<td>Relative risk ratio (95% CI)</td>
<td>1.7 (1.2-2.3)</td>
<td>7.7 (3.9-13.7)</td>
</tr>
</tbody>
</table>

Characterisation of South Africa’s Xpert MTB/RIF Ultra “Trace” Laboratory Results

Lesley Scott1, Pedro da Silva2, Kyle Fyvie1, Gabriel D. Eisenberg1, Silence Ndlovu1, Puleng S. Marokane2, Wendy Stevens1

1University of the Witwatersrand, Johannesburg, South Africa, 2National Health Laboratory Service, Johannesburg, South Africa

Background: South Africa introduced Xpert-MTB/RIF Ultra (Ultra) assay into their national TB program in October 2017. Increased sensitivity of the Ultra over the previous Xpert MTB/RIF assay is attributed to the inclusion of IS6110/ISt018I, improved chemistry, and larger PCR reaction volume. The lower limit of detection of Ultra is 15.6cfu/ml, and a new semi-quantitative category “trace” is introduced in Ultra.
756 URINE-BASED TB SCREENING WITH TB-LAM AND ULTRA IN HIV+ UGANDANS WITH MENINGITIS

Jayne Ellis1, Enock Kagimu1, Ananta Bangdiwala2, Michael Okirwoth2, Gerald Mugoynu3, Vincent Wadda4, David R. Boulware3, Nathan C. Bahr5, Fiona V. Creswell2.

1University College London, London, United Kingdom, 2Infectious Diseases Institute, Kampala, Uganda, 3University of Minnesota, Minneapolis, MN, USA, 4Infectious Disease Institute, Kampala, Uganda, 5University of Kansas Medical Center, Kansas City, KS, USA.

Background: Tuberculosis (TB) is a common cause of HIV-related death, yet diagnosis is often missed, particularly with concurrent illness such as meningitis. In one study, use of urine TB-lipoarabinomannan lateral flow assay (LAM) reduced missed TB diagnoses and mortality in HIV- infected patients with CD4 <100 or suspected TB. The utility of the novel Xpert MTB/RIF Ultra (Ultra) assay on urine has not been evaluated. We sought to determine the prevalence of disseminated TB by testing urine with LAM and Ultra in hospitalized adults with meningitis in Uganda.

Methods: We prospectively enrolled HIV+ adults with meningitis in Kampala or Mbarara, Uganda. Participants were tested for meningitis etiologies using a stepwise algorithm. In parallel, participants underwent systematic urine-based screening for TB using the LAM (Alere) and Ultra (Cepheid). 60 μL of urine was tested with the LAM. All remaining urine was centrifuged and the cell pellet resuspended in 2mL of urine for Ultra testing. Results were reported to clinicians in real-time.

Results: From Jan 2018 to Sept 2019, we enrolled 251 HIV+ inpatients. Table 1 shows baseline characteristics. Median CD4 was 37 cells/mcL, IQR 12-85. The majority had cryptococcal meningitis (59%, 148/251), and 15% (38/251) had definite/probable TB meningitis (Table 1). Overall, 25% (63/251) had evidence of disseminated TB by either urine assay. In cryptococcal subjects, 20% (29/145) had evidence of disseminated TB by LAM and 5% (5/96) by Ultra. In definite/probable TB meningitis, 32% (12/37) had a positive urine LAM and 33% (12/36) had a positive Ultra (Table 1). 178 participants had both urine LAM and Ultra results. TB meningitis was confirmed in 18% (32/178) with LAM, 13% (20/155) by Ultra, and 3% (6/178) by bothUltra. Mortality was higher in patients with evidence of disseminated TB by either urine assay (table 1).

Conclusion: In hospitalized Ugandans with advanced HIV disease and suspected meningitis, systematic screening with urine LAM and Ultra found a high prevalence of disseminated TB (25%). Cryptococcosis and TB co-infection was common (20%). Given the overlap in symptoms, TB may be missed in this setting without systematic testing. In those with TB meningitis, urine tests were positive in one-third; these tests may represent rapid, non-invasive adjunctive tests for TBM diagnoses. There was little concordance of Ultra and LAM, the reason for which warrants further investigation.

757 APPLICABILITY OF URINE LAM TEST IN ADVANCED HIV-INFECTED ADULTS IN UKRAINE

Marta Vasylyev1, Svitlana Antonyak2, Sergii Antoniak1, Natasha Rybak1, Vira Buhichyk1, Oleksandra Szuzychyna1, Maryana Szuzychyna1, Viktor Tretiakov4, Tetiana Ismagilova1, Iryna Dizha1, Yana Sherepetna1, Dymtro Skiriako1, Anastasiia Mazurenko1, Justyna D. Kowalska1.

1Lviv Regional Public Health Center, Lviv, Ukraine, 2Clinic of the Gromashovsky Institute of Epidemiology and Infectious Diseases, Lviv, Ukraine, 3Brown University, Providence, RI, USA, 4SALUS Charitable Foundation, Lviv, Ukraine, 5Lviv Regional AIDS Centre, Lviv, Ukraine, 6All-Ukrainian network of people living with HIV/AIDS, Kyiv, Ukraine, 7Hospital for Infectious Diseases, Warsaw, Poland.

Background: Tuberculosis (TB) remains the leading cause of death among HIV-infected adults in Ukraine. Urine lipoarabinomannan (LAM) antigen testing is a new rapid TB diagnostic that recently was implemented by Ukrainian National Public Health Center. We evaluated the utility of urine LAM in high TB prevalence and resource constrained settings.

Methods: Between March-August 2019, 1770 consecutive HIV-infected patients presenting for routine follow-up visits had LAM testing performed in Kyiv (North), Odessa (South), Dnipro (East) and Lviv (West) regions of Ukraine. The inclusion criteria were: HIV+, ≥18 years, CD4 < 200 cells/mm, and or clinically advanced HIV disease, regardless of TB symptoms. TB was confirmed by chest radiography, CT and/or bacteriological methods. The project was funded by All-Ukrainian Network of People Living with HIV/AIDS.

Results: In total 918 patients with both TB assessment and LAM performed were included in preliminary analyses. Mean age of participants was 41.0 years, 56.9% were male, and the mean baseline CD4 count was 157 cells/mm, IQR 30-156 confirmed TB cases. 400 (43.0%) had positive LAM test failed to detect 186 (26.3%) TB cases. TB prevalence in the sample was 63.83%. Sensitivity of LAM tests - 68.26%, Specificity – 87.35%. Positive predictive value - 90.5%. Negative predictive value – 60.29% (Table). Kappa statistics provided an estimate of moderate agreement (kappa 0.51, p-value <0.001, 95% CI: 0.46, 0.56).
Conclusion: LAM urine test is useful as an add-on rapid diagnostic method in Ukraine for HIV patients with a CD4 of <200. Sensitivity was satisfying, however for accurate and quick diagnosis LAM should be used in combination with other TB diagnostics.

### Table: LAM test results by TB confirmation.

<table>
<thead>
<tr>
<th>TB confirmation</th>
<th>0</th>
<th>1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>790</td>
<td>186</td>
<td>976</td>
</tr>
<tr>
<td>Percent</td>
<td>31.59</td>
<td>20.26</td>
<td>31.85</td>
</tr>
<tr>
<td>Positive</td>
<td>40.92</td>
<td>30.28</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>67.35</td>
<td>31.74</td>
<td></td>
</tr>
</tbody>
</table>


discussion: Specimen | 42 | 400 | 442 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>17.15</td>
<td>43.77</td>
<td>60.93</td>
</tr>
<tr>
<td>Percent</td>
<td>8.5</td>
<td>50.5</td>
<td>59</td>
</tr>
<tr>
<td>Positive</td>
<td>12.15</td>
<td>60.26</td>
<td>72.4</td>
</tr>
<tr>
<td>Negative</td>
<td>54.67</td>
<td>39.74</td>
<td>94.4</td>
</tr>
</tbody>
</table>

| Total | 392 | 566 | 958 |

### Results:

- **Sensitivity** of the Xpert Prototype as a triage test (fixed sensitivity value closest to 90%), the corresponding specificity was 55.8% (CI 47.2–64.1). Comparing to Xpert® MTB/Rif and the Xpert-Prototype as a confirmatory test at fixed value of sensitivity closest to 90%,

- **Accuracy** of the Xpert Prototype as a triage test, at a specificity of 95%, the test achieves a sensitivity of 65.7% (CI 53.7-75.9).

- **Specificity** of the Xpert Prototype as a triage test, at a specificity of 95%, the test achieves a sensitivity of 65.7% (CI 53.7-75.9).

- **Combination analysis**: The encouraging diagnostic performance of this score is the highest so far using immunological tests. In addition, the score is independent of the HIV status of the child.

### Conclusion:

The encouraging diagnostic performance of this score is the highest so far using immunological tests. In addition, the score is independent of the HIV status of the child.

## EVALUATION OF A BLOOD-BASED ANTIGEN TEST FOR TUBERCULOSIS IN INFANTS

### Background:

Immunological tests have been developed to discriminate active tuberculosis from other respiratory illnesses and healthy controls. Cepheid (Sunnyvale, CA, USA) has developed an early prototype GeneXpert PCR test ('Xpert Prototype'), that quantifies relative mRNA-levels of the 3-gene signature in a patient whole blood sample.

### Methods:

Whole blood from symptomatic people living with HIV (PLHIV) in South Africa were collected from February 2016 to August 2017 and biobanked in PAXgene tubes. The accuracy of the Xpert Prototype on these biobanked samples was compared against a comprehensive microbiological reference standard (culture and Xpert® MTB/RIF). The performance was also compared against Xpert® MTB/RIF alone, as Xpert will be the most likely confirmatory assay used in programmatic settings in high-burden countries. We depict results in ROC curves and for pre-set cut-points based on performance targets set for a triage test by the World Health Organization (WHO). The target product profile defines a minimum of 90% sensitivity and 70% specificity for the test to be used by first-contact providers to identify patients who need further confirmatory testing. A combinatory score based on a novel 3-gene host-signature has shown promise in discriminating TB disease from other respiratory illnesses and healthy controls. Cepheid (Sunnyvale, CA, USA) has developed an early prototype GeneXpert PCR test ('Xpert Prototype'), that quantifies relative mRNA-levels of the 3-gene signature in a patient whole blood sample.

### Results:

- **Sensitivity** of the Xpert Prototype as a triage test, at a specificity of 95%, the test achieves a sensitivity of 65.7% (CI 53.7-75.9).

- **Specificity** of the Xpert Prototype as a triage test, at a specificity of 95%, the test achieves a sensitivity of 65.7% (CI 53.7-75.9).

- **Combination analysis**: The encouraging diagnostic performance of this score is the highest so far using immunological tests. In addition, the score is independent of the HIV status of the child.

### Conclusion:

The encouraging diagnostic performance of this score is the highest so far using immunological tests. In addition, the score is independent of the HIV status of the child.

## PROMISING COMBINED IMMUNOLOGICAL ASSAYS TO DIAGNOSE CHILDHOOD TUBERCULOSIS

### Background:

Children account for a substantial part of the tuberculosis (TB) burden. However, the real burden of the disease is imprecise because the diagnosis of active tuberculosis remains a challenge in children. The development of non-sputum-based diagnostics assays and triage assays to rule-out TB are considered as especially critical to improve TB diagnosis in children. We aimed at constructing an algorithm aimed to improve the diagnostic of TB in children using a combination of immunoonasays based on the T cells and serologic response against cytokine and interferon-γ release assays.

### Methods:

We designed an early proof-of-principle evaluation phase including children with confirmed TB and healthy controls in Zambia. The confirmed TB group consisted of children with positive clinical signs (prolonged cough, unexplained weight loss or fever, lethargy) and tested positive for MBT culture or GeneXpert® MTB/RIF assays. The control group consisted of healthy children without any clinical signs and no history of direct exposure to TB. Blood specimens were tested using the QuantiFERON Gold IT-assay (QFT®) and cytokines released in supernatants were quantified using a 25-plex cytokine multiplex test and ELISA assays. Serological response direct against Ag85A, B and D were tested by ELISA. A Random Forest classification analysis using values of all biomarkers was used in order to identify the most discriminant biological factors. Thresholds for each variables were first checked with ROC curves. A simplified score was constructed out of these values.

### Results:

The TB confirmed group consisted of 37 children with 51% being HIV infected, for the control group, 70 children were enrolled, 44% being HIV coinfected. We identified anti-Ag85B Abs, IL2/IFNg ratio, MIG and IP10 as the most sensitive biomarkers for TB diagnosis. Because MIG and IP10 responses were strongly correlated, we kept only MIG in further analysis. Using ROC curves and the Youden index, the threshold of 151 pg/mL, 0.76 and 48.6, discriminated best confirmed TB children from controls, for MIG, Ag85B Ab and IL2 E/IFNg ratio respectively. According to our combined tests, a child was declared with TB if (i) IL2/IFNg <48.6 or (ii) both MIG (from QTF® supernatant) >151 pg/ml and Ag85B Ab > 0.76. The ROC curve derived from our score showed an AUC of 0.94 (0.90-0.99), giving 86% sensitivity and 87% specificity.

### Conclusion:

The encouraging diagnostic performance of this score is the highest so far using immunological tests. In addition, the score is independent of the HIV status of the child.

## WITHDRAWN

### ACCURACY OF NOVEL BLOOD ASSAY FOR IDENTIFICATION OF TB DISEASE IN PEOPLE WITH HIV

### Background:

A non-sputum triage test to rule out tuberculosis disease has been identified as a high-priority need for diagnostic development to reach the End-TB targets of the World Health Organization (WHO). The target product profile defines a minimum of 90% sensitivity and 70% specificity for the test to be used by first-contact providers to identify patients who need further confirmatory testing. A combinatory score based on a novel 3-gene host-signature has shown promise in discriminating TB disease from other respiratory illnesses and healthy controls. Cepheid (Sunnyvale, CA, USA) has developed an early prototype GeneXpert PCR test ('Xpert Prototype'), that quantifies relative mRNA-levels of the 3-gene signature in a patient whole blood sample.

### Methods:

Whole blood from symptomatic people living with HIV (PLHIV) in South Africa were collected from February 2016 to August 2017 and biobanked in PAXgene tubes. The accuracy of the Xpert Prototype on these biobanked samples was compared against a comprehensive microbiological reference standard (culture and Xpert® MTB/RIF). The performance was also compared against Xpert® MTB/RIF alone, as Xpert will be the most likely confirmatory assay used in programmatic settings in high-burden countries. We depict results in ROC curves and for pre-set cut-points based on performance targets set for a triage test by the World Health Organization.

### Results:

- **Sensitivity** of the Xpert Prototype as a triage test, at a specificity of 95%, the test achieves a sensitivity of 65.7% (CI 53.7-75.9).

- **Specificity** of the Xpert Prototype as a triage test, at a specificity of 95%, the test achieves a sensitivity of 65.7% (CI 53.7-75.9).

- **Combination analysis**: The encouraging diagnostic performance of this score is the highest so far using immunological tests. In addition, the score is independent of the HIV status of the child.

### Conclusion:

The encouraging diagnostic performance of this score is the highest so far using immunological tests. In addition, the score is independent of the HIV status of the child.
762B PROSPECTIVE VALIDATION OF A BLOLOOD RNA TB BIOMARKER IN AMBULANT HIV-INFECTED ADULTS

Simon C. Mendelsohn1, Andrew Fiore-Gartland2, Adam Penn-Nicholson3, Humphrey Mulenga4, Chris Hikuam5, Katie Hadley6, Michele Tameris7, Craig Innes8, William L. Brunsmeine9, Gerhard Waltz10, Kogiepleum Naidoo11, Gavin Chuchyard1, Thomas J. Scriba12, Mark Hatherill13, for the CORTIS-HR Study Team14
1University of Cape Town, Cape Town, South Africa, 2Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 3The Aurum Institute, Johannesburg, South Africa, 4Stellenbosch University, Cape Town, South Africa, 5CAPRISA, Durban, South Africa

Background: New non-sputum tuberculosis (TB) biomarkers for predicting progression to active TB disease are needed to achieve the goals of the WHO End TB Strategy. We previously developed and validated a blood transcriptional correlate of risk, RISK11, that identified individuals with active TB or high risk of progression to active TB in case-control studies. This study aimed to test diagnostic and predictive RISK11 performance for prospective community-based TB screening in HIV+ individuals, and to compare predictive performance with QuantiFERON-TB Gold Plus (QFT).

Methods: Ambulant HIV+ adults were enrolled across 5 sites in South Africa. ART naïve participants were referred for ART and isoniazid preventive therapy per country guidelines. RISK11 status was assessed at baseline and was double-blinded; RISK11 positivity was pre-defined at 60% score threshold. Participants were assessed at enrollment and underwent active surveillance for microbiologically-confirmed TB for up to 15 months. Here we report preliminary results.

Results: Among 861 participants (median age 35; 72% female; 11% symptom+; 78% ART experienced with median ART duration 3 years; median CD4 count 529 [IQR 350–725]), 33.1% were RISK11+ and 45.6% QFT+. Ten cases of TB were identified at baseline; prevalence was 2.5% in RISK11+ vs 0.2% in RISK11- participants (diagnostic risk ratio 13.1, 95%CI 2.1-81.6; AUC 88.2%, 95%CI 77.6-96.7; sensitivity 87.5%, 95%CI 57.1-95.8; specificity 65.8%, 95%CI 62.4-69).

Nine cases of incident TB were identified through median 15 months follow-up; incidence was 2.5% in RISK11+ vs 0.2% in RISK11- participants (RISK11 cumulative incidence ratio 16.6, 95%CI 2.1-133.9; AUC 80.3%, 95%CI 70.7-87.1; sensitivity 88.9%, 95%CI 44.4-98.8; specificity 69.1%, 95%CI 65.3-72.5). TB incidence was 1.6% in QFT+ vs 0.7% in QFT- participants (QFT CIR 2.3, 95%CI 0.6-9.3; AUC 72.6%, 95%CI 57.8-83.7; sensitivity 65.8%, 95%CI 30.5-89.5; specificity 56.1%, 95%CI 52.3-59.9).

Conclusion: RISK11 screening identified ambulant HIV+ adults with prevalent TB and predicted risk of progressing to active TB within 15 months. RISK11 performance approaches the WHO screening (sensitivity 90%; specificity 70%) and predictive (sensitivity and specificity 75%) test target product profiles (TPP) among HIV+ adults at the pre-specified score threshold. QFT performance falls short of the predictive TPP. RISK11 translation to a point-of-care assay may allow early identification of HIV+ adults that would benefit from further TB testing, therapy, or intensified follow-up.

764 DETECTABLE HIV RNA IN LATE PREGNANCY ASSOCIATED WITH LOW TFV HAIR LEVELS AT BIRTH

Jillian Pintye1, Yanling Huo2, Deborah Kacanek1, Karen Kuncz1, Kevin Zhang1, Hideaki Okochi3, Monica Gandhi1
1University of Washington, Seattle, WA, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3University of California San Francisco, San Francisco, CA, USA

Background: Adherence to antiretroviral therapy (ART) is vital to prevention of mother-to-child transmission of HIV (PMTCT) and maternal health, although peripartum life events can disrupt adherence. Hair levels measure cumulative ART exposure and are associated with viral suppression in nonpregnant and postnatal populations. We evaluated correlates of peripartum tenofovir (TFV) exposure via hair measures among women living with HIV (WLHIV) in the United States.

Methods: Hair samples were collected at or shortly after childbirth among WLHIV enrolled in the Surveillance Monitoring for ART Toxicities Study of the United States.
**Schouten 3, Thokozani Kalua 4, Andreas Jahn4, Beth A. Tippett Barr5**

odds ratios for detectable VL at 24 months were 10.1 among women with 1
measures/67 women vs 19/357; p<0.01). In multivariable analysis, adjusted
detectable VL at enrollment than with undetectable VL (74 detectable VL
those lost to follow-up (LTFU). Of 573 women on ART (median 29.7 mos.(IQR
p=0.02) and have undetectable VL at enrollment (79.7 vs 70.8%, p<0.01) than
more likely to be >30 years (51.6 vs 41.4%, p<0.01), parity =>4 (41.0 vs 33.5%,
implementation across Malawi.

DNA testing. Venous samples determined maternal plasma VL (<40 copies/ml
12 and 24 months PP, socio-demographic and prevention of mother to child
screened and enrolled with their infants in Malawi clinics. At enrollment,
infant HIV transmission. We report trends in postpartum (PP) VL for Malawian
reproductive-aged women on antiretroviral therapy (ART) is key to eliminating
PMTCT outcomes could incorporate drug exposure monitoring using hair or
other metrics and include adherence promotion strategies that address issues
unique to the peripartum period.

**Methods:** From 2014-2016, 4-26 week PP HIV-positive mothers were
screened and enrolled with their infants in Malawi clinics. At enrollment,
12 and 24 months PP, socio-demographic and prevention of mother to child
transmission of HIV (PMTCT) indicators were collected and infants had HIV-1
DNA testing. Venous samples determined maternal plasma VL (<40 copies/ml
= "undetectable"), standard national VL monitoring guidelines were in early
implementation across Malawi.

**Results:** 585 women were retained to 24 months (N=1281,45.7%), and were
more likely to be >30 years (51.6 vs 41.4%, p<0.01), parity >=4 (41.0 vs 33.5%,
p=0.02) and have undetectable VL at enrollment (79.7 vs 70.8%, p<0.01) than
those lost to follow-up (LTFU). Of 573 women on ART (median 29.7 mos.(IQR
26.8-61.3), 424 (74%) with VL at all 3 visits were included in analysis.
Table 1 shows 341 (80.4%) women had durable undetectable VL, 83 (19.5%) had
>= 1 detectable VL and 32 (7.5%) had persistent detectable VL. Cumulative
incidence of detectable VLs over 24 months was higher among women with
detectable VL at enrollment than with undetectable VL (74 detectable VL
measures/67 women vs 19/357; p<0.01). In multivariable analysis, adjusted
odds ratios for detectable VL at 24 months were 10.1 among women with 1
prior detectable VL (95%CI 3.7-28.1, p<0.001) and 240.4 for women with 2
prior detectable VLs (95%CI 68.0-849.8, p<0.001) (adjusted for age, parity,
education, partner disclosure, time on ART and adherence). Women with
durable undetectable VL (N=341) had no infant transmissions and 2 infant
deaths (0.6% combined outcome). Women with persistent detectable VL
(N=32) had 4 infant transmissions and 1 infant death (15.6%; p<0.01).

**Conclusion:** Detectable VL in early PP signals a risk of ongoing PP viremia
with major implications for infant HIV transmission, in a setting with limited
high VL management. These findings suggest differentiated VL monitoring
and targeted adherence support may be required during pregnancy and
breastfeeding.

**Table 1. Adjusted associations of covariates with TFV concentration (N=111)**

<table>
<thead>
<tr>
<th>Co-variate</th>
<th>N</th>
<th>% of mother</th>
<th>% of Child</th>
<th>% Change (95% CI)</th>
<th>β value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART regimen containing 3 or more classes</td>
<td>90.5</td>
<td>10.7</td>
<td>-1.1 (-66.8, 89.7)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks) per one week increase</td>
<td>36.97</td>
<td>2.6</td>
<td>-2.6 (-11.1, 6.3)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>INSTI use during pregnancy</td>
<td>43.9</td>
<td>11.2</td>
<td>-32.7 (-6.8, 56.5)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Late HIV RNA (copies/mL) during pregnancy (≥400 copies/mL)</td>
<td>9.6</td>
<td>1.5</td>
<td>-85.7 (-82.3, -88.7)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Achieved at least high school graduation</td>
<td>59.6</td>
<td>21.6</td>
<td>-38.5 (-21.5, -55.1)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><em>TFV</em> levels in infant's hair (copies/mL)</td>
<td>1.9</td>
<td>0.2</td>
<td>-98.6 (-97.8, -99.3)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

1 Estimated percent of range in TFV concentration: 1 per unit increase in continuous covariate measure; or 2 between categorical covariates with TFV concentration as the reference group for categorical outcome measures. Covariates with p-value > 0.25 in univariable models were included in multivariable models.

**Conclusion:** Early postpartum viremia predicts long-term nonsuppression and infant transmission

**Megan Landes1, Monique Van Lettow2, Joep J. Van Oosterhout 2, Erik Schouten1, Thokozani Kalua1, Andreas Jahn3, Beth A. Tippett Barr4**

**Early postpartum viremia predicts long-term nonsuppression and infant transmission**

**Background:** Long-term viral load (VL) suppression among HIV-positive reproductive-aged women on antiretroviral therapy (ART) is key to eliminating infant HIV transmission. We report trends in postpartum (PP) VL for Malawian women on ART, factors associated with detectable VL, and associations with cumulative infant HIV transmission and/or death.

**Methods:** Pediatric HIV/AIDS Cohort Study between 6/2014-7/2016. Among WLHIV on TFV-based regimens during pregnancy, TFV hair levels were analyzed using validated liquid chromatography/tandem mass spectrometry methods. Weight-normalized TFV hair concentrations were log transformed. Correlates of TFV hair concentrations were identified using multivariable linear regression. Covariates with p<0.25 in univariable models were included in multivariable models.

**Results:** Among 370 WLHIV with TFV-based ART use during pregnancy, hair collection acceptability was high (only 65/370 (18%) of all WLHIV using TFV declined); 111 women had TFV hair levels and were included in the final analysis. Median age at delivery among the 111 WLHIV was 31 years (IQR 26-36); 70% self-identified as non-Hispanic black, 71% had achieved high school graduation, 13% reported recreational drug use during pregnancy, and 9% had un

**Conclusion:** Unsuppressed VL among WLHIV in the U.S. during late pregnancy, a critical period for PMTCT, was strongly associated with low maternal TFV hair levels at birth. Over two-thirds of WLHIV had VL suggestive of imperfect adherence although viremia in late pregnancy was rare (9%). Efforts to improve PMTCT outcomes could incorporate drug exposure monitoring using hair or other metrics and include adherence promotion strategies that address issues unique to the peripartum period.

**Table 1: VIRAL LOAD MONITORING IN PREGNANCY TO PREDICT PERIPARTUM VIRAEMIA IN SOUTH AFRICA**

**Jasantha Odayar1, Siti Kabanda2, Thokozile R. Malaba3, Maia Lessky4, Landon Myer1**

1 University of Cape Town, Cape Town, South Africa

**Background:** WHO guidance recommends VL monitoring in pregnant women on ART to help identify high-risk infants for enhanced prophylaxis but there are few data evaluating this approach in routine care.

**Methods:** Data come from the screening procedures of a RCT of postpartum HIV care strategies at a large primary care clinic in Cape Town. In this setting VL monitoring takes place at the earlier of 12 weeks on ART, or 34 weeks’ gestation. In this context we identified consecutive HIV+ women initiating ART (TDF+ FTC+ EFV) who underwent VL testing during pregnancy, and for women with VL<400 copies/mL documented during pregnancy, repeated a VL within 4 weeks postpartum. All VL testing was done by the National Health Laboratory Services using the Abbott RealTime HIV-1 assay (Abbott Laboratories, Waltham, MA). We calculated sensitivity (SE), specificity (SP) and positive and negative likelihood ratios (LR+ and LR–) for antenatal VL<100 copies/ml in predicting peripartum VL<100 and <400 copies/mL, with sensitivity analyses examining subgroup of gestation at antenatal VL and prior ART exposure.

**Results:** In 323 women (median age 28y, 40% with a history of prior ART), antenatal VL was taken at a median gestation of 33w (IQR 30-36), and at that time, 89.2% of women had a VL<100 copies/mL and 10.9% had a VL 100-400 copies/mL. Peripartum VL was taken at a median of 9 days (IQR 6-17) postpartum, at which point women were on ART for a median duration of 23w (IQR 18-28), and at that time 91.6%, 6.8% and 1.6% had VL<100, 100-400 and >400 copies/mL, respectively. The SE of antenatal VL<100 copies/mL in predicting postpartum VL<100 and <400 copies/mL, with sensitivity analyses examining subgroups of gestation at antenatal VL and prior ART exposure.

**Conclusion:** These novel data suggest that antenatal VL<100 copies/mL is a useful predictor of peripartum viremia and may be used to target enhanced PMTCT interventions in this setting. The high SE and low LR suggest few women who are virologically suppressed during antenatal care subsequently become viremic peripartum.
767 HIGH VIRAL SUPPRESSION AMONG HIV-POSITIVE POSTPARTUM WOMEN: CLUSTER RANDOMIZED TRIAL

Appolinaire Tiam1, Lauren Greenberg1, Vincent Tukei1, Thabelo Ramatlapeng1, Tsetsebo Mots’oane1, Matseliso Masitha1, Matsapieli Ncchephe1, Mammatli Chabela1, Laura Guay1, Heather Hoffmann1, Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA, Ministry of Health, Maseru, Lesotho, George Washington University, Washington, DC, USA

Background: HIV-positive women are particularly vulnerable to poor retention and ART adherence in the postpartum period with low viral suppression that poses risks to maternal health and to transmission of HIV to their infants. We assessed the effect of a multidisciplinary integrated management team intervention on viral suppression in a cohort of HIV-positive pregnant women in Lesotho.

Methods: The IMPROVE cluster randomized study evaluated an intervention that included a multidisciplinary management team with maternal child health staff, village health workers, and peer mentor mothers to work together to support HIV-positive and negative women in uptake and retention in HIV and MCH services. Training together, using job aids, and adding early home based follow-up of new ANC attendees were included in the intervention. Twelve facilities were randomized to intervention or control arms. HIV-positive pregnant women were enrolled at their first ANC visit with prospective follow-up for at least 12 months postpartum. Study nurses conducted interviews with participants, extracted medical record information and collected dried (whole) blood spots from HIV-positive women for viral load testing. We compared viral load (VL) results at 12 months postpartum using Chi-square tests to test for differences between study arms.

Results: 613 HIV-positive women were enrolled in the study, 308 in the interventional arm and 305 in the control arm. 570 women had delivery information, all of whom were on ART at the time of delivery. VL results from 11-15 months postpartum were available for 351 (57%) women. There was no difference in follow-up (pregnancy losses/births, transfer to facilities outside the district, and loss to follow-up) by study arm. Overall 325 (93%) women were suppressed with a VL < 1000 copies/ml. A greater proportion of women in the intervention group had a suppressed VL (166/175, 95%) compared to women in the control arm (159/176, 90%) but the difference was not statistically significant (p=0.106). Significantly more women in the intervention group had an undetectable viral load (83% intervention vs. 72% control, p=0.016).

Conclusion: The multi-component IMPROVE intervention led to a small but not significant increase in viral suppression in HIV positive women one year after delivery, with high rates of suppression in both arms.

768 CHANGES IN BONE MINERAL DURING AND AFTER LACTATION IN UGANDAN WOMEN ON OPTION B+ ART

Florence Nabwire1, Ann Prentice1, Matthew M. Hamill1, Mary Glenn Fowler1, Josaphat Byamugisha1, Adeodata Kiikintwafi1, Gail R. Goldberg1

1MRC Elsie Widdowson Laboratory, Cambridge, UK, Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda

Background: Antiretroviral therapy (ART) in persons living with HIV (PLW) is associated with bone loss and increased risk of fracture, but data are limited in pregnant and lactating women when physiological bone mobilisation is also occurring. This research investigated changes in areal bone mineral density (aBMD) in breastfeeding HIV+ve Ugandan women initiated on lifelong ART in pregnancy compared to HIV-negative (HIV-ve) counterparts.

Methods: Two groups of pregnant Ugandan mothers planning to breastfeed, 95 HIV+ve (on Option B+ triple ART [TDF-3TC-EFV], previously ART naive) and 96 HIV-ve took part. Measurements were made postpartum at 2 (L02), 14 (L14), and 26 (L26) weeks of lactation, and at 14 weeks post-lactation when neither pregnant nor lactating (NPNL). Lumbar spine (LS), total hip (TH), femoral neck (FN) and whole body-less-head (WB-LH) areal bone mineral density (aBMD) was measured by DXA.

Results: Median age was 24.5 (IQR 21.1, 26.9) yrs. HIV+ve women had lower body weight and a shorter duration of breast feeding (47.8±13.4 vs 65.6±18.1 weeks, p<0.05). Both groups experienced lactational bone mobilisation but HIV+ve women had greater decreases in TH, FN and WB-LH aBMD during lactation, and a trend towards a smaller reduction in LS aBMD at L14. Both groups had recovered LS aBMD by NPNL. Hip and WB-LH aBMD had returned to L02 values in HIV-ve women but not in HIV+ve women (Figure 1). Adjusting for parity, age, body size, breastfeeding practices, duration of breastfeeding, use of depo-provera, resumption of menses, and other potential confounders did not attenuate the results.

Conclusion: These data show accentuated mobilisation of hip and WB-LH bone mineral during lactation, and slower skeletal recovery post-lactation in HIV+ve Ugandan women initiated on lifelong ART (TDF-based) in pregnancy, compared to HIV-ve women. Studies are ongoing to understand the mechanisms and long term consequences for bone health and growth of the child, to inform interventions aimed at reducing bone loss in pregnant and lactating HIV+ve women on ART.

Figure 1: Change in aBMD during and after lactation in HIV+ve and HIV-ve Ugandan women

HIV+ve: HIV-positive women on ART (median, IQR: L02=14 weeks of lactation, L14=14 weeks of lactation, L26=26 weeks of lactation). HIV-ve: women on ART (median, IQR: L02=14 weeks of lactation, L14=14 weeks of lactation, L26=26 weeks of lactation). WOMEN ON OPTION B+ ART

769 HIGH BLOOD PRESSURE AND ADVERSE BIRTH OUTCOMES IN HIV+ AND HIV- AFRICAN WOMEN

Angela Bengtson1, Stanza M. Le Roux1, Tasmin K. Phillips2, Kirsty Brittain2, Angela Bengtson1, Stanza M. Le Roux1, Tasmin K. Phillips2, Kirsty Brittain2

1Brown University, Providence, RI, USA, 2University of Cape Town, Cape Town, South Africa, 3Columbia University, New York, NY, USA

Background: HIV+ women on ART are at increased risk of some adverse birth outcomes. Both HIV and ART may increase the risk of high blood pressure (BP) outside of pregnancy, but little is known about the prevalence and impact of high BP in pregnancy among HIV+ women.

University, Kampala, Uganda, "Baylor College of Medicine Children’s Foundation, Kampala, Uganda
**Methods:** We followed a cohort of HIV- and HIV+ pregnant women initiating TDF+ FTC+ EFV from first antenatal care visit (ANC) through delivery in Cape Town. Gestational age (GA) was estimated from ultrasound and BP from automated monitors. BP was categorized as normal (<120/80 mmHg), elevated (120–129/<80), stage 1 (>130–139/80–89) or stage 2 hypertension (>140/ >90). Multivariable modified Poisson regression was used to estimate associations between high (elevated or higher) versus normal BP and HIV status, as well as birth outcomes. We explored modification by HIV status for associations between BP and adverse birth outcomes. We addressed missing data with multiple imputation (n=50 imputations).

**Results:** In 1116 women (HIV+ 43%) with singleton live births (median gestation at 1st ANC, 20 weeks), 48% presented with high BP (53% HIV+ vs. 43% HIV-) at 1st ANC. HIV+ + women were more likely to have high BP (RR: 1.24, 95%CI 1.04-1.49), controlling for estimated pre-pregnancy body mass index (BMI), maternal age, gravidity, socioeconomic status, alcohol use and education. Overall 12% of infants were preterm (<37 weeks’ gestation), 12% were low birthweight (LBW, <2500g), and 11% were small-for-GA (SGA, <10th percentile for GA). Compared to HIV- women, HIV+ women had more SGA (12% vs. 9%) and LBW (14% vs. 10%) infants, and a similar proportion of preterm births (13% vs. 12%). In multivariable analyses, there was no evidence that high BP increased the risk of preterm birth (RR 1.17, 95% CI 0.83-1.66), LBW (RR 1.14, 95% CI 0.82-1.57) or SGA (RR 1.00, 0.70-1.41), overall or when stratified by HIV status (Table). There was a trend towards high BP increasing the risk of preterm birth (RR 1.43, 95% CI 0.85-2.36) and LBW (RR 1.30, 95% CI 0.83-2.04) in HIV-women, but not HIV+ women.

**Conclusion:** In this setting nearly half of all women had high BP at 1st ANC. HIV+ women initiating ART were more likely to have high BP, compared with HIV- women. There was no strong evidence that high BP increased the risk of LBW, SGA or preterm birth overall, but results differed somewhat by HIV status. The high prevalence of high BP in pregnancy, particularly in HIV+ women, requires further investigation.

<table>
<thead>
<tr>
<th>BP Trajectory</th>
<th>Normal</th>
<th>Elevated</th>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA</td>
<td>15%</td>
<td>22%</td>
<td>17%</td>
<td>48%</td>
</tr>
<tr>
<td>LBW</td>
<td>12%</td>
<td>14%</td>
<td>14%</td>
<td>24%</td>
</tr>
<tr>
<td>Preterm</td>
<td>12%</td>
<td>12%</td>
<td>12%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**Figure 1:** Joint salient and holistic group trajectory membership.

**Table:** The relationship between high (elevated or higher) blood pressure (BP) levels versus normal BP at entry into antenatal care and adverse birth outcomes among 1116 pregnant women in Cape Town, South Africa, overall and by HIV status.

**Methods:** We recruited HIV+ and HIV- women at first antenatal visit at a large primary care facility in Cape Town, South Africa. HIV+ women, predominately on TDF+ FTC+ EFV regimen, initiated either pre-conception or during pregnancy. Automated BP measurements were used and a combination of ultrasound, last menstrual period and clinical exam for pregnancy dating. Group-based trajectory analysis identified distinct joint systolic and diastolic BP trajectory groups among women with ≥3 antenatal BP measurements. Multinomial regression assessed BP trajectory group associations with HIV/ART status and adverse birth outcomes. We addressed missing data with multiple imputation (n=50 imputations).

**Results:** In 1116 women (median age 28y; median gestation at 1st ANC 20w), 37% were HIV+ of whom 54% initiated ART pre-conception (n=306) and 46% during pregnancy (n=265). We identified 7 systolic and diastolic joint trajectory groups combinations based on Bayesian information criterion, then classified as consistent normal (50%), low normal (25%), high normal (20%), and increasing abnormal (5%) (Figure 1). The proportion of women in the low normal group was higher among HIV+ than among HIV- women (28% vs. 23%), but differences were not statistically significant in multivariate analysis (RR 1.27, 95% CI 0.98-1.63, reference category: consistent normal). Among HIV+ women, more women initiating ART in pregnancy were in the abnormal trajectory group than those initiating ART preconception (5% vs 2%), however association was observed (RR 2.40, 95% CI 0.54-1.61). Older (RR 1.52, 1.11-2.00) and obese (RR 2.06, 1.31-3.25) women were at increased risk of being in the high normal group. In multivariable analyses, low normal trajectory (RR 0.59, 0.41-0.85) was associated with decreased risk of PTD, while high normal (RR 1.47, 1.11-1.94) and abnormal trajectories (RR 3.18, 2.32-4.47) were associated with increased risk of PTD, and abnormal with increased risk of LBW infants (RR 3.25, 2.18-4.87).

**Conclusion:** We identified pregnant women with distinct antenatal BP trajectories, which were not associated with HIV/ART status. Further work is required to inform understanding of different BP trajectories in pregnancy, particularly in high HIV prevalent settings.

**771 POSTPARTUM WEIGHT CHANGES IN WOMEN INITIATING DTG VS EFV IN PREGNANCY: DOLPHIN-2**

**Thokozile R. Malaba1, Tao Chen1, Kenneth Kintu1, Christiana Papamichael2, Helen Reynolds3, Jesca Nakibuka4, Catriona Waitt4, Eva Maria Hodel4, Angela Colbers1, Catherine Orrell1, Durolo Wang1, Mohammed Lamorde5, Saye Khoo2, Landon Myer1, for the DolPHIN-2 Trial Team**

1University of Cape Town, Cape Town, South Africa, 2Liverpool School of Tropical Medicine, Liverpool, UK, 3Makerere University, Kampala, Uganda, 4University of Liverpool, Liverpool, UK, 5Radboud University Medical Center, Nijmegen, Netherlands, 6Desmond Tutu HIV Foundation, Cape Town, South Africa

Background: There are growing concerns about weight gain with dolutegravir (DTG) use, with some suggestion of heterogeneity of effects across populations especially among women. However there are no data from pregnancy and the postpartum (PP) period.

**Methods:** DolPHIN-2 (NCT03249181) is an open label trial randomising (1:1) pregnant women from Uganda and South Africa (SA) initiating ART from 28w gestation to DTG vs efavirenz (EFV) plus 2 NRTIs. Maternal weights were measured using standardized procedures at enrolment, <14 days of delivery and at 6, 12, 24 and 48 weeks PP. For this secondary analysis we examined changes in PP weight and body mass index (BMI) between study arms.

**Results:** Enrolment took place between Jan and Aug 2018, and follow-up data were censored Sept 2019: 210 women (mean age, 28y) were included with median follow-up of 60 months. At enrolment (median gestation, 31w) the mean weight and BMI was 74 kg and 28 kg/m^2, respectively, with no differences between trial arms but higher third trimester weight in SA (mean, 81g) versus Uganda (mean, 68g) sites. 73%, 61% and 3% of women reported breastfeeding the infant at 12, 24 and 48w PP, respectively, with no differences by arm. Across both arms and sites, mean change in weight from enrolment to...
Dolutegravir Use Is Associated with Higher Postpartum Weight Compared to Efavirenz

Jennifer Jao¹, Shan Sun¹, Justine Legbedzé¹, Denise Jacobsen¹, Keolebogile N. Mmasa¹, Samuel W. Kgoe¹, Gosego Masasa¹, Joseph Makhema¹, Sikhullele Mayo¹, Mampati G. Mmalane¹, Francis Banda², Barnaparte Nkomo³, Mariama Gerschenson¹, Elaine J. Abrams⁴, Kathleen M. Powis⁴
¹Northwestern University, Chicago, IL, USA, ²Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, USA, ³Harvard T.H. Chan School of Public Health, Boston, MA, USA, ⁴Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, ⁵Botswana Ministry of Health, Gaborone, Botswana, ⁶University of Hawaii, Honolulu, HI, USA, ⁷ICAP at Columbia University, New York, NY, USA

Background: Postpartum weight retention impacts cardiometabolic risk. Recent studies show higher weight gain with dolutegravir (DTG)-based antiretroviral therapy (ART) compared to other ART. We assessed the association of DTG with postpartum weight over time in women with HIV (WHIV) in Botswana using comparator groups of women on efavirenz (EFV) and HIV-negative (HIV-) women.

Methods: The Tshilo Dikotla study enrolled pregnant HIV- women and WHIV on either tenofovir (TDF)/emtricitabine or lamivudine (XTC)/DTG or TDF/XTC/EFV initiated during or before pregnancy. This analysis included women with weight measurements 1 to 18 months postpartum. Mixed models were fit to assess the association between ART status and postpartum weight over time, adjusting for confounders. Interaction terms between time and HIV/ART group were evaluated to assess for differences in weight trajectories. Subgroup analysis was performed among WHIV to further assess the association of DTG vs EFV and postpartum weight, adjusting for HIV-specific factors.

Results: Of 406 women, 170 received DTG and 114 EFV. Women on DTG or EFV were older than HIV- women (median age 28 vs 33 vs 25 years respectively, p<0.01), and fewer had a college education (13.5% vs 4% vs 29.5% respectively, p<0.01). Average weight gain per week (wk) between 2nd and 3rd trimester was highest in HIV- women (0.3 vs 0.2 for DTG vs 0.1 kg/wk for EFV, p<0.01) as was breastfeeding duration (35.7 vs. 19.0 for DTG vs 22.6 wks for EFV, p<0.01). No differences in income, gestational diabetes (GDM), gestational age at delivery, or BMI at 1 month postpartum were noted across groups. Among WHIV, no differences in CD4 or log viral load at enrollment were noted between ART group; more women on EFV were on their ART at conception (86% vs. 35.3%, p<0.01). Compared to HIV- women, WHIV on DTG had similar postpartum weight through 18 months but were on average 5 kg heavier postpartum than WHIV on EFV (β=0.50, p<0.01) after adjusting for age, GDM, breastfeeding duration, and weight gain between 2nd and 3rd trimester. (Fig) No differences in slope trajectories were noted between groups. This association persisted in subgroup analysis of WHIV even after further adjusting for CD4, viral load, and ART at conception (β=2.4 for DTG vs. EFV, p=0.04).

Conclusion: WHIV on DTG have persistently higher weight through 18 months postpartum than those on EFV in Botswana but similar weight to HIV- women. Further studies to assess mechanisms of postpartum weight retention are needed.

Obesity, Gestational Weight Gain, and Adverse Birth Outcomes in South African Women

Hlengiwe P. Madlala¹, Thokozile R. Malaba¹, Marie-Louise Newell¹, Landon Myer¹
¹University of Cape Town, Cape Town, South Africa, ²University of Southampton, Southampton, UK

Background: HIV and/or ART may increase adverse birth outcomes including low birthweight (LBW) and small for gestational age (SGA) infants. In parallel, there are increasing concerns regarding obesity (BMI ≥30 kg/m²) in HIV+. Individuals on ART, in pregnancy obesity is known to contribute to high birthweight (HBW) and large for gestational age (LGA) infants. However, there are few data on obesity and gestational weight gain (GWG) in HIV+ pregnant women on ART.

Methods: We examined obesity and high GWG (>75th percentile), and associations with birth outcomes in HIV+ (predominantly using TDF+XTC+EFV) and HIV- women in Cape Town. We consecutively enrolled 2828 pregnant women ages ≥18y at 1st antenatal visit. Follow-up was through routine medical records, with repeated GWG assessments available for the subset of 471 HIV+ women enrolled (n=24 weeks gestation in an intensive study. Associations between obesity, high GWG and birth outcomes (birthweight and size for GA) were assessed via multinomial logistic regression adjusting for age, ART status, GA at enrolment and parity.

Results: At 1st antenatal visit (median gestation, 19w), median BMI was 30 kg/m², (IQR, 26-35) in both HIV+ (36% of all participants) and HIV- women, with obesity prevalence of 49% and 50%, respectively. In the HIV+ subset, median GWG was 0.25 kg/week (IQR, 0.11-0.42); high GWG prevalence was 25%. In adjusted models, obesity in HIV- women was significantly associated with reduced risk of LBW (aOR 0.47, 95% CI 0.26-0.84) and SGA (aOR 0.51, 95% CI 0.32-0.82), and with increased risk of HBW (aOR 3.00, 95% CI 1.13-7.99) and LGA (aOR 2.13, 95% CI 1.28-3.55). In HIV+ women, obesity was also significantly associated with reduced risk of LBW (aOR 0.43, 95% CI 0.23-0.80) and SGA (aOR 0.59, 95% CI 0.35-0.99), and non-significantly with increased risk of HBW (aOR 1.30, 95% CI 0.46-3.65) and LGA (aOR 1.34, 95% CI 0.73-2.48). In the HIV+ subset, high GWG was associated with increased risk of HBW (aOR 4.51, 95% CI 1.67-12.15) and LGA (aOR 2.52, 95% CI 1.13-5.59).

Conclusion: Obesity in pregnancy and high GWG are prevalent in this setting in both HIV+ and HIV- women. High GWG in HIV+ women was associated with increased risk of HBW and LGA, while obesity was associated with reduced risk of LBW and SGA. Outcomes of HIV+ women may now parallel those of HIV- women.

Table 1. Association between obesity, high GWG and adverse birth outcomes among HIV+ women with four singleton births in the overall and subgroups of women in Cape Town, South Africa

<table>
<thead>
<tr>
<th>Birth weight (g)</th>
<th>Normal (n=239)</th>
<th>Obese (n=203)</th>
<th>p-value</th>
<th>Normal (n=312)</th>
<th>High (n=128)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;2500)</td>
<td>1.00 (Ref)</td>
<td>0.81 (0.62-1.03)</td>
<td>0.009</td>
<td>1.00 (Ref)</td>
<td>1.88 (0.50-7.42)</td>
<td>0.050</td>
</tr>
<tr>
<td>High (≥4000)</td>
<td>1.00 (Ref)</td>
<td>1.80 (0.60-4.93)</td>
<td>0.661</td>
<td>1.00 (Ref)</td>
<td>4.33 (1.67-11.21)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size for GA (cm)</th>
<th>Normal (&lt;10%)</th>
<th>SGA (≥10%)</th>
<th>p-value</th>
<th>Normal (&lt;10%)</th>
<th>SGA (≥10%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;38)</td>
<td>1.00 (Ref)</td>
<td>0.59 (0.35-0.99)</td>
<td>0.047</td>
<td>1.00 (Ref)</td>
<td>1.17 (0.64-2.18)</td>
<td>0.603</td>
</tr>
<tr>
<td>Large (&gt;40)</td>
<td>1.00 (Ref)</td>
<td>1.34 (0.73-2.48)</td>
<td>0.544</td>
<td>1.00 (Ref)</td>
<td>2.52 (1.13-5.69)</td>
<td>0.023</td>
</tr>
</tbody>
</table>
**FACTORS ASSOCIATED WITH GESTATIONAL DIABETES IN HIV+ AND HIV− WOMEN IN PUNE, INDIA**

Puja Chebrolu1, Mallika Alexander2, Ramesh Bhosale3, Shilpa Naik1, Nikhil Patil1, Amita Gupta1, Joyti S. Mathad3

1Weill Cornell Medicine, New York, NY, USA, 2Johns Hopkins University, Baltimore, MD, USA, 3Byramjee Jeejeebhoy Government Medical College, Pune, India

**Background:** Pre-pregnancy BMI was significantly higher among cases than controls. Among HIV+, weight at study entry, MUAC at study entry and 3rd trimester, and pre-pregnancy BMI were significantly higher among cases than controls. Among HIV−, only pre-pregnancy BMI was significantly higher. Use of PIs showed a trend toward significant association.

**Conclusion:** In our study of pregnant women in India, HIV+ women had a higher prevalence of GDM than HIV− women, which was incompletely explained by PI use. Higher MUAC, weight, and BMI were associated with increased risk of GDM in HIV+ and HIV− pregnant women among the whole cohort. Ongoing studies are identifying the pathogenesis behind this increased risk.

**RILPIVIRINE IN HIV−-INFECTED WOMEN INITIATING PREGNANCY: TO SWITCH OR NOT TO SWITCH?**

Pierre Frange1, Roland Tubiana1, Jeanne Sibiude2, Ana Canestri3, Cedric Arvieux1, Cecile Brunet-Cartier1, Laurent Cotte1, Sophie Matheron1, Jacques Reyes1, Laurent Mandelbrot1, Josiane Warszawski1, Jérôme Le Chenadec1, for the ANRS EPF C01/C011 Study Group

1Necker Hospital, Paris, France, 2AP−HP, Hôpitaux Universitaires Pitié Salpêtrière, Paris, France, 3Hôpital Louis-Mourier, Colombes, France, 4Tenon Hospital, Paris, France, 5CHU de Rennes, Rennes, France, 6CHU Hôtel-Dieu, Nantes, France, 7Hospices Civils de Lyon, Lyon, France, 8AP−HP, Hôpital Bichat-Claude Bernard, Paris, France, 9INSERM, Le Kremlin-Bicêtre, France

**Background:** Data about safety and efficacy of rilpivirine (RPV) during pregnancy remain scarce. Because RPV plasma concentrations are reduced during 2nd and 3rd trimesters of pregnancy and viral breakthroughs were observed, French guidelines recommend switching to RPV-free cART during pregnancy. This study aimed to describe the characteristics of women initiating pregnancy while on RPV and to compare the outcome of virologically suppressed subjects continuing RPV until delivery or switching to RPV-free cART.

**Methods:** We included all women in the French Perinatal HIV cohort receiving RPV at the time of conception in 2010-2018, with prospective, monthly follow-up of pregnant women and pediatric follow-up from birth to 18–24 months. We compared maternal and infant characteristics in case of maintain of RPV through pregnancy or switch to RPV-free cART. In women with available results of HIV−1 viral load (VL) before 14 weeks of gestation (WG) and viral suppression (VL<50 copies/mL) while on RPV, we compared the probability of viral rebound (≥50 copies/mL) during pregnancy between those continuing RPV versus those switching to RPV-free cART.

**Results:** Overall, 248 women were receiving RPV, mostly combined with TDF/FTC in single-tablet regimens (93.5%). At the beginning of pregnancy, most women were virologically suppressed (88.2%) and median CD4 count was 564/µL (IQR: 431–716). During pregnancy, 185 women (74.6%) switched to RPV-free cART (mostly PI−+ NRTI(s)), at a median gestational age of 6.0 WG (IQR: 6.0 – 12.0). The VL nearest delivery was <50 copies/mL in 95.7% of women. Few adverse events occurred during pregnancy (birth defects: 3.6%; ectopic pregnancies: 0.4%; stillbirths: 1.6%; preterm deliveries: 8.9%; very preterm deliveries: 2.8%) with similar proportions in patients continuing RPV and in those switching to RPV-free cART. The characteristics of newborns were similar between groups. No child was infected with HIV. Among 69 women with 9 weeks of gestation. No cases of birth defects have been reported. Three HIV-infected women receiving CAB LA 400mg IM monthly injections (range: 16–176 weeks on therapy) became pregnant with subsequent live birth outcomes. All were virologically suppressed with pre-dose CAB concentrations of 2.41–4.63 µg/mL just prior to pregnancy and 2.10–5.04 µg/mL at time of pregnancy confirmation. Following CAB LA discontinuation, residual CAB concentrations remained measurable throughout pregnancy with a predicted concentration of ~0.5 µg/mL (3x PA-IC90 [0.166 µg/mL]) at delivery and remaining detectable post-partum (range: 2.2–23 weeks) in 2/3 women. These data are consistent with absorption-rate limited PK.

**Conclusion:** Pre-pregnancy CAB trough concentrations were consistent with population estimates for monthly dosing and declined slowly following drug discontinuation in pregnancy with predicted concentration 3x PA-IC90 at time of delivery in 2 of 3 HIV-infected women with live birth outcomes. CAB PK tail in pregnancy was within the expected range for non-pregnant women. Pregnancy surveillance in the treatment and prevention program continues.
documented viral suppression before 14 WG, the risk of viral rebound during pregnancy was significantly higher when switching to a RPV-free cART than when continuing RPV until delivery (21.0% versus 0.0%, p = 0.046) (Figure).

**Conclusion:** Continuing RPV in virologically-suppressed women initiating pregnancy may be associated with better virological outcome than changing cART. Larger studies are required to confirm these results and establish the safety of fetal exposure to RPV in the long term.

**RISK OF VERTICAL TRANSMISSION FROM MOTHERS WITH PERINATAL HIV INFECTION IN ZIMBABWE**

**Tafadzwa Sibanda**, 1 Tsitsi G. Monera-Penduka, 1 Enerst Chikwati, 1 Jan Van Den Hombergh, 1 Juan Gonzalez Perez 1

**Background:** Data from all PHIV women 18 years and above active in care by April 2019 in Mpilo ART Clinic (Zimbabwe) with at least one pregnancy in the last five years were included in the study and compared with a sample of HIV+ women not perinatally infected meeting the same criteria. Demographic and clinical data was extracted from databases and complemented with individual interviews to get information of pregnancy outcomes and HIV status of exposed infants. For data analysis, proportions were compared using Chi square. Logistic regression was used to identify predictors of MTCT.

**Methods:** Data from all PHIV women 18 years and above active in care by April 2019 in Mpilo ART Clinic (Zimbabwe) with at least one pregnancy in the last five years were included in the study and compared with a sample of HIV+ women not perinatally infected meeting the same criteria. Demographic and clinical data was extracted from databases and complemented with individual interviews to get information of pregnancy outcomes and HIV status of exposed infants. For data analysis, proportions were compared using Chi square. Logistic regression was used to identify predictors of MTCT.

**Results:** Out of 564 PHIV women in the ART clinic database, 148 accepted to be interviewed and provided complete information on 166 pregnancies. Similarly, 152 non-Perinatally infected HIV positive (non-PHIV) women were interviewed yielding 174 pregnancies. Women in the PHIV group were younger (median age 20 years old versus 34 in non-PHIV) and have been longer in HIV care at the time of pregnancy (median 9 years versus 6 in non-PHIV). 81% of all participants have a VL test in the previous 12 months, with 66.4% of PHIV women and 87.2% of non-PHIV women achieving a VL < 1,000 copies/mL. On pregnancy outcomes, risk of abortion/stillbirth was double in the PHIV group (24.1% [40/166] vs. 13.8% [24/174], OR: 2.0, p < 0.01). MTCT rate was slightly higher in PHIV women (8.7% [11/126] vs. 7.3% [11/150]) but the difference was not statistically significant. When adjusting for age, education, last VL and time in HIV care at the time of pregnancy, mode of acquisition of HIV of the mother was not independently associated with the risk of MTCT.

**Conclusion:** Our results from a large ART clinic in Zimbabwe do not confirm findings from a US-based cohort where MTCT rate was more than double in PHIV mothers compared with those with horizontally acquired HIV. We identified, however, an increased risk of abortion/stillbirth in PHIV women, as well as, a high prevalence of unsuppressed VL what highlights the importance of intensive VL monitoring to optimize ART in that group.
779 HIV SEROCONVERSION DURING PREGNANCY AT ROUTINE ANTENATAL CARE CLINICS IN BOTSWANA

Katrina F. Ortblad,_Shreshth Mawandia, Odirile Baka, Lenna Tau, Matias Grande, Goabaoke Mogomotsi, Esther Mmatli, Modise Ngombo, Laura Seckel, Renee Heffron, Jillian Pintye, Jenny Ledikwe

1University of Washington, Seattle, WA, USA, 2International Training and Education Center for Health, Gaborone, Botswana, 3Botswana Ministry of Health, Gaborone, Botswana, 4Emory University, Atlanta, GA, USA, 5Massachusetts General Hospital, Boston, MA, USA

Background: Risk of HIV acquisition during pregnancy and postpartum is high in sub-Saharan Africa. While current prevention of mother-to-child HIV transmission (PMTCT) programs are designed to detect and treat women with chronic HIV infections, women who are newly infected or acquire HIV after initial antenatal testing may have infections that go undetected. Botswana was the first African country to routinize HIV testing for pregnant women attending antenatal care (ANC) and ANC attendance in Botswana is high at 97%. Repeat HIV testing during ANC is both time and cost intensive. We evaluated the frequency of detecting previously undiagnosed HIV infections among routine ANC attendees in Botswana.

Methods: From January 2018 to September 2019, a national HIV testing program was implemented at 139 ANC clinics in 15 districts in Botswana. Electronic data captured information on demographics (age, sex, citizenship), HIV testing (date, location, result) and linkage to antiretroviral treatment (ART). For this analysis, individuals who previously tested HIV-positive prior to their first identified ANC visit were excluded, enabling an evaluation of frequency of detecting previously undiagnosed HIV. Among HIV-negative individuals who had a repeat HIV test at a subsequent ANC visit, we measured time to re-testing and frequency of HIV seroconversion during ANC follow-up.

Results: In total, 29,583 women (median age 26 years, IQR 22-31) were tested for HIV at ANC clinics and 97% tested HIV-negative (28,735). Women who tested HIV-negative were similar in age, citizenship, and urban testing location to those who tested HIV-positive; (8,005) had a repeat HIV test at a subsequent ANC visit; median time to HIV re-testing was 92 days (IQR 70-112) and frequency of HIV seroconversion was 0.3% (23). ART initiation among all women who tested HIV-positive at ANC (854) was 88% (686/782). Women who tested HIV-negative were similar in age, citizenship, and urban testing location to those who tested HIV-positive; women who initiated ART were similar in age and urban testing location, but not citizenship status (99% vs 52% non-citizens, p<0.001), to those that did not initiate ART, Fig. 1.

Conclusion: In this large evaluation, we detected previously undiagnosed HIV infection and seroconversion among ANC attendees in Botswana, despite high ANC testing and PMTCT coverage. To reach elimination of MTCT, repeat HIV testing and primary prevention during ANC remain key components of PMTCT programs.

780 TRENDS IN MARIJUANA, ALCOHOL, AND OPIOID USE IN PREGNANT AND POSTPARTUM HIV+ WOMEN

Lynn M. Yee, Deborah Kacanek, Chase Brightwell, Lisa B. Haddad, Jennifer Jao, Kathleen M. Powis, By Jyun Yao, George R. Seage, Ellen G. Chadwick

1Northwestern University, Chicago, IL, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3Emory University, Atlanta, GA, USA, 4Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, USA, 5Massachusetts General Hospital, Boston, MA, USA

Background: Concurrent with the opioid epidemic in the United States (US), rates of marijuana use have risen among pregnant and non-pregnant women of reproductive age. Amid evolving legal and social changes, little is known about substance use among pregnant and postpartum women living with HIV (WLHIV). Our objective was to evaluate trends over time in marijuana, alcohol, and opioid use during pregnancy and the first year postpartum among US WLHIV.

Methods: We analyzed data on marijuana, alcohol, and/or opioid use from the Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study. SMARTT has been enrolling pregnant WLHIV at 22 US sites since 2007. SMARTT-enrolled pregnant WLHIV from 2007-2019 with self-reported substance use data available in pregnancy, 1 year postpartum, or both were included (postpartum opioid use not collected). Prevalence of any marijuana, alcohol, opioid, and concomitant alcohol and marijuana use was calculated by calendar year, separately for pregnancy and postpartum periods. We fit log binomial general estimating equation models to evaluate linear trend in use over time, accounting for repeat pregnancies.

Results: Substance use data were available for 2,926 pregnancies from 2,310 WLHIV. Women were primarily non-Hispanic black (63.5%) or Hispanic (28.1%) and aged 25-39 years (67.6%). Between 2007 and 2019, marijuana use during pregnancy increased from 7.1% to 11.7% (Figure 1a). Alcohol and opioid use in pregnancy were unchanged over this period (mean prevalence 4.9% and 5.2% respectively). Alcohol and marijuana use were more prevalent in the 1st trimester compared to the 2nd or 3rd, while opioid use was similar across trimesters. In the postpartum period, alcohol and marijuana use were common (mean prevalence 44.4% and 13.6% respectively), with marijuana use increasing over time (Figure 1b). On average, risk of marijuana use increased each year by 6% and 11% for pregnancy and postpartum, respectively (Relative Risk [RR] 1.06, 95% Confidence Interval [CI] 1.03-1.10; RR 1.11, 95% CI 1.06-1.16). Postpartum combined alcohol and marijuana use increased from 6.7% to 16.4%, a 10% per year increase (RR 1.10, 95% CI 1.05-1.15).

Conclusion: Opioid use among pregnant and postpartum WLHIV in SMARTT remained low and stable despite the US opioid epidemic, whereas the prevalence of marijuana use increased between 2007 and 2019, as did postpartum concomitant alcohol use. Increasing marijuana use in pregnant and postpartum WLHIV warrants further attention.

781 TRANSMISSION, VARIATION, AND EVOLUTION OF IN UTERO TRANSMITTED HIV-1

Manukumar Honayakanahalli, Michael Mengual, Amit Kumar, Elena E. Giorgi, David R. Martinez, Joshua J. Tu, Xiaojun Li, Sallie Permar, Feng Gao
**Background:** HIV-1 can be transmitted from infected mothers to their fetuses during pregnancy. However, the transmission timing, viral diversity, and selection pressure on fetal viruses during pregnancy is poorly understood. A better understanding of transmission mechanisms will be key to further reduce the mother-to-child-transmission (MTCT) rate.

**Methods:** Viral RNA was extracted from plasma of 12 mothers (at birth) and their in utero infected infants (from birth to 3 months after delivery). All infants were HIV-1 positive by detecting HIV-1 DNA genome in infant or cord blood at birth. Multiple env gene sequences were obtained from each sample using single genome amplification (SGA). Genetic diversity, phylogenetic trees, highlighter plots were used to infer transmitted/founder (T/F) viruses in the infants and to study the viral populations in both mothers and infants. Infection time was estimated using the Poisson-Fitter tool. Selection signatures in paired maternal viruses were analyzed using SNAP and amino acid sequence alignments.

**Results:** A total of 846 env gene sequences (317 from mothers and 529 from infants) were obtained. Homogenous viral populations were found in 6 infants and 2 were infected with 2 to 3 T/F viruses. The estimated time of infection for these infants is within 2 months (37-3 days) before delivery. High genetic diversity was found in 4 other infants. The time of infection for these 4-infants could not be reliably estimated by current computational analysis tools, possibly due to extensive recombination in the samples. The high genetic diversities strongly suggest that the fetuses were infected in early pregnancy. SNAP and amino acid sequence analysis showed that C1, V1 and V5 regions in the infant env sequences were highly variable. Some of these signatures in infant viruses were distinct from mother, indicating that placentally-transmitted viruses were under strong selection pressure in fetuses. Higher IgG-mediated neutralization potency was found in some placental plasma compared to that of peripheral plasma from the same mother, suggesting possible selection of HIV-neutralizing IgG subpopulations for placental transfer.

**Conclusion:** The majority of in utero transmissions occur in the late third trimester during pregnancy, possibly due to the thinning placenta membrane. The variable regions in the infant env sequences suggest that immune system in fetuses is able to exert strong selection pressure on fetal viral population.

---

**782 MATERNAL RISK STRATIFICATION TO IDENTIFY HIGH-RISK INFANTS FOR HIV BIRTH TESTING**


**Background:** In 2017, Zimbabwe adopted a modified version of the World Health Organization 2016 recommendation on HIV birth testing by offering HIV testing at birth only to infants at “high risk” of HIV transmission (criteria based on timing of maternal diagnosis, viral load, and ART adherence). However, there is paucity of evidence on sensitivity, specificity, and predictive value for this approach. This study focuses on assessing the sensitivity and specificity of birth testing “high risk” infants only compared to birth testing of all HIV-exposed infants.

**Methods:** This was an analytic cross-sectional study. A five-question maternal risk screening tool based on the national guidelines definition of risk was administered to mothers of all HIV-exposed infants identified within 48 hours of birth at 10 study sites from November 2018 to July 2019. At these sites, a nucleic acid HIV test was performed on all HIV-exposed infants irrespective of risk status. Univariate and bivariate analysis were used to estimate the performance of the risk screening tool.

**Results:** A total of 2,080 infants were enrolled. A nucleic acid test for HIV was successfully performed on 1,970 infants (95%) of whom 266 (13.5%) were classified as high risk infants. HIV prevalence for all infants tested was 1.5% (95% CI: 1%—2%) while prevalence among high risk infants and low risk infants was 6.8% (95% CI: 3.7%—9.8%) and 0.6% (95% CI: 0.3%—1%) respectively. There was a significant association between maternal HIV transmission risk status and HIV infection (p-value < 0.001). Sensitivity and specificity of the maternal risk screening tool was at 62.1% (95% CI: 44.4%—79.7%) and 87.7% (95% CI: 85.7%—88.7%), respectively; positive and negative predictive values were 6.8% (95% CI: 3.7%—9.8%) and 99.4% (95% CI: 99.0%—99.7%) respectively. Sensitivity and specificity in detecting HIV status varied for different individual screening questions. A ‘yes’ response to starting ART after 32 weeks’ gestation had the highest sensitivity in predicting HIV infection 58.6% (95% CI: 40.7—76.5) and a ‘yes’ to non-adherence to ART had the lowest sensitivity 7.1% (95% CI: 2.4%—16.7%).

**Conclusion:** Although there was a significant association of maternal risk stratification with risk of infant infection and the negative predictive value of the risk screening tool was relatively high, the sensitivity was relatively low, and 38% of infants infected at birth would be missed if birth testing was based solely on a positive risk screen.

---

**783 POINT-OF-CARE TESTING IMPROVES EARLY INFANT DIAGNOSIS IN THE PUBLIC HEALTH SECTOR**


**Background:** Despite progress in the scale-up of early infant diagnosis (EID) programs in the last decade, in 2018 only 51% of HIV-exposed infants received a diagnostic nucleic-acid test within the recommended two months of birth. Point-of-care (POC) testing has been shown to dramatically increase rates of early diagnosis and initiation of ART for HIV-positive infants. As national programs in sub-Saharan Africa incorporate POC EID technologies, it is critical to document the impact of POC EID within routine public sector programs and understand implications for national scale-up.

**Methods:** A 6-month pre-/post-evaluation comparing conventional laboratory (pre) to POC (post) testing using either Cepheid GeneXpert or Abbott mPima devices was conducted in 36 facilities across three countries, Cameroon, Ethiopia and Zimbabwe, between 2018-2019. On-site trainings for POC devices were held for facility and laboratory staff prior to implementation. Data were retrospectively extracted from routine records at health facilities for all infants (aged 0-2 years) tested. The primary outcome was the proportion of infants tested in which the infant’s caregiver received the test results within 28 days of sample collection (WHO recommendation, 2010). ART initiation within 28 days of sample collection was also analyzed for HIV-positive infants.

**Results:** Before POC introduction, 2465 EID tests were conducted, of which 123 (5.0%) were HIV-positive. After POC implementation, 4288 tests were conducted, 189 (4.4%) of which were HIV-positive. POC EID resulted in faster turnaround times (median of 0 days (POC) vs. 40 days (conventional)) and POC EID results were more than four times as likely to be received by a caregiver within 28 days of sample collection (19.5% for conventional vs. 86.1% for POC; RR: 4.67; 95% CI: 1.51-7.83). The proportion of caregivers receiving results within 28 days of POC sample collection varied from 76.0% in Cameroon to 96.2% in Ethiopia (Table 1). Infants tested on POC had a much greater probability of initiating ART within 28 days (9.8% for conventional vs. 67.2% for POC; RR: 6.72; 95% CI 2.13-11.32).

**Conclusion:** POC EID significantly improved rates of test result returned to caregiver and ART initiation within routine care at public health facilities. However, in some settings gaps remained in timely results return and treatment initiation. To maximize the impact of faster testing through POC, programs must focus on ensuring test results are used and follow-on care is provided.
784 EVALUATION OF PERFORMANCE AND UsABILITY OF CEPHEID XPERT HIV-1 Qual ASSay IN MALAWI

Maggie N. Nyang’Wa1, Augustine Choko1, Angela Obasi2, Chisomo Msafud1, Maganizo Chagomera1, Sarah Wattess1, Kevin Mortimer1, Neil Kennedy1, Derek Fairley1, Nigel Klein1, Dagmar Albe1

1University College London, London, UK; 2Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Lilongwe, Malawi; 3Liverpool School of Tropical Medicine, Liverpool, UK; 4University of Malawi, Blantyre, Malawi; 5University of North Carolina Project—Malawi, Lilongwe, Malawi; 6Queen’s University Belfast, Belfast, United Kingdom

Background: As countries work towards attaining UNAIDS 90–90–90 targets, challenges related to Early Infant Diagnosis (EID) of HIV should be addressed. In Malawi, EID programmes use dried blood spot (DBS) and HIV PCR with turn-around-times (TAT) of 2–3 months with 33% of exposed infants lost to follow-up. There is an urgent need for point-of-care tests (POCTs) which can improve TAT and reduce loss to follow-up. We evaluated the feasibility, sensitivity and specificity, turn-around-time, acceptability and usability of Cepheid Xpert HIV-1 Qual assay (Xpert HIV) whole blood protocol in a rural district hospital compared to HIV PCR.

Methods: This prospective diagnostic study consecutively recruited children aged 0–14 years attending Mulanje District Hospital (MDH) in Malawi between July–September 2018. All POCT were done on site using Xpert HIV. DBS were prepared for HIV PCR testing at a central facility, Queen Elizabeth Central Hospital (QECH). Xpert HIV was also sent to Thyolo District Hospital (TDH) for testing by PCR. We compared the sensitivity and specificity between Xpert HIV and PCR. Turn-around times for TAT comparison between MDH and PCR from QECH and TDH were calculated.

Results: Of 600 participants, 324 (54%) were female. 272 (45.3%) were aged 5 years or younger. 227 (37.8%) between 5–9 years and 101 (16.8%) <1 year. Most of the participants aged >1 year (11/13(85%)) started antiretroviral therapy in 1 day and 4/15 (26%) of all HIV positives were lost to follow-up. Xpert HIV was well accepted by caregivers and nurses; and was deemed easy to use by laboratory technicians in comparison to PCR.

Conclusion: These results suggest that implementing Xpert HIV may improve EID and linkage into HIV care.

785 EARLY INFANT DIAGNOSIS: STRENGTHEN EXISTING SYSTEMS OR INVEST IN POIN-OF-CARE?

Nicole McCann1, Jennifer Cohn1, Clare Flanagan1, Emma Sacks1, Sushant Mukherjee1, Addmore Chadambuka1, HAurowi Mafaune1, Rochelle P. Walenkys2, Collins O. Odhiamba1, Kenneth Freedberg1, Oluwaraminti Adetunji3, Christopher Panella1, Andrea L. Ciaramello1

1Massachusetts General Hospital, Boston, MA, USA; 2Elizabeth Glaser Pediatric AIDS Foundation, Geneva, Switzerland; 3Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA; 4Elizabeth Glaser Pediatric AIDS Foundation, Harare, Zimbabwe; 5University of Nairobi, Nairobi, Kenya

Background: To improve early infant HIV diagnosis (EID) programs, options include replacing lab-based tests with point-of-care (POC) assays or investing in strengthened systems for sample transport and return of results. We projected the clinical benefits and cost-effectiveness of these approaches.

Methods: We used the Cost-Effectiveness of Preventing AIDS Complications-Pediatric model, with programmatic and published data, to examine clinical benefits and costs of three strategies for EID in Zimbabwe for infants 6 weeks of age: 1) lab-based EID (LAB), 2) strengthened lab-based EID (S-LAB), defined as improved sample transport, two additional lab staff, and increased lab maintenance, and 3) POC EID. Assays differed in sensitivity (LAB and S-LAB 100%, POC 96.9%) and specificity (LAB and S-LAB 99.6%, POC 100%). LAB/S-LAB/POC algorithms also differed in: probability of result return (79/91/98%), time until result return (61/53/0 days), probability of linking to ART after confirmed positive result (52/71/86%), and total cost/return ($719/$298.0/$31.26), which included transport, salary, training, and maintenance costs derived from a resource utilization analysis in Zimbabwe.

Conclusion: Current EID programs will attain greater benefit for additional investments by integrating POC EID rather than strengthening lab-based systems; decreases in POC test cost will amplify the benefits of POC EID.
group, 70.5% in the control groups B and 70.0% in group C), among those tested (n=501), 85.0% of the intervention (A) children were tested at 7-90 days of age, 69.0% in group B and 75.3% of group C (adjusted Risk Ratio (aRR)=1.13 for the MI intervention vs. group C; 95% Confidence Interval (CI): 1.0-1.3) and aRR 1.2 vs. group B (95% CI: 1.1-1.4). Overall only 58 (8.2%) children were tested at 18-months (10.7% group A, vs. 5.5% in group C, aRR 2.0, 95 CI: 1.0-3.7) with a final vertical transmission rate of 0.7%. Maternal retention and VL suppression rates were similar against randomisation groups at 349 (95%) retained at six months (180/226 VL suppressed), 151 (21%) at 12 months (93/144 VL suppressed), 130 (18%) at 18-months (99/111 suppressed).

Conclusion: MI retention counselling by unskilled lay personnel is feasible and can reduce delays in the uptake early infant diagnostic tests for HIV-exposed infants. However, greater efforts are needed to improve adherence to the 18-months child antibody test, postpartum maternal retention in HIV care and viral monitoring.

787 MOTHERS’ ADHERENCE HELPS IN IDENTIFYING MORE INFANTS IN NEED OF EXTENDED PROPHYLAXIS

Sara Dominguez Rodriguez¹, Pablo Rojo Conejo¹, Maria G. Lain², Afaaf Liberty², Shaun Barnabas³, Elica López Varela¹, Kennedy N. Otwormbe³, Siva Danavah⁴, Elieni Nastouli⁵, Miquel Serna Pascual⁵, Viviana Gianuzzi⁶, Carlo Giaquinto⁴, Louise Kuhni⁷, Alfredo Tagarro⁸, for the EPICAL Consortium ¹Hospital Universitario 12 de Octubre, Madrid, Spain, ²Fundación Ariel Glaser Contra o SIDA Pediatrica, Maputo, Mozambique, ³Perinatal HIV Research Unit, Soweto, South Africa, ⁴Tygerberg Hospital, Cape Town, South Africa, ⁵Global, Barcelona Institute for Global Health, Barcelona, Spain, ⁶Africa Health Research Institute, Mthubatuba, South Africa, ⁷University College London, London, UK, ⁸PENTA Foundation, Padova, Italy, ⁹University of Padova, Padova, Italy, ¹₀Columbia University Medical Center, New York, NY, USA

Background: The WHO recommends extended HIV prophylaxis (ePCP) for infants at high-risk of PMTCT. High risk is defined by maternal factors: a mother first identified as HIV-infected at delivery or postpartum, a known HIV+ mother not on ART, viral load (VL)> 1000 copies/mL <1 month before birth, or unavailable VL but ART for <4 weeks by delivery. Well controlled cohorts of pregnant women show that 10% of pregnancies are high risk and contribute to 57% of vertical infections. 90% of pregnancies are low risk and result in 43% of infections. In practice, some of the high-risk infants are miscategorized and treated with standard prophylaxis instead of ePCP. The aim is to evaluate the sensitivity of WHO algorithm to correctly identify high risk infants, based on the given outcome which is HIV infected infant, and to assess the improvement of adding extra information to the algorithm.

Methods: EARTH is a multicenter prospective cohort, part of the EPICAL consortium, enrolling HIV perinatally infected infants diagnosed in the first 3 months of life and treated in the first 3 months after diagnosis, in Mozambique and South Africa. We categorized infants as high risk or low risk, based on WHO criteria and then re-categorized infants after including mother self-reported adherence.

Results: 135 children were analyzed. Median age at enrolment was 38 days (31-75), and median age at ART was 33 days (19-66). Prophylaxis after birth was prescribed to 80%. Only 26% of high-risk infants received extended ePCP with NVP and AZT. Median mother’s age at enrollment was 28 years and only 68% had detectable VL. Of those, their last median VL was log10 4.21. To date, no mothers died. Only 58 (43%) mothers were classified as high risk and 77 (57%) as low risk. Of these, 74/77 (96%) had not a recent VL prior to delivery but were on ART for >4 weeks. Maternal self-reported adherence was good in 52% and 56%, respectively. After adding maternal self-reported adherence to risk definition, 67% of perinatally infected infants became high risk, increasing a 24% of high-risk patients the WHO classification, while low risk reduced to 33% (Figure 1)

Conclusion: In our cohort, 24% HIV infants were miscategorized as low risk using the current WHO algorithm. Including self-reported adherence information can help to provide ePCP to all eligible infants.

788 IMPROVED HEMATOLOGICAL OUTCOMES WITH NEVIRAPINE FOR INFANT HIV POSTNATAL PROPHYLAXIS

Catherine Dolfus¹, Jérôme Le Chenadec¹, Laurent Mandelbrot¹, Roland Tubiana¹, Albert Fayet¹, Stephane Blanche¹, Pierre Frange¹, Josiane Warszawski², for the ANRS C01 et C011 ¹AP–HP, Paris, France, ²INSERM, Le Kremlin-Bicêtre, France, ³Assistance Publique – Hôpitaux de Paris, Paris, France

Background: With combination antiretroviral therapy (cART) in HIV-infected women, mother-to-child transmission rates declined to less than 1%. For postnatal infant prophylaxis, in situations of low risk of perinatal HIV transmission, high income countries use zidovudine (ZDV), whereas low income countries use either nevirapine (NVP) or ZDV. Given the low transmission risk and the concerns about the toxicities of ZDV in newborns, French national guidelines recommend since 2015 the use of NVP as an alternative to ZDV for post-natal prophylaxis in full term babies born to HIV1-infected mothers with suppressed viral load and no history of NVP resistance. We compared hematological outcomes between ZDV-exposed and NVP-exposed infants.

Methods: In the French prospective national Perinatal Cohort Study, we compared hematological outcomes (blood cell counts and differentials) at birth, 1 and 3 months among the infants born in 2016-2017, at >37 weeks gestation. We included only mothers treated with cART without ZDV, to exclude a potential impact of maternal treatment on infant outcomes. ZDV was prescribed for 4 weeks, NVP for 2 weeks; mothers did not breastfeed.

Results: 137 infants were exposed to NVP and 251 to ZDV. None became infected. 68% of mothers were born in sub-Saharan Africa (79.4% in NVP group, 62.9% in ZDV group). Median hemoglobin levels were respectively 17.4 g/dL vs 17.0 at birth (p=0.49), 11.7 vs 11 g/dL at 1 month (p=0.003) and 11.4 vs 11.2 g/dL at 3 months(p=0.02). Anemia grade >2 was observed in 0.8% vs 1.7% of infants at birth (p=0.66), 1.2% vs 9.4% at 1 month (p=0.014), 3.6% vs 7.3% at 3 months(p=0.40). Median neutrophil counts were similar, grade >2 neutropenia was found in 4.2% vs 2.7% infants at birth (p=0.53),15.9% vs 13.1% at 1 month(p=0.56), and 12.2 vs 13.4% at 3 months(p=0.84). No difference was found in platelets counts.

Conclusion: In this population of HIV-exposed uninfected infants, post-natal prophylaxis with NVP, compared to ZDV was associated with higher hemoglobin levels at 1 and 3 months and a 9-fold lower incidence of anemia at 1 month of age. These findings support the use of nevirapine as a first choice for single drug post-natal prophylaxis in low risk situations.
TOXICITY OF INTEGRASE INHIBITORS IN A HUMAN EMBRYONIC STEM-CELL MODEL
Marie-Soleil R. Smith1, Hélène C. Côté1
1University of British Columbia, Vancouver, BC, Canada

Background: Women living with HIV give birth to ~1.5M infants each year, 80% of them exposed to ARVs in utero. Most ARVs can cross the placenta, but their safety has not been fully elucidated in the context of pregnancy. The Tsepamo study reported a signal for risk of neural tube defects in infants exposed to the INSTI dolutegravir (DTG) from conception. Many ARVs affect mitochondria, which could impact embryonic development. Our objective was to characterize and compare the effects of 14 ARV regimens on cultured human embryonic stem cells (hESCs), with respect to pluripotency, and cellular and mitochondrial health.

Methods: C4A5 hESCs were cultured (n=5 independent experiments) in the presence of 0.1% DMSO or 1X Cmax of the following regimens: DTG, raltegravir (RAL), bicaptegravir (BIC), cobicistat-booster elvitegravir (EVG/Cobi), or efavirenz (EFV) on a TDF/FTC backbone; DTG, RAL, BIC, EVG/Cobi or rilpivirine (RPV) on a TAF/FTC backbone; DTG, RAL, or ritonavir-boosted darunavir (DRV) on an ABC/3TC backbone; cabotegravir (CAB)/RPV. After 3 days, cells were assessed via flow cytometry using markers for mitochondrial mass, intermembrane potential, reactive oxygen species (ROS), cell viability, and apoptosis. Two markers of pluripotency, specifically SSEA-3 (lost early in differentiation) and TRA-1-60 (a later marker), were also assessed. Regimens were grouped according to base ARV and compared to DMSO control using Kruskal-Wallis with Dunn’s correction.

Results: hESCs exposed to DTG or BIC had a 3-fold reduction in cell counts (p<0.005) compared to controls. BIC exposure resulted in a 5-fold decrease in viability (p=0.026) and a 6-fold increase in apoptosis (p=0.01). In regards to pluripotency, exposure to regimens containing DTG or CAB resulted in a >80% loss of SSEA-3 expression compared to controls (p<0.02). There were no significant differences between regimens with respect to mitochondrial mass, intermembrane potential, ROS, or loss of TRA-1-60 expression. No effects were detected for the backbones, RAL, EVG/Cobi, EFV, RPV, or DRV.

Conclusion: These data indicate that exposure to some ARV regimens at pharmacological concentrations, especially DTG or BIC, appear toxic to cultured hESCs. Our results further suggest that exposure to the INSTIs DTG and CAB can induce hESC differentiation. Given the increasing use of DTG and other INSTIs, it is imperative to investigate their long-term safety in the context of pregnancy and embryonic development.

OUTCOMES FOLLOWING PRENATAL EXPOSURE TO DOLUTEGRAVIR: THE DOLomite-EPPICC STUDY
Claire Thorne1, Virginia Rasi1, Karoline Aebi-Popp1, Luminita Ene1, Marco Floridia1, Natalia Mendoza Palomar1, Luis M. Prieto1, Leigh Ragone1, Rebecca Sconza1, Carlo Giaquinto1, Yani Vinappagari1, for the Dolomite-EPPICC Study Group
1University College London, London, UK, 2University Hospital of Bern, Bern, Switzerland, 3Victor Babes Private Medical Clinic, Bucharest, Romania, 4Istituto Superiore di Sanità, Rome, Italy, 5Vall d’Hebron Research Institute, Barcelona, Spain, 6Hospital Universitario 12 de Octubre, Madrid, Spain, 7VIV Healthcare, Research Triangle Park, NC, USA, 8University of Padova, Padova, Italy

Background: Dolutegravir (DTG) was approved for treating HIV in adults and adolescents in 2013. In 2018, the Tsepamo Study reported a significantly increased neural tube defect (NTD) risk in women conceiving on DTG (0.94%), leading to a safety alert. In July 2019, additional data showed NTD prevalence with periconceptional DTG to be lower than in the initial analysis, but still greater than seen for other antiretroviral exposures (0.3% vs 0.1%). We aimed to assess birth outcomes following prenatal DTG exposure using real-world data.

Methods: We estimated U.S. periconceptional INSTI exposures as follows. We used hospital discharge data from the Healthcare Cost and Utilization Project from 2007-2014 to predict the number of deliveries in 2015-2017 to women with diagnosed HIV using Poisson regression. We used National Vital Statistics Report estimates of proportions of all pregnancies resulting in live births (65%) and the proportions of pregnant women with HIV diagnosed prior to pregnancy (80%) (Nesheim, et al, PIDJ, 2019) and antiretroviral treatment (ART) (58%-74%) (CDC) to estimate annual pregnancies to women on ART at conception. We then utilized data from the North American AIDS Cohort Collaboration on Research and Design from 2007-2016, the most current years available, (Jennifer Lee, personal communication, February 4, 2019) and factored the proportion of women aged 15-45 years with ≥ 1 month exposure to each INSTI to estimate periconceptional INSTI exposures by year.

Results: In 2007-2016, women with diagnosed HIV in the United States had an estimated 63,085 pregnancies and 41,005 live births. Among 29,272-37,346 pregnancies conceived by women on ART, an estimated 6,727-8,583 (23%) had periconceptional INSTI exposure, of which 3,694-4,713 (55%) were exposed to raltegravir (RAL), 1,610-2,055 (24%) to DTG, 1,413-1,801 (21%) to elvitegravir (ELV) and none to bictegravir. Periconceptional INSTI use among women on ART increased steadily with 1% exposed in 2007 and 61% in 2016. In 2016, among 1,353-1,959 periconceptional INSTI exposures, 15% were exposed to RAL, 52% to DTG and 33% to ELV. An additional 3,314 pregnancies among women with HIV occurred in 2017; assuming same proportion on INSTIs as in 2016, there would have been an additional 1,492-1903 periconceptional INSTI exposures (746-801 DTG exposures).

Conclusion: INSTI use by U.S. women on ART at pregnancy conception has increased. This is the first U.S. national estimate, and ascertainment of exposures will be an important component of monitoring safety of new pharmacologic agents used in pregnancy.

ESTIMATES OF PERICONCEPTIONAL EXPOSURES TO INTEGRASE INHIBITORS UNITED STATES
Margaret A. Lampe1, Jeff Wiener1, Jennita Reefhuis1, Steven R. Nesheim1
1CDC, Atlanta, GA, USA

Background: Toxidine of periconceptional exposures to integrase inhibitors (INSTI) exposures are needed to understand the potential to study the impact of INSTI use on pregnancy and birth outcomes in the United States.

Methods: We estimated U.S. periconceptional INSTI exposures as follows. We used hospital discharge data from the Healthcare Cost and Utilization Project from 2007-2014 to predict the number of deliveries in 2015-2017 to women with diagnosed HIV using Poisson regression. We used National Vital Statistics Report estimates of proportions of all pregnancies resulting in live births (65%) and the proportions of pregnant women with HIV diagnosed prior to pregnancy (80%) (Nesheim, et al, PIDJ, 2019) and antiretroviral treatment (ART) (58%-74%) (CDC) to estimate annual pregnancies to women on ART at conception. We then utilized data from the North American AIDS Cohort Collaboration on Research and Design from 2007-2016, the most current years available, (Jennifer Lee, personal communication, February 4, 2019) and factored the proportion of women aged 15-45 years with ≥ 1 month exposure to each INSTI to estimate periconceptional INSTI exposures by year.

Results: In 2007-2016, women with diagnosed HIV in the United States had an estimated 63,085 pregnancies and 41,005 live births. Among 29,272-37,346 pregnancies conceived by women on ART, an estimated 6,727-8,583 (23%) had periconceptional INSTI exposure, of which 3,694-4,713 (55%) were exposed to raltegravir (RAL), 1,610-2,055 (24%) to DTG, 1,413-1,801 (21%) to elvitegravir (ELV) and none to bictegravir. Periconceptional INSTI use among women on ART increased steadily with 1% exposed in 2007 and 61% in 2016. In 2016, among 1,353-1,959 periconceptional INSTI exposures, 15% were exposed to RAL, 52% to DTG and 33% to ELV. An additional 3,314 pregnancies among women with HIV occurred in 2017; assuming same proportion on INSTIs as in 2016, there would have been an additional 1,492-1903 periconceptional INSTI exposures (746-801 DTG exposures).

Conclusion: INSTI use by U.S. women on ART at pregnancy conception has increased. This is the first U.S. national estimate, and ascertainment of exposures will be an important component of monitoring safety of new pharmacologic agents used in pregnancy.
conducted. Periconception exposure was defined as being within the first 6 weeks of gestation (WG).

**Results:** A total of 453 pregnancies in 428 women from 6 cohorts were included. Women were mainly of black African (229, 54%) and white (129, 30%) ethnicity. Most (326/428, 76%) women had heterosexual HIV acquisition, 42 women were vertically infected and 11 had injecting drug use history. Of 443 singleton pregnancies, 16 were terminated (1 for birth defects at 29 6/7 weeks for neural migration disorder and severe microcephaly, with periconception DTG exposure) and 22 ended in spontaneous abortion; of 10 twin pregnancies, 1 was terminated and in 1, a fetus miscarried. There were 417 live-born infants (229 male, 185 female, 3 missing), born at median 39 6/7 weeks (IQR 38–40). Five infants were stillborn, all exposed to periconception DTG, none with birth defects. The Table shows birth outcomes for the 400 live-born singleton infants (no twins had birth defects); 266 (67%) had periconception DTG exposure. One neonate died at 2 days (born at 23 GW) with periconception DTG exposure. Among the 417 live-born infants there were 17 with reported birth defects (4.1%, 95% CI 2.4, 6.5); 1 infant had 2 defects. The 18 defects were in the following systems: genitourinary (7), heart (3), limb addition (polydactyly, 3), gastrointestinal (2), other (3); no CNS defects were reported. There were no vertical transmissions (106 infants still indeterminate).

**Conclusion:** The birth defect rate and pattern add further support to current evidence on safety of periconception DTG use. This study is ongoing, in order to provide robust pharmacovigilance data in Europe.

### Table 1: Birth outcomes for the 400 live-born singleton infants

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live born infants</td>
<td>417 (100%)</td>
</tr>
<tr>
<td>Birth defects</td>
<td>17 (4.1%)</td>
</tr>
<tr>
<td>Stillborn infants</td>
<td>5 (1.2%)</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500g)</td>
<td>20 (4.8%)</td>
</tr>
<tr>
<td>Very low birth weight (≤1500g)</td>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>Infant death at delivery</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

**973 METABOLITES, PRETERM LABOR, AND ANTIRETROVIRAL THERAPY**

Nicole H. Tobin, Aisling Murphy, Fan Liu, Sean S. Brummel, Mary-Gale Fowler, James A. McIntyre, Judith S. Currier, Tsungai Chipato, Patricia M. Flynn, Brian Koo, Grace M. Alfordoni, for the 1077BF/1077FF PROMISE (Promoting Maternal and Infant Survival Everywhere) Team  
1University of California Los Angeles, Los Angeles, CA, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4Anova Health Institute, Johannesburg, South Africa, 5University of Zimbabwe, Harare, Zimbabwe, 6St. Jude Children’s Research Hospital, Memphis, TN, USA

**Background:** Antiretroviral treatment (ART) has significantly reduced AIDS-related deaths, however, ART, including protease inhibitors, has been associated with an increased risk of preterm birth (PTB). In PROMISE, PTB (<37 weeks) occurred in 20.5% of pregnancies where mothers received zidovudine, lamivudine, lopinavir-ritonavir (PI) versus 13.1% where mothers received zidovudine alone (ZDV), p < 0.001. To date the mechanisms involved in ART-associated PTB remain elusive.

**Methods:** Untargeted metabolomics was performed on maternal plasma and dried blood spots (DBS), and infant DBS from 100 mother-infant pairs enrolled in PROMISE, 50 preterm and 50 term deliveries, divided evenly between ZDV or PI. Maternal samples were obtained at the timepoint closest but prior to preterm delivery with controls matched for gestational age (GA) at sampling. Infant DBS were earliest available. Linear regression and random forests (RF) models were used to identify metabolic predictors of PTB.

**Results:** The mean GA at delivery was 33.1 weeks (Preterm) and 40.0 weeks (Term) and at sample collection 30.4, 30.5, 31.0 and 31.0 weeks for Preterm ZDV, Term ZDV, Preterm PI, and Term PI, respectively. DBS from one collection site separated from all others and were dropped because they were deemed unreliable (N=21 pairs, 9 preterm and 12 term). RF models for PTB using maternal plasma metabolite levels achieved out-of-bag accuracies of 86.1% and 79.1% for the ZDV and PI groups, respectively. Similar results were achieved with maternal DBS profiles (83.3% and 83.7% accuracy). Key predictors of PTB in the ZDV group identified by both RF and linear regression analyses included increased levels of 17a-hydroxyprogrenolone glucuronide, methionine sulfone, pantetheine, and urate. PTB in the PI group was associated with increased nucleotide and amino acid metabolism (7-methylguanine, N2,N2-dimethylguanosine, N-acetylputrescine, methionine sulfone). RF models using infant metabolite profiles from the first 3 days of life (N=61) achieved 79.2% and 83.8% accuracy for PTB classification showing decreases in infant steroid metabolism in both the ZDV and PI groups.

**Conclusion:** Program guidance based on individual counselling regarding pregnancy intention had no apparent impact on the number of women who conceived on DTG-based ART in 2018-2019 in Botswana. However, pregnant women frequently initiated non-DTG-based ART, or switched off DTG-based ART, despite being beyond the NTD risk period. Evaluation of clinician and patient perceptions of the NTD risk, and improvement in understanding pregnancy intention and barriers to pregnancy planning, will be critical for developing treatment guidelines within DTG-based ART programs.
794 GENITAL TRACT & PLASMA CYTOKINES & SYSTEMIC T-CELL ACTIVATION IN HIV+ PREGNANT WOMEN

Charlotte-Eve S. Short1, Rachael A. Quinlan1, Robin J. Shattock1, Judith Russell1, Brenton Wait1, Christopher Wood1, David Hawkins1, Rimi Shahr1, Pippa Farrugia1, Phillip R. Bennett1, Graham P. Taylor2, for the London HIV Pregnancy Research Group

1Imperial College London, London, UK, 2Lewisham and Greenwich NHS Trust, London, UK, 3Homerton University Hospital NHS Trust, London, UK, 4North Middlesex University Hospital, London, UK, 5Chelsea and Westminster Hospital, London, UK, 6Royal Free Hospital, London, UK, 7Guy’s and St Thomas’ NHS Foundation Trust, London, UK

Background: Term and preterm labour are inflammatory events. Early data indicate that PBMCs migrate to the genital tract to influence inflammation. The genital mucosa-systemic cytokine gradient has been proposed as a surrogate for the migration of PBMCs to the genital mucosa. No data in HIV infected pregnancy are available. We characterized the gradient of cervicovaginal (CVF) cytokines to plasma cytokines in HIV infected and uninfected pregnant women.

Methods: CVF, plasma and PBMCs were isolated from HIV uninfected (n=27) and cART treated, infected (n=48) pregnant women in the 2nd trimester. Concentrations of 10 cytokines in CVF and plasma were measured using multiplex immunoassays. Flow cytometry was performed for T cell surface markers: CD4, CD8, HLA-DR and CD25. Maternal characteristics, immunovirologic parameters and pregnancy outcome were recorded. Gradients were compared by HIV status, cART exposure, prematurity and correlations with T cell subsets and gestational age at delivery were explored.

Results: All measured genital-plasma cytokine gradients were greater in HIV infected than uninfected pregnant women p<0.0001, largely driven by high CVF cytokine concentrations (Table). In HIV infected women: the greatest gradients observed were for pro-inflammatory cytokine IL-1β and chemokine IL-8, followed by IL-2; CD4 cell % correlated positively with inflammatory IL-2 gradient (r=0.28, p=0.01) and immune-regulatory IL-13 (r=0.23, p=0.04); CD25 + T cell subsets associated inversely with IL-1β gradient (CD4+CD25+%; r=-0.30, p=0.003; CD8+CD25+%; r=-0.26, p=0.03); CD4:CD8 ratios correlated positively with IL-2 gradient (r=0.25, p=0.02) and CD4+HLA-DR+4% correlated inversely with IL-2 gradient (r=-0.28, p<0.01). In this small sample no association between genital-plasma cytokine gradient with cART treatment, infected or preterm status or timing. Women starting ART during pregnancy had higher log10 VCAM1 levels than those on ART before conception, regardless of whether the sample was collected before or after ART initiation. Ninety-eight women (91 WLHIV and 7 HIV-negative) had stillbirth (total 9 mothers) or baby with SGA (total 89 babies). Univariate and adjusted analyses did not show significant associations between levels of any of these biomarkers and adverse birth outcomes (stillbirth or SGA).

Conclusion: Maternal HIV infection, and lack of ART or recently starting ART, were associated with one marker of greater endothelial activation (VCAM1), but not with other markers (ICAM1 or E-selectin) in pregnancy. Markers of endothelial activation were not associated with SGA or stillbirth.

Table: Median genital-plasma cytokine gradients during second trimester by HIV status

<table>
<thead>
<tr>
<th>Cytokine gradient Medians</th>
<th>HIV-infected pregnant</th>
<th>Uninfected pregnant</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>61.1 (49.0)</td>
<td>1.30 (4.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-2</td>
<td>1.65 (1.50)</td>
<td>1.27 (1.35)</td>
<td>0.0001</td>
</tr>
<tr>
<td>IL-4</td>
<td>3.15 (2.50)</td>
<td>1.94 (2.10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-6</td>
<td>94.6 (64.9)</td>
<td>4.70 (3.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>90.1(28.1)</td>
<td>2.08 (1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-12</td>
<td>107.4 (97.1)</td>
<td>57.4 (54.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TNF-α</td>
<td>321.9 (375.5)</td>
<td>23.4 (18.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-13</td>
<td>297.1 (303.4)</td>
<td>65.3 (41.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MCP-1</td>
<td>408.2 (410.1)</td>
<td>168.1 (155.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TGF-β</td>
<td>121.0 (120.2)</td>
<td>3.10 (3.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-23</td>
<td>8.9 (8.9)</td>
<td>1.2 (1.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

795 MATERNAL BIOMARKERS OF ENDOTHELIAL DYSFUNCTION BY HIV/ART STATUS AND BIRTH OUTCOMES

Gaoerolwe Masheto1, Sihkullie Moyo1, Terence Mohammed1, Christina Banda2, Charlene Raphaka1, Mompapi O. Mmalane1, Joseph Makhema1, Roger L. Shapiro2, Masepele Mosepele1, Rebecca Zash2, Shahn Lockman1

1Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3University of Botswana, Gaborone, Botswana, 4Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: Women living with HIV (WLHIV) are at higher risk of having an adverse birth outcomes, with underlying mechanism(s) unknown. We hypothesized that HIV-associated endothelial activation could adversely impact placental function and lead to impaired fetal growth or stillbirth.

Methods: We used previously-collected data and samples from WLHIV and HIV-negative women enrolled during pregnancy in the observational Botswana Tshipidi cohort. We measured plasma levels of markers endothelial activation [soluble vascular adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and E-selectin] from samples taken during pregnancy. We compared log biomarker levels by maternal HIV status and by timing of ART initiation (prior to conception vs. during pregnancy/prior to sample collection vs. no ART prior to sampling) using t-tests and Kruskal-Wallis rank test. We also evaluated the association between these biomarkers and adverse birth outcomes (composite of stillbirth or SGA <10th percentile weight-for-GA) using univariate and multivariate log-binomial regression controlling for age and timing of ART start.

Results: Specimens were available for 414 women (372 WLHIV and 42 HIV-negative), with median age 28 years and median gestational age at sample collection 30 weeks (Q1,Q3: 26,35). WLHIV had statistically significantly higher median VCAM1 (p=0.002) than HIV-negative women. HIV-negative women had higher median ICAM1 (p=0.01); there was no statistically significant difference in E-selectin levels. ICAM1 and E-selectin were not statistically different by ART status or timing. Women starting ART during pregnancy had higher log10 VCAM1 levels than those on ART before conception, regardless of whether the sample was collected before (p=0.02) or after (p=0.03) ART initiation. Ninety-eight women (91 WLHIV and 7 HIV-negative) had stillbirth (total 9 mothers) or baby with SGA (total 89 babies). Univariate and adjusted analyses did not show significant associations between levels of any of these biomarkers and adverse birth outcomes (stillbirth or SGA).

Conclusion: Maternal HIV infection, and lack of ART or recently starting ART, were associated with one marker of greater endothelial activation (VCAM1), but not with other markers (ICAM1 or E-selectin) in pregnancy. Markers of endothelial activation were not associated with SGA or stillbirth.
Maternal and Cord Plasma Bioactive Eicosanoid Profiles Differ in HIV+ and HIV− Women

Kayode Balogun1, Lauren Balmert2, Jennifer Jao2, Shan Sun3, Richard Bazinet4, Lena Serghides5

1University Health Network, Toronto, ON, Canada, 2Northwestern University, Chicago, IL, USA, 3University of Toronto, Toronto, ON, Canada

Background: Pregnant women with HIV (WHIV) are more likely to experience adverse birth outcomes, through mechanisms not fully understood. Eicosanoids play important roles in pregnancy and fetal growth and development, but data are lacking in the context of pregnancy, HIV, and antiretroviral therapy (ART). We examined bioactive eicosanoids (cell-signaling molecules derived from polyunsaturated fatty acids) in maternal and cord plasma from a Canadian cohort of WHIV and HIV negative (HIV−) pregnant women.

Methods: 76 maternal samples at gestational week 33-38 (39 WHIV, 37 HIV−) and 55 cord samples (31 WHIV, 24 HIV−) were included. All WHIV received protease inhibitor (PI)-based ART. Levels of 139 eicosanoids were measured using liquid chromatography-mass spec and quantified against standard curves with a lower limit of 0.025ng. Differences between groups for each eicosanoid were assessed using Mann-Whitney test corrected for multiple comparisons using a false discovery rate of 0.05. Orthogonal partial least squares discriminant analysis (OPLS-DA) was used to differentiate groups by maternal HIV status. Correlations between eicosanoids in maternal and cord plasma were examined using Spearman r.

Results: A total of 53 eicosanoids were detected in maternal and 58 in cord plasma. Cord and maternal eicosanoid profiles differed, with only 3 correlating between compartments among HIV− women and none among WHIV. Compared to the HIV− group, maternal plasma in WHIV had higher levels of circulating arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), and elevated levels of lipoxygenase pathway metabolites including several hydroxyeicosatetraenoic acids (HETEs), which have been associated with inflammatory and vasoconstrictive properties. In cord plasma, only 3 eicosanoids differed significantly between groups. All were vasodilating and pro-angiogenic dihydroxyeicosatrienoic acids (DHETs) (CYP/epoxygenase/soluble epoxide hydrolase metabolites of AA), and were lower in WHIV. OPLS-DA analysis indicated group separation by eicosanoids with maternal (see figure) and cord specimens.

Conclusion: Bioactive eicosanoid profiles differ in maternal and cord plasma, and are altered in pregnant WHIV. Elevated maternal levels of inflammatory lipoxygenase metabolites and lower cord levels of DHETs in the context of HIV/PI exposure may indicate or contribute to poor placenta function. Our findings also suggest an altered in utero environment that could contribute to fetal programming.

Breastmilk Microbiome/Virome of HIV+ Kenyan Women is Not Altered by Immunosuppression

Rabia Maqsood1, Jennifer Slyker2, LaRinda A. Holland1, Lily I. Wu1, Ruth Ndiiati3, Dorothy Mbori-Ngacha4, Grace John-Stewart1, Dana Lehman5, Efrem Lim1

1Arizona State University, Tempe, AZ, USA, 2University of Washington, Seattle, WA, USA, 3University of Nairobi, Nairobi, Kenya, 4UNICEF, New York, NY, USA, 5Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Breast milk (BM) harbors a diverse community of bacteria (microbiome) and viruses (virome) that are transmitted from mother-to-infant during breastfeeding and are important for establishing a healthy infant gut flora. Whether the BM microbiome and virome of women living with HIV are altered by immunosuppression and influence morbidity in HIV-exposed infants are unknown. We hypothesized that immunosuppression, as measured by low maternal CD4 count, alters BM virome and microbiome.

Methods: We performed next-generation sequencing (NGS) to comprehensively define the virome and microbiome in BM samples collected during the pre-ART era in Kenya (2003-2005) from 53 HIV-infected women at 1 month postpartum: 30 women with CD4 <250 and 23 women with CD4 ≥250. Illumina sequencing was performed on Phi29-amplified nucleic acid (virome) and the 16S rRNA gene V4 region (bacterial microbiome). Quantitative real-time PCR (qPCR) was used to quantify select viral species.

Results: Among 53 HIV+ women, BM bacterial microbiomes were highly diverse and shared a core bacterial microbiome composed of Streptococcaceae (18.1%), Staphylococcaceae (10.1%), Moraxellaceae (4.1%) and Eubacteriaceae (3.6%) families. There was no significant difference in the diversity of BM bacterial microbiome between women with CD4<250 compared to CD4≥250
in terms of ecological measurements of richness (p>0.65), alpha-diversity (p=0.14) and beta-diversity (p=0.17).

The BM virome was dominated by cytomegalovirus (CMV). The average proportion of CMV virome sequences did not differ between women with CD4 >500 and <250, with an average of 55.6% vs 69.4%, respectively (p=0.21). These NGS results were corroborated by qPCR measurements of CMV viral loads in BM (p<0.09). All women had a high abundance of bacteriotherapy families: Myoviridae (20.7%), Siphoviridae (11.6%) and Podoviridae (3.4%). Other eukaryotic viruses detected include papillomaviruses and adeno-viruses. There was no significant difference in the BM virome richness (p=0.68), alpha-diversity (p=0.15) or beta-diversity (p=0.30) between women with CD4>500 compared to CD4<250.

Conclusion: In this cohort of HIV+ Kenyan women from the pre-ART era, BM harbors a core bacterial microbiome and a diverse virome that is dominated by CMV. Diversity and richness of the BM microbiome and virome were not significantly influenced by immunosuppression at 1 month postpartum.

798 REDUCED BASAL GANGLIA AND TOTAL GREY MATTER VOLUME IN HIV-EXPOSED UNINFECTED NEONATES

Catherine J. Wedderburn1, Nynke A. Groenewold2, Annerine Roos3, Shunmay EXPOSED NEONATES

Background: Evidence suggests HIV-exposed uninfected (HEU) children have impaired early growth and development compared to HIV-unexposed (HU) children. However, little is known about the neurobiological mechanisms underlying adverse developmental outcomes in this population. We examined the effects of in utero exposure to HIV and ART on the neuroanatomy of uninfected neonates in a South African birth cohort.

Methods: A subgroup of neonates in the Drakenstein Child Health Study (DCHS), born after 36 weeks' gestation, without medical comorbidities or neonatal intensive care admission, had magnetic resonance imaging (MRI) at the Cape Universities Brain Imaging Centre, South Africa. Mother-child pairs received antenatal and postnatal HIV testing and ART per local guidelines. Acquired structural T2-weighted images were processed using statistical parametric mapping software. Subcortical-regions-of-interest were defined using the automated anatomical labeling atlas and volumes were extracted from grey matter segmented images bilaterally. Subcortical and total grey matter volumes were compared between groups using multivariable linear regression adjusting for intracranial volume, infant age and sex.

Results: 183 neonates in the DCHS had multimodal MRI between October 2012 and September 2015. Following quality control, 143 structural images were included (HEU n=39; HU n=104) (mean age 3.2 weeks, 51% male). All HEU infants were exposed to ART (87% to maternal triple ART). HEU infants had smaller caudate volumes bilaterally compared to HU (left hemisphere p<0.006, adjusted Cohen's d effect size -0.50 (95% CI -0.87 to -0.13); right hemisphere p<0.001, adjusted Cohen's d =0.68 [-1.06 to -0.31]). There were no group differences in other subcortical volumes (all p>0.2). Total grey matter volume was also reduced in HEU infants (p=0.039, adjusted Cohen's d =-0.33 [-0.70 to 0.40]). The associations remained significant after further adjusting for maternal age and education, household income, and prenatal alcohol exposure.

Conclusion: In utero exposure to HIV and ART without infection was associated with reduced basal ganglia and total grey matter volume in early infancy. For unclear reasons, HIV exposed uninfected children (HEUs) are at risk of malnutrition, which increases childhood infections and mortality. Stunting, particularly in the first 2 years of life, potentially affects cognitive functioning and educational achievement, adult height and future risk of metabolic disease. Stunting in girls may be passed on to their future offspring. We set out to establish the rate of severe growth faltering and correlates of stunting in a cohort of HEUs aged 2-5 years in follow-up since birth in four African countries.

Methods: Child anthropometric parameters were measured six-monthly using standardized procedures in the ongoing PROMOTE observational study of women with HIV and their children. Enrolment occurred between December 2016 and June 2017. The WHO child-growth standards (2006) were used to calculate age- and sex-appropriate Z-scores for weight (WAZ), height (HAZ), and weight-for-height (WHZ). Severe growth-faltering (stunting, underweight and wasting) was defined as more than two standard deviations below the WHO population median, respectively. Generalised estimating equations (GEE) were used to assess correlates of stunting including maternal factors (age, education), country, infant sex, and surrogate measures of household level sanitation and socioeconomic status (tap water usage, size of the house).

Results: Of the 1495 HEUs aged 2-5 years during the study period included in this analysis, 48.5% were female. Mean (sd) Z-scores were below population norms for height (-1.2 +1.2) and weight (-0.5 +1.0) across all 4094 repeated measurements; 954 (22.9%) were stunted, 208 (5.1%) underweight and 72

800 MALNUTRITION IN HIV-EXPOSED UNINFECTED CHILDREN IN LONG-TERM OBSERVATIONAL FOLLOW-UP

Lynda Strainix-Chibanda1, Jim Azie1, Nonhlanhla Yende-Zuma1, Hasena Cassim1, Sherika Hanley1, Taha E. Taha2, Mary Glenn Fowler3, for the PROMOTE study team

Background: For unclear reasons, HIV exposed uninfected children (HEUs) are at risk of malnutrition, which increases childhood infections and mortality. Stunting, particularly in the first 2 years of life, potentially affects cognitive functioning and educational achievement, adult height and future risk of metabolic disease. Stunting in girls may be passed on to their future offspring. We set out to establish the rate of severe growth faltering and correlates of stunting in a cohort of HEUs aged 2-5 years in follow-up since birth in four African countries.

Methods: Child anthropometric parameters were measured six-monthly using standardized procedures in the ongoing PROMOTE observational study of women with HIV and their children. Enrolment occurred between December 2016 and June 2017. The WHO child-growth standards (2006) were used to calculate age- and sex-appropriate Z-scores for weight (WAZ), height (HAZ), and weight-for-height (WHZ). Severe growth-faltering (stunting, underweight and wasting) was defined as more than two standard deviations below the WHO population median, respectively. Generalised estimating equations (GEE) were used to assess correlates of stunting including maternal factors (age, education), country, infant sex, and surrogate measures of household level sanitation and socioeconomic status (tap water usage, size of the house).

Results: Of the 1495 HEUs aged 2-5 years during the study period included in this analysis, 48.5% were female. Mean (sd) Z-scores were below population norms for height (-1.2 +1.2) and weight (-0.5 +1.0) across all 4094 repeated measurements; 954 (22.9%) were stunted, 208 (5.1%) underweight and 72
(1.8%) wasted. We found that Malawi location when compared to South Africa (adjusted odds ratio; 95% CI: 2.50; 1.74-3.60) and being born to a mother who did not complete secondary school (1.47; 1.11-1.95) were associated with higher odds of stunting; whereas older children had lower odds of stunting (0.96; 0.95-0.96).

**Conclusion:** High rates of growth faltering were observed in this large multi-country cohort of predominantly breastfed African children who survived to at least 2 years and escaped HIV infection. Early interventions are necessary to address malnutrition in the growing population of HEUs in order to optimize their health and future human capital. Maternal factors, specifically education may be a key area of focus.

---

**801** HIGH BODY MASS IN HIV+ & HIV− WOMEN AND THEIR HIV-UNINFECTED INFANTS IN SOUTH AFRICA

Angela Bengtson 1, Stanzi M. le Roux 2, Tamisin K. Phillips 3, Kirsty Brittain 3, Allison Zerbe 1, Thoko Malaba 2, Greg Petro 2, Hlengiwe Madlala 2, Elaine J. Abrams 3, Landon Myer 4

1 Brown University, Providence, RI, USA, 2University of Cape Town, Cape Town, South Africa, 3Columbia University, New York, NY, USA, 4University of Mississippi Medical Center, Jackson, MS, USA

**Background:** HIV-exposed uninfected (HEU) infants may have altered growth relative to HIV-unexposed (HU) infants. Maternal body mass index (BMI) and obesity are strongly linked to child growth, but there are few data on associations between maternal BMI and HEU infant growth.

**Methods:** We followed cohorts of HIV+ (initiating TDF+XTV+EFV) and HIV- women from first antenatal visit (ANC) through 12 months postpartum with their breastfed infants. We estimated pre-pregnancy maternal BMI (kg/m²) from routine antepartum measures; trained staff collected postpartum anthropometry (maternal BMI and infant BMI Z-scores). Virological testing excluded infant HIV infection. We examined relationships between a combined exposure of maternal HIV/ART (HIV+ vs HIV−) and pre-pregnancy BMI (not overweight (BMI<25) vs overweight/obese (BMI ≥25)) with mean infant BMI Z-scores using multivariable linear mixed models and the probability of infant overweight (BMI<25) vs overweight/obese (BMI >25) using modified Poisson regression.

**Results:** In 780 mother-infant pairs (49% HIV+ mothers), 68% had pre-pregnancy BMI ≥25; 4% were underweight (BMI<18.5). HIV+ women were less likely to breastfeed for ≥6 months (44% vs 25%); breastfeeding ≥6 months was not associated with BMI status (~54%). Throughout follow-up, infant BMI Z-scores were more likely to be positively associated with maternal BMI (rho=0.64, p<0.01 vs HIV−) and lower among HIV+ not overweight women (0.10; 95% CI 0.05, 0.15).

**Conclusion:** In this setting of high maternal BMI, HEU infants had lower mean BMI during the first year of life than HU infants, regardless of maternal BMI status. By 12 months postpartum, the probability of being overweight was >10% for all groups. However, infants born to overweight/obese women, compared to not overweight women, were more likely to be overweight, regardless of HIV status. Future research should examine if maternal HIV and BMI status increase the risk of cardio-metabolic complications for HEU infants later in life.

---

**802** DISTINCT CORD C-PEPTIDE, ADIPOKINE, AND LIPIDOMIC SIGNATURES BY IN UTERO HIV EXPOSURE

Jennifer Jao 1, Lauren Balimert 1, Shan Sun 2, Thomas Kraus 3, Brian Kirnse 4, Mitchell Geffrin 3, Yungping Qiu 3, Stephen M. Arapdi 2, Elaine J. Abrams 3, Derek LeRoi 3h, Rhoda Sperling 1, Irwin J. Kurland 4

1 Northwestern University, Chicago, IL, USA, 2Amm & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, USA, 3Icahn School of Medicine at Mt Sinai, New York, NY, USA, 4University of Mississippi Medical Center, Jackson, MS, USA, 5University of Southern California, Los Angeles, CA, USA, 6Albert Einstein College of Medicine, Bronx, NY, USA, 7Columbia University, New York, NY, USA, 8ICAP at Columbia University, New York, NY, USA

**Background:** Metabolic derangements early in life of HIV-exposed uninfected (HEU) infants have been reported.

**Methods:** Pregnant HIV+ and HIV− women were enrolled with their infants in a US cohort from 2009–15. We measured insulin, C-peptide, and adipokines [metabolic (resistin, leptin) and inflammatory (Interleukin (IL)-6, Tumor Necrosis Factor-a (TNFa)] in cord blood of HIV+ and HIV− infants using multiplex ELISA. Demographic, clinical, and in utero antiretroviral therapy (ART) exposure data were collected. Metabolites and lipid subspecies were measured via mass spectrometry. Linear regression models were fit to assess the association of in utero HIV exposure with cord insulin and C-peptide. Orthogonal partial least squares discriminant analysis (OPLS-DA) was used to assess if differences in metabolites and lipid subspecies discriminate between HEU and HUU infants. Elastic net regression was used to identify factors including metabolites and lipid subspecies most associated with increased cord C-peptide, stratified by in utero HIV exposure.

**Results:** Of 118 infants, 56 were HEU. No differences in maternal race/ethnicity, pre-pregnancy BMI, gestational diabetes (GDM) or infant preterm birth (PTB), birth weight/length were noted. All HEU were ART-exposed (52% PI, 21% NNRTI, 9% INSTI). After adjusting for maternal age, GDM, family diabetes history, pre-pregnancy BMI, as well as infant sex, PTB, and birth weight z score, mean cord insulin (B=0.295, p=0.03) and C-peptide (B=0.522, p<0.01) were significantly higher in HEU vs HUU infants. IL-6 correlated positively with C-peptide in HEU (rho=0.30, p<0.05) but not HUU infants (rho=0.08, p=0.52) while resistin correlated inversely with C-peptide in HUU (rho=0.08, p=0.52) but not HEU infants (rho=0.52, p<0.01) but not HUU infants. Leptin correlated positively with C-peptide in both groups (rho=0.64, p<0.01 in HEU; rho=0.26, p<0.04 in HUU). OPLS-DA showed clear group separation by metabolites and lipid subspecies. Elastic net regression identified pre-pregnancy BMI, gestational diabetes, antidepressants, preterm birth, and birth weight as factors including metabolites and lipid subspecies associated with increased cord C-peptide.

**Conclusion:** Compared to HUU, HEU infants manifest with insulin resistance. Differences in cord metabolite, lipid subspecies, & adipokines are significant between HEU and HUU infants, suggesting altered fetal metabolic programming due to in utero HIV exposure.
803 MORE SEVERE DISEASE IN HOSPITALIZED HIV-EXPOSED UNINFECTED VS HIV-UNEXPOSED NEONATES

Kim Anderson1, Emma Kalk1, Hlungwe Madlala1, Dorothy C. Nyemba1, Nisha Jacob1, Amy L. Slogrove1, Mariette Smith1, Max Kroon1, Michael Harrison1, Brian Eley1, Andrew Bouille1, Landon Myer1, Mary-Ann Davies1, 2University of Cape Town, Cape Town, South Africa, 3Stellenbosch University, Cape Town, South Africa, 4Western Cape Provincial Department of Health, Cape Town, South Africa

Background: Compared to children HIV unexposed and uninfected (CHUU), children HIV exposed and uninfected (CHEU) may have an increased risk of adverse birth outcomes, morbidity and hospitalization, but there are few insights into patterns of morbidity during the neonatal period.

Methods: We followed a prospective cohort of HIV+ and HIV- pregnant women recruited from a large antenatal clinic in Cape Town, South Africa. Their infants (CHEU = 457; CHUU = 475; n=2 HIV+ neonates excluded) were followed up from delivery. Medical records were reviewed to investigate all admissions during the neonatal period (day 0–28 of life). Infants who were in hospital for routine post-delivery observation were excluded.

Results: Rates of neonatal admission were similar between CHEU (59/457, 13%) and CHUU (75/475, 16%) (p = 0.210). Most admissions occurred directly after birth (CHEU 88% vs CHUU 85%), and mode of delivery was by caesarean section in 64% CHEU vs 57% CHUU. Infectious causes were identified in 37% CHEU vs 35% CHUU (p = 0.099); bloodstream infections accounted for most infectious admissions (34/48, 71%). Neonatal respiratory distress was the most common cause of non-infectious admissions, and did not differ between CHEU and CHUU (32% vs 33% of non-infectious admissions; p = 0.20). Very preterm births (<32w) occurred more frequently among CHEU admissions (27% vs 9%; p = 0.006) as well as very low birthweight (<1500 g) (36% CHEU vs 16% CHUU; p < 0.001). Among those hospitalized, 54% CHEU required admission to an intensive care unit (ICU) vs 28% CHUU. Hospitalized CHEU had a 1.94 times increased risk of ICU admission compared to CHUU (95% CI 1.26–2.98). After adjusting for very preterm delivery, the risk of ICU admission remained higher among CHEU (RR=1.60; 95% CI 1.04–2.47).

Conclusion: There were no significant differences in overall hospitalization rates or frequency of infectious events during the neonatal period between CHEU and CHUU. However, hospitalized CHEU had increased risk of very preterm birth and very low birthweight, indicating increased severity of adverse birth outcomes. In addition, and independent of very preterm birth, hospitalized CHEU had higher risk of ICU admission, indicating increased disease severity during the neonatal period.

804 INFECTIOUS MORBIDITY OF BREASTFED, HIV-EXPOSED UNINFECTED INFANTS IN SOUTH AFRICA

Stanzi M. Le Roux1, Elaine J. Abrams2, Kirsty Donald1, Tamsin K. Phillips1, Allison Zerbe1, David M. Le Roux1, Max Kroon1, Landon Myer1, 1University of Cape Town, Cape Town, South Africa, 2ICAP at Columbia University, New York, NY, USA

Background: Without breastfeeding and maternal antiretroviral therapy (ART), HIV-exposed uninfected (HEU) infants experience greater infectious morbidity than HIV-unexposed (HU) infants. We hypothesized that with universal maternal ART, breastfeeding HEU and HU infants experience similar morbidity.

Methods: We recruited and followed infants through delivery and with breastfeeding infants for ≥12 months. All HIV+ women initiated ART in pregnancy. Infection-related hospitalisation data abstracted from routine health records were analysed using incidence rate ratios (IRR) from Poisson regression.

Results: Mother-infant pairs (n=410 HU, n=459 HEU; pre-ART median 64 count, 354 cells/µL; HIV viral load, HIV-VL <40 log10, copies/mL; gestation, 22 weeks) were followed for median 12 months. HEU (vs HU) infants experienced more infection-related hospitalisations between 7 days and 3 months (incidence/100 child-years, cy: 34.2 [95%CI 24.4–47.9] vs 9.8 [95%CI 5.1–18.8]; IRR 3.50 [95%CI 1.64–7.51]), but rates were similar at other ages. Rates for HEU infants with healthier mothers (n=84; ART initiation <24 weeks’ gestation, CD4 count <350 cells/µL; HIV-VL <40 log10, copies/mL; 15/88 [100cy] [95%CI 5.1–24.99]) approached those of HU infants (IRR vs HU, 1.62 [95%CI 0.44–6.00]); HEU infants of mothers with late ART initiation and advanced disease had the highest rates (n=44; ART≥24 weeks’ gestation, CD4 count ≥350 cells/µL; HIV-VL ≥40 log10, copies/mL; 40/44 [900cy] [95%CI 15–187.04]; IRR vs HU, 4.14 [95%CI 1.27–13.44]). Reduced rates were seen among exclusively breastfed, timely-vaccinated HEU infants (n=165;16–82/100cy [95%CI 5.08–18.78]; IRR vs HU, 1.72 [95%CI 0.53–5.49]).

Conclusion: Despite ART in pregnancy, breastfeeding HEU vs HU infants had transiently increased infectious morbidity risks in early infancy. However, differences were driven by advanced maternal disease with late ART initiation, alongside suboptimal breastfeeding and vaccination. Interventions to increase early maternal HIV diagnosis and ART initiation, optimize vaccination and promote optimal breastfeeding should be prioritized to improve HEU child health.

805 HIV EXPOSURE AND HUMAN MILK OLIGOSACCHARIDES MODULATE THE INFANT GUT MICROBIOTA

Sarah L. Brooker1, Nicole H. Tobin1, Fan Li1, Louise Kuhn1, Grace M. Aldrovandi1, 1University of California Los Angeles, Los Angeles, CA, USA, 2Columbia University Medical Center, New York, NY, USA

Background: HIV-exposed, uninfected (HEU) infants experience almost twice the morbidity and mortality of their HIV-unexposed uninfected (HUU) counterparts. The mechanisms by which maternal HIV-infection alters infant immune development are under investigation. Maternal HIV infection is associated with alterations of breast milk human milk oligosaccharide (HMO) composition and the gut microbiome of HEU infants. Whether perturbations in maternal HMO composition in HIV-infected mothers alter the infant gut microbiome or whether infant gut microbial populations and maternal HMO profile are correlated for other reasons remains unknown.

Methods: 50 maternal-infant pairs were enrolled, half with maternal HIV, in a cross-sectional study at 1-3 months postpartum. 17 HEU and 25 HUU had...
stool shotgun metagenomics performed and maternal breast milk HMO data available. Host DNA removal followed by taxonomic classification using kraken v2.0 against the NCBI database resulted in 14.5 million reads assigned to 3720 taxa. 17 unique HMO isoforms were quantified using high-performance liquid chromatography. Statistical tests were performed in the R environment. 

**Results:** Alpha diversity tended to be lower in HEU compared to HIVU infants. In contrast, maternal HMO alpha diversity tended to be increased in HIV-positive compared to HIV-negative mothers. In HEU infants, negative correlations were observed between bifidobacterium breve and Lactobacillus, Bifidobacterium having and Lactobacillus having a positive correlation with CD4. The presence of clinical and virological parameters was assessed by multivariable time-dependent Cox-proportional hazards model, including time-dependent coefficient for follow-up VL and CD4. Results: To date, 135 infants were enrolled. Currently, the median follow-up time is 5.5 months (IQR 2.7-6.9). Median age at enrolment was 38 days (31-75), and median age at ART was 33 days (19-66). Fifty-four percent were male, 37% were premature and 30% had baseline weight-for-age Z-Score (WAZ) <-2SD. Prophylaxis after birth was prescribed to 80%. Median baseline VL was 5.1 logs (4.66-1.355). 18/30 (60%) reached viral suppression at 12mo and 73% at 18mo (Fig1). Among 18 infants adherent to ART who reached VL<2mo of age and were followed with frequent plasma virus load (VL) measures for two years under a NIH funded grant. VL monitoring was performed at 1, 2, 4, 5, 6, 7, 8, 9, 11, 17, 18 and 23mo and those with >4 measurements were included in the analysis. Kaplan–Meier estimator and descriptive analyses were used to summarize infants virologic response. Results: Thirty infants started ART with ZDV/3TC/LPVr at 34 days (IQR 18), Median pre-ART VL was 1,988,708 c/ml (IQR 4,661,355) at 18mo (60%) reached viral suppression (VS), defined as HIV RNA plasma < 1000copies/ml with a median time of 7.86mo (1-24mo) after ART initiation. 9/18 (50%) infants who initially achieved VS had a rebound within 3.3 mo (1-10mo); 5/9 re-suppressed within 3mo (1-7mo). 14/30 (47%) infants had sustained VS defined as ≥ 2 consecutive VS measures. Cumulative probability of VS of among all infants was 43% at 6mo, 56% at 12mo and 73% at 18mo (Fig1). Among 18 infants adherent to ART who reached VLs, the median time to control the virus was 3mo (0.92-16.41mo); at 12mo the probability of VS was 89%. There was no statistically significant difference in time to VS among infants with pre-ART VL>Log6 compared to those with VL<Log6. Strategies to promote adherence included intensified adherence and psycho-social sessions, but they showed limited success. Conclusion: Despite early ART initiation and adherence efforts, only 60% HIV+ infants achieved viral suppression, and of these, about 50% had a virus rebound demonstrating adherence challenges in sustaining undetectable virus load faced by caregivers. Research to understand barriers to ART initiation and ART adherence in mothers along with innovative approaches to address problems that prevent timely delivery of medications to infants in low resource countries are urgently needed.
**Background:** Markers for sustained viral suppression over time are not available for HIV infection. We evaluated whether HIV serology was a useful marker for sustained RNA suppression or low cell-associated HIV reservoir among HIV-infected children treated very early in life.

**Methods:** The Early Infant Treatment Study (EIT) started antiretroviral treatment (ART) for HIV-infected children at < 7 days of age. Quantitative HIV RNA was measured every 1-3 months in PBMCs, and at 84 weeks with repeat qualitative whole blood DNA PCR testing and dual enzyme immunosorbent assay (EIA). Children starting ART at age 30-365 days in the Botswana ART program and sampled at 24-36 months of age served as controls. Comparisons were by Wilcoxon Rank Sum testing.

**Results:** Of 40 HIV+ children enrolled in EIT, 30 had reached 84 weeks by the time of this analysis; 14 (47%) had sustained RNA < 40 copies/mL at all visits from 24 to 84 weeks, including 12 (86%) with negative EIA at week 84, and 2 (14%) with indeterminate EIA. Among the 16 with > 40 copies/mL at one or more visits from 24 to 84 weeks, 5 (31%) had negative EIA, 10 (63%) had positive EIA, and 1 (6%) were indeterminate (Table). For a threshold of 40 copies/mL, the negative predictive value of the EIA was 71% (12/17) for sustained viral suppression from 24 to 84 weeks, and the positive predictive value was 100% (10/10) for lack of sustained suppression. For a threshold of 400 copies/mL, the negative predictive value was 100% (17/17), and the positive predictive value was 90% (9/10). Whole blood qualitative HIV DNA PCR at 84 weeks was negative for 14 (47%) children, positive for 15 (50%), and indeterminate for 1 (3%), and the DNA result was concordant with EIA testing for 73% (19/26) with interpretable results for both tests (Table). Among the first 17 EIT children with quantitative cell-associated DNA testing available at 84 weeks, the median DNA reservoir was significantly lower than among 10 control children (10.9 vs. 981.4 copies/million cells; p < 0.001). However, unlike plasma RNA, cell-associated DNA was not associated with the EIA test result at 84 weeks (p = 0.63) in this first group of EIT children tested.

**Conclusion:** HIV serostatus at 84 weeks was a marker for sustained RNA suppression among HIV-infected children treated from the first week of life, and may be useful in longitudinal follow-up. Very low viral reservoirs continue to be noted among early-treated children.

**Table:** HIV viral suppressor/supervivorman and 84-week qualitative DNA result**

<table>
<thead>
<tr>
<th>Nucleic Acid</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**810 MARKERS OF HIV RESERVOIR SIZE IN INFECTED CHILDREN ON LONG-TERM VIRAL CONTROL**

**Sonia Zicari**, Margherita Doria, Sara Dominguez Rodriguez, Nicola Cotugno, Alfredo Tagaro, Pablo Rojo Conejo, Eleni Nastouli, Kathleen Gartner, Nigel Klein, Caroline Foster, Savita Pahwa, Anita De Rossi, Carlo Giaquinto, Paolo Rossi, Paolo Palma, Sutika Pahwa

**Background:** Curative strategies for HIV will need to eliminate the replication competent latent reservoir. Immune Checkpoint molecules (ICP) are promising therapeutic targets for the elimination of the HIV latent reservoir, as CD4 T cells expressing ICP have been shown to preferentially harbor latent, replication-competent HIV. T cells expressing ICP are also considered as being exhausted. T follicular helper cell subset of CD4 T cells are critical for B cell differentiation for which induction of IL-21 is favorable while IL-2 is inhibitory. Here a cohort of HIV vertically infected children and young adults under durable viral control (PHIV) were investigated for CD4 ICP, immune activation (IA) markers and function in relation to HIV reservoir size.

**Methods:** 40 PHIV (4-19 yrs age) who started ART < 2 years of life and had undetectable viremia (< 50 HIV copies/mL) for the past 5 years, were enrolled in 7 European research centers. HIV DNA copies per million peripheral blood mononuclear cells (PBMC) were measured by real-time PCR. Flow cytometry was used to investigate CD4 T cells for 1) co-expression of PD1 with IA (ICOS, CD38, Ki67 and HLA-DR); 2) co-expression of PD1 with ICP (TIGIT, LG3, TIM3 and CTLA4); 3) intracellular cytokine production (IL2, IFNγ, TNFα, IL21) after stimulation with Env peptides. Pearson correlations and 2 group comparisons were performed using the Mann-Whitney U Test. P value < 0.05 was considered significant.
Results: Total PD1+ CD4 T cells positively correlated with HIV-DNA (r=0.46) as did CD4 T cells co-expressing PD1 with other ICP or IA (table 1). We then divided our cohort based on HIV DNA distribution into those with high (4th quartile) and low (1st quartile) HIV DNA. We found that PD1+ CD4 T cells co-expressing IA or ICP were higher in participants with high HIV DNA compared to low HIV DNA (table 1). PD1+ CD4 T cells (unstimulated) also showed correlations with ENV antigen activated circulating T follicular helper cells (Tfh) expressing CD40L (r = 0.14, p<0.05) with selective induction of IL2 (r = 0.47, p<0.05) suggesting that PD1+ expression on CD4 can be associated with dysfunctional T:B cells interaction in response to HIV antigens.

Conclusion: This study confirms that vertically HIV infected children and young adults under long-term viral control maintain the association between expression of PD1 on CD4 T cells and size of viral reservoirs and also implicates the size of the viral reservoir in altered Tfh functionality.

Table 1: Association of ICP with HIV DNA in CD4 T cells

<table>
<thead>
<tr>
<th>CD4+ T cell markers</th>
<th>HIV DNA (ng/mL)</th>
<th>Comparison of participants with high versus low HIV DNA (r value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD1+</td>
<td>0.002</td>
<td>r = 0.46, p &lt; 0.05, N/S</td>
</tr>
<tr>
<td>PD1+</td>
<td>0.01</td>
<td>r = 0.54, p = 0.02, N/S</td>
</tr>
<tr>
<td>PD1+</td>
<td>0.03</td>
<td>r = 0.45, p = 0.04, N/S</td>
</tr>
<tr>
<td>PD1+</td>
<td>0.05</td>
<td>r = 0.45, p = 0.05, N/S</td>
</tr>
<tr>
<td>PD1+</td>
<td>0.07</td>
<td>r = 0.49, p = 0.03, N/S</td>
</tr>
<tr>
<td>PD1+</td>
<td>0.09</td>
<td>r = 0.51, p = 0.03, N/S</td>
</tr>
<tr>
<td>PD1+</td>
<td>0.11</td>
<td>r = 0.49, p = 0.03, N/S</td>
</tr>
<tr>
<td>PD1+</td>
<td>0.13</td>
<td>r = 0.49, p = 0.03, N/S</td>
</tr>
</tbody>
</table>

NS: Not Significant

811 PROVIRAL LANDSCAPE IN CHILDREN PARALLELS ADULTS AND ENABLES RESERVOIR RECONSTRUCTION

Jenna M. Hassen1, Mary Grace K. Katusiime2, Samuel Smith2, Michael J. Bale3, Liliana Perez-Rodriguez2, Divya Klam3, Wei Shao2, Mark Cotton3, Eli A. Boritz4, John M. Coffin5, John W. Mellors6, Sean Patro1, Gert U. van Zyl2, Mary F. Kearney1, Liliana Perez-Rodriguez2, Divya Klam3, Wei Shao2, Mark Cotton3, Eli A. Boritz4, John M. Coffin5, John W. Mellors6, Sean Patro1, Gert U. van Zyl2, Mary F. Kearney1

Background: Characterizing HIV-1 proviruses that lead to viral rebound upon ART interruption could inform design strategies towards a functional cure. Methods for measuring the HIV-1 reservoir, such as the quantitative viral outgrowth assay, require collecting large sample volumes that are difficult to obtain from children. Here, we profile the proviral landscape in children and demonstrate the utility of "viral reconstruction" to characterize the genetics of the HIV-1 reservoir when sample volumes or proviral copy numbers are low.

Methods: We performed near-full length (NFL) single-genome sequencing on 210 amplicons from PBMC of two children treated relatively early (9.0 and 9.3 months) and on ART for 7 years. The proviral landscape was compared to that of adults on ART (1056 genomes in the Proviral Sequence Database).

Results: Similar to adults, ~98% of the proviruses were defective including 60% with large 3' deletions of env/tat/rev. Proviral diversity (0.3% and 0.7% in p6-PR-RT) and proviral copy number (47 and 182 copies/10^6 PBMC) were low. In the child with the lower HIV-1 diversity and fewer 3' deletions, we identified defective proviruses with sequences identical except for non-overlapping deletions, allowing reconstruction of the ancestor that infected these cells and is likely similar to both the founder virus and to variants comprising the HIV-1 reservoir. Indeed, the reconstructed virus matched an intact provirus from the same sample, demonstrating the accuracy of the approach.

Conclusion: Despite very different immune systems, the HIV-1 proviral landscapes on ART were not obviously different between children and adults, with most proviruses containing large 3' deletions. The low numbers of infected cells in children and in early-treated adults makes it difficult to detect intact proviruses. Here, we demonstrate the utility of viral reconstruction to infer the genetics of possible transmitted founder viruses and intact proviruses that may comprise the HIV-1 reservoir. Characterizing the genetics of the HIV-1 reservoir in early-treated individuals can help guide the design of therapeutic interventions towards HIV remission.

812 CELL-ASSOCIATED HIV-1 DNA/RNA IN CHILDREN: PERFORMANCE OF REAL-TIME AND DIGITAL PCR

Kathleen Gärntner1, Triantafylia Gkouleli1, Judith Heaney1, Paul Grant1, Sara Dominguez Rodriguez2, Eloise Busby4, Denise O'Sullivan, Moira J. Spyer1, Caroline Foster1, Pablo Rojo Conejo1, Deborah Persaud1, Anita De Rossii1, Jim Huggett1, Elleni Nastouli1, for the EPICAL Consortium1, University College London, London, UK, 2University College London Hospitals NHS Trust, London, UK, 3Hospital Universitario 12 de Octubre, Madrid, Spain, 4National Measurement Laboratory, Teddington, United Kingdom, 5Imperial College Healthcare NHS Trust, London, UK, 6Johns Hopkins University School of Medicine, Baltimore, MD, USA, 7University of Padova, Padova, Italy

Background: Children perinatally infected with HIV-1 (PaHIV) require life-long antiretroviral treatment (ART). Despite ART, HIV persists in a latent reservoir, the cause of viral rebound after treatment interruption (TI). Robust methods to quantify the reservoir in perinatal infections are required. To detect cell-associated HIV-1 DNA (CA-DNA) and cell-associated HIV-1 RNA (CA-RNA) in suppressed PaHIV we compared two methods: quantitative Real Time PCR (qPCR) and digital droplet PCR (dPCR).

Methods: In the CARMA EPICAL study, 40 European PaHIV on suppressive ART for ≤5 years were recruited. Total CA-DNA, total CA-RNA and unsuppressed (US) CA-RNA were quantified using qPCR (C1000, Bio-Rad) and dPCR (QX100 Droplet Analyser, Bio-Rad). Nucleic acids were extracted from PBMCs using the DSP virus/pathogen mini kit (Qiagen) on the Qiasymphony. Quantitative qPCR and dPCR were performed using primers in the LTR region for total CA-DNA and total CA-RNA and the pol region for US CA-RNA. To normalise copy numbers of CA-DNA and CA-RNA per 10^9 PBMCs reference genes were included in multiplex reactions. For qPCR a standard curve with known copy numbers was used in a 10-fold dilution series. The concordance analysis of qPCR and dPCR was determined with the Bland–Altman test and significance with Wilcoxon rank test.

Results: HIV-1 CA-DNA could be detected in 36 of 40 PaHIV (<10^-410 c/10^6 PBMCs for qPCR, <10^-1420 c/10^6 PBMCs for dPCR). In seven of the 36 PaHIV CA-DNA copy numbers were below 10 c/10^6 PBMCs. Total CA-DNA was detected in 31 (<1^-5789 c/10^6 PBMCs for qPCR, 11^-857 for dPCR) and US CA-RNA in 23 of 40 patients (<1^-11^-857 c/10^6 PBMCs for qPCR, 11^-325 for dPCR). Copy numbers of CA-DNA were significantly higher than CA-RNA, total CA-RNA copy numbers were significantly higher than US CA-RNA (see figure). Concordance analysis showed 97.4% agreement between qPCR and dPCR for total and US CA-RNA.

Conclusion: We have demonstrated the detection of very low HIV CA-DNA and CA-RNA levels using both qPCR and dPCR in well suppressed PaHIV. The high agreement of concordance analysis suggests comparability of qPCR and dPCR for detecting low copy numbers of CA-RNA and validates use of both methods for diagnostic applications. The very low levels of CA-RNA expression could contribute to chronic immune activation and/or lead to production of infectious viruses. Further work to determine the sensitivity of both methods and validate lower thresholds for CA-DNA and CA-RNA will be done.
ASSESSMENT OF HIV-1 DNA BY SINGLE-GENOME SEQUENCING IN CHILDREN ON SUPPRESSIVE ART

Kathleen Gartner1, Triantafylia Gkouleli1, Matthew Bytt1, Judith Heaney1, Moira J. Spyer1, Anita D. Rossii, Deborah Persaud2, Paolo Palma3, Carlo Giaquinto4, Pablo Rojo Conejo5, Caroline Foster6, Anne-Geneviève Marcelin8, Paolo Rossi1, Eleni Nastouli1, for the EPICAL Consortium

1University College London, London, UK, 2University College London Hospitals NHS Trust, London, UK, 3University of Padova, Padova, Italy, 4Johns Hopkins University School of Medicine, Baltimore, MD, USA, 5Bambino Gesu Children’s Hospital, Rome, Italy, 6Hospital Universitario 12 de Octubre, Madrid, Spain, 7Imperial College Healthcare NHS Trust, London, UK, 8Pitie-Salpetriere Hospital, Paris, France

Background: Perinatally HIV-1 infected children on early suppressive ART (PaHIV) represent an important population in the era of cure. Reservoir characteristics can determine criteria and cut-offs in future trials. We present unique HIV-1 DNA single genome sequencing (SGS) data in PaHIV from a multicentre cross-sectional study. We describe the presence of intact proviruses, defective genomes and ART resistance associated mutations (RAMs).

Methods: In the CARMA-EPICAL study, PaHIV on ART since <2 years of life and suppressed for ≥5 years were recruited in 7 centers. HIV-1 DNA was measured by real-time PCR. Near full-length SGS was performed in positive samples: manual extraction and limiting dilution touchdown PCR generated amplicons across the genome using in house and published primers. Products were analysed by gel, libraries generated by Nextera XT DNA Kit and sequenced on the MiSeq (Illumina). De novo assembly of genomes was performed, using an in-house bioinformatics pipeline with open source software. SMALT and LASTZ for alignment and the HIVSeqinR pipeline were utilised to describe intact genomes. De novo assembly of genomes was performed, using an in-house bioinformatics pipeline with open source software. SMALT and LASTZ for alignment and the HIVSeqinR pipeline were utilised to describe intact genomes.

Results: The majority of patients, 34/40, had detectable HIV-1 DNA (median 115.1 c/106 PBMCs, range 49.1-260.7 c/106 PBMCs). Initial findings on 4 patients, where 10 near full-length sequences were generated, are included in the figure. 2 viruses were subtype B, 1 subtype G and 1 CRF02_AG. Tropism assignment was possible in 9/10 sequences, 4/9 were CCR5, 5/9 were CXCR4. Intact sequences were identified in 4/10, however all contained APOL1 mutations. In 2 patients (3/10 sequences) RAMs in the pol/RT region were found. Defective genomes were frequent, 6/9 genomes contained deletions (4/6 were large), while 2/9 sequences had frameshift mutations. Inversions and stop codon mutations were not detected.

Conclusion: Our preliminary findings in this cohort suggest that the HIV-1 DNA landscape in PaHIV can be complex. Defective genomes with large deletions can be frequent but intact genomes are also present suggestive of a pool of virus that can rebound post treatment interruption. However, host driven APOL1 related hypermutations are present in long standing treated infection as well as RAMs.

814 DIFFERENCES IN THE INDUCED LATENT HIV RESERVOIR IN PERINATAL AND ADULT INFECTIONS

Adit Dhummakupt1, Jessica Rubens2, Thuy Anderson2, Laura Powell2, Bareng Nonyane3, Lilly V. Siems3, Aleisha Collinson-Streng1, Tricia Niles4, Richard Jones4, Vicki Tepper5, Allison Agwu6, Deborah Persaud6

1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3Abb Associates, Inc, Cambridge, MA, USA, 4George Washington University, Washington, DC, USA

Background: The HIV latent reservoir in resting memory CD4+ T cells prevents cure. Novel therapies to reactivate and eliminate the reservoir are in clinical trials in adults, but not yet in pediatric populations.

Methods: HIV proviral reservoir size was determined in perinatal (N=11) and adult infections (N=10) by digital droplet PCR (ddPCR) and with the intact proviral DNA assay (IPDA) in perinatal samples. The inducibility of the latent reservoir was determined with the Tat/rev Induced Limiting Dilution Assay (TILDA) that uses single-round (12 hr) T cell stimulation of CD4+ T cells with PMA/ionomycin to maximally activate cells to induce proviral expression, measured as multiply-spliced HIV RNA Units per 106 CD4+ cells (msRUPM). Markers of immune activation (CD69, CD25 and HLA-DR) and exhaustion (PD-1, TIM-3 and TIGIT) were also assessed. An enhanced TILDA with addition of PHA and for 18 hours was performed to enhance proviral expression in perinatal infections. Non-parametric tests were used for differences between paired and unpaired measurements; correlations were quantified by Spearman rank coefficient.

Results: The median age was 15.8 yrs with a median duration of suppression of 6.7 yrs for perinatal infections, and 40.5 yrs with a median duration of suppression of 7.3 yrs for adult infections. We found that despite a higher proviral reservoir size (median 132.1 vs. 66.7 c/106 PBMCs) and similar rates of T cell activation with PMA/ionomycin (median %CD69 = 96.7% and 93.0%) in perinatal and adult infections, respectively, the size of the induced reservoir was significantly lower in perinatal than in adult infections (median msRUPM of 2.99 vs 11.92, p=0.034), but not in adult infections. The proportion of induced provirus was significantly lower in perinatal infections at 1.6% compared with 4.0% in adult infections (p=0.030). At baseline, the proportion of HLA-DR+ T cells was significantly lower in perinatal compared with adult infections (median HLA-DR+ cells = 4.56% vs 10.5%, p=0.012), but not correlated with the induced reservoir size.

Conclusion: The inducibility of the latent reservoir is substantially lower in perinatal compared with adult infections, possibly due to differences in baseline states of immune activation, with implications for latency reversal strategies towards ART-free remission.
815 CHILDREN <15 ARE LESS LIKELY TO BE AN INDEX TESTING CONTACT COMPARED TO ADULTS

Hilary T. Wolf1, Melissa Bochnowicz1, Kayla Zhang1, Teeb Al-Samarrai1, Joseph S. Cavanaugh1, Shabeen Ally1
1Office of the Global AIDS Coordinator, Washington, DC, USA

Background: According to UNAIDS, half of children with HIV globally remain undiagnosed. Children with HIV are being diagnosed after the first five years of life, and thus may have no routine contact with the health system until they become symptomatic. In April 2017, PEPFAR began to rapidly scale index testing of sexual contacts and biological children of people living with HIV across all sites and communities, as it has shown the highest testing yield across all countries.

While some countries have been successful in scaling index testing among sexual contacts, many have struggled with using index testing effectively to find children with HIV who remain undiagnosed. This report evaluates the index testing cascade of pediatric contacts from October 2018 to June 2019.

Methods: A descriptive analysis was used to assess the number of children (aged 1-14) and adults (aged 15-49) who newly tested positive for HIV and accepted index testing services in eight countries in sub-Saharan Africa. We then evaluated the number of pediatric contacts and adult contacts of index participants who were elicited for HIV testing, the number of children who received an HIV test, and the number of children who were seropositive for HIV (yield).

Results: Each index case elicited more adult contacts than pediatric contacts in all 8 countries, with noteworthy geographic variation. The percent of elicited contacts who were children ranged from 0.8% in Uganda to 40% in South Africa. For South Africa, Zambia and Malawi, >37% of elicited contacts were children, while for the Democratic Republic of Congo (DRC), Kenya, Lesotho, Nigeria, and Uganda, <25% of elicited contacts were children. HIV testing yield among children identified as contacts ranged from 1.1% in Lesotho to 10.1% in DRC, with an average yield of 4.5% across the 8 countries.

Conclusion: Our results demonstrate high yields of new pediatric cases in specific geographic regions from index testing services. Failure to identify all pediatric contacts of index clients represents a missed opportunity to find undiagnosed children. Although we are unable to link the number of clients who accept index testing with the number of contacts that are elicited from index testing and ultimately the number of children who test positive; attention to pediatric contacts of new adult cases will allow life-saving therapy to be delivered to a vulnerable population.

816 THE CASCADE OF HIV CARE FOR CHILDREN AND ADOLESCENTS IN WEST AFRICAN COHORTS

Désiré L. Dahourot1, Karen Malatestede1, Sophie Desmonde1, Tanoh Eboua1, Elom Takassi1, Lorna Renner1, Marcelline D’Almeida1, Madeleine Amorissani-Folquet1, Mariam Sylla1, Valérienera1
1Institut de Recherches en Sciences de la Santé, Ouagadougou, Burkina Faso, 2INSERM, Bordeaux, France, 3INSERM, Toulouse, France, 4CHU de Yopougon, Abidjan, Côte d’Ivoire, 5CHU Sylvanus Olympio, Lomé, Togo, 6Karle Bu Teaching Hospital, Accra, Ghana, 7Centre National Hospitalier Universitaire Hubert Koutougou Maga de Cotonou, Cotonou, Benin, 8CHU de Cocody, Abidjan, Côte d’Ivoire, 9Hôpital Gabriel Touré, Bamako, Mali

Background: The attrition across the continuum of care for children and adolescents living with HIV (CALHIV) from their HIV diagnosis is unknown in West Africa. We assessed the progress to the second and third 90-90-90 targets in the International epidemiological Databases on AIDS (IeDEA) paediatric West African Cohort (pWADA).

Methods: The pWADA database, involves nine paediatric clinics in five countries (Benin, Côte d’Ivoire, Ghana, Mali, Togo). All CALHIV aged 0-18 years, ART-naive at enrolment except for prevention of mother-to-child transmission, and diagnosed between 2004 and 2018 were included. We described the proportions of the CALHIV initiating ART, and attrition (death, loss to follow-up [LTFU]; last clinical visit >12 months) and the proportion of those on ART virally suppressed (first viral load <500c/mL after 6-month post-ART). We presented cumulative incidence and factors associated with ART initiation, with death/ LTU as competing risks.

Results: Overall, 7570 CALHIV were enrolled in pWADA; 65% were enrolled before 2013. At enrolment, 49% were females, median age was 3.5 years (interquartile range [IQR]: 1.2–7.6 years), 37% were <2 years, and 73% were eligible to initiate ART according to the WHO guidelines in effect at enrolment. During follow-up, 3% died, 3% were transferred out and 19% were LTU before ART initiation: 3% were alive but had not initiated ART while 72% (5475/7570) initiated ART. The median time between baseline and ART initiation was 1.4 months [IQR: 0.3–7.2 months]. At ART initiation, median age was 5.1 years (IQR: 2–9 years) and 80% were treated with a non-nucleoside reverse transcriptase inhibitors regimen. Adjusted for center, gender, clinical/ immunological ART eligibility, children aged <2 years (Adjusted Hazard ratio [aHR]: 0.59, 95% Confidence Interval (95%CI): 0.54–0.65) and aged 2–4 years (aHR: 0.84; 95%CI: 0.77–0.92) at baseline were significantly less likely to initiate ART compared to those aged 5–10 years, as well as CALHIV enrolled before 2016 compared to those enrolled later. Among CALHIV on ART, 65% (3362/5475) performed at least one viral load test during follow-up. The cumulative probability of reaching viral suppression was 17%, 26%, 36% and 43% at 6, 12, 24 and 36 months, respectively.

Conclusion: In West Africa, CALHIV had low retention in care, low access to viral load and far to meeting the second and third stages of the 90-90-90 targets. Additional supports is needed for this population to initiate ART earlier, using more potent drugs and to strengthen treatment adherence.

817 HIV VIRAL SUPPRESSION IN ADOLESCENTS AND YOUNG ADULTS: A NATIONAL SURVEY IN KENYA

Irene Njuguina1, Jillian Neary2, Caren Mburu2, Danae Black2, Kristin Beima-Sofie3, Anjuli Wagner2, Cyrus Mugo4, Yolanda Evans4, Brandon Guthrie2, Janet Itindi1, Alvin Onyange1, Laura Oyiengo1, Barbra A. Richardson2, Dalton Wamalwa1, Grace John-Stewart2
1Kenya National Hospital, Nairobi, Kenya, 2University of Washington, Seattle, WA, USA, 3INSERM, Bordeaux, France, 4CHU de Cocody, Abidjan, Côte d’Ivoire, 5Korle Bu Teaching Hospital, Accra, Ghana, 6Centre National Hospitalier Universitaire Hubert Koutougou Maga de Cotonou, Cotonou, Benin, 7Centre National Hospitalier Universitaire Hubert Koutougou Maga de Cotonou, Cotonou, Benin, 8CHU de Cocody, Abidjan, Côte d’Ivoire, 9Ministry of Health, Nairobi, Kenya

Background: Adolescents and young adults (AYA) living with HIV are at high risk of virologic failure. While HIV clinics have developed innovative approaches to address unique AYA challenges, it is unclear if these influence viral suppression. To achieve UNAIDS 95-95-95 goals, there is need to understand modifiable and fixed individual and clinic correlates of suppression.

Methods: We conducted a multi-level cross-sectional analysis using viral load data and facility surveys from HIV treatment programs throughout Kenya. We abstracted medical records of AYA in HIV care, analyzed the subset on ART for >6 months between January 2016–December 2017, and collected information on AYA services at each clinic. We used multi-level logistic regression models
to determine individual- and clinic-level correlates of viral suppression at most recent assessment.

**Results:** In 99 HIV clinics, among 10,096 AYA on ART >6 months, 2,683 (27%) had un suppressed viral load (VL). Adjusted for individual-level factors, clinic-level correlates of individual suppression included designated adolescent spaces (aOR: 1.32, [95%CI: 1.07, 1.63]) and faster VL turnaround time (TAT) (aOR: 1.06 [95%CI: 1.03, 1.09]) per 10-day shorter TAT. Adjusted for clinic-level factors, AYA age 10-14 and 15-19 had lower odds of suppression compared to AYA age 20-24 years (aOR: 0.61 [95%CI: 0.54, 0.69] and 0.59 [95%CI: 0.52, 0.67], respectively). Compared to females, males had lower odds of suppression (aOR: 0.69 [95%CI: 0.62, 0.77]).

Compared to ART duration of 6-12 months, ART for 2-5, >5-10 or >10 years was associated with poor suppression (p<0.001).

In 16% of clinics, ≥80% of AYA were suppressed. Clinics with ≥80% AYA viral suppression were more likely to be in hyper-endemic counties (56% versus 22% p=0.04), have separate adolescent space, and a shorter viral load TAT (39% versus 15% and 9 days versus 12 days p=0.03, <0.001, respectively).

**Conclusion:** Dedicated adolescent space, rapid VL TAT, and tailored approaches for specific groups may improve suppression. Routine summarization of VL suppression in clinics could provide benchmarking to motivate innovations in clinical- and individual-AYA care strategies.

**818 CAN ADHERENCE INTERVENTIONS BE COST-EFFECTIVE AMONG YOUTH WITH HIV?**

**Methods:** Using the Cost-Effectiveness of Preventing AIDS Complications Adolescent model, we simulated a cohort of YWH ages 13-24 using published YWH-specific data: cohort-level VS 59% (RNA <50c/mL), mean CD4 654/μL (SD 276). We compared 2 strategies: usual care (standard-of-care, SOC) and a clinic-level adherence intervention to determine individual-and clinic-level correlates of viral suppression at most recent assessment.

**Results:** In 99 HIV clinics, among 10,096 AYA on ART >6 months, 2,683 (27%) had un suppressed viral load (VL). Adjusted for individual-level factors, clinic-level correlates of individual suppression included designated adolescent spaces (aOR: 1.32, [95%CI: 1.07, 1.63]) and faster VL turnaround time (TAT) (aOR: 1.06 [95%CI: 1.03, 1.09]) per 10-day shorter TAT. Adjusted for clinic-level factors, AYA age 10-14 and 15-19 had lower odds of suppression compared to AYA age 20-24 years (aOR: 0.61 [95%CI: 0.54, 0.69] and 0.59 [95%CI: 0.52, 0.67], respectively). Compared to females, males had lower odds of suppression (aOR: 0.69 [95%CI: 0.62, 0.77]).

Compared to ART duration of 6-12 months, ART for 2-5, >5-10 or >10 years was associated with poor suppression (p<0.001).

In 16% of clinics, ≥80% of AYA were suppressed. Clinics with ≥80% AYA viral suppression were more likely to be in hyper-endemic counties (56% versus 22% p=0.04), have separate adolescent space, and a shorter viral load TAT (39% versus 15% and 9 days versus 12 days p=0.03, <0.001, respectively).

**Conclusion:** Dedicated adolescent space, rapid VL TAT, and tailored approaches for specific groups may improve suppression. Routine summarization of VL suppression in clinics could provide benchmarking to motivate innovations in clinical- and individual-AYA care strategies.
Background: Poor linear growth (i.e., stunting), is common in perinatally-acquired HIV infection, yet effects of HIV on adolescent musculoskeletal development remain poorly characterized in sub-Saharan Africa. We hypothesize that bone and muscle growth in children living with HIV (CWH) are impaired, putting them at risk of low bone mass and functional disability, which may increase future fracture risk. We aimed to determine the impact of HIV on size-adjusted (important in context of small stature) bone density and muscle function in peri-pubertal children in Zimbabwe.

Methods: CWH aged 8-16 years, established on ART for ≥2 years, from two public sector HIV clinics and sex and aged-band frequency-matched uninfected children from schools were recruited. Musculoskeletal assessments included grip strength, standing long jump and dual-energy X-ray absorptiometry (DXA). Total-body less-head (TBLH) bone mineral content (BMC) for lean mass adjusted for total height (TBLH BMC/LSMBM) and lumbar spine bone mineral apparent density (LS BMAD) values and Z-Scores were calculated. Differences by HIV status, and risk factors for impaired musculoskeletal measures, were determined using linear and logistic regression.

Results: A total of 284 CWH and 222 children without HIV were recruited (Table 1). CWH were more likely to have pubertal delay, stunting and wasting than children without HIV. Calcium and vitamin D intake were not significantly different between the three groups. However, CWH had significantly lower muscle mass, muscle strength, TBLH BMC/LSMBM and LS BMAD compared to the uninfected controls.

Conclusion: This study, for the first time, investigated the effect of HIV on bone and muscle development sub-Saharan African children. HIV was found to have a profound effect on muscle function and bone mass. Whilst pubertal delay is more common in HIV, it does not account for these differences. The effect of HIV on musculoskeletal health may result in long-term disability and impaired quality of life in the future.
as overweight by WHO criteria. Before ART switch, median (IQR) LS Z-score and TB Z-score were -1.15 (-2.3/-0.3) and -1.05 (-2.0/-0.3), respectively. Mean change (SD) in LS Z-score was -0.03 (0.25) and TB Z-score was 0.02 (0.24). None had a decrease in LS Z-score from >-2 to < -2, but 1 ALWH had this outcome in TB Z-score. Among participants with 24 week DXA results, 15/47 (32%) had either no change or decreased LS BMD after switch, with a mean change of -1.6% (14/15 (93%) of this group were female. Overall, a greater proportion of females than males had either no change or decreased LS BMD (50% vs 4%, p=0.0001; Fisher Exact). Overall, statistically significant increases in serum creatinine and decreases in eGFR were observed (p<0.0001 and 0.0003, respectively; however, final levels remained within clinically acceptable limits.

Conclusion: South African ALWH switching from ABC to TDF experienced statistically significant decreases in eGFR but not in LS and TB BMD overall. However, female ALWH experienced greater decreases in LS BMD and may require closer monitoring.

823 EPIGENETIC AGE IN YOUNG AFRICAN AMERICAN ADULTS WITH PERINATALLY ACQUIRED HIV
Stephanie Shiau1, Michael T. Yin1, Christian Vivar Ramon2, Grace Jang1, Anayelina Cantos1, Jyesh Shah1, Stephen M. Arpadi2
1 Rutgers University, Piscataway, NJ, USA, 2 Columbia University Medical Center, New York, NY, USA

Background: Prior studies have measured accelerated aging in people living with HIV (PLWH) using a DNA methylation (DNAm)-based biomarker of aging, "epigenetic age", but data are limited in African Americans (AA). We assessed perinatally-acquired HIV infection (PHIV) is associated with accelerated epigenetic age in AA young adults (20-35 years of age).

Methods: We enrolled 61 AA young adults living in NYC, including 31 youth living with PHIV and 30 youth confirmed to be HIV seronegative (Controls) and measured DNAm from whole blood samples using the Illumina EPIC Array. DNAm age (years) was estimated by the Horvath method. We estimated four age acceleration measures, where positive values indicate that the blood sample is older than expected based on chronological age: 1) age acceleration residual (AAR), considered to be robust with respect to cell composition changes; 2) extrinsic epigenetic age acceleration (EAA), up-weights the contributions of age-related blood cell counts; 3) intrinsic epigenetic age acceleration (IEAA), adjusts for cell type counts; 4) Houmanan-adjusted age acceleration residual (HAAAR), adjusts for cell type proportions estimated by the Housman method.

Results: PHIV and Controls did not differ by sex (45% vs 40% male), chronological age (26.2 vs. 28.0 years), or ethnicity (90% not Hispanic or Latino in both groups). Among PHIV, 63.0% had a viral load (VL) <50 copies/mL (cpm) and 37% >50 cpm. Blood cell composition differed between PHIV and Controls, largely driven by differential proportions of CD8 (0.36 vs. 0.25, p<0.01) and CD4 T-Cells (0.18 vs. 0.36, p<0.01). Chronological age and DNAm age were positively correlated (r=0.56, p<0.01). PHIV had a higher mean AAR (2.86±6.5 vs. -2.96±3.9, p<0.01) and EAA (4.57±13.0 vs. -4.72±6.0, p<0.01) compared to controls. Among PHIV, AAR was higher in those with VL >50 cpm than those with VL <50 cpm (8.52±5.3 vs. 0.66±5.1, p<0.01). However, IEAA and HAAAR, the two age acceleration measures that adjust for blood cell composition did not differ between PHIV and Controls.

Conclusion: Epigenetic age acceleration in blood was observed in AA young adults with PHIV using measures unadjusted for blood cell composition. However, after accounting for blood cell composition, there was no longer evidence of age acceleration associated with HIV. Future studies of accelerated aging in PLWH should consider the relationships between CD8 and CD4 T-cells and epigenetic age.

824 GLOBAL VARIATIONS IN PUBERTAL GROWTH IN ADOLESCENTS LIVING WITH PERINATALLY ACQUIRED HIV
Siobhan Crichton1, Julie Jesson2, Marie-Hélène Akré-Assi3, Erik Belfrage4, Mary-Ann Davies5, Jorge Pinto6, Chloe A. Teasdale7, Nguyen Van Lam8, Rachel Spoulou8, Vinicius A. Vieira3, Intira J. Collins1, for the CIPHER Global Cohort Collaboration
1 MRC Clinical Trials Unit at UCL, London, UK, 2 Great Ormond Street NHS Foundation Trust, London, UK, 3 University of Oxford, Oxford, UK, 4 UCL Great Ormond Street Institute of Child Health, London, UK, 5 University of Cape Town, Cape Town, South Africa, 6 Instituto de Ciencias de la Salud, Universidad de la República, Montevideo, Uruguay, 7 Centro Hospitalar de Póvoa de Varzim, Porto, Portugal, 8 National Hospital of Pediatrics, Hanoi, Vietnam, 9 Indian Institute of Technology, Bombay, India, 10 University of California, Los Angeles, USA, 11 Harvard T.H. Chan School of Public Health, Boston, MA, USA, 12 The Ohio State University, Columbus, OH, USA

Background: Adolescents living with perinatally-acquired HIV experience puberty later than HIV-exposed uninfected young people. This study describes growth during adolescence including regional variations.

Methods: The CIPHER Cohort Collaboration pooled observational data from 1994-2015 from 48 countries. Adolescents who initiated a combination ART regimen before age 10 years and had ≥4 height measurements aged ≥8 years (including ≥1 measurement aged ≥12 years for females and ≥14 years for males based on expected age at peak height velocity) were included. We used SITAR (Super Imposition by Translation And Rotation) models to describe growth from age 8-19 years using 3 parameters; mean height, timing and intensity (i.e. shape of the growth velocity curve) of the growth spurt. We then used multivariable regression models to explore characteristics (region, year of birth, initial ART regimen, age, height-for-age z-score (HAZ), and BMI-for-age z-score (zBMI) at ART initiation (baseline)) associated with the growth parameters from SITAR models.

Results: Of 9397 female and 9585 males on ART by age 10, 4535 and 2202, respectively, were included. 1125(17%) were from Botswana and South Africa, 3312(49%) Eastern and rest of Southern Africa, 442(7%) Western and Central Africa, 880 (13%) Europe and North America, 649(10%) Asia, 329(5%) Latin America.

Timing of the growth spurt varied by region and sex (Figure). In multivariable analyses the association between baseline HAZ and timing of growth spurt in females differed by region (p=0.017): a 1SD decrease in HAZ was associated with a 0.30(95%CI 0.21,0.39) year delay in Asia and 0.11(0.07,0.14) year delay elsewhere. In males, there was an interaction between baseline age and HAZ (p=0.009); for males starting ART age <4 years, baseline HAZ was not associated with timing but for those initiating ART at older ages, lower baseline HAZ was associated with later growth spurt.

Longer calendar year of birth was associated with earlier growth spur (in males (-0.04(-0.07,-0.02)) but not in males. A 1SD decrease in zBMI was associated with a delay of 0.04(0.01,0.07) years in females and 0.07 (0.02,0.12) years in males. Differences in intensity of the growth spurt were observed across regions, age and HAZ at ART initiation.

Conclusion: Starting ART when stunted is associated with delayed pubertal growth spurt globally. Longer term follow-up is important to understand the impact of these delays on outcomes later in life.

825 LONG-TERM NONPROGRESSION IN CHILDREN WITH PERINATALLY ACQUIRED HIV
Charlotte Jackson1, Alasdair Barnard2, Siobhan Crichton1, Ruth Goodall1, Philip J. Goulder3, Nigel Klein4, Laura Marques5, Paolo Paioni6, Andrew Riordan7, Vana Spoulou8, Vinicius A. Vieira3, Intira J. Collins1, for the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group
1 MRC Clinical Trials Unit at UCL, London, UK, 2 Great Ormond Street NHS Foundation Trust, London, UK, 3 University of Oxford, Oxford, UK, 4 UCL Great Ormond Street Institute of Child Health, London, UK, 5 Centro Hospitalar do Porto, Porto, Portugal, 6 University Children's Hospital Zurich, Zurich, Switzerland, 7 Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, 8 University of Athens, Athens, Greece

Background: Long-term non-progression (LTNP) refers to long-term survival with HIV without disease progression or antiretroviral treatment (ART). LTNP
prevalence estimates in children range from 2-42% using varied definitions, often in small samples. Understanding LTNP in children can potentially inform HIV cure research. We assessed the prevalence of paediatric LTNP in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC).

**Methods:** 16 cohorts from 12 European countries and Thailand contributed follow-up data from 1980-2016. Confirmed LTNP was defined as having none of these events during the first 3 (or 8) years of life: AIDS diagnosis, initiating ART, death or ever meeting defined CD4 progression criteria. Possible LTNP was defined as no clinical events but unclear timing of CD4 progression relative to age/ART initiation. We explored 4 different CD4 criteria: a)CD4 z-score < -2 relative to HIV-exposed uninfected children, b)CD4 z-score < 3, c)CD4 count < 500 cells/µL, d)WHO advanced/severe immunodeficiency for age (CD4% < 30, < 25, < 20, < 15 at age < 11m, 12-35m, 36-59m, > 5y, or CD4 count < 350/µL at > 5y). Inclusion criteria for analysis were perinatal infection or < 10 years at first visit, ≥1 CD4 record, born pre-2011 (or 2008), not lost to follow-up by age 5/8y.

Associations between LTNP and sex, region and birth year were assessed with logistic regression. Data were analysed separately for children born domestically (country of reporting cohort) vs abroad.

**Results:** Of 9621 children followed in EPPICC, 6642 (69%) met the inclusion criteria. Median age at entry to HIV care was 1.6y [IQR 0.2-4.3] and follow-up duration 10.5y [6.6-15.1]. 1468 (22.1%) were born abroad. LTNP prevalence was 9.2-38.9% at 5y and 3.6-24.6% at 8y, 2-3 times higher in those born abroad vs domestically (Figure). In multivariable analysis, for all CD4 criteria and those born domestically and abroad, prevalence was lower in Thailand and Western/Central Europe, higher in Eastern Europe (vs UK/Ireland, p<0.01) and lower in children born in later years.

**Conclusion:** This is the largest multi-country paediatric collaboration to explore LTNP prevalence. Higher prevalence in children born abroad likely reflects selection bias of survivors well enough to migrate. Age 5y may be too early to define LTNP, as prevalence falls by 8y. Introduction of “treat all” approaches likely explains recent declines in prevalence. Data before these changes allow selection bias of survivors well enough to migrate. Age 5y may be too early to define LTNP, as prevalence falls by 8y. Introduction of “treat all” approaches likely explains recent declines in prevalence. Data before these changes allow selection bias of survivors well enough to migrate. Age 5y may be too early to define LTNP, as prevalence falls by 8y. Introduction of “treat all” approaches likely explains recent declines in prevalence. Data before these changes allow selection bias of survivors well enough to migrate.
concentration of glucose, total and fractionated cholesterol and triglycerides were measured at baseline and after 3, 6 and 12 months. Body composition was evaluated by dual-energy X-ray absorptiometry and body mass index (BMI) was calculated at baseline and after 12 months. Statistical comparisons were performed by ANOVA for repeated measures.

**Results:** Mean blood concentration of glucose and HDL cholesterol did not change significantly during the follow-up. Conversely, mean total cholesterol concentration was 190, 159, 161 and 168 mg/dL at baseline, 3, 6 and 12 months, respectively (p = 0.0057). Mean LDL cholesterol values were 109, 90, 92 and 96 mg/dL at baseline, 3, 6 and 12 months (p = 0.025). Mean triglycerides concentration decreased significantly after 3 months of therapy (114 and 64 mg/dL, p = 0.007). BMI was 20.4 at baseline and 20.9 Kg/m² after 12 months (p = 0.09). Body fat percent did not change significantly during the study (p = 0.16), but we observed a remarkable increase in trunk body fat percent (p = 0.0413). In particular, trunk/total body less head (TBH) fat ratio increased significantly (p = 0.0485), while limbs/trunk fat ratio decreased significantly (p = 0.0495) (Table 1).

**Conclusion:** Our study shows that a dolutegravir-based regimen induces a significant improvement in lipids blood concentration, but no interference on glucose metabolism. On the other hand, we observed a relevant increase in trunk fat without alterations of BMI and body fat percent. Future studies are needed to evaluate if this increase in trunk fat could impact on body metabolism.

### Table 1: Body composition measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>12 months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBH</td>
<td>111.7</td>
<td>77.0</td>
<td>0.18</td>
</tr>
<tr>
<td>Trunk</td>
<td>39.0</td>
<td>37.5</td>
<td>0.011</td>
</tr>
<tr>
<td>Arms</td>
<td>27.0</td>
<td>27.0</td>
<td>0.87</td>
</tr>
<tr>
<td>Waist</td>
<td>87.7</td>
<td>84.0</td>
<td>0.46</td>
</tr>
<tr>
<td>Waist/TBH</td>
<td>0.67</td>
<td>0.65</td>
<td>0.0046</td>
</tr>
<tr>
<td>BMI</td>
<td>20.4</td>
<td>20.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Body fat</td>
<td>19.6</td>
<td>20.6</td>
<td>0.016</td>
</tr>
</tbody>
</table>

### 828 CHER TRIAL COHORT SHOWS GREATER INSULIN RESISTANCE INTO ADOLESCENCE

Claire Davies, Steve Innes, Mark Cottrell, Sara H. Browne, Birhanu Ayale
Stellenbosch University, Tygerberg, South Africa, University of California San Diego, San Diego, CA, USA

**Background:** Few longitudinal studies have examined insulin resistance in HIV-infected children, and of those most have been conducted in developed countries. Our aim was to examine whether the trajectory of insulin resistance differs in perinatal-HIV-infected children (PHIV) who received early antiretroviral therapy (ART) below 12 weeks of age; HIV-exposed uninfected children (HEU); and HIV-unexposed uninfected children (HU).

**Methods:** This longitudinal cohort study consists of 90 PHIV, 317 well-matched controls (156 HEU and 161 HU) from the same communities and socio-economic background, attending the Family Clinical Research Centre with Ubuntu (FAM-CRU) at Tygerberg Children's Hospital, South Africa. This cohort was the first to begin ART from below 12 weeks of age with normal CD4 percentages and without clinical HIV disease (CHER trial, Lancet 2013). The cohort has now been followed until 16 years of age. For the present study, children required ≥1 set of simultaneously-obtained fasted serum glucose and insulin measurements. The main outcome was the Homeostatic Model Assessment (HOMA) insulin resistance index (HOMA-IR) (Insulin/mU/L x glucose mg/dL modelled using log HOMA-IR given skewness).

**Results:** Using linear mixed effects modelling, PHIV had a geometric mean HOMA-IR 1.2 (95% CI 1.1 – 1.3) times above HU (table 1), after adjusting for gender, height (as a surrogate for age, puberty onset and growth), waist circumference (as a surrogate for visceral adiposity), and the random effect of child, given each child had multiple measurements. Elevated HOMA-IR was found between the HOMA-IR of HEU and HU.

**Conclusion:** Our findings demonstrate the independent contribution of detectable VL on cardiovascular risk in YLH.
and 24 months. RHI was measured at 24 months. Spearman correlations were used and quantile regression models assessed associations with RHI.

**Results**: We included 283 YLPHIV and 69 HIV- participants. At baseline, median (Q1, Q3) age was 12 years (11, 13), 53% were females. There was no difference in age, sex or Tanner stages between the groups. At baseline, median CD4 cell count was 744 cells/µL (603, 951). PHIVs had poorer endothelial function compared to HIV- (RHI=1.36 vs 1.52, p<0.01). At baseline and 24 months, YLPHIV had lower BMI but higher waist-to-hip ratio, LDL cholesterol, triglycerides, markers of monocyte activation (sCD14), gut barrier dysfunction (intestinal fatty acid binding protein, IFAB-P) and oxidized LDL cholesterol (p<0.04). Several biomarkers decreased at 24 months in YLPHIV but remained elevated compared to HIV- (Figure). In univariate analyses, higher levels of IFAB-P at baseline and sCD14 at 24 months correlated with endothelial dysfunction at 24 months (p<0.04). In quantile regression analyses, in YLPHIV with endothelial dysfunction, sCD14 remained associated with lower RHI after adjusting for age, sex, Tanner stage, viral load and ART duration (β=0.05, p=0.01).

**Conclusion**: Despite viral suppression, South African YLPHIV have poor endothelial function and persistent evidence of monocyte activation and gut barrier dysfunction compared to uninfected youth. A key finding in our results is that higher sCD14 is independently associated with endothelial dysfunction in this population. The long-term clinical significance of gut integrity and monocyte activation needs to be further assessed in YLPHIV.

833 VASCULAR DISEASE, IMMUNE ACTIVATION, AND GUT DYSFUNCTION IN HIV+ UGANDAN CHILDREN

Sahera Dirajal-Fargo1, Emily Bowman2, Danielle Lobbato3, Zainab Albar1, Christine Karungi6, Rashidah Nazzinda4, Abdus Sattar1, Nicholas Funderburg2, Cissy Kityo1, Victor Musiime4, Grace A. McComsey3

Case Western Reserve University, Cleveland, OH, USA, 2The Ohio State University, Columbus, OH, USA, 3University Hospitals Cleveland Medical Center, Cleveland, OH, USA, 4Joint Clinical Research Centre, Kampala, Uganda

**Background**: Sub-Saharan Africa is facing new challenges in HIV care including management of non-communicable diseases and a growing younger generation. The risk of cardiovascular disease (CVD) and its mechanisms in children living with perinatally acquired HIV (PHIV) in sub-Saharan Africa has been understudied.

**Methods**: Mean common carotid artery intima-media thickness (IMT) and pulse wave velocity (PWV) were evaluated in 101 PHIV and 96 HIV negative participants (HIV-). Participants were between 10-18 years of age with no active infections including tuberculosis. PHIVs were on ART with HIV-1 RNA level ≤400 copies/mL. We measured plasma (soluble CD14 and CD163) and cellular markers of monocyte activation (proportions of monocyte subsets), T-cell activation (expression of CD38 and HLA-DR on CD4+ and CD8+), as well as plasma markers of systemic inflammation, oxidized lipids, gut integrity.

**Results**: Overall median (Q1, Q3) age was 13 years (11, 15) and 52% were females. Groupswere similar by age, sex and BMI. Median CD4+ cell counts were 988 cells/µL (638, 1308), 86% had viral load < 20 copies/mL and median ART duration was 10 years (8, 11). 72% were on an NNRTI based regimen. PHIVs were more likely to have traditional CVD risk factors including higher waist-hip ratio, triglycerides, and insulin resistance (p≤ 0.03). Median IMT was slightly thicker in PHIVs compared to controls, while PWV did not differ between groups (Figure). PHIVs had higher monocyte and T-cell activation; higher CD14 (p<0.01), higher frequencies of non-classical monocytes (p=0.02) and activated CD4+ and CD8+ T-cells (p<0.001 for both). In univariate analyses, lower BMI and oxidized LDL, and higher waist-hip ratio, hsCRP and zonulin correlated with thicker IMT in PHIV (p≤0.05). After adjustment for age, BMI, sex, CD4 cell count, triglycerides, HOMA, sCD163 and hsCRP were added separately, higher levels of intestinal permeability (zonulin) remained associated with IMT (β=0.02, p≤0.03).

**Conclusion**: Our study shows for the first time that African PHIV with viral suppression have evidence of worse CVD risk, structural vascular disease, ongoing immune activation and a leaky gut compared to age matched uninfected children. Gut barrier dysfunction may be involved in the pathogenesis of subclinical vascular disease in this population.

832 DEPRESSION ASSOCIATED WITH LOWER EXECUTIVE FUNCTIONING IN ASIAN YOUTH LIVING WITH HIV

Wipaporn Natalie Songtaweesin1, Christina Chandra2, Jiratchaya Sophonphan1, Ly Penh Sun1, Pradthana Ounchanum5, Pope Kosalaraks3, Linda Aurpibul7, Suparat Kanjanavanit8, Chaiwat Ngampiyaskul9, Kathleen Malee10, Robert Paul11, Jintanat Ananworanich12, Claude A. Mellins13, Thanyawee Puthanakit1, for the PREDICT and Resilience Study Group
Background: Adolescents and young adults living with HIV are situated within a dynamic confluence of behavioral, developmental, and care transitions that pose unique challenges to provide optimal healthcare. Depression and substance use may impact antiretroviral therapy (ART) adherence, but data from Latin America are scarce. We evaluated the prevalence and factors associated with depression, substance use, and self-reported adherence among youth in HIV care.

Methods: Cross-sectional study including adolescents (10 to <18 years) and young adults (18 to <25 years) on ART for ≥6 months within the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) in Brazil, Chile, Haiti, Honduras, Mexico and Peru. Individuals were screened for depression (Patient Health Questionnaires, PHQ-2/9/A), substance use (The Alcohol, Smoking and Substance Involvement Screening Test) and ART adherence (The Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol). Multivariable logistic regression models were used to evaluate factors associated with each outcome.

Results: Of 592 participants included in the analysis, 308 (52%) were female, 235 (40%) were 10-17 years old and 355 (60%) had undetectable viral load. The prevalence of depression was 16%. Regarding substance use in previous 3 months, 338 (57%) used alcohol, 170 (29%) tobacco, and 110 (19%) illicit drugs. Non-adherence in previous week was reported by 213 (36%) participants. Females were more likely to report depression (adjusted odds ratio (aOR) 2.9, 95% CI 1.6–5.1) and less likely to report illicit drug use (aOR 0.34, 95%CI 0.2–0.7) than males. Alcohol use in previous 3 months was associated with the use of tobacco (aOR 10.4, 95%CI 4.6–23.9) and illicit drugs (aOR6.9, 95%CI 1.8–26.4). Tobacco was the only substance associated with non-adherence (Table).

Conclusion: The prevalence of substance use was higher than found among CCASAnet adults in a previous analysis. Youth reporting alcohol and tobacco use should be screened for illicit drug use. Although alcohol and illicit drugs were not associated with ART adherence, youth using these substances may be at increased risk for mortality related to violence and traffic accidents - which are the main cause of death in many Latin American countries. Further studies and interventions are needed.

Table: Factors associated with depression, substance use, and non-adherence to antiretroviral therapy (ART) among, adult, adolescent, and young adult (AMA) in multicentric logistic regression analyses. 2016-2019

<table>
<thead>
<tr>
<th>Factor</th>
<th>Depression</th>
<th>Alcohol use ≥1 times per week</th>
<th>Tobacco use in previous 3 months</th>
<th>Any illicit drug use ≥1 times per month</th>
<th>Last week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 18-24 vs. 10-17</td>
<td>1.0</td>
<td>1.8–26.4</td>
<td>0.8</td>
<td>0.32–2.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Tobacco use ≥1 times per week</td>
<td>0.89</td>
<td>0.80–1.00</td>
<td>0.82</td>
<td>0.22–2.74</td>
<td>0.91</td>
</tr>
<tr>
<td>Age: 14-16 vs. 10-13</td>
<td>1.0</td>
<td>1.0–26.4</td>
<td>1.0</td>
<td>1.0–26.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcohol use ≥1 times per week</td>
<td>0.89</td>
<td>0.80–1.00</td>
<td>0.82</td>
<td>0.22–2.74</td>
<td>0.91</td>
</tr>
<tr>
<td>Age: 12 years</td>
<td>1.0</td>
<td>1.0–26.4</td>
<td>1.0</td>
<td>1.0–26.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcohol use ≥1 times per week</td>
<td>0.89</td>
<td>0.80–1.00</td>
<td>0.82</td>
<td>0.22–2.74</td>
<td>0.91</td>
</tr>
<tr>
<td>Age: 10-13 vs. 10-13</td>
<td>1.0</td>
<td>1.0–26.4</td>
<td>1.0</td>
<td>1.0–26.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcohol use ≥1 times per week</td>
<td>0.89</td>
<td>0.80–1.00</td>
<td>0.82</td>
<td>0.22–2.74</td>
<td>0.91</td>
</tr>
<tr>
<td>Age: 8-9 years</td>
<td>1.0</td>
<td>1.0–26.4</td>
<td>1.0</td>
<td>1.0–26.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcohol use ≥1 times per week</td>
<td>0.89</td>
<td>0.80–1.00</td>
<td>0.82</td>
<td>0.22–2.74</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Conclusion: Substance use was more common among adolescents, but there are few longitudinal data exploring the prevalence among perinatally-infected adolescents living with HIV (PHIV+) in sub-Saharan Africa, including comparisons with HIV- adolescents.
835 VIRAL SUPPRESSION AND MARIJUANA MODULATE TRANSCRIPTOME BIOPROFILE IN YOUTH WITH HIV
Li Yin1, Ashok R. Dinasarapu1, Kai-Fen Chang1, John W. Sleasman1, Maureen Goodenow1
1NIAID, Bethesda, MD, USA, 2Duke University, Durham, NC, USA
Background: Viral suppression by antiretroviral therapy (ART) modulates many inflammatory pathways perturbed by HIV, but does not completely normalize inflammation. Substance use, particularly marijuana, affects pro-inflammatory pathways. A systems biology approach was used to define the transcriptome profiles associated with viral suppression and marijuana use in youth with HIV (YWH).
Methods: The study included 20 YWH with long-term (3 years) viral suppression on ART (viral load < 50 copies), 8 virally suppressed YWH who regularly used recreational marijuana based on toxicology and self-report, 7 age-balanced YWH who failed the same 3-year ART regimen (median viral load 2,379 copies/ml), and 25 healthy, HIV-uninfected youth balanced for age, gender and race. Peripheral blood cell mRNA was profiled using Affymetrix HG-U133 Plus 2.0 Arrays. Differentially expressed genes (DEGs) were identified by Significance Analysis for Microarrays (FC > 1.3). Pathway enrichment analysis was performed using Ingenuity Pathways Analysis to identify enriched pathways (p < 0.001).
Results: Active HIV-1 replication in 7 viral failures perturbed 127 pathways including 602 DEGs. Sustained long-term viral suppression by ART significantly reduced the perturbed pathways to 25 with 70 DEGs. Although 22 pathways remained perturbed in viral suppressors, ~70% genes dysregulated in viral failures were normalized, while DEGs identified in viral suppressors, including up-regulation of RAP2B, ITGB1, KL1R1 and KLRC1, and down-regulation of SLC8A1, E2F3 and COL4A3B, were not observed in viral failures. Three pathways, including IL-6 signaling, macrophagocytosis signaling and GDN family ligand-receptor interactions, were unique to viral suppressors. Four genes, RAP2A, RAP2B, PHK3C2A and PIK3CB, were enriched in all pathways perturbed in viral suppressors, potentially serving as networking hubs. Among virally suppressed YWH, marijuana normalized all pathways and genes except for Protein Ubiquitination Pathway.
Conclusion: HIV replication and long-term viral suppression display unique blood transcriptome bioprofiles. Surprisingly recreational use of marijuana normalized many pathways and genes dysregulated by HIV.

836 PROMISING RESULTS FROM A PILOT RCT MENTAL HEALTH INTERVENTION FOR HIV-INFECTED YOUTH
Dorothy E. Dow1, Blondina T. Mmbaga2, John A. Gallis1, Elizabeth L. Turner1, Monika Gandhi1, Coleen K. Cunningham1, Karen O’Donnell1, 1Duke University School of Medicine, Durham, NC, USA, 2Kilimanjaro Christian Medical Centre, Moshi, Tanzania, 3Duke Global Health Institute, Durham, NC, USA, 4University of California San Francisco, San Francisco, CA, USA, 5Duke University, Durham, NC, USA
Background: There are increasing numbers of youth living with HIV (YLWH) with unaddressed mental health challenges. Mental health challenges are associated with poor antiretroviral therapy (ART) adherence which lead to unacceptably high mortality. Few evidence-based mental health interventions exist to address mental health challenges and improve HIV outcomes specifically for YLWH.
Methods: This pilot group treatment trial, which individually randomized YLWH from two clinical sites in Tanzania, evaluated a mental health intervention, Sauti ya Vijana (SYV), compared to standard-of-care (SOC) for improving ART adherence and virologic suppression. SYV consisted of ten group and two individual sessions held weekly, delivered by lay counselors. Participants were living with HIV and 12-24 years of age. Demographics, mental health questionnaires (PHQ-9, SDQ, UCLA Trauma), stigma, self-report and objective measures of adherence (ART concentration in hair), and HIV RNA were obtained at baseline and 6-months (post-intervention). Potential effectiveness was assessed by comparing outcomes between arms in exploratory analyses using mixed effects modeling.
Results: Between June 2016 and July 2017, 128 YLWH enrolled, of whom 105 were randomized and 93 (55 in SYV) followed-up at 6 months and were included in this analysis. Mean age of participants was 18.1 years with 51% female; 84% were infected perinatally. Exploratory analyses of effectiveness outcomes demonstrated change in mental health symptoms and internal stigma improved in both arms baseline to 6-months, but were not significantly different between arms. Self-reported adherence improved by 7.3 percentage points (95% CI: 2.2, 12.3) more in SYV compared to SOC, standardized levels of ART concentration increased by 0.17 ng/ml (95% CI: -0.52, 0.85) more in SYV compared to SOC. Virologic suppression (HIV RNA <400 copies/mL) at baseline was 65% in both arms, but increased to 75% in the SYV arm and stayed the same in the SOC arm (RR 1.13; 95% CI: 0.94, 1.36).
Conclusion: YLWH worldwide are an important population, but often have poor HIV outcomes due to stigma and mental health difficulties. Very few
837 LONGITUDINAL STUDY OF NEUROCOGNITIVE DISORDERS AND BRAIN STRUCTURE IN ADOLESCENT HIV
Jackie Hoare 1, Landon Myer 1, Sarah Heaney 1, Jean-Paul Fouche 1, Nicole Phillips 1, Heathet Zar 1, Dan Stein 1
University of Cape Town, Cape Town, South Africa

Background: Neurocognitive disorders (NCD) despite ART are well known in perinatally-infected HIV+ adolescents (PHIV) but there are few data on longitudinal changes in NCD and brain structure in PHIV over time.

Methods: Within this sub-study of the Cape Town Adolescent Antiretroviral Cohort, PHIV on ART >6m completed baseline and 3-year follow-up assessments including a comprehensive neurocognitive battery assessing function in 10 domains. We applied the youth HIV-associated NCD diagnostic criteria to classify each as having either a major NCD, a minor NCD, or no impairment. Diffusion tensor imaging and structural brain magnetic resonance imaging was done to determine fractional anisotropy (FA), mean diffusivity (MD), grey and white matter volumes, cortical thickness and cortical surface area. In analysis we examined changes over the 3-year period in NCD and neurostructural measures in PHIV compared to age- and sex-matched HIV- controls.

Results: Overall 122 PHIV ages 9-12 years (mean CD4 cell count 953 cells/µL and 85.3% VL<50 copies/mL) and 37 age-matched HIV- controls completed baseline and 3-year follow-up assessments, 48% PHIV had a NCD at baseline and 60% at follow-up: NCD diagnosis was stable over time in 60 (49%) of participants, 22 (18%) improved NCD status and 40 (33%) deteriorated. At baseline, PHIV with a major NCD showed the highest whole brain MD (p=0.007); at follow-up whole brain grey (p=0.004) and white matter volumes (p=0.032) were lowest in PHIV, with a major NCD showed the highest whole brain MD (p=0.02). Higher MD is suggestive of inflammation and myelin loss. In significant regional brain changes were observed at follow-up compared to baseline in PHIV vs controls. Structural changes over time were observed mainly in cortical surface area of the bilateral orbitofrontal, anterior cingulate, medial orbitofrontal, middle frontal, superior temporal, transverse temporal gyri and insula (all p<0.05). White matter microstructural changes over time were observed in the internal capsule, cerebral peduncle and the cingulum (all p<0.05).

Conclusion: NCD and brain structural alterations in PHIV increased over the 3 years of follow-up compared to HIV- controls. Studying the participants who improved vs deteriorated over time may provide insight into future interventions for NCD in PHIV.

838 BRAIN DEVELOPMENT IN TREATED PERINATAL HIV: A LONGITUDINAL NEUROIMAGING STUDY
Malon Van den Hof 1, Pien Jellema 1, Anne Marleen Ter Haar 1, Henriëtte J. Scherpbier 1, Anouk Schrantee 2, Antonia Kaiser 2, Matthias W. Caan 2, Peter Reiss 3, Ferdinand Wit 1, Henk-Jan M. Mutsaerts 2, Dasja Pajkrt 4
1Emma Children’s Hospital/Academic Medical Center, Amsterdam, Netherlands, 2Academic Medical Center, Amsterdam, Netherlands, 3Stichting HIV Monitoring, Amsterdam, Netherlands, 4Emma Children’s Hospital/Academic Medical Center, Amsterdam, Netherlands

Background: Cross-sectional studies, including our NOVICE study (Neurological Visual and Cognitive performance in treated perinatally HIV-infected [PHIV] children compared to age-, sex-, ethnicity- and socioeconomic status [SES]-matched HIV-uninfected controls), have reported lower white matter (WM) and grey matter (GM) volumes, higher WM hyperintensity (WMH) volume and poorer WM integrity measures in treated PHIV children. It is however unknown whether these differences originated before treatment initiation, or may be progressive over time. This longitudinal study compares the rates of change over time.

Methods: We approached all NOVICE participants, to repeat 3T magnetic resonance imaging (MRI) at the Amsterdam University Medical Centers, the Netherlands, after a mean of 4.6±0.3 years. We repeated GM and WM volume, WMH volume and WM integrity measures (total fractional anisotropy [FA], mean diffusivity [MD], radial diffusivity [RD], and axial diffusivity [AD],) obtained by T1-weighted, FLAIR and DTI MRI, respectively. We compared rates of change between groups using multivariable linear mixed effects models, adjusted for sex and age at first MRI, and we investigated disease- and treatment related factors as determinants of poorer outcomes.

Results: 20 out of 31(65%) PHIV and 20 out of 37(54%) controls completed a second MRI examination. Those who gave consent for follow-up MRI were not statistically different compared to those who did not give consent in volumetric outcomes and FA at first MRI (all p-values>0.05). Those who completed both MRI examinations had a mean age of 13.0±2.3 years and 17.6±3.3 years at first and second MRI, respectively. PHIV and controls were not statistically different in age, sex, ethnicity, and SES (all p-values>0.05). At p<0.01, WMH volume increased significantly more in PHIV participants (group*time 0.10±0.01, 95%CI 0.02–0.18, p=0.017) compared to controls (figure 1), which was not associated with disease- and treatment related factors (all p-values>0.05). GM volume decreased significantly less in PHIV (group*time 0.01±0.01, 95%CI -0.01–0.020, p=0.078). We found no statistically different changes over time in WM volume (group*time 0.001, 95%CI -0.006–0.008, p=0.795), nor in WM integrity measures (group*time p-values>0.356).

Conclusion: Results indicate progressive cerebral differences as WMH progress over time in long-term cART-treated PHIV adolescents. Future analyses should further investigate determinants of WMH progression.
for treatment and prophylaxis within neonatal populations. The safety and pharmacokinetics (PK) of BIC have previously been studied in children older than 6 years and adolescents but not neonates. The aim of this study was to use PBPK modelling to inform identification of an age-appropriate dose within this population.

Methods: A whole-body PBPK model was constructed in Simbiology (MATLAB 2018b) using neonatal physiological and anatomical descriptors. Neonatal PK simulations also utilised published experimental in vitro data for BIC. The ontogenies of key metabolic enzymes such as CYP3A4 and UGT1A1 were refined and validated using observed neonatal clinical data for raltegravir (RAL) and midazolam (MDZ). Published adult PK data for BIC were used to partially validate the simulated parameters, where the model was assumed to be qualified if simulated values were within 0.5 - 1.5-fold of the mean reported values as per modelling convention.

Results: All models were acceptably qualified with RAL, MDZ and BIC exhibiting absolute average fold errors of 1.05, 1.31 and 1.12, respectively. Several multi-dose regimens for orally administered BIC were simulated in 100 healthy neonates with the aim of achieving equivalent plasma concentrations to therapeutic exposures observed in adults (C_{\text{avg}}: 2.61 mg/L and AUC24: 102 mg.h/L). These regimens and their resulting PK parameters are summarised in Table 1. Regimens 2 & 3 resulted in exposures comparable to that observed in adults, and involved starting neonates on a 5 mg once daily dose, increasing to 7.5 – 10 mg once daily after day 1.

Conclusion: Dose adjustments are predicted between adult and paediatric patients. Drug approval in infants and neonates is often hindered by a lack of suitable formulations and difficulty in examining drug exposure. Several potential regimens have been identified, which are worthy of empirical validation within this infant population with HIV.

Table 1. Summary of pharmacokinetic parameters of oral adminstered bictegravir (BIC) in neonates

<table>
<thead>
<tr>
<th>Regimen</th>
<th>C_{\text{avg}} [mg/L]</th>
<th>AUC_{24} [mg.h/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen 1</td>
<td>2.61</td>
<td>102</td>
</tr>
<tr>
<td>Regimen 2</td>
<td>3.55</td>
<td>140</td>
</tr>
<tr>
<td>Regimen 3</td>
<td>4.76</td>
<td>200</td>
</tr>
</tbody>
</table>

840 SAFETY, PK, AND EFFICACY OF LOW DOSE B/F/TAF IN CHILDREN ≥2 YEARS OLD LIVING WITH HIV

Carina Rodriguez1, Kulkanya Chokephaibulkit1, Afaaf Liberty2, Renate Strehla3, Rianna Van Zyl4, Pope Kosalaraks4, Coleen K. Cunningham5, Eric J. McGroth5, Natella Rahamanina6, Heather Maxwell6, Danielle Potter6, Sophia R. Majeed6, Shaolan S. Xiang7, Deqing Xiao8, Michael Keeney1, Joanna Koziara1, PJ Costales1, Jenna Scott1, Hiba Graham1, Cheryl Pikora1, Anita Mathias1, Gilead Sciences, Inc, Foster City, CA, USA

Background: Bictegravir (BIC)/emtricitabine (FTC)/tenofovir alafenamide (B/F/TAF) is FDA-approved for the treatment of HIV in adults and pediatrics ≥25 kg. A low-dose monolayer B/F/TAF tablet (LDT) has been developed; the relative bioavailability (rBA) and food-effect of the LDT were evaluated in a Phase 1 study. The PK of the LDT was then confirmed in children with HIV 14–<25 kg.

Methods: Adult healthy volunteers (HV) received single doses of adult-strength B/F/TAF 50/200/25 mg fasted, or B/F/TAF 30/120/15 mg fasted or fed (high-fat meal) in a randomized, 3-period, crossover study. PK parameters of BIC, FTC and TAF were compared between test and reference treatments using geometric least-squares mean (GLSM) ratios and 90% confidence intervals (CI) with a stringent 70-143% equivalence boundary. The PK of the B/F/TAF LDT was then assessed in virologically suppressed children ≥2 yrs, 14–<25 kg (N=12) at W2. BIC exposures in children were compared to B/F/TAF-treated adults using clinically relevant boundaries of 50–200%. The PK of FTC, TAF and TAF-metabolite tenofovir (TFV) were compared descriptively to historical data. Safety was assessed throughout the studies.

Results: SV454 HVS completed the Ph1 study. GLSM ratios and 90% CIs for BIC, FTC, and TAF PK parameter comparisons between LDT and adult tablet were within 70–143% (Table). Compared to fasted, high-fat meal did not alter BIC or FTC PK; TAF AUCinf increased 42%, C_{\text{max}} decreased 44%, 15% (adult tab fasted, or LDT fed) and 19% (LDT fasted) of HVs had an AE (all Grade 1). There were no discontinuations due to AEs. GLSM ratios and 90% CIs for BIC AUC_{\text{tau}} and C_{\text{max}} in children vs adults were within 50–200%. Mean BIC C_{\text{max}} was 32% lower (Table). Exposures of FTC (mean AUC_{\text{tau}}=14,900 h*ng/mL), mean AUC_{\text{tau}}=305 h*ng/mL and TFV (mean AUC_{\text{tau}}=339 h*ng/mL) were within the range of historical data. 75% had an AE (all Grade 1/2).

Conclusion: B/F/TAF was well tolerated in HVs and children with HIV. The B/F/TAF LDT provided exposures equivalent to adult tablet with no clinically relevant food-effect. Like the adult tablet, LDT can be taken without regard to food. In children 14–<25 kg with HIV taking the LDT, no clinically meaningful differences in PK were identified compared to adults; mean BIC C_{\text{max}} was 12-fold above paEC95, supporting its continued evaluation in pediatric trials.

841 B/F/TAF LOW-DOSE TABLET RELATIVE BIOAVAILABILITY IN HVs AND PK IN CHILDREN WITH HIV

Sophia R. Majeed1, Polina German1, Steve K. West1, Shaolan S. Xiang1, Deqing Xiao1, Michael Keeney1, Joanna Koziara1, PJ Costales1, Jenna Scott1, Hiba Graham1, Cheryl Pikora1, Anita Mathias1, Gilead Sciences, Inc, Foster City, CA, USA

Background: Bictegravir (BIC)/emtricitabine (FTC)/tenofovir alafenamide (B/F/TAF) is approved for the treatment of HIV in adults and pediatrics ≥25 kg. A low-dose monolayer B/F/TAF tablet (LDT) has been developed; the relative bioavailability (rBA) and food-effect of the LDT were evaluated in a Phase 1 study. The PK of the LDT was then confirmed in children with HIV 14–<25 kg.

Methods: Adult healthy volunteers (HV) received single doses of adult-strength B/F/TAF 50/200/25 mg fasted, or B/F/TAF 30/120/15 mg fasted or fed (high-fat meal) in a randomized, 3-period, crossover study. PK parameters of BIC, FTC and TAF were compared between test and reference treatments using geometric least-squares mean (GLSM) ratios and 90% confidence intervals (CI) with a stringent 70-143% equivalence boundary. The PK of the B/F/TAF LDT was then assessed in virologically suppressed children ≥2 yrs, 14–<25 kg (N=12) at W2. BIC exposures in children were compared to B/F/TAF-treated adults using clinically relevant boundaries of 50–200%. The PK of FTC, TAF and TAF-metabolite tenofovir (TFV) were compared descriptively to historical data. Safety was assessed throughout the studies.

Results: SV454 HVS completed the Ph1 study. GLSM ratios and 90% CIs for BIC, FTC, and TAF PK parameter comparisons between LDT and adult tablet were within 70–143% (Table). Compared to fasted, high-fat meal did not alter BIC or FTC PK; TAF AUCinf increased 42%, C_{\text{max}} decreased 44%, 15% (adult tab fasted, or LDT fed) and 19% (LDT fasted) of HVs had an AE (all Grade 1). There were no discontinuations due to AEs. GLSM ratios and 90% CIs for BIC AUC_{\text{tau}} and C_{\text{max}} in children vs adults were within 50–200%. Mean BIC C_{\text{max}} was 32% lower (Table). Exposures of FTC (mean AUC_{\text{tau}}=14,900 h*ng/mL), mean AUC_{\text{tau}}=305 h*ng/mL and TFV (mean AUC_{\text{tau}}=339 h*ng/mL) were within the range of historical data. 75% had an AE (all Grade 1/2).

Conclusion: B/F/TAF was well tolerated in HVs and children with HIV. The B/F/TAF LDT provided exposures equivalent to adult tablet with no clinically relevant food-effect. Like the adult tablet, LDT can be taken without regard to food. In children 14–<25 kg with HIV taking the LDT, no clinically meaningful differences in PK were identified compared to adults; mean BIC C_{\text{max}} was 12-fold above paEC95, supporting its continued evaluation in pediatric trials.
842 MARAVIROC SAFETY & PHARMACOKINETICS IN HIV-EXPOSED NEONATES
Julia C. Rosebush1, Brooke Best1, Ellen G. Chadwick1, Jack Moye1, Elizabeth Smith1, Kevin Butler2, Sarah Bradford3, Kyle Whitsain4, Sisimanya R. Mathiba4, Sherika Hanley5, Mariam Aziz6, Katy Hayward7, Mark Mirochnick8, Pearl Samson1, for the IMPAACT 2007 Study Team
1University of Chicago, Chicago, IL, USA, 2University of Texas Medical School, Houston, TX, USA, 3Stellenbosch University, Cape Town, South Africa, 4Medical University of South Carolina, Charleston, SC, USA, 5National Institute of Child Health and Human Development, Bethesda, MD, USA, 6National Institute of Child Health and Human Development, Bethesda, MD, USA, 7FHI 360, Durham, NC, USA, 8Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, 9University of Cape Town, Cape Town, South Africa, 10Boston University, Boston, MA, USA, 11University of California San Diego, La Jolla, CA, USA, 12ViiV Healthcare, Research Triangle Park, NC, USA, 13Boston University, Boston, MA, USA

Background: Lack of adequate safety and pharmacokinetic (PK) data limits antiretroviral (ARV) prophylaxis and treatment options in HIV-exposed neonates. Maraviroc (MVC), a CCR5 receptor antagonist approved for use in adults, has potential for use in prophylaxis and treatment of HIV-exposed or infected neonates.

Methods: IMPAACT 2007 is an ongoing Phase I, multi-center, open-label study of MVC safety and PK in HIV-exposed neonates on standard ARV prophylaxis. Study design includes two sequential dosing cohorts starting MVC by day 3 of life. Cohort 1 infants received two single 8mg/kg MVC doses one week apart with intensive PK sampling after the initial dose. Based on PK data from Cohort 1, Cohort 2 infants receive 8 mg/kg MVC twice daily through 6 weeks of life with intensive PK sampling at Weeks 1 and 4. Due to a known PK interaction between MVC and efavirenz (EFV) in adults, cohorts were stratified by exposure to maternal EFV. PK samples were analyzed for MVC concentration by validated high-performance liquid chromatography. PK parameters were estimated using standard non-compartmental methods. MVC exposure target is Cavg ≥ 75ng/ml.

Results: Forty-seven MVC-naive, HIV-exposed neonates have enrolled; 15 in Cohort 1, 32 in Cohort 2 (median gestational age 39 weeks, 51% male) from the USA(20), Thailand(3), Kenya(2), and South Africa(22). PK data are available for 13 Cohort 1 infants and 21 Cohort 2 infants; data from 4 additional infants pending. All Cohort 1 infants (n=13) met the PK target after the initial dose. Median exposure for Cohort 2 infants (n=22) exceeded the PK target but variability in exposure was high, with 17-33% of infants below the PK target at Weeks 1 and 4, respectively (Table 1). The proportion of infants who achieved the PK target was similar between EFV-naïve and EFV-exposed infants. No Grade 3+ toxicities or early study discontinuations noted due to MVC.

Conclusion: Maraviroc appears safe when used in the first 6 weeks of life. MVC exposures met treatment PK targets in most infants receiving 8 mg/kg twice daily, but with considerable variability in exposure. Maternal EFV use appeared to have no effect on MVC exposure and there were no study discontinuations due to toxicity or intolerance. The final MVC dose recommendation will be determined accounting for patient variability.

843 ABACAVIR SAFETY AND PHARMACOKINETICS IN NORMAL AND LOW BIRTH WEIGHT INFANTS WITH HIV
Tim R. Cressey1, Adrie Bekker2, Mae Cababasay3, Jiajia Wang3, Firdose Nakwa4, Elizabeth Smith5, Jack Moye5, Ayev Viulor5, Mark Cotton5, Bobbie Graham5, Lubbe Wiesen5, Helena Rabie5, Mark Mirochnick6, Edmund V. Capparelli6, for the IMPAACT P1106 Team
1Chiang Mai University, Chiang Mai, Thailand, 2Stellenbosch University, Cape Town, South Africa, 3Harvard T.H. Chan School of Public Health, Boston, MA, USA, 4University of the Witwatersrand, Johannesburg, South Africa, 5NIH, Rockville, MD, USA, 6NIH, Bethesda, MD, USA, 7Perinatal HIV Research Unit, Soweto, South Africa, 8Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, 9University of Cape Town, Cape Town, South Africa, 10Boston University, Boston, MA, USA, 11University of California San Diego, La Jolla, CA, USA

Background: Abacavir (ABC) is licensed for infants >3 months of age while WHO recommends use in HIV-infected children 2-4 weeks of age and ≥3 kg. ABC is metabolized in the liver via UDPGT and ADH enzymes, and information describing ABC disposition during the first few months of life is lacking. We describe ABC pharmacokinetic (PK) and safety data in HIV-infected normal and low birth weight (LBW) infants initiating ABC within the first 3 months of life.

Methods: IMPAACT P1106 is an opportunistic, multi-arm study of PK and safety in LBW infants conducted in South Africa on antiretroviral and antituberculosis medicines. Arm 5 included HIV-infected infants receiving ABC, lamivudine and lopinavir/ritonavir. Plasma samples for ABC PK assessment were collected pre-dose (CO), 1.5- and 4-hours post-dose at study weeks 2, 10, and 24, with CO samples at weeks 6 and 16. ABC concentrations were measured by LC-MS/MS and ABC PK parameters estimated using a population approach. Adverse events (AE) were evaluated from entry to week 24.

Results: Twenty-five infants (18 LBW) were included in the analysis. Median entry age was 44 days (range 11 to 78 days). Twelve (48%) infants were male and 22 (88%) black African. Median ABC dose was 10 (6-13) mg/kg BID and ABC concentrations were available for 24 (95%) observations in infants with median (range) birth weight 2190 g (1360-3260) and median gestational age 36 weeks (32-37). ABC plasma concentrations were described by a 1-compartment model. Infant body weight (BW) and post-natal age (PNA) influenced ABC PK parameters. ABC oral clearance (CL/F) increased by 2% per PNA week. Infant characteristics and ABC PK parameters estimated using a population approach. Adverse events (AE) were evaluated from entry to week 24.

Conclusion: Abacavir was well tolerated in LBW infants. ABC exposures were relatively high compared to older infants during the first 3 months of life but decreased rapidly as infants matured.
ABACAVIR DOSING, EFFECTIVENESS, AND SAFETY IN YOUNG INFANTS LIVING WITH HIV IN EUROPE

Siobhan Crichton1, Intra J. Collins1, Anna Turková2, Luminita Ene3, Luisa Galli3, Magdalena Marczyńska4, Maria Luisa Navarro1, Lars Naver5, Antoni Noguerà-Julian6, Yulia Plotnikova7, Henriëtte J. Scherpbier8, Alla Volokha9, Evgeny Vorošin10, Ali Judd1, for the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Background: The World Health Organization recommends abacavir (ABC) as the preferred/alternative backbone for 1st line regimens in children with HIV from age 28 days. There are limited data available on safety and tolerability of ABC in young infants aged <3 months.

Methods: All children in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) who initiated ABC aged <3 months between 2000-2016 were included. We describe infant and regimen characteristics at the start of ABC (including drug combinations and dosing) and outcomes up to 12 months after first use of ABC. Outcomes include drug discontinuations (defined as interruption of treatment for >30 days), clinical adverse events (AE, reported from start of ABC up to 30 days after discontinuation) and viral suppression <400c/ml (VS) at 6 and 12 months of treatment for children who remained on ABC.

Results: Of 498 children in EPPICC who received antiretroviral therapy (ART) whilst aged <3 months, 139/28% (received an ABC-containing regimen (n=20 aged <28 days) and were followed for median 4.6 (IQR 1.5, 9.7) years. Median year of birth was 2010/2006,2012, age at HIV diagnosis was 39/11,62 days and 84/60% were female. 53/38% were from UK and Ireland, 23/17% Ukraine, 19/14% Spain, 14/10% Russia, 12/9% Belgium and 18/13% elsewhere in Europe. 63/45% received post-exposure prophylaxis (PEP) prior to ABC-based treatment (4 PEP regimens included ABC, with the ABC continuing following HIV diagnosis). 54/39% were taking ABC with lamivudine and lopinavir/ritonavir and for 44 infants with ABC dosing/weight data available, 30/68% started on an 8mg/kg twice daily (BD) dose (Table). Overall 66/92/70% and 59/77/77% on ABC-containing regimens had VS after 6 and 12 months, respectively. During the first 12 months on ABC, AEs overall 66/92 were reported in 8 infants with 4 events leading to discontinuation of ABC, all occurring within the first 7 days of treatment (Table). By 12 months after start of ABC, cumulative incidence of discontinuation of ABC due to a safety concern was 3.6% (95% CI 1.4, 7.8%). A further 11 infants discontinued ABC for other reasons (5 of 11 later restarted ABC) and the cumulative incidence of any discontinuation by 12 months was 11.8% (7.3, 18.9%). There were no deaths reported during follow-up.

Conclusion: ABC is safe and well tolerated in infants, with rare discontinuations for safety concerns, supporting WHO treatment recommendation. More data on ABC use are required in neonates.

ABACAVIR SAFETY AND EFFICACY IN YOUNG INFANTS IN SOUTH AFRICAN OBSERVATIONAL COHORTS

Reenee De Waal1, Helena Rabie1, Karl Technau1, Brian Eley2, Nosisa Simaboomo3, Mark Cotton4, Andrew Boull2, Robin Wood1, Frank Tanser5, Geoffrey Fatti6, Matthias Egger7, Mary-Ann Davies1, 1University of Cape Town, Cape Town, South Africa, 2Stellenbosch University, Tygerberg, South Africa, 3University of the Witwatersrand, Johannesburg, South Africa, 4Desmond Tutu HIV Foundation, Cape Town, South Africa, 5Africa Health Research Institute, Mntubatuba, South Africa, 6Khehi Impilo, Cape Town, South Africa, 7Institute of Social and Preventive Medicine, Bern, Switzerland

Background: While HIV treatment guidelines recommend abacavir as part of the preferred first line antiretroviral treatment (ART) regimen in children aged >28 days. However, there is no approved dose under 3 months of age, and with increasing access to early infant HIV diagnosis, more data are necessary to guide dosing recommendations in neonates. We describe the safety and effectiveness of abacavir in young infants in 9 South African cohorts participating in the leDEA collaboration.

Methods: We included all infants who initiated ART (>3 antiretroviral drugs from ≥2 classes) before 3 months of age, between 2006–2017. In those who received abacavir we described characteristics at abacavir initiation; the proportion who discontinued abacavir; and viral load suppression at 12 months. We compared infants who started abacavir aged <28 days with older infants, and those who weighed <3 kg in terms of abacavir discontinuations and viral load suppression, using Chi-squared or Fisher’s exact tests.

Results: Of 1847 infants who started ART aged <3 months, 931 (50%) received abacavir: 96 were aged <28 days. At abacavir start, median (interquartile range, IQR) age was 67 days (48 to 80), CD4 percentage was 26.9 (19.0 to 37.0), viral load was 1 000 000 copies/ml (146 036 to 3 792 175), and weight was 4.2 kg (3.2 to 5.0). ART regimens included lamivudine and ritonavir-boosted lopinavir in 858 infants (92%), lamivudine and nevirapine in 9 (1%) and other antiretrovirals in 64 (7%). In those with ≥1 month’s follow-up after abacavir initiation, 61789 (8%) infants discontinued abacavir permanently, at a median of 13.3 months (IQR 6.4 to 26.8). There were no significant differences in the proportion of discontinuations by age or weight category (p=0.6 and 0.9 respectively, Table 1). Reasons for discontinuation were documented in 20 infants (33%); non-compliance or transfer out in 11, treatment failure in 6, and hypersensitivity in 1. Viral load was measured at 12 months in 353/527 infants with ≥12 months’ follow up. The proportion of infants with viral load <400 copies/ml was 15/27 (56%) and 188/326 (56%) in those who started abacavir aged >28 days and 28 days to 3 months respectively (p=0.8), and 17/24 (71%) and 67/11 (60%) in those who weighed <3 kg and ≥3 kg respectively (p=0.4).

Conclusion: Half of the infants who started ART before three months of age in our cohort received abacavir. Our data suggest that abacavir may be used safely in infants <28 days old or who weigh <3 kg.

Table 1: Infant characteristics and adverse events and drug discontinuations in infants who initiated ABC aged <3 months

<table>
<thead>
<tr>
<th>Age (months) at ABC start</th>
<th>&lt;3</th>
<th>3-5</th>
<th>6-9</th>
<th>10-12</th>
<th>Missing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight at abc start (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>22</td>
<td>24</td>
<td>289</td>
</tr>
<tr>
<td>Discontinuation (%)</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Age ≥12 months at ABC start</td>
<td>8</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Discontinuation (%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Age 28 days to 3 months at ABC start</td>
<td>29</td>
<td>55</td>
<td>42</td>
<td>23</td>
<td>404</td>
<td>113</td>
</tr>
<tr>
<td>Discontinuation (%)</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>
846 PHARMACOKINETICS OF RALTEGRAVIR IN HIV/TB COINFECTED INFANTS AND YOUNG CHILDREN

Paul Krogstad1, Pearl Samson2, Edward F. Acosta3, Jack Moye4, Ellen Townley5, Jeremy Altmeyer6, Sarah Bradford7, Emily Brown8, Bobbie Graham9, Laura Hovind10, Hediy Teppler11, Sissiyana R. Mathiba12, Mark Cotton13, Jana L. Winckler14, Tammy Meyers15, for the IMPAACT P1101 Study Team

1University of California Los Angeles, Los Angeles, CA, USA, 2Harvard University, Cambridge, MA, USA, 3University of Alabama at Birmingham, Birmingham, AL, USA, 4National Institute of Child Health and Human Development, Bethesda, MD, USA, 5NIADD, Rockville, MD, USA, 6FHI 360, Durham, NC, USA, 7Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, 8Merck & Co, Inc, Paoli Alto, CA, USA, 9Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 10Stellenbosch University, Cape Town, South Africa, 11University of the Witwatersrand, Johannesburg, South Africa

Background: Current antiretroviral (ARV) options for HIV/TB co-infected children are limited. Rifampin (RIF) induces UDP-glucuronosyltransferase activity, increasing clearance of raltegravir (RAL). We sought to establish the optimal and safe dose of RAL when administered with RIF in HIV/TB co-infected infants and children.

Methods: P1101 is a dose finding study of RAL in HIV-infected children at four South African sites receiving RIF-containing TB therapy for at least 1 week, with three age cohorts spanning 4 weeks to <12 years of age, aiming to enroll 12 evaluable participants for PK and safety in each. At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose) and two nucleoside reverse transcriptase inhibitors. Intensive RAL PK sampling is done 5-8 days after initiation of ARV therapy and then a fourth ARV is added. RAL is stopped at the end of TB treatment with follow-up for another 3 months. PK targets are a geometric mean (GM) AUC0-12h of 14-45 μM*h and GM C12h ≥75 nM. Here we report the results from Cohort 3 (4 weeks to <2 years) using RAL chewable tablets as a dispersible tablet; Cohorts 1 and 2 (ages 2 years to <12 years) were previously reported.

Results: Of 13 participants, 8 were male with a median age 12.3 mo and baseline log10 HIV (RNA cpy/mL) of 5.13 (5.01-5.60), CD4 count/μL of 1513 from Cohort 3 (4 wks to <2 yrs) using RAL chewable tablets as a dispersible reverse transcriptase inhibitors. Intensive RAL PK sampling is done 5-8 days after ARV initiation and then a fourth ARV is added. RAL is stopped at the end of TB treatment with follow-up for another 3 months. PK targets are a geometric mean (GM) AUC0-12h of 14-45 μM*h and GM C12h ≥75 nM. We aimed to include 12 evaluable participants for PK and safety in each. At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose) and two nucleoside reverse transcriptase inhibitors. Intensive RAL PK sampling is done 5-8 days after ARV initiation and then a fourth ARV is added. RAL is stopped at the end of TB treatment with follow-up for another 3 months. PK targets are a geometric mean (GM) AUC0-12h of 14-45 μM*h and GM C12h ≥75 nM. We aimed to include 12 evaluable participants for PK and safety in each. At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose). At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose). At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose). At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose).

At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose). At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose). At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose).

Conclusion: A 12 mg/kg dose twice daily of RAL chewable tablets appears to safely achieve PK targets in HIV/TB co-infected children 4 weeks to <2 years receiving rifampin, with high rates of virologic suppression by Week 8.

847 ADEQUATE DOLUTEGRAVIR EXPOSURE EXPOSED BID WITH RIFAMPICIN IN CHILDREN 6 TO <18 YEARS

Hylke Waalewijn1, Hilda Mujuru2, Pauline Amuge3, Mark Cotton4, Pauline Boller5, Man Chun6, Shababin Ali7, Ebrahim Varani8, Shafiq Makumbi9, Angela Colbers10, Diana Gibb11, Deborah Ford12, David M. Burger13, Anna Turkova14, for the IMPAACT P1101 Study Team

1Radboud University Medical Center, Nijmegen, Netherlands, 2University of Zimbabwe, Harare, Zimbabwe, 3Baylors College of Medicine Children's Foundation, Kampala, Uganda, 4Stellenbosch University, Cape Town, South Africa, 5MRC Clinical Trials Unit at UCL, London, UK, 6University of the Witwatersrand, Johannesburg, South Africa, 7Alto, CA, USA, 8National Institute of Child Health and Human Development, Bethesda, MD, USA, 9University of York, York, UK, 10Rakai Health Sciences Program, Kalisizo, Uganda, 11Biomedical Research and Training Institute, Harare, Zimbabwe, 12Kenya Medical Research Institute, Kisumu, Kenya, 13Africa Health Research Institute, Mtwatate, South Africa, 14National Institute of Medical Research, Mwanza, Tanzania, United Republic of Tanzania

Background: Adults with HIV/TB co-infection on dolutegravir (DTG)-based antiretroviral therapy (ART) can overcome the induction effect of rifampicin (RIF) by doubling the DTG dose (50mg twice daily) versus once (QD) daily. We undertook a pharmacokinetic (PK) study to find out the possibility of doubling the DTG dose (50mg twice daily) versus once (QD) daily. We undertook a pharmacokinetic (PK) study to find out the possibility of doubling the DTG dose (50mg twice daily) versus once (QD) daily. We undertook a pharmacokinetic (PK) study to find out the possibility of doubling the DTG dose (50mg twice daily) versus once (QD) daily. We undertook a pharmacokinetic (PK) study to find out the possibility of doubling the DTG dose (50mg twice daily) versus once (QD) daily. We undertook a pharmacokinetic (PK) study to find out the possibility of doubling the DTG dose (50mg twice daily) versus once (QD) daily.

Methods: Children aged 6-<18 years receiving DTG BID+RIF were eligible; we aimed to include 6 children aged 6-<12 years and 6 children 12-<18 years. A 12h PK curve was constructed for children on DTG BID in the last month of RIF treatment and subsequently, a 24h PK curve on DTG QD ≥4 weeks after stopping Rif. Geometric mean ratios (GMRs) were estimated comparing DTG PK parameters between the 2 periods and individual Ctrough levels below EC90 (0.32 mg/L) were summarised. All children who received DTG BID+RIF aged ≥6 years were followed for serious adverse events (SAEs), grade 3/4 clinical/laboratory adverse events (AEs) and any AEs resulting in ART modification from start of DTG BID to 30 days after return to DTG QD.

Results: Of 30 eligible children, 17 were enrolled in the PK substudy; 13/17 participants undergoing PK had ≥2 evaluable PK curves. Of 12/13 were black African, median (range) age 11.3 (6.8-16.1) years and 51.3 (19.8-48.5) kg. 12 PK curves were evaluable for DTG BID+RIF (5 on 25mg BID and 7 on 50mg BID) and 11 for DTG QD (5 on 25mg QD and 6 on 50mg QD). GMRs (90% CI) for DTG BID versus DTG QD (reference) for Ctrough, AUC0-24h and GM C12h were 1.00 (0.9-2.33), 1.20 (0.9-1.59), and 0.98 (0.79-1.2), respectively. Oral clearance of DTG with RIF was increased 1.7-fold, with 41% reduction in elimination half-life. Findings were similar in children above and below 12 years old. AUC0-24h GMRs in children ≥20kg receiving WHO 2019-recommended DTG 50mg dose was 1.00 (0.61-1.62) and 1.47 (0.99-2.19) for children on 25mg dose. One child on DTG 25mg QD without RIF had Ctrough below EC90 ≤12 yrs were followed for serious adverse events (SAEs); grade 3/4 clinical/laboratory adverse events (AEs) and any AEs resulting in ART modification from start of DTG BID to 30 days after reversion to DTG QD.

Conclusion: Twice daily dolutegravir dosing was safe and sufficient to overcome rifampicin enzyme-inducing effect in HIV co-infected children aged 6-<18 years, including in children ≥20kg receiving new WHO doses (DTG 50mg).

848 RISK FACTORS FOR NEW HIV INFECTIONS IN THE GENERAL POPULATION IN SUB-SAHARAN AFRICA

Emma Slaymaker1, Kathryn A. Risher2, Ramadhani Abdui3, Milly Marston4, Keith Tomlin5, Robert Newton6, Anthony Nydahano7, Estelle McLean8, Tawanda Dadirai9, Daniel Kwarda10, Kathy Baisley11, Coleman Kishnamave12, for the ALPHA Network

1London School of Hygiene & Tropical Medicine, London, UK, 2Ifakara Health Institute, Dar es Salaam, Tanzania, United Republic of, 3University of York, York, UK, 4Rakai Health Sciences Program, Kalisizo, Uganda, 5Biomedical Research and Training Institute, Harare, Zimbabwe, 6Kenya Medical Research Institute, Kisumu, Kenya, 7Africa Health Research Institute, Mtwatate, South Africa, 8National Institute of Medical Research, Mwanza, Tanzania, United Republic of Tanzania

Background: Previous work identified risk factors for new HIV infections in sub-Saharan African populations but patterns of association are not consistent across studies. Different risk factor definitions and low power may explain some inconsistencies. Statistical power has not previously been estimated in these risk factor analyses. We harmonised population-based longitudinal data from general population studies in 6 sub-Saharan African countries, partners in the Network for Analysing Longitudinal Population-based HIV/AIDS data on Africa, to assess risk factors for new HIV infections. Potential risk factors were identified from the literature and a modified version of the proximate determinants framework.

Methods: Individual level data covering 2005 to the end of follow up (2012-2016) were obtained for each study. Data were arranged for survival analysis with first HIV negative test as the start of observation and HIV seroconversion as the failure event. Individuals were censored at death, out migration and end
of follow up. 70 imputations of seroconversion date were used to overcome interval censoring.

Time-varying risk factors were: residence, residential mobility, time since first sex, marital status, numbers of partners in lifetime and last year, acquisition of new partners, types and combinations of partnerships, male circumcision, condom use and age gaps between partners. Piecewise exponential regression models were fitted separately by study for men and women aged 15-24 and 25-49. Crude hazard ratios were compared between studies. We estimated the statistical power to detect each association. Study- and sex- and age-specific multivariate models were fitted and consistency of risk factors evaluated.

Where warranted, the pooled effects of risk factors are estimated.

Results: 99097 people contributed 351457 person years (203266 from women). There were 5274 seroconversions (3711 among women). Figure 1 shows the crude hazard ratio for HIV infection by selected risk factors. Most consistent findings across studies were that new & multiple partners and being formerly married increased risk whilst being circumcised decreased risk. Condom use was protective among people who had higher risk partnerships.

Conclusion: Effect size and strength of evidence varied across studies and age groups and for each risk factor. Whilst lack of statistical power explains some heterogeneity there are likely to be real differences in the importance of some risk factors between populations.

850 HIV INCIDENCE AND VIRAL BURDEN AT THE COMMUNITY LEVEL IN HPTN 071 (POPART)

Timothy Skalland1, Helen Ayles2, Ethan A. Wilson3, Ayana Moore4, Nomtha Mandla5, Justin Bwalya6, Nkatya Kasese7, Rory Dunbar2, Estelle Piwowar-Manning8, Susan H. Eshleman1, Peter Bock4, Sarah Fidler9, Richard J. Hayes1, Deborah J. Donnell1

1Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 2Zambart, Lusaka, Zambia, 3HFI 360, Durham, NC, USA, 4Desmond Tutu TB Centre, Western Cape, South Africa, 5Johns Hopkins University School of Medicine, Baltimore, MD, USA, 6Imperial College London, London, UK, 7London School of Hygiene & Tropical Medicine, London, UK

Background: HPTN 071 (PopART) was a 3-arm cluster-randomized trial that evaluated use of a combination HIV prevention strategy to reduce HIV incidence. The intervention package included universal HIV testing and treatment (UTT). The trial was conducted in 21 high HIV prevalence communities in Zambia and South Africa (7 matched community triplets). The study primary outcome was HIV incidence in the period 13 to 36 months after the start of the study, measured in a Population Cohort (PC) of ~2000 randomly-selected adults per community (aged 18-44). The intervention effect was greatest in the study arm that included treatment according to national guidelines (Arm B); a lesser effect was observed in the full UTT arm (Arm A), compared to standard of care (Arm C).

Methods: For each community, HIV incidence was estimated in the primary analysis period (PC12-PC36), weighted by age and sex. HIV viral load was measured in all HIV-positive PC participants 2 years after the start of the study (PC24). Viral suppression was defined as a viral load $<400$ copies/mL. Viral burden was defined as the estimated proportion of the entire community (both HIV positive and HIV negative persons) that were not virally suppressed at PC24, weighted by age and sex. We examined associations of viral burden at PC24 with HIV incidence, and whether it mediated the PopART intervention effect on HIV incidence.

Results: HIV viral burden at PC24 was strongly associated with HIV incidence (Figure 1; p<0.001). We estimated a mean difference of -1.2% viral burden in Arm A vs C (95% CI: -2.8%, 0.4%) and a mean difference of -0.85% for Arm B vs C (95% CI: -2.5%, 0.8%). The average causal mediated effect of viral burden on HIV incidence was not significant (Arm A vs C: p=0.50; Arm B vs C: p=0.77).

Conclusions: In HPTN 071 (PopART), higher HIV incidence was associated with higher viral burden. However, the reduction in viral burden did not explain the differential reduction of HIV incidence observed in the two trial intervention arms.

<table>
<thead>
<tr>
<th>Measures of mobility at baseline &amp; year 3</th>
<th>Total population</th>
<th>Adusted HIV incidence by sex</th>
<th>p</th>
<th>95% CI</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 months lived outside community in past 12 months, baseline</td>
<td>3.2</td>
<td>0.003</td>
<td>1.55</td>
<td>1.91</td>
<td>1.41</td>
<td>0.009</td>
</tr>
<tr>
<td>24 months lived outside community</td>
<td>1.47</td>
<td>0.001</td>
<td>1.05</td>
<td>2.09</td>
<td>1.27</td>
<td>0.014</td>
</tr>
<tr>
<td>Change in residence in past 12 months</td>
<td>1.57</td>
<td>0.004</td>
<td>1.24</td>
<td>1.91</td>
<td>1.46</td>
<td>0.009</td>
</tr>
<tr>
<td>Change in residence in past 3 years</td>
<td>1.10</td>
<td>0.025</td>
<td>0.81</td>
<td>1.48</td>
<td>0.97</td>
<td>0.058</td>
</tr>
<tr>
<td>Change in residence in past 12 months &amp; years</td>
<td>2.50</td>
<td>0.002</td>
<td>1.33</td>
<td>4.58</td>
<td>2.50</td>
<td>0.002</td>
</tr>
<tr>
<td>Change in residence in past 3 years &amp; years</td>
<td>3.40</td>
<td>0.001</td>
<td>1.72</td>
<td>6.69</td>
<td>3.40</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in residence in past 12 months &amp; years, past 3 years</td>
<td>4.40</td>
<td>0.001</td>
<td>1.67</td>
<td>1.02</td>
<td>4.40</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in residence in past 12 months &amp; years, past 3 years, past 15 years</td>
<td>1.41</td>
<td>0.025</td>
<td>1.02</td>
<td>1.99</td>
<td>1.41</td>
<td>0.025</td>
</tr>
<tr>
<td>Change in residence in past 12 months &amp; years, past 3 years, past 15 years, past 3 years</td>
<td>1.78</td>
<td>0.035</td>
<td>1.32</td>
<td>2.43</td>
<td>1.78</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Note: All models were adjusted for study arm, study community, age, sex, marital status, education level, household wealth index, occupied category, and clustering (median sampling unit), and adjusted for clustering by community.

Figure 1: Crude hazard ratios for new HIV infections by study, sex and age group. Poisson regression models adjusted for study arm, community, age, sex, marital status, education level, household wealth index, occupied category, and clustering (median sampling unit), and adjusted for clustering by community.
**AGE-SPECIFIC HIV INCIDENCE PATTERNS AMONG POPULATION COHORTS IN SUB-SAHARAN AFRICA**

Kathryn A. Risher1, Georges Reniers1, Emma Slaymaker1, Alain Vandormael1, Mark Urassa1, Robert Newton1, Tom Lutalo1, Louisa Moorhouse2, Tawanda Dadiral2, Amelia C. Crampin3, Christophe Fraser3, Anne Cori3, Milly Marston3, Jeffrey Eaton4, for the ALPHA Network

1London School of Hygiene & Tropical Medicine, London, UK, 2University of KwaZulu-Natal, Durban, South Africa, 3National Institute for Medical Research, Kisesa HDSS, Mwanza, Tanzania, United Republic of, 4University of York, York, UK, 5Rakai Health Sciences Program, Kalisizo, Uganda, 6Imperial College London, London, UK, 7Biomedical Research and Training Institute, Harare, Zimbabwe, 8University of Oxford, Oxford, UK

**Background:** As the HIV epidemic in sub-Saharan Africa matures, it is unclear how patterns of HIV incidence by sex and age have changed.

**Methods:** We used a Bayesian model to jointly reconstruct age-specific HIV incidence and mortality from population-based sero-survey and HIV survival data collected among rural population HIV cohorts in Tanzania (Kisesa), Uganda (Masaka and Rakai), Malawi (Karonga), Zimbabwe (Manicaland) and South Africa (uMkhanyakude). HIV incidence hazard was flexibly modelled using penalised B-splines with knots every 5 years over age and time. The model was fit separately for each sex in each site. Modelled incidence and prevalence results are applied to national standard populations to estimate average age of infection and percentage of new infections at given ages.

**Results:** Age-specific incidence decreased over time across age groups in most studies (Figure). In the earlier years of the epidemic, almost all studies had peak incidence among 20-24 year old women and 25-29 year old men. Over time, age-specific incidence flattened in Masaka, Kisesa, Karonga and Rakai men, while in Manicaland the age-specific incidence peaks at a later age and uMkhanyakude and Rakai women maintained the same peaks. Average age at infection is higher in men than women across all studies. While relatively stable across time, average age at infection increases from 2000 to 2017 (or max year of data collection) in Kisesa (+1.8 years among men and +2.7 among women), Masaka (+1.3 men, +1.2 women), Manicaland (+2.3 men, +1.7 women), and Karonga women (+0.2), though there were decreases in Karonga men (-0.2), Rakai (-0.1 men, -0.3 women) and uMkhanyakude (-2.0 men, -2.4 women). The percentage of women’s infections occurring among 15-24 year olds, the age range targeted in major HIV prevention, is above 50% in the most recent year of data collection in Kisesa (74%, 95% CI=67-81%), Masaka (64%, 95% CI=58-70%), and Manicaland (58%, 95% CI=55-62%), and Masaka (51%, 95% CI=35-64%). In the other three sites, this proportion was: Kisesa (38%, 95% CI=26-53%), Karonga (35%, 95% CI=25-44%), and Manicaland (41%, 95% CI=33-49%).

**Conclusion:** Our evidence suggests that age-specific incidence is declining over time in these six study sites, though the magnitude and timing of this decline varied by site. Among adult women, between 35-65% of new infections occurred among adolescent girls and young women aged 15-24.

852 HIGH HIV INCIDENCE AND VOLUNTEER RETENTION IN A BANGKOK-BASED COHORT OF MSM AND TGW

Tanyaporn Wansom1, Sant Muangnoicharoen1, Sorachai Nitayaphan1, Suchai Kitsiripornchai2, Trevor A. Crowell3, Leilani Francisco1, Qun Li4, Peter Dawson5, Merlin L. Robb1, Kirsten Smith1, Elizabeth A. Heger6, Punnpee Pitsutthithum7, Robert J. O’Connell8, Sandhya Vasan9, for the RV348 Study Group

1Henry M Jackson Foundation, Bethesda, MD, USA, 2Mahidol University, Bangkok, Thailand, 3Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, 4Emmes Corporation, Rockville, MD, USA, 5United States Army Medical Materiel Agency, Frederick, MD, USA

**Background:** Men who have sex with men (MSM) and transgender women (TGW) bear a disproportionate burden of new HIV infections. We characterized HIV incidence and retention in MSM and TGW in Bangkok, Thailand, to evaluate suitability and preparedness for potential future efficacy trials of preventive HIV vaccines.

**Methods:** From April to October 2017, HIV-uninfected Thai MSM and TGW aged 18-35 years were recruited into an 18-month prospective cohort at two sites independently: Royal Thai Army (RTA) and Vaccine Trial Centre at Mahidol University (VT). Participants had been assigned male sex at birth and reported anal intercourse in the preceding six months with at least one of the following: condomless anal intercourse with a man or TGW living with HIV or of unknown HIV status; ≥3 sexual partners; exchange of sex for money or goods; or diagnosis of any sexually transmitted infection. Participants answered comprehensive behavioral questionnaires and were screened for HIV using sequential rapid tests. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) associated with HIV acquisition.

**Results:** Of 1184 screened, 87 (7.1%) were excluded due to prevalent HIV infection, and 1017 were prospectively enrolled with median age 22 years (interquartile range 20-25), including 349 (34.3%) TGW. At enrollment, syphilis was diagnosed in 39 (3.8%), hepatitis B in 15 (1.5%), and hepatitis C in 2 (0.2%). 805 (79%) participants expressed willingness to participate in a HIV vaccine trial, 532 (55.2%) reported having heard of pre-exposure prophylaxis (PrEP), and none reported current PrEP use. A total of 942 (92.6%) participants were retained through the end of the study. During 1422 person-years (PY) of observation, 53 incident HIV infections were diagnosed (3.73 [95% CI 2.79-4.87] cases/100PY). Among 256 candidate models evaluated, the one with the lowest Akaike’s information criterion contained age, site, and prior HIV testing (Fig.1). Increased age was associated with lower hazard of incident HIV (HR 0.84 [95%CI 0.76-0.93]) and prior HIV testing was associated with increased hazard of incident HIV (2.16 [95%CI 1.23-3.79]).

**Conclusion:** Thai MSM and TGW in this study demonstrated high HIV incidence and are in need of effective HIV prevention interventions. Good retention in this cohort demonstrates the feasibility of future efficacy testing of such interventions.
HIV AMONG FEMALE SEX WORKERS: RISK FACTORS AND LESSONS FROM A NATIONAL SURVEY

Adedayo O. Adeyemi1, Emmanuel Abatta1, Olubunmi Fakunle1, Ogbonna O. Amanze1

1 University of Abuja Teaching Hospital, Abuja, Nigeria; 2 Ministry of Health, Abuja, Nigeria; 3 National Agency for the Control of AIDS, Abuja, Nigeria

Background: HIV prevention programming among female sex workers (FSW) is of national priority in the implementation of Nigeria HIV Research Agenda. FSWs are high risk group with the second highest HIV prevalence among the key populations in Nigeria. Generating evidence needed for implementable prevention strategies is vital to future national prevention and control efforts. The 2014 Integrated Biological Behavioral Surveillance Survey (IBBSS) provided the most recent national progress and performance data among the key populations. This study assessed HIV prevalence among FSWs and risk factors to HIV infection.

Methods: Secondary data analysis of 2014 IBBSS was undertaken among 8050 FSWs in brothels (BFSW) and non-brothels (NBFSW). Two-stage cluster and time location sampling techniques were used in selecting the FSWs in 13 states and Federal Capital Territory in the six geo-political zones. The survey involved HIV testing, and collected information on demographic, and sexual and reproductive health indicators. A random-effects logistic regression model was fitted with HIV infection as the outcome, and was used to ascertain state level variation.

Results: The mean age of FSW was 27.1±6.2years; mean age at first sex was 170±2.8years and average number of clients/day was 4.4. About 36.1% were married. About 38.8% had sex partners that were 10 years older. Condom use at last sex was 91.8% among the BFSWs; 43.0% experienced condom breakage in the last month prior to the survey and consistent condom use was 29.1%. About 55.0% completed at least secondary education, 46.2% had been away from home for more than one month and 72.6% received information/education on HIV/STIs in the last 12 months. HIV prevalence among FSW was 14.4% (BFSW was 19.4% and NBFSW was 8.6%). Factors associated with HIV infection were brothel-based FSW (OR=2.6, 95% CI 1.4-4.2); being away from home for at least one month OR=1.8, 95% CI 1.1-2.9; consistent condom use OR=0.7, 95% CI 0.5-0.8 and receiving information/education on HIV/STIs OR=0.7, 95% CI 0.4-0.8. The estimated variance between states was 0.4 with a standard error of 0.1.

Conclusion: Although consistent condom use was low, it was protective against HIV in addition to information materials given to FSWs. There was state-level variation. Thus, there is a need for state-level intervention with more emphasis on BFSWs. Also, targeted health education programs are needed to increase consistent condom use.

TRANSACTIONAL SEX WITH OLDER PARTNERS HEIGHTENS HIV RISKS AMONG AGYW IN TANZANIA

Katherine Rucinski1, Gaspar Mbita1, Kelly Curran1, Albert Komba1, Caterina Casalini2, Esther Majani1, Mary Drake1, Anthony Galishi1, Yeronimo Mlawa1, Upendo Kategile1, William Kafura1, Sherre Schwartz2, Stefan Baral2, John Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; 1Jhpiego, Dar es Salaam, Tanzania, United Republic of; 2Jhpiego, Baltimore, MD, USA; 3USAID Tanzania, Dar es Salaam, Tanzania, United Republic of

Background: Across sub-Saharan Africa, transactional sex and sexual relationships with older partners both affect HIV risk in adolescent girls and young women (AGYW). The extent to which these behaviors operate either independently or together to impact HIV acquisition is not well known.

Methods: Data were collected through the Sauti Project, a PEPFAR/USAID funded project which provides combination HIV prevention services to AGYW and key and vulnerable populations across Tanzania. Out-of-school AGYW aged 15-24 years who were accessing HIV-prevention services through Sauti completed a questionnaire to assess demographics and other psychosocial measures between 2016-2018. AGYW were tested for HIV and those who tested positive were linked to HIV care and treatment as per Tanzania national guidelines. We estimated adjusted prevalence ratios (APR) and 95% confidence intervals (CI) for the associations of transactional sex (any sex in exchange for money, services or gifts) and intergenerational sex (reporting a sexual partner ≥10 years older) with prevalent HIV infection. We assessed potential synergism between both exposures by comparing their observed and expected joint associations using additive and multiplicative criteria.

Results: Among 12,708 sexually active AGYW, median age was 21 years (IQR 19, 23). Transactional sex and intergenerational sex were common (43% and 33%, respectively); 5% reported engaging in both behaviors. Two percent of AGYW knew their HIV status, and the proportion taking ART varied by site. Testing programmes specifically aimed at the needs of young women aged 16-19 years, which increases rapidly by age, often report high alcohol and drug use, and have commonly experienced both sexual and physical violence and, as a consequence, are extremely vulnerable. Among HIV positive AGYS just over 50% knew their HIV status, and the proportion taking ART varied by site. Testing rates in HIV negatives were high. Programmes specifically aimed at the needs of AGYS are urgently needed, offering regular HIV testing to improve knowledge of HIV status.

HIV RISK, BEHAVIOUR, AND SERVICE UPTAKE IN ADOLESCENT GIRLS SELLING SEX IN ZIMBABWE

Mariken M. De Wit1, Brian Rice2, Elizabeth Fearon3, Tendayi Mharadze2, Sitholubuhle Magutshwa4, Joanna Busza1, Sithembile Musemburi4, Amon Mpofu1, Owen Mugurungi1, Casalini2, Esther Majani1, Mary Drake1, Anthony Galishi1, Yeronimo Mlawa1, Upendo Kategile1, William Kafura1, Sheree Schwartz2, Stefan Baral2, John Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; 1Jhpiego, Dar es Salaam, Tanzania, United Republic of; 2Jhpiego, Baltimore, MD, USA; 3USAID Tanzania, Dar es Salaam, Tanzania, United Republic of; 4USAID Council Zimbabwe, Harare, Zimbabwe; 2Zimbabwe Ministry of Health and Child Care, Harare, Zimbabwe; 3United Nations Populations Fund, Harare, Zimbabwe

Background: Adolescent girls who sell sex (AGSS) in sub-Saharan Africa are disproportionally affected by HIV, yet little is known about how these vulnerabilities intersect and its implications for programming. Using a representative sample of AGSS in Zimbabwe, we estimate population size, determine risk factors for, and the prevalence of, HIV infection, and explore engagement with HIV services.

Methods: In 2017 rapid ethnographic mapping of the spatial and social organization of AGSS (aged 16-19 years) was conducted, followed by a bio-behavioural survey using respondent driven sampling (RDS) in Harare and Bulawayo, and a census method in Gokwe, and Beitbridge. Unique objects were distributed to all women at sites identified as sex work locations during mapping in Harare and Bulawayo. All recruited women were tested for HIV and completed an interviewer administered questionnaire. Data were analysed using RDS-II weighting in Harare and Bulawayo and pooled across sites to run a logistic regression examining sociodemographic and sex work characteristics associated with being HIV-positive.

Results: In total, 615 AGSS were recruited. HIV prevalence varied between 7.2% and 38.0% by site. HIV prevalence rose sharply with age from 2.1% among AGSS aged 16 to 26.9% among those aged 19 years. AGSS who were in school and had more years of education were less likely to be infected. Overall, more than half of HIV positive AGSS were aware of their HIV status (<5.5% by site). Of those, 68.2% to 100% were on antiretroviral treatment (ART). Among HIV negative women, rates of HIV testing in the preceding 6 months was 62.0-71.4%. Reported alcohol and drug use was common, as was past history of physical and sexual violence. The size of the population of adolescent girls selling sex was estimated to be 1342 (95% CI 498-2186) in Harare and 1462 (95% CI 845-2079) in Bulawayo using the unique object multiplier method. For Gokwe (n=41) and Beitbridge (n=79) all AGSS were contacted.

Conclusion: AGSS aged 16-19 years in Zimbabwe have a high HIV prevalence that increases rapidly by age, often report high alcohol and drug use, have commonly experienced both sexual and physical violence and, as a consequence, are extremely vulnerable. Among HIV positive AGSS just over 50% knew their HIV status, and the proportion taking ART varied by site. Testing rates in HIV negatives were high. Programmes specifically aimed at the needs of AGSS are urgently needed, offering regular HIV testing to improve knowledge of HIV status.
were living with HIV. The association of transactional sex with HIV prevalence was 1.27 (95% CI 0.97, 1.67) and the association of intergenerational sex with HIV prevalence was 0.97 (95% CI 0.50, 1.89) when setting AGYW who reported neither behavior as a reference category. AGYW who reported both transactional sex and intergenerational sex had nearly twice the HIV prevalence of AGYW who reported neither behavior (aPR 1.74, 95% CI 1.03, 2.94). Evidence of interaction was present, suggesting transactional sex and intergenerational sex operate synergistically to heighten HIV risks in AGYW.

Conclusion: Transactional sex was not strongly associated with HIV prevalence in the absence of intergenerational sex, and intergenerational sex was not associated with HIV prevalence in the absence of transactional sex. Targeting AGYW who are likely to engage in commodified sex with older partners, such as AGYW who are economically and socially vulnerable, may maximize effectiveness of behavioral and biomedical HIV prevention efforts.

Table 1. Unadjusted and adjusted joint associations of transactional sex and intergenerational sex with HIV prevalence among AGYW in Transkei, South Africa, 2010-2019

<table>
<thead>
<tr>
<th>Exposure Status</th>
<th>HIV Prevalence (%)</th>
<th>Unadjusted PR</th>
<th>Adjusted PR</th>
<th>p for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No transactional sex, no intergenerational sex</td>
<td>10 (2.0)</td>
<td>1.0</td>
<td>1.0</td>
<td>0.81</td>
</tr>
<tr>
<td>Transactional sex, no intergenerational sex</td>
<td>16 (3.2)</td>
<td>1.66 (1.17-2.36)</td>
<td>1.67 (1.18-2.36)</td>
<td>0.37</td>
</tr>
<tr>
<td>Transactional sex, intergenerational sex</td>
<td>22 (4.4)</td>
<td>2.22 (1.45-3.39)</td>
<td>1.87 (1.26-2.79)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* p < 0.05 unless otherwise specified.

858 FACTORS ASSOCIATED WITH HIV SEROCONVERSION IN YOUNG WOMEN IN SOUTH AFRICA

Lara Lewis1, Ayeshia B. Kharsany1, CHERIE CAV Lord1, HILTON HUMPHRIES1, BRENDAN MAUGHAN-BROWN1, David Khanyile1

1CAPRISA, Durban, South Africa, 2Epicentre, Cape Town, South Africa, 3University of Cape Town, Cape Town, South Africa

Background: High HIV incidence in young women in Sub-Saharan Africa remains a key challenge to HIV epidemic control. HIV incidence rates in young women exceed those of men and older women, and the proportion of young HIV-positive women who know their status and are virally suppressed falls well short of the UNAIDS '90-90-90' targets. This study examined the factors associated with seroconversion in young women in a hyperendemic area of South Africa.

Methods: We analysed prospective cohort data of HIV-negative women (15-24 years) from the HIV Incidence Provincial Surveillance System conducted in KwaZulu-Natal, South Africa. Participants (n=2,710) completed a questionnaire and provided blood samples for laboratory testing (pregnancy, HIV and other STIs) at enrolment and follow-up approximately 18 months later. The association between risk factors and HIV seroconversion was assessed using Cox proportional hazards models.

Results: The incidence rate of young women was 3.92 (95% confidence interval: 3.27-4.69) per 100 women-years; 3.74 (95% CI: 2.87-4.86) and 4.13 (95% CI: 3.27-5.03) per 100 women-years for young women aged 15-19 and 20-24 years respectively. At follow-up, median (interquartile range) viral load of seroconverters was 4,400 (280-50,000) copies/ml and 17% reported knowing their HIV-positive status. Risk of seroconversion in young women increased significantly with the number of lifetime partners reported at baseline. Among teen-age girls (15-19), risk of seroconversion was positively associated with being an orphan (adjusted hazard ratio (aHR)=4.38, p=0.005) and having a baseline STI (aHR=2.37, p=0.016), and negatively associated with having family support (aHR=0.46, p=0.022) and having a circumcised partner (aHR=0.58, p=0.047). For women aged 20-24 years, failure to complete high-school (aHR=1.78, p=0.042) and inconsistent condom use (aHR=2.72, p=0.024) were associated with HIV acquisition.

Conclusion: This study suggests that structural factors contribute to the high HIV incidence rates observed in young women in this population. However, programs supporting sexual health, male circumcision and condom use remain effective ways to reduce risk. In addition to supporting such programs, it is imperative that HIV testing frequency of young women be increased so that infections can be diagnosed timely, treatment can be provided and transmission risk reduced.

857 SOCIOECONOMIC DISPARITIES ARE ASSOCIATED WITH HIV IN YOUNG MSM WITHIN LATIN AMERICA

Thiago S. Torres1, LARA COEHL1, KELILIA K. KONDA1, E. Hamid Vega-Ramirez2, Oliver A. Elobreaga3, Dulce Diaz-Sosa1, Brenda Hoagland1, Cristina Pimenta1

1Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, 2University of Peruna Cayetano Heredia, Lima, Peru, 3National Institute of Psychiatry Ramon de la Fuente Muñiz, Mexico City, Mexico, 4Candesa-Iztopalapa Specialized Clinics, Mexico City, Mexico, 5Ministry of Health, Brasilia (DF), Brazil

Background: Despite efforts to stop HIV epidemic in Latin America, new HIV cases continue to increase in the region especially among young MSM (YMSM). This study aims to assess social-economic and behavioral factors associated with HIV self-reported prevalence among YMSM participating in a survey conducted in Brazil, Mexico and Peru.

Methods: Through March to May, 2018, MSM were recruited to complete a web-based survey through advertisements on geosocial network (GSN) dating apps (Grindr and Hornet) and Facebook. Inclusion criteria were cisgender men, ≥18 years, living in Brazil, Mexico or Peru. For this analysis, we included YMSM aged 18-24 years who self-reported their HIV status (negative/positive). Multivariable logistic regression models assessed factors associated with HIV self-reported prevalence among YMSM for each country. The models were adjusted for geographical region within each country, race (only Brazil and Peru: white vs. non-white), monthly income (low vs. middle/high, according to countries definition), schooling (≥secondary school vs. ≤), steady partner (yes/no), sexual attraction (men, women or both) and time since last HIV testing (<1 year vs. ≥1 year).

Results: Among 43,687 MSM that started the questionnaire, 27,475 (62.9%) reported their HIV status; 7,055 (25.7%) were YMSM and were included in the analysis. The majority of YMSM (83.1%) were recruited on GSN apps. Most (83.3%) reported an HIV test in the past year, and 15.3% reported HIV positive status in Peru, 8.4% in Mexico and 7.7% in Brazil. Among YMSM, low-income was associated with higher odds of HIV self-reported prevalence in Brazil (aOR=1.31, 95%CI:1.00-1.74) and Peru (aOR=1.59, 95%CI:1.04-2.48) but not in Mexico (aOR=0.81, 95%CI:0.56-1.38). Lower education was also associated with higher odds of HIV self-reported prevalence in Brazil (aOR=1.34, 95%CI:1.03-1.76) but not in Mexico nor in Peru. YMSM from the three countries sexually attracted to men had at least twice higher odds of HIV self-reported prevalence than those preferring women or both (Table 1).

Conclusion: In this large, cross-country study, HIV prevalence among YMSM was high. Social-economic disparities were associated with higher odds of HIV self-reported prevalence. Interventions to increase awareness to prevention technologies including PrEP targeting socio-economic disadvantaged YMSM are urgent in Latin America.

Table 1. Factors associated with HIV self-reported prevalence among YMSM aged 18-24 years in Brazil, Mexico and Peru, 2018.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Brazil</th>
<th>Mexico</th>
<th>Peru</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low income</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Low education</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>White race</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Monthly income</td>
<td>Low</td>
<td>Middle</td>
<td>High</td>
</tr>
<tr>
<td>Schooling</td>
<td>≥secondary school</td>
<td>≤</td>
<td></td>
</tr>
<tr>
<td>Steady partner</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sexual attraction</td>
<td>Men</td>
<td>Women</td>
<td>Both</td>
</tr>
</tbody>
</table>

858 FORCED SEX IN HAITI: IMPLICATIONS FOR THE HIV EPIDEMIC AMONG MSM AND TRANS WOMEN

Nicole Y. Frascino1, LAUREN Y. ZALLA1

1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Sexual violence is an often perpetrated, but rarely studied risk factor for HIV, particularly among men who have sex with men (MSM) and transgender women (TW) living in the Caribbean. This study aimed to describe the prevalence of forced sex and HIV among MSM and TW and the association between forced sex and HIV prevalence in Haiti.

Methods: Five-hundred and twenty MSM and 109 TW were recruited from 2,339 venues where men and women meet new sexual partners, such as bars, nightclubs, and hotels, in nine of the ten departments in Haiti. Venues were selected using the Priorities for Local AIDS Control Efforts (PLACE) methodology. All MSM and TW completed an interview and HIV test. History of forced sex was defined as ever having experienced forced sexual intercourse or forced sex without a condom.

Results: HIV prevalence among MSM and TW in the study population was 2.15% and 27.64%, respectively, while 40.77% and 64.22% reported a history of forced sex. In general, MSM and TW were young, educated, in a primary relationship,
and received money or gifts in exchange for sex in the past 12 months (MSM: 54.62%, TG: 59.63%). In an unadjusted log binomial regression, MSM with a history of forced sex were 0.19 (95% CI, 3.00-21.67) and TW were 7.02 (95% CI 1.90-26.00) times more likely to be HIV positive than those without a history of forced sex. When adjusting for age, education, in a primary relationship, receiving money or gifts for sex in the past 12 months, the number of sexual partners in the past four weeks, if a condom was used at last anal sex and perceived risk of acquiring HIV in a log Poisson regression, TW with a history of forced sex were 4.83 (95% CI, 1.59-14.61) times as likely to be HIV positive than those with a history of forced sex.

Conclusion: Understanding the pathways through which history of forced sex influences mental health and sexual risk behaviors can provide evidence for integration of mental health services in HIV-prevention efforts among MSM and TW in Haiti.

859 SEXUAL HEALTH OF RURAL AND URBAN YOUNG MALE COUPLES IN THE UNITED STATES

Elissa L. Sarno1, Kyle Jozsa1, Emily Bettin1, Michael E. Newcomb1
‘Northwestern University, Chicago, IL, USA

Background: Young men who have sex with men (YMSM) are disproportionately affected by HIV, and main partnerships account for a large proportion of new HIV infections among YMSM (35-68%). The number of YMSM living with HIV is highest in urban areas; thus, HIV prevention is largely focused on urban YMSM and less is known about sexual health of rural YMSM in relationships. Rural YMSM are less likely to be tested for HIV/STIs than urban YMSM, and inconsistent condom use is common. The present study used baseline data from a randomized controlled trial of a relationship education and HIV prevention program for male couples to test associations of rurality with HIV risk and prevention behaviors among YMSM. We hypothesized that higher rurality would be associated with fewer HIV risk and prevention behaviors.

Methods: Participants were 430 YMSM in relationships. Participants’ average age was 28.70 years (SD = 7.34). Participants’ HIV status was negative (75.3%), positive (10.7%), or unknown (14%). Couples were eligible based on HIV risk criteria (i.e., at least one member reports having condomless anal sex with a known serodiscordant serious partner or with any casual sexual partner). Participants completed measures of HIV/STI testing history, PrEP use, number of sex partners outside of their main relationship, and condomless anal sex (CAS) acts with those partners. Rurality was measured using the Index of Relative Rurality, a continuous and threshold-free measure of rurality. Data were analyzed using multilevel mixed models. Analyses controlled for age and race.

Results: Results are summarized in Table 1. YMSM in more rural areas (i.e., higher rurality) were less likely to have been tested for HIV/STIs, and to have used PrEP, compared to urban YMSM. Higher rurality was also associated with fewer outside partners and fewer CAS acts; however, rates of CAS in the past three months were high for YMSM in both the top (i.e., most rural; M = 4.65, SD = 4.26) and bottom (M = 4.72, SD = 4.90) quartiles of rurality.

Conclusion: Rural YMSM lack access to sexual health-related services and face stigma associated with same-sex sexual behavior and HIV, which may act as barriers to HIV/STI testing and PrEP use. Although rural YMSM had fewer sex partners outside their relationship and fewer CAS acts than urban YMSM, CAS was not infrequent, highlighting the need for increased HIV prevention geared toward young male couples living in more rural, less resourced areas.

860 BURDEN OF HIV AMONG MEN ATTENDING EMERGENCY DEPARTMENTS IN SOUTH AFRICA

George Mwininnya, Elizabeth Hahn, Aditi Rao, Steven J. Reynolds, Andrew D. Reddi, Reinaldo Fernandez, Jemelle Miller, Morgan P. Keruly, Roshen Maharaj, Pamela Mda, David Stead, John Black, Thomas C. Quinn, Oliver Laeyendecker, Bhakti Hansoti
‘Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, ’NIAID, Baltimore, MD, USA, ’NIAID, Bethesda, MD, USA, ’Johns Hopkins University School of Medicine, Baltimore, MD, USA, ’Walter Sisulu University, Mthatha, South Africa

Background: We sought to identify factors associated with HIV infection, HIV diagnosis, and lack of antiretroviral treatment (ART) among men attending emergency departments (EDs) in the Eastern Cape region of South Africa.

Methods: Men aged ≥18 years were approached in three EDs, between June 2017 and July 2018. Study staff offered HIV testing, completed testing and collected demographic data on participants. HIV positive patients were consented for a blood sample, which was tested for the presence of antiretrovirals (ARVs) and quantification of HIV viral load. Log-binomial models were used to characterize male’s engagement in ART and care cascade and to determine factors associated with HIV prevalence.

Results: Overall, 21% (302/1458) of men tested positive for HIV, of which 47% (124/302) were unaware of their status. Of the HIV positive males that underwent further testing only 47% (104/222) tested positive for the presence of ARVs, and 43% (101/236) were virally suppressed (defined as a viral load ≤1000 copies/ml). HIV prevalence increased with age, with 4% of men aged <20 years testing positive to a peak of 35% of those aged between 36–45 years. Factors significantly associated with being HIV+ include presenting with generalized weakness (adjusted prevalence ratio [aPR] 1.49, 95% CI 1.16,1.92), signs of tuberculosis (aPR 1.95, 95% CI 1.52,2.44), and being admitted to the hospital (aPR 1.26, 95% CI 1.03,1.54) relative to males with no weakness, tuberculosis or admissions, respectively. Men diagnosed with HIV in the ED were more likely to be younger (>50%) were less than <35 years of age), trauma patients (vs. medical) (aPR 1.69, 95% CI 1.11,2.57), or presenting with fever (vs. no fever) (aPR 1.90, 95% CI 1.18,3.08). Less than 30% of men under the age of 35 years had evidence of ART and none of the 19 HIV+ men <25 years of age were virally suppressed. Furthermore, those with concurrent alcohol problems had lower frequency of being virally suppressed (38%, 36/96).

Conclusion: There is a high burden of HIV among men visiting EDs in the Eastern Cape, with almost half unaware of their HIV status. Furthermore, none of the youngest men were virally suppressed. The ED is a critical venue to identify HIV infected men not on treatment. HIV service providers, program implementers and policy makers, should consider how to leverage the ED as a venue to provide HIV services to young men in order to meet the 90-90-90 targets particularly in South Africa.

861 ROLE OF KEY POPULATIONS AND PAST INTERVENTIONS ON HIV TRANSMISSION IN CAMEROON

Romain Silhol, Sharmistha Mishra, Anna L. Bowring, Christina Mukandavire, Amrita Rao, Sheree Schwartz, Ubald Tamoufe, Serge Billong, Peter Vickerman, Stefan Baral, Marie-Claude Boily
1Imperial College London, London, UK, 2University of Toronto, Toronto, ON, Canada, 3Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 4Metabiota, Yaoundé, Cameroon, 5University of Yaoundé, Yaoundé, Cameroon, 6University of Bristol, Bristol, UK

Key populations (KP) such as men who have sex with men (MSM), female sex workers (FSW) and their clients are at high risk of HIV. We estimated the impact of past interventions and the contribution of risks stemming from unmet HIV prevention/treatment needs of KP and lower-risk groups to HIV transmission in Yaoundé, Cameroon.

Methods: We developed and calibrated a deterministic model of HIV transmission within a Bayesian framework to reproduce the HIV epidemic in Yaoundé over time, based on a comprehensive review of site-specific demographic, behavioural, HIV and intervention coverage data. We estimated the fraction of incident HIV infections averted by condoms and antiretroviral therapy (ART) and the fraction of all transmitted infections over 10-year periods attributable to sex within different partnerships.

Results: Condoms and ART together averted 33% (95% uncertainty interval: 21–47) of infections over 1980–2018. Rising condom use among FSW had the largest historical impact (18% (9–37) of infections averted from 1980–2018);
recent ART scale-up averaged 36% (31-41) over 2009-2018. With increasing condom use during paid sex, the contribution of sex between FSW and their partners fell from 37% (17-61) of all transmitted infections over 1989-1998 to 22% (8-36) over 2009-2018 (Table). In the last decade, sex between clients (7%) of all people living with HIV (PLHIV) and their partners; MSM (8% of PLHIV) and their male and female partners; and between lower-risk individuals (82% of PLHIV) contributed to 39% (26-56), 42% (17-52), and 43% (31-60) respectively. By 2018, ART coverage was estimated to be highest among FSW (86% (79-91)), followed by lower-risk groups (51% (46-56)), MSM (47% (40-52)), and clients: (44% (34-48)). Consequences of unmet HIV prevention/treatment needs of MSM are predicted to contribute to 44% (17-57) of new transmissions occurring in the coming decade (Table).

Conclusion: Increases in condom use among FSW, and recent ART scale-up have had a large transmission impact in Yaoundé and changed the relative contribution of different partnerships to onward transmission over time. Findings highlight the need to prioritize HIV prevention and treatment interventions to MSM and clients of FSW whose unmet needs are now contributing the most to onward transmission, while maintaining achievements in reducing HIV transmission in the context of sex work.

862 SEX-SPECIFIC ANALYSES IN ORAL ABSTRACTS FROM CROI 2019


Results: Estimation of sex-specific analyses was done for clinical studies at CROI 2019 included sex-adjusted results, which was slightly higher than the 30% reporting at CROI 2018. Sex-adjusted analyses were higher among observational studies (64%, 29 of 45) than in clinical trials (29%, 10 of 34); see Table.

Conclusion: While there was some improvement in reporting sex-specific analyses among oral presentations at CROI 2019 compared to 2018, there is still much room for improvement. Consistent failure to report sex distribution in clinical studies needs to be addressed. Reporting of sex distribution in clinical studies needs more emphasis since 15% of oral presentations failed to include this. Education regarding the difference between sex and gender is necessary, and titles should indicate whether findings are restricted to one sex. Finally, enrolling adequate numbers of women to perform meaningful sex-stratified analyses and performing such analyses require additional guidance and even mandates given that over half of PHLW worldwide are women.

863 HIGH PROBABILITY OF SURVIVAL IN PATIENTS WHO MAINTAIN VIRAL LOADS <200 COPIES/ML


Methods: We followed adults who newly initiated ART and achieved initial suppression (first VL under assay limit of detection (LOD)) under observation. Patients were followed from initial suppression until death, loss to follow-up (no VL for 15 months), or administrative censoring. Nearly 80% of VLs after initial suppression fell under varying LODs (LOD range: 20–500 copies/mL); multiple imputation based on demographic and clinical factors was used to address VLs <LOD. We estimated cumulative incidence (risk) of 2-year all-cause mortality at 0, 2, and 4 years after initial suppression. At each time point, analysis was restricted to patients who remained under observation and maintained all VLs <200 copies/mL up to that time. Patients were categorized as: a) those with all VLs <200 copies/mL; and b) those with ≥1 VL 20–199 copies/mL. Multiple imputation based on demographic and clinical factors was used to account for confounders (see fig.).

Results: At initial suppression, 2-year crude mortality risks for 19463 patients with VL <200 copies/mL and those with VL 20–199 copies/mL were 1.9% and 2.5%, and weighted risks were 1.9% and 2.0%, respectively. Of the 11444 patients under observation with a VL measurement 4 years after initial suppression, 77% had maintained all VLs <200 copies/mL. Among those patients, 2-year crude risks for those with all VLs <200 copies/mL and those with ≥1 VL 20–199 copies/mL were 1.6% and 1.9%, and weighted risks were 1.7% and 1.7%, respectively. Of the 6100 patients under observation with a VL measurement 4 years after initial suppression, 69% had maintained all VLs <200 copies/mL. Among those patients, 2-year crude risks for those with all VLs <200 copies/mL and those with ≥1 VL 20–199 copies/mL were 1.3% and 2.4%, and weighted risks were 1.5% and 2.2%, respectively.
864 FIRST HIV VIRAL LOAD REMAINS STRONG PREDICTOR OF TREATMENT SUCCESS IN SOUTH AFRICA

Lauren R. Violette,1 Jienchi Dorward,2 Justice Quame-Amaglo,3 Katherine Thomas1, Connie L. Celum,1 Nigel Garrett,2 Paul K. Drain1
1University of Washington, Seattle, WA, USA, 2CAPRISA, Durban, South Africa

Background: In the Simplifying HIV Treatment and Monitoring (STREAM) trial, point-of-care (POC) HIV viral load (VL) testing and task shifting significantly improved retention in care and viral suppression in South Africa. We sought to determine risk factors for poor retention and HIV viremia among trial participants.

Methods: STREAM was a randomized controlled trial in Durban, South Africa among people living with HIV (PLHIV) who were clinically stable and on antiretroviral therapy (ART) for six months. Participants (N=390) were randomized to receive either POC VL testing (Xpert® HIV-1 VL, Cepheid) and task shifting or standard laboratory VL testing. A composite primary outcome of retention in care and viral suppression (<200 copies/mL) was assessed 12 months after enrolment. We estimated relative risks using modified Poisson models with robust standard errors to evaluate the association between participant baseline characteristics and 1) not achieving the composite primary outcome and 2) 18-month HIV VL ≥50 copies/mL.

Results: Among 390 participants, median age was 32 years (IQR 27-38), 60.3% were female, and 93.1% had VL <200 copies/mL at study baseline. After 18 months on ART, 67 participants (17.2%) failed to achieve the composite primary outcome and 2) 18-month HIV VL ≥50 copies/mL.

Conclusion: Patients in care who maintained all VLs <200 copies/mL experienced a 2-year survival probability that exceeded 97% up to 4 years after initial suppression. After accounting for confounders, participants with ≥1 VL 20–199 copies/mL had a similar 2-year risk of death as patients who maintained all VLs <20 copies/mL, which suggests that estimated VLs 20–199 copies/mL did not have a notable impact on near-term risk of death.

865 POPULATION-LEVEL HIV VIRAL LOAD VARIES BY GENDER, AGE, AND LOCATION IN RAKAI, UGANDA

Imogen Kyle1, Joseph Kagaayi2, Godfrey Kigozi3, Gertrude Nakigozi3, Robert Ssekubugu4, Fred Nakagudza2, Mary K. Grabowski3, Larry W. Chang2, Maria Wawer1, David Serwadda4, Ronald H. Gray3, Thomas Quinn5, Steven J. Reynolds5, Oliver Ratmann6, for the Rakai Health Sciences Program1,2, Imperial College London, London, UK, 3Rakai Health Sciences Program, Kalisizo, Uganda, 4Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 5National Institutes of Allergy and Infectious Diseases, Bethesda, MD, USA

Background: In the ART era, population HIV viral load (PVL) quantifies gaps in the HIV care cascade, as well as the residual transmission potential from population subgroups.

Methods: Between January 2015 and September 2016, we measured HIV viral load among HIV+ individuals aged 15-49 years in 40 communities of the Rakai Community Cohort Study, Uganda (Figure 1A). To measure PVL and viral suppression, we respectively quantified the proportion of individuals in the total population with detectable viral load above 1000 copies/mL plasma blood (PVL) and the geometric mean viral load (PMVL), assigning a VL measurement of zero to HIV uninfected individuals. Sub-analyses were conducted among HIV infected individuals, and infected individuals with detectable viral load. Spatial heterogeneity in PVL measures was assessed with Gaussian kernel maps and spatial scan statistics.

Results: Of 18,656 participants, 3,467 (18.6%) were HIV-positive, of whom 3,454 (99.6%) had VL measured. Despite higher HIV prevalence among women (21.8% [21.0%-22.6%]) than men (15.0% [14.2%-15.7%]), PMVL was 1.4 [1.2-1.7] times higher among men than women. This reflected higher PVL among women (5.8% [5.3%-6.3%] compared to men (4.8% [4.4%-5.2%]), and 7 (5-10) times higher geometric mean VL among infected men with detectable viral load compared to their female counterparts. PMVL peaked at age 20-24 in men and at age 15-19 in women (Figure 1B). In contrast PVL peaked later, at age 30-34 in men and at 25-29 in women. Spatial foci of high PVL coincided with fishing communities along Lake Victoria.

Conclusion: Population-viral load analysis revealed marked differences in viral load suppression across demographic sub-groups and geography, with viral load burden greater in men than women, and concentrated in young age groups. Intensified interventions to improve health and reduce future infections are warranted especially among men and women aged <25 years, and geographic areas with excess detectable viral loads.
Background: The Ending the HIV Epidemic (EHE) initiative focuses on rapid & effective treatment of people with HIV to achieve viral suppression, which is associated with improved health outcomes & reduced HIV transmission risk. Assessing disparities in viral suppression among persons with recent HIV diagnoses has the potential to guide practice and research. Using nationally representative data from the Medical Monitoring Project (MMP), we explored characteristics associated with viral suppression among adults with recent HIV diagnoses.

Methods: During 2015-2018, MMP conducted interviews among adults with diagnosed HIV. Viral load test results were abstracted from medical records. Viral suppression was defined as <200 copies/mL or undetectable based on the most recent viral load. Generalized anxiety disorder (GAD) in the past 2 weeks was assessed using a validated scale and categorized based on clinically meaningful cutpoints. Persons who reported needing but not receiving services had unmet needs for these services. All characteristics were based on the past 1 year unless otherwise indicated. Among persons with HIV diagnosed in the 5 years prior to interview (N=1,869), we assessed differences in viral suppression by selected characteristics using Rao-Scott χ2 tests (p<0.05).

Results: Of persons with recent HIV diagnoses, 31% were not virally suppressed, and 5% reported not currently taking ART. The proportion not virally suppressed varied by race/ethnicity (blacks: 37%, whites: 27%, Hispanics/Latinos: 26%) and age (18-24 years: 50%, 25-34 years: 35%, 35-44 years: 26%, 45-54 years: 23%, and ≥55 years: 22%). Persons who had a history of homelessness (40% vs. 30%), used non-injectable drugs (37% vs. 27%), had GAD (38% vs. 29%), and had unmet needs for HIV medicine (63% vs 29%), HIV case management (55% vs. 28%), and patient navigation services (67% vs. 28%) were less likely to be virally suppressed.

Conclusion: More than a quarter of persons with newly diagnosed HIV were not virally suppressed. Providers should ensure all persons with HIV are virally suppressed, including those newly diagnosed. Focusing efforts on programs, including comprehensive engagement, adherence support, & peer navigation, may result in improved health outcomes and reduced number of new HIV infections and supports the EHE initiative.

Background: The social networks of HIV+ persons may facilitate access to HIV testing and care. We constructed community-wide social networks and assessed association between social connectedness and knowledge of HIV status, ART use, and HIV viral suppression among baseline HIV+ residents of rural Ugandan communities in the SEARCH Study (NCT01864603).

Methods: From 2013-2014, adults (≥15 yrs) in 10 communities in Uganda West and 10 in Uganda East were enumerated using a census and named social contacts in five domains: health, money, emotional support, food, and free time. Social networks were constructed by matching named contacts to other enumerated residents; 90% of residents were tested for HIV. We evaluated whether HIV+ persons in the lowest tercile of connectedness, based on in-degree (number of persons who named an individual as a contact) and out-degree (number of contacts an individual named), would be less likely to know their HIV status, have initiated ART, and be virally suppressed (HIV RNA<500 cps/ml) than their more connected counterparts. We used generalized estimating equations to adjust for sociodemographic risk factors including mobility and for clustering by community.

Results: A total of 57% of named within-community contacts in Uganda West and 63% in Uganda East were matched to enumerated residents, resulting in 20 networks with 108,521 nodes (enumerated persons) and 216,213 edges (social connections). Among 4,587 HIV+ persons who named ≥1 contact, 39% were not aware of their HIV status, 50% had not initiated ART, and 55% had viral non-suppression. HIV+ persons in the lowest tercile of in-degree (<1-2 contacts, depending on community) were less likely to know their status (Uganda West aRR:0.89 (95%CI:0.83, 0.96); Uganda East aRR:0.85 (0.76, 0.96)); to have initiated ART (Uganda West aRR:0.88 (0.80, 0.98); Uganda East aRR:0.81 (0.72, 0.92)), and to have viral suppression (Uganda West aRR:0.84 (0.73, 0.96); Uganda East aRR:0.74 (0.58, 0.94)) than those in the highest tercile (>3-7 contacts) (Figure).

Conclusion: HIV+ persons with fewer people naming them as contacts were less likely to know their HIV status, have initiated ART, or have a suppressed viral load. Interventions targeting HIV+ persons with fewer social connections may contribute to improved clinical outcomes.
LIFE EXPECTANCY GAINS WITH ART IN LATIN AMERICA, 2003-2017
Casey Smiley1, Peter Rebeiro1, Carina Cesar2, Francisco Belanazauran3, Brenda Crabtree-Ramírez3, Denis Padgett4, Eduardo Gotuzzo5, Claudia P. Cortes6, Jean W. Pape2, Valdéea Veloso1, Catherine McGowan1, Jessica L. Castilho1
1Vanderbilt University, Nashville, TN, USA, 2Fundación Huésped, Buenos Aires, Argentina, 3Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, 4Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras, 5Universidad Peruana Cayetano Heredia, Lima, Peru, 6University of Chile, Santiago, Chile

Methods: We included PLWH started on ART and ≥20 years old between 2003-2017 from CCASAnet sites in Haiti, Mexico, Honduras, Peru, Argentina, Chile, and Brazil. PLWH contributed person-time until the first of death, last cohort contact, database closure, or December 2017. Due to differences in general population life expectancy and clinical sites, we stratified analyses by Haiti vs. all other sites. We used the Chiang method for abridged life tables to calculate life expectancy at age 20 for three eras (2003-2008, 2009-2012, and 2013-2017) overall and by demographic and clinical characteristics at ART initiation. As mortality ascertainment varies by country, mortality rates were weighted for probability of loss to follow-up (LTU) using adjusted Poisson regression models. Results: Among 30,688 PLWH included, 17,491 (57%) were from Haiti, of whom 57% were female, 23% initiated ART in 2003-2008, 32% in 2009-2012, and 45% in 2013-2017. Of those from other sites, 23% were female, and 7% initiated ART before 2003, 29% in 2003-2008, 26% in 2009-2012, and 38% in 2013-2017. At ART initiation, 36% of PLWH from Haiti and 46% from all other sites had CD4+ count <200 cells/µL. There were 1,470 LTUs and 7,154 LTU among PLWH from Haiti and 1,167 deaths and 3,174 LTU at other sites. Crude and weighted mortality rates markedly decreased among all age groups over calendar eras. There were accompanying significant improvements in life expectancy, approaching that of the general population (61 years in Haiti and 69 years at other sites, in 2013-2017), though disparities by sex were significant in Haiti (Figure). While life expectancy improved over time, disparities by CD4+ count, education, and tuberculosis at or prior to ART persisted.

Conclusion: Life expectancy among PLWH on ART has significantly improved in Latin America and approaches that of the general population. Persistent disparities in life expectancy by sex, CD4+ count, education, and history of tuberculosis highlight vulnerable populations in the region.

EXCESS MORTALITY AMONG PLWH WITH MULTIMORBIDITY COMPARED TO HIV-NEGATIVE CONTROLS
Ni Gusti Ayu Nanditha1, Grace Zheng1, Hiwot M. Tafessu1, Taylor McLinden1, Andreea Bratu1, Robert S. Hogg1, Julie S. Montaner1, Viviane D. Lima1
1Vanderbilt University, Nashville, TN, USA, 2University of California San Francisco, San Francisco, CA, USA, 3Kaiser Permanente Southern California, Pasadena, CA, USA, 4Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, 5Harvard Pilgrim Health Care Institute, Boston, MA, USA

Background: Antiretroviral therapy (ART) and gains in life expectancy have increased the likelihood of people living with HIV (PLWH) developing comorbidities. We examined which chronic comorbidities, experienced in isolation or in combination, led to higher mortality rates among PLWH compared to HIV-negative controls. Secondly, we assessed the impact of multimorbidity on all-cause mortality among PLWH.

Methods: This population-based cohort study used longitudinal individual-level data on all treated PLWH and 1.5 age-sex-matched HIV-negative controls in British Columbia (BC), Canada. Eligible participants were ≥19 years old and enrolled in the Comparative Outcomes and Service Utilization Trends Study between 2001 and 2012 for ≥1 year. Comorbidities were identified from provincial administrative health databases (i.e., hospitalizations, outpatient physician, and pharmacy records). Selected comorbidities included liver, cardiovascular (CVD), renal, non-AIDS-defining cancers (NADC), hypertension, diabetes, and chronic obstructive pulmonary disease. Marginal structural models estimated the risk of all-cause mortality among PLWH with 1, 2, and ≥3 comorbidities (versus none).

Results: Overall, 51% of 8,405 PLWH, and 30% of 42,025 HIV-negative individuals developed ≥1 comorbidity by the end of follow-up. With the exception of the CVD-NADC combination, PLWH had higher all-cause mortality rates for all singular and combinations of diseases (see Figure). The largest disparity in mortality rate was related to renal disease (in isolation), where PLWH had a rate >30 times higher than that of HIV-negative controls. Among PLWH and the HIV-negative controls, a liver-NADC combination was associated with the highest mortality rate per 1000 person-years: 106.6 (95% confidence interval: 73.5-139.64) and 78.2 (46.24-110.16), respectively. After adjustment for demographic and time-dependent treatment-related confounders, PLWH with 1, 2, and ≥3 comorbidities were, respectively, 3.15 (2.57-3.86), 5.95 (4.65-7.61) and 12.96 (15.59-40.80) times more likely to die than PLWH without comorbidities.

Conclusion: Compared to HIV-negative controls, after adjusting for similar morbidities, PLWH experienced substantial excess in mortality rates. Additionally, we observed a strong positive dose-response between the number of morbidities and the risk of mortality among PLWH. These results highlight the critical role that additional morbidities continue to pose as drivers of mortality among PLWH within a publicly funded province-wide ART program.
Table: Increases in mortality rates after a cancer diagnosis among PWH and uninfected persons

<table>
<thead>
<tr>
<th>Cancer group</th>
<th>Rate difference (RD)</th>
<th>Excess mortality rate (per 1,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cancer</td>
<td>8.3%</td>
<td>20.6 (9.0-25.0)</td>
</tr>
<tr>
<td>ADC</td>
<td>4.3%</td>
<td>10.0 (4.6-16.3)</td>
</tr>
<tr>
<td>NADC</td>
<td>16.8%</td>
<td>30.3 (8.0-50.9)</td>
</tr>
<tr>
<td>Virus-unrelated NADC</td>
<td>20.3%</td>
<td>30.6 (8.0-50.8)</td>
</tr>
<tr>
<td>Virus-related NADC</td>
<td>21.1%</td>
<td>31.1 (9.0-50.9)</td>
</tr>
<tr>
<td>HIV-Related NADC</td>
<td>22.9%</td>
<td>32.7 (9.0-50.8)</td>
</tr>
</tbody>
</table>

1AIDS-defining cancers, non-HIV-infected lymphoma, and central nervous system cancer; NADCs: all cancers not classified as AIDS-defining cancers.

Results: The study included 39,000 PWH (with 697 cancers) and 387,767 uninfected adults (with 2,876 cancers). Any cancer increased mortality for PWH with an RD of 62.2 deaths per 1,000 py, and for uninfected persons with an RD of 45.5 deaths per 1,000 py. This difference by HIV status persisted with adjustment for confounders with an adjusted excess mortality rate for any cancer of 20.5 per 1,000 py (P<0.001) for PWH compared with uninfected persons. Excess mortality rates for PWH with cancer varied by cancer group (Table) with the lowest for ADCs (11.8) and the highest for NADCs (30.3), virus-unrelated NADCs (30.6), and HIV-related NADC (24.7).

Conclusion: Even with access to comprehensive HIV and cancer care, PWH have excess mortality after cancer, especially NADCs. Additional research is needed to understand this disparity, including studies evaluating effectiveness and tolerability of cancer treatments in PWH.

Table: Demographics of PLWH relative to 2009-2010, King County, Washington

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Male</th>
<th>Female</th>
<th>% difference</th>
<th>% difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>54</td>
<td>46</td>
<td>-8%</td>
<td>7%</td>
</tr>
<tr>
<td>30-59</td>
<td>45</td>
<td>55</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>60-80</td>
<td>37</td>
<td>63</td>
<td>-53%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Methods: We analyzed records of deaths in Massachusetts from 1999-2017 excluding non-residents. Using ICD-9 and -10 codes, we dichotomized deaths as with HIV or AIDS (ICD-9: 42, 43, 44, ICD-10: B20) or without HIV. We aggregated causes of death into broader system groupings (e.g. circulatory, digestive, respiratory, etc.) using WHO and CDC standards. We calculated the difference in the mean age at death for specific comorbidities during the earliest three-year period (1999-2001) with the most recent period (2015-2017) to assess improvements in longevity among individuals with HIV infection.

Results: There were 1,018,132 deaths in Massachusetts from 1999-2017; of these, 3,384 (0.3%) were among HIV infected individuals. The number of deaths among infected individuals declined from 1,319 deaths in 1999-2003 to 565 deaths in 2013-2017; deaths among uninfected individuals increased from 274,625 to 275,744. Mean age of death increased from 42.5 years in 1999-2003 to 565 deaths in 2013-2017; deaths among uninfected individuals declined from 1,319 deaths in 1999-2003 to 275,744. Mean age of death increased from 42.5 years in 1999-2003 to 52.5 years in 2013-2017.

Conclusion: A gap in longevity remains.

872 A DETAILED LOOK AT HIV MORTALITY IN KING COUNTY, 2016-2018

Andrea L. Martin¹, Meena Ramchandani¹, Susan E. Buskin²

¹University of Washington, Seattle, WA, USA

Background: While mortality among people living with HIV (PLWH) has declined 43% over the past decade in King County, death rates have remained stable over the past 5 years, from 1.0 to 1.1 deaths per 100 PLWH. Though some deaths among PLWH can be directly attributed to HIV, an increasing proportion of deaths are due to other factors, including the aging of PLWH. We compared a population based cohort of all PLWH 2016-2018 to decedents with HIV over those years, and conducted in death investigations of causes of death, comorbidities, and social determinants of health for 2017 deaths.

Methods: Data were collected by provider interviews, medical record abstractions, and analysis of the CDC's HIV/AIDS surveillance system (NHSS). 268 deaths occurred among King County PLWH 2016-2018 relative to 7,922 PLWH. Of 98 deaths in 2017 82% had a local death certificate and of these 85% had a local medical record available for review; medical providers completed surveys for 56% of these.

Results: One third (34%) of decedents had CD4 counts <200 relative to 5% of PLWH. 44% of decedents were 60+ years relative to 18% of PLWH; and 57% of decedents were diagnosed with HIV in 2000 or earlier relative to 33% of PLWH (Table). Decedents were roughly twice as likely to have a history of injection drug use. Of the 68 patients whose medical records were abstracted, 10 (15%) had causes of death related to HIV; half had an AIDS-defining Opportunistic illness (0c; 7%). Non-AIDS cancers were associated with death for 26%, heart disease for 18%, self-harm for 12%, and liver disease for 6%. An additional 10% had an AIDS related death within a year of death (making 22% total). More than half, 65% had a mental health diagnoses (mostly depression/anxiety), and 86% had some treatment of their mental health. One quarter had HCV and one quarter of these had been treated, all of whom had sustained viral response. Provider interviews suggest roughly 1/3 of decedents had some social isolation. Those experiencing stigma (24%) had 9-fold higher odds of an HIV-related death relative to decedents without known stigma.

Conclusion: Expectedly, decedents were older, had been diagnosed with HIV longer, had lower CD4 counts, and were more likely to have used injection drug use than PLWH. The deaths of the majority of PLWH in King County are from non-HIV/AIDS related causes though AIDS-OIs contributed to 7% of deaths and were present for 22%. Data suggest stigma may be associated with HIV-related deaths, but a larger study is needed to validate this finding.

873 USING MULTISTATE MODELS TO DISENTANGLE MORTALITY & LOSS TO FOLLOW-UP IN HIV+ PATIENTS

Nanina Anderegg¹, Jonas Hector², Juan Burgos², Laura Jefferys², Michael A. Hobbins³, Jochen Ehmer³, Matthias Egger³

¹Institute of Social and Preventive Medicine, Bern, Switzerland, ²SolidarMed, Pemba, Mozambique, ³SolidarMed, Luzern, Switzerland

Background: Estimating mortality in HIV-positive patients starting antiretroviral therapy (ART) is challenging, as clinics often face substantial loss to follow-up (LTFU). Many studies ignore LTFU, leading to biased estimates.
874 INCREASED MORTALITY AMONG PEOPLE AT HIGH RISK FOR HIV IN THE UNITED STATES

Fatma Shebl1, Julia H. Foote1, Krishna P. Reddy1, Yiqi Qian2, Kenneth Freedberg1, Rochelle P. Walensky1, Emily P. Hyle1

1Massachusetts General Hospital, Boston, MA, USA

Background: People with and at risk for HIV have competing risks of mortality independent of their HIV status, such as smoking, injection drug use (IDU), and serious mental illness. We sought to quantify the non-HIV-associated mortality risks among people from the major HIV transmission categories compared to those without the relevant risk factor: men who have sex with men (MSM); high-risk heterosexuals; and people who inject drugs (PWID).

Methods: We used the National Health and Nutrition Examination Survey (NHANES) (cycles 2001–14) and the National Health Interview Survey (NHIS 1991) with linked mortality data (through 2015) to examine independent associations of mortality with sexual orientation, low-socio-economic status (SES), and IDU among adults (>18y). We considered male respondents to be MSM if they reported a history of male sexual partner or self-identified as gay or bisexual and compared them to heterosexuals (in NHANES). We considered low socio-economic status (SES) as a proxy for the mortality risk experienced by high-risk heterosexuals and characterized low/high SES as poverty income ratio (PIR) ≤1 or ≥1 to examine associations between SES and mortality (in NHANES). We categorized individuals as ever PWID if they reported ever using heroin and compared them to never IDU (in NHIS). We included all major causes of death but excluded the “other” category to avoid double-counting HIV-associated causes of mortality. We used Cox proportional hazards models to estimate age- and race-adjusted mortality rates and hazard ratios (HR) with 95% confidence intervals (CI). Analyses were stratified by age at risk (≤55y vs >55y).

Results: MSM older than 55y had a non-significant higher risk of mortality compared to male heterosexuals (HR, 1.62) (Table). For females of low SES, mortality was higher for both ≤55y and >55y compared to females of high SES (HR, 2.61/3.41). Mortality was increased only among males of low SES older than 55y compared to males of high SES (HR, 2.47). Mortality was higher among ever PWID compared to never PWID. This was significant among ever PWID ≤55y (M/F HR, 2.75/4.09).

Conclusion: People from many of the major HIV transmission categories had a higher risk of non-HIV-associated mortality compared to those without the relevant risk factor. Interventions for people with HIV should also focus on reducing non-HIV-related causes of death to achieve maximum impact.

875 CD4 COUNT PATTERNS OVER TIME IDENTIFY LONG-TERM HIV CARE TRAJECTORIES IN SOUTH AFRICA

Ingrid V. Basset1, Ai Xu1, Janet Giddy1, Sue Candy1, Laura M. Bogart1, Andrew Boule2, Lucia Millham3, Robert A. Parker4, Elena Losina5

1Massachusetts General Hospital, Boston, MA, USA, 2McCord Hospital, Durban, South Africa, 3National Health Laboratory Service, Johannesburg, South Africa, 4RAND Corporation, Santa Monica, CA, USA, 5University of Cape Town, Cape Town, South Africa, 6Brigham and Women’s Hospital, Boston, MA, USA

Background: Predicting long-term care engagement at HIV diagnosis would allow targeted interventions for those at high risk of poor outcomes. Our objective was to uncover distinct CD4-based trajectories and determine baseline contextual, clinical and sociobehavioral factors associated with higher risk of being in a worse CD4 trajectory.

Methods: We used data from the Sizanani trial (NCT01188941) in which adults (≥18y) were enrolled prior to HIV testing at 4 Durban outpatient sites from Aug 2010-Jan 2013. We ascertained longitudinal CD4 count data over 5y follow up using probabilistic matching with data from the National Health Laboratory Service. We used group-based statistical modeling to identify groups with similar CD4 count trajectories over time and Bayesian information criteria to determine distinct CD4 trajectories. We then evaluated baseline risk factors that predict membership in a specific (worse) trajectory using multinomial logistic regression. We examined year of enrollment, age, gender, whether people lived alone, TB positivity at enrollment, and number of domains of self-identified barriers to care (related to service delivery, financial, personal health perception, logistical, and structural) and accounted for ART initiation within 3 months of diagnosis and mortality.

Results: 688 participants had longitudinal data available by NHLS crossmatch; 555 (81%) were women and median baseline CD4 count was 218 (IQR 94–368). Group-based trajectory modeling identified 4 distinct trajectories (Figure); Group 1 (19.5% of sample), with a consistent very low CD4 count that did not increase (red); Group 2 (20.7%), with a very low at baseline but increasing over time CD4 count (green), Group 3 (44.6%) with a medium-low but increasing CD4 count (blue), and Group 4 (15.9%) with a high baseline CD4 count that increased steadily overtime (black). Earlier year of enrollment, younger age, failure to start ART within 3 months, male sex, TB positivity and a greater number of self-identified barriers to care domains predicted membership in groups with poorer outcomes (Groups 1 and 2) compared to Group 4 (reference).
Conclusion: One-fifth of people newly-diagnosed with HIV presented with low CD4 counts that failed to rise over time. Factors available in early clinical encounters, including potentially modifiable healthcare barriers, can predict long-term outcomes. Identifying those at high risk for poor care engagement can inform design of differentiated interventions to improve long-term clinical outcomes.

877 EFFECT OF ERECTILE DYSFUNCTION DRUGS ON T CELLS AND IMMUNE MARKERS IN MEN

Jee Won Park1, Adrian Dobs2, Ken Ho1, Frank J. Palella3, Eric C. Seaberg4, Onyebuchi A. Arah5, Otoniel Martínez-Maza6, Roger Detels1
1University of California Los Angeles, Los Angeles, CA, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA, 3University of Pittsburgh, Pittsburgh, PA, USA, 4Northwestern University, Chicago, IL, USA, 5Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: Erectile dysfunction (ED) drugs are frequently used in men who have sex with men (MSM). Although commonly associated with increased vasodilation, there is evidence of beneficial immunomodulatory effects of these drugs in animal studies. However, studies on the effect of ED drugs on immune capacity and function in MSM are limited.

Methods: A total of 1,391 HIV positive men and 307 HIV negative men were included from the Multicenter AIDS Cohort Study (MACS), an ongoing prospective HIV/AIDS cohort study in the U.S., from 1998 onwards, with ages ranging from 19 to 70 years. We used marginal structural models in the form of g-computation in complex longitudinal setting to assess the causal mean differences (MD) in CD4 and CD8 T cells for 10 years, as well as other immune biomarkers up to 4 observations.

Results: ED drug use over time was associated with an increase in the number of CD4 cells in HIV positive men. After controlling for important confounding variables such as age, viral load and ART, the causal MD in CD4 cell counts in HIV positive men after 1 year of ED drug use was 57.6 cells/µL and increased to 117.7 cells/µL after 10 years. CD8 cell counts were higher among ED drug users over a 10-year period compared to non-users in the HIV positive group but showed almost no significant differences in HIV negative group. Positive ED drug users also showed reduced levels of pro-inflammatory markers, IL-6 (MD: -1.98, 95% CI: -2.22 – -1.75) and TNF-α (MD: -2.31, 95% CI: -2.48 – -2.14) after one year of observation. An anti-inflammatory cytokine, IL-10, was higher in ED drug users compared to non-users. HIV negative subjects showed similar effects with ED drug use over time with respect to inflammatory markers.

Conclusion: ED drug use was associated with a significantly higher CD4 T cell outcome in HIV positive MSM. Furthermore, analyses of immune biomarkers showed ED drug use to have been associated with lower pro-inflammatory and higher anti-inflammatory markers over time. This observation suggests a favorable immunomodulatory effect of ED drugs in MSM.

878 PREEXPOSURE PROPHYLAXIS ADHERENCE AND PERSISTENCE IN KENYAN TRANSGENDER WOMEN AND MSM

Makobo Kimani1, Elisabeth M. van der Elst1, Oscar Chirro1, Fauz Ibrahim2, Nana Mukuria3, Tobias F. Rinke de Wit4, Susan M. Graham4, Eduard Sanders1
1KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya, 2Kilifi County Department of Health, Kilifi, Kenya, 3Academic Medical Center, Amsterdam, Netherlands, 4University of Washington, Seattle, WA, USA

Background: Transgender women (TGW) and men who have sex with men (MSM) in sub-Saharan Africa have high HIV acquisition risks and can benefit from daily pre-exposure prophylaxis (PrEP) if taken regularly. We set out to assess PrEP adherence by measuring tenofovir-diphosphate (TFV-DP) levels and explore motives for PrEP persistence in a sample of TGW and MSM in coastal Kenya.

Methods: Participants enrolled in a one-year PrEP programme and made quarterly visits irrespective of whether they were still using PrEP. At their month 6 visit, participants provided a dried blood spot to be tested for TFV-DP levels; protective levels were defined as those compatible with ≥2 pills per week (700-1249 fmol/punch). Before TFV-DP levels were available, sub-set of these participants completed in-depth interviews (IDIs). All TGW and purposively selected MSM participated in the IDIs. We used semi-structured topic guides to explore motives to start and adhere to PrEP, and reasons to stop it.IDI data were analyzed thematically.

Results: Fifty-three participants (42 MSM and 11 TGW) were enrolled. At month 6, 12 (22.6%) participants (9 MSM and 3 TGW) were lost to follow up. Any TFV-DP was detected in 62.5% (5/8) of TGW vs. 15.2% of MSM (5/33, p=0.004). Protective levels were detected in 37.5% of TGW (3/8) but not in any MSM. Nineteen IDIs were conducted, with 7 TGW and 8 MSM on PrEP, and 1 TGW and 3 MSM off PrEP. Unplanned or frequent risky sexual risk behaviour, including condomless anal intercourse, were the main motives for PrEP uptake. Among TGW, the notion that PrEP reinforced their female gender identity seemed to aid adherence. Inconsistent PrEP use was attributed to situational factors and...
Results: Of the 562 individuals, 254 (44%) were sero-negative for all three infections. The prevalence of HIV, HSV-2, and HCV were 29%, 48%, and 5% respectively. 130 (23%) had laboratory-confirmed HIV-2 only, 5% were HIV only, and 1% HCV only. 21% (119/562) were co-infected with HIV and HSV-2, and 2% were infected with all three. Compared to Boston, the prevalence of having one or more infections was higher in New York (adjPR 1.88, 95%CI 1.36, 2.60), Baltimore (adjPR 1.51, 95%CI 1.12, 2.04), Atlanta (adjPR 1.38, 95%CI 1.02, 1.98), and Miami (adjPR 1.49, 95%CI 1.10, 2.01). The frequency of disease burden increased with age, as having any one or more infections increased from 27% for those <26 to 81% for those older than 45 years of age. Compared to white TW, Black, Hispanic and mixed race TW had a higher burden of disease (adjPR 3.21 95%CI 2.25, 4.59; 2.46 95%CI 1.68, 3.61; 2.28 95%CI 1.74, 3.54, respectively). Though those who ever experienced unstable housing or were without full-time employment had higher burdens of disease, these associations were attenuated in the full model. Of note, family support was associated with a higher burden of disease (adjPR 1.29, 95%CI 1.08, 1.55). This finding can be partially explained by the greater level of family support for Black TW (69%) vs. White TW (52%).

Conclusion: We found a high burden of disease among TW. Difference in disease burden were found geographically, by race and ethnicity, family support studies and with age. Surprisingly, employment status and lifetime unstable housing status were not associated with an increased risk of infection. Findings highlight the need for prospective research to further evaluate TW vulnerabilities, including for incident infections.
Background: Transwomen (TW) are uniquely vulnerable to poor HIV control due to gender identity-related stigma and discrimination. Standard HIV care continuum estimates ignore how long people spend in each stage and may artificially inflate positive outcomes by excluding people who die.

Methods: We included antiretroviral therapy (ART)-naive TW, ciswomen (CW) and cismen (CM) who engaged in care between 2000-2016 in 15 United States (US)-based NA-ACCORD cohorts that contributed data on transgender patients. We estimated the proportion of the cohort alive, engaged-in or lost-to-clinic, ART-initiated, and virally suppressed or not over the first 7 years in care. We summarized over time by reporting the average years over 7 years that each gender identity group spent in each stage. To do this, we added and subtracted series of cumulative incidence functions for death (from registry or medical record data); loss-to-clinic (12 months without a clinic visit, CD4 cell count, or viral load) and subsequent return-to-clinic; ART initiation; and viral suppression or loss of suppression after ART initiation. We report crude estimates and also adjusted for age, race/ethnicity, and calendar year. We report 95% confidence intervals (CI) around these estimates from 1000 non-parametric bootstrap resamples.

Results: We included 123 TW, 6979 CW, and 35751 CM. TW were younger (median age=30 years, vs. 39 and 40 years for CW and CM) and enrolled into care later during the study period (2009 vs. 2007 and 2007). Over the first 7 years in care, TW spent an average of 3.2 (95% CI: 2.7, 3.7) years virally suppressed after ART initiation, 1.1 (0.8, 1.4) years not virally suppressed after ART initiation (includes gaps in treatment, poor adherence, and virologic failure), 1.2 (0.9, 1.6) years in care prior to ART initiation, and 1.3 (0.7, 1.8) years lost-to-clinic, and they lost 0.3 (0.0, 0.6) years to death (figure). Compared with CW and CM, respectively, TW spent 0.7 (95% CI: 0.2, 1.2) and 0.2 (-0.3, 0.8) more years virally suppressed. After adjustment, differences between TW and CW and CM were generally smaller.

Conclusion: In several US clinics, longitudinal engagement in HIV care among TW was similar to that seen for CW and CM. Many of the HIV clinics in this analysis provide gender-affirming care; these results may not generalize to other contexts. Given the small sample of TW, further studies are recommended to explore other care outcomes in this highly vulnerable population.
884 IMPROVING DATA ON THE NYC HIV EPIDEMIC BY IDENTIFYING TRANSGENDER PEOPLE ON MEDICAID
Cristina Rodriguez-Hart1, Beverly Obeng2, Asa Radix2, Zil Goldstein3, Gagarin Zhao1, Lucia V. Torian1
1New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, 2Callen–Lorde Community Health Center, New York, NY, USA
Background: Since 2005, the New York City Department of Health and Mental Hygiene HIV Surveillance Program has ascertained transgender status among people living with HIV (PLWH) using data on sex assigned at birth and gender identity. Due to challenges in data availability, undercounting of transgender PLWH in NYC remains prevalent. In order to improve our ability to accurately enumerate transgender PLWH and address their needs for gender-affirming HIV care, we used claims data to identify transgender Medicaid enrollees and match these persons to the HIV registry.
Methods: Medicaid claims do not specify gender identity inclusive of transgender status. In consultation with clinical experts on HIV and gender-affirming care, we developed an algorithm to identify transgender Medicaid enrollees using diagnoses, prescriptions and sex at birth from claims records in 2013-2017. In order to identify those living with HIV, we matched Medicaid enrollees to individuals diagnosed with HIV before 2018 in the registry.
Results: Our algorithm identified 6,043 unique transgender persons who accessed Medicaid in 2013-2017, with 1,472 (24%) reported to the HIV registry, 1,168 (79%) of whom were identified as transgender in the registry. We found an additional 292 transgender individuals in the registry that had accessed Medicaid during this period but were not identified by our algorithm, for a total of 6,335 transgender individuals accessing Medicaid during this period (0.1% of the NYC Medicaid population) and 1,764 transgender PLWH (28% of transgender individuals accessing Medicaid). From 2013 to 2017, there was a 35% increase in transgender Medicaid enrollees. From 2013 to 2017, there was a 35% increase in transgender Medicaid enrollees. From 2013 to 2017, there was a 35% increase in transgender Medicaid enrollees. From 2013 to 2017, there was a 35% increase in transgender Medicaid enrollees. From 2013 to 2017, there was a 35% increase in transgender Medicaid enrollees.
Conclusion: Our algorithm highlights that TW are infected younger than other gender groups, but without lower CD4 cell count at initiation of care. They are not at an increased risk of loss of follow-up or later VR than other groups.

885 BUPRENORPHINE TREATMENT IS RELATED TO DECREASED HIV RNA LEVELS AMONG PEOPLE WITH HIV
Jongyeon Kim1, Geetanjali Chander1, Catherine R. Lesko1, Anthony T. Fojo1, Richard D. Moore2, Bryan Lau1
1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA
Background: Initiation of buprenorphine (BUP) for people with HIV (PWH) and opioid use disorder (OUD) may improve HIV clinical outcomes. We examined level of HIV RNA among PWH initiating BUP in an urban HIV clinic.
Methods: In the Johns Hopkins Hospital HIV Clinic Cohort (JHHCC), we identified 207 PWH who started buprenorphine treatment between 2002 and 2018. We allowed multiple number of treatment episodes (defined as continuous buprenorphine prescription with gaps less than 30 days). A quantile linear model was used to assess the relationship between buprenorphine (BUP) and viral load considering skewed distribution and the large proportion of individuals who were suppressed. We estimated quantiles with cluster bootstraps to account for repeated observations within participants. We included CD4 counts, sex, race, age, injection drug use, and men who have sex with men as covariates. Each individual contributed viral loads one year before and one year after their BUP initiation. We present difference in the 25th, 50th, and 75th percentiles comparing prior and subsequent to any episode of BUP treatment.
Results: The 207 PWH were primarily male (69%), black (88%), with median age of 49 (IQR: 44-53) at their initial BUP treatment. Individuals contributed a median of 1 (IQR:1-2) treatment episodes. HIV viral loads before and after initial treatment were a median of 80 (IQR: 50-6690) and 50 (IQR: 50-1721) copies/mL respectively. The figure shows a scatterplot and the unadjusted quantiles of HIV RNA as time prior to and subsequent to initial BUP treatment. In the model in which we considered time-varying treatment status, the estimated difference in the four quantiles comparing before and after treatment were 25th: 0 [95% CI: -4.675, 3.889], 50th: -43.94 [95% CI: -156.7 , 1.208], and 75th: -4360 [95% CI: -10930, -195.8]. Approximately 74% of viral loads were below 1500 copies/mL (a meaningful cutoff for the risk of HIV transmissibility) after the BUP treatment compared to 69% before treatment. Restriction to individuals who started BUP treatment after 2011 similarly suggested difference of viral loads in higher quantiles, but was limited in sample size (61).
Conclusion: These data suggest that BUP treatment for OUD among PWH is likely to have beneficial effects on HIV RNA. By increasing the proportion of PWH below 1500 copies/mL, it would lower the overall risk for HIV transmission.
AFFORDABLE CARE ACT’S IMPACT ON SUBSTANCE-USE TREATMENT IN PEOPLE WHO INJECT DRUGS

Erik M. Hendrickson1, Tarik Benmarhnia1, Steffanie A. Strathdee1, Jazmine Cuevas-Mota1, Richard S. Garfein1
1University of California San Diego, La Jolla, CA, USA

Background: Substance use treatment (SUT) for Persons Who Inject Drugs (PWID) can reduce the risk of HIV and HCV transmission, yet the lack of health insurance or insurance plans that cover these services is a major barrier to PWID entering SUT. Provisions in the U.S. Patient Protection and Affordable Care Act (ACA) were expected to increase the use of SUT in PWID by increasing access to health insurance and including these services as an essential health benefit. Methods: We analyzed SUT use before and after the implementation of the ACA in California on January 1, 2014 among participants enrolled in STAIR-II (2012-2016)—a longitudinal cohort study of PWID in San Diego, California that included a baseline and up to 4 semi-annual follow-up interviews. We examined changes in self-reported SUT within participants pre- and post-ACA implementation. We included participants who had both a baseline visit and a follow-up visit before and after the implementation of the ACA in California. We excluded visits with referent time periods that overlapped with the ACA implementation date. In bivariate analysis, we used McNemar’s test for paired comparisons to determine the association between the ACA and SUT, as well as potential confounders. We used multivariable logistic regression analysis with Generalized Estimation Equations (GEE) for repeated measures to assess the association between the ACA and SUT, adjusting for baseline covariates: age, sex, race, education, HIV, HCV, chronic disease, prior SUT use, past 6-month daily injection, past 6-month homelessness, perceived need for SUT. Insurance status was a time-updated covariate. Results: Of 170 participants who had both baseline visit and a follow-up visits before and after the implementation of the ACA in California, 71% were male, 50% were White and mean age was 45 years. There was an 11.8% increase in SUT use after the ACA, compared to before (52.4% vs. 40.6%, p=0.01) and a 10.6% increase in the proportion who had insurance after the ACA compared to before (81.2% vs. 70.6%, p<0.01). The positive impact of the ACA on SUT remained after adjusting for age, race, ever using SUT, perceived need for SUT, and insurance status (AOR: 1.85, 95%CI: 1.25-2.76). Conclusion: Implementation of the ACA in California was associated with an increase in SUT use among PWID in San Diego, suggesting that the ACA successfully achieved the objective of increasing access to SUT.

UNMET NEED FOR MEDICATION-ASSISTED TREATMENT AMONG PERSONS WHO INJECT DRUGS

Senad Handanagic, Dita Broz1, Cyprian Weinert1, for the NHHS Study Group
1CDC, Atlanta, GA, USA

Background: Persons who inject drugs (PWID) are at increased risk of HIV and hepatitis C virus (HCV) infections and premature mortality due to drug overdose. Medication-assisted treatment (MAT) reduces high-risk injecting behaviors, HIV and HCV transmission, and mortality from opioid overdose among PWID with opioid use disorder. Using data from National HIV Behavioral Surveillance (NHBS), we evaluated self-reported unmet need for MAT among PWID in 23 US cities in 2018. Methods: PWID were recruited by respondent-driven sampling in 2018 and interviewed. This analysis includes PWID who reported injecting drugs in the past 12 months, were 18 years or older and reported opioid use (including heroin) in the past 12 months. Unmet need for MAT was measured by asking participants if they tried to get methadone or buprenorphine to treat drug use but were unable to in the past 12 months. We used log-linked Poisson regression with generalized estimating equations to examine the association between self-reported unmet need for MAT and high-risk injecting practices and nonfatal opioid overdose. Models were adjusted for complex survey design and for confounding for age, race/ethnicity, city of residence, peer network size, current homelessness, having health insurance and being enrolled in MAT in the past year; we obtained adjusted prevalence ratios (aPR) and 95% confidence intervals (CI). Results: Of 10,965 PWID who reported opioid use in the past 12 months, 30% were female, and the median age was 44 years. In total, 28% of PWID reported unmet need for MAT in the past 12 months, and 82% of those reported visiting a health care provider in the previous year. After adjusting for confounding, PWID who reported unmet need for MAT were more likely to report injecting more than once a day (aPR 1.09, 95% CI: 1.07-1.12), receptive sharing of syringes (aPR 1.11, 95% CI: 1.04-1.19) and opioid overdose (aPR 1.33, 95% CI: 1.24-1.43) in the past 12 months. Conclusion: More than 1 in 4 PWID reported unmet need for MAT and more than 80% of those had seen a health care provider in the past 12 months. PWID with reported unmet need for MAT were more likely to report high-risk injecting behaviors and experiencing opioid overdose. These findings highlight a missed opportunity for enrolling PWID on MAT as part of a comprehensive prevention approach to reduce the risk of HIV and HCV transmission and opioid overdose among PWID. Health care providers engaging with PWID could be an important source for linkage to MAT.

UNMET NEEDS AND BARRIERS TO CARE SERVICES AMONG HIV-POSITIVE PERSONS WHO INJECT DRUGS

Sharoda Dasgupta1, Yunfeng Tie1, Linda Beer1, Dita Broz1, Quan M. Vu1, Hanna B. Demeke2
1CDC, Atlanta, GA, USA
2CDC Atlanta, GA, USA

Background: HIV-positive persons who inject drugs (PWID) have poorer clinical outcomes compared with other persons, and limited access to medical care services may be a contributing factor. Data on use of and barriers to services can inform interventions intended to improve access to care but estimates are lacking. We report nationally representative estimates on use of, need for, and barriers to services among HIV-positive PWID. Methods: We used data from the Medical Monitoring Project, a national surveillance system that reports representative estimates of characteristics among adults with diagnosed HIV. During 6/2015–5/2018, interviews were conducted to assess injection drug use, use of and need for services, and barriers to care in the past 12 months. Among persons who injected drugs during the prior 12 months (n=340), we reported the percent who received certain services and percent of persons who needed, but did not receive those services during the past 12 months (i.e., experienced unmet need). Of those with unmet needs, we reported barriers to care for each service. We reported weighted percents to account for complex survey design. Results: Of adults with diagnosed HIV, 3% injected drugs in the past 12 months. Almost all (99%) HIV-positive PWID received ≥1 service; most commonly used services included those for HIV care management (61%) and mental health (55%) (Figure). Forty percent received drug/alcohol treatment. Overall, 79% had an unmet need for ≥1 service. The services with the highest unmet need were for dental care (38%), drug/alcohol treatment (20%), transportation assistance (20%), and HIV peer group support (20%). Of those with unmet needs, 46% of persons needing dental care did not seek services because they could not pay for services; 79% of those needing drug/alcohol treatment did not seek services due to personal reasons, such as fear or embarrassment; 53% of those needing transportation assistance did not have information on services; 57% of those needing HIV peer group support also did not seek services due to personal reasons. Conclusion: Almost all HIV-positive PWID received ≥1 medical service, but a substantial proportion had unmet needs, including for drug/alcohol treatment. Barriers to care varied by service type. Addressing barriers to receiving services, including for drug/alcohol treatment, may help improve ART adherence and viral suppression among HIV-positive PWID.
889 ESTIMATING HIV INCIDENCE AMONG PWID: POPULATION- AND FACILITY-BASED APPROACHES
Allison M. McFall, Sunil S. Solomon, Oliver Laeyendecker, Syed Iqbal, Shanmugam Saravanan, Handagopal Paneerselvam, Pachamuthu Balakrishnan, Aylur K. Srikrishnan, David D. Celentano, Gregory M. Lucas, Shruti H. Mehta
1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2YR Gaitonde Center for AIDS Research and Education, Chennai, India, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4NIAID, Baltimore, MD, USA, 5Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: Monitoring HIV incidence is vital for characterizing the epidemiology and trajectory of HIV epidemics and impacts of prevention efforts. Standard methods for measuring incidence such as cohort studies take considerable time and cost and are often not feasible in settings, leading to a reliance on new HIV diagnoses, inherently a biased measurement. We compare HIV incidence estimation using 3 different methods/data sources which might leverage available program data in a variety of settings.

Methods: We used data derived from a cluster-randomized trial among people who inject drugs from 12 Indian cities to estimate HIV incidence. First, we used a validated multi-assay algorithm (MAA) to define recent HIV infection within the trial’s follow-up cross-sectional samples (Aug 2016-Apr 2017) accrued using respondent-driven sampling (RDS). Second, we estimated incidence from PWID that participated in two (confirmed via biometrics) cross-sectional RDS samples - baseline (Jan-Dec 2013) and follow-up (Aug 2016-Apr 2017) - and were serologically HIV negative at baseline. Third, we estimated incidence from initially HIV-negative PWID clients who received one or more repeat HIV tests at integrated care centers (ICCs) (Jun 2014-Feb 2017) in 6 of the 12 cities. The goal was to test clients every 6 months. ICCs also provided opioid agonist therapy and other PWID services (e.g., needle exchange).

Results: Across all cities, MAA-estimated incidence was generally highest, followed by the serial cross-sectional, with ICC estimates being substantially lower. MAA annual incidence ranged from 18.5% (New Delhi) to zero (Imphal), serial cross-sectional incidence from 16.1% (Kanpur) to 0.3% (Imphal), and ICC incidence from 7.3% (Alizawal) to 0.1% (Imphal). On average, the serial cross-sectional estimate was 19% lower than the MAA (range: -60% to +190%) and 20% higher than the ICC (range: -32% to +953%). While estimates were variable, rank order generally stayed the same across the estimates (Figure). Spearman rank correlation was 0.94 for the MAA-serial cross-sectional estimates, 0.83 for MAA-ICC, and 0.66 for serial cross-sectional-ICC estimates.

Conclusion: While HIV incidence estimates within a given city were variable by method, the rank order by incidence was consistent. While use of facility-based data will generally underestimate population incidence, using cross-sectional population-based data to estimate HIV incidence can prioritize where resources may optimally be directed.

890 OPTIMIZING SOCIAL-NETWORK SAMPLING TO FIND UNDIAGNOSED HIV-INFECTED PWID
Allison M. McFall, Bryan Lau, Carl A. Latkin, Aylur K. Srikrishnan, Santhanan Anand, Canjeevaram K. Vasudevan, Shruti H. Mehta, Sunil S. Solomon
1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3YR Gaitonde Center for AIDS Research and Education, Chennai, India, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: People who inject drugs (PWID) experience high HIV burden and lag behind in UNAIDS 95-95-95 targets, particularly at diagnosis. We evaluated whether identification of undiagnosed HIV-infected PWID via respondent-driven sampling (RDS), a chain referral approach that leverages social networks, can be enhanced through a precision RDS (pRDS) approach.

Methods: We identified characteristics that predicted recruitment of an undiagnosed HIV-infected PWID using previously collected RDS data from PWID in north India. We developed a multivariable prediction algorithm comprised of factors identified by the area under the receiver operator curve from logistic regression models and a random forest. pRDS was tested in Morinda, Punjab where participants were randomly assigned (1:1) to standard or pRDS. In the standard approach, all participants received 2 coupons. For pRDS, an individual’s probability of recruiting an undiagnosed PWID was determined by the algorithm and they received 2 (if low probability) or 5 (if high probability) coupons. The identification rate and number needed to recruit (NNR) - average number recruited in order to find one undiagnosed PWID - of each approach were compared.

Results: Predictors of recruiting an undiagnosed HIV-infected PWID included HIV/HCV infection, network size, use of syringe services, and the injection environment. Among 1631 PWID recruited in Morinda, HIV prevalence was 10%, of whom 70% were undiagnosed. From the standard approach, 615 were recruited including 39 who were undiagnosed; from pRDS, 1012 were recruited including 77 who were undiagnosed. pRDS had a significantly higher identification rate of undiagnosed PWID (1.5/week) compared to the standard (0.8/week; difference: 0.7, 95% CI: 0.3, 1.1). However, the NNR for pRDS (13.1) was not significantly lower than the standard coupon system (15.8; difference=2.6, 95% CI: -2.6, 10.0). NNR differences were more substantial in the first four months but decreased over time (test for trend p-value=0.002) (Figure). Cost to identify one undiagnosed PWID was ~10 USD lower in the pRDS approach vs. the standard.

Conclusion: A precision RDS approach identified nearly twice as many undiagnosed PWID significantly faster than the standard. While the NNR was not lower in pRDS, given the importance of timely identification and linkage to antiretroviral therapy, pRDS may be particularly useful in outbreaks when rapidly reaching undiagnosed people living with HIV is needed.
LATENT CLASS ANALYSIS OF SUBSTANCE USE AND HIV VL TRAJECTORY PATTERNS AMONG PWH IN DC

Morgan Byrne, Anne K. Monroe, Lindsey J. Powers Hopp, Rupali K. Doshi, Michael A. Horberg, Amanda D. Castel, for the DC Cohort Executive Committee 1George Washington University, Washington, DC, USA

Background: People with HIV (PWH) with substance use disorders (SUD) have worse health outcomes than PWH without SUD. Our objective was to characterize substance use (SU) patterns and their impact on Viral Load (VL) trajectories among PWH.

Methods: Data from PWH aged ≥18 years enrolled Jan 2011-Mar 2018 in the DC Cohort, a longitudinal observational study of PWH in care at 14 clinics in Washington, DC, were analyzed. Data were abstracted from participants’ electronic medical records. SU was defined as documented SU at DC Cohort enrollment and/or the presence of SU-related ICD-10 codes during study follow-up. Treatments for alcohol and opioid use were also used to identify PWH receiving care for SU. Participants with at least 3 VL were included in analysis. Latent class analysis (LCA) was used to determine classes with similar patterns of SU. HIV RNA values were examined using discrete mixture models to determine classes of group-based logVL trajectories and constructed using 3 VL measures. The number of classes for both SU patterns and VL trajectory were chosen using Bayesian Information Criterion, MLE, and maximized model fit. Differences in demographic and clinical characteristics between the SU classes were evaluated using a multivariable-adjusted multinomial model. The relationship between classes of SU patterns and classes of VL trajectories was examined using a χ² test.

Results: 6,301 participants were assigned to one of three LCA SU classes based on posterior probability: (1) No illicit SU, (2) limited SU and (3) polysubstance use. There were 4 VL trajectory classes: (a) always undetectable, (b) achieved undetectable VL, (c) always VS, and (d) high VL. In multivariable models, individuals in both the polysubstance and limited SU classes were less likely to have private insurance (P<0.05), more likely to be current smokers (P<0.001) and homeless (P<0.01) compared to the no illicit SU class after adjusting for cohort demographics. Polysubstance use participants were most likely to be categorized in the trajectory that did not achieve VS, followed by participants in the limited SU class (28% and 24% respectively; p-value <0.001). Proportions of participants in each trajectory are shown given membership in SU classes (Fig). LCA identified distinct patterns of SU among PWH, with limited and polysubstance users having higher proportions of high VL trajectories. These results may guide planning of SU treatment especially for newly diagnosed PWH to improve their ability to achieve and sustain VS.

Conclusion: LCA identified distinct patterns of SU among PWH, with limited and polysubstance users having higher proportions of high VL trajectories. These results may guide planning of SU treatment especially for newly diagnosed PWH to improve their ability to achieve and sustain VS.

MORTALITY AMONG PERSONS WITH HIV WITH A HISTORY OF INJECTION DRUG USE, NEW YORK CITY

Chitra Ramaawardy, Sarah L. Braunstein 1 New York City Department of Health and Mental Hygiene, Long Island City, NY, USA

Background: Persons with HIV (PWH) who reported a history of injection drug use (IDU) have disproportionately higher mortality than those who did not report a history of IDU despite decreasing trends in all-cause mortality as well as new HIV diagnoses.

Methods: We used New York City (NYC) Surveillance data for PWH age ≥20 years and alive at end of 2017 or who died during 2008-2017, and data on underlying cause of death for decedents from the Vital Statistics Registry or National Death Index, to examine the characteristics, cause of death and age-standardized mortality rates of PWH with a history of IDU.

Results: There were 145,799 PWH included in the analysis, representing 1,192,752 person-years. Of these, 25,144 (17%) reported a history of IDU, of whom 6,733 (27%) died by the end of 2017. Although mortality rate decreased substantially among NYC PWH overall and among all transmission risk groups during 2008-2017, the mortality rate was persistently higher among PWH with IDU history compared to PWH in other HIV transmission risk groups (Figure 1). Of decedents with IDU history, nearly nine out of ten were either non-Hispanic Black or Hispanic (88%), nearly half were age 50-59 years (44%); median age 55 (interquartile range: 47-61)), and nearly two-thirds lived in high or very high poverty neighborhoods (62%). Of IDU PWH decedents, nearly two-thirds (60%) died from a non-HIV-related cause and 39% died from an HIV-related cause. The top causes of non-HIV-related deaths were cancer (n=976, 24%); liver and lung most common) and cardiovascular diseases (CVD) (n=946, 24%; ischemic heart disease and hypertensive heart disease most common). Adjusting for demographic factors, PWH with IDU history age 50-59 (hazard ratio (HR) 1.6, 95% CI 1.5-1.8), Hispanics (HR 1.5, 95% CI 1.4-1.7) and those living in high or very high poverty neighborhoods (HR 1.4, 95% CI 1.3-1.5) had higher risk of death.

Conclusion: Although it declined, mortality among NYC PWH with IDU history remained high during 2008-2017. Older IDU PWH, Hispanic IDU PWH and IDU PWH living in high poverty neighborhoods had elevated mortality risk. Since over a third of deaths were due to HIV, improvement in HIV outcomes in this population should reduce HIV-related mortality. Additionally, interventions are needed for IDU PWH to reduce the prevalence of factors such as smoking, high-risk sexual behaviors, and co-infections such as hepatitis C given their role in CVD- and cancer-related mortality.

HCV, AIDS, LIVING IN SOUTH ARE RISK FACTORS FOR MORTALITY IN HIV+ SUBSTANCE USERS

Mamta K. Jain, 1 Mark A. Vasquez, 1 Lauren Gooden, 1 Rui Duan, 1 Cindy Minding, 1 Nelson, 1 Daniel J. Feaster, 3 Ank E. Nijhawan, 1 Megan Sullivan, 1 Allan Rodriguez, 3 Gerogina Osorio, 1 Robinia Walker, 1 Petra Jacobs, 7 Carlos del Rio, 1 Lisa R. Metsch, 2

1University of North Texas Southwestern, Dallas, TX, USA, 2Columbia University, New York, NY, USA, 3Emory University, Atlanta, GA, USA, 4Boston University, Boston, MA, USA, 5Icahn School of Medicine at Mount Sinai, New York, NY, USA, 6NIH, Bethesda, MD, USA

Background: Hospitalized HIV substance users were enrolled into Project HOPE to evaluate the effect of patient navigation (PN) vs. PN with financial incentives vs. usual care on HIV viral suppression. Those who provided consent for future treatment with PWH receiving care for SU. Participants with least 3 VL were included in analysis. Latent class analysis (LCA) was used to determine classes with similar patterns of SU. HIV RNA values were examined using discrete mixture models to determine classes of group-based logVL trajectories and constructed using 3 VL measures. The number of classes for both SU patterns and VL trajectory were chosen using Bayesian Information Criterion, MLE, and maximized model fit. Differences in demographic and clinical characteristics between the SU classes were evaluated using a multivariable-adjusted multinomial model. The relationship between classes of SU patterns and classes of VL trajectories was examined using a χ² test.

Results: LCA identified distinct patterns of SU among PWH, with limited and polysubstance users having higher proportions of high VL trajectories. These results may guide planning of SU treatment especially for newly diagnosed PWH to improve their ability to achieve and sustain VS.
contact were invited to participate in a follow-up study to evaluate hepatitis C virus (HCV) infection and the impact of care facilitation vs. usual care on progression along the HCV care continuum. We examined overall mortality and predictors of death which occurred during the primary study and through the end of the follow-up study.

Methods: Retrospective cohort study conducted among 801 HIV-infected participants enrolled in Project HOPE between July 2012 and January 2014; they were followed for a maximum of 62 months. Kaplan-Meier estimates with a Renyi type test were used for the survival curves and an Accelerated Failure Time (AFT) model assuming a log logistic distribution was used to examine predictors of all-cause mortality.

Results: Participants were 33% women, 73% black, 59% lived in the South, 40% had <high school education, average age was 44.6±10 years, and 38% were HCV coinfected. Overall, 243 (30%) died during follow-up. Estimated median survival time was 54 months (95%CI 52-58). Participants with HCV had worse survival time with a slight reversal at the end of the survival curves (Fig.1; Renyi test statistic=3.58, p=.001). In the multivariate AFT model, Project HOPE randomization group, baseline age, race, gender, education, HCV, low CD4 count (CD4 <200), active drug use, homelessness, health insurance and living in the South were included. Participants with HCV, low CD4 count and living in the South had worse survival time. Average survival time for participants with HCV was 27% lower than those without (p=0.049), with low CD4 count was 40% lower than those with higher CD4 count (p=0.002), and for those located in the South was 38% lower than those not in the South (p=0.002).

Conclusion: One out of three HIV substance users died over a 5-year follow-up. HCV, having AIDS, and living in the South significantly increased the risk of death. Inadequate access and fragmented care, often seen in the South, may decrease survival in HIV substance users. To achieve End the Epidemic goals, new strategies are needed to improve the care process for this population.

895 ASSOCIATIONS OF ALCOHOL CONSUMPTION WITH VIRAL SUPPRESSION AND ALL-cause MORTALITY

Adam Trickey1, Suzanne Ingle1, Lei Zhang1, Mario Sacriletti2, Matthias Cavassini3, Michael Saag4, Heidi M. Crane5, Derek Satre6, Michael J. Silverberg6, Amy C. Justice1, Jonathan Sterne1, for the ART-CC and the COMPAAS consortium

1University of Bristol, Bristol, UK, 2Innsbruck Medical University, Innsbruck, Austria, 3Lausanne University Hospital, Lausanne, Switzerland, 4University of Alabama at Birmingham, Birmingham, AL, USA, 5University of Washington, Seattle, WA, USA, 6Kaiser Permanente Division of Research, Oakland, CA, USA, 7Yale University, New Haven, CT, USA

Background: Unhealthy alcohol use may lead to higher morbidity and mortality among people living with HIV (PLWH), either directly or by influencing the success of antiretroviral therapy (ART). We investigated associations of alcohol intake with viral suppression and all-cause mortality.

Methods: We assembled data from 5 cohorts participating in the Antiretroviral Therapy Cohort Collaboration that provided AUDIT-C alcohol measures (categorised as no drinking and low (reference group), medium and high intake). Eligible PLWH were aged ≥16 years and started ART 1996-2018. The date of AUDIT-C measure after ART start was taken as baseline, with follow up censored at the first of loss to follow-up or death. We used logistic regression to estimate adjusted odds ratios (aOR) for detectable viral load at baseline and Cox models (stratified by cohort) to estimate adjusted hazard ratios (aHR) for virological failure among those with undetectable baseline viral load (censoring at 3 years after ART start) and for all-cause mortality. Models were adjusted for baseline CD4 count, age, gender and transmission risk group with mortality analyses additionally adjusted for baseline viral load.

Results: Of 33206 PLWH, 4056 died during 183,683 person-years follow-up, 9,623 (28.7%) of PLWH were non-drinkers, whilst 19,738 (58.9%), 3,320 (9.9%), and 857 (2.6%) had low, medium, and high alcohol intake, respectively. PLWH with medium and high alcohol intake had higher odds of detectable viral load at baseline (aORs 1.14 [95%CI 1.05, 1.24] and 1.57 [1.36, 1.83], respectively) compared with low intake (figure). Medium- and high-drinkers had faster time to detectable viral load than those with low intake, anHRS 1.13 (1.02, 1.26) and 1.60 (1.35, 1.90), respectively. For mortality, anHRS compared with low intake were 1.33 (1.24, 1.42) for non-drinkers, 1.20 (1.06, 1.36) for medium intake, and 1.99 (1.70, 2.33) for high intake.
Conclusion: Among PLHIV, high or medium alcohol intake is associated with higher mortality than low intake. Higher mortality risk for non-drinkers is likely due to a “sick-quitter” effect. PLHIV with medium or high alcohol intake were more likely than those with low intake to have a detectable viral load at baseline. Interventions to reduce unhealthy alcohol use among PLHIV should be considered.

DEPRESSION AND VIROLOGIC REBOUND AMONG PATIENTS WITH HIV IN THE UNITED STATES
Quan M. Vu1, R. L. Shouse2, John Weaver3
1CDC, Atlanta, GA, USA

Background: The relationship between depression and HIV virologic rebound among persons with HIV has not been characterized. We analyzed nationally representative data from the Medical Monitoring Project (MMP) to examine the association between depression and virologic rebound among adults with diagnosed HIV in the United States.

Methods: We used data collected during 6/2015-5/2018 from MMP, a surveillance system that produces nationally representative estimates of behavioral and clinical characteristics among adults with diagnosed HIV. Demographic characteristics were collected through interview. Data on viral loads and diagnoses including clinical depression and substance use disorder were abstracted from medical records during the two years prior to interview. A total of 7133 patients who were prescribed antiretroviral therapy (ART), had an initial HIV RNA viral load [VL] level <50 copies/ml, and had at least 1 subsequent VL measure during 2 years of follow-up were included in the analysis (9232 person-years). We estimated weighted incidence rates of virologic rebound (defined as having a VL ≥200 copies/mL following viral suppression during follow-up) and used Cox proportional hazards modeling to estimate the association between depression and the time to first virologic rebound, adjusting for selected covariates and accounting for sample weights and design.

Results: Overall, 27% of patients had depression. The weighted incidence rate of virologic rebound was 9.2 per 100 person-years (95% confidence interval [CI] = 9.1-9.4) among patients with depression, and was 6.8 per 100 person-years (95% CI = 6.7-6.9) among patients without depression. In a multivariable Cox proportional hazards model that accounted for sample weights and design, and controlled for age group, gender, race/ethnicity, and diagnosis of substance use disorder, factors known to be associated with viral rebound, patients with depression had a significantly higher hazard of virologic rebound (hazard ratio = 1.35, 95% CI = 1.13-1.61, p < 0.001; Figure). In a multivariable Cox proportional hazards model that accounted for sample weights and design, and controlled for age group, gender, race/ethnicity, and diagnosis of substance use disorder, factors known to be associated with viral rebound, patients with depression had a significantly higher hazard of virologic rebound compared with patients without depression (adjusted hazard ratio = 1.35, 95% CI = 1.13-1.61, p < 0.001; Figure).

Conclusion: Among US patients with HIV who achieved viral suppression to <50 copies/mL, those with depression had a 35% higher risk of virologic rebound compared with patients who had similar demographic and substance use characteristics without depression. Patients with HIV and depression may need closer monitoring and support to avoid virologic rebound.

PREVALENCE AND FACTORS RELATED TO TRAUMA SYMPTOMS AMONG PEOPLE WITH HIV
Bryan Lau1, Karine Yenokyan2, Catherine R. Lesko3, Mary McCaul4, Richard D. Moore5, Heidi Hutson6, Geetanjali Chander2
1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: Among persons with HIV (PWH), trauma symptoms (TS) are a barrier to achieving HIV control. We sought to determine factors associated with TS among PWH and the association of TS with viral suppression.

Methods: In the Johns Hopkins HIV Clinical Cohort (JHHCC) between 2013-2018, we measured trauma symptoms using the Primary Care Post Traumatic Stress Disorder Screen (PC-PTSD). We categorized TS as a PC-PTSD score ≥3. Prevalence of TS was examined by model based recursive partitioning allowing for repeated measures. Factors hypothesized to be associated with TS included age, race, depressive (PHQ-8≥5), anxiety symptoms (GAD-7≥5), cocaine, heroin, and hazardous alcohol. Logistic regression with generalized estimating equations was used to examine the association of TS with viral suppression. Models were stratified by gender.

Results: Our analytic sample included 666 cis-gender women (89% African American [AA], 30% IDU as risk factor for HIV acquisition, 65%<55 years old), and 1154 cis-gender men (78% AA, 33% IDU, 59%<55 years old). At baseline, prevalence of TS was 10.4% among women and 8% among men. PWH with TS at baseline had lower ART adherence (visual analogue scale<90 35 vs 7%, p<0.001), less viral suppression (56 vs. 76% p=0.3), more depression (88 vs. 39%, p<0.001), and anxiety (85 vs. 16%, p<0.001), and greater substance use (hazardous alcohol: 31 vs 17%; cocaine: 13 vs 4.4%; heroin: 20 vs. 8.3%, all p<0.001) compared to PWH without TS. Among women, the co-occurrence of anxiety and depressive symptoms was associated with an increased prevalence of TS reaching 41% (figure, node 5) TS compared to 1% (node 2) among those without anxiety irrespective of depressive symptoms. For men, the prevalence of TS among those with anxiety and depressive symptoms was 38% (node 9), followed by those without anxiety, but with co-occurring depressive symptoms and hazardous alcohol use (20%, node 6). Among both women and men, those with TS were had similar risk of being virally suppressed as compared to those without TS (women: risk difference= -11%, 95%CI: -27, 5; men: RD= -2%, 95%CI: -13, 7).

Conclusion: Overall prevalence of TS is high and related to other psychiatric comorbidities among PWH. Adding TS screening would significantly increase identification of overall psychiatric morbidity. While TS by itself was not related to non-suppression, it is likely that treatment of overall psychiatric morbidity together may potentially decrease the risk of viral non-suppression.
Mental Health and Substance Abuse Services and Retention in HIV Care in North America

Cassandra Oliver1, Bryan Lau2, Keri N. Althoff1, Kate Buchacz1, Heidi M. Crane1, Michael John Gill1, Michael A. Horberg3, Kenneth H. Mayer4, Angela M. Mayor5, Bryan Lau2, Keri N. Althoff1, Kate Buchacz1, Heidi M. Crane1, Michael John Gill1, Michael A. Horberg3, Kenneth H. Mayer4, Angela M. Mayor5, Richard D. Moore6, Asher Schranz7, Timothy R. Sterling8, April Pettit9, Peter Rebeiro10, for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

1Vanderbilt University, Nashville, TN, USA, 2Johns Hopkins University, Baltimore, MD, USA, 3CDC, Atlanta, GA, USA, 4University of Washington, Seattle, WA, USA, 5Southern Alberta Clinic, Calgary, AB, Canada, 6Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, 7The Fenway Institute, Boston, MA, USA, 8Universidad Central del Caribe, Bayamon, Puerto Rico, 9University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Retention in care (RIC) is associated with reduced HIV transmission and mortality. Mental health and substance abuse services are associated with better RIC and uptake differs by sex, but few studies include diverse clinics or assess sex as an effect modifier. We quantified the association between availability of mental health and substance abuse services on-site or by referral and individual RIC within the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), assessing sex as an effect modifier.

Methods: Adults (≥18 years) with HIV who had ≥1 clinic visit at 13 NA-ACCORD sites in the US and Canada from 2000-2017 were included. Availability of mental health and substance abuse services were assessed by site survey in 2000, 2005, and 2010 and carried forward in other years. RIC was defined as ≥2 encounters per year, ≥90 days apart, recorded until death, administrative censoring (December 31, 2017), or loss to follow-up (no visit for >12 months with no future visits). Modified Poisson regression stratified by sex, clustered by site using generalized estimating equations, and adjusting for calendar year, age, race, and HIV risk factor, was used to estimate risk ratios (RR) with 95% confidence intervals (CI) for the association between clinic services and RIC.

Results: Among 28,831 individuals contributing 205,937 person-years (p-y), 67% of p-y were spent in care. The median age was 44 years and males contributed 76% of p-y. Almost half were white (46%), 44% black, non-Hispanic, and 4% Hispanic. The most common HIV transmission risk was MSM (52%), though 11% reported injection drug use as a risk factor. Overall, 97% of patients had access to mental health and substance abuse services for ≥1 year; availability increased over time, and 99% had access at these sites by 2017 (Figure). There was heterogeneity of effects by sex (p=0.05). Available mental health and substance abuse services were associated with better RIC among both males (RR=1.11; 95% CI: 1.07-1.14) and females (RR=1.05; 95% CI: 1.01-1.10).

Conclusion: Among patients receiving HIV care at NA-ACCORD clinical sites between 2000 and 2017, mental health and substance abuse services were associated with better individual RIC. These results may imply that mental health and substance abuse services themselves, or other services for which they are proxies, may enhance RIC in diverse settings, and males may benefit slightly more than females.

Mortality in People Living with HIV and Mental Health Disorders in South Africa

Andreas D. Haas1, Yann Ruffieux1, Ernest Mokotoane2, Johannes P. Mouton2, Mpho Tlali2, Mary-Ann Davies1, Matthias Egger1, Gary Maartens1, for the IeDEA Southern Africa Collaboration

1University of Bern, Bern, Switzerland, 2University of Cape Town, Cape Town, South Africa

Background: People with mental and substance use disorders (MSD) often die prematurely from suicide, accidents or chronic comorbidities. We quantified mortality from natural and external causes in people living with HIV and MSD enrolled in the Aid for AIDS (AFA) program in South Africa.

Methods: AFA is a large South African private sector HIV management program. AFA collects demographic, clinical and laboratory data. We linked the AFA data with mortality and cause of death information (natural vs. external cause) from the South African national population registry and with ICD-10 diagnoses from hospitalization records covering the period 2011-2018. We left-truncated ART records in 2011. HIV+ children and adults who initiated cART from 2001-2018 were followed up for 15 years on ART. We estimated cumulative mortality using the Kaplan-Meier method. We calculated adjusted hazard ratios (aHR) for associations between MSD and mortality using Cox regression. HR were adjusted for age, gender, CD4 count at ART initiation and year of ART initiation.

Results: Out of 219,686 individuals who initiated ART, 9,527 (4.3%) were admitted for an MSD for a median duration of 7 days (IQR 4-14). The cumulative mortality from natural and external causes 15 years after ART initiation was 15.5% (95%CI 14.9-16.1) and 2.3% (CI 2.1-2.6), respectively. The Figure shows aHRs and 95% CIs comparing mortality in ART patients with and without MSD. AHRs for mortality from natural causes were 3.65 (CI 3.33-4.01) for people with mental disorders and 2.27 (CI 1.61-3.20) for people with substance use disorders. AHRs for mortality from external causes were 2.13 (CI 1.57-2.89) for people with mental disorders and 3.79 (CI 2.18-6.59) for people with substance use disorders. Individuals with mental disorders due to organic causes (e.g. dementia) had the largest increase in risk of mortality from natural 13.52 (CI 11.57-15.80) and external 7.04 (CI 3.83-12.94) cause. The risk of mortality from natural causes was about four times higher for people with psychotic, anxiety, other psychiatric disorder, or drug use disorder, and about double for people with mood or alcohol use disorders, compared to people without those disorders.

Conclusion: Excess mortality of people with MSD is a major public health concern that warrants action. Differentiated care models that account for the special needs of people living with HIV and MSD might be a promising approach to reduce excess mortality in this vulnerable population.
Comparing Methods for Estimating Sexual Transmission Risk Among US Adults with HIV

Yunfeng Tie, Sharoda Dasgupta, Linda Beer, Jennifer Fagan, Qian An, R. L. Shouse

CDC, Atlanta, GA, USA

Background: An accurate assessment of sexual risk behaviors associated with HIV transmission is important for informing the Ending the HIV Epidemic (EHE) initiative. The Medical Monitoring Project (MMP) produces nationally representative estimates for high-risk sex using information from all past year partnerships. To potentially reduce data collection burden, we explored whether most recent sexual partner data was enough to accurately assess high-risk sex among adults with diagnosed HIV.

Methods: MMP staff interviewed adults with diagnosed HIV to collect information on demographic characteristics and sexual behaviors with the last 5 partners during the past 12 months (P12M); for those with >5 partners, aggregated information on sexual behaviors with additional partners was also collected. Viral load results were abstracted from medical records. Using weighted data collected 6/2015–5/2018 (n=11,914), we estimated the prevalence of high-risk sex, defined as 1) having >1 detectable viral load (≥200 copies/mL) over P12M and 2) having condomless anal or vaginal sex with an HIV-negative or HIV-unknown partner not reported to be using pre-exposure prophylaxis (PrEP). We reported the incremental contributions of each sexual partner to the measure, and compared prevalence of high-risk sex overall and by age, race/ethnicity, and sexual behaviors using data from the most recent partner compared with all partners.

Results: Of adults with diagnosed HIV, 58% had anal or vaginal sex in P12M, of whom 44% reported >1 partner and 12% reported >5 partners. A higher percentage of men who had sex with men (MSM), whites, and people aged 18-29 reported having multiple partners. The prevalence of high-risk sex was 6% overall, 11% among MSM, 13% among women who had sex with men, and 15% among persons aged 18-29. Estimates of high-risk sex were lower when information of the last partner only vs. all partners was assessed (4% using last partner vs. 6% using all partners), particularly for MSM (6% vs. 11%), persons aged 18-29 (9% vs. 15%), and Hispanics/Latinos (3% vs. 6%) (Figure).

Conclusion: Estimates of high-risk sex using last partnership were not adequate to accurately describe the prevalence of HIV transmission risk—particularly for groups highly affected by HIV, such as MSM and young adults. Using information on all sexual partners may be helpful to identify key populations in need of additional support for HIV prevention and can help inform EHE initiative activities.

Figure. Prevalence of high-risk sex by number of partners among U.S. adults with diagnosed HIV, 2013–2018.
903 THE CD4 DEPLETION MODEL DOES NOT DIFFERENTIATE INCIDENT FROM CHRONIC INFECTION

Michael E. Tang1, Sanjay R. Mehta1, Susan J. Little1, Christy M. Anderson1
1University of California San Diego, San Diego, CA, USA

Background: The Ending the HIV Epidemic (EtHE) initiative targets a 75% decline in HIV incidence in 5 years and a 90% decline in 10 years. Available estimates for U.S. population incidence are derived from a CD4 depletion model developed by investigators at the Center for Disease Control. We evaluated this model in a cohort with well-characterized estimated dates of incident infection.

Methods: We evaluated 702 antiretroviral (ART)-naive, newly HIV-1 diagnosed individuals with acute and early HIV infection enrolled in the San Diego Primary Infection Resource Consortium (PIRC). We calculated the positive predictive value (PPV), negative predictive value (NPV), and specificity for various proportions of incident infections, ranging from 5% to 50%, in a setting of 1000 newly diagnosed infections. For a test on a single individual, PPV ranged from 95.9% to 56.0%, NPV ranged from 95.9% to 55.1%, and specificity was 60% (95% CI 52%-67%).

Conclusion: Although the CD4 model is not designed to predict if an infection is incident at an individual test level, the uncertainty in this test also impacts population scale estimates. As interventions to prevent HIV transmission are scaled up as part of the EtHE effort, we need more accurate estimates of incident infections for a population of 10000 (true value 2500).

904 ESTIMATING INCIDENCE AT A REGIONAL LEVEL WITH THE CD4 DEPLETION MODEL

Sanjay R. Mehta1, Michael E. Tang1, Christy M. Anderson1, Susan J. Little1
1University of California San Diego, La Jolla, CA, USA

Background: Of the 702 newly HIV diagnosed individuals (age 16-71), 234 (33.3%) were diagnosed during acute infection, 468 (66.7%) during recent infection; 90.8% estimated by limiting-antigen (LAg) avidity assay in combination with viral load information (PIRC EDI model) and 9.2% by interval HIV seroconversion (documented negative HIV serology in prior year). The PIRC EDI was weakly correlated with the CD4 model EDI (R2 = 0.017) (Figure). Among the 159 (23%) PIRC participants with follow-up CD4 data for ≥1 year prior to starting ART, we also used the pre-ART CD4 to calculate the CD4 model EDI (i.e., sampled during chronic infection). The pre-ART CD4 EDI was also weakly correlated with the PIRC EDI (R2 = 0.00058). When using the PIRC EDI as the gold standard, the sensitivity of the CD4 model was 51% (95% CI 47%-55%) and specificity was 60% (95% CI 52%-67%).

Conclusion: The CD4 model EDI was not better than the PIRC EDI in terms of accuracy and may not be an appropriate model for monitoring incidence trends among smaller sample sizes.
incidence that can be applied at smaller population scales, so that we will be able to measure the impact of our outcomes.

905 KEY POPULATION SIZE ESTIMATION IN NIGERIA: NOVEL APPROACHES TO SAMPLING AND ANALYSIS
Anne McIntyre1, Andrew Mitchell1, Samuel Nwafor2, Victor Sebastian3, Amee M. Schwitters4, Julia Lo5, Ibrahim Dalhatu5, Mahesh Swaminathan5, Kristen D. Marquart5, 1CDC, Atlanta, GA, USA; 2University of Maryland, Baltimore, MD, USA; 33CDC Nigeria, Abuja, Nigeria

Background: Nigeria has the fourth largest HIV burden globally. Key populations (KP), including female sex workers (FSW), men who have sex with men (MSM), and people who inject drugs (PWID), are more vulnerable to HIV than the general population owing to stigma and discrimination, and often have poor social visibility. Previous population size estimates (PSE) in Nigeria were based on programmatic mapping of hotspots with enumeration of KP at venues. The results failed to account for KP who were not present at venues, resulting in underestimates of population sizes that also lacked precision. Reliable PSE are needed to guide focused and appropriately scaled HIV epidemic response efforts for KP. We used novel approaches for sampling and analysis to calculate PSE in Nigeria.

Methods: We used three-source capture-recapture (3S-CRC) to estimate the size of KP in seven states in Nigeria (October–December 2018). Hotspots were mapped just before 3S-CRC sampling. We independently sampled FSW, MSM, and PWID 3 times approximately 1 week apart. During encounters at KP hotspots, distributors offered inexpensive and memorable objects to FSW, MSM, and PWID that were unique to each capture round and KP. In subsequent rounds, participants were offered an object and asked to describe those received during previous rounds; we tallied correct identifications of the object. Distributors recorded responses on tablets using REDCap® software and uploaded data to a secure central server. Data were aggregated by KP and state for analysis. Median PSEs were derived using Bayesian nonparametric latent-class models with 80% highest density intervals (HDI) for precision.

Results: During three rounds of independent captures in each state, there were approximately 310,000 encounters in 13,899 hotspots. Table 1 summarizes median PSE by KP and state.

Conclusion: We are the first to implement 3S-CRC to calculate median PSE with 80% HDI in Nigeria. Overall, our PSEs were larger than previously documented for each KP in each state. Empirical methods and analysis using Bayesian models that account for factors (i.e., social visibility and stigma) that influence heterogeneous capture probabilities may produce more accurate PSE. The large estimates suggest a need for programmatic scale-up to reach these populations with high HIV risk. 3S-CRC methods, in similar epidemic settings, could help estimate critical population denominator data needed to inform HIV prevention and treatment programs.

Table 1: Median population size estimates* (80% Highest Density Intervals) for female sex workers, men who have sex with men, and people who inject drugs in seven U.S. President’s Emergency Plan for AIDS Relief–Supported states in Nigeria (October–December 2018)

<table>
<thead>
<tr>
<th>State</th>
<th>Female Sex Workers (PSE)</th>
<th>People Who Have Sex With Men (PSE)</th>
<th>People Who Inject Drugs (PSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Federal Capital Territory (FCT)</td>
<td>45,900 (33,000–50,900)</td>
<td>8,200 (5,000–10,700)</td>
<td>3,400 (2,500–4,800)</td>
</tr>
<tr>
<td>Abuja City</td>
<td>64,500 (44,100–84,800)</td>
<td>11,000 (6,300–16,700)</td>
<td>23,500 (11,500–35,900)</td>
</tr>
<tr>
<td>Ilorin City</td>
<td>48,700 (37,500–61,900)</td>
<td>10,800 (8,800–12,800)</td>
<td>7,600 (5,200–10,600)</td>
</tr>
<tr>
<td>Cross River</td>
<td>35,500 (28,500–43,000)</td>
<td>6,200 (3,200–7,900)</td>
<td>20,100 (11,500–29,700)</td>
</tr>
<tr>
<td>Lagos City</td>
<td>48,500 (38,000–59,100)</td>
<td>5,600 (3,900–8,400)</td>
<td>5,900 (3,700–10,900)</td>
</tr>
<tr>
<td>Kano State</td>
<td>59,000 (49,700–71,700)</td>
<td>5,000 (3,700–6,800)</td>
<td>6,900 (5,200–9,700)</td>
</tr>
<tr>
<td>Rivers State</td>
<td>54,100 (41,100–68,100)</td>
<td>4,400 (3,200–5,900)</td>
<td>36,000 (17,000–64,800)</td>
</tr>
</tbody>
</table>

*Estimates are demonstrating Bayesian nonparametric latent-class models with 80% highest density intervals. FSW: female sex workers; MSM: men who have sex with men; PWID: people who inject drugs.

906 5GEOSPATIAL HIV DYNAMICS IN FRANCE: A GRAVITY EFFECT MODEL
Marie-Laure Chaix Baudier1, Benoît Visseaux1, Lambert Assoumou2, Marc Wirden3, Lot Florence4, Laurence Morand-Joubert2, Stephanie Raymond5, Laurence Bocket1, Constance Delaugerre1, Francis Barin6, Diane Descamps1, Davey M. Smith7, Angela L. Hernandez1, Anne Marie France1
1CDC, Atlanta, GA, USA; 2ICF International, Atlanta, GA, USA; 3University of California San Diego, San Diego, CA, USA

Background: HIV prevalence in the population is crucial in tracking the leading edge of HIV epidemics. We explored the geospatial dynamics of the HIV epidemics across mainland France to identify factors associated with HIV dispersal for guiding prevention efforts.

Methods: We applied a multistep phylogenetic approach on a large set of HIV-1 pol sequences from PHI individuals diagnosed in mainland France in ANRS AC43 laboratories performing genotypic resistance tests between 2014-2017. (1) We first performed an overall maximum likelihood phylogenetic inference to identify well-supported monophyletic clades; (2) All clades of size≥3 were used to perform a discrete phylogeographic inference to evaluate the dispersal history across mainland France; (3) We then applied a generalized linear model (GLM) to test the association of demographic, geospatial factors and connectivity (i.e. geographic distances and the intensity of air traffic passenger flow) with lineage dispersal.

Results: A total of 1,545 pol sequences were collected. After combining these with 48,658 publicly available sequences, we identified 71 clusters from 37 counties. The discrete phylogeographic analysis revealed varying levels of virus exchange between counties (Fig.A). The GLM analysis revealed that viral migration was strongly associated with limited driving time (BF=142, Fig.B). These observations illustrate the HIV dynamics across mainland France with Paris and Lyon areas (the 2 largest cities) being major sources and recipients of viral dispersal. It suggests the role of local human migration and large urban area in sustaining the HIV epidemics.

Conclusion: The combined use of phylogeography and GLM provides deeper insights into geospatial transmission patterns and factors associated with viral flows. Phylogeographic analyses confirm that highly populated areas could have a gravity effect on the French epidemic. These results may help to more efficiently allocate prevention resources and will allow to evaluate the impact of changes in demographic trends and policies.

907 INCREASING CAPACITY FOR DETECTING CLUSTERS OF RAPID HIV TRANSMISSION: UNITED STATES
Alexandra M. Oster1, Nivedha Panneer1, Sheryl Lyss1, Neeraja Saduvala1, Tianshi Zhang2, Cheryl B. Ochamia2, Laurie Linley1, Meg Watson1, Robert P. McClung2, William M. Switzer3, Joel O. Wertheim3, Ellisworth M. Campbell1, Angela L. Hernandez2, Anne Marie France3
1CDC, Atlanta, GA, USA; 2ICF International, Atlanta, GA, USA; 3University of California San Diego, San Diego, CA, USA

Background: Responding to HIV clusters and outbreaks is a pillar of the U.S. Ending the HIV Epidemic (EHE) initiative, which will initially focus on 48 counties; Washington, D.C.; San Juan, Puerto Rico; and 7 states with substantial rural burden. Molecular cluster detection uses HIV sequence data and can identify rapid transmission for public health response; in 2015–2016, most persons involved in U.S. clusters were men who have sex with men (MSM) — only 1% were persons who inject drugs (PWID). In 2018, requirements to collect HIV sequence data expanded to 27 to all CDC-funded health departments. We described changes in molecular cluster detection capability in EHE and non-EHE areas and geographic variation in transmission dynamics.

Methods: We examined HIV-1 pol sequence data completeness in the National HIV Surveillance System from December 2015 (first implementation of molecular cluster detection) to March 2019 for people with HIV diagnosed in the past 3 years. Clusters of rapid transmission were identified quarterly among persons with HIV diagnosed in the past 3 years using HIV-TRACE with a pairwise genetic distance threshold of 0.5%. Priority clusters had ≥ 5 diagnoses in the past 12 months. We described people in clusters first detected in 2015–2016 and allocative prevention resources and will allow to evaluate the impact of changes in demographic trends and policies.
3-28). However, most clusters (65%) involved ≥1 Prompt case and the Prompt connectivity was associated with more recent diagnoses in clusters (Figure). A prioritization threshold of ≥5 recent diagnoses and connectivity ≥5 per cluster, yielded 39 priority clusters (698 members) with 187 Prompt cases (4.8 vs. 1.6 Prompt cases/cluster in non-priority clusters).

**Conclusion:** We detected a high rate of clustering among recent diagnoses with frequent involvement of past diagnoses. Harnessing longitudinal VL and sequence data allows for timely detection and monitoring of such clusters. Clusters with rapid growth and high network connectivity with past diagnoses without viral suppression can be prioritized for intensified care re-engagement and retention support.

**Figure.** Clusters with HIV diagnoses 2017-2019.

### DO PARTNER SERVICES INITIATED FROM MOLECULAR CLUSTERS YIELD NEW OR VIREMIC HIV CASES?


1University of Chicago, Chicago, IL, USA, 2Northwestern University, Chicago, IL, USA, 3Chicago Department of Public Health, Chicago, IL, USA, 4University of California San Diego, San Diego, CA, USA, 5Houston Health Department, Houston, TX, USA, 6Argonne National Lab, Chicago, IL, USA, 7University of Texas at Houston, Houston, TX, USA

**Background:** Molecular HIV surveillance is increasingly utilized as an approach to identify new HIV diagnoses linked to clusters. Health departments employ partner services to interview people newly diagnosed with HIV—index clients—to elicit named sexual/injection drug-use partners. We examined whether the yield of new diagnoses or viremic named partners varied by molecular cluster (versus not in a cluster) when attempting to interview index clients with HIV pol sequences.

**Methods:** We matched and analyzed HIV surveillance (including HIV pol sequences) and partner services data from HIV diagnoses in Chicago from 2012 through 2016 from the Chicago Department of Public Health. We constructed molecular clusters using HIV-TRACE at a pairwise genetic distance threshold 0.5%. We compared the normalized proportion of partners reported by index clients who were a new HIV diagnosis or recently had detectable viremia (yield of partner services) in a molecular cluster vs. those whose HIV sequences did not cluster.

**Results:** Of 2,404 newly diagnosed index clients, 1,015 (42%) had HIV sequence data available and partner services initiated within 12 months of diagnosis. Of these, 336 (33%) had HIV pol sequences that clustered and 96 (29%) of them named at least one partner. The average age of index clients in clusters was 28, 47% were Black, 29% Latinx, 6% female and 89% men who have sex with men. Of the 539 named partners, 162 (36.6%) were linked to index clients in a molecular cluster (versus not in a cluster) when attempting to interview index clients with HIV pol sequences.

**Conclusions:** Partner services that were initiated from the subset of index clients whose HIV sequences are in a molecular cluster vs. those whose HIV sequences did not cluster. Future research should examine the yield among growing molecular clusters as well as partner services originating from molecular clusters that identify HIV clients co-infected with syphilis and other STIs, and by consideration of compositions by transmission categories in molecular clusters.

---

**STATEWIDE HIV-1 TRANSMISSION CLUSTER DETECTION AND PRIORITIZATION FOR RESPONSE**


1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2Cambridge University, Cambridge, UK, 3The Ohio State University, Columbus, OH, USA, 4North Carolina Division of Public Health, Raleigh, NC, USA

**Background:** New HIV diagnoses continue in the Southern US despite widespread prevention efforts; underreporting the need for innovative deployment of prevention tools. Detection and response to genetically clustered infections is a pillar to the Ending the Epidemic initiative. We combined viral load (VL) and surveillance data to prioritize genetic clusters where re-engagement to care activities could be intensified.

**Methods:** We developed automated cluster analyses to prospectively monitor clusters in North Carolina: the system is routinely updated with pol sequences (from clinical and public testing sites), demographic, and clinical data. Clusters were constructed from pairwise genetic distances (TN-93), connecting edges <1.5% difference. Prioritization metrics were assessed for clusters with recent diagnoses (2017-2019) and based on the adjacent nodes to recent diagnoses (edges <1.5%), including members potentially disengaged from care (“Prompt” cases). Prompt cases were defined as members without VLS or persistent/rising viremia (VL>200 c/mL) in the prior 12 months. Connectivity of Prompt cases in clusters was estimated by number of edges to all adjacent nodes (i.e. node degree) per prompt case.

**Results:** Of 15,558 persons with 25,509 sequences in the pipeline, 2195 had recent diagnoses; 59% (1294) of these were identified in 532 clusters. Clusters involved 2512 members: 1218 (48%) were past diagnoses (≥2016). Recent diagnoses in clusters were more likely to be MSM (65% vs. 46%), younger (33% vs. 15% 18-24 years), and have acute infection (9% vs. 5%) compared to non-clustered recent diagnoses (all p<0.01). Recent diagnoses tended to cluster with other recent diagnoses: 60% (775) clustered with ≥3 recent diagnoses (range 3-28). Of 756 people in these 87 clusters, 71% were MSM and 11% were PWID; 53% resided in EHE areas at diagnosis. State-by-state analysis showed tremendous variation in risk and racial/ethnic groups included in clusters of rapid transmission (Figure).

**Conclusion:** Sequence completeness has increased nationwide. Molecular cluster analysis demonstrates ability to identify recent and rapid transmission in varied populations, including capacity for detecting the rapid transmission among PWID that has occurred in recent years. Molecular cluster detection offers an opportunity for a focused, local approach to identify populations experiencing rapid transmission and tailor response to scale up services for these populations. These results demonstrate great potential for public health response to clusters and outbreaks in jurisdictions identified for the EHE Initiative.

**Figure.** Characteristics of people involved in clusters of rapid transmission first detected in 2018-2019, overall and for three selected states.

---

**909 PARTNER SERVICES: A NEW APPROACH TO IDENTIFY NEW HIV CASES VIA MOLECULAR CLUSTERS**

**Jonathan Ozik, Anna Hotton, Nanette Benbow**

1University of Chicago, Chicago, IL, USA, 2Northwestern University, Chicago, IL, USA, 3Chicago Department of Public Health, Chicago, IL, USA, 4University of California San Diego, San Diego, CA, USA, 5Houston Health Department, Houston, TX, USA, 6Argonne National Lab, Chicago, IL, USA, 7University of Texas at Houston, Houston, TX, USA

**Background:** Clusters identified during December 2015–March 2019, 87 were first detected in 2018–19. Of 756 people in these 87 clusters, 71% were MSM and 11% were PWID; 53% resided in EHE areas at diagnosis. State-by-state analysis showed tremendous variation in risk and racial/ethnic groups included in clusters of rapid transmission (Figure).

**Conclusion:** Sequence completeness has increased nationwide. Molecular cluster analysis demonstrates ability to identify recent and rapid transmission in varied populations, including capacity for detecting the rapid transmission among PWID that has occurred in recent years. Molecular cluster detection offers an opportunity for a focused, local approach to identify populations experiencing rapid transmission and tailor response to scale up services for these populations. These results demonstrate great potential for public health response to clusters and outbreaks in jurisdictions identified for the EHE Initiative.
910 THE RELATIONSHIP BETWEEN THE HIV TRANSMISSION NETWORK AND CARE CONTINUUM IN LA COUNTY
Adiba Hassan1, Victor De Gruttola2, Yunxin W. Hu1, Zhijuan Sheng3, Kathleen Poortinga5, Joel O. Wertheim1
1University of California San Diego, San Diego, CA, USA, 2Harvard University, Cambridge, MA, USA, 3Los Angeles County Department of Public Health, Los Angeles, CA, USA
Background: Successful public health action combatting HIV relies on navigation through the HIV care continuum: timely diagnosis of infection followed by linkage to care and initiation of antiretroviral therapy to achieve and maintain suppression of viral replication. Molecular epidemiology can identify rapidly growing HIV genetic transmission clusters. How these clusters relate to the care continuum has not been previously characterized.

Methods: We performed a population-based retrospective study on HIV/AIDS surveillance data from 5226 adult living with HIV, who had reported HIV pol sequence, resided in Los Angeles County, and were diagnosed between January 2010 through December 2014 with laboratory data reported through 2016. An HIV genetic transmission clusters was constructed using HIV-TRACE based on these pol sequences using a pairwise genetic distance threshold of 0.015 substitutions/site. We characterized cluster growth as the number of cases added to a cluster in the previous year divided by the number of cases in the cluster. Separate Cox proportional hazard models assessed the time to each event along the care continuum and gamma frailty models accounted for heterogeneity between genetic transmission clusters.

Results: Of the cases linked to care, 92% achieved viral suppression and 26% experienced post-suppression viral rebound. Median time from diagnosis to suppression was six months (IQR 4-13). Contrary to expectation, there were no differences in time to these events among individuals in clusters with different growth dynamics. However, upon achieving viral suppression, cases in high growth clusters were less likely to rebound (Hazard Ratio 0.83, p=0.011) compared with cases in low growth clusters. Heterogeneity due to cluster membership in the timing to each of event in the care continuum was highly significant (p<0.001), even after adjusting for transmission risk and demographics.

Conclusion: Combining molecular epidemiology and HIV surveillance approaches, we characterized the relationship between the HIV transmission network and the rates of linkage to care, viral suppression, and post-suppression viral rebound. Individuals within the same transmission cluster have similar trajectories through the HIV care continuum. These findings suggest molecular epidemiology can assist public health officials in identifying clusters of individuals who may benefit from assistance navigating the HIV care continuum.

911 SOCIODEMOGRAPHIC FACTORS ASSOCIATED WITH HIV CLUSTERING ACROSS BOTSWANA COMMUNITIES
Sikhulile Moyo1, Kara Bennett2, Simani Gaseitsiwe3, Melissa Zahraban-Steel1, Tapiwa Nkhisang1, Joe D. Leidner1, M. Neilds P. R. Molefe1, Tendani Gaolathe3, Kathleen Wirth3, Joseph Makhema1, Max Essex1, Deborah S. R. Dodds1, Samyas M. V. S 1
1University of California San Diego, La Jolla, CA, USA, 2National Institute of Allergy and Infectious Diseases, National Institute of Health, Bethesda, MD, USA, 3Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 4Harvard T.H. Chan School of Public Health, Boston, MA, USA
Background: Understanding HIV transmission networks is important for intervention programming. However, factors associated with molecular HIV clusters in southern Africa are not well-studied. We sought to identify independent predictors of being part of a molecular HIV cluster using data from HIV-positive persons enrolled in a large community-randomized HIV prevention trial in Botswana.

Methods: The Botswana Combination Prevention Project was conducted in 30 communities across Botswana in 2013-2018. At study enrollment, near-full length HIV-1 genome sequences were obtained (from RNA or DNA) from HIV-positive persons and analyzed for genetic relatedness. We defined an inferred molecular HIV cluster (transmission network) as a phylogenetically distinct viral lineage giving rise to a monophyletic subtree of the overall phylogeny with bootstrap support of splits >0.80. Multivariate logistic regression models (adjusted for clustering) were constructed using a backwards elimination procedure to select from pre-specified set of candidate socio-demographic and behavioral variables.

Results: Among the 6,536 HIV-positive BCPP participants, sequences were obtained from 4,069 (61%) and 1,904 (46%) of 4,009 were in one or more of the 850 unique molecular HIV clusters identified. The majority of cluster members were female (73%) with a median (IQR) age of 40 years (33, 48). Factors associated with being in a cluster included: age 25-34 years (aOR:1.29, 95%CI:1.01–1.65), transactional sex (aOR:1.51, 95%CI:1.09-2.10), and viremia (aOR:1.37, 95%CI:1.16-1.61). In sensitivity analyses examining factors associated with membership in a cluster with a seroconverter also identified lack of religious affiliation as an independent predictor (aOR:1.56; 95%CI:1.02-2.41) in addition to age (P=0.03) and viremia (P=0.047).

Conclusion: Molecular epidemiology can be applied to characterize HIV transmission networks. Clustering was associated with younger age group, and lack of viral suppression. These findings reinforce the importance of enhanced targeted HIV testing programs and scale-up of ART to increase viral suppression in persons living with HIV.

912 ASSOCIATIONS BETWEEN PHYLOGENETIC TRANSMISSION CLUSTERS AND HLA PROFILES IN MEXICO
Sanjay R. Mehta1, Santiago Avila-Rios2, Matthew Strain1, Humberto Valenzuela Ponce1, Maribel Soto-Nava1, Margarita Matías-Florentino1, Alicia Piñeirúa1, Florentino Badal-Hernández1, Andrea González Rodríguez2, Davey M. Smith1, Gustavo Reyes-Terán1, Antoine Channon1
1University of California San Diego, San Diego, CA, USA, 2National Institute of Respiratory Diseases, Mexico City, Mexico, 3Clinica Especializada Condesa, Mexico City, Mexico
Background: Class I Human leukocyte antigen (HLA-I) is a major driver of HIV evolution, both at the individual and population level, promoting HIV adaptation to cellular immune responses. The extent to which HIV adaptation to HLA-I plays a role in transmission is still not well understood. Here, we examined associations between HLA-I profiles and HIV transmission in the Mexico City HIV epidemic.

Methods: 1,049 HIV-1 subtype B pol sequences sampled between 2016 and 2018 from unique, HLA-I-typed individuals in Mexico City were analyzed. Genetic transmission networks were inferred using HIV-TRACE, establishing putative transmission linkage below a genetic distance threshold of 1.5%. High-resolution HLA profiles were determined using next-generation sequencing. Newman’s assortativity coefficients were estimated using igraph. Fisher’s exact tests were used to determine whether there was enrichment of specific HLA alleles in clustering vs. non-clustering individuals. P-groups, known to bind similar peptides, were used for HLA-match analyses.

Results: 286/1,049 (27%) individuals were genetically linked with at least one other person, forming 120 clusters (range: 2-8 individuals). All but 2 clustering individuals were male. Clustering and non-clustering individuals did not differ by age, baseline CD4 or HIV RNA level. HLA-C*02:02 was enriched in clustering individuals (p=0.02). Overall 30% (86/286) of clustering individuals shared ≥2 HLA-I P-groups/alleles in any of the three loci (Fig. 1A), and 26 had fully concordant (i.e. two matching alleles) HLA-A (13; 4.5%), HLA-B (2; 0.7%) or HLA-C (11; 3.8%) loci (Fig. 1B). Rates of HLA-I allelic concordance among clustering individuals were significantly higher than among the full cohort at all three loci (<0.01).

Conclusion: HLA-I haplotypes were significantly more concordant than expected among clustering individuals in Mexico City. These findings suggest that viral adaptations may enhance transmissibility. However, further work is needed to determine if this increased concordance is due to viral factors (i.e. adaptation) or sociodemographic factors (i.e. ancestry, racial assortativity).

Figure 1: HIV Transmission Network and HLA Concordance. (A) Inferred transmission clusters. All edges represent a genetic distance of ≤1.5%. Lines in bold red indicate individuals who shared any HLA-I P-group. (B) Individuals are colored according to number of shared alleles in persons with at least 1 match. B: individuals sharing both HLA-A,-B or -C alleles are shown.
913 HIV RISK INCREASES WITH POSITIVE TIES IN HIGHLY CONNECTED
SOCIOSPATIAL PWID NETWORK

Steven J. Clipman1, Shrut H. Mehta1, Aylur K. Srikrishnan1, Katie J. Zook1, Priya Duggal1, Shobha Mohapatra1, Shanmugam Saravanan1, Nandagopal Paneerselvam1, Muniratnam S. Kumar1, Elizabeth Ogburn2, Allison M. McFall1, Gregory M. Lucas1, Carl A. Latkin1, Sunil S. Solomon1
1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2YR Gaitonde Center for AIDS Research and Education, Chennai, India, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: People who inject drugs (PWID) bear high HIV and hepatitis C virus (HCV) burden and account for some of the most explosive epidemics globally. While individual risk factors for infection are well understood, less is known about network and spatial factors. Moreover, network studies have been limited by focusing on immediate ties (egocentric network) rather than the broader sociometric/spatial networks.

Methods: 2,512 PWID were recruited via a chain referral method in 2017-19 in New Delhi, India. An index initiated sampling and was asked to recall who they injected with in the past month and was provided referrals for those partners (index’s egocentric network). Similarly, each recruit named and recruited their recent injection network (recruit’s egocentric network and index’s sociometric network). Participant biometrics identified duplicates and cross-network linkages. All completed a survey, provided blood and information on injection locations; these data were used to generate spatial networks. Sociometric injection networks were created and analyzed using bespoke Python code.

Results: Median age was 26; 99.1% were male. HIV prevalence at baseline was 36.9% and 7.4% were virally suppressed; HCV antibody prevalence was 65.1%. The networks of 8 of 11 indexes merged into one network (Figure). Average degree (number of injection partners) was 2.1 (range: 0–47), network diameter was 39 and average path length was 14. Of 928 HIV-positive participants at baseline, 64.6% were directly connected with at least one other HIV-positive PWID. Of 1,634 HCV-positive participants at baseline, 64.6% were directly connected with at least one other HCV-positive PWID. The odds of HIV increased with each additional HIV-infected ego in a network (OR=1.21) and injecting at a specific hotspot (OR=1.86). Factors that were independent of individual needle sharing (OR=1.86) and injection frequency (OR=1.36; all p<0.001).

Conclusion: These are among the first data to comprehensively characterize the complete sociometric injection network of PWID in an urban setting. We observed a highly connected network structure where HIV and HCV prevalence were associated with network connections and spatial overlap after adjusting for other predictors. These data have implications for the success of network-based prevention/treatment strategies.

914 USING MOLECULAR EPIDEMIOLOGY TO CHARACTERIZE HIV TRANSMISSION NETWORKS OF TW AND MSM

Jessica E. Long1, Joshua T. Herbeck1, Hugo Sanchez2, Sari Reisner1, Kenneth H. Mayer3, James Mullins1, Javier R. Lama4, Ann Duerr1
1University of Washington, Seattle, WA, USA, 2Epicentro, Lima, Peru, 3Harvard T.H. Chan School of Public Health, Boston, MA, USA, 4The Fenway Institute, Boston, MA, USA, 5Asociacion Civil Impacta Salud y Educacion, Lima, Peru, 6Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Transgender women (TW) are highly vulnerable to HIV, yet little is known about their sexual networks. TW are often conflated with men who have sex with men (MSM), with the implicit assumption that the sexual networks of MSM and TW overlap, resulting in HIV transmission between the populations. However, sex partners of TW (PTW) are largely cisgender men who have sex with cis- and transgender women, suggesting that the sexual networks of MSM and TW/PTW may be separate. We examined the genetic similarity of HIV sequences from TW, male PTW, and MSM from research cohorts in Lima, Peru to determine whether the imputed transmission network, and therefore the sexual network, of TW/PTW overlaps with that of MSM.

Methods: We used HIV-1 pol sequences and epidemiologic data collected through 3 research studies conducted among primarily high-risk MSM, TW, and PTW in Lima from 2013–2017. A transmission network and phylogenetic tree were constructed using all study sequences (n=303 MSM, n=139 TW, n=25 PTW) as well as all South American sequences from the Los Alamos HIV Database (n=552). Molecular clusters were identified within the transmission network, with cluster membership defined as ≥2 sequences linked to each other based on a TH03 pairwise genetic distance threshold of 0.015 substitutions/site, and patterns in clustering were assessed with chi squared tests.

Results: 200 participants (43%) were found in 62 clusters (Fig 1), with no difference in probability of clustering by group. Both MSM and TW were more likely to cluster with members of their own group than would be expected based on chance alone. While only 28% of the sample were TW, 77% of TW found in a cluster were clustered with TW (p<0.001). Similarly, while 67% of the sample were MSM, 91% of clustered MSM were found in clusters with MSM (p<0.001). TW were less likely to be found in clusters with MSM than would be expected (57% observed vs 67% expected, p=0.086), but frequency of co-clustering of TW and MSM did suggest transmission occurring between the two populations. No characteristics were predictive of men clustering with TW, including reporting a TW sex partner.

Conclusion: Co-clustering of TW/MSM was less common than expected but still signified sizable overlap in transmission networks. This contrasts with reported sexual behavior among TW and their sex partners, and may indicate that a subset of high-risk men who have sex with both TW and men drive HIV transmission between these two populations.
915  **PHYLOGENETIC EVIDENCE OF HIV-1 MIXING BETWEEN KEY RISK GROUPS IN COASTAL KENYA**

**NDUVA M. GEORGE**, Amin S. Hassan, Susan M. Graham, Joakim Esbjörnsson, Eduard Sanders

1 KEMRI Wellcome Trust Rsr Prog, Kilifi, Kenya, 2 KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya, 3 University of Washington, Seattle, WA, USA, 4 Lund University, Lund, Sweden

**Background:** HIV-1 transmission patterns within and between populations at high-risk of HIV-1 acquisition in Kenya are not well understood. We investigated HIV-1 subtype distribution and transmission dynamics in men who have sex with men (MSM), female sex workers (FSW) and heterosexuals (HET) in coastal Kenya.

**Methods:** We used maximum-likelihood and Bayesian phylogenetics to analyze new (N=163) and previously published (N=495) HIV-1 pol sequences collected 2005-2019 from treatment-naïve individuals. To perform a subtype-specific cluster analysis of the coastal Kenyan sequences, we obtained reference sequences (N=1079) from GenBank based on similarity. Transmission networks were classified based on the number of sequences per cluster into dyads (2 sequences), networks (3-14 sequences) and large clusters (>14 sequences).

**Results:** Of 658 sequences, 131 (20%) were MSM, 58 (9%) IDU, 109 (17%) FSW, and 360 (55%) HET. The majority (66%) of the sequences were sub-subtype A1, with lower fractions of subtypes D (10%), C (7%), G (<1%), and recombinant forms (17%). Overall, 206 (31%) sequences formed 39 dyads, 21 networks, and 360 (55%) HET. The majority (66%) of the sequences were sub-subtype A1, with lower fractions of subtypes D (10%), C (7%), G (<1%), and recombinant forms (17%)

**Conclusion:** Our work suggests that in addition to frequent transmission within-risk-groups, HIV-1 transmission between MSM, FSW and HET is also common in coastal Kenya. Targeting HIV-1 prevention programmes to FSW, MSM and IDU will be necessary to reduce HIV-1 transmission in coastal Kenya.

916  **PHYLDYNAMIC EVIDENCE OF HIV TRANSMISSION BETWEEN AGE-DISCREPANT MSM IN KING COUNTY**


1 University of Washington, Seattle, WA, USA, 2 Public Health–Seattle & King County, Seattle, WA, USA

**Background:** Sexual mixing is typically age-assortative. Mathematical modeling studies conducted in the 1990s suggested an important role for age-disassortative mixing in HIV transmission dynamics among men who have sex with men (MSM), suggesting that young MSM (YMSM) may acquire HIV from older partners. We compared molecular epidemiology methods with phylodynamic methods to examine the frequency of HIV transmission between age discrepant MSM.

**Methods:** Using 2000-2018 HIV surveillance data from Public Health–Seattle & King County, HIV-pol gene sequences were linked to demographic, clinical, and epidemiological information. We identified genetic similarity clusters of 2+ individuals using TN93 pairwise genetic distance with a 0.015 threshold, and assessed correlates of clustering using multivariate logistic regression. We conducted probabilistic phylodynamic modeling to estimate transmission flows between YMSM (age <25) and older MSM (categorized for analyses as age 25-34, 35-44, and >45).

**Results:** From 2000-2018, 4597 MSM were diagnosed with HIV in King County, with 654 (14%) diagnoses among YMSM. Among 2851 (62%) of MSM with an available sequence, 1435 (50%) clustered in 277 genetically similar clusters: 9 clusters were comprised of only YMSM, 166 of only older MSM, 102 of both older and YMSM. YMSM had higher odds of clustering compared to those >25 years old (AOR 1.6; 95% CI: 1.3, 2.0). Older MSM were more likely to cluster with other MSM >25 years old (AOR 4.3; 95% CI: 2.3, 3.1) and less likely to cluster with YMSM (AOR 0.4; 95% CI: 0.3, 0.5), compared to YMSM. Phylodynamic modeling suggest that the majority (47%) of HIV transmissions occurs among MSM age 25-34 and 35-44 years old. The overall assortativity coefficient was 0.08. YMSM had the highest probability of acquiring HIV from MSM aged 25-34 years old (39%) and 35-44 years old (31%), with a 19% probability of acquiring HIV from other YMSM. Phylodynamic models estimated that YMSM acquire HIV from MSM with probability-weighted mean age difference of 11.2 years older (IQR 4 to 18 years).

**Conclusion:** Both molecular epidemiology and phylodynamic methods were suggestive of age-assortative mixing among older MSM, among whom the majority of HIV transmissions occurred. However, molecular cluster analyses were suggestive of high relative rates of transmission among YMSM. Phylodynamic models also found that YMSM frequently acquire HIV from older partners, suggesting that age-discrepant partnerships play an important role in HIV dynamics among YMSM.

917  **HOMOPHILY IN THE SOCIOSEXUAL NETWORKS OF GAY AND BISEXUAL MEN**


1 British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

**Background:** Kenyon & Delva (2018, “It’s the network, stupid”) argue that the elevated prevalence of sexually transmitted infections (STIs) in sub-populations is due to the structure of their socio-sexual networks. Homophily, which measures the degree to which individuals associate with those like themselves, has been regularly identified as a key determinant of socio-sexual network structure. Thus, we aim to describe patterns of homophily within the networks of gay and bisexual men (GBM).

**Methods:** Sexually-active GBM, aged 16+, were recruited between 2/2012 and 2/2015 using respondent-driven sampling. Participants recruited up to six participants in their social or sexual networks. Homophily estimates (h), based on recruitment patterns, were calculated in RDSAT and ranged from -1.00 (completely heterophilous) to + 1.00 (completely homophilous).

**Results:** Among 774 GBM, high homophily (h>0.50) was observed by HIV serostatus (Positive: h=.62; Negative: h=.31; unknown h=.03), gender (Cis-man: h=.59; Trans-man: h=.57), and age (Age < 30: h=.57; Age > 30: h=.55). Moderate homophily (h>0.30) was observed for ethnicity (White: h=.39;
919 NON-B SUBTYPE HIV INFECTIONS IN GERMANY BEFORE AND AFTER THE EUROPEAN MIGRANT CRISIS

Melanie Stecher1, Antoine Chaillou1, Christoph Stephan1, Jan-Christian Wasmuth2, Josef Ebeler1, Georg M. Behrens1, Julia Roider1, Christoph D. Spinner1, Matthias C. Muller2, Elena Knoops3, Guido Schaller4, Sanjay R. Mehta2, Joerg Wasmuth4, Josef Eberle5, Georg M. Behrens6, Julia Roider7, Christoph D. Spinner8, Ruxandra-Ilinca Ibanescu1, Isabelle Hardy1, Nadine Kronoti1, David Stephens5, Bluma G. Brenner1, Nathan Osman1, Ernesto Cuadra Foy1, Antoine Chaillou1, Ruxandra-Ilinca Ibanescu1, Isabelle Hardy1, Nadine Kronoti1, David Stephens1, Michel Roger1

1Lady Davis Institute for Medical Research, Montreal, QC, Canada, 2University of California San Diego, La Jolla, CA, USA, 3Centre de Recherche du CHUM, Montreal, QC, Canada, 4Research Institute of McGill University Health Centre, Montreal, QC, Canada, 5McGill University, Montreal, QC, Canada

**Background:** Phylogenetic analyses of the interrelationships of viral sequences, using novel statistical tools, provide molecular epidemiological frameworks to reconstruct HIV transmission networks. We applied these methods to gain novel insights on HIV transmission patterns in Quebec, uncover cryptic at-risk populations, and elucidate epidemic drivers that cannot be identified by traditional epidemiological approaches.

**Methods:** Genetic analyses were performed on subtype B pol sequences derived from newly-infected men having Sex with Men (MSM, n=4800) and Heterosexuals subgroups, including People who Inject Drugs (PWID) and Migrants from Haiti and the Americas (n=1836). Phylogenetic analyses were also conducted on non-B viral subtypes originating from Migrants from Africa, Asia and Europe (n=1578). Growth trajectories of transmission networks (6+ members/cluster) were analyzed using Maximum-Likelihood in MEGA10 and/or HIV-TRACE (Transmition Cluster Engine) platforms.

**Results:** Half of new infections (n=2328) among MSM segregated as solitary “dead-end” transmissions (n=1478) or small transmission networks having 2-5 members/cluster (n=850). The remaining half of new infections (n=2371) were in large transmission networks (6-150 members, mean 42 members/cluster). Phylogenetics showed a marked decline in singleton transmissions (n=48) compared to 5.6% (11/195), p<0.001] increased significantly after 2015. However, there were only three new non-B diagnoses after 2015 among individuals from the top 5 countries of origin of the 2015 immigrants (i.e. Syria, Kosovo, Afghanistan, Albania, Iraq). Of the 686 non-B HIV infected individuals, 119 (13.7%) were genetically linked, forming 42 transmission clusters (size 2-19 sequences) with heterosexual risk (36.1%; 43/119) and injection drug use (20.1%; 24/119) being predominant. There was an increase in genetically linked men who have sex with men (MSM) with two male only clusters before 2015 and the emergence of six more male only clusters (including 9/18 males, of whom 8/9 originating from Eastern Europe) after 2015 (Figure 1A&B).

**Conclusion:** The proportion of HIV-1 non-B diagnoses increased after 2015, particularly driven by individuals originating from Eastern Europe, North Africa, and Middle East. However, the number of new diagnoses among migrants originating from the top 5 countries of the European migrant crisis was minimal.

**Figure 1:** Transmission network of HIV-1 non-B subtypes in Germany (sequences are from individuals who received care at the University Hospital’s Bonn, Cologne, Freiburg, Hamburg, Hannover, and Munich, between 2001 and 2018). All edges represent a genetic distance of 25%. A) Color indicates the period prior 2015 (yellow) and after 2015 (blue). B) Color indicates the risk group: men having sex with men (MSM) in blue; heterosexuals (HTS) in red; people originating from an endemic country (Columbia) in yellow; people who inject drugs (PWID) in green, and others unreported in gray.
Background: Migrants account for nearly 30% of all new diagnoses of HIV infection in Italy in the last years. Aim of this study was to evaluate the characteristics of HIV-1 molecular transmission clusters (MTCs) among natives and foreign individuals diagnosed between 1998 and 2018 enrolled in the ICONA cohort.

Methods: Phylogenetic analyses were performed on HIV-1 pol sequences (seq) to characterise subtypes (Neighbor Joining method, 1000 replicates) and identify MTCs, divided into small (SMTCs, 2-3 seq), medium (MMTCs, 4–9 seq) and large (LMTCs, ≥10 seq). MTCs were first identified by the HIV-TRACE tool (genetic distance ≤0.01). The robustness of MTCs was further tested using the Maximum Likelihood method, using MEGA6 software. Factors associated with MTCs were evaluated using logistic regression.

Results: Among 3,499 drug-naive participants in the ICONA cohort (2,804 natives; 695 migrants), 726 (20.8%) 644 natives, 82 migrants) were involved in 228 MTC, including 6 LMTCs (N=140 subjects), 36 MMTCs (N=184) and 186 SMTCs (N=402), respectively. Subjects involved in MTCs were prevalently native (88.7%) vs 77.8%, p<0.001), male (94.3% vs 78.9%, p<0.001) and MSM (74.7% vs 45.0%, p<0.001), younger (median [IQR] yrs: 32 [27–40] vs 38 [31–46], p<0.001), more recently diagnosed (median [IQR] yrs: 2012 [2009–2014] vs 2011 [2007–2014], p<0.001), and with higher CD4 count were significantly associated with MTCs (Table). The presence of both natives and foreigners was found in 66.7% of LMTCs, 33.3% of MMTCs and 23.1% of SMTCs. By focusing on migrants, they contributed 14.4% to SMTCs, 7.6% to MMTCs and 7.1% to LMTCs, respectively. The 24 migrants involved in LMTCs and MMTCs were mainly from Central/South America or other European countries.

Conclusion: HIV-1 newly diagnosed subjects are involved in several MTCs in the last two decades in Italy. Clustering transmission, especially for large clusters, is prevalently driven by natives, mainly MSM and frequently infected with HIV-1 non-B subtype. Our findings can contribute to monitoring of the HIV epidemic and guiding the public health response.

Background: Almost half of the new HIV diagnoses were among people originating from outside the reporting country (migrants) in Europe the last few years. We aimed to trace the geographic origin of HIV-1 CRF02_AG infections, the most prevalent non-B clade in France, for migrants in Paris, using molecular epidemiology methods.

Methods: We studied the first available pol gene sequence for all patients infected with HIV-1 CRF02_AG (N=2,146) diagnosed in two large Parisian University hospitals. HIV-1 typing was carried out using automated subtyping tools (COMET, REGA). We analyzed phylogenetically the CRF02_AG sequences from migrants (N=567) along with all the available CRF02_AG sequences from non-migrant patients (N=1,579). We also included all publicly available CRF02_AG sequences (N=3,476), and unpublished CRF02_AG sequences from Spain, Italy and Greece (N=1193), as references. Local transmission networks (LTNs) were phylogenetic clusters including sequences from France at proportions ≥70%, receiving bootstrap value >70% or SH-support >0.8. Phylogenetic trees were estimated by the maximum likelihood method (RAxML, FastTree). The origin of HIV transmissions was traced by phylogenetic analysis using the criterion of parsimony (Mesquite).

Results: Phylogenetic analysis revealed that 198 (34.9%) sequences from migrants clustered within LTNs. The distribution of transmission risk group in migrants infected with CRF02_AG strains was: Heterosexuals (N=447, 78.8%), MSM (N=37, 6.5%), Others/Unknowns (N=83, 14.7%). The proportion of migrant MSM within CRF02_AG LTNs was significantly higher (83.8%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogeographic analysis showed that 29.3% of the CRF02_AG HIV-transmissions within migrants occurred in France. Multivariate analysis showed that parameters associated with clustering within the large LTNs (≥10 sequences) were MSM risk group (MSM vs heterosexual OR 10.3, 95% CI: 6.5-16.5) and French origin (non-migrants vs migrants OR 2.4, 95% CI: 1.5-3.9).

Conclusion: We found that 29.3% of CRF02_AG HIV-transmissions within migrants originated in Paris. Transmissions among migrants within LTNs were associated with MSM risk group. Moreover, transmissions within large clusters are more frequent among MSM and non-migrants. This is one of the few molecular studies showing that even for CRF02_AG, which is prevalent in Sub-Saharan Africa, a large proportion of transmissions among migrants occur in Paris.

921 MOLECULAR ANALYSIS SUGGESTS POST-MIGRATION HIV-1 ACQUISITION AMONG MIGRANTS IN PARIS

Evangelia G. Kostaki1, Cathia Soulée1, Benoit Vissereau1, Alexandre Storto1, Charlotte Charpentier1, Marc Wierden1, Roland Landman1, Christine Katlama1, Vincent Calvez2, Diane Descamps1, Federico García3, Maria M. Santoro4, Dimitrios Paraskevis1, Anne-Geneviève Marcelin1,2

1University of Athens, Athens, Greece, 2AP–HP, Hopitaux Universitaires Pité Salpétrière, Paris, France, 3AP–HP, Hôpital Bichat-Claude Bernard, Paris, France, 4IMEA, Paris, France, 5Hospital Universitario San Cecilio, Granada, Spain, 6University of Rome Tor Vergata, Rome, Italy

Background: Previous studies showed that even for CRF02_AG, which is prevalent in Sub-Saharan Africa, a large proportion of transmissions among migrants occur in Paris. The molecular origin of HIV-1 CRF02_AG variants in migrants in Paris has been unclear.

Methods: We studied the first available pol gene sequence for all patients infected with HIV-1 CRF02_AG (N=2,146) diagnosed in two large Parisian University hospitals. HIV-1 typing was carried out using automated subtyping tools (COMET, REGA). We analyzed phylogenetically the CRF02_AG sequences from migrants (N=567) along with all the available CRF02_AG sequences from non-migrant patients (N=1,579). We also included all publicly available CRF02_AG sequences (N=3,476), and unpublished CRF02_AG sequences from Spain, Italy and Greece (N=1193), as references. Local transmission networks (LTNs) were phylogenetic clusters including sequences from France at proportions ≥70%, receiving bootstrap value >70% or SH-support >0.8. Phylogenetic trees were estimated by the maximum likelihood method (RAxML, FastTree). The origin of HIV transmissions was traced by phylogenetic analysis using the criterion of parsimony (Mesquite).

Results: Phylogenetic analysis revealed that 198 (34.9%) sequences from migrants clustered within LTNs. The distribution of transmission risk group in migrants infected with CRF02_AG strains was: Heterosexuals (N=447, 78.8%), MSM (N=37, 6.5%), Others/Unknowns (N=83, 14.7%). The proportion of migrant MSM within CRF02_AG LTNs was significantly higher (83.8%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogeographic analysis showed that 29.3% of the CRF02_AG HIV-transmissions within migrants occurred in France. Multivariate analysis showed that parameters associated with clustering within the large LTNs (≥10 sequences) were MSM risk group (MSM vs heterosexual OR 10.3, 95% CI: 6.5-16.5) and French origin (non-migrants vs migrants OR 2.4, 95% CI: 1.5-3.9).

Conclusion: We found that 29.3% of CRF02_AG HIV-transmissions within migrants originated in Paris. Transmissions among migrants within LTNs were associated with MSM risk group. Moreover, transmissions within large clusters are more frequent among MSM and non-migrants. This is one of the few molecular studies showing that even for CRF02_AG, which is prevalent in Sub-Saharan Africa, a large proportion of transmissions among migrants occur in Paris.

922 GEOGRAPHIC PATTERNS IN HIV TRANSMISSION CLUSTERS IN LOS ANGELES COUNTY

Britt Skaathun1, Manon Ragonnet-Cronin1, Kathleen Poortinga2, Zhijuan Brits Skaathun2

1University of California San Diego, La Jolla, CA, USA, 2Los Angeles County Department of Public Health, Los Angeles, USA

Background: The geographic spread of HIV-1 is driven by both human movement and local heterosexual spread. In Los Angeles County, HIV-1 in men who have sex with men is predominantly driven by migration, while for MSM in Los Angeles and San Diego counties, the geographic origin of HIV-1 is predominantly driven by migration.

Methods: We estimated the proportion of sexual partnerships within Los Angeles County HIV genetic transmission networks that are likely to be driven by migration. We used a dynamic transmission modeling framework to estimate the geographic origin of HIV-1 CRF02_AG infections, the most prevalent non-B clade in France, for migrants in Paris, using molecular epidemiology methods.

Results: Phylogenetic analysis revealed that 198 (34.9%) sequences from migrants clustered within LTNs. The distribution of transmission risk group in migrants infected with CRF02_AG strains was: Heterosexuals (N=447, 78.8%), MSM (N=37, 6.5%), Others/Unknowns (N=83, 14.7%). The proportion of migrant MSM within CRF02_AG LTNs was significantly higher (83.8%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogeographic analysis showed that 29.3% of the CRF02_AG HIV-transmissions within migrants occurred in France. Multivariate analysis showed that parameters associated with clustering within the large LTNs (≥10 sequences) were MSM risk group (MSM vs heterosexual OR 10.3, 95% CI: 6.5-16.5) and French origin (non-migrants vs migrants OR 2.4, 95% CI: 1.5-3.9).

Conclusion: We found that 29.3% of CRF02_AG HIV-transmissions within migrants originated in Paris. Transmissions among migrants within LTNs were associated with MSM risk group. Moreover, transmissions within large clusters are more frequent among MSM and non-migrants. This is one of the few molecular studies showing that even for CRF02_AG, which is prevalent in Sub-Saharan Africa, a large proportion of transmissions among migrants occur in Paris.
**923 HUMAN MOBILITY PATTERNS GENERATE GEOGRAPHICALLY STRUCTURED SUB-EPIDEMICS IN NAMIBIA**

Eugenio Valdano¹, Justin Okano¹, Vittoria Colizza¹, Sally Blower¹
¹University of California Los Angeles, Los Angeles, CA, USA; ²INSERM, Paris, France

**Background:** Populations in Sub-Saharan Africa are highly mobile. Therefore, an individuals’ “social/sexual community” can consist of multiple communities: we define such a social/sexual community as a mega-community (MC). If MCs exist, they would geographically structure a generalized HIV epidemic into loosely connected sub-epidemics. This would have significant implications for designing effective epidemic control strategies. Here we use mobile phone data from Namibia, where HIV prevalence is ~14%, to search for MCs.

**Methods:** We first evaluated HIV transmission dynamics within Namibia: Genetic network analyses found that 23% (18/78) had a putative linkage with ≥1 sequence forming 6 clusters (size: 2-5 PWH). We then used a technique from network science (a community-detection algorithm) to determine if MCs exist.

**Results:** Residents of Namibia spent ~22% (median, Interquartile range: 18-26%) of their time outside their home constituency, over a year. Population-level travel patterns divide Namibia’s population of 2.5 million into eight MCs that vary in size (15,000 to 650,000 individuals) and compactness (figure). Namibia’s generalized epidemic consists of eight connected sub-epidemics: each contained within a MC. We were also able to identify “bridges” that link sub-epidemics: a bridge is a constituency in one MC that is linked, by travel, to another MC. We identified two “types” of bridges (figure): short bridges (linked constituencies are spatially contiguous) and long bridges (linked constituencies are separated by at least one constituency). Notably, the capital of Namibia (Windhoek) is a long bridge and connects to six MCs and sub-epidemics. Oshakati, the capital of one of 14 regions in Namibia, is also a long bridge; it is connected to five MCs and sub-epidemics.

**Conclusion:** As a result of travel patterns, the population of Namibia is divided into MCs. These MCs are not visible, but they spatially structure Namibia’s generalized epidemic into eight loosely connected sub-epidemics. This suggests that interventions may be the most effective if they are implemented at the level of the MC. Furthermore, it may be very difficult to reduce incidence in Windhoek and Oshakati, as they are connected (by travel) to multiple other sub-epidemics.

---

**924 LOCAL AND REGIONAL DYNAMICS OF HIV EPIDEMICS AMONG HIGH-RISK POPULATIONS IN HAITI**

Frantz Jean-Louis¹, Jean Wysler Domercan¹, Caroline Ignacio¹, Sara Gianella¹, Guethrina Galbaud¹, Davey M. Smith³, Antoine Chaillon¹
¹Equipment-MatCH, Petion-Ville, Haiti; ²Wits Health Consortium, Johannesburg, South Africa; ³University of California San Diego, San Diego, CA, USA

**Background:** Although the overall HIV prevalence in Haiti has been stable around 2% for the past 15 years, the prevalence in high risk groups, such as men having sex with men (MSM) and female sex workers (FSW), are much higher, 12.9% and 8.7% respectively. To characterize the HIV epidemics in the Caribbean, we explored: (1) the dynamics of HIV transmission among persons with HIV (PWH) from high risk groups in Haiti, and (2) viral dispersal across the Caribbean.

**Methods:** 78 HIV-1 pol sequences were newly sampled and analyzed from MSM, FSW and sexual partners of FSW from Haiti. We also analyzed 3,908 publicly available HIV-1 pol sequences from the Caribbean and 33,100 from the rest of the world. Phylogenetic and network analyses were performed to infer local HIV transmission in Haiti. Sequences were screened for drug resistant mutations (DRM). Next, we applied a multistep phylogeographic approach to evaluate dispersal across the Caribbean: (1) identify all well-supported monophyletic clades; (2) all clades of size ≥3 identified were used to perform a discrete phylogeographic inference to evaluate the dispersal history across Caribbean countries; (3) we applied a linearized model (GLM) to test the association of epidemiologic factors and connectivity (i.e. geographic distances and air traffic passenger flow) with lineage dispersal.

**Results:** We first evaluated HIV transmission dynamics within Haiti: Genetic network analyses found that 23% (18/78) had a putative linkage with ≥1 sequence forming 6 clusters (size: 2-5 PWH). Further analyses revealed viral trafficking from the Dominican Republic (DR) toward Haiti but also from Puerto Rico (PR) and Trinidad and Tobago toward DR and PR respectively. Next, we evaluated geospatial patterns in the Caribbean’s: Discrete phylogeographic inference revealed viral trafficking from the Dominican Republic (DR) towards Haiti but also from Puerto Rico (PR) and Trinidad and Tobago toward DR and PR respectively. As might be expected, the GLM analysis showed that closer countries were the most likely to show viral exchange.

**Conclusion:** HIV transmissions occurs across risk groups in Haiti with high rates of shared DRM's. This study also found that local epidemics are likely sustained by regional human migration. Thus, prevention efforts to curb local epidemics will need to consider all risk groups and also epidemics from other countries.
925 MAPPING AND CHARACTERISING HIV TRANSMISSION HOTSPOTS IN SUB-SAHARAN AFRICA
Caroline Bulstra1, Jan A. Hontelez1, Federica Giardina2, Richard Steen3, Nico Nagelkerke1, Till Bärnighausen4, Sake de Vlas1
1Heidelberg University, Heidelberg, Germany, 2Erasmus University Medical Center, Rotterdam, Netherlands, 3Africa Health Research Institute, Mbabane, South Africa
Background: In the generalised epidemics of sub-Saharan Africa (SSA), HIV prevalence shows patterns of clustered micro-epidemics. We mapped and characterised these so-called ‘hotspots’ for young adults (15-29 years of age), as a proxy for transmission hotspots, for seven countries in Eastern and Southern Africa: Kenya, Malawi, Mozambique, Tanzania, Uganda, Zambia, and Zimbabwe.
Methods: We used geolocated survey data from the most recent USAID Demographic and Health Surveys and AIDS Indicator Surveys, which included 53,234 young adults from 3,665 sample locations. Ordinary kriging was applied to predict HIV prevalence at unmeasured locations. We explored to what extent behavioural, socioeconomic and environmental factors explain HIV prevalence at the individual- and sample location-level, by developing a series of multilevel multivariable logistic regression models. We then compared and geospatially visualised how heterogeneity and hotspots can be explained by the models, using the sample location random effect estimates from each model.
Results: We found substantial HIV prevalence heterogeneity among both adults (Figure 1A) and young adults (Figure 1B) throughout all countries, with clear geospatial hotspots among young adults characterised by areas with prevalences of over 11% or 15% alternating with areas of prevalences between 0% and 2%. The heterogeneity in young adults could be explained for 15.6% by an interplay of known behavioural, socioeconomic and environmental factors. Maps of the interpolated random effect estimates show that environmental variables, representing indicators of economic activity, were most powerful in explaining HIV hotspot locations.
Conclusion: In young adults, micro-epidemics of relatively high HIV prevalence alternate with areas of very low prevalence, clearly illustrating the existence of transmission hotspots. These hotspots are partially characterised by high economic activity, relatively high socioeconomic status, and risky sexual behaviour. Localised HIV prevention interventions specifically tailored to the populations at risk will be essential to curb transmission. More fine-scale geospatial mapping of key populations, such as sex workers, and migrant populations, could help to further understand the drivers of these transmission hotspots, and to determine to what extent they fuel the generalised epidemics in SSA.

926 GEOGRAPHIC CHARACTERISTICS OF HIV GENETIC CLUSTERS AMONG NEWLY DIAGNOSED CASES IN NC
Andrew E. Cressman1, Erika Samoff1, Victoria L. Mobeley1, Simon Frost1, Kimberly Enders1, Shuntai Zhou1, Ronald Swansstrom1, Joseph J. Eron1, William C. Miller1, Myron S. Cohen1, Richard Steen1, Nico Nagelkerke1, Till Bärnighausen4, Sake de Vlas1
1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2North Carolina Division of Public Health, Raleigh, NC, USA, 3Cambridge University, Cambridge, UK, 4The Ohio State University, Columbus, OH, USA
Background: Identifying both geographic clusters and genetic clusters are routine parts of HIV surveillance aiming to help focus prevention efforts. Integrating geographic and genetic analyses, especially beyond traditional surveillance borders, will inform the ability of geographic clustering to identify linked HIV transmission networks and help allocate prevention efforts.
Methods: We assessed genetic clusters among those >=13 years old newly diagnosed with HIV in North Carolina (NC) between 2016 and 2019. Data of those with complete residential address information at the time of HIV diagnosis and either a pol sequence reported to NC or from sequence analysis of the diagnostic specimen received from the NC State Lab of Public Health were assessed (n=2,679 persons, approximately 69% of new diagnoses reported in NC). Clusters were constructed with <1.5% pairwise genetic distance (TN-93) between two members and restricted to >=5 total members for this analysis. Addresses were geocoded, and planar distances between those with genetically linked infections were calculated using address coordinates.
Results: In total, we identified 67 genetic clusters involving 565 persons. Cluster members were mostly male (93%), African American (67%), and men who have sex with men (78%). The median cluster size was 7 members (range: 5-28), and most clusters were composed of a majority of members who lived in the same NC Field Services Unit Region (87%), of which there are seven, or county (58%), of which there are 100 with a median area of 436 square miles, at the time of diagnosis. The median geographic distance among linked members across all clusters was 25 miles (range: 0, 234), and 40 genetic clusters (60%) had a median geographic distance <25 miles among their linked members. Most clusters had maximum distances >100 miles (54%) and minimum distances <10 miles (97%) among linked members. Genetic clusters with median geographic distances >25 miles among linked members were more likely to have members who were African American (71% vs. 63%), younger at HIV diagnosis (53% vs. 46%) 18-24 years old), and in non-metropolitan (micropolitan, small town, or rural) areas (16% vs. 6%) compared to clusters with median geographic distances <25 miles among linked members.
Conclusion: While most genetic clusters had a majority of members located within traditional surveillance borderlines of regions and counties, most also included greater geographic distances between genetically-linked infections.

927 HIV TRACE VS PHYLOGENETIC ANALYSIS: UNRAVELING TRANSMISSION CLUSTERS IN SPAIN
Carlos Guerrero Beltrán1, Evangelia G. Kostaki2, Luca Carioti3, Marta Alvarez1, Julian Olalla1, Maria Carmen Vidal Ampurdanes1, Marta Montero1, Silvia García-Bujalance1, Jose-Ramón Blasco1, Maria Rivero1, Lucio Jesus Garcia-Fraile Fraile1, Maria M. Santoro1, Dimitrios Paraskevis1, Federico García1
1Hospital Universitario San Cecilio, Granada, Spain, 2University of Athens, Athens, Greece, 3University of Rome Tor Vergata, Rome, Italy, 4Hospital Costa del Sol, Marbella, Spain, 5Hospital Universitario de Son Espases, Palma de Mallorca, Spain, 6Hospital Universitario La Fe, Valencia, Spain, 7Hospital La Paz Institute for Health Research, Madrid, Spain, 8Hospital San Pedro, La Rioja, Spain, 9Clínica Universidad de Navarra, Pamplona, Spain, 10Hospital Universitario de La Princesa, Madrid, Spain
Background: The HIV-1 TRACE (TRAnsmission Cluster Engine) is a new computational tool to identify molecular transmission clusters in large databases. This approach is based on viral genetic relatedness to a reference sequence in order to construct and visualize the connections among clusters. Our objective was to identify transmission clusters in CoRIS cohort (2018 update) by using HIV-1 TRACE computational tool focusing on subtype B patients and to compare TRACE identified clusters with phylogenetic approaches.
Methods: We used the RT available regions from newly HIV diagnoses in 2018 in CoRIS. HIV-1 TRACE (http://hivtrace.datamonkey.org/hivtrace) was used to estimate transmission clusters in 484 subtype B antiretroviral-naive patients enrolled in the CoRIS cohort. Phylogenetic analysis was conducted by maximum likelihood method (ML) with bootstrap using the GTR + G as nucleotide substitution model. Sequences were phylogenetically analysed along with all the most similar sequences as identified by a BLAST search. Local transmission networks (LTNs) were defined as phylogenetic clusters including sequences from Spain at proportions >70%, receiving bootstrap value >70%.

Results: HIV-1 TRACE results showed that 354 patients (73.1%, n=354/484) were not involved in any cluster and 130 patients (26.9%, n=130/484) were grouped in 54 clusters: 39 clusters with 2 nodes, 11 clusters with 3 nodes, 2 clusters with 4 nodes, 1 cluster with 5 nodes and 1 cluster with 6 nodes (range 2-6). Phylogenetic analysis revealed that 330 (68.2%, n=330/484) and 154 patients (31.8%, n=154/484) were involved in 63 clusters: 48 clusters with 2 nodes, 7 clusters with 3 nodes, 4 clusters with 4 nodes and 4 clusters with 5 nodes (range 2-5). Overall, the concordance between phylogenetic approaches and HIV-1 TRACE tool was 84.4%. The discrepancies were not observed only in the number of clusters, as previously described, but also in the distribution, since phylogenetic tools identified 8 clusters with more than 3 nodes and HIV-1 TRACE tool identified only 4 of these clusters.

Conclusion: The implementation of HIV-1 TRACE is an easy to use tool and it allows identification of transmission clusters. Our results revealed that HIV-1 TRACE identified fewer clusters among B-subtype patients than traditional phylogenetic approaches. Those discrepancies were due to the non-use of a threshold in the patristic distances in phylogenetic analysis.

928 RECONSTRUCTION AND ESTIMATION OF DIRECTED HIV-1 TRANSMISSION USING DEEP SEQUENCES

Nicholas Bbsosa1, Deogratius Ssemwangwa2, Alfred Ssekagiri1, Yunia Mayanja1, Ubaldo M. Bahemuka1, Janet Seeley3, Deenan Pillay4, Christophe Fraser5, Pontiano Kaleebu6, Oliver Ratmann3, for the PANGEA Consortium

MRC/UVRI and LSHTM Uganda Research Unit, Entebbe, Uganda; MRC/UVRI and LSHTM Uganda Research Unit, Entebbe, Uganda; Uganda Virus Research Institute, Entebbe, Uganda; Africa Health Research Institute, Mbabune, South Africa; University of Oxford, Oxford, UK; Imperial College London, London, UK

Background: Key population in Uganda are disproportionately affected by HIV-1 relative to the general population (GP). Serial cross-sectional surveys were carried out in several HIV-1 high-risk and general population cohorts of the MRC/UVRI & LSHTM Uganda research unit to generate near full length (NFL) deep sequences. The aim of this study was to perform a source attribution analysis in the sampled populations to assess the extent to which high-risk groups contribute to the HIV epidemic in the general population and to further inform location focused interventions in key populations.

Methods: We used the phyloscanner program developed to phylogenetically infer transmission from with-in and between-host HIV genetic diversity to reconstruct directed HIV-1 transmission networks from NFL deep sequences (n=2,531) from communities of women at high risk to HIV (WHR), the fisherfolk (FF) and the general population (GP). We used the phylosfows package implemented in the R software to correct for sampling heterogeneity and estimate HIV transmission flows between the three populations.

Results: Of the 2,531 HIV-1 NFL deep sequences analyzed in phyloscanner, 105 highly supported HIV transmission pairs were identified with phylogenetic evidence for the direction of transmission (criteria for linkage: >60% and >60% for one direction). Our observed transmission counts showed majority of HIV-1 transmissions to be intra-population (GP-GP (34%): FF-GP (31%): WHR-GP (10%)): Between populations, transmission counts were more prevalent from the GP to FF (11%) followed by those from the FF to the GP (10%) (Figure 1). An estimation of HIV transmission flows showed results that were comparable to the observed counts within and across populations with the exception of transmissions within the WHR that increased more than four-fold.

Conclusion: Major HIV-1 transmissions were largely localized within the three studied populations. An estimation of the viral transmission flows suggests that the high-risk FF population considered a hotspot for HIV infection could act as a sink of virus flowing from the GP. Although consistent with our earlier findings, interpretation of these results highlights the importance of correcting for sampling heterogeneity that could underestimate transmission flows. Results further imply that location focused interventions could be key for effective epidemic control in high-risk populations but should not negate the need for broader prevention.
930 USE OF PHYLOGENETIC ANALYSIS TO INFER THE DIRECTION OF HIV TRANSMISSION

Yinfeng Zhang1, Chrys Wymant2, Oliver Laeyendecker1, Kate Grabowski3, Matthew D. Hall4, Sarah E. Hudelson5, Estelle Piwowar-Manning1, Marybeth McCauley4, Johnstone Kumwenda5, Mina C. Hosseinipour6, Ying Qin Chen7, Myron S. Cohen1, Christophe Fraser8, Susan H. Eshleman1, for the HPTN 052 Study Team

1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2University of Oxford, Oxford, UK, 3FHI 360, Washington, DC, USA, 4Malawi College of Medicine-Johns Hopkins University Research Project, Blantyre, Malawi, 5University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 6Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Phylogenetic analysis can provide important information about the spread of HIV in cohorts and populations. Methods are well established for identifying genetically-linked viral infections and clusters. Improved methods are needed to infer the direction of HIV transmission. We used next-generation sequencing (NGS) to generate whole-genome HIV sequences from couples with known linked HIV infection and known transmission direction. These data were used to evaluate methods for inferring the direction of HIV transmission.

Methods: NGS was performed using samples from 32 index-partner pairs (couples) enrolled in the HIV Prevention Trials Network (HPTN) 052 trial (up to two samples per person, collected on different dates). Index samples were obtained up to 5.5 years before partner infection; partner samples were obtained near the time of HIV seroconversion. The bioinformatics method, phylocoder, was used to infer transmission direction. We evaluated inferred transmission direction using whole-genome NGS data for individual couples, for all couples as a group (one sample/person; group analysis) and for all couples using all available samples (multi-sample group analysis). We also evaluated inferred transmission direction using NGS data from individual HIV genes (gag, pol, env).

Results: Ultra-deep whole-genome NGS data was obtained for 116 samples from indexes and partners, including 105 unique index-partner sample pairs. Transmission direction was correctly inferred (index to partner) for 98/105 (93.3%) of the individual sample pairs, 99/105 (94.3%) of the sample pairs using group analysis, and 31 (96.9%) of the 32 couples using multi-sample group analysis. For the remaining cases, linkage was established but transmission direction could not be inferred. There were no cases where the incorrect transmission direction (partner to index) was inferred. The methods were more likely to infer transmission direction when there was a longer time between index and partner sample collection. Pol region sequences performed better than env or gag sequences for inferring transmission direction.

Conclusion: Accurate predictions of transmission direction were obtained using whole-genome and pol NGS data. Further research is needed to evaluate the performance of these methods in other settings and cohorts and in cases where whole-genome and pol NGS data. Further research is needed to evaluate the performance of these methods in other settings and cohorts and in cases where whole-genome and pol NGS data were used to evaluate methods for inferring the direction of HIV transmission.

932 IMPLICATIONS OF NEXT-GENERATION SEQUENCING FOR DRUG RESISTANCE AND CLUSTER DETECTION

Randall V. Collura1, Wendy Patterson1, Carol-Ann Swan1, Eva Pradhan1, William M. Switzer1, Alexandra M. Oster1, Bridget J. Anderson1

1New York State Department of Health, Albany, NY, USA, 2CDC, Atlanta, GA, USA

Background: HIV-1 polymease (pol) sequences from routine HIV drug resistance (DR) testing are used to monitor DR and identify molecular transmission clusters as part of public health (PH) surveillance. Proximal DNA DR testing using next-generation sequencing (DNA-NGS) has been used clinically since 2015 to provide DR information in the setting of viral suppression. Since DNA-NGS covers the same part of the HIV genome and DNA-NGS consensus sequences mimic traditional RNA-Sanger (RNA-S) sequences, they have likely been reported to PH as RNA-S sequences. Some clinical labs are also using (and others are considering) NGS for RNA-based DR testing (RNA-NGS). We evaluated whether shifts in testing methods and sequencing technology have implications for PH surveillance of DR and transmission clusters.

Methods: We identified ~115,000 RNA-S, ~11,000 DNA-NGS, and ~5,000 RNA-NGS sequences reported to New York during 2010-2019 from a single commercial lab. Inferred DR was compared for 1,350 persons with two or more sequence types. For cluster analyses, pairwise genetic distances were calculated...
between sequences for the same person with collection dates within 1 year (n=7,771 comparisons from 2,823 individuals) using Secure HIV-TRACE default settings and a 2% genetic distance threshold, stratified by sequence type.

**Results:** Overall, DR was 37% more likely to be inferred from DNA-NGS sequences than RNA-based sequences from the same individual. Time between tests was not a significant factor, and individual drug classes showed similar results. For clustering, over 25% of DNA-NGS were rejected by Secure HIV-TRACE due to high levels of ambiguities compared to RNA-NGS (11%) and RNA-S (8%). Based on pairwise distances for sequences from the same individual, RNA-NGS and especially DNA-NGS sequences, clustered less frequently than RNA-S sequences and at a higher distance threshold if they did cluster. Mean number of years since diagnosis was high and varied by sequence types but did not explain the results (Table 1).

**Conclusion:** We found significant differences between consensus DNA-NGS and RNA-NGS sequences compared to RNA-S sequences for cluster inference and between DNA-NGS and RNA-based sequences for DR. Hence, reporting of sequence type for PH surveillance is critical for ensuring appropriate inclusion of sequences for accurate HIV DR and transmission cluster analyses. Monitoring changes in sequencing technology is critical for assessing impact on PH and clinical decisions.

**Table 1: Within-individual pairwise TN93 distances by sequence type**

<table>
<thead>
<tr>
<th>Sequence Comparison</th>
<th>N</th>
<th>% clustering at &lt;1.5% distance level</th>
<th>% clustering at ≤0.5% distance level</th>
<th>Mean DNA identity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA-NGS to DNA-NGS</td>
<td>229</td>
<td>93.7</td>
<td>19.2</td>
<td>99.8</td>
</tr>
<tr>
<td>DNA-NGS to RNA-NGS</td>
<td>123</td>
<td>97.8</td>
<td>26.0</td>
<td>99.5</td>
</tr>
<tr>
<td>DNA-NGS to RNA-S</td>
<td>857</td>
<td>99.7</td>
<td>23.0</td>
<td>97.9</td>
</tr>
<tr>
<td>RNA-NGS to RNA-NGS</td>
<td>262</td>
<td>95.9</td>
<td>16.4</td>
<td>99.5</td>
</tr>
<tr>
<td>RNA-NGS to RNA-S</td>
<td>707</td>
<td>97.5</td>
<td>20.7</td>
<td>99.4</td>
</tr>
<tr>
<td>RNA-S to RNA-NGS</td>
<td>5,955</td>
<td>79.0</td>
<td>10.5</td>
<td>92.1</td>
</tr>
</tbody>
</table>

*Comparisons are with n individuals from pol sequence collected = 1 year apart
1. 2% distance threshold is the lowest TN (FASTA) default
2. Clustering above the 2% distance threshold indicates recent and rapid transmission per CDC.*

**934 JACKHAMMER RT-PCR RECOVERS DIVERSE ARCHIVAL VIRAL GENOMES FROM KINSHASA, 1983**

Sophie Gryseels1, Thomas D. Watts1, Thomas Quinn2, Philippe Lemey3, Henry Francis1, Oliver Laeyendecker4, Michael Worobey1

1University of Arizona, Tucson, AZ, USA, 2Johns Hopkins University, Baltimore, MD, USA, 3Katholieke Universiteit Leuven, Leuven, Belgium, *4FD, Silver Spring, MD, USA, 5Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** Viral genome data are a key means for characterizing current epidemics as well as reconstructing past epidemiological and evolutionary histories. To reliably infer the past, genome data stored in archival samples can provide essential calibration points for dated phylogenetic analyses. In the case of epidemics with a long pre-discovery history, such as the HIV/AIDS pandemic, specimens from early phases in the epidemic are very scarce, and the remaining viral genetic material are by now often degraded, thus warranting very sensitive sample-to-sequence procedures.

**Methods:** Here we expand our ‘jackhammer’ multiplex PCR approach to amplify and sequence HIV-1 RNA from 45 serum/plasma specimens from Democratic Republic of Congo (DRC) sampled in 1983 from the very first diagnosed AIDS patients of Africa. A sequential set of 63 primer pairs, compatible with most known subtypes, were designed that target 63 150-300 nucleotide overlapping regions across the coding HIV-1 genome. Primers with non-overlapping targets were combined into six pools, so that reverse transcription and a pre-amplification PCR could efficiently be performed in only six reactions per sample, before the final amplifications in 63 reactions.

**Results:** On average 80% of PCRs produced reliable (sanger) sequences after this <2 day general procedure, resulting in an average of ~7,000 nt of HIV-1 sequence data per sample. Performing additional PCRs with shuffled primers from an augmented primer set resulted in complete coding genomes for all samples. Twenty of the sequenced genomes were designated as a ‘pure’ subtype (A1, D, C, F1), two genomes were of an unknown subtype, six were known circulating recombinant forms (01_AE, 02_AG, 13_CPX, 25_cpx), and the remaining seventeen were each unique recombinants.

**Conclusion:** The recovered diversity spans essentially the entire global HIV-1 group M diversity, which (1) provides direct evidence that the breadth of HIV-1 group M diversity was already present when AIDS was first identified in the DRC, and (2) indicates our method can efficiently recover virtually any (even degraded) HIV-1 group M genome. We analyze these genomes together with other time-stamped sequences from central Africa in a phylodynamic framework to refine the timings of the major early growth phases of the HIV-1 epidemic in this region.

**935 A THIRD COMPLETE GENOME ESTABLISHES HIV-1 SUBTYPE L**

Julie Yamaguchi1, Ana Vallani1, Carole McArthur2, Larry Shrestley1, Gavin Cloherty1, Michael Berg3, Mary A. Rodgers1

1Abbott Labs, Abbott Park, IL, USA, 2University of Missouri–Kansas City, Kansas City, MO, USA, 3Presbyterian Church (USA), Louisville, KY, USA

**Background:** As part of the region where HIV-1 initially expanded early in the global pandemic, the Democratic Republic of Congo (DRC) is where the most diverse HIV isolates have been found, including all recognized Group M subtypes and many unclassifiable sequences. Two divergent non-recombinant sequences, 83CD003 and 90CD121E12, collected in 1983 and 1990 in DRC were previously proposed as a new subtype, L. However, HIV nomenclature standards require three epidemiologically distinct genomes for a new classification.

**Methods:** Specimen CG-0018A-01 was collected in DRC in 2001 as part of an HIV prevention of mother to child transmission (PMTCT) study. Previous subgenomic HIV-1 sequences branched closely with the proposed subtype L references, but small sample volume and low viral load limited efforts to expand genome coverage. In the present study, the complete genome was assembled through
application of metagenomic Next-Generation-Sequencing (mNGS) and target enrichment (HIV-xGen) methods. Neighbor-joining phylogenetic and recombinant analyses were completed to classify the genome using PhyIip v3.5 and Simplot v3.5.1.

**Results:** The combined mNGS and HIV-xGen approach yielded 4,363,031 of 11,046,542 total reads (39.5%) that mapped to the final 9681 bp complete genome at an average coverage depth of 47,783x. The CG-0018a-01 genome branched with the putative subtype L references with a bootstrap value of 100 in a phylogenetic tree. Notably, the CG-0018a-01 branch was basal to the junction of 83C.D003 and 99C012E12, which suggests CG-0018a-01 may be more closely related to an ancestral strain. Recombinant analysis did not identify any breakpoints and indicated the putative subtype L references had the highest percent identity to CG-0018a-01 across the genome except in the well-conserved pol region. Subgenomic phylogenetic analysis of the pol region confirmed that CG-0018a-01 branched with L references with bootstrap support of 97.

**Conclusion:** The subtype L classification has now been established by the non-recombinant HIV-1 genome of CG-0018a-01 as the third isolate in this divergent Group M branch. The identification of CG-0018a-01 decades after the two first subtype L strains were collected suggests transmission of subtype L may be ongoing in DRC. Although it was collected most recently, CG-0018a-01 appears to be more closely related to the ancestral subtype L strain than the other two isolates and will be important for determining the origins of subtype L.

936 WHOLE-GENOME SEQUENCING SHOWS INCREASING HIV-1 SUBTYPE COMPLEXITY AMONG MSM IN THE UK

Jean L. Mbisa1, Juan Ledesma1, David F. Bibby1, Carmen M. Fernandez Manso1, Peter Kirwan1, Alison E. Brown1, Hodan Mohamed1, Yuen T. Chan1, Gary Murphy1, David Dunn1, Caroline Sabin1, Valérie Delphch1, Kate El Bouzidi1, Anna Maria Geretti2, for the UK HIV Drug Resistance Database

**Background:** Recombination in HIV can occur following co-infection with two or more different strains. HIV whole genome sequencing (WGS) provides a better understanding of the recombination process and characterization of circulating strains. This helps to better define virus evolution and transmission dynamics.

**Methods:** The UK whole genome sequencing (UK-WGS) project undertook WGS analyses on 382 samples from men-who-have-sex-with-men (MSM) collected between 2000-2006 (n=201) and 2015-2016 (n=181). The former consisted of chronic (n=157) and recent (n=44) infections whereas the latter were recent infections only. Recency of infection was defined by avidity assay. More than 110,000 partial pol gene sequences from routine HIV-1 genotyping in the UK were obtained from the UK HIV Drug Resistance Database (UKHDRV). Subtyping was performed using REGA HIV subtyping tool and Cluster Picker was used for transmission cluster analysis (1.5% genetic distance and 90% bootstrap support). Linked clinical and demographic data were extracted from the HIV and AIDS Reporting System at PHE.

**Results:** Partial pol gene sequence data shows a gradual increase in diagnosed infections involving complex recombinants among MSM in the UK from 0.8% (n=630) in 2000 to 9.3% (n=2655) in 2014 (p<0.001). Among recently infected MSM the proportion of complex recombinant infections was 11.0% (55/501) in 2000 to 9.3% (n=2655) in 2014 (p>0.001). Furthermore, 32.4% (11/34) of WGS sequences classified as complex recombinants were similarly classified using partial pol gene only. The most common subtypes involved in recombination were A and B (n=17 each; 50.0%). Most men infected with complex recombinants were born in the UK (63.6%; n=21) and probably acquired HIV in the UK (84.8%; n=25). Using WGS data only, 18.2% (n=6) of the complex recombinants formed 2 transmission clusters, containing 2 and 4 sequences. When analyses included partial pol sequences from the UKHDRV, 27.3% (n=9) of the complex recombinants were in 3 transmission clusters, each containing 2-9 sequences. Partial pol sequences were classified as pure subtypes or CRFs (B or CRF02_AG) in 3 clusters and complex recombinants in 2.

**Conclusion:** WGS shows that routine HIV-1 genotyping significantly underestimates the prevalence and complexity of circulating recombinant strains among MSM in the UK. These data suggest an evolving MSM epidemic and transmission dynamics.

937 ASSISTED PARTNER NOTIFICATION SERVICES IN KAMPALA, UGANDA

Florence Namimbi1, Faridah Akuj1, Martin Susuna1, Esther Nasuuna1, Rhoda Mwandha1, Stella Alamo1, Madina Apolot1, Nelson Kalema1, Alice Namale1, Joanita Kigozi1

1Infectious Disease Institute, Kampala, Uganda, 2CDC Uganda, Kampala, Uganda

**Background:** Of the estimated 1.2 million people living with HIV (PLHIV) in Uganda, 77% knew their status as of 2017, falling short of the UNAIDS 95% target of PLHIV who know their status. To address this gap, we implemented World Health Organization-recommended assisted partner notification (APN) in routine clinical services.

**Methods:** Health workers were trained to implement APN at 69 health facilities in two urban Ugandan districts (October 2017—September 2018). Health workers identified eligible HIV-positive clients aged >15 years who had sexually transmitted infections, or a non-suppressed viral load and notifiable sexual partners with unknown HIV status. Eligible index clients provided written consent for an interview to elicit partner information and eventual notification. Health workers contacted partners through a phone call or home visit and notified them of their possible exposure and offered HIV testing. All those tested were linked to treatment and prevention services. We followed up with index clients to determine whether they experienced gender-based violence (GBV) after partner notification. We also determined APN acceptability and completion of the HIV cascade.

**Results:** Of 55,312 index clients eligible for APN, 37,289 (67.4%) participated. Of these, 20,752 (55.6%) were men aged ≥25 years. APN teams identified 49,314 sexual partners, and 40,177 (81.5%) were notified of their exposure. Of those notified, 6925 (17.2%) knew they were HIV positive and were on treatment. Of those with previously negative or unknown status, 20,284 (61.0%) were tested at the notifying facility, and 6028 (29.7%) were HIV positive. APN identified more HIV-positive women across all age groups than men. Following testing, 5803 (96.3%) of all newly identified HIV-positive partners initiated ART. 368 (0.9%) of index clients (women, 258 (70.1%)) reported experiencing post-notification GBV.

**Conclusion:** We found moderate APN acceptability and high linkage to care for HIV-positive partners. However, we need to understand why fewer partners were elicited than suggested in the literature and why 40% of notified partners declined testing at notifying facilities. A follow-up of those who declined facility testing is needed to ascertain if they tested elsewhere and were linked to care. Also, although <1% of index clients reported GBV, our findings suggest that monitoring and strengthening linkage to GBV services could help improve APN programs.

938 TARGETED PEER MOBILISATION AND ASSISTED PARTNER NOTIFICATION SERVICES IN KENYA

Maartje Dijkstra1, Khamsi Mohamed1, Alex Kigoji1, Mahmoud Shally1, Abdalla Wesonga1, Teresa Mumba1, Nana Mukuria1, Margaret Juma1, Evans Gichuru1, Shaun Palmer1, Susan M. Graham1, Elisabeth M. van der Elst1, Eduard Sanders1

1Public Health Service Amsterdam, Amsterdam, Netherlands, 2Kenya Medical Research Institute, Kilifi, Kenya, 3University of Washington, Seattle, WA, USA

**Background:** Peer mobilisation, HIV self-testing, acute HIV infection (AHI) screening, and assisted partner notification services (APNS) among gay, bisexual, other men who have sex with men and transgender women (GBT) may have great potential in penetrating hidden epidemics, and identifying GBT and their sexual partners with undiagnosed HIV. We operationalised these strategies in coastal Kenya and assessed safety, feasibility and linkage to antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) services after testing.

**Methods:** Twenty-seven lay GBT mobilisers offered OraQuick HIV self-tests to at-risk peers and immediate clinic referral for peers with AHI symptoms in April-August 2019. Regardless of the self-test result, mobilised GBT received HIV testing and counselling (HTC) with two HIV antibody rapid tests in series, according to Kenyan guidelines. GBT with negative or discordant rapid tests received GeneXpert point-of-care HIV RNA testing. GBT newly diagnosed with HIV were offered immediate ART and APNS. HIV-negative GBT were offered PrEP. A subgroup of index participants returned to the study clinic one month after initiating APNS to assess potential social harms.

**Results:** Of 584 GBT mobilised for self-testing and 188 for AHI symptoms, 453 GBT (76.2%, 445/584 self-tests, and 4.3%, 8/188 AHI referrals) completed HTC (Figure 1). Median age was 26 (IQR: 22-30) years. Of these, 5.3% (24/453) were
newly diagnosed with HIV, including 2 with positive HIV-RNA and negative (n=1) or discordant (n=1) rapid tests. 91.7% (22/24) initiated ART following a median of 2 (IQR: 1-7) days. In addition to the 24 newly diagnosed GBT, 9 partners and 4 GBT diagnosed through routine HTC were offered APNs and 70.3% (26/37) accepted. Of 41 enrolled partners, 26.8% (11/41) were newly diagnosed and 39.0% (16/41) were known positive. Of these, 90.9% (10/11) initiated ART, while all 16 known positive partners were on ART. Among 17 index participants, no social harm (100%, 17/17) was reported. PYEPI initiation among HIV-negative participants was 25.4% (109/429) for mobilised GBT and 21.4% (3/14) for partners.

Conclusion: A targeted peer mobilisation approach offering self-tests, screening for AHI symptoms, and APNs for newly diagnosed GBT appears feasible and safe. These strategies can effectively penetrate hidden epidemics among GBT and link newly diagnosed GBT to care.

939 SCALE-UP OF ASSISTED PARTNER SERVICES (APS) IN BOTSWANA
Matthew R. Golden1, Matias Grande1, Sreenath Mawanda2, Odile Baké2, Lenna Tau2, Gobaabo Mogomotsi1, Esther Mmatl1, Modicse Ngombo3, Jenny Ledikwe1
1University of Washington, Seattle, WA, USA, 2International Training and Education Center for Health - Botswana, Gaborone, Botswana, 3Botswana Ministry of Health, Gaborone, Botswana

Background: Controlled studies have shown that APS is efficacious, and World Health Organization guidelines recommend that all persons diagnosed with HIV be offered APS. We evaluated APS implementation in the PEPFAR supported districts of Botswana to define program coverage and outcomes.

Methods: Starting in October 2018, the Government of Botswana Ministry of Health and Wellness and the International Training and Education Center for Health implemented a new APS program in 52 clinical sites. Guidelines during the evaluation period recommended that all persons with newly diagnosed HIV infection be offered APS; APS recipients (index cases [IPs]) chose to notify partners themselves or to notify partners in collaboration with counselors. Counselors used structured paper registers to record information about each named partner, including if the partner HIV tested and their test result. Aggregate outcomes from registers were entered into a database. We analyzed data collected between October 2018 and June 2019 to define conventional partner notification indices. These indices measure the number of partners named, tested and testing HIV positive per IP (i.e. contact index, testing index and case-finding index, respectively).

Results: Staff at 52 clinics performed 130,889 HIV tests during the evaluation period, of which 7015 (5.4%) were positive. A total of 6959 (99%) persons who had received a diagnosis were offered APS and were named, tested and testing HIV positive per IP (i.e. contact index, testing index and case-finding index, respectively).

Conclusion: Botswana clinics have successfully implemented APS, with high levels of program coverage and high HIV positivity among tested partners. However, fewer than one partner is named and tested per index case, suggesting areas for program improvement. The case-finding index was 0.12 (range 0.0-0.17).

940 OPTIMIZING TESTING INCREASES YIELD IN HIV CASE FINDING IN 24 COUNTRIES, 2018–2019
Shahul Hameed Ebrahim1, Arielle Lasry2, Randy Yee2, Wayne A DuPuis3, John Abellera2, Shane T Diekman1, Jacqueline Rurangirwa1, Bakary Drammeh1, Tiffany Ahoulou1, Michael Grillo2, Vincent Wong1, Stephanie Bebeli1, CDC, Atlanta, GA, USA, 2Defense Health Agency, San Diego, CA, USA, 3United States Agency for International Development, Washington, DC, USA

Background: In 2019, the U.S. President’s Emergency Plan for AIDS Relief prioritized the scale-up of testing contacts of HIV-positive index patients (contact testing) and optimizing provider-initiated testing and counseling services (PTC) to boost the first 90 goal (90% of people living with HIV know their HIV status) of the UNAIDS strategy. We assessed the impact of changes in HIV-testing modalities on the first 90 goal.

Methods: We used PEPFAR data from 24 countries that reported at least 2,000 HIV-positive test results per quarter. We compared second quarter (Q2) HIV testing data from 2018 and Q2 2019 and calculated the number of HIV tests and the yield (percentage of HIV-positive tests) by testing modality.

Results: Overall, HIV test volume decreased by 12%, and the number of HIV-positive results decreased by 4%, whereas overall yield increased by 9% (3.6% to 3.9%). In 2019, the 5 modalities that contributed to most (85%) of the HIV test volume were routine PTC in outpatient departments (OPDs); excluding emergency rooms, in-patient services, and tuberculosis and sexually transmitted infection clinics; 50%; voluntary counseling services (11%), mobile clinics (6%), contact testing (4%), and prenatal clinics (14%). Between 2018 and 2019, test volume increased in contact testing but decreased in others (Table). PTC in OPDs remained the leading contributor to the number of HIV-positive results, but the contribution of this modality to overall HIV-positive results decreased from 54% in 2018 to 45% in 2019. By modality, contact testing had the highest yield (9.9%, 2018, 14.3%, 2019) and was the second largest contributor to overall HIV-positive results (112,433/709,544 [15.8%]) in 2019. Increased test volume in other modalities (emergency wards, pediatricians, and TB and malnutrition clinics; 15% of all tests in 2019) did not increase yield (2018, 3.5%; 2019, 3.2%).

Conclusion: Overall, contact testing and optimization of other testing modalities increased HIV testing yield between 2018 and 2019. Increased yield and scale from contact testing was, however, insufficient to compensate for the decrease in HIV-positive results. Both yield and absolute number of cases should be considered in assessing the impact of scale-up of contact testing and optimization of case-finding approaches.

Table: HIV testing and yield in 24 PEPFAR countries, 2018-2019

<table>
<thead>
<tr>
<th>2018 Q2</th>
<th>2019 Q2</th>
<th>Change in yield (% of total yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>345,278</td>
<td>324,847</td>
</tr>
<tr>
<td>OPDs</td>
<td>252,065</td>
<td>232,493</td>
</tr>
<tr>
<td>Non-OPDs</td>
<td>93,213</td>
<td>92,354</td>
</tr>
<tr>
<td>Contacts</td>
<td>1,601</td>
<td>1,356</td>
</tr>
<tr>
<td>PTCs</td>
<td>1,601</td>
<td>1,356</td>
</tr>
</tbody>
</table>

**Note:**
- PTC - Provider-initiated testing and counseling services.
- OPD - Outpatient Department.
- O/E - Other/Estimated.
941 PARTNER TESTING SERVICES TO ACHIEVE HIV EPIDEMIC CONTROL IN 9 PEFFAR COUNTRIES, 2019

Bakary Drammeh1, Shahul Ebrahim1, Andrew L. Baughman1, Arielle Lasry1, Randy Ye1, Wayne A. Duffus1, Jacqueline Runarungwa1, Shane T. Diekman1, Amy M. Medley1, Tiffany Michelle Aholou1, G. Laisa Ouedraogo1, Isabelle Tondoh-Kour1, Ismelda Pietersen2, Stephanie Behel1, for the HIV Testing Services CDC, Atlanta, GA, USA, Ministre de la Santé et de l’Hygiène Publique, Abidjan, Côte d’Ivoire, IUS CDC Whinfock, Windhoek, Namibia

Background: The US President’s Emergency Plan for AIDS Relief (PEPFAR) supports HIV prevention in most HIV endemic countries. Programs provide partner notification services (PNS) or index testing as an HIV case finding strategy. Data is collected on PNS, contacts of index cases and HIV indicators as Monitoring, Evaluation and Reporting (MER) data. These data measures progress towards HIV epidemic control by reaching the first UNAIDS 90.

Methods: To evaluate progress towards reaching the 1st 90, we performed a descriptive analysis of MER data reported by 9 countries during October 2018 - March 2019 through a Data for Accountability, Transparency and Impact Monitoring database. The 9 countries were prioritized based on HIV prevalence and the need to scale up HIV prevention activities. The five variables selected represented key elements of the HIV testing cascade indicators.

Results: Three countries that were within 6% of achieving the 1st 90 (Namibia 4%, South Africa 5%, Rwanda 6%) had the lowest proportion of HIV-positive cases who accepted partner notification services (Namibia 66%, South Africa 52%, Rwanda 28%). In contrast, countries that had a larger gap to the 1st 90 target (Mozambique 18%, Nigeria 23%, Cote d’Ivoire 40%) showed a higher index case acceptance (Mozambique 87%, Nigeria 44%, Cote d’Ivoire 94%). Three countries met the PEFPAR benchmark of 1.5 contacts per index (Namibia 1.6, Uganda 1.7, Mozambique 1.5) but only two countries showed a high percentage of HIV positives as a result of the index exposure to contacts (Namibia 98%, Mozambique 94%). Despite being high HIV prevalence countries (Eswatini 27.4%, Namibia 12.1%, (South Africa 18.8% and closest to the 1st 90, these countries reported low HIV pos per 100 index (Eswatini 14, Namibia 19, South Africa 3).

Conclusion: These findings suggest that select countries closer to achieving the 1st 90 target with high HIV burden (Namibia, Southern Africa and Rwanda) tend to have a lower rate of index case acceptance. However, index testing is an important modality for countries that have a large gap to achieving the 1st 90s. Non-aggregated data within these countries should be evaluated to fully understand the most effective modality in each country.

943 EXPANDING HIV IDENTIFICATION BY TESTING CONTACTS OF DECEASED HIV INDEX CLIENTS

Neema Makyao1, Parthi Ramesh1, Peris L. Utzara1, Leonard Subi1, Neusta Kwasigabo1, Christopher Obong’2, Neema Makyao1

1National AIDS Control Program, Dar es Salaam, Tanzania, United Republic of, 2Tanzania Ministry of Health, Community Development, Gender, Elderly, and Children, Dar es Salaam, Tanzania, United Republic of

Background: Tanzania is at 61% and among countries that lag behind on UNAIDS first 95 target, which requires 90% of all people living with HIV (PLHIV) to know their status. Index HIV testing is an optimized HIV testing modality, aimed at accelerating progress towards UNAIDS first 90, which targets identification of undiagnosed HIV infected individuals through testing of sexual contacts, and biological children of index PLHIV. There is, however, a missed opportunity in reaching contacts of deceased HIV clients. In October 2018, THPS extended Index Testing Initiative (TeI) was designed, an innovation where sexual contacts and biological children of deceased PLHIV were reached and given opportunity to test for HIV infection.

Methods: The study aimed to expand HIV positive clients’ identification, through testing index contacts of deceased HIV positive clients. Details of deceased HIV clients, at 24 supported health facilities in Kigoma (15) and Pwani (9) regions were accessed through CTCC cards and HIV status of sexual partners, testing supporter’s mobile number and home address documented. Peer educators contacted sexual partners through mobile phone and arranged home visits for HIV testing sensitization and education. HIV testing was performed by healthcare providers.

Results: A total of 906 archived files of deceased HIV clients were reviewed and a list of 530 sexual partners extracted, among whom 168 (32%) had known HIV status. The remaining 362 sexual partners had unknown HIV status, 233 (64%) were reached for HIV testing whereby 45 (19%) were newly identified HIV positive. All 45 positives were linked to HIV care and treatment.

Conclusion: There is an opportunity to expand HIV identification from deceased HIV clients. Correct contact information documentation improves tracing of index contacts. We recommend scale up of this initiative to reach potential groups of HIV infected individuals such as contacts of deceased clients.

944 NONENROLLMENT AMONG HIV-POSITIVE KENYAN FEMALE INDEX CLIENTS IN PARTNER NOTIFICATION

Beatrice Wamut1, Monisha Sharma1, Emily Kemunto1, George Otieno1, Christopher Obong’2, Judith Onsomu1, Cecilia Audo1, Dominic Mutai1, Paul Macharia1, Rose Bosire2, Sarah Masyuko1, Karinithi Edward1, Mary Mugambi1, Carey Farquhar1

1University of Washington, Seattle, WA, USA, 2PATH, Seattle, WA, USA, 3Ministry of Health, Nairobi, Kenya

Background: Assisted partner services (APS) involves notification and HIV testing for sexual partners of persons diagnosed HIV-positive (index cases).
Since the impact of aPS is contingent on high acceptance rates, we sought to assess the characteristics and reasons for non-enrollment of female index cases in an ongoing implementation science study of aPS scale-up in western Kenya.

**Methods:** We analyzed data from HIV-positive females (age ≥15 years) who were offered aPS in 31 health facilities in western Kenya from May 2018 to August 2019. Socio-demographics of females were compared by aPS enrollment status (accepted, refused, ineligible) and reasons for refusal and inelegibility were tabulated. We used multivariate binomial regression to assess the association between demographics and aPS refusal.

**Results:** Across facilities, 28,031 females received HIV testing and 1,050 tested HIV-positive (yield: 3.8%). Overall, 839 females accepted aPS (80%), 59 refused (6%) and 152 were ineligible (14%). APS acceptance did not differ by age, testing history or testing type (provider vs. client initiated). Females who refused aPS were more likely to have completed secondary school (adjusted relative risk (aRR) 2.03, 95% CI: 1.13 - 3.68) or single (2.66 95% CI: 1.31 - 5.42) compared to married/cohabitating. The most common reason for refusing aPS was not feeling emotionally ready (31%) and claiming not to have any sexual partners (15%). Common reasons for aPS inelegibility included fear or risk of intimate partner violence (9%), previous HIV testing (9%) or not enough time for aPS provision (3%).

**Conclusion:** aPS has high acceptability among HIV-positive females regardless of age or testing history. More counseling may be needed to increase uptake among females with higher education and those who are separated or single. Follow-up for females who are not emotionally ready for aPS or had insufficient time for aPS in their clinic visit can improve program coverage.

945 **SCALING UP ASSISTED PARTNER NOTIFICATION SERVICES IN WESTERN KENYA**

**Sarah Masyuko1, Monisha Sharma2, Emily Kemunto3, George Otieno4, Christopher Obong'o3, Judith Onsomu3, Cecilia Audo3, Dominic Mutai4, Paul Macharia3, Beatrice Warnuti3, Rose Bosire3, Mary Mugambi3, Karithi Edward4, Carey Farquhar4**

1Ministry of Health, Nairobi, Kenya, 2University of Washington, Seattle, WA, USA, 3Program for Appropriate Technology in Health, Kikuyu, Kenya, 4Program for Appropriate Technology in Health, Kikuyu, Kenya, 5Kenya National Hospital, Nairobi, Kenya, 6Kenya Medical Research Institute, Nairobi, Kenya

**Background:** Despite high HIV prevalence in Kenya, a substantial proportion of persons living with HIV are not aware of their status. Assisted partner services (APS), or notification for sexual partners of persons diagnosed HIV-positive, has been shown to increase HIV testing and linkage to care. The World Health Organization (WHO) guidelines recommend scale-up of partner notification services in Africa yet optimal strategies for implementation and APS performance in a real-world setting are not well-defined.

**Methods:** We report findings from an ongoing implementation science study of aPS in western Kenya. Starting in May 2018, aPS was scaled up by the Ministry of Health in 31 health facilities in Kikuyu and Homa Bay counties. Newly diagnosed HIV-positive females ≥15 age years were offered aPS. Those who accepted provided contact information for all male sexual partners in the past 3 years. Healthcare providers notified partners of their potential HIV exposure and provided HIV testing and referral services.

**Results:** From May 2018 to mid-September 2019, 29,249 females tested for HIV across facilities and 1,120 were diagnosed HIV-positive (yield: 3.8%). Overall, 899 HIV-positive females were enrolled into aPS (acceptance rate: 80%) and reported an average of 1.7 male partners each (1,497 male partners total). Healthcare workers located and tested 68% of reported male partners, of whom 19% were newly diagnosed HIV-positive. At 6 weeks follow-up, 90% of female index cases and 87% of male partners reported to be on antiretroviral therapy (ART) with few adverse events (2% of female indexes reported relationship dissolution and 0.7% reported intimate partner violence).

**Conclusion:** APS has been safely incorporated into healthcare facilities in western Kenya, with high coverage among female index cases and their male partners and high linkage to ART. APS is a promising strategy to increase HIV testing and linkage and achieve the 95-95-95 targets in Kenya.

946 **HIV TESTING AND INTEGRATED HIV/STI/HEPATITIS TESTING, OREGON, 2016**

**Tim W. Menza1, Lindsay Hixson2, Jeff Capizzi3**

1Oregon Health Authority, Portland, OR, USA

**Background:** Both the US Preventive Services Task Force and the Centers for Disease Control and Prevention recommend routine, voluntary, “opt-out” HIV testing for all adolescents and adults. Despite these recommendations, HIV testing is not routine practice. Furthermore, integrated HIV, STI, and hepatitis testing is even less common.

**Methods:** We analyzed outpatient HIV, STI, and viral hepatitis-related insurance claims from the Oregon All Payers All Claims Database (APAC) for 2016. Using ICD-10 and CPT codes, we identified the number of patients that had an HIV test, an STI test, and a hepatitis B or hepatitis C test. We excluded those aged <13 years and >64 years, pregnant women, and those previously diagnosed with HIV. We examined demographic, healthcare, and geographic predictors of HIV testing and integrated HIV, STI, and hepatitis testing.

**Results:** In 2016, 4.8% of the sample (n=1,780,612) had an HIV test, 13.0% had a test for an STI or hepatitis B or C. 4.2% had integrated HIV and STI or hepatitis testing. At visits that included an HIV test, 88.3% were tested for an STI or hepatitis. Conversely, at visits that included an STI or hepatitis test, 31.5% were tested for HIV. HIV tests were most commonly accompanied by gonorrhea/chlamydia (62.4%), syphilis (53.0%), and hepatitis B (47.2%) testing. Women were more likely to be tested for HIV and experience integrated testing than men. Those aged 18-29 were most likely to have an HIV test and HIV/STI/hepatitis co-testing, while those aged 50-64 were least likely to be tested. Black/African Americans were most likely to be tested for HIV and to have integrated testing while Native American/Alaska Natives were least likely to experience these testing services. Compared to those with other insurance coverage, those with Medicaid were more than two times more likely to be tested for HIV and to have integrated testing. Those in rural and frontier regions were less likely to be tested for HIV and STI/hepatitis than those in urban areas.

**Conclusion:** Routine HIV testing and integrated HIV/STI/hepatitis testing are not widespread practice. Routine, rather than risk-based, testing, is critical to the timely diagnosis and treatment and, thus, prevention of onward HIV, STI, and hepatitis transmission.
any positive response and all participants between 50 and 70 years. Two multivariable models were created, one for participants younger than 50 and another for those older than 50. These models included the questions that exhibited the strongest association with a positive HCV result in the univariate analysis.

**Results:** A total of 7,936 questionnaires were completed and 4,705 HCV tests were performed, 46 of these (0.98%) were positive. Model identified, four out of the 22 questions, that predicted 90% of HCV status for participants younger than 50: HIV- or HCV-infected partner OR 26.6 (9.5% CI (7.6–92.9), Male Sex Male 3.3 (0.8–13.5), illicit or recreational drug use 18.1 (4.2–77.8), and hepatitis or unexplained liver disease 51.0 (17.4–154.9). For patients over 50, five questions predicted 89% of HCV status: male gender 3.1 (1.4–7.2), illicit or recreational drug use 3.3 (0.8–13.5), illicit or recreational drug use 23.6 (4.2–131.8), and hepatitis or unexplained liver disease 20.8 (8.6–50.3). Nomograms appear in Figure 2.

**Conclusion:** Two easy-to-implement models that are age adapted can predict the majority of HCV status, in general population. This work contributes to the implementation of integrated, bundled, rapid HCV/HIV testing programs.

---

**Table – Predictors of HCV Test Positivity, Botswana testing data**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.54 (1.05 – 2.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (≥60-year-old)</td>
<td>2.38 (1.05 – 5.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Testing Strategy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigative</td>
<td>2.56 (1.30 – 4.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient</td>
<td>1.06 (0.75 – 1.49)</td>
<td>0.73</td>
</tr>
<tr>
<td>Testing Place</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accident/Emergency</td>
<td>0.88 (0.52 – 1.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outpatient: Departments</td>
<td>1.01 (0.52 – 1.97)</td>
<td>1.00</td>
</tr>
<tr>
<td>Outpatient: Specialty Clinics</td>
<td>0.83 (0.48 – 1.42)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital: General</td>
<td>0.35 (0.14 – 0.84)</td>
<td>0.19</td>
</tr>
<tr>
<td>ICU</td>
<td>3.15 (1.10 – 9.15)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hospital: Medical</td>
<td>0.76 (0.36 – 1.63)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hospital: Obstetrics</td>
<td>1.25 (0.69 – 2.25)</td>
<td>0.47</td>
</tr>
<tr>
<td>Hospital: Surgical</td>
<td>1.07 (0.46 – 2.50)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Reference = OPO; General

**948** HIV TESTING CRITERIA TO REDUCE TESTING VOLUME AND INCREASE POSITIVITY IN BOTSWANA

Emily Rowinson1, Jenny Ledikwe2, Shreeshth Mawandia2, Odirile Bakae2, Lenna Tau1, Matias Grande1, Laura Seckel1, Gaboabe Mogomotsi1, Esther Mmatli1, Modise Ngombo1, Matthew R. Golden1

1University of Washington, Seattle, WA, USA; 2International Training and Education Center for Health, Gaborone, Botswana; 3Botswana Ministry of Health, Gaborone, Botswana

**Background:** Recent PEPFAR guidance seeks to diminish HIV testing volume and focus testing on higher positivity populations. We sought to define testing criteria to reduce total tests performed and increase positivity in Botswana.

**Methods:** We analyzed data collected October 2018-August 2019 as part of routine HIV testing provided in 134 Botswana Ministry of Health facilities supported by the International Training and Education Center for Health (I-TECH). We randomly split the data into prediction and validation datasets of equal size and used multivariate logistic regression to identify demographic characteristics, testing strategies, and testing sectors (e.g., antenatal) associated with HIV positivity; factors with significant adjusted odds ratios (aOR) ≥1.5 were included in the testing criteria. Testing strategies and sectors where cessation of testing was deemed unacceptable a priori (TB, STD, VCT, partner services, antenatal, labor & delivery, pediatrics and gynecology) were excluded from model development and included in the testing criteria. We applied the new testing criteria to the validation dataset to determine the number of tests performed, test positivity, proportion of positives missed, and costs averted. Costs were derived based on total budgets allocated to I-TECH to support HIV testing and estimated costs of test procurement.

**Results:** The analysis included 262,230 tests of which 4.3% were HIV positive. Model derivation analysis identified ages 23-29, 30-39, and 40+, non-citizenship, and emergency department testing as significantly associated with positivity. Among 131,115 tests in the validation analysis, 5,580 (4.3%) were HIV positive. Restricting testing to persons age >30 years and other defined criteria would reduce testing volume by 23% and increase positivity to 4.9%; 649 (2.1%) of the 30,178 persons who would not be tested were HIV positive representing 11.6% of all positive tests in the validation dataset. Positives missed by the criteria had a median age of 25 years and were mostly female (67%) and tested in the general outpatient department (86%). Assuming no changes in staffing, implementing the new testing criteria would decrease total HIV testing costs by 13%, a savings of $518 per positive test missed.

**Conclusion:** In Botswana, a targeted approach to HIV testing could reduce testing volumes by 23% and modestly increase HIV test positivity while missing 11.6% of positive tests. Cost saving would be modest unless implementation was accompanied by changes in staff costs.

---

**949** FREQUENT HIV TESTING OF MSM AND TGW OF COLOR RESULTS IN EARLIER DIAGNOSIS

Karen W. Hoover1, Weiming Zhu2, Kenneth L. Domínguez3, Kirk D. Henny3, Ya-Lin A. Huang3, Kashif Iqbal2, Mary Tanner1, Kevin P. Delaney2

1CDC, Atlanta, GA, USA

**Background:** Few clinical studies exist to support recommendations for more frequent than annual HIV testing of persons at increased risk for HIV. Frequent testing provides more opportunities for PrEP counseling and initiation, and earlier diagnosis of HIV and initiation of ARV medications to preserve immune function and prevent HIV transmission. We studied the effect of HIV testing frequency on time to diagnosis and yield of testing among MSM and TGW of color in the THRIVE demonstration project.

**Methods:** We analyzed a longitudinal database that included HIV tests and results for a cohort of persons enrolled in THRIVE from September 2016 to March 2019. All MSM and TGW of color in THRIVE were at increased risk for HIV. We excluded those who were PrEP users. Among persons who had an initial negative HIV test and at least one additional test, we estimated the median time to diagnosis among MSM and TGW of color in the THRIVE demonstration project.

**Results:** In THRIVE, 20,956 clients received an HIV test. Of these, 26% (5,408) had an initial negative test and at least one additional test. Among these 5,408 persons, 1,338 were MSM or TGW of color who did not use PrEP and 47 (4%) had a subsequent positive test. Overall, the median time to diagnosis was 235 days (IQR 92–364). Frequent testers were diagnosed earlier than non-frequent testers (p<0.001) (Figure). Among 34 frequent testers, the median time to diagnosis was 120 days (IQR 83–278), the median number of tests was 3 (IQR 2–4), and the median interval between tests was 84 days (IQR 53–119). Among 13 non-frequent testers, the median time to diagnosis was 364 days (IQR 358–551).
255–569), the median number of tests was 2 (IQR 2–3), and the median interval between tests was 255 days (IQR 198–325). The diagnostic yield among MSM or TGW of color who were frequent testers was 1.2% (34/2846) and among non-frequent testers 1.0% (13/1281). Among all other THRIVE clients, the yield was 0.2% (12/6506).

**Conclusion:** The diagnostic yield was similar for MSM and TGW of color who were tested frequently or non-frequently, but frequent testing was associated with a shorter time to diagnosis. These data support the CDC recommendation to test persons at risk of HIV more often than annually.

---

**950 INDETERMINATE HIV RAPID-TEST RESULTS: OUTCOMES AND RISK FACTORS**

George Mwineya, Mary K. Grabowski, Ronald H. Gray, Maria Wawer, Larry W. Chang, Joseph Sekasawanu, Joseph Kagaayi, Godfrey Kigozi, Ronald M. Galliwaango, Anthony Ndyabanob, David Serwadda, Thomas C. Quinn, Steven J. Reynolds, Oliver Laeyendecker, 1 for The Rakai Community Cohort Study 1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA, 3Rakai Health Sciences Program, Kalisigo, Uganda, NH, Bethesda, MD, USA, SNAID, Baltimore, MD, USA

**Background:** Little is known about the frequency, subsequent outcomes and factors associated with indeterminate HIV rapid results. We assessed final HIV serological outcomes for individuals with rapid indeterminate test results and associated risk factors in Rakai, Uganda.

**Methods:** 54,469 HIV rapid test results, defined by two parallel rapid tests, among 31,413 participants aged 15–49 years in the Rakai Community Cohort Study were assessed. 8361 participants were tested on two separate visits and 7354 had three time points tested. Each visit was approximately 18 months apart. Indeterminate results were defined as contradictory rapid test results or inconclusive concurrent rapid test results. The final HIV status for each indeterminate observation was determined using previous HIV status information and additional testing, including PCR, ELISA and Western blot when necessary. Generalized estimating equations together with modified Poisson regression models with robust variance were used to assess prevalence ratios (PRs) of subsequent HIV serological outcomes and factors associated with indeterminate rapid test results.

**Results:** The prevalence of HIV rapid test indeterminate results was 2.7% (1490/54,469). Of the 1,490 rapid indeterminate observations, 26% were eventually classified as HIV positive. The proportions of persons with rapid indeterminate results progressing to HIV rapid positive, negative, or still indeterminate at the subsequent visit were 19%, 40% and 41%, respectively. For individuals with two consecutive indeterminate results who had a third follow-up visit (67 individuals), 21% (14/67) tested negative, 9% (6/67) were positive and 70% (47/67) were still indeterminate.

Factors associated with higher risk of an indeterminate result were: women vs. men (adjPR 2.07, 95% CI 1.77,2.41); 44 yrs vs. <20 yrs of age (adjPR 1.69, 95% CI 1.26,2.26); student vs. farmer (adjPR 0.62, 95% CI 0.46,0.83); shopkeeper vs. farmer (adjPR 0.81, 95% CI 0.68,0.96); ART vs. not (adjPR 1.29, 95% CI 1.10,1.51).

In total, 4.4% of individuals on ART had indeterminate test results.

**Conclusion:** The frequency of indeterminate rapid results was low (<3%), and a quarter ultimately tested HIV positive. 41% of individuals with an indeterminate result had an indeterminate result on a follow-up visit and 0.64% of the population had continuous indeterminate results over a 3 year period.

---

**951 SIGNIFICANT UNDERQUANTIFICATION OF HIV RNA WITHIN ROUTINE SETTINGS IN SOUTH AFRICA**

Ahmad Haeri Mazanderani, Tendayai Kufa-Chakezha, Tanya Murray, Aurelie Mukendi, Faith Mayo, Kate Braithwaite, Karl Technau, Sergio Carmona, Gayle G. Sherman

1National Institute for Communicable Diseases, Johannesburg, South Africa, 2University of the Witwatersrand, Johannesburg, South Africa

**Background:** The extent to which pre-analytical variables impact HIV viral load (VL) accuracy is unknown. We describe VL log difference between paired point of care (POC) and centralized laboratory (lab) results within routine clinical settings, and determine whether result variability was associated with time to result, facility or season.

**Methods:** Secondary analysis of data from a POC implementation study at four tertiary facilities in South Africa between March 2018 – August 2019. Two 4ml EDTA tubes were collected from HIV-positive women at time of delivery. One sample was centrifuged and plasma tested within 24 hours on an HIV VL assay at POC (Cepheid Xpert) and the other sent for routine lab testing (Cobas 8800 or Abbott RealTime) but only centrifuged at the testing lab. Results were transformed into log scale with those below limit of detection assigned a log value of 0.001 and results below limit of quantification assigned value of lower limit of quantitation. Median log differences were calculated as POC - lab result. Ranksum and K-tests for equality of medians were used to determine if log differences varied significantly by time to lab result, facility, and season.

Proportion of paired results with >0.5log difference and discrepancy at 1000 RNA cps/ml threshold were compared using X2 tests. Multivariable binomial regression was performed to identify variables associated with discrepant VL results at 1000 cps/ml threshold.

**Results:** Among 1600 paired results, median POC VL was 2.1 (1.6–3.9) and lab VL was 2.0 (1.3–3.6) log (p<0.001), with median time to result of 1.6 (1.5–4.6) and 67.5 (45.5–99.1) hours, respectively. 475 (29.7%) specimen pairs had a VL difference >0.5log. Longer duration to lab result (p<0.001) and facility (p<0.001) were associated with >0.5log difference (Table 1). 59 (3.7%) paired samples had discrepant results at 1000 cps/ml threshold, of which 53 (3.3%) had a POC VL ≥1000 cps/ml but lab VL <1000 cps/ml. There was significant misclassification of lab VL results ≥5 days compared to <5 days (aRR 1.82: 1.01–3.30).

**Conclusion:** Longer time to lab result and facility, but not season, increased likelihood of underquantifying HIV VL by >0.5log and misclassifying results as <1000 cps/ml. Timely centrifugation and testing should be prioritized.

---

**952 EVALUATION OF A TRUE POC VIRAL LOAD TEST: SAMBA LEUCO-DEPLETED WHOLE BLOOD HIV ASSAY**

Gary Brook, Tsetena Stephenkenova, Innocent M. Ali, Sandra Chipuka, Helen Lee

1London North West University Healthcare NHS Trust, London, United Kingdom, 2Hyvääty AIDS centre, Kiev, Ukraine, 3University of Dschang, Dschang, Cameroon, 4Harare Central Hospital, Harare, Zimbabwe, 5Cambridge University, Cambridge, UK

**Background:** To meet the UNAIDS 90-90-90 targets, patients in developing countries require better access to HIV viral load (VL) testing to confirm antiretroviral (ART) treatment success. Current laboratory-based assays are confined to cities with high infrastructure, limiting access to patients in remote settings. The SAMBA II HIV-1 Semi-Q Whole Blood (WB) Test is a portable, robust, heat-stable, point-of-care (POC) VL assay that automatically leuco-depletes 3 logs of cellular RNA and DNA, thus providing clinically meaningful results (VL <or> 1000 cp/ml) using a finger-prick blood sample.

**Methods:** Secondary analysis of data from a POC implementation study at four tertiary facilities in South Africa between March 2018 – August 2019. Two 4ml EDTA tubes were collected from HIV-positive women at time of delivery. One sample was centrifuged and plasma tested within 24 hours on an HIV VL assay at POC (Cepheid Xpert) and the other sent for routine lab testing (Cobas 8800 or Abbott RealTime) but only centrifuged at the testing lab. Results were transformed into log scale with those below limit of detection assigned a log value of 0.001 and results below limit of quantification assigned value of lower limit of quantitation. Median log differences were calculated as POC - lab result. Ranksum and K-tests for equality of medians were used to determine if log differences varied significantly by time to lab result, facility, and season.

Proportion of paired results with >0.5log difference and discrepancy at 1000 RNA cps/ml threshold were compared using X2 tests. Multivariable binomial regression was performed to identify variables associated with discrepant VL results at 1000 cps/ml threshold.

**Results:** Among 1600 paired results, median POC VL was 2.1 (1.6–3.9) and lab VL was 2.0 (1.3–3.6) log (p<0.001), with median time to result of 1.6 (1.5–4.6) and 67.5 (45.5–99.1) hours, respectively. 475 (29.7%) specimen pairs had a VL difference >0.5log. Longer duration to lab result (p<0.001) and facility (p<0.001) were associated with >0.5log difference (Table 1). 59 (3.7%) paired samples had discrepant results at 1000 cps/ml threshold, of which 53 (3.3%) had a POC VL ≥1000 cps/ml but lab VL <1000 cps/ml. There was significant misclassification of lab VL results ≥5 days compared to <5 days (aRR 1.82: 1.01–3.30).

**Conclusion:** Longer time to lab result and facility, but not season, increased likelihood of underquantifying HIV VL by >0.5log and misclassifying results as <1000 cps/ml. Timely centrifugation and testing should be prioritized.

---

**Table 1. Distribution of viral load differences between point-of-care and centralized laboratory results.**
953 MODELING POINT-OF-CARE NUCLEIC ACID TESTS (POC NAT) TO MINIMIZE HIV MISTAKES

Anne M. Neilan1, Jennifer Cohn2, Emma Sacks2, Aditya Gandhi1, Patricia Fassino2, Kenneth Freedberg1, Marc N. Kouadio2, Rochelle P. Walensky1, Andrea L. Carannillo1
1Massachusetts General Hospital, Boston, MA, USA, 2Cambridge University, Cambridge, UK

Background: The World Health Organization (WHO) adult HIV diagnostic testing strategy requires up to 4-7 rapid diagnostic tests (RDTs) prior to ART initiation. Although more expensive than RDTs, adding POC NAT to current testing strategies may minimize misdiagnoses and attrition, permitting ART initiation with fewer tests.

Methods: Using the Cost-Effectiveness of Preventing AIDS Complications model, we simulated a one-time HIV test in addition to status quo (SQ) testing practices in a low HIV-undiagnosed prevalence setting (1.3%): Côte d’Ivoire (CI). Model inputs included mean age (37y), SQ HIV testing (74 tests/1,000PY), and costs of ART ($6,500) and HIV care ($3,278-38m), and assays (RDT $1.50; POC NAT $27.92). We assessed 3 testing strategies: RDT-based strategies recommended by the WHO (RDT-WHO) and CI (RDT-CI), and a novel strategy: POC NAT to resolve RDT discordancy (NAT-Resolve). We calculated the number of true/ false positive/negative (TN, TP, FN, FP) results for each strategy. We modeled 3 scenarios: A) sensitivity/specificity from WHO prequalification reports and no attrition between tests, B) sensitivity/specificity from WHO prequalification reports and reported attrition and result-delay rates, and C) field-based RDT sensitivity/specificity and reported attrition and result-delay rates. We reported life expectancy (LE) and costs per misdiagnose and per person in the tested population, as well as incremental cost-effectiveness ratios (ICERs), in 5-year-of-life saved (YLS); threshold ≤$1,720 (CI per-capita GDP).

Results: Relative to the tested population, there were few misdiagnoses in Scenarios A and B (Table 1). A FN diagnosis led to a LE loss of 5y (vs. a TP); this LE loss was most sensitive to HIV detection rates after developing an opportunistic infection. A FP diagnosis increased costs by $6,500 (vs. a TN); this cost increase was most sensitive to costs of HIV care and ART, and time spent misdiagnosed. In Scenarios A and B, for the entire tested population, LE and costs were very similar between all 3 strategies. In Scenario C, with field-based RDT characteristics and attrition, NAT-Resolve averted more misdiagnoses and was cost-saving compared to RDT-WHO and RDT-CI.

Conclusion: With HIV Rapid Diagnostic Testing-based strategies, the impacts of misdiagnoses may be substantial. In combination with RDTs, in practice in a low HIV prevalence setting, POC NAT-based testing strategies will minimize misdiagnoses, improve attrition, and be cost-saving.
Conclusion: SAMBA’s high concordance in this population suggests a role for POC NATs when starting and monitoring PrEP, detecting acute infection, and for monitoring potential virologic failure among PWH on ART.

Background: HIV testing may serve as an entry point for youth to engage with the HIV prevention and care cascade. Several barriers have been identified for youth attending for facility based HIV testing, thereby delaying knowledge of their HIV diagnosis and subsequent linkage to care. Here, we assess the uptake of a HIV oral mucosal transudate (OMT) self-testing amongst youth attending tertiary level colleges in Zimbabwe.

Methods: Youth aged 16-24 years of age, of unknown HIV status and not having had a HIV test in the past 3 months were offered an OMT HIV self-test. Distribution points were chosen through social mapping involving students and staff at tertiary level campuses in Harare and Masvingo, Zimbabwe. Youth had the option to perform the self-test onsite, unsanised, in a private booth or offsite in a location of their choice. From 16th July 2019, blood based confirmatory testing was offered on site using SD Standard Q HIV 1b Ab 4-Line® and Chembio HIV 1/2 Stat-Pak® in parallel. Linkage to care (either confirmation of reactive test or attendance for ART initiation) was determined through phone call follow up.

Results: Distribution took place over 57 days in a three-month period, 2,760 youth received a self-test kit, 1,310 (63%) female, median age 21 years (IQR 20-23). In total, 1792 (65%) said they previously had sex, median number of partners in past one year, 1 (IQR 1-2), 1140 (65%) reported condom use at last sex. Close to one third (30%) of males had been circumcised. In total, 917 (33%) were first-time testers. Of those who had previously tested, 422 (23%) had used a HIV self-test kit. Overall, 1206 (44%) of youth said they had heard of a HIV self-testing before. In total, 1592 (58%) opted to test themselves off-site, 5 had confirmatory testing on site (n=4 of positive, n=1 negative), 2 refused confirmatory testing reactive. Of these, 6 reported confirmatory testing off site, 5 had confirmatory testing on site (n=4 of positive, n=1 negative), 2 refused confirmatory testing reactive. Of these, 6 reported confirmatory testing off site, 5 had confirmatory testing on site (n=4 of positive, n=1 negative), 2 refused confirmatory testing reactive. Of these, 6 reported confirmatory testing off site, 5 had confirmatory testing on site (n=4 of positive, n=1 negative), 2 refused confirmatory testing reactive.

Conclusion: Community based HIV self-test distribution in tertiary colleges is an opportunity to reach youth who may be at risk of HIV acquisition. Given the low HIV prevalence, linkage to prevention services is key for those testing reactive. Further research needs to invest in ensuring seamless linkage to care for those testing reactive.

957 IS AN UNASSISTED PHARMACY-BASED HIV SELF-TESTING STRATEGY IN MOZAMBIQUE SUFFICIENT?

Caroline De Schacht1, Carla L. Fonseca1, Paula Paulo1, Noela Chicuecue2, Anibal Fernando3, Jalilo E. Chinai3, Wilson Da Silva1, Sofia Viegas 4, Sara Van Rompaey1, Aleny Couto5, C. William Wester1

1Friends in Global Health, Maputo, Mozambique, 2Ministry of Health, Maputo, Mozambique, 3Provincial Health Directorate, Quelimane, Mozambique, 4Instituto Nacional de Saúde, Maputo, Mozambique, 5Vanderbilt University, Nashville, TN, USA

Background: HIV self-testing (HIVST) is a strategy recommended by WHO to increase testing, especially among key populations, men and young people. In May 2019, an HIVST pilot began in Zambia province involving 14 public/private pharmacies (4 urban, 10 rural), allowing clients to purchase up to two oral HIV self-tests at a subsidized price of 50Mzn (~$US 0.80). The study assessed the acceptability and use of this strategy.

Methods: Exit-surveys were conducted in a random sample of 20 clients per pharmacy, independently from test purchase. A survey was also done for a random sample of up to 10 clients per pharmacy who bought a test and accepted being contacted later. Structured questionnaires were used assessing perceptions on HIVST; clients contacted after test purchase were additionally asked about its use. Analysis (X2-test) was done for each variable comparing clients who purchased versus not. Sales were monitored using pharmacy-based registers.

Results: During the first 3 months, 517 adults purchased 603 tests (70% male, 41% <30 years). A total of 351 pharmacy clients participated in the surveys: 259 who did not buy a test and 92 who bought one. Median age was 29 years (IQR 23-37), 65% male, 60% married and 63% with a ≥12th grade education level. The most frequently reported advantage of HIVST was confidentiality, while primary disadvantages were lack of counseling and fear of test result (Table 1). Eighty-five (24%) clients found the test expensive.

From the 92 who bought a test, 73 participated in the additional survey, of whom 67 (93%) performed the test. Self-reported easiness of test instructions and test performance was 34% and 45%, respectively. Almost all (97%) were confident in the result, but 27 (40%) felt they needed additional information or counseling. Before doing the test, 49% felt very anxious, and 32% felt very anxious.

958 UPTAKE OF HIV SELF-TESTING AMONGST YOUTH IN TERTIARY EDUCATION COLLEGES IN ZIMBABWE

Grace McHugh, Andrea L. Kori1, Totsi Bandason1, Katharina Kranner1, Rashida A. Ferrand1

1Biomedical Research and Training Institute, Harare, Zimbabwe, 2Duke Global Health Institute, Durham, NC, USA, 3London School of Hygiene & Tropical Medicine, London, UK

Background: HIV testing is recommended by WHO as a key component of the HIV prevention and care cascade. However, in high epidemic settings, uptake of HIV self-testing (HIVST) among young men is suboptimal.

Methods: We conducted an implementation study from October 2018 to June 2019 among 1628 men in 30 villages of Mpingi district in Uganda. Community health workers distributed one HIVST-kit and a tailored linkage-to-care insert to each consenting male aged 15+ years and living in a sampled household. We allowed up to 10 days to use the kit, 30 days to seek confirmatory testing at a health facility (HF) and up to 60 days to start care if confirmed HIV+. We collected baseline data including demographics, testing history and HIV risk behavior. At follow up, we measured HIVST-uptake (by proof of used kit) and linkage-to-care as HF-confirmation of HIV sero-positive status (by proof of HIV test result slip) and ART initiation. We summarized categorical data as proportions and used Poisson regression to determine predictors of HF-confirmation of HIV sero-positive status and improve the HIV care cascade among men. We implemented a community-led oral HIV self-testing (HIVST) intervention among men in a peri-urban district in Uganda and assessed uptake of HIV testing, identification of HIV+ persons and linkage to care.

Results: At baseline, 19.8% (322/1628) of participants had never tested for HIV and only 37.2% (606/1628) had tested in the last 12 months. HIVST-uptake was 93.5% (1551/1628) with 2.5% (41/1628) testing HIV+. Of those who received a test kit, 1637 (59%) reported their results, 29 (1.8%) were reactive. Of these, 6 reported confirmatory testing off site, 5 had confirmatory testing on site (n=4 of positive, n=1 negative), 2 refused confirmatory testing reactive. Of these, 6 reported confirmatory testing off site, 5 had confirmatory testing on site (n=4 of positive, n=1 negative), 2 refused confirmatory testing reactive. Of these, 6 reported confirmatory testing off site, 5 had confirmatory testing on site (n=4 of positive, n=1 negative), 2 refused confirmatory testing reactive. Of these, 6 reported confirmatory testing off site, 5 had confirmatory testing on site (n=4 of positive, n=1 negative), 2 refused confirmatory testing reactive.

959 COMMUNITY-LED HIV SELF-TESTING INCREASES TESTING AND LINKAGE TO CARE OF MEN IN UGANDA

Joanita Nangendo1, Joan Kalyango1, Gloria O. Odei1, Jane Kabami1, Fred Semitela1, Anne Katahoire1, Charles Karamagi1, Rhoda Wanyenze1, Moses R. Kamya1

1Makerere University College of Health Sciences, Kampala, Uganda

Background: Targeted strategies are needed to increase knowledge of HIV sero-status and improve the HIV care cascade among men. We implemented a community-led oral HIV self-testing (HIVST) intervention among men in a peri-urban district in Uganda and assessed uptake of HIV testing, identification of HIV+ persons and linkage to care.

Methods: We conducted an implementation study from October 2018 to June 2019 among 1628 men in 30 villages of Mpingi district in Uganda. Community health workers distributed one HIVST-kit and a tailored linkage-to-care insert to each consenting male aged 15+ years and living in a sampled household. We allowed up to 10 days to use the kit, 30 days to seek confirmatory testing at a health facility (HF) and up to 60 days to start care if confirmed HIV+. We collected baseline data including demographics, testing history and HIV risk behavior. At follow up, we measured HIVST-uptake (by proof of used kit) and linkage-to-care as HF-confirmation of HIV sero-positive status (by proof of HIV test result slip) and ART initiation. We summarized categorical data as proportions and used Poisson regression to determine predictors of HF-confirmation of HIV sero-status among men using HIVST.

Results: At baseline, 19.8% (322/1628) of participants had never tested for HIV and only 37.2% (606/1628) had tested in the last 12 months. HIVST-uptake was 93.5% (1551/1628) with 3.9% (63/1628) testing HIV+. Of those who used HIVST, 81.0% (1257/1551) sought HF-confirmation of HIV sero-status (by proof of HIV test result slip) and ART initiation. We summarized categorical data as proportions and used Poisson regression to determine predictors of HF-confirmation of HIV sero-status among men using HIVST.

Conclusion: Community-led HIVST may be an efficient way to increase male HIV testing and linkage to care of newly diagnosed HIV+ and known HIV+ who had fallen out of care. Further research is needed to assess cost-effectiveness and scalability of this intervention in resource-limited settings.
anxious after the test awaiting results. Self-test result was revealed by 40 (60%) (one HIV-positive), with 15% reporting linking to a health facility to confirm their result.

**Conclusion:** HIVST at public/private pharmacies was successfully employed, reaching male and young people. The cost, although small, might be a barrier. The perceived lack of counseling is concerning, suggesting a need for specific tools at pharmacies and/or offering assisted testing. Moreover, to attain the first 95 of the UNAIDS 95-95-95 goals, other strategies (e.g. index-case HIVST) should also be considered.

**958 HIV SELF-TESTING AMONG KEY POPULATIONS AND SEXUAL PARTNERS OF NEW MOTHERS IN UGANDA**

Esther M. Nasuuna1, Florence Namimbi2, James Wanyama1, Alice Namale2, Martin Ssuna3, Alex Muganza4, Joanita Kigozi5

1Infectious Diseases Institute, Kampala, Uganda, 2COC Uganda, Kampala, Uganda

**Background:** HIV self-testing (HIVST) was adopted for hard to reach populations (key populations and partners of pregnant and lactating women) in Uganda in September 2018. We report the preliminary findings from this program in Kampala, Uganda.

**Methods:** HIVST was rolled out to 38 facilities in Kampala in September 2018 using two distribution approaches. The facility-based approach targeted sexual partners of pregnant and lactating mothers with unknown HIV status. Before giving HIVST kits to female participants, we provided information about performing an HIV self-test through demonstration and videos in the local language. Women distributed the kits to their partners. The community-based approach targeted key populations (KPs), including female sex workers (FSWs) and men who have sex with men (MSMs) with unknown HIV status. Trained peers were given test kits at the facility to distribute to clients at KP hotspots. Clients who accepted were recorded in access-restricted distribution logs. Self-testers were asked to report results within 2 days; clients from the facility and the community who did not report results received a follow-up phone call from a trained health worker. Those who reported HIV-positive results were offered confirmatory testing using the standard HIV testing algorithm. Data on kits distributed from October 2018 to June 2019, target population, testing yield, and linkage to care were summarized and analyzed in Excel.

**Results:** We distributed 9378 HIVST kits. In the facility, mothers received 5212 (56%) kits for their sexual partners. In the community, KPs received 4166 (44%) kits (MSMs, 2192 [53%]; FSWs, 1974 [47%]). Of the 9378 kits distributed, 9126 (97%) were HIV negative and 252 (3%) clients reported HIV-positive results: 74 (29%) were partners of mothers, 126 (50%) were FSW, and 52 (21%) were MSM. There were 17 (7%) known positives among those who reported. Of the 170 (67%) clients that returned for confirmatory HIV testing: 36 (49%) partners of mothers, 99 (79%) FSW, and 35 (67%) MSM. Linkage to treatment (126 [74%]) was <95% of the program target: 22 (61%) partners of mothers, 78 (79%) FSW, and 26 (74%) MSM. Fig 1

**Conclusion:** HIVST can identify patients with HIV among hard-to-reach populations. However, confirmatory testing and linkage to care are challenging. Further research is needed to determine barriers to confirmatory testing and linkage to care for HIV-positive self-testers.

**Figure 1:** clients that tested HIV positive on self-test

**959 ACCEPTABILITY OF HIVST DISTRIBUTION BY PREGNANT WOMEN TO MALE PARTNERS: A CLOSER LOOK**

Norma C. Ware1, Monique A. Wyatt1, Emily E. Pisarski1, Andrew Mujugira1, Connie L. Celm2

1Harvard Medical School, Boston, MA, USA, 2Infectious Diseases Research Collaboration, Kampala, Uganda, 3University of Washington, Seattle, WA, USA

**Background:** Provision of HIV self-test kits (HIVST) to HIV-positive pregnant women attending antenatal care for secondary distribution to partners of unknown HIV status may increase knowledge and linkage to HIV care and prevention among African men. Research to date indicates secondary distribution of HIVST by pregnant women greatly increases partner testing, but studies have not focused on experiences of women living with HIV who distribute HIVST to their partners.

**Methods:** The Obumu study is a randomized trial of secondary distribution of HIVST and linkage of male partners to HIV care or pre-exposure prophylaxis, compared to invitation letters as standard of care, among 500 pregnant women living with HIV in Kampala, Uganda. Women randomized to deliver HIVST to their partners are trained and given two kits to take home. Obumu includes qualitative interviews with a subset of 45 women. Interviews explored: 1) the partnered relationship; 2) HIV testing experiences; 3) discovery of HIV status; 4) experiences taking antiretroviral therapy; 5) pregnancy; 6) disclosure; 7) HIVST delivery; and 8) partner responses to HIVST. In this content analysis, qualitative data were examined inductively to characterize themes in the distribution process.

**Results:** Women in the qualitative sample were eager to have their partners test and receptive to HIVST. However, they were apprehensive about disclosing their own HIV status to their partners, believing disclosure would result in abandonment during pregnancy, when they felt vulnerable and dependent on their partner’s support. Women were anxious to avoid the questions about HIV they feared delivering the kit would raise, and coped by: 1) delivering HIVST but misrepresenting its purpose; 2) avoiding explanations by leaving the kit—without comment—where it would be seen; or 3) not delivering HIVST at all. When women delivered kits that were used by male partners, they often avoided discussing test results, and chose not disclose their own status when their partners asked. Women whose partners knew their HIV status delivered HIVST more easily.

**Conclusion:** Disclosure emerges as a major barrier to HIVST distribution to male partners by Ugandan pregnant women living with HIV. Counseling and support for disclosure as part of the distribution process may help to alleviate this barrier. HIVST distribution may be different, and more challenging, for HIV positive pregnant women than for women not living with HIV.

**960 “FIRST TO KNOW MY STATUS”: ACCEPTABILITY OF HIV SELF-TESTING AMONG SOUTH AFRICAN MEN**

Monique A. Wyatt1, Emily E. Pisarski1, Adrienne E. Shapiro1, Kombi Sausi1, Alastair Van Heerden3, Oluwafemi A. Adeagbo4, Janet Seeley5, Connie L. Celum2, Ruanne V. Barnabas1, Norma C. Ware6

1Harvard Medical School, Boston, MA, USA, 2University of Washington, Seattle, WA, USA, 3Human Sciences Research Council, Pretoria, South Africa, 4Africa Health Research Institute, Mtubatuba, South Africa, 5London School of Hygiene & Tropical Medicine, London, UK

**Background:** We distributed 9378 HIV self-test kits (HIVST) to HIV-positive pregnant women attending antenatal care for secondary distribution to partners of unknown HIV status may increase knowledge and linkage to HIV care and prevention among African men. Research to date indicates secondary distribution of HIVST by pregnant women greatly increases partner testing, but studies have not focused on experiences of women living with HIV who distribute HIVST to their partners.

**Methods:** The Obumu study is a randomized trial of secondary distribution of HIVST and linkage of male partners to HIV care or pre-exposure prophylaxis, compared to invitation letters as standard of care, among 500 pregnant women living with HIV in Kampala, Uganda. Women randomized to deliver HIVST to their partners are trained and given two kits to take home. Obumu includes qualitative interviews with a subset of 45 women. Interviews explored: 1) the partnered relationship; 2) HIV testing experiences; 3) discovery of HIV status; 4) experiences taking antiretroviral therapy; 5) pregnancy; 6) disclosure; 7) HIVST delivery; and 8) partner responses to HIVST. In this content analysis, qualitative data were examined inductively to characterize themes in the distribution process.

**Results:** Women in the qualitative sample were eager to have their partners test and receptive to HIVST. However, they were apprehensive about disclosing their own HIV status to their partners, believing disclosure would result in abandonment during pregnancy, when they felt vulnerable and dependent on their partner’s support. Women were anxious to avoid the questions about HIV they feared delivering the kit would raise, and coped by: 1) delivering HIVST but misrepresenting its purpose; 2) avoiding explanations by leaving the kit—without comment—where it would be seen; or 3) not delivering HIVST at all. When women delivered kits that were used by male partners, they often avoided discussing test results, and chose not disclose their own status when their partners asked. Women whose partners knew their HIV status delivered HIVST more easily.

**Conclusion:** Disclosure emerges as a major barrier to HIVST distribution to male partners by Ugandan pregnant women living with HIV. Counseling and support for disclosure as part of the distribution process may help to alleviate this barrier. HIVST distribution may be different, and more challenging, for HIV positive pregnant women than for women not living with HIV.
Background: HIV self-testing (HIVST) is increasingly being used as a strategy to improve HIV testing coverage in sub-Saharan Africa, particularly in men, who are less likely to test for HIV in traditional health care settings. Understanding acceptability of HIVST is necessary to achieve optimal uptake of these new testing modalities.

Methods: HIVST kits were distributed to 4495 men in community-based venues in two regions in Kwazulu Natal, South Africa as part of a large implementation study. Individuals were offered self-administered oral fluid or blood-based tests and chose to use the tests on-site or at home. A subsample of 30 men who received and used HIVST kits took part in a single in-depth qualitative interview. Interviews covered: distribution of the test, experiences of HIVST, previous testing experiences, and preferences for HIV testing. Qualitative data were coded and inductively analyzed to identify themes representing men’s perspectives on and experiences using HIVST.

Results: Men who participated in qualitative interviews responded positively to both types of HIVST and overwhelmingly preferred self-testing over testing at a health facility. Despite initial concerns about being able to administer the test correctly on their own, they found the HIVST kits easy and simple to use. Lack of familiarity with HIVST and the newness of the technology fueled some doubts about test efficacy, particularly oral tests. However, men gained confidence in the accuracy of HIVST when their results confirmed prior clinic-based tests.

The fear of newly discovering an HIV-positive status through HIVST was an important concern for men, but this was far outweighed by the appeal of testing alone, in private. Being able to know their results “first,” without having to trust a health care worker to protect the confidentiality of their results, was unexpectedly empowering for men. They reported that HIVST gave them a sense of independence and control over decisions about testing circumstances and disclosure. This, in turn, led them to talk about the experience of HIVST to others, generating additional interest in self-testing among their peers.

Conclusion: Our findings suggest that HIVST is an acceptable testing strategy among men. Men’s perceptions of self-testing appear to evolve from an initial reluctance to an overall endorsement of HIVST through the experience of using the tests. Peer distribution of HIVST may be an effective method for scaling up HIV testing in communities where men do not test for HIV.

961 THE IMPACT AND COST OF HIV SELF-TEST DISTRIBUTION IN WORKPLACES IN SOUTH AFRICA

Cyprian Mostert1, Trishanta Kisten1, Linda Sande1, Marc D’Elbee1, Mohammed Majum1, Vincent Zishiri1, Willem D. Venter1, Karin Hatzold1, Cheryl Johnson1, Joel Meyer-Rath1


Background: Awareness of HIV status is critical for achieving UNAIDS targets, particularly for sub-populations at high risk of acquiring and transmitting HIV. The sub-populations require targeted, resource-intensive strategies for HIV test uptake, a challenge when resources are limited. We conducted a trial-based cost-effectiveness analysis on offering the choice of HIV self-testing (CHIVST) in a high-risk population—long-distance truck drivers—in Kenya.

Methods: We leveraged data from a randomized controlled trial of CHIVST (intervention, n=150) vs provider-administered testing—standard of care (SOC) (control, n=155). CHIVST included choice of SOC or clinic- or home-based self-test. Economic cost data (HIV test kits, medical supplies, labor, capital and overhead costs, patient time) included upper and lower bounds, came from the literature and reflected a societal perspective. Generalized Poisson and linear gamma regression models estimated the effectiveness (relative risk) and incremental costs (2017 US$) over the number needed to receive CHIVST for an additional HIV test uptake. We reported incremental cost-effectiveness ratios, with 95% confidence intervals (CIs) calculated using Fieller’s theorem. Deterministic sensitivity analysis identified key cost drivers; non-parametric bootstrapping generated cost-effectiveness acceptability curves to assess uncertainty in the ratio. We determined cost-effectiveness according to a willingness-to-pay threshold of 3x GDP per capita for Kenya (US$774).

Results: HIV test uptake was 23% more likely for CHIVST vs SOC, with six individuals needed to receive CHIVST for an additional HIV test uptake (6.25, 95% CI 5.00-8.33). The mean cost per patient was more than double for CHIVST ($262.56) compared to the SOC ($104.79). The incremental cost-effectiveness of CHIVST was $974.21 (95% CI 65.74-120.98) per additional HIV test uptake compared to SOC. Self-test kits and patient time were the main cost drivers, with findings robust even in a worst-case scenario of all upper bound economic
costs. The probability of CHIVST being cost-effective at a given willingness-to-pay threshold approached one at a threshold of $140 (Figure).

**Conclusion:** CHIVST is a highly efficient use of resources for improving HIV test uptake among high-risk populations. Policies supporting CHIVST in these populations may expedite achievement of country-specific UNAIDS targets.

---

**Table 1: Characteristics of study participants, overall and according to prior HIV testing**

<table>
<thead>
<tr>
<th>Age</th>
<th>N (%)</th>
<th>N (%)</th>
<th>Age</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24</td>
<td>235 (48)</td>
<td>142 (46)</td>
<td>25-34</td>
<td>370 (49)</td>
</tr>
<tr>
<td>35-44</td>
<td>234 (28)</td>
<td>176 (24)</td>
<td>45-54</td>
<td>57 (7)</td>
</tr>
<tr>
<td>55+</td>
<td>4 (0.5)</td>
<td>4 (0.5)</td>
<td>65+</td>
<td>2 (0.3)</td>
</tr>
</tbody>
</table>

**Notes:**

- Male/female: declared for 216 participants; 36 were missing.
- Ethnic identity: declared for 216 participants; 36 were missing.
-ever HIV tested: declared for 216 participants; 36 were missing.
- Current PrEP use: declared for 216 participants; 36 were missing.

---

**Figure: Cost-effectiveness acceptability curve**

---

**CHARACTERISTICS OF MSM WHO REGISTER FOR HIV SELF-TESTING IN SAO PAULO, BRAZIL**

Ricardo D. Vasconcelos,1 Vivian I. Avelino-Silva,2 Ivoine P. de Paula,3 Leda Jamal4,5 Maria Clara Gianna2, Flavio Santos1, Cristina Santos1, Robson Camargo1, Eduardo Barbosa2, Gilvan Cascemi,6 Maria Cristina Abbaté,6 Marly M. Cruz,6 Aluisio C. Segurado,6 for the A Hora é Agora - SP1

1Universidade de São Paulo, São Paulo, Brazil, 2Centro de Referência e Treinamento DST/AIDS-SP, São Paulo, Brazil, 3Secretaria Municipal da Saúde de São Paulo, São Paulo, Brazil, 4Centro de Referência da Diversidade, São Paulo, Brazil, 5Ministry of Health, Brasilia, Brazil, 6Escola Nacional de Saúde Pública, Brasilia, Brazil

**Background:** HIV testing is a critical step of both HIV care and prevention. Since 2015 WHO recommends HIV self-testing (HIVST) as an additional screening strategy to improve testing coverage among key populations. Prior to implementation of HIVST in the public health system in Brazil, the demonstrative study “A Hora é Agora” evaluated the acceptance, interest in use and logistics of distribution of free HIVST kits among men who have sex with men (MSM) in Curitiba and Sao Paulo, two state capitals in Brazil. We here analyze the characteristics and prevention attitudes of participants registered to undertake HIVST in Sao Paulo.

**Methods:** Between April–December 2018 potential participants were invited through social media and gay venues to complete a web-based anonymous survey on prevention attitudes, HIV infection risk and risk perception. We explored demographic and vulnerability characteristics associated with reported lifetime HIV testing using univariate analyses. We also compared participants with and without prior testing for their preferred testing strategy.

**Results:** 6,477 respondents who provided valid answers were included. All were MSM, with median age of 28 years (IQR 23-34); 54% self-declared as white and 68% had at least 12 years of schooling. Sexual orientation was homosexual for 81%. Fifty percent of the participants reported at least 1 episode of unprotected anal intercourse in the past 6 months; 25% reported illicit drug use in the same period. Despite a high-risk profile, the perception of risk for HIV infection in the next year was high for only 4%. 78% reported being previously tested for HIV, with factors such as facility working hours (53%), exposure of personal issues to a provider (34%) and gender identity/sexual orientation-related stigma (21%) cited as barriers for testing. Older age, higher education, illicit drug use and gay orientation were associated with higher percentage of lifetime HIV testing (p<0.001). Most participants (67%) reported not knowing of the availability of HIVST before enrolling in the study. The preference for HIVST was higher among participants who had never been tested (71%) compared to those with previous HIV testing (61%; p<0.001).

**Conclusion:** In this study including high risk MSM, HIVST was the preferred testing strategy among participants who had never been tested. This shows HIVST may be an important tool to improve HIV testing, particularly among hard-to-reach key populations.

---

**DOES PROVISION OF FREE HIV SELF-TESTING KITS INCREASE HIV DIAGNOSIS IN MSM?**

Alison Rodger1, Leanne McCabe1, Andrew N. Phillips1, Fiona Lampe1, Fiona M. Burns1, Denise Ward1, Valerie Delpech2, Peter Kirwan3, Peter Weatherburn1, T. Charles Witzel2, Roger Pebody3, Roy Trevelion4, Yolanda Collaco-Moraes5, Sheena McCormack1, David Dunn1


**Background:** High levels of HIV testing in men who have sex with men (MSM) remain key to reducing incidence, particularly in men who have condomless anal intercourse (CAI) with multiple partners. There is little evidence about the effectiveness of free HIV self-testing (HIVST) to increase HIV diagnosis rates in MSM. We aimed to assess if the offer of a single free HIVST kit led to increased diagnosis of HIV infections that linked to care.

**Methods:** SELPHI is an internet based, open-label, randomized controlled trial that used online advertising to recruit men potentially interested in HIVST. Enrolment criteria were male (including trans), aged ≥16 years, ever had anal intercourse (AI) with a man, not known to be HIV positive and consent to link to national HIV surveillance databases (to ascertain new HIV diagnoses and linkage to care). Participants were randomly allocated 3:2 at enrolment to a free HIVST (Baseline Test (BT)) versus no free HIVST (BT only). Online surveys collected data at baseline, 2 weeks (BT only) and 3 months (BT only) post-enrolment. Men in BT were asked about HIVST use and linkage to care if reactive. Primary outcome was a confirmed new HIV diagnosis within 3 months of enrolment.

**Results:** 10,111 men were randomized (6049 BT; 4062 NT); median age 33 years (IQR 26–44); 89% white; 20% born outside UK; 0.8% trans men; 47% degree educated; 15% never HIV tested; 8% ever and 4% currently on PrEP. At enrolment 89% reported AI and 72% CAI with ≥1 male partner in previous 3 months. 4194/4695 (89%) in BT reported using the HIVST kit. No significant difference at 3 months (p=0.64, 19 [0.3%] in BT vs 15 [0.4%] in NT) in nBT. Men randomized to BT were more likely to HIV test in 3 months after enrolment (96% vs 42%; risk ratio 2.27 95%CI 2.13, 2.40), but a higher proportion in nBT tested for HIV in the 3 months after enrolment (42%) compared to 3 months before (21%). STI testing rates between arms were similar (22% in BT vs 25% in nBT).

**Conclusion:** Reflecting national declines in MSM, new HIV diagnoses were low in both arms by 3 months after enrolment, with no significant difference between men randomized to receive an HIVST kit (BT) and those who were not (nBT). Men randomized to nBT may have been motivated to HIV test through other routes in the 3 months after enrolment. However, HIV testing rates were overall higher in the 3 months after enrolment in those offered HIVST, with similar rates of STI screening.
THE RATIONALE FOR A 3-TEST HIV DIAGNOSTIC ALGORITHM: BALANCING ACCURACY AND COST

Jeffrey Eaton, Anita Sands, Magdalena Barr-Dichiera, Muhammad S. Jamil, Thokozani Kala, Andreas Jahn, Rachel Baggaley, Cheryl Johnson

Imperial College London, London, UK, WHO, Geneva, Switzerland, Malawi Department of HIV and AIDS, Lilongwe, Malawi

Background: To ensure >99% positive predictive value (PPV) for HIV testing strategies (HTS) in all settings, WHO 2015 Guidelines recommended two consecutive reactive HIV tests to diagnose HIV infection in high-prevalence (≥5%) and three consecutive reactive tests in low-prevalence (≤5%) settings. As awareness of HIV status and treatment coverage reaches high levels, positivity among HTS clients is now below 5% even in high HIV prevalence settings. Consequently, countries employing the ‘high-prevalence’ strategy should consider, when, and how to transition to a strategy with three-assays for HIV diagnosis. We estimated the HIV testing outcomes, commodities required, and incremental cost for the 3-test versus 2-test strategy.

Methods: We created a probability model to simulate HIV testing outcomes of the high- and low-prevalence strategies recommended in WHO 2015 HTS Guidelines, including recommended repetition of discrepant assays. We assumed each assay in the algorithm had 99% sensitivity and 98% specificity, minimum thresholds required to obtain WHO prequalification. Fully loaded costs indicative of a low/middle-income setting were US$2 per client plus commodity costs of $1.30, $2.30, and $2.50 per A1, A2, and A3 assay used, respectively. We calculated expected HIV testing outcomes per 100,000 persons tested with positivity ranging from 0.1% to 20%: expected number of false-positive and false-negative misclassifications, positive and negative predictive value, number of each assay used, and total cost.

Results: The expected number of false-positive misclassifications reduced from around 45 to fewer than 1 per 100,000 tested for the 3-test strategy at all positivity levels (Table 1). The PPV of the testing strategy was well above the 99% target at all positivity levels for the 3-test strategy. The number of A1 and A2 assays utilized did not change; the number of A3 assays required was expectedly greater with the 3-test strategy but still much lower than the number of A2 required. The total cost of the 3-test strategy was only 2.5% greater than the 2-test strategy at 5% positivity, reflecting that HTS cost programme cost is primarily determined by the number of A1 conducted.

Conclusion: The 3-test strategy ensured high PPV at all HIV positivity levels for a modest incremental cost relative to the 2-test strategy. In light of low positivity, we suggest all countries transition to a unified strategy with three reactive tests for HIV diagnosis in accordance with latest WHO guidance.

Table 1: Characteristics and clinical features of individuals with false-positive (FP) HIV test results.

<table>
<thead>
<tr>
<th>Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median [IQR])</td>
<td>0.110</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Race (%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td>0.120</td>
</tr>
<tr>
<td>MSM (%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current pregnancy (%)</td>
<td>0.040</td>
</tr>
<tr>
<td>History of IDU (%)</td>
<td>0.040</td>
</tr>
<tr>
<td>DCE (%)</td>
<td>0.030</td>
</tr>
<tr>
<td>FLU (% of HIV-positive patients)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

966 FALSE-POSITIVE 4TH GENERATION HIV TEST RESULTS IN THE EMERGENCY DEPARTMENT

Gabriel A. Wagner, Ryan Anson, Nicole Gamache-Kool, Kushagra Mathur, Megan Lo, Jeffrey H. Burack, Annette Shaib, Jill Blumenthal, Susan J. Little, Martin Hoening

University of California San Diego, San Diego, CA, USA, East Bay AIDS Center, Oakland, California, East Bay AIDS Center, Oakland, CA, USA

Background: Universal opt-out HIV screening in low prevalence settings such as emergency departments (EDs) has increased identification of persons with HIV infection. However, false positive (FP) 4th generation HIV test results may impact the positive predictive value (PPV) and lead to a delay of disclosure of HIV diagnosis. The objective of this analysis was to assess factors associated with false-positive test results.

Methods: Opt-out HIV screening was conducted among adults at four California locations (two EDs at UC San Diego from July 2017 - March 2019 and two EDs at Alta Bates Summit Medical Center in Oakland from May 2017 - March 2019) using a 4th generation HIV Ag/Ab combination assay. We identified all individuals with FP HIV Ag/Ab results. Demographics, clinical data (ED chief complaints, discharge diagnoses, and medical conditions), and HIV risk factors were extracted from electronic medical records and compared with data from individuals with true positive (TP) HIV test results using non-parametric statistical tests.

Results: A total of 32,450 HIV tests were performed across four EDs using a 4th generation Ag/Ab assay (Architect® and Roche Elecsys®) resulting in 104 FP cases and 34 FP cases (PPV: 75.4%; FP rate: 0.1%). Among FP cases, the median age was 42 (IQR: 32-55), more than half (64.7%) were female, and more than half (58.8%) were White (Table). In univariate analyses, FP cases were significantly more likely than TP cases to be female (64.7% vs 28.9%, p < 0.05), White (63.6% vs 35.6%, p < 0.05), and pregnant (9.7% vs 0%, p < 0.05). None of the false-positive cases were in men who have sex with men and none were persons who inject drugs. Several factors were common (>20%) but not statistically significant: history of flu vaccination (lifetime) (65.5%), history of multiparity (30.0%), and obesity (24.2%). Additionally, 3 cases had a history of FP HIV tests and 1 case had autoimmune hepatitis.

Conclusion: The PPV of 4th generation HIV tests was suboptimal during universal opt-out HIV screening in EDs at two medical centers in California. Individuals who were female, White, and pregnant were more likely to have FP tests. Understanding these factors associated with FP test results in a population with low pretest probability may be important for early HIV disclosure as universal HIV testing in low-prevalence settings becomes more commonplace.

Table 2: Demographic and clinical features among individuals with false-positive (FP) HIV test results.

<table>
<thead>
<tr>
<th>Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median [IQR])</td>
<td>0.110</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Race (%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td>0.120</td>
</tr>
<tr>
<td>MSM (%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current pregnancy (%)</td>
<td>0.040</td>
</tr>
<tr>
<td>History of IDU (%)</td>
<td>0.040</td>
</tr>
<tr>
<td>DCE (%)</td>
<td>0.030</td>
</tr>
<tr>
<td>FLU (% of HIV-positive patients)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

967 EVALUATION OF VIRAL SUPPRESSION ON RAPID HIV TEST REACTIVITY AMONG MSM, NHBS, 2017

Shamaya Whitby, Amanda Smith, Johanna Chapin-Bardales, Rebecca Rossetti, Cyprian Wejnert, Silvina Masciotra, for the for the NHBS Study Group

Oak Ridge Institute for Science and Education, Atlanta, GA, USA, CDC, Atlanta, GA, USA

Background: Antiretroviral therapy (ART) leads to viral suppression (VS) and potentially seroorversion. However, the impact of sustained VS on the ability of rapid tests (RTs) to identify HIV infection has not been extensively reported. To assess RT performance in populations with likely exposure to antiretrovirals, we...
evaluated RT results among self-reported HIV-positive (SRP) men who have sex with men (MSM) in 23 U.S. cities participating in 2017 National HIV Behavioral Surveillance (NHBS).

Methods: Sites performed at least one point-of-care RT on all consenting SRP MSM. Participants with RT-nonreactive (RT-NR) results were considered discrepant and resolved with further laboratory testing using plasma or dried blood spots (DBS) at the CDC or locally. At CDC, those consenting to storage of DBS were confirmed using Abbott RealTime HIV-1 assay (VL), Bio-Rad GS HIV Combo Ag/Ab and Genieus HIV-1/2 assays. Self-reported data and valid test results were analyzed using SAS.

Results: The false-negative rate was 2.3% (45/1936). Of 1936 participants, 42.4% were tested with INSTI (21/820, 2.6% RT-NR), 31.1% with Determine (10/603, 1.7% RT-NR), 12.3% with Sure Check (5/239, 2.1% RT-NR), 11.6% with OraQuick (5/224, 2.2% RT-NR) and 2.6% with Uni-Gold (4/520, 0.8% RT-NR). The table shows reactivity of RTs from participants by VL results and self-reported ART use. Of 1655 RT-R participants, 1311 (79.2%) had undetectable VL or detected <2.92 log_{10} (copies/mL) of whom 1263 (96.3%) reported being on ART. Of 18 RT-NR participants, 17 (94.4%) had undetectable VL of whom 16 (94.1%) reported being on ART. The laboratory-based serology testing algorithm did not confirm HIV-positive status in 5 of 18 RT-NR persons self-reported to be living with HIV and on ART (2 Determine, 1 OraQuick, 1 Uni-Gold, 1 Sure Check).

Conclusion: False non-reactivity of rapid HIV tests occurred but was low and consistent across most RTs. In a small number of samples, VS was associated with non-reactivity possibly due to sequestration; however, the percent of participants virally suppressed on ART was similar among those who were RT-R and RT-NR. Given the sensitivity limitation of RTs, our results highlight challenges with relying on rapid HIV testing alone, particularly in circumstances of VS in which non-reactivity could lead to misinterpretation of HIV status. This could have implications for monitoring for virologic breakthroughs with PrEP and surveillance systems that use RTs to gauge HIV prevalence.

968 PERFORMANCE OF ORAQUICK RAPID TEST ON HIV DIAGNOSIS AMONG CADAVERS IN KISUMU, KENYA

Frankline O. Mboya1, Anthony Waruru2, Alex Sila3, Dickens Onyango4, Solomon Sava5, Lily Nyaga5, Mary Wamungwe5, Nakayiga Nakayiga5, Mutahi Junghae6, Paul K. Musingila1, Frank L. Basiye1, Kimberly McCarthy1, Boaz Oyaro6, Peter W. Young7

1University of Washington, Seattle, WA, USA, 2Human Sciences Research Council, Pretoria, South Africa, 3Africa Health Research Institute, Mbabane, Swaziland, 4Global Solutions for Infectious Diseases, San Francisco, CA, USA, 5KEMRI–Centre for Global Health Research, Kisumu, Kenya, 6KEMRI–Centre for Global Health Research, Mombasa, Kenya, 7US Department of State, Nairobi, Kenya

Background: Ascertaining HIV status at time of death can be useful for identifying missed opportunities to diagnose and treat HIV infection. Routinely testing HIV status among deaths, though not commonly practiced, may identifying missed opportunities to diagnose and treat HIV infection. Routinely testing HIV status among deaths, though not commonly practiced, may.

Methods: A series of cadaver samples from 132 cadavers > 18 months old at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOJTRH) were collected from 2017 to 2018. Autopsy samples from 100 were tested with OraQuick®. The other 32 cadavers were tested for the presence of VS in which non-reactivity could lead to misinterpretation of HIV status. This could have implications for monitoring for virologic breakthroughs with PrEP and surveillance systems that use RTs to gauge HIV prevalence.

Conclusion: OraQuick® was found to work more specific than sensitive on oral samples from cadavers. Similar performance has been reported among living subjects. It is a convenient less invasive screening test for surveillance of HIV among cadavers within a mortuary setting.

969 DRIED BLOOD SPOTS PROVIDE SIMPLIFIED ACCURATE MEASUREMENT OF HIV VIRAL LOAD

Torin Schaafsma1, Katherine Thomas1, Heidi Van Ruyzee2, Maryam Shahmanesh3, Jared Baeten1, Connie L. Celum1, Ruviene V. Barnabas1, for the DO ART Study Team

1University of Washington, Seattle, WA, USA, 2Human Sciences Research Council, Pretoria, South Africa, 3Africa Health Research Institute, Mbabane, Swaziland

Background: HIV viral load (VL) is a robust measure of adherence and treatment efficacy when monitoring antiretroviral therapy (ART), facilitating timely switching to second line regimes. However, collection of plasma for VL requires phlebotomy, controlled transport conditions, and is costly, thereby limiting its use in community settings. The use of dried blood spot (DBS) cards of finger-prick blood transported at ambient temperature to a central laboratory for VL testing would simplify monitoring, but requires validation against the gold standard method of plasma VL.

Methods: In a randomized study of community-based delivery of ART in KwaZulu-Natal, South Africa (the DO ART Study) persons living with HIV provided concurrent EDTA plasma and DBS specimens. Plasma VL samples were transported 100 - 250 km to Global Labs (Durban), which used the bioMérieux NucliSens EasyQ HIV-1 assay to measure plasma VL. DBS were transported 100 - 250 km to Global Labs (Durban), which used the bioMérieux NucliSens EasyQ HIV-1 assay to measure plasma VL.

Results: There was high correlation between log-transformed DBS and plasma results of -0.17 log_{10} copies/mL (95% of the differences were from -1.42 to 1.09 log_{10} copies/mL). There was high correlation between log-transformed DBS and plasma results of -0.17 log_{10} copies/mL (95% of the differences were from -1.42 to 1.09 log_{10} copies/mL).
Automated high-throughput quantification of low-level HIV-1 plasma viremia

Jana L. Jacobs1, Melissa A. Tosiano1, Dianna L. Koontz2, Andrew Worlock2, Karen Harrington1, Sonia Bakkouri1, Michael P. Busch2, John W. Mellors1

1University of Pittsburgh, Pittsburgh, PA, USA, 2Hologic Corporation, Bedford, MA, USA

Background: Low-level plasma HIV-1 viremia persists in the majority of HIV-1 positive individuals despite long-term clinically-effective ART. Clearance of HIV-1 viremia remains a critical goal towards an HIV cure, but complex and low-throughput single copy assays (SCA) limit the capacity to monitor the effects of interventions on persistent viremia. Here we report the evaluation of two high-throughput methods on the Hologic Panther platform to automate quantitation of low-level viremia in comparison with a SCA targeting integrase (iSCA2.0; Tosiano, et al. J Clin Micro 2019).

Methods: The assay methods performed on the Hologic Panther platform were: 1) testing of nine 0.5mL replicates (Panther 9x) with estimation of HIV-1 RNA concentration using statistical inference based on binary outcome; and 2) concentration of 5mL plasma to one 0.7mL replicate by centrifugation (Panther spun). Plasma HIV-1 RNA standards (20, 5, 2.5, 1.25, 0.625, and 0 copies/ml) from the Quality Assurance (VQA) at Rush University were tested in 5 independent runs of 5 replicates. Both Panther methods were compared to the manual iSCA 2.0. Mean, standard deviation and percent positive assays were calculated for each run and the 95% LOD was assessed using maximum likelihood estimation.

Results: The model based means for storage temperatures range from 4.26 – 4.42 Log10 copies/ml. The assay methods performed on the Hologic Panther platform

971 Heat-inactivated/lyophilized HIV virus for use in proficiency testing programs

Raul Louzao1, Thomas M. Denny1, Heidi M. Register1, Wes Rountree1, Ambrosia Garcia1, Cassandra Porth1, Andrea Pappas1, Clare Morris1, Sarah Gilbert1, Bhavna M. Hora1, Feng Gao1

1Duke Human Vaccine Institute, Durham, NC, USA, 2National Institute for Biological Standards and Control, South Mimms, United Kingdom

Background: Proficiency testing (PT) for labs performing HIV viral load (VL) is critical to determining that acceptable patient monitoring standards are being established. Current PT programs utilize infectious material which requires a cold chain for shipping and local laboratory storage. We set out to develop QC materials to reduce the infectious risk of the QC material and overall cold chain requirements.

Methods: A Clade C virus from the NIAID EQAPOL program was heat inactivated and shown inability to replicate, as determined by VL and p24 Ag testing; then lyophilized at 50,000 copies/ml. Testing was performed at four storage temperatures (-20°C, 4°C, 23°C, 30°C) at seven time points. Linear modeling was performed to make descriptive statistics (e.g., estimation of means) and a descriptive evaluation of the means for storage temperatures and time points at the alpha 0.05 level.

Results: The heat-inactivated non-lyophilized viral material showed a VL of 4.698 (-0.5 < 4.198 and +0.5 < 5.198) Log10 copies/ml during 12 months of repeat testing under -80°C conditions. Shown below are VL results for the lyophilized material held at different storage conditions over time and then tested. We found statistical evidence of a 0.007 Log10 increase per week of storage and that month 6 VL was higher than the average time point VL (see Figure 1). There was no statistical evidence of storage temperature differences. The model based means for storage temperatures range from 4.26 – 4.42 Log10 copies/ml and the model based means for the time points range from 4.28 – 4.49 Log10 copies/ml. Displayed in Figure 1 below are the VL results for the lyophilized material held at different storage conditions over the various time points. The average VL is 4.38 with the standard acceptance criteria of +/- 0.5 Log10 copies/ml at 3.88 and 4.88.

Conclusion: These data we collected provides a proof of concept that the heat inactivated and lyophilized material remains stable and well within a 0.5 Log10 acceptance criteria at all temperature storage conditions for up to six months. Studies are underway to determine suitability of this material for use in quality assessment of drug mutation sequencing assays. Reducing cold chain requirements, shipping costs and infectious status of QC materials offers significant improvements to current PT approaches. Work supported by NIAID EQAPOL HHSN27220170061C.

Figure 1. Lyophilization Temperature Stability Testing

- Week 1
- Week 2
- Week 3
- Week 4
- Month 1
- Month 2
- Month 3
- Month 4
- Month 5
- Month 6
- 0.5 Log10
- 0 Log10
- 0.1 Log10

5.5
5
4.5
4
3
30°C
5°C
-20°C
-40°C
972 IDENTIFYING RECENT HIV INFECTIONS IN REAL-WORLD SETTINGS IN KENYA AND ZIMBABWE

Brian Rice1, Markien M. De Wit1, Kathryn A. Risher1, Susie Welty1, Sungail T. Chabata1, Frances Cowan1, Georges Reniers1, Gary Murphy1, Jeffrey Eaton1, George Rutherford2, James R. Hargreaves2
1London School of Hygiene & Tropical Medicine, London, UK, 2University of California San Francisco, San Francisco, CA, USA, 3Centre for Sexual Health and HIV/AIDS Research Zimbabwe, Harare, Zimbabwe, 4Liverpool School of Tropical Medicine, Liverpool, UK, 5London School of Hygiene & Tropical Medicine, London, UK, 6Public Health England, London, UK, 7Imperial College London, London, UK

Background: Distinguishing recently acquired infection from “long-standing” infection among persons newly diagnosed with HIV can help guide prevention programming. Focusing on the procedures required to accurately determine recent infection, we present the results of three pilots of HIV recency testing in Kenya and Zimbabwe.

Methods: Using Maximo HIV-1 LAg-Avidity EIA dried blood spot and plasma kits, we conducted HIV recency testing in a variety of routine service-provision contexts, namely: antenatal clinics providing PMTCT services in Siaya County, Kenya, routine HIV testing clinics in Nairobi, Kenya, and a national programme for female sex workers (FSW) in Zimbabwe. Our recency test results were interpreted as part of a Recent Infection Testing Algorithm (RITA), to which we included prior testing history, viral load and ART exposure. LAg results with a normalized optical density (ODn) of <1.5 and a viral load > 1000 copies/mL were classified as testing positive for recent infection.

Results: Having tested participants for HIV, investigated HIV status and sought consent, in total 1,272 HIV positive women and men were tested for recent infection across the three pilots (see figure 1). Based on LAg test result alone, our crude recency percentages were 24.9% (106/426) in Siaya County, 11.3% (60/530) in Nairobi, and 15.6% (49/313) in Zimbabwe. Figure 1 highlights how combining our recency assay results with viral load greatly reduced the number of people classified as recent infection in all three settings. In Nairobi (ART metabolite testing) and Siaya County (linked clinic records) the number classified as recent infection was further reduced due to evidence of ART use (in Zimbabwe women with a history of a previous positive test or ART use were excluded). The final percentages of participants classified with a recent infection were 2.3% (10/426) among women in Siaya County, 8.7% (46/530) among men and women in Nairobi, and 10.5% (33/314) among FSW in Zimbabwe.

Conclusion: We successfully identified recently acquired infections among persons diagnosed with HIV in real-world settings. Our recency percentages would have been substantially inflated without the inclusion of clinical information. In using recency assays to accurately distinguish recent from long-standing infection in routine settings, we highlight the importance of considering a person’s previous HIV test history, ART use, and viral load.

Figure 1: HIV recency test results and testing

973 STAGING OF HIV-1C INFECTION AMONG PATIENTS ON ART IN BOTSWANA USING PROVIRAL DNA

Manon Ragonnet-Cronin1, Tanya Golubchik1, Sikhulile Moyo1, Christophe Fraser1, Max Essex2, Vlad Novitsky3, Erik Volz4, for the PANGEA Consortium 1Imperial College London, London, UK, 2University of Oxford, Oxford, UK, 3Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, 4Harvard T.H. Chan School of Public Health, Boston, MA, USA

Background: HIV genetic diversity increases during infection and can be used to infer time since infection; however published analyses have included only antiretroviral treatment (ART) naïve individuals.

Methods: Demographic and clinical information from HIV-1C-infected patients were collected within the Botswana Combination Prevention Project from 2013 to 2018. HIV genetic sequencing efforts have been intensified under the PANGEA-HIV initiative. The vast majority of participants were on ART. Amplification and near full-length HIV genome sequencing were performed from proviral DNA. Duration of HIV infection was dichotomized, as < or ≥ 1 year for 1153 participants based on longitudinal follow-up before and after diagnosis. We calculated viral diversity at each nucleotide site and for gag, pol and env based on nucleotide frequency files. We optimized a logistic regression model to predict recency < 1 year and assessed model performance by cross-validation.

Results: In our dataset, 140 individuals had been infected for less than a year at diagnosis. Most patients (954/1143, 83.5%) were on ART at the time of sampling. We split our data randomly into training (70%) and testing (30%) subsets. Our best predictive model included genetic diversity for pol, gag and env, viral load, age, gender and ART-status. Prediction accuracy in the test dataset was 94.4% (91.3%–96.6%) compared to a null model accuracy of 87.8% (p<0.0001). Model sensitivity was 74.4%, specificity 97.2% and positive predictive value was 78.4%. Accuracy was consistent across 1000 cross-validation tests. The model including only genetic diversity measures, without any demographic or clinical variables, was not significantly better than the null model (p=0.05) because of the confounding effect of ART-status.

Conclusion: In contrast to previous analyses, most of our sequences came from proviral DNA from individuals on suppressive ART. Among treated patients, genetic diversity measures (e.g. entropy) displayed overlap between recent and chronic infections (Figure 1) but including clinical and demographic data improved prediction of recency. We are currently evaluating whether machine learning can incorporate additional information (e.g. sites under selection) to further distinguish between recent and chronic infections in treated individuals.

Figure 1. Violin plot displaying entropy (a measure of viral diversity) for patients based on time since infection (recent, i.e. <1 year, or chronic) and antiretroviral treatment (ART) status. Entropy was averaged across all informative sites in the genome.

974 NOVEL CRITERIA FOR DIAGNOSING ACUTE HIV IN A MULTINATIONAL ART-INITIATION STUDY

Trevor A. Crowell1, Justin Ritz1, Robert Coombs1, Lu Zheng1, Joseph J. Erion1, John W. Mellors1, Gert U. van Zyl2, Javier R. Lama3, Kiat Ruxrungtham3, Beatriz Grinsztejn3, Roberto Arduino4, Lawrence Fox5, Jintanat Anawaranch6, Eric Daar7, for the AIDS Clinical Trials Group (ACTG) A5354 Study Team 1US Military HIV Research Program, Silver Spring, MD, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3University of Washington, Seattle, WA, USA, 4University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 5University of Pittsburgh, Pittsburgh, PA, USA, 6Stellenbosch University, Cape Town, South Africa, 7Asociacion Civil Impacta Salud y Educacion, Lima, Peru, 8Thai Red Cross AIDS Research Center, Bangkok, Thailand, 9Instituto de Pesquisa Clinica Evandro Chagas, Rio de Janeiro, Brazil, 10University of Texas at Houston, Houston, TX, USA, 11DAIDS, NIH, Bethesda, MD, USA, 12Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA

Background: HIV genetic diversity increases during infection and can be used to infer time since infection; however published analyses have included only antiretroviral treatment (ART) naïve individuals.

Methods: Demographic and clinical information from HIV-1C-infected patients were collected within the Botswana Combination Prevention Project from 2013 to 2018. HIV genetic sequencing efforts have been intensified under the PANGEA-HIV initiative. The vast majority of participants were on ART. Amplification and near full-length HIV genome sequencing were performed from proviral DNA. Duration of HIV infection was dichotomized, as < or ≥ 1 year for 1153 participants based on longitudinal follow-up before and after diagnosis. We calculated viral diversity at each nucleotide site and for gag, pol and env based on nucleotide frequency files. We optimized a logistic regression model to predict recency < 1 year and assessed model performance by cross-validation.

Results: In our dataset, 140 individuals had been infected for less than a year at diagnosis. Most patients (954/1143, 83.5%) were on ART at the time of sampling. We split our data randomly into training (70%) and testing (30%) subsets. Our best predictive model included genetic diversity for pol, gag and env, viral load, age, gender and ART-status. Prediction accuracy in the test dataset was 94.4% (91.3%–96.6%) compared to a null model accuracy of 87.8% (p<0.0001). Model sensitivity was 74.4%, specificity 97.2% and positive predictive value was 78.4%. Accuracy was consistent across 1000 cross-validation tests. The model including only genetic diversity measures, without any demographic or clinical variables, was not significantly better than the null model (p=0.05) because of the confounding effect of ART-status.

Conclusion: In contrast to previous analyses, most of our sequences came from proviral DNA from individuals on suppressive ART. Among treated patients, genetic diversity measures (e.g. entropy) displayed overlap between recent and chronic infections (Figure 1) but including clinical and demographic data improved prediction of recency. We are currently evaluating whether machine learning can incorporate additional information (e.g. sites under selection) to further distinguish between recent and chronic infections in treated individuals.
Background: Antiretroviral therapy (ART) initiation during acute HIV infection (AHI) limits HIV reservoirs, enhances reservoir decay, restricts viral genetic diversification and may facilitate post-ART control. Identifying and treating persons with AHI is highly desirable but logistically challenging. We describe the performance of new AHI diagnostic criteria for an ongoing multi-national study of ART initiation during AHI.

Methods: ACTG 5354 enrolls adults during AHI at 29 sites in the Americas, Africa, and Southeast Asia. Participants must meet one of the following criteria: (A) detectable HIV RNA and non-reactive HIV antibody; (B) detectable HIV RNA or reactive antibody and negative/indeterminate Western blot (WB) or Geenius; (C) negative HIV RNA or antibody within 90 days and reactive antibody, WB (p31-), or Geenius (p31-) within 7 days; (D) ARCHITECT or GCOOMBO antigen/antibody (Ag/Ab) combo signal-to-cutoff ratio (S/CO) ≥ 10 and non-reactive HIV antibody. Participants start ART at enrollment. HIV infection and Fiebig stage at ART initiation are subsequently confirmed by centralized testing that includes HIV RNA, ARCHITECT Ag/Ab, Bio-Rad HIV-1/2 Ab (IgM sensitive), and Geenius HIV-1/2 lateral flow antibody assay.

Results: From January 2017 through August 2019, 174 were enrolled and completed centralized confirmatory testing. Their median age was 27 (interquartile range 23-38) years and 29 (17%) were female. ART was started by 154 (89%) on the day of enrollment and 20 (11%) the next day, mostly with study-provided elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (n=136, 78%). AHI was confirmed in 167 (96%) participants after centralized testing and varied in Fiebig stage according to the AHI criteria used (Figure Panel A). Three participants with locally detectable HIV RNA had no evidence of infection on centralized testing, discontinued ART and were withdrawn. Four others were in Fiebig VI, not AHI, at enrollment. Centralized ARCHITECT S/CO ≥ 10 combined with nonreactive or indeterminate HIV antibody on the Geenius assay correctly identified 87 of 106 (82%) Fiebig II-IV AHI cases (Figure Panel B).

Conclusion: Novel efficient AHI criteria incorporating ARCHITECT S/CO into diagnostic algorithms facilitated rapid ART initiation pending confirmation. False-positive diagnoses of AHI were rare. These new criteria may facilitate AHI diagnosis, staging, and immediate ART initiation in research studies and clinical practice.

A. Fiebig Stage of Enrolled Participants, by Criterion for Acute HIV Infection

B. ARCHITECT Signal-to-Cutoff Ratios of Participants with Negative/Indeterminate Geenius HIV-1/2 Antibody Results, by Fiebig Stage

---

**Table:**

<table>
<thead>
<tr>
<th>Fiebig Stage</th>
<th>AHI Yes</th>
<th>AHI No</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>II</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>85</td>
</tr>
</tbody>
</table>

**Figure Panels:**

A. Fiebig Stage of Enrolled Participants, by Criterion for Acute HIV Infection

B. ARCHITECT Signal-to-Cutoff Ratios of Participants with Negative/Indeterminate Geenius HIV-1/2 Antibody Results, by Fiebig Stage

---

**Image:**

The bottom and top edges of the box indicate the inter-quartile range (IQR). The line inside the box indicates the median. Filled circles represent actual data points.
Background: The Limiting Antigenic Avidity (LAg) assay is used to estimate HIV incidence in cross-sectional surveys. Testing algorithms often include low HIV viral load (VL) as a marker of non-recent infection. We compared the accuracy of cross-sectional incidence (CSI) estimates to observed incidence in the community-randomized HPTN 071 (PopART) trial, where a substantial proportion of HIV+ participants were virally suppressed.

Methods: HIV incidence was assessed in a Population Cohort (PC) 1-2 years after study initiation (between the PC12 and PC24 surveys). Observed incidence was based on confirmed seroconversion events between PC12 and PC24. The CSI analysis of the PC24 survey included 15,845 who remained HIV negative, 2,211 persons who seroconverted between PC12 and PC24 (SC12-24), 217 who seroconverted between PC0 and PC24 (SC0-24), 4,022 who were HIV+ at PC0; and 689 who enrolled HIV+ during the PC24 survey. The VL at PC24 was <1,000 copies/mL for 72.7% of HIV+ persons, including 31% (70/221) of the SC12-24 group. All HIV+ + PC24 samples were tested using the Sedia LAg-Avidity assay. Recent infections were defined as having a LAg result <1.5 normalized optical density units (ODn) and HIV VL >1,000 copies/mL. The CSI estimate was determined using a mean duration of recent infection of 130 days (95% confidence interval [CI]: 117-143) and a false recent ratio (FRR) of 4%.

Results: The LAg result was <1.5 ODn in 11.3% (582/5149) of all HIV+ persons; 74/582 had a VL >1,000 copies/mL and were classified as recently infected. These included 27% (60/221) of the SC12-24 group, 2.7% (6/217) of the SC0-24 group, 0.15% (1/689) of those who enrolled HIV+ at PC0; and 0.07% (7/4022) of those who enrolled HIV+ at PC0 (most infected for >2 years). Use of a higher cutoff for the LAg assay (2.0 or 2.5 ODn) increased the proportion of the SC12-24 group classified as recently infected from 27% to 32% or 41%, respectively, but increased the FRR among those infected >2 years from 0.17% to 0.42% or 0.72%, respectively. In each study country and overall, the CSI estimates were considerably less precise than observed incidence measured from cohort follow-up.

Conclusion: In this large community-randomized study, a widely-used CSI algorithm that included the LAg assay and HIV VL yielded accurate point estimates of incidence, despite high rates of viral suppression among those with both prevalent and incident infection. However, the CSI estimates were considerably less precise than observed incidence measured from cohort follow-up.

797 URINE TENOFOVIR LEVELS BY IMMUNOASSAY PREDICT HIV PROTECTION IN A LARGE PREP TRIAL

Randy Stalter,1 Kelly Johnson3, Andrew Mujugira1, Mark A. Marzinke6, Craig W. Hendrix6, Randy Stalter and all HIV seroconverters on PrEP, we conducted a case-cohort analysis to assess association between recent urine TFV level >1500 ng/mL, a threshold which accurately classifies recent PrEP dosing, and protection from HIV. The 1500 ng/mL cut-off would be used for the first iteration of the POC assay. Estimates of the hazard ratio for the Cox model are adjusted for age, sex, and sexual behavior.

Results: We included 292 participants in the cohort and 45 cases who contributed 722 and 91 urine samples, respectively. 39% of the cohort and 51% of cases were female. Detectable urine TFV levels showed 87% sensitivity (95% CI: 84-90%) and 73% (65-79%) specificity for detectable plasma TFV concentration, which is predictive of HIV protection. Using the urine level at first detection of seroconversion in the adjusted model, a urine TFV level >1500 ng/mL was associated with a 71% (95% CI: 24-89%; p<0.01) adjusted reduction in HIV risk.

Conclusion: In a large completed PrEP trial, urine TFV levels measured via a novel immunoassay were predictive of protection from HIV. Detection of TFV in urine showed good sensitivity and specificity for detection of TFV in plasma measured via LC-MS/MS, an established metric of short-term PrEP adherence. The urine immunoassay has now been developed into a lateral flow assay which can provide results at the POC. Our findings suggest that a real-time assay to assess TFV levels in urine could be a valuable addition to existing objective metrics for PrEP adherence.
979 POPULATION-LEVEL EFFECTIVENESS OF PrEP AMONG MSM AND TRANSGENDER PERSONS WITH STI

Jade Pagkas-Bather1, Christine M. Khosropour2, Matthew R. Golden1, Julia C. Dombrowski2
1University of Chicago, Chicago, IL, USA, 2University of Washington, Seattle, WA, USA

Background: HIV PrEP is highly efficacious, but its effectiveness may be limited by poor adherence or discontinuation. Few studies have evaluated PrEP effectiveness outside of specific clinics or healthcare organizations.

Methods: We conducted a retrospective cohort study using King County, Washington STI partner services (PS) interview data collected January 2014 to August 2018. During PS interviews, public health staff asked men who have sex with men (MSM) and transgender persons who have sex with men (TGSM) if they were taking PrEP. We used name, date of birth and sex to match STI PS data to public health HIV surveillance data to identify persons diagnosed with HIV after their interview. We calculated the incidence of HIV diagnoses per 100 person-years in PrEP users and non-users and used Cox proportional hazard regression, adjusting for age and race/ethnicity, to assess the risk of HIV diagnosis based on past PrEP use. We included PrEP use status, race, Latinx ethnicity, age, and bacterial STI diagnoses in multivariate analysis. MSM and TGSM without an identified HIV diagnosis were administratively censored on August 31, 2018. We reviewed HIV PS interview records for PrEP users who were diagnosed with HIV to assess if they were taking PrEP at the time of their diagnosis.

Results: The median time from PS interview to HIV diagnosis or censoring was 14 months (IQR 6 to 23 months). Five (0.4%) of 1206 people who reported PrEP use at the time of their STI diagnoses and 97 (3%) of 2162 persons who were not using PrEP were diagnosed with HIV infection (p < 0.001). HIV incidence was lower among PrEP users than nonusers (0.02 vs. 0.09 cases per 100 person-years, aHR 0.16, 95% CI 0.06 to 0.45). Other factors associated with incident HIV diagnosis included age <20 years (aHR 1.76, 95% CI 0.68 to 4.54), Black race (aHR 1.21, 95% CI 0.60 to 2.45), and Latinx ethnicity (aHR 2.13, 95% CI 1.30 to 3.51). All five PrEP users diagnosed with HIV after their STI PS interview reported discontinuing PrEP prior to their HIV diagnosis.

Conclusion: Based on current use in King County, PrEP is highly effective, reducing HIV incidence by 84% among MSM and transgender persons. Our findings highlight PrEP discontinuation as a key challenge limiting the effectiveness of PrEP, and the elevated risk of HIV among young and minority MSM and TGSM diagnosed with STI.

980B TFV-DP IN DBS FOR PREGNANT/POSTPARTUM ADOLESCENT AND YOUNG WOMEN ON PrEP IN AFRICA

Peter L. Anderson,1 Lynda Strain-Chibanda,2 Sharon Huang,3 Sybil Hosek,4 Deborah Kacanek1, Tecler Nematazida5, Frank Taulo,6 Violet Korutaro6, Clemensia Nakabiti7, Masebola Masenya8, Kathryn Lypen9, Nahida Dombrowski2, John H. Stroger Jr. Hospital of Cook County, Chicago, IL, USA, 2Malawi College of Medicine-Johns Hopkins University Research Project, Blantyre, Malawi, 3Baylor College of Medicine Children’s Foundation, Kampala, Uganda, 4Makerere University, Kampala, Uganda, 5Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 6FHI 360, Durham, NC, USA, 7National Institute of Child Health and Human Development, Bethesda, MD, USA, 8DADS, NIADD, Rockville, MD, USA, 9University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Pregnant/postpartum adolescent girls and young women (AGYW) in Africa are one of the populations at highest risk for HIV acquisition; yet, pharmacokinetic (PK) data for pre-exposure prophylaxis (PrEP) remains limited. Intracellular tenofovir-diphosphate (TFV-DP) concentration in red blood cells, measured via dried blood spots (DBS), has been used to monitor cumulative PrEP adherence in many settings.

Methods: The first phase of IMPAACT 2009 evaluated PK characteristics of daily oral PrEP (FTC 200mg/TDF 300mg) among pregnant/postpartum AGYW (16-24 years) in Malawi, South Africa, Uganda, and Zimbabwe. Daily FTC/TDF was administered under direct observation for 12 weeks in two groups: pregnant AGYW starting at 14-24 weeks gestation (pregnancy) or 6-12 weeks after delivery (postpartum). Weekly TFV-DP was measured from DBS using a validated liquid chromatography-tandem mass spectrometry assay. TFV-DP distributions were determined at 12 weeks and groups compared with the Wilcoxon test. Population PK models were fit to estimate half-life and steady state concentrations.

Results: From March to June 2019, we enrolled 20 pregnant (median gestational age: 18 wk) and 20 postpartum (median time after delivery: 7 wk) women at a median age of 20 years (IQR: 19.22). Of 3360 doses, 3348 (99.9%) were directly observed. TFV-DP accumulated, with a half-life of 15.3 days (95% CI: 12.8, 17.8) in pregnancy and 18.0 days (95% CI: 15.3, 20.7) postpartum, with steady state achieved by 8-10 weeks in both groups. Median TFV-DP was 965 fmol/punch (IQR: 691,1166) in pregnancy vs 1406 fmol/punch (IQR: 1035,1859) postpartum (p=0.006). Predicted median TFV-DP was 890 fmol/punch (IQR: 704,1143) in pregnancy vs 1418 fmol/punch (IQR: 1179,2139) postpartum (Figure). Two fetal demises (unrelated to study agent), two newborns <10th percentile birthweight, and one preterm birth were recorded. No HIV transmissions occurred during follow-up.

Conclusion: Under conditions of near perfect adherence, TFV-DP in African AGYW was 31-37% lower in pregnancy than postpartum. With sequential measurements and a novel measure of cumulative drug exposure, these findings extend prior studies showing lower plasma TFV during pregnancy. There are few data correlating HIV protection and TFV-DP concentrations in women; however, our results suggest that strict adherence is needed during pregnancy. They also provide guidance for assessing PrEP adherence using TFV-DP levels in DBS for pregnant/postpartum African women.
982 WAXING AND WANEING HIV RISK: DYNAMICS OF PrEP ELIGIBILITY IN RAKAI, UGANDA
Victor Ssempijja1, Robert Ssekubugye2, Godfrey Kigozi2, Gertrude Nakigozi2, Joseph Kagaayi2, Tom Lutalo1, Anthony Ndyababo2, Anna Mia Ekström1, David Serwadda3, Thomas C. Quinn4, Ronald H. Gray5, Maria Wawer5, Larry W. Chang2, Steven J. Reynolds6
1Leidos Biomedical Research, Inc, Frederick, MD, USA, 2Rakai Health Sciences Program, Kalisizo, Uganda, 3Karolinska Institute, Stockholm, Sweden, 4Johns Hopkins University School of Medicine, Baltimore, MD, USA, 5Uganda National Bonpellier Medical School, Baltimore, MD, USA
Background: PrEP is based on the presence of substantial HIV risk (SHR) behaviors making PrEP eligibility and retention dynamic. We used population-based data to describe longitudinal patterns of SHR of PrEP eligibility and identify factors associated with incidence, persistence and recurrence of PrEP eligibility.
Methods: Between August 2011 – June 2018, 4 surveys including SHR-focused questions were conducted by the Rakai Community Cohort Study among consenting adults aged 15-49 years. SHR was defined by the Uganda national PrEP eligibility as either reporting sexual intercourse with >1 partner of unknown HIV status, non-marital sex without a condom or having transactional sex. Recurrence of SHR was defined as the resumption of SHR after stopping SHR, while persistence of SHR meant SHR on >1 consecutive visit. Poisson and log-binomial regressions with generalized estimating equations and robust variance estimators were used to estimate adjusted incidence rate ratios (aIRRs) and prevalence rate ratios (aPRRs) for PrEP eligibility with 95%CIs.
Results: 25,695 HIV-negative individuals participated in the cohort, including 13,010 participants with SHR assessment data at ≥ 2 visits (24,132 person-intervals). Overtime, prevalence of SHR increased from 20.1% to 25.2% (p<0.001), and incidence of SHR increased from 6.0/100pys to 7.7/100pys (p<0.001). Persistence of SHR was 27.4%. Persistence of SHR at 24, 36 and 48 months was 67.5% (95%CI=66-69), 46.9% (95%CI=45-49) and 26.0% (95%CI=24-28), respectively. SHR was associated with male sex (aPRRs=2.81[95%CI=2.25-3.53]), and 30-34 (aIRR=1.71 [95%CI=1.55-1.87]), 25-29 (aIRR=1.29 [95%CI=1.13-1.47]), and 30-34 (aIRR=1.29[95%CI=1.13-1.47]). Persistence of SHR at 24, 36 and 48 months was 67.5%(95%CI=66-69), 6.0/100pys to 7.7/100pys (p<0.001). Recurrence of SHR was 27.4%.
Conclusion: Persistence of SHR was modest in this population while incidence and recurrence of SHR were high. The overall prevalence of SHR steadily increased. PrEP programs in similar settings should expect short and repeated PrEP eligibility periods with turnover due to incidence and recurrence of SHR.

983 IMPLEMENTATION OF MOBILE PrEP, STI, AND HIV PREVENTION SERVICES IN SOUTH FLORIDA
Mary Tanner1, Weiming Zhu1, Kashif Iqbal1, Kenneth L. Dominguez1, Kirk D. Henn1, Karen W. Hoover1
1CDC, Atlanta, GA, USA
Background: Men of color who have sex with men (MSM) and transgender women (TGW) of color are disproportionately affected by HIV. National testing guidelines state that sexually active MSM should have HIV testing annually, and persons at higher risk of acquisition may consider testing every 3-6 months. Little is known about HIV testing patterns of MSM and TGW of color. The THRIVE demonstration project promotes HIV care and prevention services through health department-led collaborative at 7 sites in the United States. We used THRIVE client data to compare HIV testing patterns for MSM and TGW of color based on PrEP screening results.
Methods: Preliminary THRIVE data from 2016-2019 were used. Inclusion criteria were: 1. HIV-negative MSM or TGW of color, 2. Received ≥2 HIV tests, 3. At least 180 days follow-up time. We calculated median and interquartile ranges (IQR) for: days from first to last test, number of tests, and days between tests. We determined what proportion of persons had testing intervals of 90, 120, 180, and 365 days among persons screened for PrEP and found to have 1. PrEP indications and 2. No PrEP indications. Chi squared tests were used for statistical comparisons.
Results: For the 2490 MSM and TGW of color, 92% had PrEP indications. Overall, the median (IQR) days to last test was 335 (167-503); median number of tests 3 (2-5); and median days between tests 110 (73-183). Overall, cumulative percentages of persons tested were 36%, 55%, 74%, and 93% for intervals of at least 90, 120, 180, and 365 days respectively. For persons with PrEP indications, cumulative percentages were 37%, 58%, 77%, and 95% for the same intervals; cumulative percentages were 36%, 47%, 63%, and 87% for the same intervals for persons without PrEP indications. Proportion tested every 90 days did not differ significantly between groups; for all other testing intervals significantly more persons with PrEP indications were tested (p<0.05).
Conclusion: The majority of MSM and TGW of color with evidence of serial HIV testing are tested at least annually, however, persons without indications for PrEP were significantly less likely to receive annual testing. Similar proportions of MSM and TGW of color with and without PrEP indications were tested every 90 days. Additional investigations are needed to understand the factors influencing HIV testing frequency among MSM and TGW of color.

Table. HIV testing patterns among MSM and TGW of color, by PrEP indications

<table>
<thead>
<tr>
<th>MSM and TGW of color</th>
<th>Persons with ≥2 HIV tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>Median days between tests (IQR)</td>
</tr>
<tr>
<td>PrEP indications</td>
<td>2490 (2175-2797)</td>
</tr>
<tr>
<td>No PrEP indications</td>
<td>1877 (1517-2239)</td>
</tr>
</tbody>
</table>

* Missing intervals are cumulative over the time (column) and do not encompass persons included in the columns before.

984 IMPLEMENTATION OF MOBILE PrEP, STI, AND HIV PREVENTION SERVICES IN SOUTH FLORIDA
Susanne Doblecki-Lewis1, Erin Kobetz1, Stefani A. Butts1, Katherine Kloes1, Angela M. McLaugh1, Brian B. Leon1, Gillanine Narici1, Jessica Moore1, Yue Pan1, Gabriel Cardenas1, John Byrne1, Patrick Whiteside1, Marco Torrealba1, Daniel J. Feaster1, Mario Stevenson1
1University of Miami, Miami, FL, USA, 2Prevention305, Miami, FL, USA
Background: Pre-Exposure Prophylaxis (PrEP) can substantially reduce HIV incidence among those at risk for acquisition. To achieve population-level impact, effective dissemination of PrEP to priority groups in areas with a high incidence of HIV, such as black and Hispanic men who have sex with men (MSM) living in South Florida, is needed. To address multiple social, logistical, and structural barriers to PrEP uptake, we implemented PrEP/HIV and sexually transmitted infections (STI) services combined with cancer screening through the Sylvester Gamechanger vehicle. We describe demographics, utilization, and early retention in PrEP care during the first year of operation.
Methods: The mobile clinic was positioned at 4 sites in Miami with high HIV incidence with input from community stakeholders. Key program personnel were a medical provider, HIV/PrEP counselors, and a pharmacist. In addition to self-referrals, Prevention305 and Latino Salud, community-based organizations, developed focused patient recruitment through social media. All services were provided at no cost. Normative demographics, risk behavior, STIs, and early-maintenance-in-care data, were collected. Descriptive statistics were compiled using SPSS.

![Image](372)
Results: From September 2018 to September 2019 services were provided to 429 clients. Of these, 266/429 (62%) sought PrEP. Of PrEP clients, 223 (83.8%) identified as Hispanic, 19 (7.1%) as non-Hispanic Black, 17 (6.4%) as non-Hispanic White, and 7 (2.6%) as other. 194/265 (73.2%) were foreign-born; 233/266 (87.6%) of PrEP clients identified as MSM (66.2% MSM only, and 21.4% MSMW). Ten (3.8%) PrEP-seeking clients were HIV positive at baseline. Of these, 2 were identified as acute/early infections. Among clients assessed for PrEP, an initial PrEP prescription was filled by 239/251 (95.2%). Of the 175 clients seen within the initial 6 months of operation, 129 (74%) completed a follow-up visit. Overall, 74/307 (24.1%) PrEP clients had positive STI results (gonorrhea, chlamydia, or syphilis) at baseline. STI treatment delivery on the mobile clinic began in August, 2019.

Conclusion: Implementation of HIV-PrEP prevention and STI services using a mobile clinic model is acceptable and effective in engaging Hispanic/Latino immigrant MSM at risk for HIV and STIs. Low-barrier-to-entry services delivered through a mobile clinic inclusive of other prevention services can be an effective method for engagement of priority populations with difficulty accessing traditional clinic settings.

985 PrEP USE APPROACHING 50% AMONG HIGH- RISK MSM IN WESTERN WASHINGTON

Darcy W. Rao1, Julia Hood1, Rachel Wittenauer1, Kelly Naismith1, Jonathon Downs1, Matthew R. Golden1

1University of Washington, Seattle, WA, USA, 2Public Health—Seattle & King County, Seattle, WA, USA, 3Washington State Department of Health, Tumwater, WA, USA

Background: To monitor progress towards a target of 50% uptake among high-risk MSM who have sex with men (MSM) by 2020, we compared estimates from two ongoing surveys of Washington State MSM.

Methods: We analyzed data collected 2017-2019 from the Washington HIV/STI Prevention Project (WHSSP), a statewide online survey, and an annual paper-based survey administered to men attending the Seattle Pride Parade in June of each year. Samples from both surveys were restricted to cisgender males residing in King, Pierce, and Snohomish counties who reported sex with a man in the past 12 months (N=213-291 for Pride surveys and 463-726 for WHSSP).

To adjust for differences in sample composition between the surveys, we used a raking procedure to standardize the samples by age, race/ethnicity, education, sexual orientation, and county. We classified respondents as high risk if they reported any of the following in the past year: bacterial STI diagnosis, use of methamphetamine or poppers, ≥10 male anal sex partners, or condomless anal sex with an HIV-positive or unknown-status partner. For each year, we calculated the proportion of high-risk men who reported sex with men (MSM) by 2020, we compared estimates from two ongoing surveys of Washington State MSM.

Results: Current use of PrEP increased from 33% in 2017 to 43-46% in 2019 (p<0.001).

Conclusion: Awareness of PrEP increased among high-risk MSM in western Washington State from 2017-2019, but did not lead to increases in demand. The proportion of high-risk men using PrEP increased, tracking well with local prevention targets. Although the representativeness of samples from both surveys is unknown, the concordance in estimates supports continued use of these low-cost methods to monitor trends and inform ongoing HIV prevention efforts.
987 NON-DAILY USE OF HIV PREEXPOSURE PROPHYLAXIS IN A LARGE ONLINE SAMPLE IN THE US

Whitney C. Sewell1, Victoria Powell, Douglas Krakower1, Kenneth H. Mayer1, Alleen Ochoa1, Apollo Taylor1
1Harvard University, Cambridge, MA, USA, 2Fenway Health, Boston, MA, USA, 3Beth Israel Deaconess Medical Center, Boston, MA, USA, 4Harvard Pilgrim Health Care Institute, Boston, MA, USA

Background: Event-driven dosing of HIV exposure prophylaxis (PrEP) using a 2-1-1 strategy has been shown to be efficacious in reducing HIV risk for men who have sex with men (MSM). However, data on interest in and use of non-daily PrEP in the US are limited.

Methods: We developed a survey to assess interest in and experiences with PrEP, including non-daily use, among HIV-negative adults in the US. We distributed the survey nationally in May 2019 on geosocial networking sites commonly used by MSM. We used chi-square tests and t-tests to identify factors associated with interest in and use of non-daily PrEP.

Results: Our study sample included 9,697 respondents. Mean age was 43 years, 67% were non-Hispanic white, and 90% were MSM. Nearly all (96%) had heard of PrEP, 40% had ever used PrEP, and 33% had used PrEP in the last 6 months. Interest in non-daily PrEP was high (67%). A greater proportion of those interested in non-daily than daily PrEP were aged <30 years (21% vs 18%, P=0.013), had no graduate degree (76% vs 77%, P<0.001), had annual income <$80,000 (76% vs 73%, P=0.02), and were uninsured (11% vs 9%, P<0.001). Of the 3232 who used PrEP in the past 6 months, only 5% used non-daily dosing. Non-daily dosing strategies included event-driven (49%), regular but not daily use (e.g., on days of the week starting with T or S, 24%), daily but only for short periods (e.g., on vacations; 19%), and other strategies (8%). Of the 85 using event-driven dosing, 65% used the 2-1-1 strategy; the remaining 35% used a variety of strategies, including daily dosing for a week before and after sex, 1 pill before and after sex, or 1 pill around the time of sex. A greater proportion of non-daily than daily users had annual income ≥$80,000 (36% vs 30%, P=0.04) and always planned sex in the past 6 months (21% vs 11%, P<0.001). Common reasons for non-daily use were not consistently engaging in sexual activity (59%), high cost of PrEP (49%), concerns about potential long-term side effects (39%), not engaging in sex perceived as high-risk for HIV (37%), and planning sex in advance (25%).

Conclusion: In this national sample, interest in non-daily PrEP was high, and 5% of recent PrEP users reported non-daily dosing. Given the use of non-daily strategies that have not been evaluated in clinical studies, there is an urgent need for US public health authorities to provide clear guidance for safe and effective non-daily dosing options.

988 EFFECTIVENESS OF PrEP NAVIGATION MODELS IN THE THRIVE DEMONSTRATION PROJECT

Kirk D. Henny1, Weiming Zhu1, Kenneth L. Dominguez2, Kashif Iqbal1, Mary Tanner1, Karen W. Hoover1
1CDC, Atlanta, GA, USA

Background: HIV pre-exposure prophylaxis (PrEP) uptake has been suboptimal among populations with the highest rates of HIV diagnoses, including men who have sex with men (MSM) of color. Effective navigation models for PrEP clinical care can help persons at risk of acquiring HIV to initiate, adhere to, and persist with PrEP. PrEP providers currently lack evidence-based models for PrEP service navigation. The THRIVE demonstration project funded seven state health departments to develop collaboratives comprised of community-based organizations (CBOs) and clinical providers to implement comprehensive HIV prevention and care services for MSM of color. THRIVE used several different PrEP navigation models in the demonstration project.

Methods: We analyzed cohort data of 8,339 MSM of color enrolled in THRIVE from September 2015 through March 2019. Study locations included Alabama, Baltimore, Louisiana, New York City, Philadelphia, Virginia and Washington (DC). We estimated the number of MSM of color who were eligible for and linked to PrEP care. We explored possible navigation models based on the following navigation components common across all seven jurisdictions: navigator education (professional with a college or higher vs. peers from the community with no formal educational requirement) and source of navigation protocol development (health department or clinic/CBO); three navigation models were identified. We conducted multivariable regression analyses (risk ratio, 95% confidence intervals [CI]) to estimate the associations between type of PrEP navigation model and linkage to care.

Results: Among 4,999 MSM of color who were eligible for PrEP, 4,227 (84.6%) were linked to care. Our analyses identified three navigation models. We found that navigation models that combined professional and peer navigators with protocols designed by clinics/CBOs were more than 3 times as likely to link eligible clients to PrEP compared to navigation models that combined peer navigators with protocols designed by health departments (88.8% vs. 21.5%; RR: 3.48, 95% CI=2.61–4.62).

Conclusion: Navigation models that included professional navigators and CBO-developed protocols were more effective for increasing linkage to PrEP healthcare services. Our analyses of interim data from the THRIVE demonstration project provide evidence to guide the development of PrEP navigation models that can be used in U.S. jurisdictions funded by the Ending the HIV Epidemic federal initiative.

989 TURNING INTENT INTO ACTION: ASSESSING PrEP UPTAKE AT A PUBLIC STI CLINIC

Kate Drezner1, B.W. Furness1, Chantil Thomas1, Jason Beverley1, Adam Allston1, Adam Visconti1
1District of Columbia Office of Health Department, Washington, DC, USA, 2CDC, Atlanta, GA, USA

Background: Consistently taking pre-exposure prophylaxis (PrEP) reduces the risk of acquiring HIV by almost 90%. Washington, DC has a high incidence of HIV (360 new cases in 2018) which disproportionately affects people of color (71.1% Black and 9.2% Latinx). The DC Health and Wellness Center began prescribing PrEP in 2016 to start and maintain men who have sex with men (MSM) and transgender women of color on PrEP at low or no cost to them. We assessed differences between patients on PrEP <1 month and those on ≥1 month.

Methods: Demographics and reasons for starting PrEP were collected in REDCap at initiation. Eligible patients received PrEP, scheduled a follow-up visit, and agreed to additional follow-ups every 3 months. REDCap data were merged with medical records to determine time on PrEP. Chart reviews were done to establish duration of therapy. Patients taking PrEP <1 month and ≥1 month were compared using chi-square analysis and multivariable logistic regression to explore the associations between race/ethnicity, age, gender identity, and insurance status.

Results: From August 2016 - December 2018, 530 people were prescribed PrEP; 81.7% were people of color (47.2% Black, 28.5% Latinx, and 6% other); 80.2% were MSM, 10.0% were cisgender women, and 3.6% were transgender women. Of these, 280 (52.8%) were still on PrEP at ≥1 month and 250 (47.2%) were not. Likelihood of being on PrEP ≥1 month increased with age (AOR: 1.02, 95% CI=1.00–1.04). Patients on PrEP ≥1 month were less likely to be transgender women (AOR: 0.089, 95% CI=0.019–0.41) or cisgender women (AOR: 0.21, 95%
DISCOVER: 96-WEEK FOLLOW-UP OF BLACK AND HISPANIC/LATINX STUDY PARTICIPANTS

Edwin DeJesus¹, Jason Halperin², Indira Brar², Eric Daar³, Jeffrey L. Stephens⁴, Yongwu Shao⁵, Lijie Zhong⁵, Ramin Ebrahimi⁵, Staci Bush⁶, Jonathon Anderson⁷, Moupali Das⁷, Scott McCallister⁷, Jeffrey H. Burack⁷, Michelle Iandiorio⁷, Gordon Crofoot⁸, Amy Martin⁹, Richard Haaland⁹, Catlainn Sionean⁹, Johanna Chapin-Bardales¹⁰, for the NHBS Study Group

¹Orlando Immunology Center, Orlando, FL, USA, 2CrescentCare, New Orleans, LA, USA, ³Henry Ford Hospital, Detroit, MI, USA, ⁴Harbor–UCLA Medical Center, Torrance, CA, USA, ⁵Mercer University, Macon, GA, USA, ⁶Gilead Sciences, Inc, Foster City, CA, USA, ⁷East Bay AIDS Center, Oakland, CA, USA, ⁸University of New Mexico, Albuquerque, NM, USA, ⁹Crofoot Research Center, Houston, TX, USA

Background: In the US, Black and Hispanic/Latina (H/Lx) men and transgender women who have sex with men (MSM, TGW) are disproportionately impacted by HIV and underutilize PrEP. Contributing factors include low access to and retention in care. Among 5,387 randomized participants in the DISCOVER study, noninferiority of F/TAF to F/TDF for HIV prevention was shown in MSM and TGW with significant risk of HIV infection.

Methods: Using descriptive statistics, 96 week (W) follow-up data from study participants who confidently self-identified as Black race or H/Lx ethnicity were analyzed for efficacy (HIV incidence, dried blood spot (DBS) adherence) and safety (renal biomarkers, serum lipids, bone mineral density).

Results: Of 5387 participants enrolled from 94 sites in North America and Europe, 474 (9%) identified as Black and 1318 (24%) identified as H/Lx. Fifty participants identified as both Black and H/Lx ethnicity and are included in both sub-populations. Through 96W, among Black or H/Lx participants, 11 individuals acquired HIV, incidence rate: 0.34 (95% CI 0.17 - 0.61). Two had suspected baseline HIV infection and the 9 remaining individuals (n=4 Black, n=5 H/Lx) had low or undetectable drug levels at diagnosis. The percent of Black participants lost to follow-up (LTFU) was 14.6 vs 7.1 among non-Black participants (p<0.001). The percent of Black participants with an adverse event (AE) leading to discontinuation was 2.3% vs 1.5% among non-Black participants (p=0.18). The percent of H/Lx participants LTFU was 8.7% vs 7.4% among non-H/Lx participants (p=0.14). The percent of H/Lx participants with an AE leading to study drug discontinuation was 0.8% vs 1.9% among non-H/Lx participants (p=0.004). While study drug adherence for the overall population was high, nonadherence was increased in Black vs non-Black participants: OR 2.4 (95%CI 1.2 - 4.8). Changes to eGFR, BMD, weight and lipids were similar in Black vs non-Black and H/Lx vs non-H/Lx participants (Table 1).

Conclusion: Through 96W, all Black or H/Lx participants who acquired HIV during follow-up had low or undetectable drug levels at diagnosis. Black vs non-Black participants were more likely to be LTFU and 2.4 times more likely to be nonadherent. The proportion of study drug discontinuations due to AE was lower among H/Lx vs non-H/Lx participants. Overall, both F/TAF and F/TDF were efficacious, safe, and well tolerated in Black and H/Lx participants.

Table: DISCOVER: 96-WEEK FOLLOW-UP OF BLACK AND HISPANIC/LATINX STUDY PARTICIPANTS

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>LTFU (%)</th>
<th>HIV Incidence Rate</th>
<th>F/TAF Adherence</th>
<th>F/TDF Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>14.6</td>
<td>0.34 (0.17 - 0.61)</td>
<td>0.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>H/Lx</td>
<td>7.1</td>
<td>0.34 (0.17 - 0.61)</td>
<td>0.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Non-Black</td>
<td>7.4</td>
<td>0.34 (0.17 - 0.61)</td>
<td>0.8%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

991 FACTORS ASSOCIATED WITH PrEP PERSISTENCE AND ADHERENCE AMONG MSM IN 4 US CITIES

Johanna Chapin-Bardales¹, Amy Martin¹, Richard Haaland¹, Catlainn Sionean¹, Ekow Kwoi Sey¹, Kathleen A. Brady¹, Henry F. Raymond¹, Jenevieve Opara¹, Irene Kuo¹, Gabriela Paz-Bailey¹, Cyprian Wojeńª, for the NHBS Study Group

¹CDC, Atlanta, GA, USA, ²Los Angeles County Department of Public Health, Los Angeles, CA, USA, ³Philadelphia Department of Public Health, Philadelphia, PA, USA, ⁴Rutgers University, Newark, NJ, USA, ⁵District of Columbia Department of Health, Washington, DC, USA, ⁶George Washington University, Washington, DC, USA

Background: Pre-exposure prophylaxis (PrEP) persistence and adherence are critical to achieving national HIV prevention goals. While there is no gold standard for measuring PrEP persistence (continued use) and adherence (effective use), biological testing for tenofovir disoproxil fumarate (TFV-DP) and emtricitabine ( FTC) is considered best practice. We conducted testing for PrEP among HIV-negative men who have sex with men (MSM) in 4 US cities as part of 2017 National HIV Behavioral Surveillance.

Methods: MSM were recruited via venue-based sampling in Los Angeles, Philadelphia, San Francisco, and Washington DC. Eligible, consenting MSM completed a survey, HIV testing, and dried blood spot (DBS) collection. DBS were tested for tenofovir (TFV), FTC, and TFV-DP by liquid chromatography mass spectrometry. Our analysis was limited to HIV-negative MSM who had CDC-based PrEP indications and self-reported PrEP use in the past year. Persistence was defined as self-reporting PrEP use in the past 12 months and having any detectable TFV, FTC, or TFV-DP in DBS collected at the interview. Among those reporting past-month PrEP use, adherence was defined as TFV-DP ≥1250 fmol/punch or TFV-DP ≥700 fmol/punch (consistent with an average of 7 doses/week or 4-7 doses/week, respectively). Poisson regression with generalized estimating equations clustering by recruitment event and adjusting for city was used to assess associations between key characteristics and persistence and adherence. Results: Overall, 81.2% (310/382) were persistently using PrEP based on biological testing. Persistence was significantly lower among MSM who were younger (p<0.03), had lower education (p<0.01), had public insurance (p=0.02), and had fewer male sex partners (p<0.01). Among MSM reporting past-month PrEP use, 66.2% (200/302) were adherent at 7 doses/week and 80.3% (245/302) were adherent at 4-7 doses/week. Adherence was significantly lower among MSM who were younger (p<0.01), had less than high school education (p=0.02, p=0.04), were black race/ethnicity (p=0.04, p=0.03), had fewer male sex partners (p=0.03, p=0.05) and lived in Philadelphia (p<0.01, p=0.01). Conclusion: Approximately 19% of PrEP-using MSM in the 4 cities had not persistently used PrEP. About 34% of MSM were not adherent at 7 doses/week and 20% were not adherent at 4-7 doses/week. Efforts to support PrEP persistence and adherence are needed for MSM and should include strategies tailored to age, education, race/ethnicity, insurance type, and city context.
992 HIV-1 INCIDENCE, PrEP UPTAKE, AND ADHERENCE AMONG KENYAN MSM

Elizabeth Wahome1, Susan M. Graham2, Alexander N. Thiongo’1, Khamisi Elizabeth Wahome2, Elisabeth M. Van Der Elst1, Eduard Sanders1, Mohamed1, Tony H. Oduor1, Evans Gichuru1, John Mwambi1, Maria Prins3, Susan M. Graham2, Alexander N. Thiong’O1, Khamisi Elizabeth Wahome2

Background: Among men who have sex with men (MSM) in sub-Saharan Africa, is not available. We assessed PrEP uptake and adherence, and HIV-1 incidence, in at-risk MSM with access to PrEP in coastal Kenya.

Methods: Since June 2017, at-risk MSM followed at monthly visits were offered daily PrEP with adherence and risk reduction counselling. At each visit, we assessed PrEP adherence, intention to continue, and HIV-1 status using rapid antibody tests. If symptoms of acute HIV-1 (e.g. fever) or risk criteria (e.g. receptive anal sex,) were met, X-pert RNA Qual testing was done. We determined tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS) were collected at months 3 and 9 for TFV-DP testing. Generalized estimating equations (GEE) with robust variance were used to detect associations with (1) TFV-DP detection and (2) protective TFV-DP levels (≥700 fmol/punch, compatible with ≥4 weekly doses).

Results: Of 167 at-risk MSM, 162 (94.9%) were eligible for PrEP, 131 (80.9%) started it, and 57 (43.5%) reported PrEP use at study censoring, for a median follow-up time of 21.2 (interquartile range: 10.2–22.1) months. Nine MSM had tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots 6–12 months after PrEP initiation, and tenofovir (TFV) concentrations and genotypic HIV-1 drug resistance in plasma samples when HIV-1 was detected. HIV-1 incidence was assessed as per reported PrEP use, and population-averaged multivariate Poisson regression with robust standard errors was used to identify predictors of HIV-1 acquisition.

Conclusion: Despite high reported adherence, drug levels were undetectable in most participants, and only 10% had protective levels. These results suggest that PrEP adherence is not aligned with risk among GBMSM in Kenya, and that tailored interventions to address PrEP adherence in this population are urgently needed.
994 PREEXPOSURE PROPHYLAXIS CASCADE AMONG MEN WHO HAVE SEX WITH MEN IN ZIMBABWE

Lauren Parmley1, Tiffany Harris1, Innocent Chimonge1, Munyaradzi Mapingure2, Owen Mugwurungu3, John R. Rogers4, Tsitsi Apollo5, Getrude Ncube6, Brian K. Moyo7, Perpetua Gozhora1, Yingfeng Wu1, Elizabeth Gonese1, Sophia Miller1, Avi Hakim1, Godfrey Musuka1
1CAP at Columbia University, New York, NY, USA, 2Zimbabwe Ministry of Health and Child Care, Harare, Zimbabwe, 3CDC, Harare, Zimbabwe, 4CDC, Atlanta, GA, USA

Background: Pre-exposure prophylaxis (PrEP) for persons at high risk of acquiring HIV, including men who have sex with men (MSM), is increasingly being scaled-up in Zimbabwe, with goals to roll-out PrEP to all public facilities by 2020. We assessed gaps in PrEP awareness, uptake, and use among HIV-negative MSM in two cities of Zimbabwe.

Methods: We used respondent-driven sampling to recruit 1538 MSM to participate in a cross-sectional survey assessing HIV-related outcomes in Harare and Bulawayo, Zimbabwe (March–July 2019). MSM were eligible for the survey if they were born male, engaged in anal or oral sex with a man in the past 12 months, and were aged ≥18 years. Consenting participants completed a questionnaire and received HIV testing. The sample did not reach equilibrium and was treated as a convenience sample. Unweighted univariate analyses were restricted to MSM who self-reported negative/unknown HIV status that was confirmed via HIV testing.

Results: Overall, 75.9% (1167/1538) of all participants tested HIV negative and self-reported HIV-negative/unknown status (Harare, 75.9%; Bulawayo, 75.9%). Awareness of PrEP was 45.8% (534/1167; Harare, 57.8%; Bulawayo, 35.2%; Figure). Of those aware of PrEP, 31.3% (167/534) had ever taken PrEP (Harare, 32.7%; Bulawayo, 29.2%). Most (71.1% [216/307]) reporting never taking PrEP were interested in starting PrEP (Harare, 65.1%; Bulawayo, 79.4%). The top 3 reasons for never starting PrEP included not knowing where to access PrEP (24.8% [91/367]), fearing side effects (20.4% [75/367]), and not feeling at risk for HIV (19.6% [72/367]). Most (74.9% [125/167]) MSM who had ever used PrEP had taken it in the last 6 months (Harare, 73.8%; Bulawayo, 76.6%). Reasons for discontinuing PrEP included side effects (59.5% [25/42]), trust in partner (71.1% [3/42]), inability to access PrEP (4.8% [2/42]), concern about others finding out (2.4% [1/42]), or other reasons (26.2% [11/42]). Most PrEP users in the last 6 months reported taking PrEP daily (70.4% [88/125]).

Conclusion: Our findings highlight gaps in PrEP awareness and use among participants. Less than half of HIV-negative MSM were aware of PrEP, and awareness was lower in Bulawayo than Harare. Despite interest among participants in starting PrEP, uptake was low. To increase awareness and uptake, demand creation messaging could be strengthened by providing information on locations where PrEP is accessible, risk behaviors for HIV and PrEP eligibility, and side effects.

996 SAFETY AND TOLERABILITY OF ONCE-DAILY BIC/FTC/TAF FOR POSTEXPOSURE PROPHYLAXIS

Kenneth H. Mayer1, Johnathon B. Holmes1, Marcy Gelmian1, Jessica C. Kraft2, Kathy Melbourne2, Douglas Krakower3, Matthew J. Mimiga4
1The Fenway Institute, Boston, MA, USA, 2Gilead Sciences, Inc., Foster City, CA, USA, 3Beth Israel Deaconess Medical Center, Boston, MA, USA, 4Brown University, Providence, RI, USA

Background: The use of antiretrovirals for post-exposure prophylaxis (PEP) is well-established, although completion rates with prior regimens have been suboptimal because of pill burden or side effects. The purpose of the current study has been to evaluate the single tablet regimen of bictegravir, emtricitabine, tenofovir alafenamide (BIC/FTC/TAF) for PEP, administered daily for 28 days after a high-risk exposure.

Methods: The analyses focused on a prospectively enrolled clinical cohort recruited through referrals from a busy medical department in a Boston community health center, specialized in HIV care, as well as from a community education campaign.

Results: Of the first 39 enrollees, the median age was 33 years (range 22-71), with 12.8% Black and 5.1% Latinx. Most (76.9%) were cisgender gay or bisexual men. Other participants included 3 heterosexual cisgender men, 1 transgender woman and 2 cisgender women. Most (76.9%) completed college +/- advanced degrees. Behaviors that led to PEP initiation included: receptive anal (49.7%), insertive anal (43.6%), insertive oral (15.4%), and insertive or receptive vaginal sex (7.7% for each). The most commonly reported adverse events were nausea (+/- vomiting) (12.8%), fatigue (10.3%), and diarrhea (10.3%). One participant noted mild gastrointestinal discomfort and another reported flatulence. All but one of the symptoms were grade 1; a grade 2 report of fatigue led to product discontinuation. The only lab abnormalities were elevated transaminases (N=2) and decreased creatinine clearance (N=1). These changes did not lead to product discontinuation, and reverted after regimen completion. Of the 39 fully evaluable participants, 92.3% completed the regimen as prescribed; 2 did
not return for follow-up, and one participant discontinued prematurely. No HIV seroconversions have been detected in the study.

**Conclusion:** The fixed drug combination of bictegravir, emtricitabine, tenofovir alafenamide appears to be safe and well-tolerated when used as PEP, with occasional, mainly mild, gastrointestinal side effects, fatigue, and infrequent laboratory abnormalities. This favorable safety profile, and the high completion rates, suggest that BIC/FTC/TAF is a potential option for PEP.

---

**997 HYPO-OSMOLAR RECTAL DOUCHE DELIVERED TVF DISTIBUTES TFV DIFFERENTLY THAN ORAL PEP**

**Peng Xiao**1, Sanjeev Gumber, Mark A. Marzinke1, Abbiit Date1, Thuy Hoang2, Justin Hanes3, Laura Ensign1, Lin Wang1, Lisa C. Rohan1, Richard Cone1, Edward J. Fuchs1, Craig W. Hendrix3, Francois Villinger1

1University of Louisiana at Lafayette, Lafayette, LA, USA, 2Emory University, Atlanta, GA, USA, 3Johns Hopkins University, Baltimore, MD, USA, 4Magee—Women’s Research Institute, Pittsburgh, PA, USA

**Background:** In spite of the PEP with tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) rolloff, the rate of new HIV infections remains a major hurdle. In the US alone, the rate of new infections has shifted to predominately men having sex with men in rural settings where access to PEP can be an issue, in addition to cost and the need for adherence. As an alternative, we have developed an on demand PrEP approach using TFV-based hypo-osmolar (HOSm) rectal douches that are congruent with sexual behavior. Using stringent intrarectal repeated exposures of macaques to SHIV, this approach has delivered significantly better protective efficacy from virus acquisition compared to oral daily TDF and TDF/FTC PrEP. We therefore attempted to delineate the parameters that may dictate such improved efficacy and tested the safety of repeated TFV douching.

**Methods:** Sodium based HOSm intrarectal douches were compared to oral daily PEP for their ability to promote uptake of TFV into the tissue and circulation.

**Results:** Analysis of HOSm formulation of TFV douche delivery demonstrated the presence of >10,000 fmol/mg TFV-DP at 3 hours 2500 fmol/mg TFV-DP in rectal tissues at 24 h post rectal douching, markedly higher than the ~200 fmol/mg steady state achieved by daily oral PEP. TFV-DP levels in all other tissues analyzed including colonic lymph nodes draining the rectal mucosa were considerably lower, between 10-30 fmol/mg irrespective of anatomical location. Of note, while single oral TDF and HOSm rectal TDF achieved the same peak of plasma TFV, general AUC were higher for the oral delivered TFV. Rapidly repeated HOSm rectal douching (xs) using 30 vs 60 ml did not cause any detectable tissue or systemic toxicity. The single vs repeated HOSm rectal douching achieved similar TFV and TFV-DP levels in colorectal tissues, but any detectable tissue or systemic toxicity. The single vs repeated HOsm rectal douching (x5) using 30 vs 60 ml did not cause any detectable tissue or systemic toxicity. The single vs repeated HOsm rectal douching achieved similar TFV and TFV-DP levels in colorectal tissues, but any detectable tissue or systemic toxicity. The single vs repeated HOsm rectal douching achieved similar TFV and TFV-DP levels in colorectal tissues, but any detectable tissue or systemic toxicity. The single vs repeated HOsm rectal douching achieved similar TFV and TFV-DP levels in colorectal tissues, but any detectable tissue or systemic toxicity. The single vs repeated HOsm rectal douching achieved similar TFV and TFV-DP levels in colorectal tissues, but any detectable tissue or systemic toxicity.

**Conclusion:** Findings from this international survey demonstrate a high prevalence of rectal douching associated with RAI and high likelihood of using a rectal microbicide douche to prevent HIV if one were available, even among those who do not currently douche. Ideally, an HIV-prevention douche should be adaptable to various devices, as enema bottles such as those used for douche administration in current clinical trials are not commonly used in regions outside of the US.

---

**998 THE POTENTIAL FOR A RECTAL MICROBICIDE DOUCHE: FINDINGS FROM AN INTERNATIONAL SURVEY**

**Rebecca Giguere**1, Alex Carballo-Diezegüez2, Cody Lentz1, Curtis Doeleza1, Edward J. Fuchs1, Craig W. Hendrix3

1New York State Psychiatric Institute, New York, NY, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** Many individuals who engage in receptive anal intercourse (RAI) regularly use cleansing rectal douches beforehand, an HIV-prevention douche could have high acceptability. Administration of tenofovir via a rectal douche results in faster and higher drug concentration in the rectal mucosa than oral administration. We aimed to describe behavioral aspects of rectal douching before RAI in different international settings to inform development of a behaviorally congruent tenofovir douche.

**Methods:** Using the social media app Grindr, we recruited individuals aged 18 or above, born male, who had engaged in RAI in the past three months. They completed an online survey about their rectal douching practices. The survey was available in English, Spanish, and French. Participants were recruited from:

1) the United States and its territories; 2) Latin America; 3) Africa. Data were analyzed using descriptive statistics.

**Results:** In total, 5,127 participants from 52 countries responded; 87% from the US, 10% from Latin America, and 3% from Africa. Among those who reported RAI, 80% in the US, 63% in Latin America, and 73% in Africa reported douching beforehand. Proportions who reported douching after RAI included 27% in the US, 37% in Latin America, and 59% in Africa. Most (90%) douches for cleanliness, though one-quarter of respondents in Latin America and Africa believe it might prevent infections. While half of US respondents used an enema bottle, reported use of this device was less common in other regions, with infrequent use in Africa (14%). Instead, a hose attached to a faucet was most popular in Latin America (51%) and Africa (45%), while a rubber bulb was used across all regions (39%). Tap water was the liquid preferred by 89% of respondents in all regions. Among those who did not douche, most had never thought about it (58%) or did not feel the need (28%). Finally, 98% of those who douch and 96% of those who did not reported likelihood of using a rectal douche to prevent HIV transmission.

**Conclusion:** Findings from this international survey demonstrate a high prevalence of rectal douching associated with RAI and high likelihood of using a rectal microbicide douche to prevent HIV if one were available, even among those who do not currently douche. Ideally, an HIV-prevention douche should be adaptable to various devices, as enema bottles such as those used for douche administration in current clinical trials are not commonly used in regions outside of the US.
BIODEGRADABLE IMPLANT FOR DELIVERY OF ANTIRETROVIRAL (ARV) AND HORMONAL CONTRACEPTIVE

Lining A. Li, Sai Archana Krovi, Chasity Norton, Ellen Luecke, Zach Demkovich, Pafio Johnson, Christine Areson, Guadalupe Jimenez, Ariane Van Des Straaten, Leah M. Johnson

Background: Women worldwide confront two frequently concurrent reproductive health challenges: the need for contraception and protection from sexually transmitted infections, including HIV. Multipurpose prevention technologies (MPTs) that simultaneously prevent unintended pregnancy and HIV could address these challenges with one product. Here, we are developing a long-acting (LA) subcutaneously administered and biodegradable implant system that provides sustained delivery of hormone and antiretroviral (ARV) with zero-order release kinetics.

Methods: Polycaprolactone (PCL) tubes were extruded and filled with various formulations and enclosed by heat sealing. In-vitro release from devices (in PBS, pH 7.4 at 37°C) was monitored over 7 months using UV-vis spectroscopy or HPLC. Devices were transferred to fresh buffer three times per week to maintain sink conditions.

Results: We selected two well-characterized progestins, levonorgestrel (LNG) and etonogestrel (ENG), as well as one ARV, tenofovir alafenamide (TAF), for MPT indication. We formulated these active pharmaceutical ingredients (APIs) with a single trocar or as a single segmented implant that houses different drug formulations in each compartment.

Conclusion: We developed a LA MPT implant system for sustained delivery of TAF, LNG and ENG with zero-order kinetics that maintains in-vitro stability of the APIs. We are currently evaluating this implant system in preclinical animal studies to correlate in-vitro and in-vivo results. This MPT platform offers the potential to address the unmet need for dual protection against unintended pregnancy and HIV infection in resource-limited areas.
1003 PRÉP SÉROCONVERSION-SEGMENTAL HAIR ANALYSIS FOR UNRAVELING TIMING OF VIRAL RESISTANCE

Brentton T. Lowery1, Hideaki Okochi2, Karen Kunczce3, Niki Phung4, Cheryl McDonald5, Matthew A. Spinelli6, Anthony Mills7, Patricia A. Defechereux8, Kathryn Jee9, Peter L. Anderson10, Robert M. Grant11, Monica Gandhi12

1Southern California Men’s Medical Group, Los Angeles, CA, USA, 2University of California, San Francisco, San Francisco, CA, USA, 3Tarrant County Infectious Disease Associates, Fort Worth, TX, USA, 4University of Colorado, Aurora, CO, USA

Background: Failure on PrEP with emtricitabine/tenofovir (FTC/TDF) disoproxil fumarate (TDF) can occur from poor adherence or acquisition of resistant virus. Here, we describe a case of seroconversion on PrEP with resistant virus but 100% self-reported adherence, with objective adherence metrics providing clues to the timing of viral resistance.

Methods: History was obtained from patient and records. PrEP adherence was assessed via self-report, TDF diphosphate (TFV-DP) levels in dried blood spots (DBS) collected at seroconversion, and measuring TFV/FTC levels with segmental hair analysis. Genotypic resistance was evaluated.

Results: A 44-year-old Latino MSM started daily FTC/TDF on 12/15/17 after a non-reactive HIV antibody (Ab) and confirmatory test on 12/14/17. He reported 100% adherence to FTC/TDF since PrEP initiation with zero missed doses. HIV antigen (Ag)/Ab test was negative x 4 in 2018, 1/15/19, 4/19/19, but indeterminate on 6/10/19. HIV RNA level was 146,000copies/ml on 6/17/2019 and 2-drug PrEP was switched to 3-drug ART (bic/TAF/FTC) that day. Viral genotyping 6/17/19 showed an M184V and a TAM (K70N) mutation in the reverse transcriptase (RT) gene, with no TDF-associated mutations or significant mutations in the protease or integrase genes. DBS collected on 6/17/19 showed a TFV-DP level of 1683 fmol/punch, consistent with high (7 doses/wk) adherence over the past ~6 weeks. A hair sample (~4 cm) was collected that day and, to evaluate adherence over preceding months, segmental analysis of TFV/FTC levels was performed in 1 cm segments from the scalp. Hair drug levels were consistent with high PrEP adherence over the preceding 2 months, but lower PrEP adherence (<4 doses/wk) from ~mid-Feb to ~mid April 2019 when he reported 4 new partners (Figure).

Conclusion: Seroconversion on PrEP can result from poor adherence or the acquisition of drug-resistant virus. However, since continuing two-drug PrEP in the face of HIV infection can lead to the emergence of new RT mutations, determining whether resistance was acquired or emerged requires timed objective adherence metrics. This patient had good adherence 6 weeks prior to seroconversion per DBS and proximal hair data, but segmental hair analysis revealed inadequate adherence 3 months prior to seroconversion, making subsequent development of M184V from consistent FTC/TDF use with active HIV infection epidemiologically most likely. Objective adherence metrics that look back over time can help unravel the etiology of PrEP failures.

1004 RENAL IMPAIRMENT IN A PREEXPOSURE PROPHYLAXIS IMPLEMENTATION COHORT IN AUSTRALIA

Hamish McManus1, Douglas Drak2, Jack E. Heron2, Tobias Vickers2, Stefanie Vaccher2, Iryna Zablotska3, Rebecca J. Guy1, Benjamin Bavinton1, Fengyi Jin1, Andrew E. Grulich1, Mark Bloch4, Catherine C. O’Connor2, David Gracey2, for the EPIC Study

1University of New South Wales, Sydney, NSW, Australia, 2University of Sydney, Camperdown, NSW, Australia, 3University of New South Wales, Sydney, NSW, Australia, 4Holdsworth House Medical Practice, Sydney, NSW, Australia

Background: Co-formulated tenofovir disoproxil fumarate/emtricitabine is prescribed as pre-exposure prophylaxis (PrEP) to prevent HIV infection. Prior studies have found low incidence of new renal impairment in people taking PrEP but have been restricted to clinical trial settings. We sought to quantify rates of renal impairment in a large prospective cohort of participants taking PrEP as part of a population-level implementation study in Australia.

Methods: Participants enrolled in the EPIC-NSW study with baseline eGFR≥60 ml/min/1.73m2, more than one PrEP dispensing visit between 1 March 2016 and 30 April 2018, and no recorded history of prior PrEP were included. Patients without eGFR monitoring during this period were excluded. Risk of renal impairment (defined as average eGFR of two consecutive tests <60) was estimated using the Kaplan-Meier method. Cox proportional hazards models stratified by study site were used to compare risk factors including baseline eGFR (60-90, >90), age (<40, 40-49, ≥50), sex, recreational drug use, and HBV and HCV infection status. Time-updated PrEP medication possession ratio (MPR) was included as a binary independent covariate (<0.95, ≥0.95). Significant covariates (p<0.05) were included in a multivariable model.

Results: Of 9,596 participants dispensed PrEP, 4,514 met the inclusion criteria for this analysis. Most were aged ≥50 (88%), male (99%), and had baseline eGFR ≥90 (76%). Baseline eGFR<90 was observed in 55% of participants aged ≥50 compared to 20% aged <50 (p<0.001). The observed rate of renal impairment was 8.0/1,000 person-years (95%CI: 5.86-10.99) over 4,853 person-years follow-up, with two-year cumulative risk of 1.7% (95%CI: 1.11-2.70) (Figure 1). Renal impairment was highest in patients aged ≥50 at 44.7/1,000 person-years (95%CI: 30.65-65.16) and two-year cumulative risk of 8.3% (95%CI: 5.35-12.69). The rate of renal impairment was also increased in participants with baseline eGFR<90 (32.0/1,000 person-years (95%CI: 23.20-44.20) and with MPR<0.95 (11.2/1,000 person-years, (95%CI: 7.95-15.72)). A multivariable model showed increased risk associated with age ≥50 compared to <40 (HR: 12.9 [95%CI: 4.31-38.58], p<0.001) and baseline eGFR<90 (<HR: 23.5 [95%CI: 5.99-109.18], p<0.001) after adjustment for MPR (HR: 2.3 [95%CI: 0.96-5.68], p=0.060).

Conclusion: In a large real-world PrEP cohort, risk of renal impairment increased over two years of PrEP, with older patients and those with pre-existing renal dysfunction at significantly higher risk.

1005 DEVELOPMENT OF A PrEP EQUITY INDEX TO SET LOCAL TARGETS FOR PrEP COVERAGE

Julie Myers1, Sarah L. Braunstein2, Zoe R. Edelman3, Alexis Rivera1, Nijideka Motanya1, Oni J. Blackstock1

1New York City Department of Health and Mental Hygiene, Long Island City, NY, USA

Background: Scaling up PrEP is a priority in ending the HIV epidemic plans, yet progress remains inequitable. Indicators are needed to drive PrEP programming, guide resource allocation, and quantify inequities. We developed a PrEP equity index (PEI) to support local target development for PrEP coverage among MSM, focusing on racial equity.

Methods: To calculate the PEI, we first estimated PrEP coverage using a PrEP-to-need ratio, where the numerator was prevalence of PrEP use in the past 6-months (derived either from the Sexual Health Survey (SHS) among NYC MSM aged 18-40, 2018, or the National HIV Behavioral Surveillance (NHBS) study among NYC MSM, 2017) and the denominator was epidemiologic need (derived either from HIV diagnosis rate per 100,000 for men ages 13-59 from NYC HIV surveillance data and US Census data, or the number of new diagnoses among...
Implementation of On-Demand PrEP in a Large Integrated Health Care System

J. Carlo Hojilla, Julia L. Marcus, Rachel Herbers, Charles B. Hare, Leo Hurley, Michael J. Silverberg, Derek Satre, Jonathan E. Volk
Kaiser Permanente Division of Research and University of California, San Francisco, CA, Oakland, CA, USA, Harvard Pilgrim Health Care Institute, Boston, MA, USA, Kaiser Permanente San Francisco Medical Center, San Francisco, CA, USA

Background: Data describing real-world implementation of on-demand (2-1-1) HIV pre-exposure prophylaxis (PrEP) are limited. In this study, we report on the experiences of early 2-1-1 adopters in Kaiser Permanente San Francisco (KPSF).

Methods: KPSF started offering 2-1-1 PrEP in February 2019. We abstracted data from the electronic health record, including demographics, reasons for selecting 2-1-1, and self-reported challenges, adherence, and persistence. These were collected by clinicians at baseline and at follow-up visits using standardized notes. We examined data descriptively and, for those with available data, we used pharmacy fill data to assess recent PrEP use and adherence.

Results: Of the 3,281,965 members, recent PrEP use ranged from 0.02% to 40.4%, and ever PrEP use from 0.02% to 51.4%, among those with low and very high risk scores, respectively (Table). Of the 8,840 with very high risk scores, mean age was 38 years, 97.7% were male, 19.1% were Black, and 18.6% were Hispanic. Recent PrEP use among those with very high risk scores was higher among males than females (41.2% vs. 7.3%), higher among those aged 30-49 than 18-29 (44.8% vs. 33.8%), higher among those in the highest quintile of neighborhood-level socioeconomic status compared with the lowest (45.3% vs. 32.9%), and higher among Asian (50.8%), White (47.9%), and Hispanic members (42.4%) than Black members (14.1%; P<0.001 for all comparisons). Demographic differences were similar for ever PrEP use.

Conclusion: HIV risk prediction models can be used to monitor progress toward PrEP scale-up and equity goals in healthcare settings. Of those identified by our model as being at very high risk of HIV acquisition, nearly 60% had not recently used PrEP and there were substantial disparities in use. Efforts are needed to increase PrEP uptake in insured populations, particularly among females, younger age groups, those with lower socioeconomic status, and Black individuals.

Table: Recent and ever PrEP use by HIV risk score, Kaiser Permanente Northern California

<table>
<thead>
<tr>
<th>HIV risk score</th>
<th>Recent*</th>
<th>Ever*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>3,218,566</td>
<td>11,733 (0.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2,827,737</td>
<td>513 (0.01)</td>
</tr>
<tr>
<td>High</td>
<td>402,923</td>
<td>1,066 (0.3)</td>
</tr>
<tr>
<td>Very high</td>
<td>42,820</td>
<td>1,564 (3.7)</td>
</tr>
</tbody>
</table>

*Recent PrEP use was defined as any PrEP fill during January 1, 2019–June 30, 2019. Ever PrEP use was defined as any PrEP fill during our entire follow-up period.


Tim W. Menza, Jeff Capizzi, Lea Bush
Oregon Health Authority, Portland, OR, USA
Background: PrEP is an important HIV prevention modality. Population-based metrics of PrEP uptake and access are critical to the evaluation of public health efforts to increase PrEP use.

Methods: Using the Oregon All Payers All Claims administrative dataset, we determined the number of unique individuals at least 16 years of age starting PrEP, defined as at least one prescription of >30 days of Truvada, each year from 2012-2016. People with HIV or hepatitis B were excluded. We created two metrics of PrEP access in 2016: the number of individuals starting PrEP per 100K population and the number of individuals with a PrEP prescription in each of the four quarters of 2016 per 100K population (i.e., prevalent users). Using public health surveillance data, we created three metrics of PrEP need in 2016: the number of HIV diagnoses per 100K population; the number early syphilis and gonorrhea diagnoses per 100K population; and the number of acute or chronic hepatitis C diagnoses among patients aged 16-30 years per 100K population. We calculated six metrics of PrEP access-to-need by dividing each of the access measures by the need measures.

Results: The number of individuals with a new PrEP prescription increased from 8 in 2012 to 571 in 2016. Most new PrEP users were men, aged 25-34 years, identified as white, lived in an urban area, had commercial insurance, and had an internal medicine PrEP prescriber. In 2016, there were 17.2 PrEP starts and 9.9 individuals with a PrEP prescription in all four quarters of 2016 per 100K population. There were 6.7 HIV cases, 136.0 early syphilis and gonorrhea cases, and 109.1 acute and chronic hepatitis C cases per 100K population. Per HIV diagnosis, there were 2.6 PrEP starts and 1.5 prevalent users. However, there were 0.13 PrEP starts and 0.07 prevalent users per early syphilis and gonorrhea diagnosis and 0.16 PrEP starts and 0.09 prevalent users per hepatitis C diagnosis. Women, people aged 16-24, people of color, and people in rural areas experienced lower PrEP access-to-need.

Conclusion: Access metrics based on prevalent users (a measure of longer-term adherence to PrEP), STI diagnoses (a measure of HIV acquisition risk), and HCV diagnoses among those less than 30 years of age (a measure of need among people who inject drugs) may provide a more complete assessment of PrEP access-to-need than those based on PrEP starts and HIV diagnoses.

Background: With the goal of ending the HIV epidemic in the United States, access to HIV Pre-exposure Prophylaxis (PrEP) is essential to curb new HIV infections. There has been differential regional uptake of PrEP with the South experiencing the highest rates. PrEP is an important HIV prevention modality. Population-based metrics of PrEP uptake and access are critical to the evaluation of public health efforts to increase PrEP use. The design was a cross-sectional study of all individual Qualified Health Plans (QHPs) offered in the 2019 Affordable Care Act Marketplace. QHP PA requirement for combined tenofovir disoproxil fumarate and emtricitabine (PrEP) was our primary outcome. Log binomial regression was used to estimate the association between region and PA requirement, and assess whether other plan characteristics (national issuer, high deductible, PrEP cost sharing structure, PrEP specialty drug tier status, plan level, rating area urbanity, and rating area competition) may explain regional disparities in PA.

Results: 16,833 QHPs were analyzed (18% Northeast, 20% West, 25% Midwest, and 37% South). Overall, 19% of plans required PA for PrEP. Compared to plans in the Northeast, a plan in the South was 53.9% less likely to require PA (RR 0.47, 95% CI, 0.45-0.48) as well as 13.8% less likely to require PAs (RR 0.86, 95% CI, 0.83-0.89). Multivariable analyses found the association between region and PA requirement, and assess whether other plan characteristics (national issuer, high deductible, PrEP cost sharing structure, PrEP specialty drug tier status, plan level, rating area urbanity, and rating area competition) may explain regional disparities in PA.

Conclusion: QHPs in the South are 16 times as likely to require PrEP PA. PA reduces the chance of obtaining a prescribed medication. High PA rates are a possible barrier to PrEP access in the South, which is the region with the most new HIV diagnoses. Due to PrEP’s USPSTF Grade A rating, QHPs must start offering PrEP without cost-sharing starting in 2021. However, there is no regulation on QHP’s use of PA for PrEP. We have the tools to end the HIV epidemic, and we will need robust health policies to end the HIV epidemic.
Pre-exposure prophylaxis (PrEP) with daily tenofovir disoproxil fumarate/emtricitabine is an effective HIV prevention tool. While the cost of PrEP is high, information about how the costs are distributed across payers is limited. We estimated average third-party payer and out-of-pocket (OOP) costs of PrEP by third-party payer type using a national pharmacy database.

**Methods:** Using a previously validated algorithm to distinguish TDF/FTC prescription as PrEP prescriptions in the IQVIA Longitudinal Prescriptions database, we compiled nationwide PrEP prescriptions from the year 2017. We further excluded prescriptions paid for by AIDS Drug Assistance Programs since these prescriptions were for HIV-positive patients. We classified third-party payers as commercial, Medicaid, Medicare, Gilead’s Medication Assistance Program (MAP), or other. We compared the mean cost for 30 pills and total number of pills prescribed for each third-party payer by state.

**Results:** In 2017, 280.0 million pills of TDF/FTC for PrEP were prescribed to 146,064 patients in the United States. The total annual cost of PrEP was $1.59 billion of which $1.51 billion (94.8%) were paid by third party payers and $83 million (5.2%) were OOP costs paid by patients. Among the $1.51 billion paid by third party payers, $1.21 billion (80.2%) were paid by commercial insurance, $0.15 billion (9.9%) by Medicaid, $35 million (2.3%) by Medicare, and $68 million (4.5%) by Gilead’s MAP. Mean third-party payer costs were $1,622 for 30 pills for commercial insurance, $1,653 for Medicare, and $1,596 for Medicaid (p<0.001). The mean cost for Medicaid per 30 pills varied by state (range $1,411 to $1,795 for 30 pills, p<0.001 for mean state costs being equal) (Table 1). Mean OOP costs were $101 for 30 pills for commercial insurance compared to $72 for Medicare and $4 for Medicaid (p<0.001).

**Conclusion:** Commercial insurers cover most PrEP prescriptions costs. The mean cost to Medicare for 30 pills varied by state. OOP costs were lower for public insurance programs compared to commercial insurance. The pharmacy database could not account for 340B, Medicare, or Medicaid rebates and may overestimate the overall cost of TDF/FTC for PrEP to the healthcare system.

**Table 1. Quantities of Medicinal cost for PrEP by state, United States 2017**

<table>
<thead>
<tr>
<th>Quarter</th>
<th>States*</th>
<th>Mean Payment Range per 30 Pills</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CA, GA, IA, MA, MD, NV, SC, UT, VA, VT</td>
<td>$1,011 - $1,557</td>
</tr>
<tr>
<td>2</td>
<td>CO, DC, FL, GA, HI, IL, IN, MI, NY, OH, OR, PA, TX, WA, WY</td>
<td>$1,335 - $1,719</td>
</tr>
<tr>
<td>3</td>
<td>AL, AR, CA, FL, HI, ID, MD, MT, NC, NE, NH, NJ, NY, PA</td>
<td>$2,594 - $6,622</td>
</tr>
<tr>
<td>4</td>
<td>AZ, CT, DE, HI, ID, KS, KY, LA, NH, RI</td>
<td>$1,623 - $2,667</td>
</tr>
<tr>
<td>5</td>
<td>IL, IN, MI, MN, MS, MO, NC, TN, TX, VA, WI</td>
<td>$1,673 - $2,755</td>
</tr>
</tbody>
</table>

*p*PrEP prescriptions paid by Medicaid were not included in the database for South Dakota or Wisconsin.

**1013 SOCIAL MEDIA INFLUENCERS ENHANCE RECRUITMENT OF YOUNG THAI MSM INTO PrEP INTERVENTION**

**Chris Beyrer**1, Brian Weir2, Andrea L. Wirtz1, Hsu Hnin Mon1, Midnight Poonsakewattana1, Patrick S. Sullivan1, Stefan Baral1, Chen Dun2, for the COPE4YMMS Study Team

1 Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2 Asia Pacific Community of MSM Organizations, Bangkok, Thailand, 3 Emory University, Atlanta, GA, USA

**Background:** Engagement of HIV at-risk young persons who might benefit from PrEP is an urgent prevention priority. Young male sex workers (MSW) aged 18-26 in Bangkok, and Pattaya, Thailand, are at very high risk for HIV acquisition and have had low rates of PrEP use. COPE is an NIH-funded Thai-US collaborative effectiveness and cost effectiveness intervention for young Thai MSM recruited through venue, street, and community outreach; HIV VCT referral; and a web-based portal.

**Methods:** Eligible Thai MSW selected a prevention package with or without daily oral Truvada for PrEP and could stop or start PrEP at any time. SMS messaging was used to support adherence and collect weekly PrEP use data. Enrollment in the first 12 mos averaged 17/month—too slow to meet study aims. Of these recruits, 23.0% reported learning of the project through social media. We then implemented a social media influencers (SMI) campaign with a community partner, APCOM. Short, (< 1 minute) scenario-based videos were developed with MSW-specific content and were promoted by hired SMI with combined reach to over 5 million Thai LGBTQ followers. We also expanded recruitment sites to 3 community partner locations convenient for MSW. We
used a Poisson interrupted time-series analysis (ITSA) to estimate the impact of SMI on monthly recruitment, including coefficients to capture change in intercept and change in slope. We excluded the last 2 months of recruitment due to high enrollment prior to cessation

**Results:** SMI intervention was implemented in September 2018, with serial boosts across multiple social media platforms through August 2019 and led to 17,393 website views. The impact SMI on study recruitment and initiation of PrEp was immediate and sustained. From campaign launch to close of enrollment in August, 2019, we enrolled 63.3 men/month, for a total N = 900. Among later recruits, 36.4% reported learning of the study through social media. The majority of MSW, 75%, chose a package with Truvada for PrEP.

**Conclusion:** Social media is a key platform for health messaging and outreach. SMI further extend this reach by serving as credible advocates with high relatability and followings within target communities. The success of the COPE campaign confirms the use of SMI to increase engagement and enrollment for at-risk individuals marginalized from traditional health structures.

**Figure:** Cumulative study enrollment of young MSW in Bangkok and Pattaya, Thailand: The COPE4YMSM project.

**1014 PrEP NONADHERENCE, WHITE COAT DOSING, AND HIV RISK AMONG A HIGH-RISK COHORT OF MSM**

Cherie S. Blair1, Matthew R. Beymer1, Ryan M. Kofron1, Robert Bolan1, Willbert C. Jordan3, James F. Rooney4, Amy R. Wohl5, Raphael J. Landovitz1

1University of California Los Angeles, Los Angeles, CA, USA, 2Los Angeles LGBT Center, Los Angeles, CA, USA, 3Charles R. Drew University of Medicine and Science, Los Angeles, CA, USA, 4Gilead Sciences, Inc, Foster City, CA, USA, 5Los Angeles County Department of Public Health, Los Angeles, CA, USA

**Background:** Therapeutic drug monitoring is critical to interpretation of PrEp trials as a biomarker of adherence and correlate of protection. Perceived expectations from providers or study staff may lead individuals to participate in “white coat dosing” (WCD), or increased adherence to study products just prior to a study visit. As little is known about WCD, this analysis seeks to explore factors associated with this practice.

**Methods:** This is a secondary analysis of PATH-PrEP, an open label study evaluating TDF/FTC PrEp for MSM at high risk for HIV acquisition at two sites in Los Angeles, California. Study participants received daily oral TDF/FTC for 48 weeks. Adherence was assessed using TFV-DP and FTC-TCP in dried blood spots (DBS) and TFV in plasma. TFV concentrations were measured at weeks 4, 12, 24, 36, and 48. WCD was defined as TFV-DP < 350fmol/punch on DBS and either or both FTC-TCP > 0.3pgm/punch or plasma TFV > 40ng/mL at the same time point. Optimal and sub-constitutional levels were defined as TFV-DP > 700fmol/punch and < 700fmol/punch on DBS, respectively. CASI assessed sexual behaviors and STI screening occurred at each visit. Generalized structural equation modeling with multinomial logit compared optimal with 1) sub-optimal and 2) WCD at study visits, adjusting for demographics, incident syphilis, and risk behaviors in last 30 days: condomless anal intercourse with multiple partners, exchange sex, and discussing HIV serostatus before intercourse.

**Results:** Between April 2014 and July 2016, 300 MSM were enrolled. 281 MSM had optimal drug levels at 1,118 (89.2%) visits, sub-optimal at 122 (9.2%) and WCD at 14 (1.1%). Compared to visits with optimal levels, incident syphilis was associated with WCD. Individuals with sub-optimal and WCD had lower odds of discussing HIV serostatus before intercourse, compared to optimal levels (Table).

**Conclusion:** Individuals who participate in WCD demonstrate behavioral and STI-associated risk for HIV acquisition. Sub-optimal chronic use of PrEp with WCD in the setting of ongoing condomless sex is a precarious clinical scenario in which HIV protection may be limited, and post-infection WCD carries high rates of selection for resistant viral variants, particularly M184V/I.

**Table:** Adjusted odds ratios of factors associated with sub-optimal drug levels and white coat dosing among a cohort of men who have sex with men using PrEP

<table>
<thead>
<tr>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.93 (0.89-0.98)</td>
<td>0.05</td>
<td>0.86 (0.81-0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Hispanic</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>0.83 (0.73-0.95)</td>
<td>0.002</td>
<td>0.75 (0.62-0.90)</td>
</tr>
<tr>
<td>Latino</td>
<td>0.72 (0.59-0.87)</td>
<td>0.00</td>
<td>0.68 (0.59-0.81)</td>
</tr>
<tr>
<td>Other</td>
<td>0.72 (0.53-0.97)</td>
<td>0.05</td>
<td>0.62 (0.40-0.95)</td>
</tr>
<tr>
<td><strong>IMC</strong> with multiple partners</td>
<td>No</td>
<td>Ref</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>0.72 (0.54-0.98)</td>
<td>0.07</td>
<td>0.70 (0.53-0.90)</td>
</tr>
<tr>
<td><strong>Exchange sex</strong></td>
<td>No</td>
<td>Ref</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>2.40 (1.17-4.56)</td>
<td>0.12</td>
<td>2.16 (1.17-4.29)</td>
</tr>
<tr>
<td><strong>Incident syphilis</strong></td>
<td>No</td>
<td>Ref</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>1.00 (0.32-3.47)</td>
<td>1.00</td>
<td>0.51 (0.18-1.58)</td>
</tr>
<tr>
<td><strong>Dendritic HIV serostatus</strong></td>
<td>No</td>
<td>Ref</td>
<td>No</td>
</tr>
<tr>
<td>Always</td>
<td>2.43 (1.04-5.76)</td>
<td>0.04</td>
<td>0.85 (1.02-1.80)</td>
</tr>
</tbody>
</table>

**Keywords:** pre-exposure prophylaxis, white coat dosing, PrEP adherence, MSM

**1015 IMPACT OF THE “CHARISMA” INTERVENTION PILOT ON PARTNER DISCLOSURE, IPV, AND ADHERENCE**

Elizabeth Montgomery1, Sarah T. Roberts1, Krishnaveni Reddy2, Betsy Tolley3, Miniam Hartmann1, Ellen Wilson4, Florence Mathebula5, Danielle Wagner5, Seth Zissette6, Michele Lanham7, Rose Wilker8, Jared Baeten9, Thesla Panalene-Phillips2

1RTI International, San Francisco, CA, USA, 2Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 3HHI 360, Durham, NC, USA, 4RTI International, Research Triangle Park, NC, USA, 5University of Washington, Seattle, WA, USA

**Background:** Biomedical, female-initiated HIV prevention methods can help address disproportionately high HIV rates among women in sub-Saharan Africa, but male partner resistance and intimate partner violence (IPV) may decrease effective use.

**Methods:** To promote consistent use of the dapivirine vaginal ring, we pilot tested the CHARISMA relationship counseling intervention with women enrolled at the Wits RHI (WRHI) site (Johannesburg) of the multisite open-label MTN-025/HOPE trial. Lay counselors used a 42-item tool with 5 subscales to tailor counseling at enrolment, followed by a booster at Month 1 and follow-up (FU) checks at Months 3 and 6. Through not fully-powered, we evaluated potential impact by comparing indicators of ring disclosure to partners, partner clinic attendance, and biomarkers of ring adherence at WRHI vs. 3 comparator sites using multivariable regression models. Comparator clinical sites were purposively selected as those most similar to WRHI for baseline characteristics identified a priori.

**Results:** At WRHI, 95% (95% CI of HOPE participants enrolled into CHARISMA. Mean age was 30, 36.8% lived with a partner, and 85.3% received his financial support. During FU, CHARISMA participants reported: partner disclosure at 72.7% visits; 43% partners attending the research clinic; 1 participant-related SH; and 9.5% experiencing IPV. The mean level of dapivirine released was 3.4mg (SD 1.56), suggesting moderate adherence. In adjusted regression models (Table 1), partner clinic attendance was lower at all comparator sites; and significantly so at Site A (aRR 0.20, 95% CI 0.00-0.98). Site B women were more likely to report partner disclosure at FU visits (aRR 1.12, 95% CI 1.00-1.25). The risk of IPV report during FU was significantly lower at Site A (aRR 0.20, 95% CI 0.04-0.98).

**Conclusion:** CHARISMA participants had high IPV but were nevertheless able to adhere to ring use, and more CHARISMA male partners came to the research clinic vs. comparators. CHARISMA taught women skills to decide on levels of disclosure, address disproportionately high HIV rates among women in sub-Saharan Africa, but male partner resistance and intimate partner violence (IPV) may decrease effective use.

**Keywords:** pre-exposure prophylaxis, white coat dosing, PrEP adherence, MSM
1016 REDUCED RELIANCE ON SEX WORK FOR YOUNG WOMEN IN TANZANIA
Jenny Tiberio1, Susie Welty2, Joel Ndayongeje1, Christen Said1, Ritha Mboneko1, Tania Reza1, Willi McFarland1
1University of California San Francisco, San Francisco, CA, USA
Background: In sub-Saharan Africa, adolescent girls and young women (AGYW) account for 25% of new HIV infections, and age, and economic disparities are drivers of HIV infection. To address these factors, the PEPFAR-funded “DREAMS” program employs a holistic approach to reduce HIV incidence among AGYW, including an economic-strengthening group intervention of starting a business. We evaluated the effect of these interventions on HIV risk and vulnerability of AGYW in Tanzania.

Methods: We recruited a prospective cohort of AGYW from DREAMS communities and measured changes in economic situation and vulnerability to HIV. DREAMS interventions targeted seven districts that included urban, semi-urban, and rural communities identified as uniquely vulnerable for AGYW due to their situation along transit corridors, in major urban centers, or in proximity to mining activities. Eligible participants for the DREAMS program and the cohort were sexually-active, out-of-school AGYW aged 15-24 years. Data were collected from May 2017 to February 2019. We used conditional logistic regression to examine significant changes in HIV risk and vulnerability from baseline to 12 months in association with program interventions. A key outcome was dependence upon sex work as primary source of income.

Results: We enrolled 778 AGYW, and 598 (77%) completed follow-up (70 were lost to follow-up, 59 moved, 49 dropped, and 2 died). The economic-strengthening group intervention reduced dependence on sex work as primary source of income (OR=0.55, p<0.05). The effect was particularly strong among those whose business was established by the end of follow-up (OR=0.33, p<0.05). In the cohort as a whole, AGYW reported significantly increased food security, adult support, planning for the future, self-esteem, and condom self-efficacy. No negative effects on sexual health and well-being were observed.

Conclusion: Economic strengthening interventions offer alternative livelihoods to AGYW who previously relied on sex work. As HIV prevention strategies advance worldwide, protection of AGYW lags behind. Our study supports economic strengthening as a promising tool in the struggle to keep AGYW AIDS-free.

1017 TRANSPrEP: SOCIAL NETWORK-BASED PrEP ADHERENCE FOR TRANSGENDER WOMEN IN LIMA, PERU
Jesse L. Clark1, Sari L. Reiner, ScD1, Ayma G. Perez-Bruner1, Leyla Huerta Castillo1, Hugo Sanchez1, Hideki Okochi1, Maria Mami Lanque1, Ximena Salazar1, Matthew Mimiaga2, Monica Gandhi3, Kenneth H. Mayer4, Javier R. Lama4
1University of California Los Angeles, Los Angeles, CA, USA, 2Boston Children’s Hospital, Boston, MA, USA, 3University of Toronto, Toronto, ON, Canada, 4Association Civil Impacto Salud y Educación, Lima, Peru, 5Epícentro, Lima, Peru, 6University of California San Francisco, San Francisco, CA, USA, 7Universidad Peruana Cayetano Heredia, Lima, Peru, 8Brown University, Providence, RI, USA, 9The Fenway Institute, Boston, MA, USA
Background: While pre-exposure prophylaxis (PrEP) is an effective HIV prevention method, uptake remains poor among transgender women (TW). We conducted a pilot randomized controlled trial of a social network-based intervention to promote PrEP adherence among Peruvian TW.

Methods: From September, 2017-July, 2018, we screened 172 TW from three geographic areas of Lima, Peru. Screening visits were conducted to: assess HIV serostatus; introduce PrEP as a prevention strategy; and discuss PrEP adherence. We enrolled 89 HIV-uninfected TW into 6 groups based on pre-existing social network clusters. Clusters were randomized on a 1:1 basis to standard of care (n=44) or the TransPrEP intervention (n=45). Groups assigned to TransPrEP attended 4 weekly introductory workshops (to discuss principles of and barriers to PrEP adherence, and to construct and support group adherence goals). Biweekly maintenance workshops reviewed adherence strategies, discussed participants’ experiences taking PrEP, and encouraged network cohesion. Adherence was evaluated through self-report and by measurement of tenofovir (TFV) levels in hair. Intent-to-treat analyses compared intervention versus control conditions at baseline and 3-month follow-up.

Results: Participants’ mean age was 26.9 years (range 18-58), with 76.5% using feminizing hormones. At 3-month follow-up, we evaluated 40 TW and obtained 21 hair samples. Though no statistically significant differences were observed in ITT analysis, a higher proportion of participants in the TransPrEP arm reported taking “Most” or “All” TDF–FTC doses in the prior 30 days (90.5% [19/21] versus 73.4% [14/19]). In hair sample analysis, 36.4% (4/11) of participants in the TransPrEP arm reported taking PrEP daily versus 73.4% [14/19] of control participants. In the TransPrEP group, participants were lost to follow-up, 59 moved, 49 dropped, and 2 died. The economic-strengthening intervention reduced dependence on sex work as primary source of income (OR=0.33, p=0.05). The effect was particularly strong among those whose business was established by the end of follow-up (OR=0.33, p<0.05). In the cohort as a whole, AGYW reported significantly increased food security, adult support, planning for the future, self-esteem, and condom self-efficacy. No negative effects on sexual health and well-being were observed.

Conclusion: Pilot assessment of our network-based intervention showed improvements in PrEP adherence among TW in Peru according to both biological and behavioral adherence markers but did not achieve statistical significance. Mixed-methods data identified potential modifications to improve participant involvement and retention. Additional research to assess the TransPrEP intervention with a larger sample is needed.

1018 PrEP CONTINUUM OF CARE AMONG MSM AND TGW OF COLOR IN THE THRIVE DEMONSTRATION PROJECT
Kashif Iqbal1, Weiming Zhu1, Kenneth L. Dominguez1, Mary Tanner1, Kirk D. Henny2, Karen W. Hoover1
1CDC, Atlanta, GA, USA
Background: Pre-exposure prophylaxis (PrEP) reduces the risk of HIV acquisition when taken daily as prescribed. Access to and uptake of PrEP have been suboptimal among populations with the highest rates of HIV diagnoses, including men who have sex with men (MSM) of color and transgender women (TGW) of color. The THRIVE demonstration project funded seven U.S. health departments to lead community collaboratives that consisted of community-based organizations and clinical providers to implement comprehensive HIV prevention and care services for MSM and TGW of color. In this analysis, we estimated the PrEP care continuum among MSM and TGW in the THRIVE demonstration project.

Methods: We analyzed data collected from a cohort of 10,422 HIV-negative MSM and 1,009 TGW enrolled in THRIVE from September 2015 through March 2019. We estimated the proportions who were included at each step in the PrEP care continuum: screened, eligible, referred, linked, and prescribed PrEP, stratified by age and race/ethnicity. For both MSM and TGW, we used multivariable logistic regression models to estimate the associations of being linked, referred, and prescribed PrEP among persons who were eligible for PrEP, by race/ethnicity and age-group (aged <30 and >30 years).

Results: Among HIV-negative MSM and TGW in THRIVE, 8,339 (80.0%) were MSM of color and 916 (90.8%) TGW of color. At each step of the continuum, there were significantly larger proportions of MSM of color compared to TGW of color (Figure). In the multivariate model, among MSM eligible for PrEP, there...
were similar proportions of white MSM and MSM of color who were referred (77.8% and 84.6%, p=0.50) and linked (44.1% and 65.0%, p=0.62), but fewer MSM of color were prescribed PrEP than white MSM (40.0% and 38.9%) (p<0.05). In addition, among MSM of color, a smaller proportion of men aged <30 years were prescribed PrEP compared to men aged >30 years (35.2% and 43.1%) (p<0.05).

Conclusion: The THRIVE demonstration project expanded access to PrEP services for MSM and TGW of color, however challenges exist in prescribing PrEP to younger MSM of color. Increased use of interventions that support PrEP uptake among MSM and TGW of color are needed to improve the PrEP care continuum for these populations. Further investigation is needed to understand reasons that MSM of color were prescribed PrEP after referral and linkage to PrEP less frequently than white MSM.

1019 PrEP INDICATION AND CARE CONTINUUM AMONG TRANSGENDER WOMEN IN THE UNITED STATES

Jowanna Malone1, Sari Reisner1, Andrea L. Wirtz2, for the American Cohort to Study HIV Acquisition Among Transgender Women (LITE) Study Group 1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA

Background: U.S. transgender women (TGW) have a disproportionate burden of HIV, with an estimated prevalence of 28%. Pre-exposure prophylaxis (PrEP) is effective in preventing HIV acquisition among adherent users. However, the PrEP care continuum among TGW as well as factors associated with high risk for HIV and subsequent PrEP indication (e.g. condomless anal sex, sex partner number, having an STI, etc.) are not well understood.

Methods: The LITE study is a multi-site cohort enrolling TGW across six cities in the southern and eastern U.S. Upon screening, participants underwent HIV/STI testing and completed a socio-behavioral survey in which they reported experiences with PrEP. We identified factors associated with PrEP indication using prevalence ratios from a multivariate Poisson regression with robust variance. We also calculated descriptive statistics to depict the PrEP care continuum.

Results: As of April 2019, there were 751 participants not living with HIV at baseline. Among this group, 293 (39%) met PrEP indication based on the following: had a laboratory confirmed STI, recent partner who was known to be living with HIV, reported recent sex work, and/or recent condomless anal sex. Participants who were Non-Hispanic Black [ref: Non-Hispanic White, PR: 1.98, p<0.0001] or had self-perceived low risk of HIV [ref: no risk, PR: 2.09, p=0.012], medium risk of HIV [ref: no risk, PR: 3.33, p<0.001], or high risk of HIV [ref: no risk, PR: 3.91, p<0.001], were more likely to be indicated for PrEP. Having some college education or above was associated with being less likely to be PrEP indicated [ref: high school education or less, PR: 0.79, p=0.04]. Ultimately, among those indicated for PrEP, 42 (14%) were currently using and adherent to PrEP (Figure 1). Eighty-four percent of those indicated were aware of PrEP, 76% of those aware of PrEP had health insurance, 63% of those insured were taking PrEP, and 68% of PrEP users reported 100% adherence within the prior 7 days of the survey (14% among all who were indicated for PrEP).

Conclusion: Over a third of TGW not living with HIV at baseline were indicated for PrEP. Although most PrEP users were adherent, overall uptake and adherence among those PrEP indicated were low. Improving uptake and adherence among TGW warrants further investigation, particularly with respect to development of culturally appropriate strategies to increase uptake and adherence among Black TGW for whom PrEP indication is higher.

1020 DISCOVER: NO EFFECT OF HORMONES ON F/TAF OR F/TDF PK, EFFICACY & SAFETY IN TRANSWOMEN

Michelle S. Cespedes1, Sophia R. Majeed1, Maria Prins2, Ivanka Krznaric2, Anita Mathias1, Deqing Xiao1, Pamela Wong1, Jason Hindman1, Christoph Carter1, Diana Brainard1, Moupali Das1, Elske Hoornenborg2, Peter Ruane1, John Phoenix1, Jason Halperin1, 1Icahn School of Medicine at Mount Sinai, New York, NY, USA, 2Gilead Sciences, Inc, Foster City, CA, USA, 3University of Amsterdam, Amsterdam, Netherlands, 4Center for Infectious Diseases, Berlin, Germany, 5Public Health Service Amsterdam, Amsterdam, Netherlands, 6Peter J Ruane MD Inc, Los Angeles, CA, USA, 7Huntridge Family Clinic, Las Vegas, NV, USA, 8CrescentCare, New Orleans, LA, USA

Background: Emtricitabine (F), tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) do not have relevant drug interactions with low-dose hormones used for contraception. The current analysis explored PK as well as efficacy and safety of transwomen receiving either F/TAF or F/TDF in the DISCOVER trial, the majority of whom were taking high-dose, gender-affirming, hormonal therapy.

Methods: Overall, 74 transwomen at risk of HIV were randomized 1:1 to receive blinded F/TAF or F/TDF once daily in DISCOVER. Efficacy and safety results are summarized. TFV-DP and FTC-TP PBMC trough levels (C_t,h, defined as 20 to 28 hours postdose) were evaluated at steady-state (W4) and compared between transwomen taking high-dose hormones concomitantly with F/TAF (N=17) and a randomly pre-selected, representative group of MSM randomized to F/TAF not using high-dose hormones (N=161) using geometric least squares means (GLSM) ratios and 90% confidence intervals (CIs). Comparisons were made using a lack of PK alteration boundary of 50 to 200% to identify potentially clinically relevant differences. Levels of TFV-DP and FTC-TP with F/TDF in transwomen on high-dose hormones (N=10) were compared descriptively to levels in MSM randomized to F/TDF (N=155) due to a smaller sample size.

Results: No transwomen acquired HIV. Transwomen had similar numerical improvements in dipstick proteinuria and markers of tubular proteinuria as MSM. No transwomen developed clinically significant proteinuria (UPCR>200 mg/g). There were no differences between F/TAF and F/TDF in change from baseline in weight or eGFR in transwomen. GLSM ratios and 90% CIs for comparisons of PBMC TFV-DP and FTC-TP levels with F/TAF between transwomen taking high-dose hormones and MSM were within the 50 to 200% boundary, indicating no clinically significant interaction. In transwomen taking F/TDF and high-dose hormones, TFV-DP and FTC-TP levels were comparable to MSM, suggesting no interaction (Table).

Conclusion: The absence of infections suggests that both F/TAF and F/TDF were effective for HIV prevention in transwomen. Both F/TAF and F/TDF were safe and well-tolerated in transwomen and MSM. No clinically meaningful differences in PBMC TFV-DP and FTC-TP levels with F/TAF or F/TDF were observed between transwomen taking high-dose hormone therapy and MSM, suggesting that both F/TAF and F/TDF are effective and safe options for PrEP in transwomen on gender-affirming, high-dose hormone therapy.
1022 ASSOCIATIONS BETWEEN HORMONE USE, PReP USE, AND STIGMA IN US TRANSGENDER WOMEN

Jessica L. Maksut1, John Mark L. Wiginton1, Maria Zlotorzynska2, Carrie E. Lyons1, Travis Sanchez1, Ayden Scheim3, Stefan Baral1, Augustus Klein1, Lila A. Starbuck1, Alexander Harris2, Amiyah Guerra2, Christopher A. Rincon1, Pedro Carneiro2, Asa Radix2

1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2Emory University, Atlanta, GA, USA, 3Drexel University, Philadelphia, PA, USA

Background: The association between hormone therapy and PReP use among transgender women is unclear. Qualitative research suggests that hormone use may facilitate PReP use for some, while others may prioritize hormone therapy or have concerns about hormone-PReP interactions.

Methods: We analyzed data (collected March-May 2019) from 330 sexually active transgender women aged ≥15 years who resided in the US. We used bivariate multinomial regression to estimate the association between self-reported past-year hormone use (i.e., no hormone use, provider-prescribed hormone use, and non-prescription hormone use) with past-year PReP use. We used Chi-squared (χ²) tests to compare past-year sexual practices (i.e., condomless anal intercourse [CAI], condomless vaginal intercourse [CVI], and transactional sex) and past-year healthcare engagement across the provider-prescribed and non-prescription groups.

Results: Median age was 24 (IQR: 20, 31) and 72.7% (240/330) of the sample was White, non-Hispanic. 104 (31.5%) participants reported no hormone use while 190/330 (57.6%) reported provider-prescribed hormone use, and 35/330 (10.6%) reported non-prescription hormone use. 22 participants (6.66%) used PReP. 115 individuals (34.85%) reported CAI, 128 (38.79%) CVI, and 29 (8.79%) engaging in transactional sex. 303 (91.8%) reported a past-year healthcare provider visit. Compared to no hormone use individuals, provider-prescribed participants had 10.78 times the odds (95% CI 1.42–81.94), and non-prescription participants had 6.17 times the odds (95% CI 1.38–29.8) of reported PReP use while 190/330 (57.6%) reported provider-prescribed and 35/330 (10.6%) non-prescription participants.

Conclusion: TGW who are engaged in care can successfully uptake and adhere to PReP. Research should focus on interventions to enhance patient-provider communication about PReP for TGW, and adherence support for TGW should be provided consistently with findings on adherence across priority populations and medications.

1023 HIV PREVENTION AND DRUG-USER HEALTH CARE ON SITE AT A SYRINGE EXCHANGE PROGRAM

Andrea L. Jakubowski1, Irene L. Soloway1, Mercedes L. Guzman2, Christine Fitzsimmons3, Leonardo Dominguez-Gomez4, Franklin Ramirez5, Bracketts Kaplan2, Breni Gibson6, Jessica DeLucia7, Julia H. Armsten8, Brianna L. Norton9, 1Montefiore Medical Center, Bronx, NY, USA, 2New York Harm Reduction Educators, Bronx, NY, USA, 3BronxWorks Hospital, Bronx, NY, USA, 4New York University, New York, NY, USA, 5Bronx, NY, USA

Background: Syringe exchange programs (SEPs) serve populations who use drugs (PWUD) onsite at an SEP.

Methods: A Montefiore Medical Center clinic was opened within the drop-in center of a local SEP on February 11, 2019. In this setting clients are able to access clean syringes, laundry, showers, group education, and psychosocial counseling. We conducted a retrospective chart review of patients seen at the drop-in center clinic from 2/11/2019-5/29/2019 using the electronic medical record.

Sexual risk factors for HIV were defined: multiple sex partners, unprotected sex, sex worker, STD in the last 12 months, and/or sexual partners who are anonymous, HIV+, or currently injecting drugs. Adherence to offsite healthcare referrals is low. We describe a novel partnership between an academic medical center and an SEP to deliver low barrier healthcare to people who use drugs (PWUD) onsite at an SEP.

Results: A total of 118 patients were seen by a provider during the study period. The mean age was 43 (IQR: 17) and the majority of patients were female (53%) and Hispanic (44%) or non-Hispanic Black (32%). 30% of patients were homeless. 61% of patients had ever injected drugs and 61% of patients also had one or more sexual risk factors for HIV. The most common current substances used were heroin (50%) and crack/cocaine (44%). The primary reason for a patient's first visit to the clinic was for buprenorphine treatment (32%), followed by PReP (20%), hepatitis C treatment (20%), and PEP (8%). Of those who initiated buprenorphine treatment, 50% were retained in treatment at 90 days. 27% of patients who initiated PReP were retained in treatment at 90 days. Of the 8 patients who received PEP, 3 initiated PEP afterward. Of the 22 patients who were HCV positive, 20 (91%) were evaluated for treatment and had fibrosis staging, 10 (50%) initiated treatment.

Conclusion: Through a novel SEP-academic medical center partnership, PWUD received well-established HIV-prevention services (buprenorphine and PReP/PEP), as well as HCV treatment on-site at an SEP, demonstrating the feasibility of such initiatives. Rates of retention in buprenorphine treatment are comparable to retention rates at other low-barrier programs. PReP retention was slightly lower than reported in other populations, but few studies have evaluated PReP.
engagement among PWUD. Low barrier care delivered onsite at an SEP should be further explored to improve access to care and HIV and HCV prevention for PWUD who may otherwise never receive them.

1024 HIGH PREVALENCE OF PrEP INDICATION IN PEOPLE WHO INJECT DRUGS IN BOSTON, MA, 2018
Joel I. Earlywine1, Katie Bliedt1, Angela R. Bazzi1
1Boston University, Boston, MA, USA, 2Brown University, Providence, RI, USA
Background: PrEP is recommended for HIV prevention in people who inject drugs (PWID) in the US. In Massachusetts, increasing prevalence of injection drug use has contributed to outbreaks of HIV, potentially identifying missed opportunities for PrEP. Understanding PrEP need, knowledge, and use among PWID will help inform and evaluate PrEP as an HIV prevention tool.
Methods: We used the 2018 National HIV Behavioral Surveillance (NHBS) data from PWID in Boston, MA. Eligible participants were ≥18 years old, reported past year injection drug use, lived in the Boston Metropolitan statistical area, could complete the interview in English or Spanish, and consented to be interviewed. Based on US Preventive Services Task Force (USPSTF) guidelines, we estimated the proportions of PWID with PrEP indication by types of HIV acquisition risk: injection risks only (i.e., sharing syringes or injection equipment), sexual risks only (i.e., past-year sexually transmitted infections, being in serodiscordant relationships, or inconsistently using condoms with known MSM or PWID), and overlapping injection and sexual risks. We then evaluated PrEP awareness, conversations with healthcare providers about PrEP, and actual (self-reported) PrEP use among those with and without PrEP indications.
Results: Overall, among 433 HIV-uninfected PWID, 399 (92%) had PrEP indication based on USPSTF guidelines as follows: 298 (69%) were indicated for injection risks only, 3 (1%) were indicated for sexual risks only, and 98 (23%) were indicated for both injection and sexual risks. As shown in Figure 1, among the 399 PWID with PrEP indication, 155 (39%) had PrEP awareness, 42 (11%) had discussed PrEP with a healthcare provider, and 9 (2%) had used PrEP in the last year.
Conclusion: The majority of PWID in the Boston 2018 NHBS had PrEP indication based on current guidelines. Although most PWID were indicated for PrEP due to high risk injection-related behaviors, nearly a quarter also reported high risk sexual behaviors. PrEP awareness was suboptimal, conversations about PrEP with providers were uncommon, and PrEP use was extremely low. These findings highlight important areas for clinical and community-based interventions to improve PrEP uptake among PWID.

1025 PROPHYLACTIC EFFECT OF PrEP AGAINST HBV INFECTION AMONG MSM
Daisuke Mizushima1, Misao Takano1, Haruka Uemura1, Yasuyuki Yanagawa1, Takahiro Aoki1, Koji Watanabe1, Hiroyuki Gatanaga1, Shinichi Oka1
1National Center for Global Health and Medicine, Tokyo, Japan
Background: Universal HBV vaccination had not been available in Japan until 2015. We evaluated incidence of HBV infection and prophylactic effect of pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF/FTC) against HBV infection among a non-HIV-infected MSM cohort, sexual health clinic (SHC) in Tokyo.
Methods: MSM over 16 years old were included in SHC cohort. Participants were examined for HIV infection, syphilis (quantitative RPR/TPHA), pharyngeal and rectal Chlamydia trachomatis and Neisseria gonorrhoeae infections, and HBs antigen/antibody and HBc antibody, HCV antibody and HAV IgG antibody every 3 months. Entry criteria of the study were HBc antibody negative (<

1026 AV AND HBV VACCINATION COVERAGE AND ACCEPTABILITY AMONG MSM ON PrEP
Paul Le Turnier1, Isabelle Charreau1, Audrey Gabassi2, Diane Carrette1, Laurent Cotte1, Gilles Pialoux3, Cécile Tremblay3, Bruno Spire3, Marie-Laure Chaux Baudrier1, Laurence Meyer1, Catherine Captant1, Constance Delaugerre1, Jean-Michel Molina4, François Raffi5, for the ANRS IPERGAY study group
1CHU de Nantes, Nantes, France, 2INSERM, Villejuif, France, 3Assistance Publique – Hôpitaux de Paris, Paris, France, 4CHU de Lyon, Lyon, France, 5Tenon Hospital, Paris, France
Background: Sexually transmitted viral hepatitis have a rising incidence in MSM. During the ANRS IPERGAY PrEP trial (NCT 01473472), vaccination against HAV and HBV was offered free of charge to non-immune participants. We assessed baseline immune status, vaccine acceptability and efficacy in IPERGAY participants.
Methods: All subjects included in the IPERGAY blind and/or open phases were studied. HAV and HBV immune status were assessed at baseline and after vaccination. Anti-HAV IgGs and anti-HBs antibodies (Abs) were analyzed on available samples taken 1 to 3 months after each vaccine dose and on the latest available sample. The vaccination scheme was analyzed in subjects with a follow-up ≥6 months after receiving the 1st vaccine dose. Vaccination was considered incomplete when the last dose was not administered (3rd if HBV, 2nd if HAV). Subjects who started vaccination before trial initiation were excluded from acceptability and efficacy analyses. Sociodemographic factors associated with baseline immune status were explored by univariate analysis.
Results: A total of 429 subjects were analyzed. Two subjects were excluded because of isolated anti-HB Abs at baseline. The median follow-up was 2.2 years.
1027 HIGH PrEP ADHERENCE BASED ON TFV-DP LEVELS IN THAI 15-19-YEAR-OLD MSM AND TRANSWOMEN

Wiraporn Natalie Songtaweesin1, Thanyawee Puthanakit1, Surinda Kawichai1, Tim R. Cressey1, Prisaca Wongharn2, Taantip Theerawit1, Somsong Teeratakulpisam3, Danai Linjrongrut4, Surang Janyam5, Nittaya Phanuphak3,4, Rainbowsky Association of Thailand, Bangkok, Thailand, 5Service Workers In Group Foundation, Bangkok, Thailand

Background: Thailand initiated the first regional pre-exposure prophylaxis (PrEP) program in 2014, which has reached 10,000 PrEP users, including adolescents. Our objective was to assess 6-month adherence to oral tenofovir-diphosphate/emtricitabine (TDF/FTC) PrEP among adolescent men who have sex with men (MSM) and transgender women (TGW) in Bangkok.

Methods: MSM and TGW aged 15-19 years were provided free daily TDF/FTC with condoms funded by the Princess Preexposure prevention project and CIPHER program at youth-friendly clinics. Monthly contact was via clinic visits (months 0, 1, 3, 6) or telephone calls (months 2, 4, 5) after PrEP initiation. Clients were counselled on PrEP adherence and behavioral risk reduction. Self-reported sexual risk behaviors including sex acts and condom use were recorded. Dried blood spots (DBS) were collected for quantification of TFV-DP levels at months 3 and 6 using a validated LC-MS/MS assay. Behavioral risk data were summarized into 3-month blocks to assess HIV protection (PrEP and/or 100% condom use). TFV-DP levels of <100, ≥100-349, ≥350-699 and ≥700 fmol/l were taken to be ‘not protective’, ‘partly protective’, ‘protective’ and ‘highly protective’ respectively against HIV.

Results: Between March 2018 and June 2019, 148 MSM (74%) and 52 TGW (26%) were initiated on PrEP. Twenty-two percent had a sexually transmitted infection at enrollment. Median (IQR) sex acts per 3-month block was 8 (4-14). Retention at months 3 and 6 was 86% and 75%, respectively. There were 199 DBS samples collected (123 and 76 at months 3 and 6 respectively). TFV-DP levels were ≥700, ≥350-699, 100-349 and <100 fmol/l in 47%, 17%, 20% and 16%, respectively. Among 199 risk periods, 46% were protected by PrEP only, (12% and 34% of samples with TFV-DP levels of ≥350-699 and ≥700 fmol/l, respectively). 15% were protected by PrEP and condom use, 11% were protected by condoms alone, and 28% remained at risk of HIV acquisition. Of the 76 adolescents who completed the study, 66% were protected at month 3, and of these, 37/50 (74%) remained protected at month 6 (see table 1). There were 8 adolescents (11%) whose adherence improved and 13 (17%) whom declined when comparing the first and second periods of PrEP use.

Conclusion: Youth-friendly clinics and monthly follow-up in adolescent MSM and TGW provided a 72% HIV risk reduction by either ‘protective’ TFV-DP levels and / or 100% condom use. PrEP rollout should be encouraged in adolescent MSM and TGW.

1028 DRUG LEVELS, ADHERENCE, AND RISKS FOR LOW ADHERENCE IN THE DISCOVER PrEP STUDY

Susanne Doblecki-Lewis1, Olamide Dosekun2, Moti Ramgopal1, Jay Gladstein1, Mezegebe Berhe1, Kevin Nguyen1, Jason Hindman1, Yongwu Shao2, Ramin Ebrahimi3, Diana Brainard1, Moupal Di3, Scott McCallister4, Adriano Lazzarin5, Gerald F. Lang1, Peter L. Anderson9
1University of Miami, Miami, FL, USA, 2Imperial College Healthcare NHS Trust, London, UK, 3Midway Immunology and Research Center, Fort Pierce, FL, USA, 4APLA Health, Los Angeles, CA, USA, 5North Texas Infectious Diseases Consultants, Dallas, TX, USA, 6Gilead Sciences, Inc, Foster City, CA, USA, 7Ospedale San Raffaele, Milano, Italy, 8Medical University of Graz, Graz, Austria, 9University of Colorado, Aurora, CO, USA

Background: In over 8,700 person-years (PY) follow up in the DISCOVER PrEP trial, the HIV incidence rates in the emtricitabine/tenofovir alafenamide (F/TAF) and emtricitabine/tenofovir disoproxil fumarate (FTD/FAR) arms were 0.16 and 0.34/100 PY, demonstrating noninferiority for HIV prevention. Study investigators and site staff provided comprehensive adherence support to study participants at all visits.

Methods: 5,387 men who have sex with men (MSM) and transgender women (TGW) at high HIV risk were randomized 1:1 to receive blinded once daily F/TAF or F/TDF. At all visits, adherence was assessed by self-report on a confidential questionnaire and also by pill count. Dried blood spot analyses of tenofovir diphosphate (TFV-DP) in red blood cells (RBCs) were assessed in a randomly selected subset of 10% participants, and in any participant who acquired HIV; peripheral blood mononuclear cell (PBMC) TFV-DP levels were assessed at W4 in the same subset. Adherence support included adherence counseling at each visit, personal communications from site staff as needed, optional text messaging daily, and email updates periodically.

Results: Of the 22 HIV infections diagnosed in DISCOVER occurred while on study; 5/22 were suspected baseline infections. Of the 17 HIV infections that occurred on study, 6/17 occurred in the F/TAF arm and 11/17 occurred in the F/TDF arm. In 15 of the 17 on study HIV infections, DBS testing demonstrated that participants had undetectable or low TFV-DP levels in RBCs. By univariate logistical regression analysis, 5 baseline variables were significantly associated with low adherence by DBS (see Table); 2/5 were selected by multivariate stepwise analysis (asterisks). In both arms, adherence of at least 95% was >80% by self-report and was 69% by pill count. In the F/TAF and F/TDF arms respectively, 86-96% and 84-93% of participants were using at least 4 tablets/week, as measured by TFV-DP levels in RBCs. Levels of TFV-DP in PBMCs strongly correlated with tablets per week adherence TFV-DP levels in RBCs.

Conclusion: DISCOVER participants had very high adherence and very low HIV incidence rates. TFV-DP levels in RBCs were significantly lower in those with low adherence than in those with high adherence. The most important risk factor for acquisition of HIV on study was low adherence. Not using PrEP at baseline, black race, US residence, age below 25, and less than 4 years of college were significant risks for having low adherence to study drugs.

<p>| Table 1: Odds ratios of risk factors associated with non-adherence (DBS), univariate logistical regression |</p>
<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>Comparison</th>
<th>Odds Ratio Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using F/TDF for PrEP at baseline</td>
<td>No v/s Yes</td>
<td>2.91 (1.14, 7.47)</td>
</tr>
<tr>
<td>Race</td>
<td>Black v/s Nonblack</td>
<td>2.37 (1.17, 4.79)</td>
</tr>
<tr>
<td>Region*</td>
<td>US v/s Other</td>
<td>2.77 (1.28, 4.41)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 25 v/s ≥ 25</td>
<td>3.12 (1.03, 9.46)</td>
</tr>
<tr>
<td>Highest Level of Education*</td>
<td>&lt; 4 Yr v/s ≥ 4 Yr College</td>
<td>2.17 (1.29, 3.63)</td>
</tr>
<tr>
<td>Recreational Drug Use</td>
<td>No v/s Yes</td>
<td>1.54 (0.92, 2.60)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hispanic v/s Non-Hispanic</td>
<td>1.53 (0.89, 2.66)</td>
</tr>
<tr>
<td>Diagnosis of Rectal Gonorrhea, Rectal Chlamydia or Syphilis (both ≥ 6 mos. prior to screening)</td>
<td>No v/s Yes</td>
<td>1.45 (0.79, 2.64)</td>
</tr>
<tr>
<td>Bisexual Alcohol Use</td>
<td>Never v/s Have had ≥ 6 Drinks on One Occasion</td>
<td>1.94 (0.87, 3.99)</td>
</tr>
<tr>
<td>Number of Condors of Sexual Partners (within 3 mos. prior to screening)</td>
<td>≥ 3 v/s &gt; 3</td>
<td>1.73 (0.79, 2.92)</td>
</tr>
<tr>
<td>Circumcision Status</td>
<td>No v/s Yes</td>
<td>0.95 (0.52, 1.73)</td>
</tr>
</tbody>
</table>
1029 COMPARISON OF TFV-DP AND WISEPILL ADHERENCE AMONG YOUNG KENYAN WOMEN USING PrEP

Maria Pyra1, Elizabeth A. Bukusi2, Nelly R. Muogo2, Kenneth Nguere1, Kevin Oware1, Catherine Kiptinness1, Katherine Thomas1, Lindsey Garrison1, Peter L. Anderson1, Jared Baeten1, Jessica E. Haberer2
1Howard Brown Health Center, Chicago, IL, USA; 2KEMRI–Centre for Global Health Research, Kisumu, Kenya; 3Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya; 4Partners in Health Research and Development, Thika, Kenya; 5University of Washington, Seattle, WA, USA; 6Harvard Medical School, Boston, MA, USA; 7University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Background: Understanding PrEP use and related barriers is dependent on good measures of PrEP adherence. We compared electronic monitoring with tenofovir-diphosphate (TFV-DP) assessed from dried blood spots (DBS) to assess consistency of both measures in a cohort of young women taking PrEP.

Methods: Participants were 18-24 year old women at high risk (by V.O.I.C.E risk score) for HIV in Thika and Kisumu, Kenya. Participants were encouraged to take PrEP for at least the initial 6 months with study visits at 1 month, 3 months, and then quarterly for 24 months. The primary adherence measure was a real-time electronic monitor (Wisepill), while a random sample (15%) of DBS collected from non-pregnant participants receiving PrEP was also tested for TFV-DP. Adherence was categorized as high (>85% or 6+ doses/week; >1,050 fmol/punch), moderate (57-85% or 4-5 doses/week; 700-1,050 fmol/punch), and low (<57% or <4 doses/week; <700 fmol/punch) for electronic monitoring and DBS, respectively. Descriptive comparisons were made between DBS and corresponding Wisepill openings over the prior 30 days.

Results: DBS results from 39 samples (representing 35 women) over the first 12 months of follow-up were available. Overall concordance between electronically monitored and DBS adherence was moderate at 59%. Of the 21 participants with low electronically monitored adherence (<4 doses/week), almost all (n=20) had TFV-DP<700 fmol/punch, with an average of 128 fmol/punch. Of the 11 with moderate electronically monitored adherence (4-5 doses/week), 4 (10%) had TFV-DP ≥700 fmol/punch and an average of 559 fmol/punch. Of the 7 participants with high electronically monitored adherence (≥6 doses per week), only 1 had the expected TFV-DP ≥1050 fmol/punch, with an average of 577 fmol/punch. Notably, among women with high electronically monitored adherence, average TFV-DP was 526 fmol/punch when hemoglobin was <11 g/dL versus 616 fmol/punch when hemoglobin was >11 g/dL.

Conclusion: Overall, these findings show moderate consistency between both adherence measures, although the established TFV-DP thresholds may be high in this African population, especially among those with lower hemoglobin level. We found no evidence that women were taking PrEP by DBS without concurrent dosing by electronic monitoring, however, overreporting by electronic monitoring is possible. Additional studies are warranted to fully characterize both adherence measures for young women who are an important key population for HIV prevention.

1030 HIV RISK AND OBJECTIVELY MEASURED PrEP ADHERENCE IN YOUNG KENYAN WOMEN

Jessica E. Haberer1, Nelly R. Muogo2, Elizabeth A. Bukusi2, Kenneth Nguere2, Kevin Oware1, Catherine Kiptinness1, Maria Pyra1, Katherine Thomas1, Lindsey Garrison1, Jared Baeten1
1Massachusetts General Hospital, Boston, MA, USA; 2Kenya Medical Research Institute, Nairobi, Kenya; 3University of Washington, Seattle, WA, USA

Background: To assess adherence to event-driven PrEP, we used a mobile-based diary application and intracellular tenofovir diphosphate (TFV-DP) levels to assess adherence event-driven PrEP users participating in the Amsterdam PrEP demonstration project (AMPPEP) in the Netherlands.

Methods: Participants could choose and switch between daily and event-driven PrEP regimens. Participants used a mobile application to record their sexual behaviour and pill use on a daily basis. We studied adherence by assessing (1) the number of condomless anal sex (CAS) acts covered by PrEP using data collected by the mobile application and (2) the correlation between TFV-DP concentrations (measured in dried blood spot (DBS) samples taken at the 3, 6 or 9, and 12 and 24 month visits; lower level of detection 12.5 fmol/punch) and CAS, and between TFV-DP concentrations and self-reported pill use. Good adherence was defined as at least one tablet before a CAS act and one tablet within 48 hours of that CAS act.

Results: Between September 2015 and February 2019, 139 of 376 (37.0%) AMPPEP participants used event-driven PrEP for at least 3 months. In this period, a total of 6,583 CAS acts were reported in the mobile application during event-driven PrEP use, of which 5,518 (83.8%) were covered by good PrEP adherence. Good PrEP adherence was more common among CAS acts with known (93.0%) and unknown (90.4%) casual partners, than with a steady partner (56.2%); p<0.001. Median TFV-DP concentration was 528 fmol/punch (IQR 222-900; levels ≥700 fmol/punch are correlated with use of at least 4 pills per week in the preceding 6 weeks) and higher TFV-DP concentration was associated with...
the number of self-reported CAS acts (β=0.15, 95% CI 0.11-0.19) and with the number of pills taken (β=-0.08, 95% CI 0.06-0.09) in the 6 weeks before the DBS.

**Conclusion:** In our PrEP demonstration study, the majority of reported CAS acts were covered by PrEP. Self-reported adherence to event-driven PrEP was very high for CAS acts with unknown and known casual sex partners, suggesting that MSM use event-driven PrEP when they are most at risk for HIV. Observed TDF levels in event-driven PrEP users are lower than those reported from studies among daily users.

### 1032 USE OF A TENOFOVIR URINE TEST TO IMPROVE PrEP ADHERENCE AND PREDICT NON-RETENTION

**Shane Hebel**1, Elijah Kahn-Woods1, Landon Larabee1, Bibiana Osorio1, Kenneth H. Mayer1, Patric S. Sullivan1, K. Rivet Amico1, Giffin Daughtridge1

1UrSure Inc, Boston, MA, USA, 2The Fenway Institute, Boston, MA, USA, 3Emory University, Atlanta, GA, USA, 4University of Michigan, Ann Arbor, MI, USA

**Background:** Daily pre-exposure prophylaxis (PrEP) effectively prevents new HIV infections. Poor adherence and retention are pervasive, undermining PrEP’s utility. Objective adherence monitoring (OAM) tools that identify non-adherent patients and drive behavioral change are urgently needed. A Liquid Chromatography Mass Spectrometry (LC-MS/MS) urine test for Tenofovir (TFV), a component of PrEP, was used clinically to identify non-adherent patients and target support services. Adherence data were analyzed to describe the association between recent adherence, missed visits, and loss to follow up (LTFU).

**Methods:** Urine samples were collected from PrEP patients at 16 clinics in the US during routine visits. The LC-MS/MS Test detected recent non-adherence (no dose in 48 hours) versus recent adherence (a dose in the last 6 days). Non-adherent patients received adherence support, per clinics’ standards of care. We assessed results from patients who attended ≥2 visits and analyzed follow-up test results to determine if non-adherent patients had repeat non-adherence or improved adherence at their next visit. Clinic visits were recorded based on dates of adherence testing. Missed visits were defined as a gap in care of >120 days since the last visit. LTFU was defined as a gap in care of >180 days since the last visit with no future visit. Rates of missed visits and LTFU were calculated based on patients’ adherence status at the previous visits.

**Results:** 688 patients received urine screening and targeted adherence support at ≥2 visits. Of Visit 1, 544 (88%) remained adherent at Visit 2. Of the 82 non-adherent patients at Visit 1, 544 (88%) remained adherent at Visit 2. Of the 82 non-adherent patients at Visit 1, 61 (74%) were adherent at their next visit. Non-adherence was associated with missed visits and LTFU. Non-adherent patients were 70% more likely to miss their next visit and 114% more likely to be LTFU than adherent patients. Individuals who were initially non-adherent but became adherent had a similar chance of missing a visit or LTFU as patients with two adherent results based on patients’ adherence status at the previous visits.

**Conclusion:** Use of OAM coupled with targeted support for non-adherent individuals was associated with increased adherence. OAM also proved to be an invaluable tool to predict future non-retention and demonstrated the potential to reduce non-retention. This evidence indicates that OAM can be a key tool to identify and improve behavioral determinants of PrEP efficacy.

### 1033 DETERMINANTS OF HIV PREEXPOSURE PROPHYLAXIS INITIATION IN WOMEN AT HIGH RISK FOR HIV

**Rachel K. Scott**1, Shawnika Hull1, Jim C. Huang1, Adam Visconti1, Megan Coleman1, Peggy Ye1, Pam Lotke1, Diksha Balaji2, Jason Beverley1, Alison Ward4, Jennifer Holiday2, Richard A. Elion1

1MedStar Health Research Institute, Hyattsville, MD, USA, 2George Washington University, Washington, DC, USA, 3District of Columbia Department of Health, Washington, DC, USA, 4Whitman-Walker Health, Washington, DC, USA, 5MedStar Health, Washington, DC, USA, 6Georgetown University, Washington, DC, USA

**Background:** Determinants of HIV Pre-Exposure Prophylaxis (PrEP) initiation in U.S. women at risk for HIV are poorly understood. We sought to identify barriers and facilitators of PrEP initiation among women at high risk for HIV in a high prevalence community. We hypothesized that there would be significant demographic, behavioral, and psychosocial barriers to PrEP initiation.

**Methods:** We offered an anonymous, validated survey to women presenting for care in a hospital-based family planning clinic and a government sexual health clinic in Washington, DC. We measured socio-demographics, HIV behavioral risk factors, knowledge, attitudes, norms, and self-efficacy regarding PrEP initiation. We used chi-squared and Fisher’s exact tests for categorical variables, t-tests for continuous variables, and Mann-Whitney U test for ordinal variables. This analysis included women at high risk for HIV acquisition (i.e. ≥3 reported behavioral risk factors).

**Results:** 1118 women completed the survey; 32.4% (N = 362) were categorized as high risk for HIV acquisition. Of women at high risk, mean age was 27. The majority were Black (71.6%), single (88.5%), had completed ≥ high school/GED (94.6%), and reported household incomes <$25,000 (51.5%). 13.4% (n=148) were committed to starting PrEP in the next 12 months. Although specific behavioral risk factors for HIV were not associated with uptake intention, composite number of reported risk factors for HIV was positively associated (r=0.18, p<0.01). 8.7% perceived moderate-high risk of HIV acquisition in the next 12 months and 15.7% moderate-high lifetime risk. Perceived risk was not associated with intention to initiate PrEP. Age, race, marital status, income, distance from clinics, insurance status, transportation, housing, illicit drug use, and prior knowledge of PrEP were not associated with uptake intention. Prior discussion about PrEP with a medical provider was associated with intention to initiate. Attitudes toward PrEP, perceptions of norms (injunctive and descriptive) and efficacy, were positively associated with uptake intention (Table 1).

**Conclusion:** Demographic factors, behavioral risks, and perceived risk were not associated with intention to initiate PrEP among women at high risk for HIV. Psychosocial factors and healthcare provider support, however, were positively associated with intention to initiate PrEP. Our findings have important implications for PrEP messaging and development of interventions that center on the role of providers and social networks in the destigmatization and provision of PrEP.
Prenatal PrEP Exposure and Longitudinal Birth Outcomes in Kenya

Julia C. Dettinger 1, John Kinuthia 1, Laurén Gómez 1, Jillian Pintye1, Joshua Stern 1, Nancy M. Ngumbau 2, Ben O. Odhiambo 2, Mary M. Marwa2, Salphine A. Wattoyi 2, Felix Abuna 2, Jared Baeten1, Grace John-Stewart1

1University of Washington, Seattle, WA, USA, 2Kenyatta National Hospital, Nairobi, Kenya

Background: PrEP is recommended for use among pregnant and breastfeeding women at risk for acquiring HIV by the World Health Organization and Kenyan Ministry of Health. As PrEP implementation continues, accruing data on birth outcomes following prenatal PrEP exposure remains important.

Methods: PrEP Implementation for Mothers in Antenatal Care (PrIMA) is a cluster randomized trial in Western Kenya (NCT03070600) evaluating different outcomes following prenatal PrEP exposure.

Results: As of September 2019, 4,445 women had enrolled during pregnancy and 3,882 had delivered; 654 (17%) used PrEP at any time during pregnancy and 3,882 had delivered; 654 (17%) used PrEP at any time during pregnancy. Birth outcomes if they were prescribed PrEP at any antenatal study visits. Birth outcomes including, miscarriage (≥20 week gestation), stillbirth (>20 week gestation), gestational age at birth, birth weight, birth length, and congenital malformations are collected on all participants at six-week postpartum. Low birthweight (LBW) was defined as birthweight ≤2.5 kg among term infants, and small-for-gestational age (SGA) as below the 10th percentile for birthweight. LBW in women included patients seen in our sexual health clinics up to 12 months, or no HIV testing, respectively. Women were more likely to have positive extra-genital tests, GU was positive only in 24% of cases. Of 41 individuals with positive extra-genital tests, 34 had a positive bacterial STI test between January 1, 2019 and June 30, 2019 at 3 hospitals affiliated with an academic medical center in northern Manhattan. Missed opportunities for CHPS remain common. Sexually transmitted infections (STI) are significant biomarkers of HIV risk and should trigger pre-exposure prophylaxis discussion. We reviewed STI testing practices outside of sexual health clinics at our center to identify opportunities for improvement in the provision of CHPS.

Methods: An electronic sexual health dashboard was used to identify patients with a positive bacterial STI test between January 1, 2019 and June 30, 2019 at 3 hospitals affiliated with an academic medical center in northern Manhattan. Women included patients seen in our sexual health clinics up to 12 months, or no HIV testing, respectively. Women were more likely to have positive extra-genital tests, GU was positive only in 24% of cases. Of 41 individuals with positive extra-genital tests, 34 had a positive bacterial STI test between January 1, 2019 and June 30, 2019 at 3 hospitals affiliated with an academic medical center in northern Manhattan. Missed opportunities for CHPS remain common. Sexually transmitted infections (STI) are significant biomarkers of HIV risk and should trigger pre-exposure prophylaxis discussion. We reviewed STI testing practices outside of sexual health clinics at our center to identify opportunities for improvement in the provision of CHPS.

Results: Patients were predominantly female (65%); median age was 24 (range 18-85). Positive tests occurred in 50 inpatient and outpatient locations; the most frequent were the family planning clinic (25%) and the three emergency rooms (27%). The most common test performed was a genitourinary (GU) gonorrhea/chlamydia nucleic acid amplification test (46% of all tests ordered). Multi-site testing was rarely performed (7.9% of PE) and was more frequent in men than women (22% vs. 0.45%, OR 62.5, 95% CI 15.1-263.2). Of 41 individuals with positive extra-genital tests, GU was positive only in 24% of cases. Of all individuals with a positive STI test, 65%, 9% and 13% had concurrent, >12 months, or no HIV testing, respectively. Women were more likely to be inadequately screened for HIV (17% vs. 23%, OR 0.61, 95% CI 0.41-0.91). Documentation of PrEP discussion was rare (6.8% of PE) compared to safe sex (4%) and condoms (50%). PrEP was discussed almost exclusively with men compared to women (7% vs. 1.3%, OR 15.03, 95% CI 6.28-35.97). Of 41 individuals with positive extra-genital tests, GU was positive only in 24% of cases. Of all individuals with a positive STI test, 65%, 9% and 13% had concurrent, >12 months, or no HIV testing, respectively. Women were more likely to be inadequately screened for HIV (17% vs. 23%, OR 0.61, 95% CI 0.41-0.91). Documentation of PrEP discussion was rare (6.8% of PE) compared to safe sex (4%) and condoms (50%). PrEP was discussed almost exclusively with men compared to women (7% vs. 1.3%, OR 15.03, 95% CI 6.28-35.97).
1036 RESULTS FROM A PrEP DEMONSTRATION PROJECT FOR AT-RISK CISGENDER WOMEN IN THE US

Jill Blumenthal1, Sonia Jain1, Feng He1, Ryan M. Kofron1, Eric Ellorin1, Jamila Stockman1, Gifty Ntim2, Peter L. Anderson3, Katya Calvo4, Richard Haubrich4, K. Rivet Amico4, David J. Moore1, Sheldon Morris1, Raphael J. Landovitz2, Jill Blumenthal6
1University of California San Diego, San Diego, CA, USA, 2University of California Los Angeles, Los Angeles, CA, USA, 3University of Colorado, Aurora, CO, USA, 4Harbor–UCLA Medical Center, Torrance, CA, USA, 5Gilead Sciences, Inc, Foster City, CA, USA, 6University of Michigan, Ann Arbor, MI, USA

Abstract: Data on TDF/FTC PrEP use by cisgender women have largely been from Africa. We report the primary results from the first US demonstration project of oral PrEP among at-risk cisgender women.

Methods: Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGiS) was a 48-week PrEP demonstration project in cisgender women ≥18 years old at-risk for HIV conducted at 5 Southern California sites. Adherence was supported using two-way text messaging (Individualized Texting for Adherence Behavior; ITAB) and titrated adherence counseling based on rapid-turnaround tenofovir diphosphate (TFV-DP) concentrations. Study visits occurred at baseline, week 4, week 12, then quarterly through week 48. Demographics were collected with computer surveys. Outcomes included PrEP adherence, retention and persistence. Adherence was assessed by quantifying TFV-DP concentrations in dried blood spots. Concentrations ≥1050 fmol/punch were considered protective, suggesting ≥6 doses on average per week. Self-reported PrEP adherence was determined by the proportion of participants responding positively to daily ITAB text prompts over 30 days prior to study visits.

Results: Between 6/2016 and 10/2018, 136 ciswomen enrolled with mean age 40 (SD 11); 38% were non-Hispanic (NH) Black and 19% Latina. Over 48 weeks, 84 (62%) participants were retained and 62 (74%) remained on PrEP. Over one-third (12/31) of those on study but off PrEP discontinued TDF/FTC due to self-reported side effects; one led to study discontinuation. Of 120 participants with drug concentrations measured, 67 (56%) had at least one protective concentration; 22 (18%) had consistently protective drug concentrations across all available study visits attended. For all visits, women with protective TFV-DP were more likely to have a higher proportion of positive iTAB responses compared to those with TFV-DP <1050 fmol/punch (p < 0.05 at all visits except week 24). There were no incident HIV infections and 4 incident bacterial STIs.

Conclusion: Cisgender women in a PrEP demonstration project had mixed adherence and retention; many had non-protective TFV-DP concentrations and over 25% were lost to follow up. US PrEP programs may need to consider offering prevention alternatives for women who discontinue or struggle with PrEP adherence. In particular, integrating PrEP delivery within other valued medical or social services may promote and augment HIV prevention efforts.

1037 LONG-TERM EFFECTIVENESS OF VOLUNTARY MEDICAL MALE CIRCUMCISION FOR HIV PREVENTION

Gideon Loevinsohn1, Godfrey Kigozi2, Joseph Kagaayi2, Fred Nalugoda2, Larry W. Chang1, David Serwadda2, Steven J. Reynolds3, Gertrude Nakigozi2, Robert Ssekubugu2, Maria Wawer1, Aaron Tobian1, Ronald H. Gray4, Mary K. Grabowski1, Ssekubugu2, Maria Wawer1, Aaron Tobian1, Ronald H. Gray4, Mary K. Grabowski1, for the Rakai Health Sciences Program
1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Rakai Health Sciences Program, Kalisizo, Uganda, 3NIAID, Baltimore, MD, USA, 4Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Abstract: While the efficacy of male circumcision for HIV prevention was demonstrated in clinical trials, evidence on the long-term effectiveness of post-childhood circumcision through voluntary medical male circumcision (VMMC) programs in sub-Saharan Africa is limited. We assessed effectiveness of VMMC in preventing HIV acquisition in a President’s Emergency Plan for AIDS Relief (PEFAR) funded program in the Rakai region of Uganda using longitudinal data from the Rakai Community Cohort study (RCCS).

Methods: A cohort of initially uncircumcised HIV-uninfected men in the RCCS were followed between 2009 and 2016 in 30 communities during scale-up of VMMC programs. Self-reported data on circumcision status was collected and rapid HIV tests were done at five surveys conducted every 18 months. Incident HIV infection was estimated to occur at the midpoint of the inter-survey interval. Multivariable Poisson regression with generalized estimating equations was used to estimate adjusted incident rate ratios (IRR) and 95% confidence intervals (CI) of HIV acquisition in circumcised versus uncircumcised men adjusting for sociodemographic characteristics and sexual behaviors.

Results: 3,916 non-Muslim men were followed for 17,088 person-years over 9,469 study visits. There were 1,338 newly reported VMMCs (10.79/100py) and 138 incident HIV infections (0.81/100py) observed. At baseline, men adopting circumcision were significantly younger and more likely to have never initiated sex, consistently use condoms, and to be unmarried compared to uncircumcised men. Over the study period, the median age of men adopting circumcision declined from 28 years (interquartile range [IQR]: 21-35) to 22 years (IQR: 18-25; p-trend < 0.001). Overall, HIV incidence was 0.40/100 person-years (py) among circumcised men compared to 0.98/100 py among uncircumcised men (unadjusted IRR = 0.4; 95% CI 0.25-0.66; adjusted IRR = 0.47; 95% CI: 0.28-0.78). The effectiveness of circumcision for HIV prevention was sustained with increasing time from surgery (Figure) and was similar across age groups and calendar time.

Conclusion: A VMMC service program was highly effective in preventing HIV acquisition. The effectiveness of VMMC in this observational study is consistent with efficacy in clinical trials and support current recommendations that VMMC is a key component of combination HIV interventions and central to efforts to reduce HIV incidence.
**1038 “STYLISH MAN” CLUSTER RCT TO INCREASE MALE CIRCUMCISION FOR ADULT MEN ≥19, UGANDA**

Maria Waiver1, Godfrey Kigozi2, Stephen Mugumba3, Amos Zikusooka2, Joseph Kagaayi2, David Serwadda4, Anthony Ndyanabo1, Joseph Seokasanev4, Larry W. Chang1, Ronald H. Gray1

1Johns Hopkins Bloomberg School of Public Health; Rakai Health Sciences Program, Baltimore, MD, USA, 2Rakai Health Sciences Program, Kalisizo, Uganda, 3Makerere University, Kampala, Uganda, 4Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** There is need to increase acceptance of voluntary medical male circumcision (VMMC) among men ≥19 years who are at highest risk of incident HIV, but who are under-represented in VMMC programs in sub-Saharan Africa.

**Methods:** Between 2015-2018, we conducted a community cluster randomized trial (5 clusters per arm) to assess community promotion of voluntary medical male circumcision mobilization using a de-medicalized messaging intervention (the “Stylish Man” intervention). In the intervention arm, VMMC was provided via mobile camps alongside a 3-4 day “Stylish Man Event” (infotainment, games, testimonials by satisfied adopters and their partners, “red carpet” VMMC services for men ≥19 years, messages stressing VMMC as an adult lifestyle choice rather than just a health service), compared to control arm services provided via standard mobile VMMC camps of the same duration. The primary endpoint was the number and proportion of men aged ≥19 accepting VMMC services, and the population prevalence/incidence of VMMC among non-Muslim men ≥19 in three population-based Rakai Community Cohort Study surveys during the trial. Differentials between intervention and control arms were estimated using rate ratios (RR) and 95% confidence intervals (CI).

**Results:** The number of men accepting VMMC in the intervention arm (5,992) was higher than in the control arm (4,394); also, the numbers and proportions of acceptors aged ≥19 was higher in the intervention (n=2,083, 34.8%, than the control arm (n=1,752, 12.1%). RR=1.96, 95%CI 1.82-2.11) and the differential was statistically significant in all cluster pairs. The population prevalence of VMMC in men ≥19 increased over time in both arms and was significantly higher in the intervention compared to the control arm during the first follow-up (RR=1.11, 95%CI 1.05-1.18). The incidence of VMMC was also higher in the intervention arm during the first inter-survey interval (RR=1.71, 95%CI 1.43-2.06), but not at later time points.

**Conclusion:** Community mobilization/de-medicalized promotion increased VMMC uptake in men aged ≥19, as reflected in service statistics. Population-level VMMC prevalence in men ≥19 was initially higher in the intervention arm, but VMMC rates increased in both arms over time and the differential between arms was not sustained. Programs should consider de-medicalized approaches to increase VMMC among older men.

---

**1040 PREVALENCE AND INCIDENCE OF STIs DURING PREGNANCY IN SOUTH AFRICA**

Dorothy C. Nyemb1, Phuti P. Ngwpe2, Remco P. Peters1, Jeffrey D. Klaassner3, Landon Myer1, Dvora Joseph Davey1, Andrew Medina-Marino1, Leigh F. Johnson1, 1University of Cape Town, Cape Town, South Africa, 2University of Pretoria, Pretoria, South Africa, 3Anova Health Institute, Johannesburg, South Africa, 4University of California Los Angeles, Los Angeles, CA, USA

**Background:** Global estimates of the prevalence of sexually transmitted infections (STIs) remain high with approximately one million new infections per day. STIs increase HIV acquisition and perinatal transmission risk. Syndromic management for STIs is standard of care in South Africa. We evaluated the incidence and prevalence of STIs in pregnancy in Tshwane District and Cape Town, South Africa.

**Methods:** We conducted two observational prospective studies of pregnant women enrolled while attending their first antenatal clinic (ANC) visit in Cape Town and Tshwane District. We interviewed women ≥18 years and tested them at first ANC visit for Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG) and Trichomonas vaginalis (TV) using Xpert® assays (Cepheid, USA) as well as at the first postnatal visit. We evaluated the prevalence of STI at first ANC visit and factors associated using logistic regression model. We estimated the incidence of STI and factors associated with time to incident STI using Poisson regression model.

**Results:** We enrolled 669 pregnant women, 427 HIV-infected (64%) from Tshwane District and 242 (36%) from Cape Town (107 HIV-infected and 135 HIV-uninfected). At enrolment, median age was 30 years (IQR 26-34 years) and median gestational age was 18 weeks (IQR 13-23 weeks). Almost all women reported having vaginal sex in pregnancy (89%). At baseline the overall prevalence of any STI was 37% (n=250). The most common infection was CT (26%) followed by TV (18%), then NG (6%). Overall 11% (n=72) were infected with ≥1 STI, and 1% (n=7) had all 3 STI infections. Reporting symptoms was not associated with having an STI. 76% participants (n=190) had asymptomatic ...

---

**1039 SEX AND THE PENILE MICROBIOME: POTENTIAL SHARING OF HIV RISK–ASSOCIATED ANAEROBES**

Cindy M. Liu1, Jessica L. Proderg1, Ronald M. Gallwango1, Godfrey Kigozi2, Aggrey Anok3, James Nnamute1, Mathias Agaba2, Deo Male2, Yahaya Isabirye3, Malinha Azi2, Daniel Park1, Tom De Man1, Abigail Onos1, Rupert Kaul4, Aaron Tobian5

1George Washington University, Washington, DC, USA, 2University of Western Ontario, London, ON, Canada, 3Makerere University, Kampala, Uganda, 4University of Toronto, Toronto, ON, Canada, 5Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** Anaerobes in the genital microbiome have been associated with HIV acquisition in both men and women. Prevotella bivia and Dialister micraerophilus are associated with HIV risk and genital inflammation in both men and women despite major differences in vaginal and penile microbiome composition. Little is known regarding the potential transmission of HIV-associated anaerobes, particularly the directionality of transmission.

**Methods:** We characterized sub-preputial microbiota in uncircumcised HIV-negative males, including non-sexually active adolescents (aged 15-17 yrs, N=95) and sexually active adult men (mean age 22 yrs, N=47) in Rakai, Uganda. Sub-preputial swabs were collected into 1% BSA in PBS with protease inhibitor. Total bacterial density was measured by qPCR and proportional and absolute abundance of penile bacteria was characterized by sequencing of the 16S rRNA V3V6 region. Overall penile microbiome composition was compared by PerMANOVA test. Prevalence and abundance of penile bacteria were compared by Chi-square test and Wilcoxon rank-sum test, respectively.

**Results:** Penile microbiome composition differed significantly between sexually active and non-sexually active uncircumcised males in both proportion and absolute abundances (PerMANOVA p<0.001 in both). However, the total bacterial density was similar in both groups. Non-sexually active adolescents had high abundances of anaerobic penile bacteria, including many Prevotella and Dialister species; however, the two species associated with HIV risk and inflammation—P. bivia and D. micraerophilus—were significantly less prevalent and abundant in non-sexually active adolescents, in contrast to sexually active men (Chi2 and Wilcoxon p<0.05 for both organisms). Pectostreptococcus anaerobius, associated with HIV risk in men, was also less prevalent and abundant in non-sexually active adolescents than sexually-active men.

**Conclusion:** Prior to initiation of sexual activity, the uncircumcised penile microbiome is dominated by anaerobic bacteria, but the specific species associated with HIV risk and genital inflammation are conspicuously rare. These data suggest that seroconversion-associated anaerobes may originate in the vaginal microbiome, which once transmitted to penile microbiome could spur foreskin inflammation and colonize the penile microbiome.

---

1039 SEX AND THE PENILE MICROBIOME: POTENTIAL SHARING OF HIV RISK–ASSOCIATED ANAEROBES
STI infection. STI infection at baseline was associated with younger maternal age (aOR=0.96, 95% CI:0.92-0.98), gestational age at booking (aOR=1.02, 95% CI:1.00-1.05), single relationship (aOR=1.58, 95% CI:1.3-2.21) and HIV status (aOR=1.91, 95% CI:1.07-3.39) adjusting for site and education. Of the 419 participants who were not infected with an STI at baseline, 21 had an incident STI during follow-up, with mean follow-up time of 81 days. The total incidence rate was 15 infections per 100 women-years (95% CI=9–23).

**Conclusion:** Our study shows high prevalence and incidence of STIs in pregnancy, demonstrating the need for STI screening and treatment in ANC to prevent infant STI and HIV transmission. More research is needed on how to move from syndromic management of STIs in South Africa which misses asymptomatic cases.

### 1041 STILLBIRTH AND PREVALENT SYPHILIS IN THE US WOMEN’S INTERAGENCY HIV STUDY, 1994-2016

**Kristal J. Aaron**, Ilene Brill, Zenoria Causey, Rachel Sinkey, Lisa B. Haddad, Anandi N. Sethi, Michael Augenbraun, Audrey French, Stephen J. Gange, Kerry Murphy, Dominika Seidman, Barbara Van Der Pol, Jeanne M. Marrazzo, Mirjam-Colette Kempf, Jodie Dionne-Odom

**University of Alabama at Birmingham, Birmingham, AL, USA, 2Emory University, Atlanta, GA, USA, 3University of California San Francisco, San Francisco, CA, USA**

**Background:** Syphilis rates have increased steadily in US women since 2013 and congenital syphilis cases are at a 20-year high. Syphilis infection during pregnancy can lead to stillbirth. The purpose of this study was to test the hypothesis that prevalent syphilis infection in women with and without HIV can identify those with elevated risk of stillbirth over time.

**Methods:** Women age 16-49 in the multisite US WIHS cohort between 1994 and 2016 with documented syphilis testing and pregnancy outcomes were included. Prevalent syphilis was defined as a positive RPR screen with confirmatory treponemal antibody testing at baseline. Birth outcomes were self-reported with stillbirth defined as an intrauterine fetal demise after 20 weeks of gestational age. History of stillbirth and stillbirth during follow up were examined separately. Logistic regression with backward selection was used to create adjusted models using HIV status, prevalent syphilis and pre-selected covariates. Information about drug use, alcohol intake and sex were used to create adjusted models using HIV status, prevalent syphilis and pre-selected covariates. Information about drug use, alcohol intake and sex were collected during biannual visits using standardized questionnaires.

**Results:** The study included 3577 women: 2687 (75%) with HIV and 879 (25%) without HIV. (Fig. 1) Mean age at enrollment was 36 years and prevalent syphilis was more common in women with HIV vs women without HIV (8% vs 4%; p<0.05). In total, 4.6% reported prior stillbirth and 2.2% of women with pregnancy during follow up had stillbirth. During follow up, 4.7% of women with prevalent syphilis had a stillbirth compared to 2.0% of syphilis seronegative women. Small numbers (n=13) did not permit modeling of stillbirth during follow up. Predictors of prior stillbirth in the unadjusted model (p<0.2) included syphilis at baseline, HIV-negative status, black race, non-heterosexual identity, income <$12000, HCV, older age, lifetime sexual partners, and younger age of sexual debut. In multivariable models, prior stillbirth was associated with syphilis at baseline (OR 1.8, 95% CI:1.0-3.0), HIV-negative status (OR 1.6, 95% CI:1.1-2.2), older age (OR 1.0, 95% CI:1.0-1.1), and younger age at sexual debut (OR 0.95, 95% CI:0.91-0.99).

**Conclusion:** Reported stillbirth rates were four times higher among US women living with and without HIV in this study compared to the general population. Women with prevalent syphilis had higher rates of prior stillbirth and stillbirth during follow-up. Early prenatal care and universal syphilis screening is critical for US women living with HIV or at risk of HIV.

### 1042 PREVALENCE OF MYCOPLASMA GENITALIUM AND PERINATAL OUTCOMES IN HIV+ PREGNANT WOMEN

**Dvora Joseph Davey**, Remco P. Peters, Carolyn Smullin, Dorothy Nyemba, Hunter Green, Andrew Medina-Marino, Jeffrey D. Klausner, Landon Myer

**University of California Los Angeles, Los Angeles, CA, USA, 2Anova Health Institute, Johannesburg, South Africa, 3University of Cape Town, Cape Town, South Africa, 4Desmond Tutu HIV Foundation, Cape Town, South Africa**

**Background:** The bacterium Mycoplasma genitalium (MG) is a sexually transmitted organism that may increase risk of adverse perinatal outcomes, including prematurity and pregnancy loss, but there are few data on the epidemiology of MG in HIV-infected pregnant women in sub-Saharan Africa.

**Methods:** We conducted two observational prospective studies of HIV+ pregnant women receiving antenatal care at two public sector facilities in Tshwane and Cape Town, South Africa. Women self-collected vulvovaginal swabs, tested using the Aptima® Mycoplasma genitalium assay (Hologic, USA). We report on prevalence (both sites) and incidence (Cape Town only) of MG, associated symptoms and perinatal outcomes in HIV+ women and using logistic regression.

**Results:** We enrolled 391 women: 299 from Tshwane (77%) and 92 from Cape Town (23%). Median age was 30 years (IQR=26-35) and gestational age was 18 weeks (IQR=14-23). Most women reported vaginal sex during pregnancy (89%). MG prevalence at first antenatal visit overall was 17% (n=66 of 391); 15% in Tshwane (n=44 of 299) and 24% in Cape Town (n=22 of 92, p=0.04). MG incidence was 5.7 infections per 100-woman-years (95% CI=0.96, 18.9) based on two newly acquired infections. Half of prevalent MG infections had another STI diagnosed at the same visit (50%, n=33) and were treated: Chlamydia trachomatis coinfection in 30% (n=20) and Trichomonas vaginalis in 26% (n=17). Most MG-infected women were asymptomatic (79%, n=52), but vaginal discharge was reported by 6% (n=4), vaginal bleeding in 6% (n=4), and pain with urination in 6% (n=4). Of 299 mono-MG-infected women (not diagnosed with other STIs) with pregnancy outcomes, 33 had adverse pregnancy outcomes including pre-term delivery, stillbirth, or low birth weight. In MG-infected women (n=57), 18% (n=10) of women had an adverse pregnancy outcome compared with 9.5% (n=23 of 242) of MG- women (age adjusted OR=2.03, 95% CI=0.90, 4.54).

**Conclusion:** We found a high prevalence and incidence of MG in HIV-infected pregnant women in this setting, and a trend towards worse perinatal outcomes.
1043 DIAGNOSIS OF SEXUALLY TRANSMITTED INFECTIONS IN PREGNANT WOMEN AND MALE PARTNERS

Nava Yeganeh1, Regis Kretschmann2, Jeffrey D. Klausner3, Karin Nielsen-Saines4, Mei Leng5, Pamina M. Gorbach6

1University of California Los Angeles, Los Angeles, CA, USA, 2Irmandade da Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Brazil

Background: Porto Alegre, Brazil has the highest rates of congenital syphilis and HIV in the country. Although studies have shown that congenital syphilis and HIV acquisition during pregnancy are associated with untreated sexual partners, male sexual partners infrequently attend clinic for diagnosis and treatment. Other treatable sexually transmitted infections (STIs) including gonorrhea (GC), chlamydia (CT), and trichomons (TV) are associated with poor pregnancy and neonatal outcomes, but are only diagnosed by syndromic algorithms.

Methods: Starting 9/2018, we offered all pregnant women and their male sexual partners clinic-based STI testing for HIV and syphilis (via lateral flow assay rapid tests provided by the Brazilian Government) and for GC, CT and TV (via PCR-based testing provided by GeneXpert, Sunnyvale CA) in 6 public health clinics in Porto Alegre. Participating women and men also answer a brief survey via audio computer assisted survey instrument regarding demographics, partnerships and sexual behaviors. All infected individuals received appropriate treatment and referrals.

Results: Of 297 pregnant women recruited, 26% were diagnosed with an STI including 2% with HIV, 11.5% with syphilis, 10% with CT, 1% with GC, 5.4% with TV (fig 1). All male partners were invited for evaluation, and 175 (60%) have attended clinic. In these male partners, 14.3% were diagnosed with an STI including 5.2% with syphilis, 8.1% with CT, 1.2% with GC, 1% with TV, and 0.5% with HIV. In our multivariate analysis, younger age (AOR 1.1, 95% CI 1.1-1.2), being non-white (AOR 2.3, 95% CI 1.3-4.4), having less education (AOR 2.9 95% CI 1.2-3.7), having a relationship <1 year (AOR 2.3 95% CI 1.2-4), were all independent predictors of women being infected with an STI. Having symptoms of an STI (ulcer, vaginal/urethral discharge) was not predictive of having a diagnosis of STI (OR 0.8, 95% CI 0.5-1.4). The concordance rate of STIs between couples where both were tested ranged from 18% for TV and 75% for CT.

Conclusion: STIs are common in pregnant women and are currently not being addressed using syndromic management. Given that most of these infections are easily treatable, they should be appropriately diagnosed and treated in both pregnant women and their sexual partners to decrease treatment failure and re-infection.

Figure 1: Schema of STI frequencies in pregnant women and their partners

1045 HIV TRANSMISSION RISK FACTORS AMONG MEN LIVING WITH HIV WANTING A PREGNANCY IN UGANDA

Pooja Chitneni1, Bosco M. Bwanwa1, Moran Owembabazi2, Deogratious Tusowski1, Alice Najjuma1, Johnmary Tumwine1, Patricia Smith1, Elijah Musinguzi2, Cathy Kyamire1, Sylvia Natzukynda2, Paul Kalyebara3, Lynn T. Matthews4, Angela Kaida3

1Massachusetts General Hospital, Boston, MA, USA, 2Mbarara University of Science and Technology, Mbarara, Uganda, 3Simon Fraser University, Burnaby, BC, Canada, 4University of Alabama at Birmingham, Birmingham, AL, USA

Background: Little is known about HIV risk behavior among men living with HIV (MLWH), who have sex with women, and want to have children. This group is of particular interest given increased HIV acquisition risks to women during periconception and pregnancy periods. We describe HIV transmission risk factors among a cohort of MLWH planning for pregnancy in rural Uganda.

Methods: We enrolled 50 MLWH accessing HIV care and planning for pregnancy with an HIV-infected or unknown female partner (Nov 2018–Mar 2019). Men were offered comprehensive safer conception counseling, HIV viral load testing via GeneXpert, and STI testing for Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis via GeneXpert, and syphilis via immunochromatographic testing confirmed by rapid plasma reagin. Men also completed a questionnaire on socio-demographics, sexual and reproductive
history, behavior, and relationship dynamics. We used descriptive statistics to analyze the data.

Results: Of the 50 study participants, the median age was 36.5 (IQR 32.4-43) years and most (N=49, 98%) were married or living as married with their pregnancy partner. Half (N=26, 52%) reported condomless sex at last sex, N=47 (94%) had HIV-uninfected partners, N=3 (6%) did not know their partners’ HIV-serostatus, and N=46 (92%) disclosed their HIV-serostatus to their partner. Most men (N=48, 96%) accessed ART, and N=8 (16%) had detectable HIV-RNA (>40 copies/mL). Eleven (22%) had curable STIs, including chlamydia-6% and syphilis-16%.

Conclusion: Among MLWH planning for pregnancy in rural Uganda, most accessed ART, 92% disclosed their HIV-serostatus to their partner, and 84% were virally suppressed. We also observed a high prevalence of curable STIs, with significant repercussions for the health of men, pregnancy partners, and neonates.

Undetectable=Untransmittable (U=U) is an important concept to support men’s reproductive goals. We found that comprehensive counseling and HIV-RNA testing are essential components of the success of U=U. Additionally, as Uganda and other settings consider laboratory-based STI screening, men and women planning for pregnancy should be a screening priority. Integration of comprehensive sexual and reproductive health into HIV care for men and women is critical to cultivating the health of individuals and families living with or affected by HIV.

1046 CHANGES IN SEXUAL RISK BEHAVIORS FOLLOWING AN STI DIAGNOSIS AMONG A COHORT OF MSM

Marjan Javanbakht1, Amy Ragsdale1, E. India Richter2, Steven Shoptaw1, Pamina M. Gorbach2
1University of California Los Angeles, Los Angeles, CA, USA

Background: Prevalence of sexually transmitted infections (STIs), rates of STI reinfections, HIV acquisition and changes in behaviors following STI diagnoses were examined in a cohort of men who have sex with men (MSM) in Los Angeles, CA.

Methods: Data from an NIH/NIDA funded longitudinal study of HIV-positive and high-risk HIV negative MSM participants enrolled from 2014 with at least one follow-up visit through May 2019 were analyzed (n=445; 1,556 study visits; 82% of parent cohort). Study visits every 6 months included computer assisted self-interviews for self-reports of behaviors and urine, pharyngeal and rectal swabs, and blood were tested for chlamydia, gonorrhea, syphilis and HIV. Changes in behaviors following an STI diagnosis were assessed using Mc Nemar’s test for paired data comparing the index visit with each of the follow-up visits. Participants not diagnosed with an STI during the study served as controls for a ‘difference of difference’ analysis of changes over time (difference in change in behaviors among those with no STI compared to difference in change in behaviors among those with an STI).

Results: Of the 445 participants, 50% (n=223) were diagnosed with an STI during the course of the study. At the first STI diagnosed visit, the average age was 31 with 41% identifying as Black/African American, 35% Latino/Hispanic, and 15% white. Following an STI diagnosis, significant declines were noted in substance use and sexual risk behaviors (see Table). Among the 91 HIV-negative participants with an STI, six seroconverted during the course of the study (incidence 6.6%). At 12-months post STI diagnosis, binge drinking declined from 50% to 38% (p value<.01), methamphetamine use declined from 50% to 40% (p value=0.03), and median number of sex partners declined from 5 (IQR: 2-12) to 3 (IQR: 1-10) (p value=0.02). No differences were noted overtime in the prevalence of PrEP use.

Conclusion: STI reinfection in this cohort of MSM was not uncommon yet was accompanied by some decreases in risk behavior. Because HIV incidence was high and PrEP use low this suggests MSM with STIs occupy a high risk sexual network where even reductions in some risk behaviors do not protect them from ongoing high risk exposures to STIs and HIV.

1047 VARIATION IN SYPHILIS AMONG BISEXUAL MEN AND ASSOCIATION WITH SYPHILIS IN WOMEN

Chase Cannon1, Matthew R. Golden1, for the CORES Group
1University of Washington, Seattle, WA, USA

Background: The rate of syphilis among U.S. men who have sex with men (MSM) has been rising for over two decades, and rates of syphilis in women and of congenital syphilis are now also increasing. The extent to which these trends are related is uncertain. We evaluated what percentage of MSM early syphilis (ES) cases occurred in men who had both male and female partners (MSMW); how that percentage varied over time and among men of different race/ethnicity and between regions of the U.S.; and the relationship of measures of MSMW syphilis with syphilis rates in women. We hypothesized that the proportion of MSM ES cases occurring in MSMW would increase over time, would be higher in Black MSM and in the southern U.S., and that measures of syphilis morbidity in MSMW would be associated with higher syphilis (all stages) rates in women.

Methods: We solicited aggregate syphilis surveillance data from areas with the highest rates of ES in 2017, limiting the sample to states with >50 female ES cases and focusing on directly-funded cities if they contributed >50% of cases in their state. The initial sample included 22 jurisdictions, of which 16 (73%) provided data for 2013-2017. ANOVA and linear regression models were used to test hypotheses.

Results: Of 122,226 male ES cases from 2013-2017, data on gender of sex partners based on standard syphilis contact periods was available in 77.3%. The median percentages of ES cases in MSM, only reporting sex with women only (MSW) and MSMW were 73.6 (range: 49.7-94.2), 14.9 (2.3-37.7) and 7.6 (1.2-26.4), respectively. The mean percentage of MSM ES cases occurring in MSMW was stable over time, but was higher in the South compared to all other regions, and was higher in Black men compared to White and Hispanic men (p<0.01, Table 1). The mean number of MSMW ES cases per 100,000 men across the five years likewise varied by region, from 5.6 in the South to 2.3 in the Midwest (p<0.01). The rate of syphilis in women was not associated with the percentage of MSM ES cases occurring in MSMW (p=0.18), but was associated with the number of MSMW cases per 100,000 men, with each 10% rise in this number yielding an estimated mean increase in syphilis among women of 0.71 per 100,000 (95% CI: 0.45-0.97).

Conclusion: Our findings are consistent with the hypothesis that syphilis rates in women are related to measures of syphilis in MSMW, and may in part explain some observed regional and racial/ethnic disparities in syphilis morbidity.

Table 1: Measures of Morbidity in MSMW with Early Syphilis by Region and Race/Ethnicity

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean Percent MSMW with Early Syphilis who are MSMW 2013-2017</th>
<th>p-value</th>
<th>Mean MSMW Early Syphilis Cases per 100000 Men 2013-2017</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>West</td>
<td>9.0%</td>
<td>&lt;0.01</td>
<td>4.6</td>
<td>0.69</td>
</tr>
<tr>
<td>Midwest</td>
<td>8.0%</td>
<td>3.5</td>
<td>3.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Northeast</td>
<td>7.0%</td>
<td>3.8</td>
<td>3.8</td>
<td>0.02</td>
</tr>
<tr>
<td>South</td>
<td>36.5%</td>
<td>0.03</td>
<td>10.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8.8%</td>
<td>1.6</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>10.5%</td>
<td></td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>16.4%</td>
<td></td>
<td>10.5</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MSMW (men who have sex with women), NMSW (men who have sex with men and women)

* p-value indicates level of significance of estimated population of men

* Denominator indicates total estimated population of men.
1050 A POINT-OF-CARE ASSAY FOR DIAGNOSIS OF NEUROSYPHILIS

Hemil Gonzalez1, Christina Marra1, Igor Koralnik1, Lauren Tantalo2, Zachary Orban1, Gregory D. Huhn1

1Rush University, Chicago, IL, USA; 2Harborview Medical Center, Seattle, WA, USA; 3Ruth M. Rothstein CORE Center, Chicago, IL, USA

Background: Neurosyphilis (NS) can cause severe disability. Globally, the burden of NS remains high, and the ability to diagnose it in resource limited settings (RLS) is limited. We tested whether a point of care test originally developed to detect serum treponemal and non-treponemal antibodies could be used on cerebrospinal fluid (CSF) to diagnose NS.

Methods: Participant characteristics (table) and ROC curve (figure) are shown; cases and controls were well matched. We detected CSF treponemal antibodies in 31/36 cases and 5/36 controls, and CSF non-treponemal antibodies in 27/36 cases and 1/36 controls. This resulted in sensitivity of 86% and specificity of 96% for the treponemal test and sensitivity of 81% and specificity of 97% for the non-treponemal test. Treponemal test false negatives and true positives had a median sRPR of 128(IQ 128-384) vs 256(IQ 64-1024), median CSF-VDRL titer of 86% for the treponemal test and sensitivity of 81% and specificity of 97% for the non-treponemal test. There were no differences in prevalence ratio (PRR) test (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP).
1051 IDENTIFYING AN HIV AND NEURO/Ocular syphilis CLUSTER IN VERMONT
Devika Singh1, Ray Belcher1, Daniel Daltry2, Abigail Crocker3, Jennifer Read1
University of Vermont, Burlington, VT, USA

Background: Since 2001, rates of syphilis in the U.S. have more than doubled, largely attributable to an increase among men who have sex with men (MSM). It is recognized that syphilis facilitates HIV acquisition, likely through a combination of biological and behavioral risk factors. National interest in neuro/ocular syphilis emerged following a cluster of cases in 2014-2015 in Seattle, Washington and San Francisco, California, with the majority of cases occurring among HIV-infected MSM. Our study characterizes a cluster of neuro/ocular syphilis cases among HIV-infected individuals in Vermont in 2017-2018.

Methods: All HIV and syphilis diagnostic test results are reported to the Vermont Department of Health (VDH). VDH Disease Intervention Specialists (DISs) conduct interviews with newly diagnosed cases of HIV and syphilis, and among HIV-infected MSM. We conducted a single arm multi-site clinical study of the efficacy of ciprofloxacin 500 mg by mouth for the treatment of wild-type gyrase A N. gonorrhoeae infections. We recruited and enrolled study participants from sexually transmitted disease clinics across the United States. We recruited and enrolled study participants from sexually transmitted disease clinics across the United States. We conducted a single arm multi-site clinical study of the efficacy of ciprofloxacin 500 mg by mouth for the treatment of wild-type gyrase A N. gonorrhoeae infections. We recruited and enrolled study participants from sexually transmitted disease clinics across the United States. We determined N. gonorrhoeae gyrA serine 91 wild type status using a previously Clinical Laboratory Improvement Act-verified laboratory-developed PCR assay with high-resolution melt analysis. We report outcomes in participants who were N. gonorrhoeae culture positive for gyrA serine 91 wild type infection at enrollment and had culture assessment 5-10 days after treatment. We also report treatment outcomes in cases with non-wild type gyrA serine 91 N. gonorrhoeae infections at enrollment.

Results: Among 106 patients with 117 urogenital, rectal or pharyngeal infections across 6 clinics, the frequency of microbiological cure was 100% (95% one-sided confidence interval 97.5-100%). The cure frequency did not vary by anatomic site of infection, sex or age of the study participant. Two cases with mutated gyrA N. gonorrhoeae infection failed therapy (0% cure). Conclusions: GyrA serine 91 N. gonorrhoeae genotyping was highly predictive of clinical outcomes in patients with gonorrhea treated with ciprofloxacin.
baseline prevalence of Syphilis, Ct and Ng as well as the cumulative incidence of each infection at 6 and 12 months after PrEP initiation using Kaplan-Meier survival analysis. We also describe the frequency and percentage of Ct/Ng detection per anatomic site and calculate the percentage of missed diagnosis if molecular testing for Ct/Ng were applied only for symptomatic patients, or if screening is done in urine only.

**Results:** 386 PrEP users under follow-up in a single institution in Sao Paulo, Brazil, were included in the study. Most (94%) were men who have sex with men, with median age of 31 years old (interquartile range [IQR] 27-37). At baseline, active syphilis was detected in 23 participants (7%); 3 symptomatic and 20 latent or unknown stage), whereas Ct and Ng were detected in 9 patients each (8% and 9%) of whom only one Ng-positive patient had symptoms. After a median follow-up of 278 days (IQR 180-370), incident syphilis was detected in 24 PrEP users, with a cumulative incidence of 12% at 12 months; of those, 10 were symptomatic (3 in primary stage and 7 in secondary stage), Ct and Ng were detected in 13 patients and 10 patients, with a cumulative incidence of 12% and 10% at 12 months respectively. Had Ct/Ng molecular testing been used for symptomatic patients only, 15/16 (94%, 95% CI 70-100) cases would have been missed at baseline and 14/20 (70%; 95%CI 46-88) cases would have been missed. Had screening been performed in urine only, 12/16 (75%; 95%CI 46-88) incident cases would have been missed.

**Conclusion:** Multiple anatomic site sampling is a powerful strategy to increment the diagnostic sensitivity of Ct/Ng molecular screening. This approach should be applied in high-risk PrEP users as to improve the capacity of accurate diagnosis and treatment.

---

**Figure 1:** Percentage of missed Ct/Ng diagnosis at baseline and follow-up if molecular testing were applied to symptomatic patients only (blue and yellow bars) or tested in urine only (grey and green bars). Whiskers represent 95% confidence intervals.

---

**1054 THE PERFORMANCE OF POOLED 3-ANATOMIC-SITE CHLAMYDIA AND GONORRHEA TESTING**

_Claire C. Bristow_1, Sanjay R. Mehta1, Martin Hoenigl1, Susan J. Little1

_1University of California San Diego, La Jolla, CA, USA_

**Background:** While molecular testing for Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) is much more sensitive than traditional culture and immunostaining approaches, the cost can be more than 20 times higher per test. These costs are amplified further, as optimal testing requires specimens from 3 anatomic sites (rectal, pharyngeal and urogenital [urine or vaginal swab]), tested individually. While individual testing of samples from all three sites is currently recommended, pooled testing may offer a cost-saving alternative. We assessed the performance of routine versus pooled 3 anatomic site testing (1 test per person versus 3) for CT and NG.

**Methods:** Using the Xpert® CT/NG assay (Cepheid, Sunnyvale, CA) we tested urine, rectal and pharyngeal swabs for CT and NG. Remnant specimens (0.34 mL from each anatomic site specimen) were combined to perform a single ‘pooled’ test. We calculated positive and negative percent agreement between the pooled testing results with the single specimen Xpert CT/NG test results as the reference.

**Results:** We conducted 403 pooled tests. Of those, 366 (90.8%) gave valid results. Of the 37 pooled tests for which a valid result was not obtained, 3 were positive for CT, 3 were positive for NG and 1 was positive for both CT and NG on individual tests. The CT positive and negative percent agreement were 95.8% (95% CI: 85.7%, 99.5%) and 99.1% (97.3%, 99.8%), respectively. The NG positive and negative percent agreement were 96.9% (95% CI: 83.8%, 99.9%) and 99.3% (95% CI: 98.3%, 100%), respectively. Pooled testing identified 3 CT and 1 NG infections that were negative at all anatomic sites by individual testing. Conclusion: Three-site pooled CT and NG testing performs similarly to single anatomic site testing among tests providing a valid result. Optimizing the pooled testing protocol (e.g. using a single elution buffer for all 3 swabs) may further enhance this approach. In addition, future studies should evaluate pooled testing with multiple reference tests to allow for a more precise infection status determination. Future cost analyses should evaluate the cost effectiveness of pooled three-site testing to determine if such a strategy improves the feasibility and accessibility of molecular STI testing in both domestic and international settings.

---

**1055 NO EVIDENCE OF CLINICAL IMPACT OF STIs ON SEMINAL HIV BURDEN DURING SUCCESSFUL ART**

_Christof Stingone_1, Rossana Scutari1, Elisabetta Teti1, Lorenzo Piermatteo1, Vincenzo Malagnino1, Marta Brugneti1, Ada Bertoli1, Valentina Sivicher1, Maria M. Santoro1, Carlo Federico Perno1, Claudia Afleti1, Loredana Sarmati1, Massimo Andreoni1, Francesca Ceccherini Silberstein1

_1Hospital of Rome For Vergata, Rome, Italy, 2University of Rome For Vergata, Rome, Italy, 3University of Milan, Milan, Italy_

**Background:** Sexually transmitted infections (STI) are known to increase the HIV shedding in semen of ART naive patients. Their role in influencing the seminal compartment despite peripheral undetectable HIV-RNA is still unclear.

**Methods:** This ongoing study includes 25 HIV-1 patients (pts) with undetectable viremia (<200cps/ml) for at least 1year. At enrolment, 10 were STI-positive (cases:3syphilis, 1M.genitalium, 1U urealyticum urethritis, 1syphilis/C. trachomatis/U.urealyticum co-infection), while 15 were STI-negative.

HIV-DNA and residual viremia (detection limits of 32cps/10^6 CD4+ and 2 cps/ml, respectively) in both blood and seminal compartments by home-made protocols using ddPCR have been analyzed.

**Results:** Pts are mainly MSM (80%), with a median(IQR) age of 37(32-47) years, and median(IQR) CD4+ 772(578-1037) cells/µL. 20 pts were on NRTI-based regimens (3rd drug:NNRTI; NNRTI; 4P), 5 pts were on a dual regimen (2DR;3DRV/c+3TC, 1DRV+/RAL, 1ETR+RAL). No baseline differences were found between cases and controls. Peripheral HIV-DNA was detectable in 20 pts (80%) with a median(IQR) of 612(154-257)1cps/10^6CD4+ (table1). Differently, seminal HIV-DNA was detectable only in 3 pts (12%) 1 case and 2 controls, always with a quantification <32cps/10^6CD4+. Peripheral HIV-RNA was detectable in 16 pts (64%) with a median(IQR) of 2.7(2.0-3.8) cps/ml, whereas 14(56%) pts had seminal detectable HIV-RNA levels (median(IQR) 3.9(2.1-7.9) cps/ml). In both compartments residual RNA levels never exceeded the 20 cps/ml with the exception of 1 2DR-control (congenital infection) who had 39 cps/ml in the seminal compartment. No differences were found when HIV-DNA and -RNA values in both compartments were compared between cases and controls (p=0.13). However, 6 out of 25pts (24%) showed a seminal HIV-RNA detectability despite the peripheral HIV-RNA undetectability. This discordance was more frequently observed in cases (40%) respect to controls (13%) (p=0.17). 7STI cases were analyzed also after antibiotic treatment and resolution. Among these, seminal HIV-RNA was maintained undetectable or showed a reduction in 6 pts (86%), while only one (16.7%) experienced an increase to 12.1cps/ml.

**Conclusion:** These preliminary data show that successful combined ART (3DR or 2DR) avoids the presence of HIV-DNA in the seminal cells in the majority of pts, maintaining HIV-RNA in seminal compartment at non-relevant levels, despite STI.
**1056 RISK OF PELVIC INFLAMMATORY DISEASE WITH CONTRACEPTIVE METHOD USE IN THE ECHO TRIAL**

Kavita Nanda¹, James Kiarie¹, Khatija Ahmed¹, Tsungai Chipato², Margaret P. Kasaro¹, Cheryl M. Lowú⁴, Charles S. Morrison³, Susan Morrison⁴, Nelly R. Mugo¹, Maricahon Onono², Thesla Palanee-Phillips³, Katherine Thomas⁵, Irina Yiannoutsos⁴, James Kiarie², Khatija Ahmed³, Tsungai Chipato⁴, Margaret P. Kasaro², Cheryl M. Lowú⁵, Charles S. Morrison¹, Susan Morrison⁴, Nelly R. Mugo¹, Maricahon Onono², Thesla Palanee-Phillips³, Katherine Thomas⁵, Irina Yiannoutsos⁴

¹University of Washington, Seattle, WA, USA, ²Moi University, Eldoret, Kenya, ³Indiana University, Indianapolis, IN, USA, ⁴University of California San Francisco, San Francisco, CA, USA, ⁵Kenya Medical Research Institute, Nairobi, Kenya

**Background:** Concerns regarding intrauterine devices (IUDs) and the risk of pelvic inflammatory disease (PID) have been debated for decades. Few data are available from high sexually transmitted infections (STI) settings or have validation methodology also highlights a way forward for other studies though the higher rates may be due to recall bias. Our robust and novel contraceptive implant effectiveness is reduced with concomitant efavirenz effectiveness, should be considered for WLHIV already using or interested in use. Dolutegravir-containing ART, which is not anticipated to reduce implant use. Nevirapine- and efavirenz-containing ART users, respectively (IRR 3.8, 95% CI 2.0-7.2).

**Conclusion:** Using probabilistic subsampling, we confirm the prior finding that contraceptive implant effectiveness is reduced with concomitant efavirenz use. Dolutegravir-containing ART, which is not anticipated to reduce implant effectiveness, should be considered for WLHIV already using or interested in contraceptive implants. Self-reports largely corroborated medical records, and we conducted two-phase random sampling with an expanded cohort of women living with HIV (WLHIV) using data from the East Africa International Epidemiology Databases to Evaluate AIDS.

**Methods:** We conducted a random sampling study of WLHIV, from 15 to 45 years of age enrolled in HIV care in western Kenya between January 2011 and December 2015, to validate the exposure of a combination of contraceptive method and ART regimen and primary outcome of incidence pregnancy. We generated a cohort of WLHIV utilizing electronic medical records, and then conducted detailed file reviews for a stratified random subset of the women. We used multivariate Poisson models to compare pregnancy rates among women using different contraceptive and ART combinations, accounting for the second phase sampling with generalized raking inverse probability weighted methods. Lastly, we conducted phone interviews with a further subset of women sampled for the file reviews to compare self-reports against medical records. 

**Results:** 85,819 women contributed 172,378 person-years (p-y) to this analysis. We conducted file reviews for 4,987 women (contributing 16,991 p-y) and phone interviews for 1,275 women (contributing 5,775 p-y). Based on data from the file review, among women using implants in the overall cohort, the pregnancy incidence was 1.1 and 3.3 per 100 p-y for nevirapine- and efavirenz-containing ART users, respectively (incidence rate ratio [IRR] 3.1, 95% CI 2.1-4.5; Table). Among the subset of women using implants with whom we conducted phone interviews, the pregnancy incidence was 2.4 and 9.0 per 100 p-y for nevirapine- and efavirenz-containing ART users, respectively (IRR 3.8, 95% CI 2.0-7.2).

**Conclusion:** Using probabilistic subsampling, we confirm the prior finding that contraceptive implant effectiveness is reduced with concomitant efavirenz use. Dolutegravir-containing ART, which is not anticipated to reduce implant effectiveness, should be considered for WLHIV already using or interested in contraceptive implants. Self-reports largely corroborated medical records, though the higher rates may be due to recall bias. Our robust and novel validation methodology also highlights a way forward for other studies conducted with electronic medical records.

**Table 1. Residual vicemina and Total HIV-DNA in peripheral and seminal compartments.**

<table>
<thead>
<tr>
<th>Residual vicemina (copies/mL)</th>
<th>Total HIV-DNA (copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 STI triple</td>
<td>3.1</td>
</tr>
<tr>
<td>2 Control triple</td>
<td>2.9</td>
</tr>
<tr>
<td>3 Control triple</td>
<td>2.8</td>
</tr>
<tr>
<td>4 Control triple</td>
<td>2.7</td>
</tr>
<tr>
<td>5 Control triple</td>
<td>2.6</td>
</tr>
<tr>
<td>6 Control triple</td>
<td>2.5</td>
</tr>
<tr>
<td>7 Control triple</td>
<td>2.4</td>
</tr>
<tr>
<td>8 Control triple</td>
<td>2.3</td>
</tr>
<tr>
<td>9 Control triple</td>
<td>2.2</td>
</tr>
<tr>
<td>10 Control triple</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**Table 2. PID incidence by study arm.**

<table>
<thead>
<tr>
<th>Study arm</th>
<th>PID incidence (copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>299</td>
</tr>
<tr>
<td>Coppper PID</td>
<td>9 (2, 11)</td>
</tr>
<tr>
<td>LNG implant</td>
<td>6.0 (4.1, 7.0)</td>
</tr>
<tr>
<td>DMPA-IM vs. LNG implant</td>
<td>4.0 (3.6, 5.5)</td>
</tr>
<tr>
<td>DMPA-IM vs. PID</td>
<td>0.7 (0.2, 2.5)</td>
</tr>
</tbody>
</table>

**1057 VALIDATING INCIDENCE PREGNANCIES AMONG WOMEN USING CONTRACEPTIVES AND ANTIRETROVIRALS**

Rena Patel¹, Beatrice Jakait¹, Gustavo Amorin¹, Bryan E. Shepherd¹, Caitlin Bernard⁴, A. Rain Mocello⁴, Beverly Musick⁴, Marisiana A. Onono², Craig R. Cohen³, Elizabeth A. Bukusi⁵, Kara K. Wool–Kaloustian⁶, Constantin T. Yiannoutsos⁴

¹University of Washington, Seattle, WA, USA, ²Moi University, Eldoret, Kenya, ³Vanderbilt University, Nashville, TN, USA, ⁴Indiana University, Indianapolis, IN, USA, ⁵University of California San Francisco, San Francisco, CA, USA, ⁶Kenya Medical Research Institute, Nairobi, Kenya

**Background:** A prior cohort study from Kenya demonstrated reduced effectiveness of contraceptive implants when used in combination with efavirenz-containing antiretroviral therapy (ART). To further validate this finding, we conducted two-phase random sampling with an expanded cohort of women living with HIV (WLHIV) using data from the East Africa International Epidemiology Databases to Evaluate AIDS.

**Methods:** We conducted a random sampling study of WLHIV, from 15 to 45 years of age enrolled in HIV care in western Kenya between January 2011 and December 2015, to validate the exposure of a combination of contraceptive method and ART regimen and primary outcome of incidence pregnancy. We generated a cohort of WLHIV utilizing electronic medical records, and then conducted detailed file reviews for a stratified random subset of the women. We used multivariate Poisson models to compare pregnancy rates among women using different contraceptive and ART combinations, accounting for the second phase sampling with generalized raking inverse probability weighted methods. Lastly, we conducted phone interviews with a further subset of women sampled for the file reviews to compare self-reports against medical records.

**Results:** 85,819 women contributed 172,378 person-years (p-y) to this analysis. We conducted file reviews for 4,987 women (contributing 16,991 p-y) and phone interviews for 1,275 women (contributing 5,775 p-y). Based on data from the file review, among women using implants in the overall cohort, the pregnancy incidence was 1.1 and 3.3 per 100 p-y for nevirapine- and efavirenz-containing ART users, respectively (incidence rate ratio [IRR] 3.1, 95% CI 2.1-4.5; Table). Among the subset of women using implants with whom we conducted phone interviews, the pregnancy incidence was 2.4 and 9.0 per 100 p-y for nevirapine- and efavirenz-containing ART users, respectively (IRR 3.8, 95% CI 2.0-7.2).

**Conclusion:** Using probabilistic subsampling, we confirm the prior finding that contraceptive implant effectiveness is reduced with concomitant efavirenz use. Dolutegravir-containing ART, which is not anticipated to reduce implant effectiveness, should be considered for WLHIV already using or interested in contraceptive implants. Self-reports largely corroborated medical records, though the higher rates may be due to recall bias. Our robust and novel validation methodology also highlights a way forward for other studies conducted with electronic medical records.
1059 A COMBINED ESTROGEN/PROGESTIN VAGINAL RING IMPROVES VAGINAL MICROBIAL COMMUNITIES
Nicole H. Tobin1, Sarah L. Brooker1, Fan Li1, Yoninah S. Cramer1, Susan L. Rosenkrantz2, Grace M. Alfordvanti1, Robert Coombs1, Susan E. Cohn1, Carmen D. Zorrilla1, Laura E. Moran1, Baiba Bezins1, Kimberly K. Scarsi1, Catherine Godfrey1, for the ACTG 5316 Team
1University of California Los Angeles, Los Angeles, CA, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3University of Washington, Seattle, WA, USA, 4Northwestern University, Chicago, IL, USA, 5University of Puerto Rico, San Juan, Puerto Rico, 6Social & Scientific Systems, Silver Spring, MD, USA, 7University of Nebraska Medical Center, Omaha, NE, USA, 8AIDS, NIAID, Bethesda, MD, USA
Background: ACTG study 5316 found that during contraceptive intravaginal ring (IVR) use over 3 weeks, efavirenz-based ART (EFV) significantly decreased both etinyl estradiol (EE) and etonogestrel (ENG) plasma exposure, while azatavir/etonavir-based ART (ATV) decreased EE, yet increased ENG. We explored the role of the IVR on vaginal microbial communities and vaginal small fatty acids (SCFA) as well as the role of the vaginal microbes/SCFA on hormone concentrations.
Methods: Of the 74 participants (25 ART naive; 25 EFV, 24 ATV), 71 had 16S rRNA sequencing of the V4 region on vaginal swabs at weeks 0 (pre-IVR insertion), 1, 2, 3, and 4 (1 week post-IVR removal); and 73 had vaginal aspirate SCFAs measured by Metalab® at weeks 0, 1 or 2, and 4. Sequences were filtered and taxon assigned using DADA2, species using SPINGO with SILVA database, and Lactobacillus using BLAST. Negative binomial and linear regression models identified differentially abundant microbiome and SCFA features, respectively. Spearman correlation assessed relationships between microbiome relative abundance and weekly EE/ENG concentrations.
Results: At baseline, microbial communities of participants could be robustly classified as L. crispatus- or L. iners-dominant (Community Type (CST) I, II, III, n=8), L. gasseri-dominant (CST II, n=2), L. iners-dominant (CST III, n=20), or mixed anaerobic communities (CST IV, n=41). Start of IVR therapy was associated with an increased probability of transition into Lactobacillus-dominant community types (OR=3.39, CI=0.36-32.15), Fisher’s exact test, p<0.001). ENG levels were negatively correlated with abundance of Prevotella tennesonii. After IVR removal, an increased probability of transition into CST IV (OR=7.75, CI=1.56-38.49, p<0.001) was observed, with a decrease in lactic acid levels (p<0.001). Negative binomial modeling of the most abundant taxa between week 1 (during IVR use) and 4 (1 week after IVR removal) showed significant increases in Gardnerella vaginalis, unclassified Prevotella sp., and P. timonensis, and decreases in L. crispatus.
Conclusion: The shift in vaginal microbial communities from Lactobacillus-dominant types (CST I-III) to CST IV following removal of the ENG/EE IVR is concerning. Some women had a favorable response to the IVR, which may suggest this IVR is a therapeutic option for women with bacterial vaginosis. Further investigation is needed to fully assess interactions and safety of vaginal hormonal contraception in women with HIV-1.

1060 CONTRACEPTIVE USE INDUCES DURABLE SHIFTS IN THE FEMALE GENITAL-TRACT MICROBIOTA
Bryan P. Brown1, Mariannan Onono2, Gonasangrie Nair3, Thesla Palanee-Bryan P. Brown1, Mariannan Onono2, Gonasangrie Nair3, Thesla Palanee-Brown1, Thesi Palanee-Phillips4, Caitlin W. Scoville1, Rubina Bunjum1, Tanko F. Ramla1, Kate Keller1, Jared Baeten1, Steven E. Bosinger1, Adam Burgenstein1, Jo-Ann Passmore1, Renee Heffron3, Heather Jaspars1
1Seattle Children’s Research Institute, Seattle, WA, USA, 2KEMRI-UCSF, Kisumu, Kenya, 3Desmond Tutu HIV Foundation, Cape Town, South Africa, 4Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 5University of Washington, Seattle, WA, USA, 6AIDS, NIAID, Bethesda, MD, USA
Background: Vaginal bacterial microbiota modulate genital immunity and susceptibility to HIV and other sexually transmitted pathogens. However, it is unclear how contraceptive use affects the composition and dynamics of these communities.
Methods: Within the ECHO trial, designed to compare the relative HIV-1 incidence among women randomized to copper intrauterine device (Cu-IUD), levonorgestrel implant (LNG-implant), or DMPA-IM, this nested three-site study aimed to evaluate the impact of these contraceptives on genital tract microbiota. 201 were randomly selected (Cape Town, Johannesburg, Kisumu) sub-study aimed to evaluate the impact of these contraceptives on genital tract microbiota. 201 were randomly selected (Cape Town, Johannesburg, Kisumu) sub-study aimed to evaluate the impact of these contraceptives on genital tract microbiota. 201 were randomly selected (Cape Town, Johannesburg, Kisumu) sub-study aimed to evaluate the impact of these contraceptives on genital tract microbiota. 201 were randomly selected from among the 430 in the sub-study for analyses of samples collected at
enrollment (pre-contraceptive initiation), 1-month, and 6-months post-contraceptive initiation. For all samples, the 16S rRNA gene was amplified and sequenced from fluid collected via lateral vaginal wall swabs.

Results: Baseline Shannon diversity was elevated in women randomized to LNG-implant compared to DMPA-IM, but not Cu-IUD. After 1 month of use, there were no differences in Shannon diversity between randomization arms. However, after 6 months of use, there were significant differences in Shannon diversity between all arms, with women randomized to DMPA-IM displaying the lowest bacterial diversity (mean 0.5833), followed by LNG-implant (mean 1.06) and Cu-IUD (mean 1.64). Lactobacillus abundance was significantly reduced between baseline and 6-months post-contraceptive initiation for women randomized to Cu-IUD, which was concurrent with a significant increase in taxa associated with Bacterial Vaginosis. Conversely, women who were randomized to DMPA-IM exhibited significant reductions in the abundance of dysbiotic Prevotella taxa. Significant differences in beta-diversity between randomization arms suggested that community-wide alterations persisted at both 1-month (p = 0.034), and 6-months post-contraceptive initiation (p = 0.004), with women assigned to Cu-IUD transitioning to more diverse bacterial communities.

Conclusion: These are the first data comparing vaginal bacteria among women randomized to effective contraceptives. That Cu-IUD elicits increases in overall bacterial diversity and abundance of dysbiotic taxa relative to DMPA-IM and LNG-Implant suggests that non-hormonal IUDs may have consequences on vaginal microbiota. These results are central to informing contraceptive options for sexual and reproductive health.

1061 GENITAL SECRETIONS FROM WOMEN WITH BACTERIAL VAGINOSIS ENHANCE HIV INFECTION EX VIVO

Maria J. Keller1, Richard Hunte1, Rebecca Barnett1, Joyce Serebrenek1, Jessica McWatters1, April Dobkin1, Jessica Goymer1, Laurie Ray1, Lilia Espinoza1, Jessica M. Atrio1, Kerry Murphy1, Betty Herold1
1Albert Einstein College of Medicine, Bronx, NY, USA, 2Montefiore Medical Center, Bronx, NY, USA

Background: Women with bacterial vaginosis (BV) are more susceptible to HIV. We hypothesized that increased HIV susceptibility is mediated by direct or indirect effects of bacteria on mucosal immunity and the epithelial barrier. To test this hypothesis, we conducted a longitudinal study in women with clinical BV before and after treatment, quantified the ability of cervicovaginal fluid (CVF) to inhibit or enhance HIV infection ex vivo, and correlated the activity with vaginal microbiota, cytokines, chemokines and other soluble immune molecules.

Methods: Cervicovaginal lavage and vaginal swabs were collected from 20 HIV negative adult women in Bronx, New York with symptomatic BV (3 or 4 Amsel criteria). Repeat sampling was done 1 week and 1 month after completion of 7 days of twice daily oral metronidazole treatment. Vaginal pH, Nugent scores, CVF cytokines and chemokines, CVF inhibitory or enhancing activity against HIV infection in a TZMBl assay with BAL, and quantities of select vaginal microbiota in swabs (qPCR) were measured. Results were compared between visits by Friedman’s test. Spearman correlation coefficients were calculated to assess associations between HIV inhibiting/enhancing activity and other measures.

Results: Proinflammatory cytokines were significantly higher and chemokines were significantly lower in women with BV compared to sampling done after BV treatment (IL-1α p = 0.001; IL-1β p = 0.04; CXCL9 p = 0.01; CXCL10 p = 0.03). CVF from women at the time of BV diagnosis enhanced HIV infection significantly by 26% (95% CI 1-8%, 128%) and enhancement decreased significantly 1 month after treatment (p < 0.05). HIV enhancement correlated positively with Nugent score (r = 0.48), IL-1α (r = 0.5), Gardnerella vaginalis (r = 0.55), Atopobium vaginae (r = 0.44), BVAB2 (r = 0.41), Neisseria (r = 0.62), and Megasphaera Type 2 (r = 0.5) and negatively with L. crispatus (r = -0.4), MIP-1β (r = -0.43), CXCL9 (r = -0.4), and CXCL10 (r = -0.43) (all p < 0.002). Preliminary mechanistic studies indicate that CVF increases the binding of HIV to target cells.

Conclusion: CVF from women with BV enhanced HIV in vitro and the enhancing activity was associated with specific BV-associated bacteria and IL-1α. Treatment with metronidazole led to a reduction in the enhancing activity. Additional mechanistic studies are in progress to better understand links between HIV enhancing activity and the vaginal microbiome.

1062 DMPA-IM DRIVES CERVICAL Th17 HIV TARGET-CELL ACCUMULATION IN WOMEN IN ECHO TRIAL

Rubina Bunjun1, Tanko F. Ramla1, Shameem Jaumdally1, Hoyam Gamiedien1, Rushil Harryparsad1, Marisana A. Onono1, Gonasangrie Nair1, Thesla Palanee-Phillips1, Carinna W. Scoville1, Kate Keller1, Jared Baeten1, Renee Heffron3, Jo-Anne Passmore3
1University of Cape Town, Cape Town, South Africa, 2Desmond Tutu HIV Foundation, Cape Town, South Africa, 3Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 4KEMRI—Centre for Global Health Research, Kisumu, Kenya, 5University of Washington, Seattle, WA, USA, 6Seattle Children’s Research Institute, Seattle, WA, USA

Background: To definitively assess the relationship between selected contraceptive methods and HIV acquisition risk, the Evidence for Contraceptive Options and HIV Outcomes (CHO) trial randomised women to the copper-T IUD, DMPA-IM and levonorgestrel (LNG) implant with HIV seroconversion as the primary endpoint. Within this trial, we nested mucosal CD4+ T cell studies to determine the impact of contraceptive initiation on Th17 HIV target cells in the genital tract as a potential mechanism for HIV risk.

Methods: Cervical cytobrushes and cervicovaginal secretions from women enrolled in the CHO trial (n = 80) were collected at baseline and within 3 months of initiating contraception. Cervical cytobrush-derived T cells were phenotyped ex vivo by multiparameter flow cytometry, staining for T cell (CD3, CD4, CD8), activation (CD38), mucosal homing (CCR5, a4b7), and Th17 subset markers (CCR6, CCR10). Soluble cytokines and chemokines were measured in secretions using 27-plex LumineX assay.

Results: DMPA-IM induced an increase in the frequency of activated (CD38+) cervical Th17-like cells (p = 0.04), while the other contraceptive arms did not. Despite no contraceptive specific changes in the overall expression of HIV receptors CCR5 or a4b7, 90% of all activated Th17 cells expressed either receptor and were therefore potentially infectable by HIV. Co-expression analyses revealed that women using DMPA-IM had a higher frequency of highly susceptible CD38+ CCR5+ a4b7+ Th17 cells compared to baseline. Neither the copper IUD nor LNG-implant induced an increase in any Th17 population expressing CD38, CCR5 or a4b7 in any combination. Increases in the frequency of susceptible Th17 populations in women using DMPA-IM were not associated with higher concentrations of T cell chemotactic markers IL-8, Eotaxin, IP10, RANTES, MIP-1α or MIP-1β, suggesting that chemotaxis was not the major mechanism for the DMPA-IM driven accumulation of target cells in the genital tract.

Conclusion: For the first time in a randomised clinical trial, we demonstrate that DMPA-IM, but not the copper IUD or LNG-implant, induced an increase in the abundance of potentially infectable Th17 HIV target cells expressing CD38, CCR5 and a4b7 in the female genital tract. Despite their possible susceptibility to HIV infection, Th17 cells play an important role in epithelial barrier repair. It is therefore interesting to speculate whether increased Th17 cell frequency and activation status associated with DMPA-IM reflect epithelial barrier damage.

1063 INCREASED GENITAL INFLAMMATION IN WOMEN RANDOMIZED TO COPPER IUD IN THE ECHO TRIAL

Tanko F. Ramla1, Rubina Bunjun1, Shameem Jaumdally1, Marisana A. Onono1, Gonasangrie Nair1, Thesla Palanee-Phillips1, Carinna W. Scoville1, Jared Baeten4, Renee Heffron3, Heather Jaspan1, Jo-Anne Passmore3
1University of Cape Town, Cape Town, South Africa, 2Desmond Tutu HIV Foundation, Cape Town, South Africa, 3Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 4University of Washington, Seattle, WA, USA

Background: The inflammatory milieu of the lower female genital tract contributes substantially to HIV acquisition risk. In the randomized ECHO trial, we investigated whether the intramuscular injectable depot-medroxyprogesterone acetate (DMPA-IM) influenced genital inflammation, relative to the levonorgestrel implant (LNG-Implant) and non-hormonal copper intrauterine device (Copper-IUD).

Methods: Cervicovaginal secretions (CVS) were collected via menstrual cups at three sites (Cape Town and Johannesburg [South Africa], and Kisumu [Kenya]) from women who participated in the ECHO trial comparing HIV incidence rates among women randomized to (1:1:1) to different types of contraceptives. For this sub-analysis, concentrations of 27 cytokines were measured by LumineX in matched CVS from 190 women (DMPA-IM: n = 67; LNG-Implant: n = 63; Copper-
IUD: n=60) with samples collected at baseline (pre-contraceptive initiation), 1 and 6 months post-contraceptive initiation.

**Results:** After adjusting for multiple comparisons, genital cytokine concentrations were significantly elevated at 6 months post-contraceptive initiation in women randomized to Copper-IUD compared to matched baseline. These included IL-1β (p=0.0002), IL-6 (p=0.0003), TNF-α (p=0.0002), MIP-1α (p=0.0002), MIP-1β (p=0.0003), IP-10 (p=0.005) and IL-8 (p=0.001). In contrast, there were no significant changes in cytokine levels in DMPA-IM and LNG-Implant users at 6 months post-contraceptive initiation. No changes in CVS cytokines were observed at 1 month post-contraceptive initiation in any arm.

**Conclusion:** Overall, these results show that use of the Copper-IUD non-hormonal contraceptive option in ECHO, appeared to be more inflammatory than the hormonal contraceptives DMPA-IM or LNG-Implant. Despite the ECHO trial showing no significant difference in HIV incidence between the three contraceptive arms, our finding of late rather than early genital inflammation in women using the Copper-IUD requires further investigation.

### 1064 ELEVATED GENITAL CYTOKINES IN HIV-INFECTED WOMEN USING COPPER AND LEVONORGESTREL IUDs

**Jo-Ann Passmore**1, Musalula Sinkala2, Nai-Chung Hu3, Shameen Jaumadally1, Hoyam Gamieldien1, Smritee Dabee1, Heidi Jones2, Donald R. Hoover3, Nontokozo Langwenya1, Landon Myer1, Catherine S. Todd4

1University of Cape Town, Cape Town, South Africa, 2City University of New York, New York, NY, USA, 3Rutgers University, Piscataway, NJ, USA, 4FHI 360, Durham, NC, USA

**Background:** Intrauterine contraceptive devices (IUCD) may increase genital inflammatory cytokine concentrations in HIV+ women despite antiretroviral therapy (ART). We compared the effect of copper (cIUCD) versus levonorgestrel intrauterine system (LNG-IUS) on genital cytokines in both ART using (ART+) and non-ART using (ART-) women.

**Methods:** In a secondary analysis of an RCT, menstrual cup cervicovaginal secretions (CVS) were collected in ART- and ART+ women randomized 1:1 to cIUCD or LNG-IUS. 28 cytokines were measured in 104 age-matched participants with CVS collected at enrollment and then 3 and 6 month post-IUCD insertion (ART- n=48; ART+ n=56). We compared cytokine clustering by IUCD and ART use by Principle Component Analysis (PCA) and Partial Least Squares Discriminant Analysis (PLSDA).

**Results:** CVS cytokines clustered separately at baseline, with 17/28 higher in ART+ than ART- women, including IL1b, IL1a, IL6, MIP1a, MIP1b, RANTES, IP10, and Eotaxin in ART+. Only genital tract VL (qVl) correlated positively with IL1b (R=0.72; 95%CI 0.55-0.84) and ILB concentrations (R=0.66; 95%CI 0.47-0.80). None of the cytokines predicted qVl in ART+. Compared to baseline CVS, cIUCD insertion in ART- women resulted in significantly elevated concentrations of IL-6, MCP-1, MIP-1a, MIP-1b, RANTES, GCSF, IL-15 at 3-month follow-up, of which MCPI, MIP1a, and GCSF remained high at 6m. A more significant increase in CVS cytokines was observed after cIUCD insertion in ART+ women, with 19/29 cytokines elevated at 3-months, of which 15 remained high at 6m. In contrast, among ART- women, LNG-IUS resulted in suppression of IL12p70, IP10, VEGF, GM-CSF at 3-months (IL12p70 and VEGF remaining low at 6 months). In contrast to baseline CVS, cIUCD insertion in ART+ women resulted in significantly elevated concentrations of IL-6, MCP-1, MIP-1a, MIP-1b, RANTES, GCSF, IL-15 at 3-month follow-up, of which MCPI, MIP1a, and GCSF remained high at 6m. A more significant increase in CVS cytokines was observed after cIUCD insertion in ART+ women, with 19/29 cytokines elevated at 3-months, of which 15 remained high at 6m. In contrast to baseline CVS, cIUCD insertion in ART+ women resulted in significantly elevated concentrations of IL-6, MCP-1, MIP-1a, MIP-1b, RANTES, GCSF, IL-15 at 3-month follow-up, of which MCPI, MIP1a, and GCSF remained high at 6m. A more significant increase in CVS cytokines was observed after cIUCD insertion in ART+ women, with 19/29 cytokines elevated at 3-months, of which 15 remained high at 6m. In contrast to baseline CVS, cIUCD insertion in ART- women resulted in suppression of IL12p70, IP10, VEGF, GM-CSF at 3-months (IL12p70 and VEGF remaining low at 6 months). In ART- women, LNG-IUS had a more moderate effect than cIUCD, with 6/28 cytokines elevated at 3 months, of which half resolved by 6 months. Despite differences in cytokine changes in cIUCD compared to LNG-IUS users, overall profiles did not differ significantly by IUCD type by PCA. PLSDA suggested that MCPI best differentiated IUCD groups, irrespective of ART status.

**Conclusion:** These data suggest that cIUCD insertion was associated with increased genital cytokine concentrations in HIV+ women irrespective of ART status. LNG-IUS was initially less inflammatory, particularly in ART- women. Although certain genital cytokines were positively associated with qVl in ART-, changes in inflammatory profiles associated with either IUCD did not increase qVl in ART-.

### 1065 MOLECULAR PERTURBATIONS INDUCED BY DMPA, COPPER IUD, AND LNG IMPLANT IN ECHO TRAIL

**Prachi M. Gupta**1, Sydney A. Nelson2, Gregory K. Tharp3, Mariciah A. Onono1, Gonasangrie Nair4, Thesla Palanee-Phillips5, Hossaena Ayle6, Laura Noel-Romaz7, Kelly Arnold1, Jared Baeten1, Jo-Ann Passmore1, Adam Burgener1, Heather Jaspan8, Renee Heffron9, Steven E. Bosinger1

1Yerkes National Primate Research Center, Atlanta, GA, USA, 2Kenya Medical Research Institute, Nairobi, Kenya, 3Desmond Tutu HIV Foundation, Cape Town, South Africa, 4Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 5University of Manitoba, Winnipeg, MB, Canada, 6University of Michigan, Ann Arbor, MI, USA, 7University of Washington, Seattle, WA, USA, 8University of Cape Town, Cape Town, South Africa

**Background:** Previous studies have suggested alterations in mucosal immunity in women using hormonal contraceptives, specifically intramuscular depot medroxyprogesterone acetate (DMPA-IM). The results of the ECHO trial found that women randomized to DMPA-IM, copper intrauterine device (IUD), and the levonorgestrel (LNG) implant experienced similar HIV incidence rates. Transcriptomics and proteomics of genital samples, collected from women in the ECHO trial, were used to characterize molecular perturbations induced in the vaginal compartment by initiation of contraception.

**Methods:** Endocervical cytobrush and vaginal soft cups were collected from a total of 202 women at enrollment and after one month of initiating DMPA, LNG or IUD for RNA-Seq and proteomic analysis. RNA exome capture beads were used to generate enriched libraries for Illumina based RNA-Seq. Paired analyses were carried out for each study-arm using DESeq2, with participant ID and visits as input factors. Gene set enrichment analysis (GSEA) was conducted for each study-arm to identify gene-sets or pathways specifically enriched in one or more study-arm.

**Results:** The number of differentially expressed genes detected between month 1 and enrollment visits were 565, 314, and 83 among women randomized to DMPA-IM, LNG and IUD, respectively. Women using DMPA-IM or LNG showed a higher perturbation in vaginal gene-expression relative to IUD users. GSEA demonstrated that prevalent antiviral signaling pathways (IFNA, IFNG, KEGG RIG-I like and T-cell signaling), had similar enrichment across the three study-arms. Gene-sets comprising genes related to inflammatory responses, NFkB target genes and serpins were differentially induced in the three study-arms. Mass spectrometry based proteomic analysis of murine fluid identified 1021 human proteins in the (150) participants profiled, identifying proteins involved in inflammation, antimicrobial activity, epithelial function, and humoral immunity.

**Conclusion:** These data demonstrate enhanced perturbation of inflammatory pathways among women using DMPA-IM and LNG that provide mechanistic insights into the biological impact of these contraceptives. While the magnitude and/or durability of these changes do not ultimately impact HIV susceptibility, they may have implications for other sexually transmitted infections.

### 1066 COPPER IUD AND LEVONORGESTREL INSERTION GENETIC INFLAMMATION IN THE ECHO TRIAL

**Jennifer Deese**1, Nina Radzyv1, Bahiah Meyer1, Pai-Lien Chen1, Sophie Gao1, Charles S. Morrison2, Celia Mehou-Loko3, Florence L D’Hellencourt4, Gregory Buck5, Jennifer Smit6, Jerome Strauss1, Kavita Nanda1, Khatija Ahmed1, Rushil Harrrypad2, Lindi Masson3

1FIH 360, Durham, NC, USA, 2University of Cape Town, Cape Town, South Africa, 3Virginia Commonwealth University, Richmond, VA, USA, 4MatCH, Durban, South Africa, 5Setshaba Research Center, Pretoria, South Africa

**Background:** The Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial found no substantial difference in HIV acquisition risk between women randomised to injectable depot medroxyprogesterone acetate (DMPA-IM), copper intrauterine device (IUD) or the levonorgestrel (LNG) implant. However, ECHO did not address whether these contraceptives increase HIV risk relative to other contraceptive methods or to no contraception. We investigated the impact of DMPA-IM, copper IUD and LNG implant on cervicovaginal inflammatory profiles previously associated with HIV acquisition, among a sub-cohort of ECHO participants.

**Methods:** This study included 168 ECHO participants at the Setshaba Research Centre in Tshwane and MRU in eThekwini, South Africa. Eleven cytokines and antimicrobial peptides were measured in duplicate using Luminex in lateral vaginal wall swabs. Changes in cytokine concentrations were assessed using Wilcoxon signed rank test and generalized linear modelling. P values were adjusted for multiple comparisons using a false discovery rate procedure.

**Results:** Baseline cervicovaginal cytokine concentrations were elevated in women with Neisseria gonorrhoeae infection and dampened among herpes simplex virus (HSV)-2 seropositive women. Younger women had higher concentrations of IL-8 and IL-1β. The copper IUD and LNG implant were associated with rapid increases in inflammatory markers following contraceptive initiation. Pro-inflammatory IL-1β and IL-6 and chemotactic IL-8,
IP-10, MIP-1α and MIP-1β were significantly elevated one month following copper IUD insertion. No changes were evident at one month post LNG implant insertion, however at three months, TNF-α, IP-10, MIP-3α and SLPI were significantly raised relative to baseline. Significant effect modification was observed by N. gonorrhoeae and HIV-2 infection.

**Conclusion:** The copper IUD and the LNG implant are associated with increased cervicovaginal inflammatory markers that have been linked to HIV infection risk. These effects are modified by STI status. Recent studies have demonstrated the important interplay between inflammation, the microbiome, contraception and HIV risk. Continued research to understand these effects are critical for safe contraceptive use and to inform novel contraceptive development.

### 1067 DOUCHING IS ASSOCIATED WITH RECTAL INFLAMMATION IN HIV-NEGATIVE SEXUAL MINORITY MEN

**Angela M. McGaugh**, Charlene Miller, Justice King, Kathryn McManus, Maria L. Alcande, Jose Bauermeister, Christian Grov, Jennifer A. Manuzak, Courtney Broedlow, Robert Parisi, Darling Martinez, Nichole Klett, Adam W. Carico1

**University of Miami, Miami, FL, USA, 2University of Pennsylvania, Philadelphia, PA, USA, 3City University of New York, New York, NY, USA, 4AIDS Healthcare Foundation, Los Angeles, CA, USA**

**Background:** Rectal douching may increase vulnerability to HIV and other sexually transmitted infections (STIs) in sexual minority men (i.e., gay, bisexual, and other men who have sex with men). However, relatively little is known about the pathways whereby rectal douching could amplify biological vulnerability to HIV and other STIs.

**Methods:** Participants were recruited in four STI clinics in South Florida operated by the AIDS Healthcare Foundation. Rectal swabs for 92 participants who reported engaging in condomless receptive anal intercourse (CRAI) and no antibiotic use in the past three months were selected to measure inflammatory cytokines using LEGENDplex. Multivariate logistic regression analyses examined the independent associations of rectal douching with detectable levels of rectal interleukin-6 (IL6), interleukin-8 (IL8), and tumor necrosis factor – alpha (TNF-α). Models were adjusted for age, pre-exposure prophylaxis (PrEP) use, and number of CRAI partners in the past three months.

**Results:** Participants were between 19 and 80 years old (mean age=34.6; SD=13.7) and 54% were ethnic minorities (37% Hispanic/Latino, 14% Black/African American, and 3% other ethnic minority). Approximately 28% of participants were taking PrEP, 90% reported testing negative for HIV in the past year, and nearly 70% reported rectal douching. Participants who douched reported more CRAI partners (Cohen’s d = 0.51; p < 0.01) and more instances of CRAI with ejaculation (Cohen’s d = 0.50; p = 0.03). As shown in the Figure, a significantly greater proportion of men who douched had detectable rectal IL-6 (80% versus 44%; p = 0.002) and IL-8 (69% versus 41%; p = 0.019). In adjusted analyses, douching was independently associated with more than 4-fold greater odds of detectable rectal IL-6 (adjusted odds ratio [AOR] = 4.78; 95% CI = 1.45 – 15.76) and more than 3-fold greater odds of detectable rectal IL-8 (AOR = 3.12; 95% CI = 1.06 – 9.19).

**Conclusion:** This study is among the first to observe that rectal douching is independently associated with rectal inflammation, which was assessed using non-invasive rectal swabs. Novel behavioral and biomedical approaches that mitigate heightened rectal inflammation in sexual minority men who douche could reduce biological vulnerability to HIV or other STIs.

### 1068 SEXUAL VIOLENCE EXPOSURE DYSREGULATES HIV-ASSOCIATED IMMUNE BIOMARKERS IN WOMEN

**Annette Aldous**, Jason Daniels, Christopher Joy, Mariel Jais, Kaleigh Connors, Hani Mohamed, Brendan Capozzi, Sam Simmens, Manya Magnus, Asfsoon Roberts, Gary Simon, Mimi Ghosh

**1George Washington University, Washington, DC, USA**

**Background:** HIV/AIDS and sexual violence act synergistically to adversely and disproportionately impact women’s health. Yet immuno-biological mechanisms linking sexual violence and increased HIV susceptibility are incompletely understood. We aimed to determine systemic and mucosal immune dysregulation in women who had experienced recent sexual violence.

**Methods:** We conducted a cross-sectional study of premenopausal, HIV-negative women from the Washington DC area, comparing 13 cases who had experienced forced vaginal penetration (FVP) within the past 12 weeks and 25 controls who had never experienced FVP. Clinical data as well as plasma and cervicovaginal lavage (CVL) samples were collected and ELISA assays performed to measure inflammatory, anti-inflammatory, anti-HIV, and wound healing biomarkers. We modeled differences between cases and controls using linear and logistic regression with inverse probability of treatment weighting based on age, race, insurance status, menstrual cycle phase, hormonal contraceptive use, and other contraceptive use. We used the Benjamini–Yekutieli method to control the false discovery rate (FDR) for 47 tests.

**Results:** In CVL, cases had reduced levels of chemokines MIP-3α (p = 0.003) and MCP-1 (p < 0.001) and anti-HIV/wound-healing marker Thrombospondin-1 (TSP-1) (p = 0.027). Conversely, they had increased inflammatory cytokine IL-1α (p = 0.001) and were more likely to have detectable levels of wound-healing platelet derived growth factor (PDGF) (OR=7.89; p=0.019). In plasma, cases had decreased levels of chemokines MIP-3α (p < 0.001) and IL-8 (p = 0.004), anti-inflammatory cytokine TGF-β (p = 0.016), anti-HIV factor beta defensin 2 (HBD2) (p = 0.017), and wound-healing protease MMP-1 (p = 0.019). They had higher levels of protease Cathepsin B (p = 0.010) and TSP-1 (p = 0.003) and were more likely to have detectable chemokine IP-10 (OR=12.24; p = 0.064). The associations of case status with reduced MCP 1 in CVL and reduced MIP 3α in plasma remained statistically significant at α = .05 after FDR adjustment.

**Conclusion:** We found indications of distinct systemic and mucosal immune dysregulation in women who had experienced recent sexual violence. As some of these biomarkers have been associated with HIV infection and pathogenesis, dysregulation may increase HIV susceptibility in these women. This data informs future studies on HIV prevention in the setting of sexual violence and directs development of novel therapeutic interventions and trauma-informed care.

### 1069 ASSESSMENT OF IMMEDIATE INITIATION OF ANTIRETROVIRAL THERAPY IN NEW YORK CITY

**Daniel Bertolino**, Erica D’Aquila, Nadia Nguyen, Denis Nash, Abigail Baim-Lance, Bisrat Abraham

**1New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, 2New York State Psychiatric Institute, New York, NY, USA, 3City University of New York, New York, NY, USA**

**Background:** Rapid or immediate initiation of antiretroviral therapy (IART) after a positive HIV test has been shown to decrease time to viral suppression (VS), in turn reducing transmission of HIV. New York City (NYC) and New York State (NYS) have expanded access to IART for people living with HIV (PLWH) through targeted programs at clinics in NYC. We evaluated IART knowledge, attitudes, and practices among clinical and non-clinical-staff in NYC clinics, as well as barriers and facilitators to IART implementation.

**Methods:** We recruited at least one clinical (i.e., medical provider) and one non-clinical (i.e., administrator or social service provider) staff member to complete an online survey from a purposive sample of 30 NYC clinics providing primary care to one or more PLWH. Clinics were selected to ensure a diverse...
representation of health outcomes (e.g., clinic VS), clinic resources (e.g., IART funding) and clinic location and type (e.g., borough, hospital-based clinic). Descriptive and bivariate analyses were performed on collected data.

**Results:** We received 46 survey responses, representing 25 NYC clinics, 98% of which reported prior knowledge of IART. Over 80% of respondents identified IART as decreasing time to VS and increasing patient retention. Overall, 80% and 67% of respondents agreed that ART should be initiated on the same-day or within three to four days of a positive HIV test, respectively. Conversely, 51% of respondents believed ART should not be initiated prior to confirmatory test results, with non-clinical staff being more likely to hold this belief (odds ratio [OR]: 4.64, 95% confidence interval [CI]: 2.41-9.33). Among all respondents, 66% reported zero to four days as the typical length of time from a positive HIV test to ART initiation. Clinics serving a majority of people of color were less likely to meet the same-day benchmark (OR: 0.15, 95% CI: 0.02-0.95). Commonly reported facility-level and patient-level barriers to IART included: insurance barriers (76%), medication prior authorization (50%), financial barriers (46%), and concern about false positives (37%). ART medication starter packs (63%) and patient education materials (52%) were the most commonly reported facilitators to IART.

**Conclusion:** Despite high levels of knowledge around the benefits associated with IART, it is not yet the standard of care across NYC clinics. The proven benefits of IART warrant further efforts to overcome barriers to implementation, with a focus on achieving health equity.

---

### Table 1. Knowledge, attitudes, and practice around immediate initiation of antiretroviral therapy (IART) by staff role and clinic-level patient demographics

<table>
<thead>
<tr>
<th>Knowledge</th>
<th>Staff Role</th>
<th>No (n=19)</th>
<th>Yes (n=27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IART offered on same day</td>
<td>Research staff</td>
<td>9 (50)</td>
<td>10 (59)</td>
<td>0.70</td>
</tr>
<tr>
<td>IART offered on same day</td>
<td>Facility staff</td>
<td>3 (16)</td>
<td>10 (59)</td>
<td>0.24</td>
</tr>
<tr>
<td>IART offered on same day</td>
<td>Research staff</td>
<td>4 (21)</td>
<td>13 (76)</td>
<td>0.019</td>
</tr>
<tr>
<td>IART offered on same day</td>
<td>Facility staff</td>
<td>1 (6)</td>
<td>14 (78)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Table 1070**

**A STRUCTURED ALGORITHM FOR SAME-DAY ART INITIATION: SLATE II TRIAL PRIMARY OUTCOMES**

Mhairi Maskew, Alana T. Brennan, Matthew P. Fox, Lungisile Vezi, Willem D. Venter, Peter Ehrenkranz, Sydney Rosen

**Health Economics and Epidemiology Research Office, Johannesburg, South Africa, Boston University, Boston, MA, USA, Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, Bill and Melinda Gates Foundation, Seattle, WA, USA**

**Background:** Many countries, including South Africa, encourage same-day initiation (SDI) of antiretroviral therapy (ART), but evidence on how to implement SDI and its impact on outcomes remains scarce. Building on the Simplified Algorithm for Treatment Eligibility trial (SLATE I), in which nearly half of participants were ineligible for same-day initiation due mainly to TB symptoms, we evaluated the revised SLATE II algorithm, which allowed SDI for patients with mild TB symptoms and other less serious reasons for delay.

**Methods:** SLATE II was a 1:1 individually randomized trial at 26 public outpatient clinics in Johannesburg that enrolled patients presenting for an HIV test or any HIV care but not yet on ART. Intervention arm patients were assessed with a symptom self-report, medical history, brief physical examination, and readiness questionnaire to distinguish patients eligible for immediate ART dispensing from those requiring further care, tests, or counseling before initiation. Standard arm patients received usual care. Using routine clinic records, we report initiation in 0 (same day), 7, and 28 days after study enrollment and retention in care 8 months after study enrollment.

**Results:** From 3/14/18–9/21/18, we enrolled 593 adult HIV+, non-pregnant patients (median[IQR] age 35 [29-43]; 63% [n=373] female; median CD4 count 293 [133-487]). In the intervention arm, 87% initiated on the same day, compared to 38% in the standard arm (Table). Initiation was higher in the intervention vs standard arm by 7 days (91% vs 68%; RD: 23%, 95% Cl: 17-29%)

and 28 days (94% vs 82%; RD: 12%; 95% Cl: 7-17%) after enrolment. By 8 months after study enrolment, 70% (207/296) intervention and 55% (163/297) standard arm patients had initiated ART ≤ 28 days and were retained in care (RD 15%; 95% CI 7-23%). Nearly half (140/296, 47%) of intervention arm patients reported no TB symptom; 39 (13%) were severe enough to require delay for further investigation, and 6 (2%) were diagnosed with TB. No serious post-initiation adverse events were reported. Nearly all patients (98.5%) stated they would like to start same-day if possible.

**Conclusion:** More than 85% of patients presenting for HIV testing or care, including those newly diagnosed, were eligible and ready for same-day initiation under SLATE II algorithm. The algorithm increased initiation in ≤ 7 days by 28% and retention in care at 8 months by 15%, offering a practical approach to enhance ART initiation in resource-limited settings.

---

**Table 1071**

**ASSOCIATION BETWEEN TIME TO ART AND LOSS TO CARE AMONG NEWLY DIAGNOSED PLHIV IN RWANDA**

Jonathan Ross, Gaid Murenzi, Donald R. Hoover, Quhu Shi, Hae-Young Kim, Benjamin Muhoza, Athanase Munyaneza, Remera Eric, Sabin Nsanzimana, Marcel Yotiebegi, Denis Nash, Kathryn Anastasi

Albert Einstein College of Medicine, Bronx, NY, USA, Rwanda Military Hospital, Kigali, Rwanda, Rutgers University, Piscataway, NJ, USA, New York Medical College, Valhalla, NY, USA, Rwanda Biomedical Centre, Kigali, Rwanda, City University of New York, New York, NY, USA

**Background:** Nearly all countries have adopted WHO “Treat All” guidelines to initiate antiretroviral therapy (ART) for all people living with HIV (PLHIV) as soon as possible after diagnosis. An emerging literature suggests it is important to characterize the relationship between time to ART initiation and subsequent clinic outcomes under Treat All. We compared loss to follow up (LTFU) and viral suppression (VS) among PLHIV in Rwanda by time from diagnosis to ART initiation.

**Methods:** Cohort study in 10 Rwandan health centers of adults ≥15 years who were newly diagnosed with HIV from 1 July 2016 to 15 September 2018. We used Kaplan-Meier survival curves and Cox proportional hazard regression to examine associations between time from diagnosis to ART initiation (same day, 1-7, 8-30, >30 days) and LTFU (>120 days since last clinic visit and did not knowingly die or transfer) in the 15 months after diagnosis. Among patients with measured viral loads after ART initiation, we used log binomial regression to calculate risk ratios for VS (<200 copies/ml on most recent viral load >3 months after ART initiation), by time to ART.

**Results:** Among 1871 patients, 1895 (96%) initiated ART. Of ART initiators, 292 (16%) initiated on the same day as diagnosis, 452 (24%) from 1-7 days, 768 (41%) from 8-30 days, and 382 (20%) >30 days after diagnosis. Compared to those initiating ART later, same day initiators were more likely to be female (70 vs 54%), had lower median age (30 vs 33 years) and had higher median baseline CD4 count (468 vs 411 cells/mm3, p<0.001 for all). LTFU occurred among 25%, 15%, and 17% of same day, 1-7, 8-30, and >30 day initiators, respectively. After adjusting for health center, age, sex, enrollment source, BMI, WHO stage, and CD4 count, compared to those initiating on the same day, hazard of LTFU was lower among patients initiating ART later (1-7 days: adjusted hazard ratio [aHR] 0.66, 95% CI 0.47-0.92; 8-30 days: aHR 0.68, 95% CI 0.51-0.92; and >30 days: aHR 0.47, 95% CI 0.32-0.68). Among 1084 patients with measured viral loads >3 months after ART initiation, 958 (88%) were suppressed; there were no differences in probability of VS by time to ART.

---

**Table 1:** Time to ART initiation by study arm

<table>
<thead>
<tr>
<th>Time to ART Initiation</th>
<th>Standard arm, n=593</th>
<th>Intervention arm, n=593</th>
<th>Risk difference</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 days (current test)</td>
<td>154 (26%)</td>
<td>237 (40%)</td>
<td>0.26 (1.35-3.89)</td>
<td></td>
</tr>
<tr>
<td>≥ 7 days</td>
<td>202 (17%)</td>
<td>270 (45%)</td>
<td>0.34 (2.34-4.5)</td>
<td></td>
</tr>
<tr>
<td>≥ 28 days</td>
<td>219 (18%)</td>
<td>267 (45%)</td>
<td>0.46 (2.67-8.4)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** authToken: eee1d8f4837c1769d1ef01a9232c5810
Conclusion: In this cohort of PLWH entering care after implementation of Treat All, patients initiating ART on the day of diagnosis were more likely to be lost to care than those initiating later. Ensuring adequate support for PLWH initiating ART rapidly is important to maintain engagement in care.

1072 SAME-DAY ART IN THAILAND: THE IMPACT OF ART INITIATION PERIODS ON TREATMENT OUTCOMES

Pich Seekeaew1, Sorawit Amatavej1, Nipat Teertatakulpirc1, Prantana Leenasirimakul1, Sawimon Khuswasuwan2, Teerarat Chuntachon2, Ampaipitil Nimlanat1, Suriyong Boopachrun3, Oranuch Nampaisarn3, Reshmie Ramautarsing4, Stephen Mills5, Ravipa Vannakiti6, Praphan Panuphak1, Nittaya Panuphak7

1Columbia University, New York, NY, USA, 2Thai Red Cross AIDS Research Center, Bangkok, Thailand, 3Nakornping Hospital, Chiang Mai, Thailand, 4Chiang Rai Prachanukroh Hospital, Chiang Rai, Thailand, 5Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand, 6Hat Yai Hospital, Songkhla, Thailand, 7Hat Yai Hospital, Songkhla, Thailand, 8University of Florida, Gainesville, FL, USA

Background: Despite the World Health Organization’s recommendation on same-day antiretroviral therapy (ART) for clients who are ready, there are still concerns around the effect of immediate ART on care outcomes. This study evaluates the influence of different ART initiation durations on retention, viral load suppression, and adverse events on clinically-eligible clients in same-day ART cohort in Thailand.

Methods: Data was obtained from HIV-positive clients from 10 facilities in 6 provinces (Chiang Rai, Chiang Mai, Chonburi, Ubonratchathani, Bangkok and Songkhla) between July 2017–July 2019. Baseline laboratory tests and chest X-rays were performed according to national guidelines. ART eligibility was determined by a physician. Clinically-eligible clients were included in the analysis, and categorized into the duration between care engagement and ART initiation: same-day, 2-7 days, 8-14 days, 15-21 days, and more than 21 days. Logistic regressions were performed to identify factors associated with loss to follow-up at months 3, 6, and 12 after ART initiation, as well as adverse events (AEs).

Results: Of 4,642 clients who agreed to start ART, 3,888 (83.8%) were clinically eligible and started ART; 30%, 64%, and 6% of these identified as general population, men who have sex with men (MSM), and transgender women (TGW), respectively. The following results presented are in order of same-day, 2-7 days, 7-14 days, 14-21 days, and more than 21 days categories. The numbers of clients were: 3,053 (78.5%), 484 (12.5%), 164 (4.2%), 67 (1.7%), and 120 (3.1%), respectively. At month 3, retention rates were: 98.8%, 94.5%, 96.2%, 95.1%, and 96.5% (p = 0.695). At month 6, retention rates were 92%, 95.5%, 96.6%, 90.9%, and 90.7% (p = 0.153). At month 12, retention rates were: 95.6%, 95.7%, 100%, and 95.2%. (p = 0.921) Reports on clinical AEs were: 15.3%, 14.4%, 13.4%, and 10.8% (p = 0.685). Reports on death were: 0.4%, 0.6%, 0.6%, 0%, and 0.8% (p = 0.895). Viral load suppression rates were: 94%, 94%, 84.4%, 100%, and 88.2% (p = 0.054). When compared to general population, TGW were more likely to be lost to follow-up (OR=1.795% CI:1.03-2.8;p<0.05) and had AEs (OR=1.52;95% CI:1.07-2.12;p<0.05).

Conclusion: Same-day ART did not lead to an increase in loss to follow-up, adverse events, or death among clinically-eligible clients, and viral load suppression did not differ by timing of ART initiation. Service for TGW may need to integrate gender-affirming care to enhance ART retention.

1073 RAPID START LEADS TO SUSTAINED VIRAL SUPPRESSION IN YOUNG PEOPLE IN THE SOUTH

Lorna Seybolt1, Katherine Conner2, Isolde Butler3, Nicholas Van Sicksel1, Jason Halperin1

1CrescentCare, New Orleans, LA, USA

Background: HIV incidence continues to increase in young men of color. Youth living with HIV, also, have lower rates of viral suppression and retention in care. Rapid Start is a linkage-to-care intervention to start people newly diagnosed with HIV immediately on ART and support equity in care. Our prior data has shown that rapid ART initiation improves linkage and viral suppression. Rapid Start data for US youth has not been published. To verify that youth were achieving similar outcomes, we developed a continuum of care for our young adult rapid start population and compared this continuum to our adult population.

Methods: Newly diagnosed patients were linked within 72 hours of diagnosis (often same-day) to CrescentCare, a Federally Qualified Health Center in New Orleans. The first dose was directly observed and patients were provided a 30-day dose pack. Labs were drawn and patients underwent expedited insurance enrollment. The proportion achieving viral suppression, time to viral suppression, sustained viral suppression 12 months post-diagnosis and engagement in care at 12 months were compared between youth (18 – 24) and adults.

Results: 124 patients were enrolled in our rapid start intervention between 12/1/2016 and 5/15/2018. Ninety-three were 25 or older with a median age of 33. Thirty-one were under 25 with a median age of 21. All patients chose to start ART, and none stopped due to adverse effects. 96.8% (30/31) of the youth population achieved viral suppression with a median of 29 days from diagnosis. 83.9% (26/31) remained virally suppressed at 12 months post-diagnosis and 96.8% (30/31) remained engaged in care. 97.9% (91/93) of the adult population achieved viral suppression with a median of 28 days from diagnosis. 92.5% (86/93) remained virally suppressed at 12 months post-diagnosis and 97.9% (91/93) remained engaged in care. There were no significant differences in these outcomes between the two groups.

Conclusion: The intervention outcomes demonstrate that starting adults and youth on ART immediately after diagnosis, before labs are obtained, is safe, well-tolerated, and effective. Viral suppression was quickly achieved and maintained. Rapid Start is a paradigm shift that upholds equity and effectively engages youth.

1074 TREAT-ALL HIV POLICIES AND PATIENT ATTENTION IN SOUTH AFRICA: A PROSPECTIVE STUDY

Dorina Onoya1, Cheryl J. Hendrickson1, Tembeke Sineke1, Mhlaiwakw Mbeke1, Lawrence Long1, Matthew P. Fox1

1Health Economics and Epidemiology Research Office, Johannesburg, South Africa, 2Boston University, Boston, MA, USA

Background: We aimed to determine whether the Universal Test & Treat (UTT) and same-day antiretroviral therapy (ART) policies, instituted in South Africa in September 2016 and 2017, resulted in improvements in patient attrition at 12-month after HIV diagnosis and viral suppression (<400 copies/ml) at six months after ART start.

Methods: We enrolled three cohorts of newly diagnosed HIV infected adults from two primary health clinics in Johannesburg from April to November 2015 (Pre-UTT, n=144), May-September 2017 (UTT, n=178) and October-December 2017 (same-day ART period, n=88). A baseline survey was administered after HIV diagnosis and clinical records were reviewed up to 12 months after HIV diagnosis. We compared patient attrition, defined as being >90 days late for a visit (lost to follow-up (LTFU)) at 12-months, between HIV policy periods using Cox regression. Six-months viral suppression was assessed using log-binomial regression.
1075 IMPACT OF UTT ON VIRAL SUPPRESSION IN SOUTH AFRICA: A NATIONAL COHORT STUDY

Jacob Bor, Matthew F. Fox, Mhairi Maskew, Dorina Onoya, Alana T. Brennan, Noah A. Haber, Till Bärnighausen, Sergio Carmona, Wendy Stevens, Adrian J. Puren, William B. MacLeod

1Boston University, Boston, MA, USA, 2Health Economics and Epidemiology Research Office, Johannesburg, South Africa, 3University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 4Heidelberg University, Heidelberg, Germany, 5National Health Laboratory Service, Johannesburg, South Africa, 6National Institute for Communicable Diseases, Johannesburg, South Africa

Background: Universal Test-and-Treat (UTT) aims to increase rates of viral suppression by extending treatment eligibility to all patients and reducing barriers to initiation of antiretroviral therapy (ART).

Methods: We developed a national HIV cohort through novel linkage of the complete historical laboratory records of South Africa's public sector HIV program, Apr 2004–Mar 2018. Using this cohort, we analyzed the longitudinal patient-level care cascade as observed through routine laboratory monitoring, and how it has changed over time within levels of presenting CD4 counts. Per national treatment guidelines, CD4 counts are collected when a patient first presents clinically with HIV. We analyzed progression from presentation (first CD4) to different stages of the HIV care cascade observed in the labs: an ART lab workflow within 90 days of presentation (ALT/HC/CR, taken prior to starting ART), HIV viral monitoring within 15 months of presentation (indicating a patient is on ART and retained in care), and viral suppression within 15 months of presentation. Patients were followed for 15 months to include routine viral loads at 6 and/or 12-months, with a 3-month buffer. Analyses were stratified by CD4 count at presentation and prevailing treatment guidelines at time of presentation.

Results: 11M patients had a first CD4 count 2004–2016, including 266,479 in the UTT era (Sept–Dec 2016). The share of patients progressing from presentation to ART workup increased over time, from 46% before Aug 2011 to 91% under UTT. These gains were due in part to expansions of ART eligibility, leading to the elimination of discontinuities at prior CD4 thresholds, and in part to improvements affecting patients at all CD4 counts (Fig 1a). Eligibility expansions — and improved access to viral monitoring — also increased the share of patients progressing from presentation to documented viral suppression within 15 months (Fig 1b). Comparing the period just prior to UTT with the UTT era (Fig 1c), the share of patients presenting for care who had an ART workup increased from 78% to 91%; the share virally monitored increased from 54% to 61%; and the share reaching documented viral suppression increased from 38% to 44%.

Conclusion: Despite high rates of progression from first CD4 to ART workup in the UTT era, many patients who present with HIV are not retained through viral monitoring and suppression. UTT has had a small impact on progression from clinical presentation to viral suppression.

1076 HIV-1 DYNAMICS FOLLOWING UNIVERSAL TESTING-AND-TREATMENT WITHIN HPTN 071 (POPART)

William Probert, Rafael Sauter, Michael Pickles, Anne Cori, Helen Ayles, Peter Bock, Deborah J. Donnell, Sarah Fidler, Richard J. Hayes, Christophe Fraser, for the HPTN 071 (PopART) Study Team

1University of Oxford, Oxford, UK, 2Imperial College London, London, UK, 3Zambart, Lusaka, Zambia, 4Desmond Tutu TB Centre, Western Cape, South Africa, 5Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 6London School of Hygiene & Tropical Medicine, London, UK

Background: A universal HIV testing-and-treatment (UTT) approach has been shown to be effective as an intervention in high prevalence areas in sub-Saharan Africa (SSA) to reduce HIV incidence. Community-wide interventions may change the dynamics of the epidemic. Understanding these changes will inform future policy towards achieving zero new infections. Using an individual-based model (PopART-IBM), developed as part of the HPTN 071 (PopART) trial, we project the impact of four scenarios of UTT to 2030 on the distribution of incident cases stratified by categories of sexual risk-taking behaviour.

Methods: Model predictions were made with the PopART-IBM calibrated to data from a representative trial community in Zambia from the HPTN 071 (PopART) trial. The model has been previously validated against the primary endpoint of the trial. The model separates the population into three groups according to sexual risk-taking behaviour based on behavioural questionnaire data, including number of sex partners and use of condoms. The proportions of individuals in each risk group (low 50%, medium 35%, high 15%) were assumed to be static through time. Model projections to 2030 are based on four scenarios: 1) PopART then continuation of UTT in the PopART community; 2) PopART then no UTT; 3) no PopART but nationwide UTT from 2020; 4) no PopART and no UTT.

Results: Making antiretroviral therapy universally accessible to all who are HIV-positive in the PopART community would lead to a decline in prevalence in all risk groups but would concentrate new cases in those with the highest levels of risk-taking behaviour (65% of incident cases vs 54% if no UTT was implemented; figure 1). While population HIV incidence to 2030 decreases, the model predicts continued persistence of an HIV epidemic in the high-risk subpopulation in all scenarios unless nationwide UTT is adopted.

Conclusion: Our results predict that even with a UTT intervention, the proportion and absolute number of new HIV cases in those with the highest levels of sexual risk-taking behaviour would increase, despite overall HIV prevalence decreasing. Our results highlight that targeting of high-risk individuals may be necessary following successful UTT interventions in order to eliminate HIV as a public health issue in SSA.
1077 DRAMATIC DECLINE OF NEW HIV DIAGNOSES IN SUBJECTS NATIVE FROM FRANCE

Adrien Le Guillou1, André Cabie2, Cyrille Delprin3, Pascal Pugliese4, Christine Jacomet5, Maxime Hentzien1, Claudine Duvivier5, Olivia Faucher-Zaegel1, Laurent Cotte1, François Raffi6, Firouze Bani-Sadr1

1CHU de Reims, Reims, France, 2CHU Fort de France, Fort de France, Martinique, 3INSERM, Toulouse, France, 4CHU de Nice, Nice, France, 5CHU de Clermont-Ferrand, Clermont-Ferrand, France, 6Assistance Publique–Hôpitaux de Paris, Paris, France, 7Assistance Publique–Hôpitaux Marseille, Marseille, France, 8Hôpitaux Civils de Lyon, Lyon, France, 9CHU de Nantes, Nantes, France

Background: In France, universal ART (TasP) was recommended at the end of 2013 and PrEP in January 2016. The 3rd UN target (90% patients on cART) was achieved in 2014. As the trends in new HIV diagnosis is a measure of HIV epidemic, we conducted a 6-year longitudinal study to evaluate the change in rates of new HIV diagnosis and describe their epidemiology in a large French multicenter cohort.

Methods: Data were obtained for subjects with a new HIV diagnosis date between 2013 and 2018 from the metropolitan centers of the French Dat’AIDS cohort. HIV diagnosis date was defined as the date of the first known positive HIV serology. Analyses were performed by place of birth (France and abroad) and by contamination route.

Results: During the study period, a total of 68,376 people living with HIV were followed in the Dat’AIDS cohort; 9,543 subjects were newly diagnosed with HIV, 4,253 born in France (90% male; 70.5% MSM), and 4,737 born abroad (39.1% female; 56.7% MSM). HIV prevalence was 12.6%, and did not differ by migration status; population VLS was 77.4%. HIV infection (adjusted odds ratio [aOR], 1.10; 95% confidence interval [CI]: 1.05–1.16) but only in communities with viremia >1%. Both EM and RM had lower proportions of VLS primarily due to less awareness of being HIV positive (Figure). If aware, there were no significant differences in proportion on ART for EM or RM. There was weak evidence that RM had less VLS than long-term in-migrants (93% vs. 88%, p=0.059). On multivariable analysis, adjusted odds of VLS were low for RM (aOR, 0.57; 95% CI: 0.35–0.92) and for those with hazardous alcohol use (aOR, 0.29; 95% CI: 0.45–0.92).

Conclusion: Namibia has achieved a high level of population VLS. Understanding how to reach at-risk migrants with prevention and treatment can help further optimize the national HIV response.

1078 MOBILITY, NEW HIV INFECTIONS, AND PROGRESS TOWARDS THE 90-90-90 TARGETS IN NAMIBIA

Andrea Low1, Karampeet K. Sachathep1, George Rutherford2, Anne-Marie Nitschke3, Adam Wolkon1, Karen M. Banda4, Keisha Jackson1, Chelsea Solmo5, Hetal Patel1, Stephen McCracken1, Sally Findley1, Nicholas Mutenda1

1ICAP at Columbia University, New York, NY, USA, 2University of California San Francisco, San Francisco, CA, USA, 3Ministry of Health and Social Services, Windhoek, Namibia, 4US CDC Windhoek, Windhoek, Namibia, 5CDC, Atlanta, GA, USA, 6Columbia University, New York, NY, USA

Background: Namibia has high HIV prevalence and migration rates, yet little is known about how migration affects HIV transmission. We assessed the impact of mobility on HIV transmission and treatment outcomes using data from the 2017 Namibia Population-based HIV Impact Assessment (NAMPHIA).

Methods: NAMPHIA included a nationally representative sample of adults aged 15–64 years. Recent infection (<130 days) was measured using HIV-1 LAg avidity combined with viral load (>1000 copies/mL) and antiretroviral (ARV) testing data. Awareness of HIV status and ARV use were based on self-report and/or detectable ARVs in blood. Viremia was defined as no viral load suppression (VLS, <1000 copies/mL) regardless of serostatus; community viremia was a weighted average across the sampled enumeration area. Ever migrants (EM) included those who had lived outside their home region, or away from home >1 month in the past 3 years. Recent in-migrants (RM) were those who moved to the community <2 years prior, even if this was an intra-regional move, compared to long-term in-migrants. Hazardous alcohol use was defined using the AUDIT-C scale. Analyses were run on weighted data.

Results: Of eligible adults, 84% (9,671/11,510) of women and 73% (7,268/9,954) of men were interviewed and tested for HIV. Overall, 6.1% reported living outside Namibia, 52.5% had lived in another region, and 28.8% had lived away from home for >1 month; for a total of 62.5% of adults classified as EM; 15.3% of adults were RM. HIV prevalence was 12.6%, and did not differ by migration status; population VLS was 77.4%. RM was associated with recent HIV infection (adjusted odds ratio [aOR], 1.46; 95% confidence interval [CI]: 1.05–1.91) but only in communities with viremia >1%. Both EM and RM had lower proportions of VLS primarily due to less awareness of being HIV positive (Figure). If aware, there were no significant differences in proportion on ART for EM or RM. There was weak evidence that RM had less VLS than long-term in-migrants (93% vs. 88%, p=0.059). On multivariable analysis, adjusted odds of VLS were low for RM (aOR, 0.57; 95% CI: 0.35–0.92) and for those with hazardous alcohol use (aOR, 0.29; 95% CI: 0.45–0.92).

Conclusion: Namibia has achieved a high level of population VLS. Understanding how to reach at-risk migrants with prevention and treatment can help further optimize the national HIV response.

1079 PROGRESS TOWARDS THE 90-90-90 HIV TARGETS IN 11 EU COUNTRIES

Georgia Yourell, Teymur Noori1, Khlodou Porter2, Josip Begovac3, Valerie Delpech2, Enrico Girardi2, Barbara Gunsenheimer-Bartmeyer4, Victoria Hernandez5, Niels Oeber1, Arnd Van Sophem6, Anders Sönnerborg7, Virginia Supervieille8, Robert Zangeleh9, Giota Touloumi10, for the European HIV Continuum of Care Working Group

1University of Athens, Athens, Greece, 2European Centre for Disease Prevention and Control, Stockholm, Sweden, 3University College London, London, London, UK, 4University of Zagreb, Zagreb, Croatia, 5Public Health England, London, London, UK, 6Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, 7Robert Koch Institute, Berlin, Germany, 8Institute of Health Carlos III, Madrid, Spain, 9Copenhagen University Hospital, Copenhagen, Denmark, 10Stichting HIV Monitoring, Amsterdam.
African countries. From January 2018-June 2019, the treatment observatory and analyze facility-level HIV treatment data from 125 health centers in 11 West Africa. Community Treatment Observatory in West Africa to increase accountability for International Treatment Preparedness Coalition (ITPC) established a Regional drug stock-outs, weak health systems and poor quality of care. In 2017, the 39% are virally suppressed. Progress is stymied by low demand for services, are aware of their status, 51% are accessing antiretroviral therapy (ART), and In West and Central Africa, 64% of people living with HIV (PLHIV) Background: In West and Central Africa, 64% of people living with HIV (PLHIV) are aware of their status, 51% are accessing antiretroviral therapy (ART), and 39% are virally suppressed. Progress is stymied by low demand for services, drug stock-outs, weak health systems and poor quality of care. In 2017, the International Treatment Preparedness Coalition (ITPC) established a Regional Community Treatment Observatory in West Africa to increase accountability for the 90-90-90 targets. Methods: ITPC trained and supported national networks of PLHIV to collect and analyze facility-level HIV treatment data from 125 health centers in 11 West African countries. From January 2018-June 2019, the treatment observatory conducted 1781 monthly monitoring visits to the health centers, complemented by 1501 interviews, and 143 focus group discussions. Feedback was provided to communities, government and health center staff on a quarterly basis to help improve performance. Results: At the monitored health centers, the number of HIV tests performed increased from 161,647 in the first six-month period, to 246,604 in the second, and fell to 223,612 in the third. HIV-positive yield rose from 3.0%, to 5.4%, to 5.5%, respectively. The frequency of ART stock-outs decreased over the course of the project. Stock-outs were recorded during 23.6% (95% CI 19.9%-27.2%) of health center visits in the first period, declining to 16.4% (95% CI 13.6%-19.3%) in the second, and 15.2% (95% CI 12.3%-18.1%) in the third. The number of viral load tests performed more than doubled, increasing from 16,532 in the first period, to 31,472 in the second, to 33,376 in the third. The rate of viral suppression also increased dramatically, from 48.3% in the first period, to 67.9% in the second, and 77.4% in the third. According to patients, the quality of services improved. The average quality of care rating rose from 3.8/5.0 in the first period, to 4.0/5.0 in the second, to 4.2/5.0 in the third. Conclusion: The treatment observatory improved data transparency, creating a culture of collective problem-solving among patients, healthcare workers and policy-makers. The project triangulated anecdotal evidence of facility-level improvements with macro data trends that show regional-level progress. This provides proof of concept for the positive effects of community-led monitoring when done at scale. The approach should be expanded to help achieve global HIV treatment targets.

1081 ROUTINE LABORATORY DATA FOR ESTIMATING POPULATION VIRAL SUPPRESSION IN SOUTH AFRICA

Elton E. Mukonda¹, Nei-Yuan M. Hsiao², Landon Myer1, Maia Lesosky1
1University of Cape Town, Cape Town, South Africa, 2National Health Laboratory Service, Cape Town, South Africa

Background: There are few population-wide data on viral suppression (VS) that can be used to monitoring programmatic targets in sub-Saharan Africa. We describe how routinely collected viral load (VL) data from ART programmes can be extrapolated to population VS and validate this using a combination of empirical and model-based estimates.

Methods: We used routine VL testing data for the Western Cape province for the January 2008 to September 2018, obtained from the South African National Health Laboratory Service. We carried out record linkage using a combination of deterministic and probabilistic linkage with hierarchical clustering to obtain linked results for individuals. Test- and individual-level VL rates were based on test VL values <1000 copies/mL, and individual VL <1000 copies/mL in a calendar year, respectively. We calculated population VS among people living with HIV (PLWH) in the province by combining census derived mid-year population estimates, HIV prevalence estimates and individual level VS estimates from routine VL data. Sensitivity analyses examined subgroups by age, year and gender.

Results: Approximately 1.9 million tests from 530 clinical sites were included, with VL testing volumes increasing by 500% between 2008 and 2018. Among individuals in care, VS increased from 84% in 2008 to 90% in 2018. Population VS among all PLWH in the province increased from 12.2% in 2008 to 51.0% in 2017. The estimates derived from this method are comparable to those from other published studies including surveys specifically designed to estimate HIV prevalence and population viral suppression (HSRC National HIV Prevalence, Incidence, Behaviour and Communication Survey - SABSSM V), where 54.7% of PLWH had VS in 2017. This method also demonstrates close alignment with National Department of Health estimates (~2% difference across all years). Sensitivity analyses showed that the results are robust to variations in linkage method, but sensitive to the extreme combinations of assumed ART coverage and population HIV prevalence.

Conclusion: While validation of this method in other settings is required, this approach provides a simple, robust method for estimating population VS using routine data from ART services that can be employed by national programmes in high-burden settings.
### 1082 POPULATION-BASED HIV IMPACT ASSESSMENTS AND VIRAL LOAD RESULTS: IMPLICATIONS FOR U=U

**Gregory C. Chang**, Trista Bingham, Katrina Sleeman, Irene Benech, Yen T. Duong, Jessica E. Justman, Suzue Saito, Melissa Metz, Anna Awo, Yohannes Mengistu, Judith Shang, Alice Maida, Optatus Malewo, Bharat S. Parekh

**Background:** Undetectable equals Untransmittable (“U=U”) is a message that conveys no risk of sexual transmission when people living with HIV (PLHIV) have a viral load (VL) <200 HIV RNA copies per milliliter of blood (cp/mL). VL assays that use dried blood spots (DBS) have a minimum detection threshold of 700-839 cp/mL, in contrast to VL assays that use plasma which can detect <200 cp/mL. Because some countries rely on DBS-based VL testing that is unable to detect the U=U threshold of <200 cp/mL, some providers are reluctant to adopt U=U messaging, especially in areas where plasma VL tests are not universally available. To address this potential barrier, we assessed the proportion of those with VL <200 cp/mL among PLHIV participants with VL <1000 cp/mL who were on ART and adhering to high-quality laboratory sample collection and systems to verify VL. PHIA data supports that the scale-up of U=U messaging may be suitable even in settings limited to DBS-based VL measures. With continued ART adherence and high-quality laboratory sample collection and systems to verify VL, PHIA data supports that the scale-up of U=U messaging may be appropriate regardless of which VL testing platform is available.

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage of HIV-positive adults on ART with VL&lt;1000 among all HIV-positive adults: 95% CI</th>
<th>Percentage of HIV-positive adults on ART with VL&lt;200 among those with VL&lt;1000: 95% CI</th>
<th>Percentage of HIV-positive individuals on ART, self-reported 12/3 months on ART, and VL&lt;200 among all individuals with VL&lt;1000: 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>83.3 (81.6-85.0)</td>
<td>92.8 (90.9-94.7)</td>
<td>94.6 (92.9-96.4)</td>
</tr>
<tr>
<td>Lesotho</td>
<td>87.3 (86.3-89.3)</td>
<td>95.6 (94.6-96.6)</td>
<td>96.7 (95.8-97.7)</td>
</tr>
<tr>
<td>Tanzania</td>
<td>87.0 (84.2-89.8)</td>
<td>95.6 (94.5-97.2)</td>
<td>97.4 (95.8-98.9)</td>
</tr>
<tr>
<td>Malawi</td>
<td>91.2 (89.1-93.2)</td>
<td>95.7 (94.3-97.1)</td>
<td>97.0 (95.6-98.4)</td>
</tr>
<tr>
<td>Zambia</td>
<td>89.2 (87.3-91.1)</td>
<td>96.1 (95.0-97.2)</td>
<td>97.4 (96.3-98.5)</td>
</tr>
<tr>
<td>Cameroon</td>
<td>79.4 (74.1-84.7)</td>
<td>95.5 (93.3-97.0)</td>
<td>97.8 (95.7-99.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>86.9 (84.4-87.4)</td>
<td>95.1 (94.7-95.4)</td>
<td>96.6 (96.2-96.9)</td>
</tr>
</tbody>
</table>

### 1083 VIRAL SUPPRESSION TRAJECTORIES AMONG HIGH-NEED PATIENTS IN LOW-BARRIER HIV CARE

**Julia C. Dombrowski**, Meena Ramchandani, McKenna C. Eastment, Matthew R. Golden

**Background:** Ending the HIV epidemic will require intensive efforts to sustain viral suppression among persons with HIV who have complex medical and social barriers to care. We previously showed that a clinic offering walk-in, incentivized care (the Max Clinic) improves viral suppression. Here we examine viremia trajectories among Max Clinic patients.

**Methods:** We included patients with ≥180 days of observation time after enrollment during Dec 2014–Jan 2019, starting on the enrollment date and ending at the time of death, relocation, or July 31, 2019. We categorized patients into groups defined a priori based on knowledge of common viremia trajectories: 1) early consistent suppression (first viral load (VL)<200 copies/mL ≤6 months (mo) after enrollment; all subsequent VL<200); 2) late consistent suppression (first VL<200>6 mo after enrollment, all subsequent VL<200); 3) transient/intermittent suppression (≥1 VL<200, subsequent VL>200); and 4) no suppression (no VL<200). We compared the characteristics of patients in each group using χ² tests for categorical variables and Kruskal-Wallis One-way ANOVA for continuous variables.

**Results:** Among 167 patients with a median observation time of 27 mo (interquartile range (IQR): 16-39 mo), 69% were homeless or unstably housed at enrollment, 54% used methamphetamine, 51% injected drugs, and 32% had a diagnosed psychotic, bipolar or personality disorder. Most patients (59%) had transient/intermittent suppression, followed by early consistent suppression (26%), no suppression (10%) and late consistent suppression (5%). The groups differed by the median observation time, which was shorter in the no suppression (15 mo) and early consistent suppression (20 mo) groups than in the transient/intermittent suppression (34 mo) and late consistent suppression (37 mo) groups (p<0.001). The groups did not differ significantly by gender, race, ethnicity, housing status, substance use or depression/ anxiety disorder diagnoses. Patients with psychotic, bipolar disorder or personality disorder were more likely to be in the late or no suppression groups (p<0.04). The median time from the first suppressed VL to a subsequent unsuppressed VL was 4 mo (IQR 1-10 mo).

**Conclusion:** The vast majority of patients in the low-barrier clinic reach viral suppression even in the context of unstable housing, substance use, or severe mental illness, but most are intermittently unsuppressed. Even with low-barrier care and high-intensity support, most patients continue to have periods of viremia.

### 1084 ROUTINE PHARMACY REFILLS PREDICT WOMEN’S PLASMA ARV DETECTION AND VIRAL SUPPRESSION


**Background:** Detection of antiretrovirals (ARV) is an objective adherence measure that predicts HIV treatment outcomes, however, routine ART testing
is currently not feasible in high-burden settings. We examined how pharmacy refill data predicts ARV detection in plasma and viral suppression (VS) in a routine care cohort in Cape Town, South Africa.

**Methods:** HIV+ women who initiated TDF+FTC+EFV during pregnancy and achieved VS (≤50 copies/mL) were followed up for 24 months. Plasma viral load and presence of ARV (>20 ARVs tested for using mass-spectrometry) were measured at multiple study visits. Patient-level routine pharmacy data were used to classify each visit as: having no ARVs in hand (i) today, (ii) for >30 days, or (iii) >90 days prior. Generalized estimating equations were used to calculate associations between ARV in hand, VS, and detectable ARV in plasma. Secondary analyses were restricted to a) women who stayed in one of three large clinics to minimize heterogeneity in routine data, and b) the first visit to calculate diagnostic characteristics.

**Results:** Across 237 women and 417 visits (median 10 months on ART, IQR=7-14) 46% were not VS. No ARV was detected in plasma at 60% of visits, of which EFV was detectable in 98%, TFV in 65% and FTC in 73% of visits. Patients were classified as having no ARV in hand at 56% of visits, with 81% and 63% of these having no ARV in hand for >30 and >90 days, respectively. Absence of any ARV in plasma was strongly associated with viremia (OR 70.6, 95% CI 35.7-139.6). No ARVs in hand today (OR 7.7, 95% CI 4.7-12.6), for >30 days (OR 15.0, 95% CI 6.5-32.3) and for >90 days (OR 19.7, 95% CI 10.8-35.6) were also associated with viiremia; similar associations were observed between drugs in hand and plasma ARV detection. Associations with VS, but not plasma ARVs, strengthened when restricted to women who were in care at one of three large clinics. At the first visit, increasing time with no ARV in hand resulted in decreased sensitivity (VL 76% to 33%; plasma ARV 83% to 35%) and increased specificity (VL 67% to 92%; plasma ARV 68% to 92%).

**Conclusion:** Although ARV detection in plasma was the best predictor of virologic outcomes, having ARV in hand was a strong predictor of VS and presence of ARV. Routine pharmacy data provides a feasible, inexpensive alternative objective measure of ART adherence for public sector programme evaluation in high-burden settings.

1086 OPTIMIZATION OF HIV CLINIC INTAKE PROCESS TO REDUCE TIME TO VIRAL SUPPRESSION

**Methods:** This study describes a novel clinic intake process to more rapidly initiate antiretrovirals (ARVs) and compares mean time to initiate ARVs as time to viral suppression from before and after the advent of this new intake process.

**Results:** In April 2018, the UC San Diego Owen Clinic developed a new intake process that included an initial visit with a multidisciplinary team to improve access while providing the opportunity for rapid initiation or optimization of ARVs at first visit using clinical pharmacy services. Prior to this process, patients only met with licensed vocational nurses (LVNs) at their initial intake visit. We conducted a retrospective study comparing time to initiate ARVs as well as time to viral suppression before and after this new intake process was implemented. We also evaluated clinic retention rates within both 1 month and 6 months of initial visit. Predictors of lack of retention in care were also evaluated.

**Results:** We included 379 patients in the analysis. Table 1 shows demographic data, psychosocial data, and baseline virologic data. In the new intake cohort, there were significant reductions in mean time to initiate ARVs (45.2 days vs. 7.8 days, p=0.0002) and mean time to viral suppression (217.9 days vs. 75.9 days, p<0.0001). There was no significant difference in the proportion of patients retained either short or long term. Although not statistically significant, after
logistic regression was there a trend that black patients were more likely to fall out of care long term (p=0.0535).

**Conclusion:** We observed significant reductions in time to initiate ARVs and time to viral suppression in the new, pharmacist driven intake cohort. Similar intake processes that facilitate rapid modification and initiation of ARVs should be routine in order to move toward more rapid viral suppression among PLWH.

**Conclusion:** Use of near-POC VL and centralized testing of $5·09 could be further reduced in patients on optimized regimens. The difference between the 'all in' cost of patients are on a second-line regimen, suggesting that routine VL results enabled prompt clinical action. According to national data, fewer than 3% of patients are on optimized regimens.

**Results:** During the 12-month study period, 2813 near-POC VL tests were conducted. 1511 (54%) tests were for onsite patients for whom results and costs are presented.

**Conclusion:** Targeted, near-POC VL testing was feasible and consistently enabled prompt clinical action. According to national data, fewer than 3% of patients are on a second-line regimen, suggesting that routine VL results are likely underutilized; near-POC VL may be an attractive modality to ensure patients are on optimized regimens. The difference between the 'all in' cost of near-POC VL and centralized testing of $5·09 could be further reduced in an optimized national program combining targeted near-POC testing and centralized testing.

**Results:** 4,800 participants were enrolled; 1919, 1335 and 1546 in 3MF, 3MC and 6MC, respectively. Retention was high and similar in all arms, 93.0%, 94.8% and 95.5% in 3MF, 3MC and 6MC, respectively (table). The pre-specified non-inferiority limit (3.25%, risk difference [RD]) was met for comparisons between all arms; 3MC vs. 3MF, adjusted RD=1.1% (95% CI: -0.5% to 2.6%); 3MC vs. 3MC: adjusted RD=1.1% (95% CI: -0.5% to 2.6%). VL completion at 12 months was 49%, 45% and 8% in 3MF, 3MC and 6MC, respectively; VS in 3MC (99.7%) was high and not different to 3MF (99.1%), relative risk=1.0 (CI: 0.9-1.0). VS was marginally reduced in 6MC (92.9%) vs. 3MF, relative risk=0.9 (CI: 0.9-1.0).

**Conclusion:** Retention in CARGs receiving three and six-monthly MMD was noninferior to standard-of-care facility-based ART delivery in Zimbabwe for stable patients, and is a strategy that can be scaled-up. VS in six-monthly MMD requires further evaluation.

**Results:** The difference in quality-adjusted life years (QALYs) was −0.01 (CI: −0.02 to −0.00) and the ICER was −$150,000/QALY. With generic F/TDF expected in 2020, we examine how much more payers should be willing to pay for the improved safety profile of branded F/TAF. With generic F/TDF expected in 2020, we examine how much more payers should be willing to pay for the improved safety profile of branded F/TAF.

**Methods:** We assembled safety data for F/TAF and F/TDF in an age-stratified population of 123,610 US MSM without HIV and from studies of people with HIV. Data were used to forecast fractures, ESRD cases, quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios (ICERs) over 5y. To determine the maximum price differential for F/TAF (currently $16,600/year, Federal Supply Schedule) over generic F/TDF, we portrayed F/TAF as favorably as possible, ignoring any ASCVD effects and overstating its safety. For example, we assumed for those on F/TDF that: 1) severe loss of bone mineral density resulted in osteoporosis-related fractures and that all fractures occurred at the hip, leading to a one year 30% quality of life (QoL) decrement and a cost of $70,400; 2) background ESRD rates were more than double their reported value and ESRD was immediate and irreversible, resulting in a 47% QoL decrement and costs of $92,100-$95,500 each year; and 3) the generic F/TDF alternative would achieve
a modest (50%) price reduction to $8,300/year. We also examined the budget impact of F/TDF vs. F/TAF, comparing PrEP coverage and transmissions.

**Results:** Compared to F/TDF, F/TAF averted 2,101 fractures and 30 ESRD cases, the ICER exceeded $7,370/QALY gained (Table). At a willingness to pay of $100,000/QALY, the maximum justifiable price for F/TDF was $68,000/year. Even among patients at highest risk of fracture and ESRD (>55y), the ICER for F/TAF exceeded $3,350/QALY and the maximum justifiable price was $9,050/year. Results were robust to alternative time horizons and PrEP using population sizes; regardless of age and F/TDF costs, the maximum justifiable markup over generic F/TDF was <$750/yr. Using the entire US HIV prevention budget ($900.8M) and base case assumptions of F/TDF and F/TAF costs, 54,270 people could receive F/TAF and 105,210 could receive F/TDF annually; this difference in PrEP coverage would result in an additional 8,610 new HIV infections with F/TDF.

**Conclusion:** Given its minimal impact on adverse events, F/TAF justifies a markup no greater than $750 over generic F/TDF in the US. At a higher price, it may well do more harm than good.

### Table 5: Five-year clinical and cost outcomes of F/TDF compared to generic F/TDF in PrEP for MSM in the US

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>PrEP coverage</th>
<th>Costs ($)</th>
<th>ESRD (n=1,000,000)</th>
<th>F/TDF Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>54,270</td>
<td>904,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>105,210</td>
<td>1,453,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td>156,240</td>
<td>1,902,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total**</td>
<td>216,820</td>
<td>3,290,500</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:**

- **Strategy for POC adoption in South Africa is likely to be a targeted approach, with a mix of GeneXpert and m-PIMA may still be cost-effective with an ICER of $1,095 compared to Scenario 3, requiring an additional $52 million annually. All other scenarios were dominated in the incremental analysis. When POC VL resulted in a reduction of viral suppression was varied in a sensitivity analysis.

- **Results:** The total cost-effectiveness (total expected number of people with suppressed VL) and incremental cost-effectiveness ratio (ICER) based on expected improvement in suppression rates from POC adoption. The effectiveness of POC VL in improving viral suppression was varied in a sensitivity analysis.

### Table 5.5: Five-year clinical and cost outcomes of F/TDF compared to generic F/TDF in PrEP for MSM in the US

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>PrEP coverage</th>
<th>Costs ($)</th>
<th>ESRD (n=1,000,000)</th>
<th>F/TDF Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>54,270</td>
<td>904,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>105,210</td>
<td>1,453,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td>156,240</td>
<td>1,902,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total**</td>
<td>216,820</td>
<td>3,290,500</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Despite free ART, most ppts reported OOP spending. OOP costs were higher for ppts with co-morbid NCD, contributing to financial distress.
END THE HIV EPIDEMIC IN BALTIMORE: A MODELING STUDY

Anthony T. Fojo1, Parastu Kasaie1, David Dowdy2, Maunank Shah1,1 Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2 Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: Last year, the US government announced a plan to reduce HIV incidence by 90% by 2030 through the “90-90-90” target. However, it is not clear how these targets will perform in local epidemics, such as the one in Baltimore City, driven by heterogeneity in HIV transmission and access to care.

Methods: We extended the Johns Hopkins HIV economic-epidemic model (JHHEM), a validated compartmental model of HIV transmission, to represent population by sex (male/female), race/ethnicity (black, non-black), age strata (13-24, 25-34, 35-44, 45-54, 55+ years old), and CDC risk groups (MSM, injection drug users), and to include pre-exposure prophylaxis (PrEP).

We calibrated the model using 10,000 simulations against CDC-reported new HIV diagnoses and persons living with HIV from 2010-2017 in the Baltimore metropolitan statistical area.

We ran each simulation multiple times from 2020-2030 under a range of potential interventions, targeting HIV testing frequency, proportion of HIV-diagnosed individuals virally suppressed, and proportion of at-risk individuals prescribed and adherent to PrEP. Interventions were targeted at different combinations of high-risk subgroups. For each intervention and target group, we estimated the reduction in total Baltimore incidence that could be achieved between 2020 and 2030.

We calculated 95% uncertainty ranges (UR) by weighting simulations according to how well they fit the observed data from 2010-2017.

Results: Continuing testing, suppression, and PrEP at current levels projected a reduction in incidence of 13% (95%UR: 2-35%) from 2020-2030. Interventions targeted at Baltimore’s highest-risk subgroups, black MSM and injection drug users, could achieve reductions of 57% (39-67%) (Table) with yearly testing, 90% suppression among people with diagnosed HIV, and 50% adherence to PrEP, and reductions up to 60% (42-71%) with 75% adherence to PrEP. Achieving close to 90% reduction in incidence from 2020 to 2030 among our tested interventions required expanding these interventions across the entire population.

Conclusion: Ending the HIV epidemic in Baltimore will be challenging, and will require several, broadly targeted interventions to achieve high levels of HIV suppression among diagnosed individuals with HIV as well as high uptake of PrEP and frequent screening across multiple subgroups.

Methods: Using a dynamic HIV transmission model calibrated with the best-available evidence on epidemiological and structural conditions for Atlanta, Baltimore, Los Angeles (LA), Miami, New York City (NYC) and Seattle, we assessed 16 evidence-based interventions (HIV prevention, testing, antiretroviral therapy (ART) engagement and re-engagement) to identify strategies providing the greatest health benefit while remaining cost-effective. Outcomes included averted HIV infections, quality-adjusted life-years (QALYs), total costs and incremental cost-effectiveness ratios (ICERs) (healthcare perspective; 3% annual discount rate; 2018US$). Interventions were implemented at previously-documented and ideal (90% coverage/adopt) scale-up, and sustained from 2020 to 2030, with outcomes evaluated until 2040.

Results: We assessed 23,040 combinations, with optimal strategies containing between eleven (NYC, Seattle) and thirteen (Atlanta, LA, Miami) interventions. Implemented at previously-documented scale-up, these would reduce incidence by 30.8% (95% credible interval: 19.2%-43.8%) (Seattle) to 50.1% (41.5%-58.0%) (NYC) by 2030, at ICERS ranging from cost-saving in Miami to $136,718/QALY in Atlanta. These rose to 39.8% (26.7%-54.1%) in Seattle to 85.1% (72.3%-88.5%) in Baltimore at ideal implementation. Combined costs of implementing strategies at previously-documented scale-up totaled $671M/year at peak levels (2.3 times the initially-proposed 2020 funding allocation); however, costs were offset by long-term reductions in new infections and delayed disease progression, with Miami projecting cost-savings over the 20-year study period.

Conclusion: Evidence-based interventions can deliver considerable value, however, complementary strategies to overcome social and structural barriers to HIV care will be required to reach national ‘Ending the HIV epidemic’ targets by 2030.

Assessing the Impact and Cost-Effectiveness of HIV and NCD Integrated Care in Kenya

Parastu Kasaie1, Brian Weir1, Melissa Schnure1, Chen Dunn1, Jeff Pennington1, Yu Teng1, Richard Wama1, Kipkoech Mutua1, David Dowdy2, Chris Beyrer1, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2 Avenir Health, Glastonbury, CT, USA, 3 Northeastern University, Boston, MA, USA, 4 National AIDS Control Council, Nairobi, Kenya

Background: With increasing ART coverage, non-communicable diseases (NCDs) are a growing cause of death and disability in many high HIV burden countries. Integrated community-based screening and treatment for HIV and NCDs is a promising approach for addressing the dual burden of these diseases. We model the national scale-up of this approach in Kenya to estimate its population-level impact and cost-effectiveness.

Methods: Coupling a microsimulation of cardiovascular diseases (CVDs) with a population-based model of HIV dynamics (the Spectrum model), we created a hybrid model of HIV/CVDs. We applied this model to estimate the impact of a community-wide integrated program for screening and treatment of HIV, hypertension and diabetes in Kenya. The intervention was projected to run from 2019 to 2023, with a model time horizon of 2033. We assumed that 20% of the population would be targeted on an annual basis, 73% of HIV-positive people would start ART if screened, and 50% of eligible post-screening NCD treatment time would be covered.
Results: At a national level in 2018, an estimated 7.62 million individuals were living with untreated hypertension, 692,000 with untreated diabetes, and 592,000 individuals in need of ART. ART coverage increased from 68% at baseline to 88% in 2033, and HIV incidence decreased by 64%. Providing NCD screening and treatment would aver t116,000 CVD events and 43,600 CVD deaths by 2033. The integrated HIV/NCD intervention could aver t1.76 million disability-adjusted life years (DALYs) over 15 years at an estimated total cost of $6.68 billion ($445.27 million per year), or $860 per DALY averted (Table 1). At a cost-effectiveness threshold of $2,010 per DALY averted, the probability of cost-effectiveness was 0.92.

Conclusion: Integrated screening and treatment of HIV and NCDs would be a cost-effective approach to avert substantial death and disability in Kenya. Substantial investments would be required to address the identified disease burdens.

Table 1: Epidemiological and economic impact of integrated services for HIV/NCD in Kenya. Values represent median difference between baseline and intervention scenarios across 2000 simulations. Models are initialized with a similar population in 2018 and are followed to year 2033. The baseline scenario assumes fixed ART coverage at 2018’s levels over time and minimal NCD treatment. The intervention scenario models an annual campaign for screening and treatment of HIV, hypertension (HTN) and diabetes (DM) running from 2019 to 2023. 

![Table 1](image)

1096 HOW SHOULD WE PRIORITIZE AND MONITOR INTERVENTIONS TO END HIV EPIDEMIC IN AMERICA?

Kevin P. Delaney,1 Samuel Jenness2, Jordan A. Johnson2, Dawn K. Smith1, Karen W. Hoover1, Norma Harris1, Elizabeth DiNenno1

1CDC, Atlanta, GA, USA, 2Emory University, Atlanta, GA, USA

Background: The goal of the US Ending the HIV Epidemic (EHE) plan is to reduce HIV incidence by 90% over the next decade. This initiative will direct a major scale-up of many prevention and care activities in high-burden areas. An important aspect for local jurisdictions will be the ability to monitor changes in their local HIV epidemic to ensure progress. Models can help inform what changes in potential indicators to expect as prevention interventions are implemented.

Methods: We developed a stochastic network-based HIV transmission model for men who have sex with men (MSM), calibrated to current surveillance-based estimates of HIV prevalence, PEP use, and HIV care continuum levels in the Atlanta area (Baseline). Two counterfactual scenarios increased HIV screening rates to annual and quarterly. Additional scenarios included increases of 10x for ART retention relative to empirical rates, with and without increases in screening. Changes in HIV incidence and indicators readily available to local HIV surveillance programs – new HIV diagnoses and the proportion of those that were acute infections — were assessed for 10 years following implementation.

Results: Compared to current HIV screening rates, increasing HIV screening to annual or quarterly for all MSM would lead to approximately 97% and 99% of all extant HIV infections (among this risk group) being diagnosed. By year 5 of the intervention new diagnoses (dashed lines) would correspond directly with the unobserved true HIV incidence (solid lines) in all scenarios (Figure). The more rapid the build-up of HIV testing, the more quickly new diagnoses approximate HIV incidence, with an increase to quarterly testing leading to new diagnoses matching true incidence by year 3. The proportion of all new HIV diagnoses identified while acute increased with testing frequency from approximately 2% at baseline, to approximately 8% and 26% of all diagnoses with annual and quarterly rescreening. However, reductions in incidence through other mechanisms such as improved retention on ART do not increase the proportion identified while acutely infected.

Conclusion: These results suggest one strategy for jurisdictions seeking to simultaneously reduce HIV incidence and improve their ability to track their epidemic would be to dramatically increase HIV screening in the earliest stages of elimination efforts. This should lead to an initial dramatic increase in new diagnoses, after which new HIV diagnoses would accurately measure incident HIV infections.

1095 ACHIEVING 95-95-95 MAY NOT BE ENOUGH TO END THE AIDS EPIDEMIC IN SOUTH AFRICA

Dobromir Dimitrov1, James R. Moore1, Deborah J. Donnell1, Marie-Claude Boly1

1Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 2Imperial College London, London, UK

Background: The ambitious 95–95–95 strategy was announced by UNAIDS in 2014, aiming to end the AIDS epidemic by 2030 by achieving 95% diagnosed among all people living with HIV (PLHIV), 95% on antiretroviral treatment (ART) among diagnosed, and 95% virally suppressed (VS) among treated. An intermediate goal of 90–90–90 was set for 2020. These targets have been adopted by many countries implying that treatment should be prioritized in resource allocation. We estimate the expected reduction in HIV incidence if the UNAIDS targets are met in South Africa by 2030 reaching different PLHIV groups by sexual risk behavior.

Methods: A risk behavior model was used to simulate annual HIV incidence by tracking the transmission from PLHIV assuming 30% of them engaged in high-risk behavior (more frequent sex with multiple partners). Two baseline scenarios with different risk group coverage were parameterized with the HIV prevalence and 85–58–76 treatment cascade (i.e. 37% viral suppression of PLHIV), estimated in 2015 in South Africa, and calibrated to the 2015 HIV incidence among adult population (15-49 years). They were compared to scenarios in which UNAIDS targets are achieved and newly diagnosed, treated and virally suppressed (VS) among treated. Additional interventions included increases of 10x for ART retention relative to empirical rates, with and without increases in screening. Changes in HIV incidence and indicators readily available to local HIV surveillance programs – new HIV diagnoses and the proportion of those that were acute infections — were assessed for 10 years following implementation.

Results: Annual HIV incidence was estimated 1.05% - 1.31% in 2015 depending on how treatment coverage was distributed between risk groups (see figure). The 90–90–90 target by 2030, resulting in 73% overall VS, may reduce annual HIV incidence to 0.29% if the cascade is predominately improved through recruitment from the high-risk group or to 0.74% if the cascade is improved with low-risk PLHIV. Reaching the 95–95–95 target, resulting in 86% overall VS, may result in 0.15% and 0.39% annual HIV incidence if the cascade is improved with high-risk and low-risk PLHIV, respectively. The HIV incidence projections in all scenarios remain above the elimination threshold of 0.01% (1 infection/1000 person-years).

Conclusion: Reaching UNAIDS treatment cascade targets does not equate the end of the HIV epidemic in South Africa. Expected HIV incidence strongly depend on the risk heterogeneity and the ART and VS coverage achieved among high-risk PLHIV. Scale-up of other HIV prevention tools is needed to bridge the gap to AIDS elimination.
HIV CARE CASCADE: MEN WHO HAVE SEX WITH MEN & TRANSGENDER WOMEN/GENDERQUEER, ZIMBABWE

Tiffany Harris1, Lauren Parmley1, Munyazadzi Mapingure2, Owen Mugurungi3, John H. Rogers4, Tsitsi Apollo2, Getrude Ncube1, Elizabeth Gones1, Brian K. May1, Perpetua Gozhora2, Godfrey Musuka1, Sophia Miller1, Yingfeng Wu1, Avi Hakim1, Innocent Chingombe1

1ICAP at Columbia University, New York, NY, USA, 2Zimbabwe Ministry of Health and Child Care, Harare, Zimbabwe, 3CDC, Harare, Zimbabwe, 4CDC, Atlanta, GA, USA

Background: Men who have sex with men (MSM) and transgender women/genderqueer (TGW/GQ) are at greater risk for HIV than the general population and face stigma and other barriers to receiving HIV services. However, little HIV data is available among these groups in Zimbabwe. We examined progress toward the 90-90-90 treatment targets (90% of HIV-positive persons know their status; of those, 90% are on antiretroviral treatment [ART]; and of those, 90% have viral load suppression [VLS]) among a sample of MSM and TGW/GQ in Harare and Bulawayo, Zimbabwe.

Methods: We used respondent-driven sampling to identify MSM and TGW/GQ individuals aged 18+ to participate in a biobehavioral survey in 2019. Consenting participants completed a questionnaire that obtained sociodemographic and HIV-related data and underwent HIV and viral load testing. VLS was defined as HIV RNA <1000 copies/mL. Univariate analyses were used to calculate sample estimates, as data did not reach convergence.

Results: In Harare, 416 MSM and 279 TGW/GQ received HIV testing (97% of those tested positive, 61.7% [MSM, 69.0%; TGW/GQ, 55.1%] had VLS). Among those testing HIV-positive, 34.9% (MSM, 33.8%; TGW/GQ, 35.9%) reported knowing their status; of these, 90.4% (MSM, 91.7%; TGW/GQ, 89.3%) reported using ART; and of these, 83.0% (MSM, 81.8%; TGW/GQ, 84.0%) had VLS. In Bulawayo, 760 MSM and 56 TGW/GQ received HIV testing (>99% of participants). Median age was 26 years. HIV prevalence was 23.4% (MSM, 23.3%; TGW/GQ, 23.0%); of those testing positive, 61.3% (MSM, 61.6%; TGW/GQ, 57.1%) had VLS. Among those testing HIV-positive, 52.9% (MSM, 53.7%; TGW/GQ, 42.9%) reported knowing their status; of these, 95.1% (MSM, 94.7%; TGW/GQ, 100.0%) reported using ART; and of these, 80.2% (MSM, 78.9%; TGW/GQ, 100.0%) had VLS.

Conclusion: HIV prevalence was higher in sampled MSM and TGW/GQ than in the general male population aged 15-64 years in both Harare (11.1%) and Bulawayo (16.1%). Self-reported awareness of HIV status was lower among MSM and TGW/GQ than among the general adult male population (68.3%) in Zimbabwe. HIV-positive participants who knew their status had high ART coverage and high VLS, indicating strong linkage to care and retention in treatment in this subgroup. Improvements in testing are needed among MSM and TGW/GQ, and programs could consider innovative approaches to optimize case finding among these populations.

1098 IMPACT OF HIV CONTINUUM OF CARE INTERVENTIONS AND PREEXPOSURE PROPHYLAXIS IN KENYA

Liem Binh Luong1, Stephen S. Wanjala2, Elisabeta Szumilin3, Pierre Mendizharat1, Yazdan Yazdanpanah1, Kenneth Freedberg1

1INSERM, Paris, France, 2MSF, Nairobi, Kenya, 3MSF, Paris, France, 4Massachusetts General Hospital, Boston, MA, USA

Background: In Western Kenya up to one quarter of the adult population was HIV-infected in 2012. Médecins Sans Frontières (MSF) has implemented an HIV care program to reach the 90-90-90 UNAIDS targets and has surpassed those. In this generalized epidemic, our objective was to compare effectiveness of Pre-exposure Prophylaxis (PreP) with improving the continuum of care coverage to 95-95-95.

Methods: We developed a time-discrete, dynamic microsimulation model to project HIV incidence and infections averted resulting from different strategies in the adult population. We used two age group risk strata, younger adults (YAs), as the age strata where HIV incidence is the highest: women 15-30y and men 20-40y, and older adults (OAs): women >31y and men >41y. We modeled 3 strategies compared to a 90-90-90 continuum of care base case: 1) Scaling up the continuum of care to 95-95-95 (85.7% suppression), 2) PreP targeting the YA with 10% coverage, and 3) Scale up to 95-95-95 and PreP. The time horizon was 2018 to 2030. Transmission parameters, including number of sexual contacts within and outside the same age group, were calibrated to fit overall prevalence (24.1%) and incidence (1.9/100 PY) in 2012. Monthly probabilities for continuum of care matched the 2012 levels (61.8% tested, 68.2% on ART among tested, and 73.0% viral suppression among ART) and 90-90-90 in 2020; PreP efficacy was set at 75%. We did sensitivity analyses on key parameters, including PreP impact starting at higher continuum levels, as obtained in 2018 (93% tested, 95.0% on ART among tested, and 97.0% suppression among ART).

Results: In the base case, by 2030 HIV incidence was 0.31/100 Person-Years (PY) in YAs, 0.35/100 PY in OAs, and 0.32/100 PY overall. Improving continuum levels to 95-95-95 averted 4.0% of infections in YAs, 9.0% in OAs, and 5.2% overall. PreP averted fewer infections: 3.7% in YAs, 1.5% in OAs, and 3.2% overall. Combining 95-95-95 and PreP averted 7.9% of infections in YAs, 9.1% in OAs and 8.1% overall. Sensitivity analysis shows that PreP coverage had to be 20% to avert as many infections as 95-95-95. With 88.0% overall suppression, as MSF has achieved, adding PreP is even less effective.

Conclusion: In a generalized epidemic with continuum of care levels at 90-90-90, improving continuum to 95-95-95 is substantially more effective than providing PreP. Continued focus on improving the continuum will have the greatest impact on decreasing new HIV infections.

Table: HIV incidence (/100 PY) and infections averted as a function of improved continuum of care and/or addition of PreP in rural Kenya

<table>
<thead>
<tr>
<th>Population</th>
<th>No Intervention</th>
<th>95-95-95</th>
<th>PreP 10%</th>
<th>95-95-95 + PreP10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger Adults</td>
<td>Incidence</td>
<td>4.0</td>
<td>3.7</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>Prevalence (%)</td>
<td>0.31</td>
<td>0.23</td>
<td>0.26</td>
</tr>
<tr>
<td>Older Adults</td>
<td>Incidence</td>
<td>9.0</td>
<td>1.2</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>Prevalence (%)</td>
<td>0.35</td>
<td>0.20</td>
<td>0.28</td>
</tr>
<tr>
<td>Overall</td>
<td>Incidence</td>
<td>13.0</td>
<td>4.9</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>Prevalence (%)</td>
<td>0.62</td>
<td>0.27</td>
<td>0.89</td>
</tr>
</tbody>
</table>

1099 DIFFERENCES IN HIV CARE OUTCOMES: US HISPANIC/LATINOS WITH DIAGNOSED HIV INFECTION

Sonia Singh1, Yonggang Li2, Alexandra Balaji1

1CDC, Atlanta, GA, USA, 2ICF International, Atlanta, GA, USA
**Background:** HIV testing, linkage to and retention in HIV medical care and achievement of viral suppression are critical to prevent disease progression. Assessing HIV care outcomes among Hispanics/Latinos is important for guiding targeted prevention efforts and monitoring progress towards national goals.

**Methods:** Data from the National HIV Surveillance System from 42 jurisdictions that reported complete CD4 and viral load laboratory results to CDC through December 31, 2018 were used to determine the numbers of Hispanics/Latinos aged ≥13 years newly diagnosed and diagnosed at Stage 3 (AIDS) and percentages linked to care within one month, retained in care and virally suppressed by sex, age and transmission category. These data provide more granularity than in HIV surveillance reports.

**Results:** Among 8,517 Hispanics/Latinos with HIV infection diagnosed in 2017, 1,825 (21.4%) had infection classified as stage 3 (AIDS). Among males, the highest percentage of infections diagnosed as stage 3 (AIDS) was at 25-34 years (34.3%) and among females, 45-54 years (28.2%). By transmission category, the highest percentage of infections diagnosed at stage 3 (AIDS) attributed to injection drug use was at 45-54 years for both males (29.1%) and females (40.9%) and for injection attributed to heterosexual contact, among males, 35-44 years (33.0%) and females, 45-54 years (26.8%). In 2017, 6,750 (79.3%) were linked to care within 1 month after diagnosis. For males, females and all transmission categories, 13-24 years had the lowest linkage to care except for males with infection attributed to male-to-male sexual contact and injection drug use [25-34 years (67.1%)] and heterosexual contact [35-44 years (75.5%)]. Among 181,145 Hispanics/Latinos living with diagnosed HIV infection at year-end 2016, 130,195 (71.9%) received any care, 106,101 (58.6%) were retained in care and 111,107 (61.3%) were virally suppressed. The lowest retention in care for females was 25-34 years (56.5%) and for males was 35-44 years (55.7%). The lowest viral suppression was among males 25-34 years with infection attributed to injection drug use (43.8%) and 35-44 years with infection attributed to heterosexual contact (43.8%), followed by females 25-34 years with infection attributed to injection drug use (47.9%).

**Conclusion:** Tailored strategies for Hispanics/Latinos that increase care and achieve viral suppression in different groups such as those <35 years and persons who inject drugs are needed as highlighted in the national HIV prevention goals.

### 100 IMPROVEMENTS ACROSS NAIROBI COUNTY’S HIV CARE CONTINUUM: CASE OF A FAST-TRACK CITY

**Sindhu Ravishankar, Eryn Macarayan, Caroline Ngunu, Molly Pezzulo Collier, Harriet Konig, Jose M. Zuniga, Ingrid Katz**

1. International Association of Providers of AIDS Care, Washington DC, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3Nairobi City County, Nairobi, Kenya, 4UNAIDS, Geneva, Switzerland, 5Harvard Medical School, Boston, MA, USA

**Background:** The Fast-Track Cities initiative is supporting municipalities to measure and monitor progress against the global 90-90-90 targets. Using 2016-2018 trend data from Nairobi County’s Fast-Track City dashboard, we assessed progress against 90-90-90 targets at county and sub-county levels.

**Methods:** HIV care continuum data from 2016 (baseline) to 2018 (current) for Nairobi County and its 17 sub-counties were obtained from the Fast-Track City dashboard. Improvements in data from baseline to current were measured using two parameters: 1. Progress made against the 90-90-90 targets; and 2. completeness of HIV care continuum data. 90-90-90 targets (which use a floating denominator) were converted to care continuum indicators (using a consistent denominator of estimated PLHIV) resulting in the following targets: 90% of PLHIV diagnosed; 81% of PLHIV on ART; and 72.9% of PLHIV virally suppressed.

**Results:** The care continuum for Nairobi County improved from 77% PLHIV diagnosed, 74% PLHIV on ART, and 41% of PLHIV virally suppressed in 2016 to 79% PLHIV diagnosed, 76% of PLHIV on ART, and 72% of PLHIV virally suppressed in 2018. Trend data between 2016 and 2018 were reported for eight of the 17 sub-counties. Of these eight sub-counties, seven demonstrated improvement across one or more indicators. As of 2018, no sub-county had surpassed the 90-90-90 targets but one sub-county had surpassed the second and third target. In 2018, two sub-counties reported surpassing all three targets, with five sub-counties surpassing one or more of the 90 targets. Ranges of improvement for the sub-counties from 2016-2018 were 4-11 percentage points on the first 90 target; 4-13 percentage points on the second 90 target; and 1-14 percentage points on the third 90 target. Between 2016-2018, the completeness of data also improved with all 17 sub-counties reporting HIV care continuum data in 2018 compared to eight sub-counties reporting such data in 2016.

**Conclusion:** Nairobi County and many of its sub-counties have seen improvements across the HIV care continuum since their 2016 baseline. Given the quickly approaching 2020 deadline to attain the 90-90-90 targets, targeted focus to improve the HIV care continua in the poorest performing sub-counties is crucial. By reporting data on all sub-counties, Nairobi County is taking the steps needed to assess gaps and subsequently address geographic priorities.
ART interruptions to include person-specific outreach support for those who remain off treatment for ≥4 months. We examined outcomes before and after launch of this re-engagement and Engagement in Treatment for Antiretroviral Interrupted and Naïve populations (RETAIn) initiative.

Methods: We analyzed DTP participants with ART interruptions triggering a physician-directed alert (ART refill ≥2 months late) in pre-RETAIn (Jul-2013 to Apr-2016) and post-RETAIn periods (May-2016 to Oct-2017) with follow-up until Oct-2018. Persons who moved out of BC, died, or were on ART through other sources were excluded. We compared the proportions who re-started ART, or achieved viral suppression (pVL<200 copies/mL) in pre- and post-RETAIn periods and the time to ART re-initiation using generalized estimating equation. Cox modelling has been used to examine associations between time to ART restarts with time period (pre-RETAIn vs. post-RETAIn) as our primary explanatory variable.

Results: A total of 1805 individuals contributed 3219 ART interruptions of ≥2 months triggering physician-directed alerts: 2059 in pre-RETAIn and 1169 in post-RETAIn periods. Participants were predominantly male (74%) had a median duration on ART of 3 years and a median age of 47 years. We found no differences between the two periods in terms of proportion who re-started ART within 4 months of a physician alert (73% vs 73%), or achieved viral suppression within six months (60% vs 60%). Among persons who remained interrupted ≥4 months after a physician-directed ART interruption alert was sent, the median time from interruption to ART re-initiation declined from 8.7 (5.8-14.9) months to 7.4 (5.5-10.9) months (p<0.001) from the pre- to post-RETAIn period. Interruptions in the post-RETAIn era were more likely to re-start ART (adjusted hazard ratio 1.50; 95% CI 1.34 - 1.69). ART re-initiation was associated with pVL suppression prior to interruption and ART duration prior to interruption (Table 1.) Similar findings were also found when examining only the first interruption in our study period.

Conclusion: Public health referrals for persons who did not re-engage in care after alerts to their physicians were sent shortens the length of ART interruptions. Similar programs should be considered in other jurisdictions.
Background: For newly diagnosed persons with HIV (NDP), early initiation of ART is essential in reducing morbidity and mortality and decreasing the risk of transmitting HIV. Two indicators have been proposed to monitor HIV care among NDP: the percentage of those linked to HIV medical care within 1 mo. of diagnosis (process) and the percentage of those achieving viral suppression (VS) within 3 mo. of diagnosis (outcome). We analyzed trends in both indicators in the Cohort of the Spanish AIDS Research Network (CoRIS).

Methods: The data source was the CoRIS database of ART-naïve adult persons living with HIV (PLWH) recruited from 2004 to 2018. VS was defined as ever having an HIV-RNA <200 copies/mL. We used logistic regression to assess differences by sex, country of origin, age, HIV transmission category, and CD4 count at diagnosis.

Results: A total of 13,260 PLWH were enrolled in the study period; 84% males, 59% native-born Spaniards, median age 34 years, median CD4+ cell count 384 cells/µL, 58% MSM. The percentage of NDP linked to care within 1 mo. of diagnosis increased from 42% in 2004 to 71% in 2018 (Figure). The percentage of NDP achieving VS within 3 mo. of diagnosis, increased from 6% in 2004 to 35% in 2018 (Figure). The odds of achieving VS within 3 mo. of HIV diagnosis was higher among females (adjusted OR, 1.42, 1.20–1.69), among non-Spanish Europeans and Latin Americans compared to native-born Spaniards (1.39, 1.20–1.62 and 1.26, 1.09–1.45, respectively), and among those older than 50 years (1.28, 1.06–1.54). Opposite, the odds of achieving VS within 3 mo. of diagnosis was lower among IDU compared to MSM (0.48, 0.36–0.65) and those with CD4 counts between 200–500 cells/µL (0.59, 0.52–0.67) and CD4 counts <500 cells/µL (0.36, 0.30–0.42) compared to those with CD4 < 200 cells/µL.

Conclusion: Progress has been made in HIV care among NDP in Spain during the 15-year analysis period, but there is still much room for improvement. The advance in the outcome indicator most likely reflects changes in treatment guidelines to offer ART to any PLWH regardless of CD4 count. These two indicators can guide our efforts to improve HIV care among NDP.

A FIELD-BASED SAMPLING STRATEGY TO REVIVE HIV TREATMENT PROGRAM RETENTION ESTIMATES

Theodora Savory1, Masuzyo Chitala2, Paul Elish3, Jake Pry1, Cynthia Lupenga1, Jacob Mutale1, Walusiku Muyinda1, Mwansa Lumpa1, Kaala Moomba2, Carolyn Bolton Moore1, Izukanji Sikazwe1, Michael Herc1

1Center for Infectious Disease Research in Zambia, Lusaka, Zambia, 2Centre for Infectious Disease Research in Zambia, Lusaka, Zambia

Background: Loss to follow-up (LTFU) in Zambia’s national treatment program threatens progress toward achieving HIV epidemic control. With CDC/PEPFAR funding, the Centre for Infectious Disease Research in Zambia (CIDRZ) supports the national program in Lusaka Province where a drop in 12-month retention was noted from 76% in FY17 to 65% in FY18. The recent CIDRZ BetterInfo study used a multi-stage sampling approach to generate revised, regionally representative estimates for mortality and LTFU in the national program. We adapted the study methodology to create a field ready “BetterInfo lite” sampling approach to ascertain true program status for patients apparently “LTFU” and drivers of retention decline.

Methods: Using routine data, we selected 10 high-volume facilities in Lusaka for “BetterInfo Lite” based on the largest net drop in program retention between Q3 and Q4 FY18. We randomly selected 15% of newly “LTFU” clients between Q3 and Q4 in each facility to be traced by phone or in person and to complete a brief vital status and retention questionnaire. Leveraging existing CIDRZ platforms, trained peer educators contacted patients or their contacts to determine patient mortality and true program status (i.e. alive in care, transferred, disengaged from care, dead, or LTFU).

Results: 1,023 of 6,968 LTFU patients (15%) were randomly selected for tracing. Tracing was attempted in 1,001 (98%), with 604 of these (80%) reached by phone or in person. 397 (40%) could not be reached. Of the 604 contacted, 491 (81%) were found alive and in care at their original clinic or a neighboring satellite health post, 80 (13%) were “silent” transfers, 17 (3%) disengaged from care and 16 (3%) were deceased (Figure 1).

Conclusion: It is feasible to adapt a rigorous sampling-based strategy used in a research context for routine program use to revise HIV treatment program retention estimates. We observed a high proportion of patients alive in care at the facility where they were flagged as “LTFU”, suggesting data quality issues, likely due to increasingly decentralized ART distribution and data collection. We also observed numerous “silent” transfers after ART initiation and identified 16 missed deaths, resulting in a mortality underestimation and LTFU overestimation. Scale up of electronic data systems to decentralized ART dispensation points, use of unique identifier tools such as biometrics, and enhanced early patient support and follow-up are needed to improve, and better monitor, program retention.

LOSS-TO-FOLLOW-UP RISK FACTORS AFTER ANTIRETROVIRAL THERAPY INITIATION IN UGANDA

Barbara Castelnuevo1, Frank Mubiru1, Grace Banturaki1, Joseph Musaazi1, Joseph Kabanda2, Michelle Adler2, Alice Namale2, Rhoda Mwondha1, Joanita Kigozi1, Agnes Kiragga1

1Infectious Disease Institute, Kampala, Uganda, 2CDC Uganda, Kampala, Uganda

Background: In sub-Saharan Africa published data seem to indicate that loss to follow-up (LTFU) is higher in men and young individuals. We described the proportion of LTFU by age and gender, and explored gender differences in different age groups. We also identified risk factors for LTFU in patients on antiretroviral therapy (ART) in urban Uganda.

Methods: This was a retrospective analysis of routine data of patients aged ≥15 years who initiated ART in 6 clinics in Kampala (2005–June 2018). Patients defined LTFU if they did not return for >90 days at any time, and did not transfer. Confirmed deaths and transfers were not included. We compared LTFU by gender, age groups (young adults [YA], 15–25 years; adults [AD], 26–50 years; and older adults [OA], >50 years), point of entry into HIV care, and year of ART initiation. We used Cox proportional hazards models to determine factors associated (P<0.05) with LTFU. We imputed missing (33%) CD4 count using multiple imputation chained equation with 30 imputations.

Results: Of the 56,304 patients: 41,847 (74.3%) were women, median age 30 years (IQR, 25–36 years), 17.2% had WHO stage 3/4 disease, median CD4 count at ART start 271 cells/µL (IQR, 147–426 cells/µL), and 80.3% started efavirenz-based ART. Overall, 20,203 (35.9%) were LTFU: LTFU was higher in women (36.6%) than men (34.5%; P<0.001). LTFU declined across age groups: 45.8% in YA, 33.1% in AD, and 31.4% in OA. In YA, LTFU was higher among women (46.5%) than men (37.9%), but lower in women AD (32.6% vs 34.3%) and OA (29.9% vs 33.0%; all P<0.001). LTFU was higher among recent ART initiators. One quarter (25.5%) women entered care through prevention of mother-to-child transmission (PMTCT) programs; LTFU among pregnant women was 55.2% among YA, 45.1% among AD, and 35.7% among OA (P<0.001). On multivariate analysis, we found that men, women who entered care through PMTCT services,
1107 HIV STIGMA PREDICTS RETENTION IN CARE AMONG US PATIENTS IN CARE

Catherine Pearson1, Mallory Johnson1, Torsten B. Neilands1, Samantha E. Dilworth1, John Sauseda1, Michael J. Mugavero2, Heidi M. Crane1, Rob Fredericksen1, W. C. Mathews5, Richard D. Moore1, Sonia Napravnik1, Kenneth H. Mayer1, Katerina A. Christopoulos1

1University of California San Francisco, San Francisco, CA, USA, 2University of Alabama at Birmingham, Birmingham, AL, USA, 3University of Washington, Seattle, WA, USA, 4University of California San Diego, San Diego, CA, USA, 5Johns Hopkins University, Baltimore, MD, USA, 6University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 7Fenway Health, Boston, MA, USA

Background: HIV-related stigma is a known barrier to engagement in care yet no large-scale, nationally representative studies have prospectively evaluated the effect of stigma on retention for those in HIV care in the United States (US).

Methods: The Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort integrates medical record and survey data from patients in primary care at 7 academic HIV clinics across the US. We added a yearly, validated 4-item assessment of internalized HIV stigma (response scale 1=strongly disagree to 5=strongly agree, α=0.91) into patient surveys for age, gender, race/ethnicity, sexual orientation, time since CNICS enrollment, and the effect of stigma on retention for those in HIV care in the United States (US).

Results: From 4/16 – 10/17, 5,825 patients completed the stigma assessment. Median age was 49 years (interquartile range [IQR]39–50 years), the median duration of ART was 6 years (IQR 5–7 years) and the median CD4 count at enrollment was 523 cells/µL (IQR 362–707). Of these, 113 (18.3%) had VLs≥1000 copies/mL at enrollment. Participants were followed for a median of 2.8 years (IQR 2.6–3.2) years during which hospitalizations occurred in 101 participants (7% of men vs. 20% of women; p<0.001). A total of 22 (3.6%) deaths occurred; 9% of men vs. 2% of women (p<0.001). Participants who were hospitalized had a lower risk of mortality in the univariate analysis (HR=0.22; 95% CI 0.03–1.63), but it was not statistically significant (p=0.138) and was not included in the final model. In the multivariate model, mortality was associated with age (adjusted hazard ratio [AHR] = 1.07 per year increase; 95% CI 1.01–1.13), male gender (AHR = 2.57; 95% CI 1.06–6.23) and time-updated CD4 counts (AHR = 0.67 per 100 cell increment; 95% CI 0.52–0.88). Virologic failure at enrollment was not associated with mortality (AHR = 1.18; 95% CI 0.40–3.47).

Conclusion: Female patients receiving ART for more than 6 years in rural Uganda were three times more likely to be hospitalized than men, but male mortality was nearly four times higher in the subsequent three years of follow-up. Facilitating care for acute medical problems may help to improve survival among male ART patients.
1109 ALCOHOL USE AND THE HIV CARE CONTINUUM IN ZAMBIA: NATIONALLY REPRESENTATIVE SURVEY

Michael J. Vinikoor1, Izukanji Sikazwe2, Anjali Sharma1, Lloyd Mulenga1, John Mayeya1, Ravi Paul1, Geetanjali Chander5, Jenala Chipungu6, Laura Murray5, Jeremy Kane1

1University of Alabama at Birmingham, Birmingham, AL, USA, 2Center for Infectious Disease Research in Zambia, Lusaka, Zambia, 3Government of Zambia Ministry of Health, Lusaka, Zambia, 4University of Zambia, Lusaka, Zambia, 1Johns Hopkins University, Baltimore, MD, USA, 5Centre for Infectious Disease Research in Zambia, Lusaka, Zambia

Background: Although increasing in sub-Saharan Africa (SSA), unhealthy alcohol use is not routinely screened for or treated within HIV prevention and treatment programs, in part due to lack of data on its intersection with the HIV epidemic. We evaluated the prevalence of unhealthy alcohol use among people living with HIV (PLWH) and its association with the HIV care continuum in Zambia.

Methods: We analyzed de-identified data from the 2016 Zambia Population-Based HIV Impact Assessment (ZamPHIA), a nationally-representative household survey. ZamPHIA included an assessment of alcohol use with the consumption questions from a modified Alcohol Use Disorders Identification Test (AUDIT-C), and rapid point-of-care HIV testing. PLWH also took an HIV care history survey and provided blood for detection of antiretroviral therapy (ART) and HIV RNA quantification. Unhealthy alcohol use was defined as an AUDIT-C score of 3-12 for women and 4-12 for men, abstinence was 0, and other scores were considered moderate use. Using multivariable regression, we identified the correlates of unhealthy alcohol use in the overall sample including sociodemographic factors and HIV status. Among PLWH, we evaluated the association of unhealthy alcohol use (versus abstinence) with HIV diagnosis, current ART use, and viral suppression (VS; RNA <1,000 copies/ml) using multinomial regression. PLWH were assumed to be diagnosed and on ART if ARVs were detectable.

Results: Among 18,796 participants included in the analytic sample, 11.9% were HIV-positive, and 15.3% (95% CI 14.6-16.1) reported unhealthy alcohol use. Male sex (relative risk ratio [RRR], 5.09), urban residence (RRR, 1.78), and HIV-positivity (RRR, 1.51) were independently associated with unhealthy alcohol use. Among PLWH, 71.4% were diagnosed, 87.1% were on ART, and 89.2% had VS. Unhealthy alcohol use (compared to abstinence) was associated with significantly lower odds of being diagnosed (adjusted odds ratio [AOR], 0.66; 95% CI, 0.49-0.87). We observed non-significant trends towards reduced odds of current ART use (AOR, 0.73; 95% CI, 0.48-1.10) and VS (AOR, 0.91; 95% CI, 0.57-1.44) among unhealthy users (versus abstinence).

Conclusion: Urban men living with HIV reported increased prevalence of unhealthy alcohol use in Zambia. Unhealthy drinking was associated with reduced awareness of HIV infection. Efforts to achieve control of the HIV epidemic in SSA should include alcohol reduction activities.

1110 RCT OF EARLY REFERRAL OF HIV+ ADULTS STARTING ART TO COMMUNITY-BASED ADHERENCE CLUBS

Janasanta Odayar1, Joanne Allerton1, siti kabanda1, Thoko Malaba1, Maia Lesosky1, Zovda Mamanzi2, Cathy Kalombo2, Landon Myer3

1University of Cape Town, Cape Town, South Africa, 2Western Cape Provincial Department of Health, Cape Town, South Africa

Background: Differentiated models of service delivery (DSD) are widely recommended to provide ART services for HIV+ patients established on ART, but there are few data on how soon stable patients may be referred to DSD after ART initiation.

Methods: We randomised adults 4 months after starting TDF+FTC+EFV in a large primary care service in Cape Town, South Africa, to either (a) immediate referral to the local DSD (‘adherence clubs’ (AC)) or (b) continued clinic-based care (NCT03199027). At randomisation all participants were eligible for ACs based on local criteria: VL<400 copies/ml, no viral load suppression, TB or other comorbidities, or HIV/ART complications. In this setting ACs are based at community venues separate from the clinic with counsellor-led services, 2-4 monthly ART refills and annual nurse checks; clinic-based services are nurse-/doctor-driven with 2-monthly ART refills and 4-monthly clinical appointments. Using study follow-up visits conducted separately from routine care in either arm, we evaluated the primary trial outcome of VL<400 copies/ml at 12 months on ART (8 months after randomisation).

Results: Between Jan 2017 and Apr 2018, 220 consecutive non-pregnant adults who met local criteria for referral to ACs were enrolled and randomised (mean age 35y; 67% female; 24% previous ART; median nadir CD4 366 cells/mm3; median time on ART 18w). 88% of patients randomised to ACs attended the club visit on schedule. VL measures for the primary outcome were available on 214 participants (97%) with no differences between those retained versus lost to follow-up, overall and by arm. By 12m on ART, VL<400 cps/ml was observed in 89% of participants randomised to be referred to ACs versus 53% of participants randomised to be retained in the clinic (risk difference, -4.3%; 95% CI, 11.9% to 3.2%). The finding for similar outcomes between AC and clinic-based care was consistent across subgroups of age, gender, previous ART use and nadir CD4 cell count; in a binomial model adjusted for the same factors; and when the outcome was examined at cutoffs of VL<50 and <1000 cps/ml.

Conclusions: These novel data suggest that referral of stable ART patients to community-based DSD may take place as early as 4 months after ART initiation in this setting with comparable virologic outcomes achieved at 12 months on ART versus clinic-based services.

1111 DIFFERENTIATED SERVICE DELIVERY FOR HIV CARE: THE FAST-TRACK EXPERIENCE FROM ZAMBIA

Samuel Bosomprah1, Isaac Zulu2, Michael Hercle1, Lloyd Mulenga1, Mihesh P. Shah1, Izukanji Sikazwe1, Annie Mwila1, Helen B. Mulenga1, Muhau Mubiana1, Mwansa Lumpa1, Pamela J. Bachanas2, Simon Agolory3

1Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, 2CDC, Atlanta, GA, USA, 3Government of Zambia Ministry of Health, Lusaka, Zambia, 4CDC Zambia, Lusaka, Zambia

Background: Differentiated service delivery (DSD) models are designed to lower barriers to HIV care for people living with HIV (PLWH). In 2017, we implemented a DSD model known as “FastTrack” (FT) within Zambia’s HIV program that provided PLWH “stable” on ART (defined as WHO stage I/II disease, on ART ≥6 months, and CD4+ >350 or viral load suppression [VLS]) with expedited clinical services. We report clinical outcomes for FT patients during the first 2 years of implementation.

Methods: We reviewed individual-level PLWH data from Zambia’s electronic health record, SmartCare. Patients 15–59 years were included in our analysis if they started ART any time from January 1, 2010 at any of 14 high-volume (>3,000 patients on ART) clinics in Lusaka. All patients in FT from its inception (January 1, 2017) through September 30, 2018 had their data reviewed to ascertain 6- and 12-month retention (i.e. any visit within 90 days of their 6- and 12-month post-ART initiation anniversaries) and VLS. To enable comparison, we reviewed records for all FT eligible patients who did not participate in FT during the same period at the same clinics. Using random-effects log binomial regression modeling, we estimated relative risk of retention in care for FT versus non-FT patients.

Results: During the review period, 3,671 patients participated in FT and 83,764 did not. FT patients were more likely to be female (64.9% vs 62.3%), ≥35 years (70.9% vs 60.2%), and on ART ≥24 months (77.6% vs 73.6%) (all p<0.01); there was no difference in the proportion with WHO I/II disease (72.6% vs 72.4%), FT patients were more likely to be retained at 6- and 12-months and to achieve VLS at 6-months compared to non-FT patients (p<0.001) (Figure). After adjusting for clinic, age, sex, WHO stage, and time on ART, FT patients were 1.23 and 1.49 times as likely to be retained in care as non-FT patients at 6- and 12-months, respectively (p<0.001).

Conclusions: We observed superior retention in care and VLS, and higher risk of care retention in adjusted analyses, among patients receiving FT versus non-FT services at ART clinics in Lusaka, Zambia. Due to limitations with routine data, we could not control for baseline CD4 and other unmeasured confounders. New DSD models, such as FT, hold promise for increasing care retention and VLS among stable ART patients in routine HIV treatment programs.
DIFFERENTIATED CARE: TIME SPENT IN DIFFERENT ART DELIVERY MODELS IN RURAL ZIMBABWE

Benedikt Christ, Jannke van Dijk, Wesley R. Mukondwa, Cordélia Kunzekwenyika, Ronald Manhibi, David Tasunga, Frédérique Chammartin, Matthias Egger, Marie Ballif, for the International epidemiology Databases to Evaluate AIDS (IeDEA), 1Institute of Social and Preventive Medicine, Bern, Switzerland, 2SolidarMed, Masvingo, Zimbabwe, 3Ministry of Health and Child Care, Harare, Zimbabwe, 4Centre for Infectious Disease Epidemiology and Research, Cape Town, South Africa

Background: Differentiated service delivery (DSD) may contribute to reaching the UNAIDS 90-90-90 targets as the number of people living with HIV (PLWH) on antiretroviral therapy (ART) increases. The implementation of differentiated ART delivery is part of the national DSD guideline in Zimbabwe, with the aim to meet the diverse needs of PLWH, to reduce the time spent at health facilities (HFs) and to decongest the health system.

Methods: We assessed 26 rural HFs in Bikita District, Zimbabwe, in 2019. At each HF, one or two nurses involved in HIV service delivery, and consecutive PLWH attending the HF on the day of data collection were recruited. We collected data on the availability of various ART delivery models and the time that PLWH spend at the HF using standardized electronic data collection forms. We used descriptive statistics and linear regression analysis on log transformed time data.

Results: We assessed 22 rural health centers, 2 rural hospitals and 2 district hospitals. Median numbers of staff and patients registered were 4 and 346 (rural health centers), 13 and 994 (rural hospitals) and 24 and 1152 (district hospitals), respectively. Twenty HFs (77%) had at least one or more differentiated ART delivery model in place. The most common model was the community-based ART refill group (CARG; 13 HFs), followed by facility-based fast track (8 HFs), family refill group (6 HFs) and facility-based club refill (1 HF). Time spent at the HF was assessed for 203 PLWH (68% female, 12% pregnant or lactating). Twenty HFs (77%) had at least one or more differentiated ART delivery model in place. The most common model was the community-based ART refill group (CARG; 13 HFs), followed by facility-based fast track (8 HFs), family refill group (6 HFs) and facility-based club refill (1 HF). Time spent at the HF was assessed for 203 PLWH (68% female, 12% pregnant or breastfeeding, median age 43 years [interquartile range: 34–52]). Fifty-seven (28%) were enrolled in a differentiated ART delivery model (34 in a facility- and 23 in a community-based or family model). Table 1 shows mean times spent at the HFs and results from multivariable regression. There was no evidence of interaction between model type and gender when controlling for patient-to-staff ratio and the type of HF. The type of HF and patient-to-staff ratios were more important determinants of the time spent at the HF than the ART delivery model.
COMMUNITY-BASED SERVICE DELIVERY OF HIV TREATMENT IN ZAMBIA: COMMUNITY PRIVATE PHARMACY ANTIRETROVIRAL THERAPY REFILL IN KAMPALA, UGANDA

Martin Ssuuna1, Shamim Nakade1, Joseph Kabanda1, Sarah Zalwango1, Daniel A. Okello1, Christopher Mugara2, Donna Kabatesi2, Alice Namale2, Alex Muganzi2, Nelson Kalemza3, Joannah Kigozi3

1Infectious Disease Institute, Kampala, Uganda, 2CDC Uganda, Kampala, Uganda, 3Ministry of Health Uganda, Kampala, Uganda

Background: Of the 1,000,000 (72%) persons living with HIV (PLHIV) on antiretroviral therapy (ART) in Uganda, 20% received care in Kampala, the capital, and its surrounding areas between April and June, 2019. The number of PLHIV attending Kampala’s mid-level public health facilities has grown four times in the last 10 years, resulting in high patient-provider ratios, congestion, and long waiting times. The Kampala private community pharmacy ART refill model is a differentiated care approach that was introduced in 2017 for stable clients to address these challenges. Here, we describe the model and evaluate its effectiveness.

Methods: The Infectious Diseases Institute in partnership with the Kampala Capital City Authority selected 6 private pharmacies to serve as community ART refill points for stable PLHIV from 4 high-volume public health facilities (8000–13,000 PLHIV on ART at each site). Virally suppressed adults on first-line ART were enrolled in this model by their primary care providers. They received ART refills at the pharmacy and attended semi-annual follow-up appointments at the primary health facility per national guidelines. A nurse-dispenser per pharmacy supported free ART refills, opportunistic infection screening, patient referrals, tracking and follow-up, ART inventory management, and reporting. Program data from pharmacy and facility records has been summarized and analysed.

Results: Over a 30-month period (Jan 17 – June 19), 9291 (29% men) PLHIV enrolled in the pharmacy refill model, representing 30% of clients at the 4 facilities. Of these, 96% had received ART refills as scheduled, and the average waiting time at the pharmacy was <10 minutes. The 12-month retention in care rate was 98%, and >99% of enrolled clients remained virally suppressed.

Conclusion: Rapid enrolment and good retention rates indicate high acceptability of this model among urban PLHIV in Uganda. Structured public-private partnerships present opportunity for delivery of simplified ART refill services for PLHIV in resource-limited settings.

COMMUNITY-BASED SERVICE DELIVERY OF HIV TREATMENT IN ZAMBIA: COSTS AND OUTCOMES

Brooke E. Nichols1, Refiloe Cele2, Lisa Jamieson2, Lawrence Long3, Zumbe Siwale3, Patrick Banda4, Crisgimoyo4, Sydney Rosen5

1Boston University, Boston, MA, USA, 2Health Economics and Epidemiology Research Office, Johannesburg, South Africa, 3University of Cape Town, Cape Town, South Africa, 4EquiP Health Zambia, Lusaka, Zambia, 5Ministry of Health, Lusaka, Zambia

Background: There are 1 million Zambians receiving antiretroviral treatment (ART) for HIV, severely straining existing healthcare infrastructure and human resources. To address this challenge, community-based differentiated service delivery (DSD) models of care have been implemented to reduce provider workload and improve quality of care. The costs and impact of these DSD models have not yet been evaluated in routine settings.

Methods: We conducted a cost and outcomes analysis of ART naïve HIV-infected adults in Aid for AIDS (AFA) cohort, an HIV health management scheme for the private sector in South Africa who initiated first line NNRTI based ART between January 2002 and July 2013. The primary endpoint was all-cause mortality; secondary endpoints included CD4 and viral load (VL) response, loss to follow-up (LTFU), and switching to home-refill. Statistical analyses included descriptive, baseline (propensity-score) model, and time-updated (marginal structural) models (MSM).

Results: 40,939 patients, contributing over follow-up 66,000 years were evaluated. In a baseline analysis only, courier was associated with improved survival (adjusted hazard ratio = 0.90 [95% CI: 0.84-0.96], p-value for log-rank test <0.001) after adjusting for baseline differences. Within an MSM framework, which addresses time-varying aspects, courier was associated with higher benefit (adjusted hazard ratio = 0.66 [95% CI: 0.55-0.78]). LTFU and switching were positively associated with lower CD4 and higher VL, explaining the improvement in the adjusted hazard ratio; CD4 response and VL suppression rates were superior for home-refill (including cases in which patients switched to home-refill). Finally, hospitalisation days and average costs, and CD4/ VL monitoring were higher in home-refill compared to the self-refill groups (p<0.001) despite improved survival, CD4 and VL responses (see figure 1), which suggests that home-refill promotes better health-seeking behaviour and better outcomes.

Conclusion: Our findings support the adoption of home-refill (courier) within the DSD models to facilitate the UNAIDS 90-90-90 targets, for HIV programs in both resource-poor and -rich settings. Further research is needed on the potential impact of home-refill in vulnerable groups with known transportation barriers such as postpartum women and adolescents.
Outcomes of Community-Based Antiretroviral Treatment Program in Namibia

Naemi Shoopala1, Andrew L. Baughman2, Assegid T. Mengistu3, Kiren Mitruka2, Godfrey Woek2, Graham Mutandi6, Michael B. De Klerk4, Isaac Zulu4, Steven Hong5, Nicholas Mutenda5, Linea Hans4, Simon Agolory5, Leigh Ann Miller1, Eric J. Dziuban1, Ndapewa Hamunime6

1Centers for Disease Control and Prevention, Windhoek, Namibia, 2Centers for Disease Control and Prevention, Atlanta, GA, USA, 3Ministry of Health and Social Services, Windhoek, Namibia, 4Elizabeth Glaser Pediatric AIDS Foundation, Washington DC, USA, 5Centers for Disease Control and Prevention, Windhoek, Namibia

Background: Namibia is a sparsely populated country of 2.5 million people, with an HIV prevalence 12.6% (persons aged 15-64 years). About 52.1% of the population lives in rural areas, having to travel, on average, 25-59 km for HIV care. During 2007-2014, communities and health care facilities (HCF) in two high HIV burden districts in northern Namibia collaborated to establish Community-Based Antiretroviral Treatment (C-BART) services. Community members constructed basic structures close to their homes where healthcare workers visited quarterly to provide HIV clinical assessment, viral load (VL) and CD4 specimen collection, and antiretroviral (ARV) refills. We evaluated clinical outcomes at these C-BART sites to inform program expansion.

Methods: We conducted a retrospective cohort review of patients who were down-referred from HCFs to C-BART sites for continued HIV care during January 01, 2007–July 31, 2017, in Okongo (16 sites) and Eenhana (18 sites) Districts. We abstracted data on demographics, clinical encounters, ARV dispensation, and VL results from electronic and paper records. We measured C-BART retention (3-60 months), defined as being alive and on ART with a documented visit within 90 days of appointment date, and viral suppression (VS) (<1000 copies/ml) on a VL test at least 3 months after down-referral and closest to data abstraction date (November 30, 2017).

Results: Of the 1031 patients (909 adults and 122 children) included in the analysis, 100% of patients were retained in C-BART at 3 months and 99% of adults (n=522) and children (n=71) were retained at 12 months (Table). In Okongo District, 91% of adults (n=141) and 96% of children (n=28) were retained at 60 months. Overall, 98% of adults (n=568) and 87% of children (n=77) retained at C-BART sites for ≥3 months had viral suppression; 98% of adults (n=427) and 84% (n=58) of children in C-BART ≥12 months, and 98% of adults (n=121) and 83% (n=23) of children in C-BART ≥60 months (Okongo) had VS. VS did not differ by the time on ART in C-BART (range: 3 months−10 years) (p=0.49 and p=0.81, respectively).

Conclusion: The C-BART program demonstrates high retention and VS among patients and alleviates concerns about providing community-based ART to children. High retention rates were sustained up to 60 months after down-referral to C-BART, demonstrating the utility of C-BART as a long-term model for managing patients on ART, particularly in rural settings.

Randomized Trial of HIV-ASSIST Versus Guidelines for ART Selection by Trainees

Jesus Ramirez1, Manoj Maddali2, Saman Nematiollahi3, Jonathan Z. Li4, Maunank Shah1

1Johns Hopkins University, Baltimore, MD, USA, 2University of California San Francisco, San Francisco, CA, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4Brigham and Women's Hospital, Boston, MA, USA

Background: Support for primary care clinicians in HIV medicine is critical in light of national HIV-provider shortages. Department of Health and Human Services (DHHS) guidelines are comprehensive but complex to apply for antiretroviral therapy.
transition to dolutegrvir-based regimen: nigerian experience

Moses Katbi1, Adefaayo Adedoyin1, Kent Klinder1, Bartholomew Ochone2, iyiola Fatuiriyele3, Michele Russell1, Oluwatosin Adeoye4, Adeoye Adedayo1, Tolu A. Alamu1


Background: Following the release of the preliminary results of the largest ever HIV/AIDS indicator and Impact survey in Nigeria, the government of Nigeria and PEPFAR launched an aggressive effort towards improving virologic supression among PLHIV. We transitioned clients from efavirenz to dolutegravir based regimen. We examined the viral load among key population groups transitioned from TLE to TLD in three high burden states.

Methods: A descriptive observational study that compared the routine viral load result of 1,327 key population (KP) clients from three high burden states who were transitioned from Tenofovir-Lamivudine-Efavirenz (TLE) to Tenofovir-Lamivudine-Dolutegravir (TLD). We carried out a repeat viral load tests on clients 1 to 3 months after transitioning to TLD using the Roche (C8800 & C8800) and Abbott PCR analyzers. We analyzed data using SPSS version 21. Paired sample t-test was used to compare the means of the viral load test results and Chi-square to compare the proportion of respondents with <1000 copies/ml and those that achieved untransmitable viral load level of <200 copies/ml before and after start of TLD. We used ANOVA to determine difference in means between the different KP groups. We set P-value at P < 0.05, being statistically significant.

Results: 64.7% (n=2153) females and 35.3% (n=1174) males were enrolled (FSW 55.9% (n=1861); MSM 24% (n=797); PWID 14.3% (n=476); sexual partners of key population 5.6%; (n=190); People in prisons 0.1%; (n=3)). Mean age of clients is 31.19 ±2.82. Lower viral load achieved when on TLD (mean = 6924.71, SD = 65687.079) than when on TLE (mean = 17059.85, SD = 11859.603). Paired sample t-test found this difference to be significant (t = 4.572, p<0.005). Chi square reveals more clients achieved viral load <1000 copies and <200 copies/ml while on TLD than while on TLE (X2 = 217491, p < .005; X2 = 175722, p < .005 respectively). ANOVA showed no significant difference in the mean of the viral load between the groups before and after start of TLD (F(4) = 1.113, p=0.35 for viral load results before start of TLD; F(4) = 0.665, p=0.62 for viral load results after start of TLD).

Conclusion: DTG-based regimen significantly suppressed viral load of KP PLHIV following transition from Efavirenz based regimen. Virologic supression and untransmitable viral levels achieved were superior with the use of TLD.

poor linkage to care among HIV+ PERSONS IN EMERGENCY DEPARTMENTS IN SOUTH AFRICA

Bhakti Hansoti1, Aditi Rao1, Elizabeth Hahn1, Sofia Ryan1, Nomzamo Mvandaba2, Yandisa Nyansia3, Victoria Chen4, Pamela Mda5, Roshen Maharaj1, David Stead1, John Black1, Steven J. Reynolds1, Jean B. Nachega2, Thomas Quinn1, for the WISE Study Group

1Johns Hopkins University, Baltimore, MD, USA, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3Walter Sisulu University, Mthatha, South Africa, 4University of Pittsburgh, Pittsburgh, PA, USA

Background: Despite efforts to extend HIV services across South Africa a significant number of persons living with HIV in the Eastern Cape remain either untested or unengaged. Even though Emergency Departments (EDs) were designed to address acute medical issues, they may also represent an under-utilized gateway for identification and engagement of HIV positive individuals at high risk for disease progression as well as onward transmission. We therefore sought to examine the feasibility and acceptability of universal HIV testing in the ED and subsequent linkage to treatment.

Methods: We conducted a prospective cohort study across four EDs in the Eastern Cape province of South Africa, for a period of six weeks each, from July 2016 to July 2018. All adult (over 18yrs) non-critical patients presenting were systematically offered HIV testing. HIV+ patients were further consented to participate in a follow up study to ascertain linkage to care (LTC) via: 1) Telephone follow-up and/or; 2) Tracking in the National Health Laboratory System (NHLS) database. LTC at one-year was defined as self-reporting linkage (telephonic) or evidence of repeated CD4/viral load testing (NHLS). All patients followed the usual down referral care pathway (follow up in local clinic near their home after receiving a letter stating their results).

Results: Over the study period 5900 patients were enrolled, of which 4846 (82.1%) accepted testing, of which 1172 (24.2%) were HIV positive of which 949 consented to participate in a LTC follow up study. Of these 633 (66.7%) had a known diagnosis of HIV and 316 (33.3%) had a new diagnosis of HIV infection. Of the known HIV positive patients, 30.9% had evidence of LTC via NHLS (72/233) and 48.6% confirmed via phone (71/146). Among newly diagnosed patients, 27.6% (40/145) had evidence of LTC in the NHLS database, and 38.4% confirmed via phone (28/73). There was no significant difference in linkage to care between those with known HIV versus those with HIV diagnosed in the ED.

Conclusion: ED-based HIV testing in South Africa identifies individuals with new HIV diagnoses and those out of HIV care. Overall LTC in this population was extremely poor. While the ED is a critical venue to identify HIV individuals not on ART there is a need to deploy novel, targeted LTC interventions in the ED.
Background: Treatment for all people with HIV and improved antiretroviral therapy and care infrastructure are expected to have improved health outcomes in the US. We aimed to describe changes in initial care outcomes for people diagnosed with HIV in the District of Columbia (DC) over time.

Methods: We used DC HIV surveillance data for people ages 13 and older diagnosed with HIV in DC in 2009-2017 to calculate linkage to care (LTC, presence of CD4 or viral load after HIV diagnosis) and viral suppression (VS, HIV RNA <200 copies/ml) as continuous variables (time from diagnosis to outcome) and dichotomous variables (LTC-0, or LTC within 30 days, and VS-90, or VS within 90 days of diagnosis). Chi square tests were used to compare demographics and CD4 at diagnosis between those diagnosed in 2009-2012 (DX09-12) vs. 2013-2017 (DX13-17). For DX13-17, multivariable (MV) logistic regression was used to calculate adjusted prevalence ratios (aPR) for LTC-30 and VS-90, adjusted for age at diagnosis, gender, race/ethnicity, mode of transmission, year of diagnosis, and CD4 at diagnosis.

Results: Compared to DX09-12 (n=3124), DX13-17 (n=2119) were more likely to be men (75.2% vs. 71.3%), Latino (10.9% vs. 7.5%), MSM (50.1% vs. 43.0%), and younger (all p<0.001). There were no differences by LTC-30 between the groups. The proportion never virally suppressed declined (22.7% DX09-12 vs. 19.6% DX13-17, p<0.0001). Median time from HIV diagnosis to initial VS declined from 250 days (DX09-12) to 157 days (DX13-17) (p<0.0001); among those with CD4>350 cells/µl at HIV diagnosis, median time from HIV diagnosis to initial VS declined from 235 days (DX09-12) to 129 days (DX13-17) (p<0.0001). Among DX13-17, achievement of VS was lowest among transgender people (TG, 67.9%), PWID (58.6%), and adolescents 13-18 (69.2%). MV analysis (Table) demonstrated that non-White races, MSM/PWID, ages 25-39, dx year 2014, and CD4>500 (aPR 1.47, 95% CI 1.13-1.90) were less likely to achieve VS-90, and women, TG, dx year 2015-2017, and those with CD4<500 (aPR 1.47, 95% CI 1.13-1.90) were more likely to achieve VS-90.

Conclusion: Time from HIV diagnosis to LTC and VS have significantly improved from 2009 to 2017 for people diagnosed in DC, but gender, race, and risk factor-based disparities were found. Results can guide interventions for focus populations, including men, MSM/PWID, Black individuals, and those with lower CD4 counts. Future research may elucidate reasons for delays.

1124 ENGAGEMENT IN CARE AND VIRAL SUPPRESSION AMONG NEWLY DIAGNOSED HIV-INFECTED PERSONS

Kashif Iqbal1, Maria Mendoza1, Anne Patala1, Robyn N. Fanfair1, Gary Marks1

1CDC, Atlanta, GA, USA

Background: Achieving and maintaining viral suppression (VS) in persons living with human immuno deficiency virus (HIV) protects their own health and prevents new infections. An important step to achieving and maintaining VS is being engaged in care. This study describes how newly diagnosed HIV-infected persons are engaging with their provider and achieving VS over a 24-month period.

Methods: Persons newly diagnosed with HIV infection from June 30, 2012-December 31, 2014 who presented at one of six HIV clinics (Birmingham, AL; Boston, MA; Houston, TX; Miami, FL; San Diego, CA; Seattle, WA) were included in the cohort. All participants had an un-suppressed viral load on their first viral load (VL) test at the clinic and observed for up to 24 months from the date of their first VL test. We examined patterns of VS (<200 copies/ml) across time and the percentage of persons who had VS on their latest VL test during the 24-month follow-up period. We used chi-squared statistics to compare persons with VS and not virally suppressed (nVS) by proportion of kept HIV care visits and by clinic, age, sex, race/ethnicity, and insurance.

Results: Overall, 76% (1111/1469) of all newly diagnosed HIV-infected patients were VS at their latest VL test with an average of 149 days to achieve VS. Examining the cohort across time revealed that after achieving VS, 69% remained VS on all subsequent VL tests and 19% were nVS on any of their tests. The percentage VS varied by clinic, race/ethnicity, age, insurance, and proportion of kept visits with their provider (Table). Notably, as the proportion of clinic visits increase, the proportion of patients who had VS on their latest VL test during the 24-month follow up period. We used chi-squared statistics to compare persons with VS and not virally suppressed (nVS) by proportion of kept HIV care visits and by clinic, age, sex, race/ethnicity, and insurance.

Conclusion: A large proportion of newly diagnosed HIV-infected patients achieved and maintained VS however nearly 20% never achieved suppression. There is a need for close clinical monitoring and identification of barriers.
impacting some newly diagnosed patients, particularly the unmet needs of minorities to increase the number who achieve stable suppression.

Table 1. Characteristics of HIV testers in Botswana from January 2018 to September 2019, by HIV testing department

<table>
<thead>
<tr>
<th>Variable</th>
<th>VCT</th>
<th>Other PITC</th>
<th>VCT/Other PITC</th>
<th>ED</th>
<th>Other PITC</th>
<th>ED/Other PITC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30 (24-36)</td>
<td>26 (23-34)</td>
<td>30 (24-36)</td>
<td>30 (35-41)</td>
<td>30 (35-41)</td>
<td>0.009</td>
</tr>
<tr>
<td>Male sex</td>
<td>66.2%</td>
<td>66.2%</td>
<td>66.2%</td>
<td>66.2%</td>
<td>66.2%</td>
<td>0.907</td>
</tr>
<tr>
<td>Urban setting</td>
<td>61.0%</td>
<td>61.0%</td>
<td>61.0%</td>
<td>61.0%</td>
<td>61.0%</td>
<td>0.001</td>
</tr>
<tr>
<td>Newly detected (HIV positivity)</td>
<td>43.7%</td>
<td>43.7%</td>
<td>43.7%</td>
<td>43.7%</td>
<td>43.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>ART initiated</td>
<td>42.9%</td>
<td>42.9%</td>
<td>42.9%</td>
<td>42.9%</td>
<td>42.9%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

1125 FREQUENT DETECTION OF UNDIAGNOSED HIV WITHIN EMERGENCY DEPARTMENTS IN BOTSWANA

Jillian Pintye1, Katrina F. Orblad2, Shreshth Mawandia1, Odirele Bakae1, Lenna Tau1, Mattas Grande1, Gbabaone Mogomotsi1, Esther Mmatli1, Modise Ngombo1, Laura Secell1, Renée Heffron1, Jenny Ledikwe1

1University of Washington, Seattle, WA, USA, 2International Training and Education

Background: Botswana has a severe generalized HIV epidemic (23% adult HIV prevalence) with a high annual HIV incidence (1.3%). In 2004, Botswana became Africa's first country to routinize "opt-out" provider-initiated HIV testing and counseling (PITC) at health facilities, though it is rarely implemented in Emergency Departments (EDs). EDs provide episodic, unplanned care to large volumes of undifferentiated patients. Thus, EDs provide an opportunity to capture patients with undiagnosed HIV infection missed by other facility-based HIV testing.

Methods: We evaluated the frequency of detecting undiagnosed HIV infection in the ED using data from a national HIV testing program in Botswana. From January 2018 to September 2019, HIV testing was conducted by program counselors at 149 facilities in 16 districts, including 55 EDs. Electronic data capture and demographic information (age, sex, citizenship) and testing date, location and result. Data were included from individuals' first HIV test during the 12-month period. HIV testing was successful within EDs in Botswana and yielded higher frequency of detecting undiagnosed HIV infections than VCT or other PITC; however, immediate ART initiation was less frequent. ED HIV testing programs should strengthen linkage to care for those who test positive.

Results: In total, 130,161 individuals were tested in ED (9,695; 7%), VCT (12,760; 10%), and other PITC (107,706; 83%) and were included in the analysis; median age was 30 years (IQR 24-30), 29% were <25 years, 53% were male, and 57% were tested in urban centers. Compared to individuals who tested in VCT or other PITC, individuals who tested in the ED differed in age, sex, and urbanicity (Table 1). Overall, frequency of detecting undiagnosed HIV infection was 3.4%; 2.2% in VCT, 3.4% in other PITC, and 4.7%; in ED, respectively. Frequency of HIV detection in EDs was 2-fold higher than in VCT (prevalence ratio [PR] =2.2, 95% CI 1.4-3.3, p <0.001) and 1.4-fold higher than in other PITC (OR=1.4, 95% CI 1.1-1.9, p=0.03). Among individuals with ART information (3,505), those who tested HIV-positive in EDs less frequently initiated same-day ART compared to VCT/other PITC (71% vs 82%, PR=0.9, 95% CI 0.8-1.0, p=0.003).

Conclusions: HIV testing was successful within EDs in Botswana and yielded higher frequency of detecting undiagnosed HIV infections than VCT or other PITC; however, immediate ART initiation was less frequent. ED HIV testing programs should strengthen linkage to care for those who test positive.

1126 COMBINATION HIV PREVENTION STRATEGIES TO MEET THE 2030 ENDING THE HIV EPIDEMIC GOALS

Samuel Jenness1, Jordan Johnson2, Karen W. Hoover1, Dawn K. Smith2, Kevin P. Delaney2

1Emory University, Atlanta, GA, USA, 2CDC, Atlanta, GA, USA

Background: The goal of the US Ending the HIV Epidemic (EHE) plan is to reduce HIV incidence by 90% over the next decade. This initiative will direct a major scale-up of prevention and care activities in high-burden areas like the Southeast US. It is unknown what interventions, alone or in combination, will have the greatest impact towards meeting the EHE 2030 targets.

Methods: We developed a stochastic network-based HIV transmission model for men who have sex with men (MSM) stratified by race. Our model was calibrated to current surveillance-based estimates of HIV prevalence, PrEP utilization, and HIV care continuum levels in the Atlanta area. Counterfactual model scenarios varied HIV screening rates relative to empirical levels, under assumptions that HIV-negative screens are linked to PrEP initiation versus no PrEP linkage, and also relative improvements to HIV care linkage and care retention for those testing HIV-positive.

Results: Compared to current HIV screening rates, a ten-fold relative increase (to approximately biannual screening for black and Hispanic MSM and quarterly for white MSM) would lead to 41.2% of infections averted under the assumption of PrEP linkage, with prevention through both increased PrEP coverage (from 14.9% to 67.0%) and increased HIV viral suppression (from 48.9% to 55.8% of all infected). At the same relative increase in screening but under the assumption of no PrEP linkage, 9.9% of infections would be averted, with prevention only relative improvements to HIV care linkage and care retention for those testing HIV-positive.

Conclusions: Interventions to improve HIV screening linked with PrEP for those screening negative and HIV care retention would have the largest impact on HIV incidence. Additional interventions beyond these improvements to HIV screening, PrEP coverage, and HIV care retention will be necessary to reach the EHE targets.

1126 COMBINATION HIV PREVENTION STRATEGIES TO MEET THE 2030 ENDING THE HIV EPIDEMIC GOALS

Samuel Jenness1, Jordan Johnson2, Karen W. Hoover1, Dawn K. Smith2, Kevin P. Delaney2

1Emory University, Atlanta, GA, USA, 2CDC, Atlanta, GA, USA

Background: The goal of the US Ending the HIV Epidemic (EHE) plan is to reduce HIV incidence by 90% over the next decade. This initiative will direct a major scale-up of prevention and care activities in high-burden areas like the Southeast US. It is unknown what interventions, alone or in combination, will have the greatest impact towards meeting the EHE 2030 targets.

Methods: We developed a stochastic network-based HIV transmission model for men who have sex with men (MSM) stratified by race. Our model was calibrated to current surveillance-based estimates of HIV prevalence, PrEP utilization, and HIV care continuum levels in the Atlanta area. Counterfactual model scenarios varied HIV screening rates relative to empirical levels, under assumptions that HIV-negative screens are linked to PrEP initiation versus no PrEP linkage, and also relative improvements to HIV care linkage and care retention for those testing HIV-positive.

Results: Compared to current HIV screening rates, a ten-fold relative increase (to approximately biannual screening for black and Hispanic MSM and quarterly for white MSM) would lead to 41.2% of infections averted under the assumption of PrEP linkage, with prevention through both increased PrEP coverage (from 14.9% to 67.0%) and increased HIV viral suppression (from 48.9% to 55.8% of all infected). At the same relative increase in screening but under the assumption of no PrEP linkage, 9.9% of infections would be averted, with prevention only relative improvements to HIV care linkage and care retention for those testing HIV-positive.

Conclusions: Interventions to improve HIV screening linked with PrEP for those screening negative and HIV care retention would have the largest impact on HIV incidence. Additional interventions beyond these improvements to HIV screening, PrEP coverage, and HIV care retention will be necessary to reach the EHE targets.
COMMUNITY HIV-PREVENTION SERVICES IMPROVE THE HIV TREATMENT CASCADE IN 5 COUNTRIES

Mansoor S. Farahani1, Andrea Lové, Karampreet K. Sachathep1, Neema M. Philip1, Wolfgang Hladik1, Andrew Voetsch2, Godfrey Musuka1, Andrew F. Auld1, Shirish Balachandra1, Jackson Okuku1, Ameer M. Schwitters2, Bharat S. Parekh1, Hetal Patel1, David Hood1, Jessica E. Justman3

1ICAP at Columbia University, New York, NY, USA, 2CDC, Atlanta, GA, USA, 3ICAP at Columbia University, Email institution information to CROIabstracts@iasusa.org, 4CDC Malawi, Lilongwe, Malawi, 5US Centers for Disease Control and Prevention, Atlanta, GA, USA, 6CDC Zambia, Lusaka, Zambia, 7CDC Nigeria, Abuja, Nigeria

Background: The effect of using HIV prevention services on using HIV treatment services has not been well documented in southern Africa. Using nationally representative data from household surveys conducted in Eswatini, Lesotho, Malawi, Zambia, and Zimbabwe (2015–2017), we examined the correlation of self-reported voluntary medical male circumcision (VMMC) and condom use among HIV-negative adults with use of treatment services by people living with HIV (PLHIV), represented by the UNAIDS 90-90-90 targets, at the community level.

Methods: Among HIV-negative adults in the surveys, we estimated the prevalence of self-reported VMMC status and condom use (during last sexual act in the prior 12 months) at the smallest geographic sampling unit (enumeration area [EA]). We used multilevel mixed-effects logistic regression, adjusted for demographic and risk behavior variables at individual level to estimate the correlation between VMMC and condom use at the EA level with the likelihood of PLHIV being aware of their status, currently on ART, or virologically suppressed (VS).

Results: Among 10,861 PLHIV aged 15–64 years (62% women) residing in 1,734 EAs across surveys, 76% had a previous HIV diagnosis, 68% were receiving ART, and 60% were VS. Median EA-level prevalence of HIV infection, VMMC, and condom use was 16% (interquartile range [IQR], 10%–24%), 16% (IQR, 6%–32%), and 72% (IQR, 55%–88%), respectively.

On multilevel analysis, the odds of knowing HIV-positive status, receiving ART, or being VS were significantly higher for PLHIV residing in an EA where ≥75% of the adults reported condom use (adjusted odds ratio [AOR], 1.3 [95% confidence interval (CI), 1.2–1.5]; 1.3 [95% CI, 1.1–1.4]; 1.2 [95% CI, 1.1–1.3], respectively). The odds of knowing HIV-positive status, receiving ART, or being VS were significantly higher for PLHIV residing in an EA where ≥15% of men reported VMMC (AOR, 1.2 [95% CI, 1.1–1.3]; 1.1 [95% CI, 1.0–1.3]; and 1.1 [95% CI, 1.0–1.2], respectively).

Conclusion: In these five countries, community utilization of prevention services was positively correlated with the individual use of treatment services, suggesting that combination prevention services can play a synergistic role in epidemic control.

OPTIMIZING HIV PREVENTION EFFORTS WITHOUT NEW INVESTMENT CAN REDUCE INCIDENCE

Evin Jacobson1, Katherine A. Hicks2, Justin Carrico2, Stephanie L. Sansom1

1CDC, Atlanta, GA, USA, 2RTI International, Research Triangle Park, NC, USA

Background: We optimized current societal spending on HIV prevention to assess how best to achieve large reductions in HIV incidence.

Methods: We used a national model of HIV transmission to estimate the potential maximum 10-year reduction in new infections from 2018 to 2027. The model applied current estimated public and private HIV prevention spending ($)2.6 billion for 2018) each year to the following intervention categories: HIV screening (high- and low-risk MSM and heterosexuals, PWID), HIV care continuum (linkage to care at and after diagnosis, prescription of ART, retention in care, viral suppression), PrEP, and SSPs. The model optimized expenditures for two consecutive 5-year periods. We compared the base case (no optimization) to two optimization scenarios: a limited-reach scenario, where all eligible persons can be reached by each intervention generally reflect current conditions; and an ideal, unlimited-reach scenario, where all eligible persons can be reached by each intervention.

Results: In the base case in which 30.0% and 16.7% of societal investments are applied to HIV screening and care-continuum interventions, there were 331,000 new cases over the next 10 years. Optimization in the limited-reach scenario in the first 5 years decreased the allocation to HIV screening to 13.4% and increased the allocation to care-continuum interventions to 35.1%. In the unlimited-reach scenario, allocations to both HIV screening and care-continuum interventions increased (to 35.4% and 64.6%, respectively).

The 10-year reduction in incidence was 69% in the limited-reach scenario and 94% in the unlimited-reach scenario. Investment in HIV screening decreased in the unlimited-reach scenario to focus on groups other than low-risk heterosexuals, whereas in the unlimited-reach scenario, screening investments increased to cover all eligible persons. In the unlimited-reach scenario, investment in PrEP was minimized because that scenario included extensive diagnosis and effective viral suppression through the increased funding of ART adherence interventions. However, under the more realistic conditions of the limited-reach scenario, continued investment in PrEP was required.

Conclusion: Optimal allocation of current societal investments in HIV prevention can achieve substantial reductions in new infections. Achieving reductions over 90% is theoretically possible, but implausible with current resources.
1129 IMPACT OF COMBINATION HIV PREVENTION IN ZIMBABWE: A MULTIDISTRICT TRANSMISSION MODEL


Background: The Zimbabwean HIV epidemic is generalized, and heterogeneous at the district level. Combination HIV prevention (CHP) has been rolled out in Zimbabwe over the past decades, including antiretroviral therapy (ART), voluntary male medical circumcision (VMMC), prevention of mother to child transmission, behavior change programmes, and condom distribution. Evaluating the impact of these programs on the HIV epidemic is important to improve intervention planning.

Methods: Together with local policy makers and stakeholders, we developed a multidistrict, individual based HIV transmission model that simulates dynamic interactions between districts to accurately represent transmission dynamics, and quantified it using Zimbabwean demographic, epidemiological, and behavioral data. We used this model to evaluate the impact and cost-effectiveness of CHP in Zimbabwe over the period 2011 – 2015. This period was chosen as it encapsulates the national HIV strategic plan, and because the two large-scale population based surveys were conducted at the end of that period. We also estimate the future impact of alternative strategies.

Results: We simulated the Zimbabwean HIV epidemic over 4 different districts, representative of rural, urban, mining, and commercial farming districts, and were able to reproduce district specific and national census data, sexual behavior in key and general populations, and HIV prevalence and incidence. We show that CHP in Zimbabwe over the period 2011 – 2015 prevented an estimated total of 90 thousand new infections, at 225 US$ per infection averted (table). Interventions were most cost-effective in urban districts, and least cost-effective in rural districts. Importantly, our model closely reproduced national HIV incidence estimates in 2015 without specifically tuning to these data, serving as an important validation of our unique approach, and shows that we managed to closely reproduce the effects of CHP on incidence.

Conclusion: We have shown that CHP in 2011-2015 in Zimbabwe was highly cost-effective, even over the short period of implementation. Our approach in modeling a geospatially dynamic representation of the Zimbabwean HIV epidemic proved successful, and could be a valuable to further understand underlying transmission dynamics, and in turn optimize location specific resource allocation, allowing for the dynamic spillover effects of these interventions to other areas. Further expanding these tools could help policy makers in Zimbabwe and other countries to develop efficient and effective strategies to end AIDS by 2030.

1130 IMPLEMENTATION OF U=U IN REAL LIFE IN ITALY: RESULTS FROM THE ICONA COHORT

Giordano Madeddu1, Andrea De Vito1, Alessandro Cozzi-Lepri2, Antonella Cingolani3, Franco Maggiolo4, Carlo Federico Perno5, Roberta Gagliardini6, Giulia Marchetti1, Annalisa Saracino1, Antonella D’Arminio Monforte5, Andrea Antonini6, Enrico Girardi6, for the ICONA Foundation Study Group 1University of Sassari, Sassari, Italy, 2University College London, London, UK, 3Catholic University of the Sacred Heart, Rome, Italy, 4Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy, 5University of Milan, Milan, Italy, 6Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, 7University of Bari, Bari, Italy

Background: Zero risk of linked HIV transmission in sero-discordant couples when the HIV-infected partner had viral load (VL)<200 copies/mL (U=U status) was observed in large observational studies. We aimed at estimating the proportion of time in which this status was maintained and identifying factors associated to the risk of losing it among people living with HIV (PLWH) enrolled in a clinical cohort.

Methods: We included participants in the ICONA cohort who had reached an established U=U status (VL<200 copies/mL for >6 months) as of December 2010. The outcome was the number of person days of follow up (PDFU) with a VL<200 copies/mL (cp/mL), relative to the total number of PDFU observed in follow-up. Logistic regression model was used to identify factors independently associated to the risk of losing U=U status. For this analysis, a participant was defined as losing his/her U=U status if he/she spent <90% of his/her PDFU on observation with a VL<200 cp/mL. The median of VL measurements was 9 (IQR: 4-15).

Results: 8,241 PLWH were included in the analysis and contributed 12,670,888 PDFU. Of these, 1,648 (20%) were female, 768 (9%) were people who inject drugs (PWID), 3,786 (46%) men who have sex with men and 3,176 (39%) heterosexuals. Overall, during the entire follow-up, 96.9% of PDFU observed were with a VL<=200 cp/mL. Thus, only 3.1% of PDFU were observed when VL was >200 cp/mL with some evidence for a decrease after 2016. The median time with VL>200 cp/mL was 47.3 days (IQR: 46.3-47.9). Of note, the proportion of PDFU with VL>200 cp/mL was higher than average in females (5.3%), unemployed (5.4%), PWID (4.7%) and in people with >3 previous virological failures (6.3%). At individual level, 617 participants (7.5%) spent <90% of PDFU with a VL<=200 cp/mL and were classified as losing their initial U=U status. Unadjusted and adjusted OR of losing U=U status from fitting the logistic regression model are shown in Table 1.

Conclusion: In our population of PLWH meeting the definition of U=U this status was maintained for 97% of the following 10 years of observation with a trend towards an increase in recent years. These findings reinforce the validity of the U=U message in real world settings. However, we identified subsets of our population, including females and foreign-born, at higher risk of not maintaining the U=U status, for whom greater efforts are needed to reduce these infrequent periods of VL>200 cp/mL.

Table 1. Logistic regression estimates of factors associated with losing U=U status

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unadjusted OR (95% CI)</th>
<th>p-value</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.11 (1.80, 2.46)</td>
<td>&lt;0.001</td>
<td>1.63 (1.26, 2.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of HIV Transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INDI vs. MSD</td>
<td>1.80 (1.65, 2.00)</td>
<td>&lt;0.001</td>
<td>1.52 (1.36, 1.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INDI vs. Heterosexual</td>
<td>1.91 (1.72, 2.14)</td>
<td>&lt;0.001</td>
<td>1.63 (1.42, 1.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MSD vs. Other/Mixed</td>
<td>1.71 (1.59, 1.85)</td>
<td>&lt;0.001</td>
<td>1.52 (1.37, 1.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign-born vs. Italian</td>
<td>1.39 (1.04, 1.70)</td>
<td>&lt;0.001</td>
<td>1.25 (1.02, 1.51)</td>
<td>0.004</td>
</tr>
<tr>
<td>Unemployed vs. Employed</td>
<td>2.34 (1.35, 3.52)</td>
<td>&lt;0.001</td>
<td>1.69 (1.15, 2.49)</td>
<td>0.004</td>
</tr>
<tr>
<td>Occasional vs. Employed</td>
<td>2.06 (1.29, 3.29)</td>
<td>&lt;0.001</td>
<td>1.57 (1.05, 2.35)</td>
<td>0.066</td>
</tr>
<tr>
<td>No sexual activity or Employed</td>
<td>2.51 (1.21, 5.18)</td>
<td>&lt;0.001</td>
<td>1.89 (1.08, 3.32)</td>
<td>0.141</td>
</tr>
<tr>
<td>CD4 count, cells/mm³</td>
<td>1.03 (1.02, 1.04)</td>
<td>&lt;0.001</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.042</td>
</tr>
<tr>
<td>CD4 count, cells/mm³</td>
<td>0.90 (0.88, 0.92)</td>
<td>&lt;0.001</td>
<td>0.89 (0.87, 0.92)</td>
<td>0.003</td>
</tr>
<tr>
<td>Previous virological failures</td>
<td>0.89</td>
<td>&lt;0.001</td>
<td>0.88 (0.85, 0.92)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Multivariable model includes all variables selected by backward selection that were retained with a p-value less than 0.05. Also adjusted for age, ART status, binary/continuous variables, smoking, ever injecting drugs, history of AIDS diagnostic, WHO/AIDS status, duration of ART, partner drug use, geographical region, duration, starting, use of statins, aspirin, blood pressure drugs, glaucoma and prior use of ART. ART: people who inject drugs; MSM: men who have sex with men;
1131 IMPACT OF PrEP and TasP ON INCIDENCE OF HIV DIAGNOSES IN 48 HIGHEST-BURDEN US AREAS

Robertino Mera Giler1, Staci Bush1, Trevor Hawkins1, Moupal Das1, Julius Asubonteng1, Scott McCallister1

1Gilead Sciences, Inc., Foster City, CA, USA

Background: Use of tenofovir disoproxil/Emtricitabine (TDF) for Pre-Exposure Prophylaxis (PrEP) has significantly reduced the HIV diagnosis rate in many US states, independent of the effect of treatment as prevention (TasP).

Methods: Using publicly available HIV surveillance data on HIV diagnoses from 105 US metropolitan statistical areas (MSAs) (2012-2017), virologic suppression data from 38 US states and DC as a proxy for Treatment as Prevention (TasP), and TDF for PrEP drug utilization obtained from a national pharmacy and medical claims database, we evaluated the independent impact of PrEP and TasP on HIV diagnosis rates in 48 counties and localities in the End the Epidemic Initiative (48-ETE). We calculated the person time at risk of HIV infection excluding time of those taking PrEP as well as those who became HIV positive. Incidence rates, rate ratios and 95% confidence intervals were assessed using a multilevel Poisson regression model for the 48-ETE and overall after adjusting for the effect of PrEP and TasP.

Results: Over this 6-year analysis, the US rate of HIV diagnoses in the 48-ETE locations decreased at a rate of 7.1% (95% CI: 6.9 to -7.3%) per year while PrEP use in those with a CDC-defined PrEP indication increased 9.9-fold in the same locations from a mean 1.31/100 individuals (95% CI 0.3-2.3) in 2012 to 13.1/100 (95% CI 12.1-14.1) in 2017. HIV viral suppression (viral load <200 c/mL) increased by 1.4% per year (95% CI 1.1 to 1.7%) during the same time among HIV treated subjects. A multivariate poisson model showed that PrEP use was significantly associated with the decline in the rate of new HIV cases in the 48-ETE locations, independent of a significant TasP effect. 48-ETE localities with an average PrEP use rate of 17.4 per 100 subjects at risk could expect a decline of 15.5% in the rate of new HIV diagnoses, 48-ETE localities with significantly higher new HIV diagnosis rate than the rest of the US MSAs (IRR 2.0, 95% 1.6 – 2.58), but the rate of new HIV diagnoses. 48-ETE localities had significantly higher new HIV diagnoses in 2017, compared to 2012 by 1.4% per year (95% CI 1.1 to 1.7%).

Conclusion: From 2012-2017, HIV diagnoses declined significantly in the 48 counties and localities selected for intervention where PrEP use was the highest. The effect of PrEP use was significantly associated with this decline and was independent of treatment as prevention. Improvements in PrEP and TasP coverage in these localities could yield important declines in the rate of new HIV diagnoses.

1132 IMPACT OF FOOD INSECURITY ON THE HIV EPIDEMIC IN SUB-SAHARAN AFRICA (2015–2017)

Andrea Low1, Elizabeth Gummerson1, Ameem Schwitters2, Rogerio Bonifacio3, Nicholas Mutenda1, Karampreet K. Sachathap1, Choice Ginindza5, Avi Hakim6, Nicholas Mutenda1, Elizabeth Gummerson1, Rogerio Bonifacio3, Choice Ginindza5, Avi Hakim6, Neena M. Philip1, Steven Hong1, Sally Findley10

1ICAP at Columbia University, New York, NY, USA, 2Kaiser Permanente Mid-Atlantic States, Silver Spring, MD, USA, 3World Food Programme, Johannesburg, South Africa, 4Columbia University, New York, NY, USA, 5World Food Programme, Johannesburg, South Africa, 6IHS Institute for Health and Social Services, Windhoek, Namibia, 7ICD Health Information Systems, MD, USA, 8Columbia University, New York, NY, USA, 9ICD Health Information Systems, MD, USA, 10ICAP at Columbia University, New York, NY, USA

Background: Food insecurity (FI) is a critical determinant of HIV-related outcomes, including infection, we used data from nationally representative population-based HIV impact assessment (PHIA) surveys in Zambia, Lesotho, Uganda, Tanzania, and Namibia (2015–2017).

Methods: We reviewed literature on the topic of food insecurity and HIV-related outcomes, including infection, we used data from nationally representative population-based HIV impact assessment (PHIA) surveys in Zambia, Lesotho, Uganda, Tanzania, and Namibia (2015–2017).

Results: Of the 112,964 enrolled adults aged 15–59 years, 23% lived in households reporting FI. It was associated with migration (away for >1 month in past 1–3 years), and in older adolescents (aged 15–17 years), lower odds of current school enrolment (Figure). Higher educational attainment was associated with lower odds of prevalent HIV in men and women aged 15–24 years. FI was associated with intergenerational sex in women aged 15–24 years and, in all women, with transactional sex, and with a two-fold increase in recent HIV infection (adjusted odds ratio [aOR] 2.08; 95% confidence interval [CI]: 1.04–4.17). FI was not associated with lower odds of VLS, but migrants were less likely to be suppressed (aOR 0.48; 95% CI: 0.35–0.67).

Conclusion: FI could negatively impact the HIV epidemic both in the short-term, by increasing high-risk sexual behaviors and HIV infection rates in women, and in the long-term, by impeding educational attainment and increasing migration.

1133 GEOGRAPHIC ESTIMATE OF SEXUAL HIV TRANSMISSION BURDEN IN ERA OF U=U: DC COHORT DATA

Hana Akserlod1, Morgan Byrne1, Anne K. Monroe2, Matthew E. Levy3, Rachel Denyer1, Adam Klein1, Michael A. Horberg4, Amanda D. Castel1, Rupali K. Doshi5, Alessandra Secco6, Jose Lucar7, Leah Squires8, Stefanie Schroeter9, Debra A. Benator1, for the DC Cohort Executive Committee

1George Washington University, Washington, DC, USA, 2Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, 3District of Columbia Department of Health, Washington, DC, USA, 4University of Mississippi, Jackson, MS, USA, 5Washington DC VA Medical Center, Washington, DC, USA

Background: Washington, DC (DC) has the highest jurisdictional prevalence of HIV in the US. Sexual transmission is the primary driver of the HIV epidemic in DC, the US, and globally. The Undetectable = Untransmittable (U=U) campaign advances the goal of ending the HIV epidemic by promoting durable viral suppression and reducing sexual transmission. On the other hand, insights into geographic areas of high HIV transmission burden allow for focused and impactful interventions. We aimed to assess HIV transmission by zip code of residence in the DC Cohort, a city-wide cohort of persons with HIV infection (PWH). We define HIV transmission burden as the number of PWH with high-risk sexual behaviors as identified by an incident STI who also are at risk for transmitting HIV.

Methods: We conducted an analysis of DC Cohort participants, ages ≥13 from April 1, 2016 to March 31, 2018. We assessed by zip code of residence, HIV transmission burden: the number of those with incident STIs (gonorrhea, chlamydia, and syphilis) and any HIV VL ≥200 copies/mL from the nine months prior to the day of STI diagnosis to 3 months post STI diagnosis (to approximate the U=U criteria for undetectable).

Results: Of the 3,467 participants, 270 (7.8%) had at least one incident STI. Compared to those without any STIs, those with ≥1 STI were younger (mean age 41.1 vs. 54.1 years without STIs), male (91.5% vs. 64.5%) and MSM (79.6% vs. 31.9%). White race was more frequently represented among those with STIs (23.3%) compared to those without STIs (8.6%) and blacks were less frequently represented (66.7% vs. 83.2% of those without STIs). Homelessness or interaction term between country and FI. We stratified by sex for transactional and intergenerational sex and for recent HIV as outcomes. As part of the analytic framework, we also assessed whether secondary or greater education was associated with HIV infection in young adults (aged 15-24).

Results: Of the 112,964 enrolled adults aged 15 – 59 years, 23% lived in households reporting FI. It was associated with migration (away for >1 month in prior 1–3 years), and in older adolescents (aged 15–17 years), lower odds of current school enrolment (Figure). Higher educational attainment was associated with lower odds of prevalent HIV in men and women aged 15–24 years. FI was associated with intergenerational sex in women aged 15–24 years and, in all women, with transactional sex, and with a two-fold increase in recent HIV infection (adjusted odds ratio [aOR] 2.08; 95% confidence interval [CI]: 1.04–4.17). FI was not associated with lower odds of VLS, but migrants were less likely to be suppressed (aOR 0.48; 95% CI: 0.35–0.67).

Conclusion: FI could negatively impact the HIV epidemic both in the short-term, by increasing high-risk sexual behaviors and HIV infection rates in women, and in the long-term, by impeding educational attainment and increasing migration.
temporary housing was more common among those with STIs, 18.9% vs. 9.1% without. (P <0.0001 for all comparisons.) Ten or more DC Cohort participants lived in 20 Washington DC zip codes. Of the 270 PWH with incident STIs, 85.6% lived in 10 zip codes (See figure). Of the 270 participants with incident STI, at least one HIV VL was available for 254 (94.1%). Overall, 69 (27.2%) of individuals with incident STIs had an HIV VL ≥200 copies/ml. Of these 69, 72.5% resided in 6 of the 20 Washington DC zip codes.

Conclusion: In Washington DC, 6 zip codes of residence accounted for 72.5% of the estimated HIV transmission burden among participants in the DC Cohort. Estimates of HIV transmission burden by zip code of residence allow for targeted, neighborhood-level interventions that may strengthen efforts to end the HIV epidemic.

Figure. Washington, DC zip code maps showing (left) number with at least one incident STI, and (right) % of participant with HIV VL ≥200 copies/ml among those with an incident STI.

1134 LATE PRESENTATION PERSISTS UNDER UTT IN SOUTH AFRICA: A NATIONAL COHORT STUDY

Jacob Bor1, Matthew P. Fox1, Cornelius Nattray2, Brendan Maughan-Brown3, Mhairi Maskew2, Dorina Onoya2, Alana T. Brennan3, Till Bärgenhäuser4, H Manisha Yapa5, Sergio Carmona6, Wendy Stevens6, Adrian J. Puren7, William B. MacLeod8

1Boston University, Boston, MA, USA, 2Health Economics and Epidemiology Research Office, Johannesburg, South Africa, 3University of Cape Town, Cape Town, South Africa, 4Heidelberg University, Heidelberg, Germany, 5Kirby Institute, Sydney, NSW, Australia, 6National Health Laboratory Service, Johannesburg, South Africa, 7National Institute for Communicable Diseases, Johannesburg, South Africa

Background: South Africa implemented Universal Test-and-Treat (UTT) in September 2016 to encourage earlier initiation of antiretroviral therapy (ART). We conducted an interrupted time series (ITS) analysis to assess the impact of UTT on median CD4 count at ART initiation among adults attending public sector primary care services in South Africa.

Methods: We analysed data from individuals >=16 years old initiating ART between 2014 and 2019 at 17 clinics in northern KwaZulu-Natal and registered on TIER.net, the national ART clinical database. Our outcome of interest was CD4 count at ART initiation, defined as the value closest to ART start date in a window from 6 months prior to 3 months after ART initiation. Our primary exposure of interest was calendar period, based on CD4 eligibility expansions: (i) <January 2015, (ii) Option B+/pre-UTT era (January 2015 - August 2016) and (iii) post-UTT era (>=September 2016). We used a segmented linear regression model with a continuous time variable, binary exposure variables for each policy change, and time-by-policy interaction terms. To distinguish between short- and longer-term effects of eligibility expansions, we allowed a change in trend 12 months after policy rollout. We fitted separate regression models for men and women.

Results: Between July 2014 and March 2019, 20,603 (54% under UTT) individuals (69% female) aged >=16 years commenced ART. Median age at ART initiation was 30 (interquartile range 25-38) years. CD4 counts within window were available for 74% individuals. In January 2015 median CD4 at ART initiation was 381 cells/µL among women and 282 cells/µL among men. After UTT implementation, there was an immediate increase in median CD4 at ART initiation of 123 cells/µL (95% CI 81.7 to 164.3, p<0.001) among women, and 98.3 cells/µL (95% CI 75.6 to 121.0, p<0.001) among men (Figure 1). However, there was a significant downward monthly trend in CD4 count at ART initiation in both women (-12.5 cells/µL, 95%CI -18.1 to -6.9, p<0.001) and men (-7.0 cells/µL, 95%CI -11.2 to -2.7, p=0.002) for 12 months after UTT implementation. The trends stabilised thereafter (Figure 1).

Conclusion: UTT led to an immediate boost in earlier initiation of ART in this rural community. However, the effect declined over time before stabilising. More efforts are needed to increase early ART initiation, particularly among men.
USING SOCIAL NETWORKS TO REACH INDIVIDUALS WITH LOW CD4 AT HIGH RISK OF DEATH

Lillian Brown, Yiqun Chen, Laura B. Balzer, Gabriel Chomiac, James Ayieko, Dalsone Kwarisiima, Jane Kabami, Nortan Sang, Edwin D. Charlebois, James Peng, Yusuf Mwinike, Elizabeth A. Bukusi, Moses R. Kamya, Diane V. Havlir, Maya L. Petersen

Background: HIV+ persons with low CD4 (<200 cells/mm³) are at high risk networks with high prevalence of HIV. We evaluated strategies for reaching this target population based on outreach to social contacts of HIV+ persons in care to identify HIV+ individuals who had CD4<200 and were out of care.

Methods: Adult (≥15 years) residents enumerated during a 2013-2014 census in 32 rural Kenyan and Ugandan communities in the SEARCH Study (NCT01864603) named social contacts in five domains: health, money, emotional support, food, and free time. Named contacts were matched to enumerated residents to build named social contacts in five domains: health, money, emotional support, food, and free time. The target population was defined as HIV+ adults with CD4<200 and out of care. We evaluated strategies for reaching this target population based on outreach to 1st degree contacts of two index populations: 1) all HIV+ adults in care, 2) HIV+ adults in care with CD4<350. For each strategy we calculated coverage (% of the target population potentially identified), number needed to screen (NNS, # of persons outreached to per target individual identified), and ratio of coverage and NNS of each index population relative to the other. Clustering was quantified with an assortative mixing coefficient; p-values were based on randomly permuting node labels.

Results: Among 10,285 adults known to be HIV+ at baseline with at least one contact, 8,168 had a record of HIV care, of whom 1,904 had CD4<350; 394 HIV+ adults had CD<200 and were out of care. HIV+ persons in care had an average of 4.3 1st degree network members; HIV+ persons in care with CD4<350 had an average of 4.4 1st degree network members. An outreach strategy to 1st degree contacts of all HIV+ adults in care would have reached 40% of target persons (p<0.001) and required outreach to 52 contacts per target individual identified (p<0.001). Outreach to 1st degree contacts of HIV+ in care with CD4<350 would have reached 35% of target persons (p<0.001) and required 31 contacts per target individual identified (p<0.001).

Conclusion: HIV+ persons with low CD4 who are out of care are socially connected to HIV+ individuals engaged in care. An outreach strategy through the social networks of HIV+ persons in care may be an effective way to reach this high-risk population.

IMPROVING HIV CASE-FINDING WITH MACHINE LEARNING

Pavlo Smyrnyov, Yulia Sereeda, Artem Lytvyn, Olga Denisiv

Background: Alliance for Public Health implements social network strategy for HIV case-finding among key populations. We developed a model to improve recruitment of undiagnosed HIV-positives in the network using machine learning (ML) algorithm.

Methods: Since 2016, 130,095 people who inject drugs and their extended risk network were recruited in 12 regions of Ukraine. Recruitment starts from HIV positive cases with following criteria: 14+ years, inject drugs. Participants provided with 3 coupons to invite their peers defined as an injecting or sexual partner or somebody from the social network who can be also at risk of HIV. Recruitment stops if there are two HIV-negative cases next to each other in a chain. Data on recruitment chains and participants’ characteristics collected in mobile application. Additional coupons are provided to participants with certain characteristics, such as “over 10 years of injecting drugs”, “history of incarceration”, “positive HIV test result”. We implemented a ML algorithm to predict in real-time the probability of recruiting an undiagnosed HIV-positive person within onestep from the participant who receives coupons. Considering the estimated probability, recommendations on a number of additional coupons are provided.

Results: Among participants who received coupons, 75.9% (n=35,965/47,404) recruited at least one peer and 15% (n=7,146/47,404) recruited at least one HIV-positive participant within onestep. In comparison with current recruitment algorithm ML model is 1.5-2.5 times more efficient (based on GINI index) in predicting chances of undiagnosed positive case (Fig.1). ML model with 42 predictors yielded a GINI index of 34% for classification of HIV-positives and negatives. The most informative predictors of recruitment of HIV-positives included “HIV test result”, “Region”, “Years of injecting drugs”, while “Age” and “Marital Status” had the lowest contribution to prediction.

Conclusion: Higher level of discriminatory power (an ability to distinguish between successful and not successful recruitment) of ML model suggests that application of ML algorithm during recruitment could improve HIV-positive yield and guide HIV testing to address gap in locating undiagnosed cases. Further steps include piloting of ML algorithm with randomizing recruiters to evaluate effectiveness of ML in improving case-finding in groups connected in risk networks with high prevalence of HIV.

HIV SCREENING IN EMERGENCY DEPARTMENTS: LINKAGE WORKS, BUT WHAT ABOUT RETENTION?

Kushagra Mathur, Jill Blumenthal, Gabriel A. Wagner, Lucy Horton, Miriam Zuazo, George Lara-Paez, Megan Lo, Gary M. Vilké, Christopher J. Coyne, Susan J. Little, Martin Hoenigl

Background: Universal opt-out HIV screening programs in emergency department (ED) settings have been successful in linking newly-diagnosed and out-of-care known HIV-positive persons into care. However, most of these programs report linkage to care but not retention rates and so the actual impact
of these programs on the HIV care cascade remains unknown. The objective of this analysis was to evaluate rates of linkage to care and subsequent retention in care associated with an ED-based universal opt-out HIV screening program in San Diego.

Methods: All newly HIV diagnosed and known HIV-positive out-of-care (i.e., >12 months without a clinic visit) individuals were identified through EMR-based universal opt-out HIV screening for persons aged 13-64 years at the University of California San Diego EDs between July 2017 and September 2019. Case managers dedicated to the program focused on relinking these individuals to care and stopped case management at the time of re-linkage. Retention in care was assessed at 6 and 12 months following initial (re)linkage to care. Univariate and multivariable logistic regression models assessed medical, and social variables (derived from existing literature) as predictors of successful linkage and retention in care (Table).

Results: A total of 47 newly diagnosed and 92 known HIV-positive out-of-care persons were identified. 40 of 47 (85%) newly diagnosed individuals were linked to care, and 48 of 92 (52%) known HIV+ out of care individuals were re-linked to care. At 6 months follow-up, 23/33 (70%) of the newly diagnosed individuals were still in care, 5 (15%) were confirmed to be out of care, and 5 (15%) were unable to be contacted. At 6 months follow-up, 14/26 (54%) of the known HIV-positive persons were still retained in care, 11 (42.3%) were confirmed to be out of care, and 1 (4%) was unable to be contacted (p = 0.04 vs new diagnoses). Methamphetamine use (within six months of ED screening; 43% of Meth users confirmed out of care) was significantly associated with falling out of care in the multivariable model (p = 0.03; Table).

Conclusion: While our universal opt-out ED HIV screening program achieved high rates of (re)linkage to care, 37% had (again) fallen out of care within 6 months. Although a majority of newly diagnosed patients (574 (94%) successfully LTC. For return to care patients 51% seen in ED and 48% LTC <60 days. Conclusion: HIV screening programs in EDs reach into the heart of the US epidemic and ensures some of the most difficult to reach individuals access testing and rapid treatment. Scale up will contribute substantially to ending the US epidemic.

1140 BUPRENORPHINE VS METHADONE AND ART PRESCRIBING IN VIETNAM: A RANDOMIZED TRIAL

P. Todd Korthuis1, Caroline King2, Gavin Bart1, Lynn Kunkel1, Thuan Nguyen1, Khuyen Tong1, Sareen Bielavitz1, Le Minh Giang1
1Oregon Health and Sciences University, 2 Hennepin Healthcare Research Institute, Minneapolis, MN, USA, 3Hanoi Medical University, Hanoi, Vietnam

Background: Integrating methadone or buprenorphine treatment of opioid use disorder (OUD) into HIV care is a recommended strategy for achieving UNAIDS 90-90-90 targets, and associated with improved antiretroviral therapy [ART] uptake in observational studies and a single-site U.S. trial, but adoption of HIV clinic-based buprenorphine has been limited in many countries. We hypothesized that HIV-infected persons with OUD in Vietnam randomized to HIV clinic-based buprenorphine versus methadone would experience comparable 12-month uptake of ART.

Methods: We conducted a non-blinded, multi-center non-inferiority trial randomizing people with HIV and DSM-5 moderate-to-severe OUD to HIV clinic-based buprenorphine versus referral for methadone for treatment of OUD in 6 Vietnam HIV clinics. The primary outcome was medical record documentation of ART prescription. Secondary outcomes included retention on OUD treatment and positive urine drug screen (UDS) for opiates, assessed at baseline, 3, 6, 9, 12 months. Generalized linear mixed models assessed buprenorphine versus methadone and change in outcomes over time in intention-to-treat analyses.

Results: Participants (n=281) were randomized to receive buprenorphine (n=141) or methadone (n=140). At baseline, 96.8% of participants were male, 45 (8.9) employed, with mean age 38.3 (SD 6.1) years and 7.4 (SD 5.7) years since HIV diagnosis. Mean CD4 count was 405 (SD 224). At baseline, 100% tested positive for heroin and 18.7% for methamphetamine. Retention in treatment at 12 months was 75.9% for buprenorphine and 82.1% for methadone and did not differ by treatment group (p = 0.92). ART use increased from 68.0% to 73.8% for buprenorphine and 67.9% to 80.7% for methadone, and was higher for participants on methadone versus buprenorphine at 12 months (p = 0.009).

Conclusion: Both buprenorphine and methadone improved ART uptake despite modest decreases in heroin use, comparable to those achieved in U.S. practice. Opioid agonist treatment can help achieve UNAIDS 90-90-90 goals for ART uptake.
1141 HRSA’S RYAN WHITE HIV/AIDS PROGRAM RESPONSE TO THE OPIOID EPIDEMIC

Nicole S. Chavis1, Pamela W. Klein1, Stacy Cohen1, Letha Healey1, Antigone Dempsey1, Heather Hauck1, Laura W. Cheever1
1HRSA HIV/AIDS Bureau, Rockville, MD, USA

Background: The U.S. is in the midst of an unprecedented opioid crisis with injection drug use (IDU)-related HIV outbreaks increasing, particularly in rural areas. The Health Resources and Services Administration’s Ryan White HIV/AIDS Program (HRSA RWHAP) is well positioned to integrate treatment for IDU-associated HIV infections with treatment for drug use disorders. The purpose of this study was to evaluate the sociodemographic characteristics and substance use service utilization of RWHAP clients with HIV attributed to IDU nationwide compared to seven southern states identified with large rural HIV epidemics. These activities will be crucial for the “Ending the HIV Epidemic: A Plan for America” initiative.

Methods: Data from the 2017 RWHAP Services Report were used to assess the sociodemographic characteristics of RWHAP clients aged 13 and older with HIV attributed to IDU (“IDU clients”). We also examined the proportion of RWHAP-funded providers who delivered substance use services and the characteristics of RWHAP clients who accessed these services. Data were examined nationally and in seven states with significant rural HIV epidemics. HRSA convened a technical expert panel to explore how the RWHAP can best respond to the opioid crisis; we identified key themes.

Results: In 2017, RWHAP 6% of clients served (31,683) had HIV attributed to IDU. When compared with IDU clients served by RWHAP nationwide, IDU clients in the seven rural states were younger (27.2% aged <45 years vs. 17.0% nationally), White (52.8% vs. 30.7% nationally) and stably housed (84.6% vs. 80.3% nationally). Nationwide, 17.5% (269) of RWHAP providers delivered substance use services, but only 3.3% (17,716) of RWHAP clients accessed substance use services. Key themes from the panel included the impact of stigma on service availability and access, workforce challenges, and social determinants of health.

Conclusion: A significant proportion of RWHAP clients are impacted by substance use disorder and the opioid crisis with sociodemographic differences observed in rural areas as compared to national trends. RWHAP data and input from experts highlight the RWHAP’s unique position to respond to the growing opioid crisis, nationally and in rural areas, and can inform the RWHAP’s approach to care delivery in areas at the intersection of the HIV and opioid crises.

1142 SEARCH TEST & TREAT INTERVENTION IMPROVES VIRAL SUPPRESSION AMONG HAZARDOUS DRINKERS

Sarah B. Puryear1, Dalsone Kwariissima2, James Ayielo1, Judith A. Hahn1, Atukunda Mucunguzi2, Sabina Ogachi3, Laura B. Balzer4, Vivek Jain1, Edwin D. Havlir2, Moses R. Kamya2, Gabriel Chami1
1University of California San Francisco, San Francisco, CA, USA, 2Infectious Diseases Research Collaboration, Kampala, Uganda, 3Kenya Medical Research Institute, Nairobi, Kenya, 4University of Massachusetts Amherst, Amherst, MA, USA, 5University of California Berkeley, Berkeley, CA, USA

Background: Hazardous alcohol use has been associated with poor HIV care cascade outcomes. We previously reported that hazardous drinkers had lower baseline viral suppression (VS) than non-drinkers in the SEARCH universal test and treat (UTT) trial. In this analysis, we sought to assess if gaps in VS persisted between hazardous drinkers and non-drinkers by arm in intervention and control communities after 3 years and to determine if the intervention improved VS compared to control among hazardous drinkers.

Methods: SEARCH randomized 32 communities in Kenya and Uganda to a UTT intervention of annual testing and universal ART eligibility via streamlined care designed to decrease barriers to engagement in care and VS, or a control of baseline universal testing with ART eligibility and delivery by evolving country standards over 3 years (2013-17). We evaluated VS at year 3 in baseline HIV+ adults. We assessed baseline alcohol use by Alcohol Use Disorders Identification Test–Concise (AUDIT-C) score: hazardous drinking was defined as a score ≥3 for women and 4 for men and non-drinking as a score of 0. Within each arm, associations between baseline alcohol use and year 3 VS were estimated using individual-level Targeted Maximum Likelihood Estimation (TMLE) to adjust for sociodemographic factors, mobility and clustering by community. Comparisons of year 3 VS between arms among hazardous drinkers were based on cluster-level TMLE.

Results: Of 9,936 HIV+ adults with baseline AUDIT-C measures, 871 (9%) reported hazardous alcohol use. Men accounted for 75% of hazardous drinkers (655/871) and 29% (2695/9065) of non-drinkers. After adjustment for confounders, year 3 VS in the control arm was lower among hazardous drinkers (77%) compared to non-drinkers (83%, aRR:0.93, 95%CI:0.86-0.99, p=0.04). In contrast, in the intervention arm, year 3 VS among hazardous drinkers (86%) was not significantly different than among non-drinkers (90%, aRR:0.96, 95%CI:0.9-1.01, p=0.11). Hazardous drinkers in intervention communities were more likely to achieve VS than hazardous drinkers in control communities (RR 1.21, 95%CI:1.1-1.3, p<0.001).

Conclusion: The SEARCH intervention reduced the gap in VS between baseline hazardous drinkers and non-drinkers, achieving high prevalence of VS regardless of alcohol use, whereas a disparity in VS in VS by alcohol use persisted in the control arm. These data suggest that the SEARCH intervention may have decreased barriers to HIV care and VS for hazardous drinkers.
END OF HIV EPIDEMIC AMONG PWID IN A LOW-MIDDLE INCOME COUNTRY: THE HAI PHONG CASE

Nicolas Naget1, Khuat T. Oanh2, Duong T. Huong3, Delphine Rapoud1, Hoang T. Giang1, Catherine Quillet1, Pham M. Khue1, Laurent Michel4, Roselyne Vallo5, Jonathan Feelemeyer1, Vu H. Vinh1, Didier Laureillard6, Philippe Van De Perre1, Jean-Pierre Molès1, Don Des Jarlais4

Background: The HIV epidemic among people who inject drugs (PWID) has been ended in many high-income countries, but no such achievement has been reported from the low-middle income countries (LMIC) where the epidemic has flared. In Vietnam, despite a persistent repressive policy regarding drug use, directly-observed methadone therapy and universal ART have been implemented, along with community-based organizations (CBO) to deliver harm reduction and assist PWID in accessing care. In this context, we assessed whether the HIV epidemic could be ended in this high-risk group, taking the case of Haiphong, a 2 million inhabitant city.

Methods: After a feasibility phase which estimated the active PWID population to 5500 in Haiphong, we implemented 3 community-based respondent driven sampling surveys (RDS) in October 2016, 2017 and 2018. We enrolled active PWID with recent injection skin marks and heroin detected in urine, recorded drug use behaviors, and tested them for HIV and plasma viral load. From each RDS, all HIV-positives and 200 to 400 HIV-negative PWID entered in two open cohorts with bi-annual follow-up. HIV incidence was calculated using follow-up accumulated from both the cohort (bi-annual HIV testing) and recaptured PWID between RDS. We also estimated the HIV cascade of care, recent infections and HIV viremia prevalence.

Results: The 3 RDS recruited 1380, 1451 and 1443 PWID, representing 3146 distinct individuals; all of them were injecting heroin, 23% for less than 5 years, and 11.8%, 32.4% and 41.5% reported being in the methadone program, respectively. Their mean age was 39 years, and 94.9% were male. Reported needles/syringes sharing was low at 3.9%, 3.2% and 3.6%, respectively. The HIV prevalence was 26.5%, similar across RDS. Overall, 1497 person-years of follow-up were accumulated with 1 HIV seroconversion, yielding a HIV incidence of 0.7/1000 person-years (95% CI: 0.02-4). At RDS1, the cascade of care was 87-93-97, improving to 91-92-95 and 95-93-95 at RDS2 and RDS3. There was no recent infection among all HIV-positives. The viremia prevalence (threshold of 1000 copies/mL) decreased from 7.2% at RDS1, to 5.4% at RDS2 and 3.1% at RDS3. Conclusion: Ending the HIV epidemic among PWID in a LMIC setting can be reached, thanks to an active CBO network and structural barriers to care.

Conclusion: Evidence-based interventions targeted to PWID can deliver considerable value, however ending the HIV epidemic among PWID will require innovative implementation strategies and supporting programs to reduce social and structural barriers to care.

Figure 1. City-level health production functions

ENDING THE HIV EPIDEMIC AMONG PEOPLE WHO INJECT DRUGS: A COST-EFFECTIVENESS ANALYSIS

Emanuel Krebs1, Xiao Zang1, Benjamin Ems1, Jeong E. Min1, Bohdan Nosyk1, for the Localized Economic Modeling Study Group

Background: In the United States, people who inject drugs (PWID) continue to be disproportionately at risk of HIV infection. We aimed to determine the cost-effectiveness of expanded access to evidence-based prevention and care interventions for PWID and to identify the highest-valued combination implementation strategies to reduce the burden of HIV among PWID in six US cities with diverse HIV microepidemics.

Methods: We identified and estimated costs, effectiveness and previously-documented scale of delivery for 14 evidence-based interventions from the US CDC’s Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention and from the published literature. Using a dynamic, compartmental HIV transmission model calibrated for Atlanta, Baltimore, Los Angeles, Miami, New York City and Seattle, we assessed combinations of evidence-based interventions implemented at either previously-described, optimistic or ideal scale. We estimated averted HIV infections among PWID, quality-adjusted life-years (QALYs), total costs and incremental cost-effectiveness ratios (ICERs) for each combination and city compared to the status quo over a 20-year time horizon (healthcare perspective; 3% annual discount rate, 2018 US$). Interventions were modeled for a 10-year period. In addition, we estimated health production functions, representing combination implementation strategies providing the greatest health benefits for incremental investment levels.

Results: Strategies that maximized health benefits while remaining cost-effective according to international standards contained between six (Atlanta and Seattle) and twelve (Miami) interventions. The ICER values for these strategies ranged from $81,679/QALY for Atlanta to $141,454/QALY for Baltimore (Figure 1). Implemented at documented scale, these would result in 1.7% (Seattle) to 27.0% (Miami) reductions in new HIV infections among PWID across cities by 2030. PEP for PWID was found to be cost-effective in Miami ($64,221/QALY). Incidence reduction reached 11.8% (New York City) to 81.9% (Miami) when strategies were implemented at ideal scale.

Conclusion: Evidence-based interventions targeted to PWID can deliver considerable value, however ending the HIV epidemic among PWID will require innovative implementation strategies and supporting programs to reduce social and structural barriers to care.

INTEGRATING ANTIRETROVIRAL TREATMENT AND HARM REDUCTION SERVICES ON HIV AND OVERDOSE

Javier Cepeda1, Annick Borquez2, Christopher Magana2, Anh T. Vo3, Claudia Rafful4, Maria Gueida Rangel-Gomez2, Maria Elena Medina-Mora5, Steffanie A. Strathdee1, Natasha Martine1

Background: The HIV epidemic in Tijuana, Mexico is concentrated in key populations, including people who inject drugs (PWID). Mexico’s drug law reform included referral to drug treatment, yet funding was provided for non-evidence based compulsory abstinence programs (CAP) associated with elevated HIV and overdose risk. However, evidence-based opioid agonist therapy (OAT) reduces overdose, HIV transmission, and reincarceration, while improving antiretroviral therapy (ART) outcomes. We assessed the potential impact of integrated ART and drug treatment (OAT or CAP) on HIV and fatal overdose among PWID in Tijuana.

Methods: We developed a dynamic model of HIV transmission, incarceration, and fatal overdose among PWID in Tijuana. We incorporated synergistic benefits of OAT on reducing injecting-related HIV transmission, increased ART recruitment and retention, reducing reincarceration, and averting fatal overdose. We also modeled harms associated with CAP on HIV and overdose. We assessed HIV incidence and fatal overdose over the next decade with the following scenarios: 1) status quo (10% ART among HIV-positive PWID and no drug treatment), 2) OAT scale-up to 40%, 3) ART scale-up (10-fold recruitment) among HIV-positive PWID, 4) scale-up OAT to 40% and ART (10-fold recruitment), 5) scale-up CAP to 40% (no ART scale-up).

Results: OAT scale-up to 40% coverage could avert 32% (95% CI: 19-45%) and 19% (95% CI: 8-26%) of new HIV infections and fatal overdoses, respectively, over the next decade (see figure). Due to low ART coverage, OAT had marginal impact on averting HIV through its effect on ART recruitment/retention.
Conclusion: HealthCall paired with CG resulted in better ART adherence than the other treatment conditions. Given the importance of ART adherence and the low costs and time required for HealthCall, pairing HealthCall with brief interventions within HIV clinics merits widespread consideration.

1146 SMARTPHONE INTERVENTION TO REDUCE HEAVY DRINKING IN HIV CARE: EFFECT ON ART ADHERENCE
Deborah S. Hasin1, Efrat Aharonovich1, Barry S. Zingman2, Malka Schlesinger3, Claire Walsh4
1Columbia University Medical Center, New York, NY, USA, 2Montefiore Medical Center, Bronx, NY, USA, 3New York State Psychiatric Institute, New York, NY, USA

Background: Heavy drinking among People Living With HIV (PLWH) reduces antiretroviral adherence and worsens health outcomes. Brief interventions to reduce heavy drinking in primary care patients are effective, but in heavy-drinking PLWH, more extensive intervention may be needed. Lengthy interventions are not feasible in most HIV primary care settings, and patients seldom follow referrals to outside treatment. Utilizing visual and video features of smartphone technology, we developed and tested HealthCall as an electronic (smartphone) means of increasing patient involvement in brief intervention to reduce drinking and improve medication adherence without making unfeasible demands on providers.

Methods: Alcohol-dependent patients at a large urban HIV clinic were randomized to receive 1 of 2 brief (~25 min) baseline drinking-reduction interventions plus ART adherence education, and then HealthCall (daily use on the smartphone, ~4-5 min/day) or standard care for 60 days. All patients had 2 brief (15 min) check-in sessions at 30 and 60 days. Baseline interventions: NIAAA Clinician’s Guide (CG) or Motivational Interviewing (MI). HealthCall included coverage of drinking and ART adherence. Patients were randomly assigned to CG+standard care (n=37), CG+HealthCall (n=38) or MI+HealthCall (39). Outcomes assessed at 30, 60, 90 days, 6 and 12 months: drinks per drinking day; ART adherence (unannounced phone pill-count method; possible adherence scores: 0%-100%). Analysis: generalized linear mixed models with pre-planned contrasts.

Results: Study retention was excellent (85%-94% across timepoints) and unrelated to treatment arm or patient characteristics. Drinking decreased overall during treatment, with continued declines at 6 and 12 months in the CG+HealthCall arm. During treatment, patients in MI+HealthCall drank less than others (p=0.07-0.003). However, at 6 and 12 months, drinking was lower among patients in CG+HealthCall (p=0.04-0.06). Overall ART adherence declined slightly by 12 months. However, at 60 days, 90 days and 6 months, ART adherence was significantly better among patients in CG+HealthCall than CG+standard care (p=0.03-0.09).