Special Issue: Abstracts From the 2020 Conference on Retroviruses and Opportunistic Infections

Abstracts

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This issue of *Topics in Antiviral Medicine* is a special issue that includes the abstracts from the 2020 Conference on Retroviruses and Opportunistic Infections (CROI). This issue is funded and supported by IAS–USA. Below is a sample of how to cite a CROI abstract:


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CROI 2020 Resources

Webcasts and electronic posters from CROI 2020 and information about CROI 2021 (to be held in Chicago, Illinois, USA from March 7 to March 10, 2021), can be found at www.CROIconference.org. The Electronic Materials page includes the following resources and more.

The CROI Program and Information Guide includes information about sessions, speakers, and other details about CROI 2020.

In addition to the Special Issue of *Topics in Antiviral Medicine™*, abstracts from CROI 2020 can be viewed in the Abstract eBook and searchable data base.

Plenaries, symposia, oral abstract sessions, and themed discussions are available as webcasts. Visit www.croiwebcasts.org to access webcasts from CROI 2014 to CROI 2020.
ABSTRACTS

How to cite the abstracts:

1 SESSION OVERVIEW: PROGRAM COMMITTEE WORKSHOP FOR NEW INVESTIGATORS AND TRAINEES
John W. Mellors1, Serena S. Spudich 2
1University of Pittsburgh, Pittsburgh, PA, USA, 2Yale University, New Haven, CT, USA
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 Koupr 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=untransmitable' 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.

2 SHIFTING FROM ACUTE TO CHRONIC, AGING, LONGEVITY, AND LIVED EXPERIENCE
Jim Pickett1, Martha Tholanah2, Gabriel Maldonado3, Celeste Watkins-Hayes4
1AIDS Foundation of Chicago, Chicago, IL, USA, 2Advocate, Harare, Zimbabwe, 3TruEvolution, Riverside, CA, USA, 4Northwestern University, Chicago, IL, USA
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 Koupr 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=untransmitable’ 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.

3 SHAPING VACCINES WITH DNA ORIGAMI
Mark Bathe, MIT, Cambridge, MA, USA
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. Scaleable 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 pre-clinical 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.

4 CONCEPTS IN RESERVOIR MEASUREMENTS
Janet M. Siliciano, Johns Hopkins University School of Medicine, Baltimore, MD, USA
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 proviral 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 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.

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 cytopathic 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 immune 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 NONINFERIORITY 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 acceptably 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
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 malignancies, 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.

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 DAA 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 inevitably arise. The approach to management of HCV treatment interruptions of varying durations at different times during therapy and retreatment for multiple DAA regimens 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 regimens failure retreatment
- Approach to treatment interruptions during DAA therapy
While FDA approved options for retreatment exist for initial DAA 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 exist—such as evidence based approaches for dealing with treatment interruptions, expert opinion and audience input will be used to offer management options.

“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.

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 HCV 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 (DAA) 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.

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, endpoints liver disease, and hepatocellular carcinoma. NASH cirrhosis is the second leading indication for liver transplantation in the United States. In addition, NASH 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 PLWH, 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.

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 adaption 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.

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, PMTCT, 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 persistence of only 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. BCCP 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 (6.2-2.3/1000/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 the 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
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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 virion 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 impaired 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 impaired 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.

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

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**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 gp160. 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/Adnectin complex clearly shows the bent conformation for CD4 while bound to gp140. Mutagenic analyses on CD4 confirmed that amino acid F202 forms a key interaction with the Adnectin. In addition, amino acid L151 was shown to be 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

**SERINCS3/5 PERTURB HIV MEMBRANE FUSION POST-HEMIFUSION AT FUSION-PORE DIATION STEPS**

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**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 cryo-Electron 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.

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

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**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 (Y103 and 37LHAL376). 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**

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**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 HIV-1 complexes and by an inability to accurately quantify capsid protein (CA) loss from the viral complexes. We analyzed the dynamics of viral complex association with 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.

**Results:** Using live-cell imaging, we observed >100 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 complexes 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**

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**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/cell. Concerted 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 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.

**Conclusion:** Starting with purified HIV-1 virions, we have reconstituted the first half of the HIV-1 life cycle in a cell-free system. This system highlights the key role of the viral capsid and should facilitate dissection of the mechanisms and host factor contributions to HIV-1 replication.

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

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**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 SIVcm, 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 SIVcm 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.
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=3) and HIV- individuals (n=4). Without batch fluid, to compare T cell transcripts differentiating ART-suppressed HIV from the HIV-negative 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%); CSF cell 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 between 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 a cut-off of >0.8.

Differences in gene expression were noted between PWH and HIV- in CSF and PBMC, 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.

Conclusion: PET imaging of synaptic density in HIV: preliminary findings from a pilot study

Preliminary results from PET imaging of synaptic density in HIV (29)

28 GREATER BURDEN OF INTRACRANIAL ARTERIAL-WALL ENHANCEMENT IN PERSONS LIVING WITH HIV

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Background: Persons living with HIV (PWH) are at higher risk of stroke compared with age-matched persons without HIV. However, the mechanisms underlying increased cerebrovascular risk in PWH are unclear. In particular, the contribution of intracranial arterial disease to HIV-associated stroke remains poorly defined. We compared intracranial vessel wall magnetic resonance imaging (VW-MRI), which can demonstrate atherosclerotic disease even when conventional angiography is normal, in treated, virologically suppressed PWH and persons without HIV.

Methods: All participants were >40 years of age with a history of cardiovascular (CV) disease or at least one CV risk factor. PWH were on 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: PET imaging of synaptic density in HIV (29)

PET imaging of synaptic density in HIV: preliminary findings from a pilot study

Julian Weiss1, Rachela Calvi1, Mika Naganawa1, Takuya Toyonaga1, Shelli Farhadian1, Michelle Chintanaphol1, Jennifer Ciarelli1, Ming-Qiang Zheng1, Jim Ropchan1, Yiyun Huang1, Richard Carson1, Serena S. Spudich1

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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 virologically 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 had a lower baseline 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), but there were no differences in VT, though lower values in PLWH were noted in the eight cortical ROIs with significantly decreased BPND. PLWH had significantly lower binding potential (BPND) in eight cortical ROIs compared with HC (p<0.05). SV2A specific binding (BPND) was higher in 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 and BPND between the groups. PLWH 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.

PET imaging of synaptic density in HIV: preliminary findings from a pilot study

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neuropsychological performance. SV2A imaging may be a promising outcome measure for interventional trials of HAND.

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

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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 granymes. This poor killing delays CTL detachment from its target, causing hypersecretion 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 cell lines 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 3BN1C17 and p<0.05 for PG121). 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.

31 HIV DNA DETECTED IN IMMUNE CELL SUBSETS IN CSF DURING ART

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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-CD204+. 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 RNA 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 4/6 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 1.8 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 CD24+ 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 is in replication-competent proviruses, and whether other CNS immune cell types are HIV-infected.

32 EFFECTS OF HIV AND AGING ON RESTING-STATE NETWORKS

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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 with respect to aging among PLWH and controls.

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 was reflective of these conditions is resting state functional connectivity (rsFC). 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.

Conclusion: Our data suggest changes in rsFC occurs as a result of HIV infection, and are primarily associated with motor, control, and attention. Further, changes exhibit specific temporal patterns between networks which is independent of reorganization that occurs due to normal aging, and these changes begin around midlife. These results will allow for a more tailored treatment approach for PLWH, and should be considered when conducting clinical trials.
MYELIN CONTENT IS ELEVATED IN VIROLOGICALLY UNSUPPRESSED PEOPLE LIVING WITH HIV

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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 the T1w to T2w ratio and assigned to the cortical surface of the brain. Individual brains were then registered to a common surface atlas. Average myelin for each FreeSurfer parcel was computed. Omnibus ANCOVA analysis with age as a covariate was used to identify the regions of interest (ROI) where myelin content was affected by disease with increases in the T1w/T2w ratio for any of the regions. Correlations were performed between viral load and myelin content in the VF group.

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 as a covariate was used to derive the cortical surface of the brain. Individual brains were then registered to a common surface atlas. Average myelin for each FreeSurfer parcel was computed. Omnibus ANCOVA analysis with age as a covariate was used to identify the regions of interest (ROI) where myelin content was affected by disease with increases in the T1w/T2w ratio for any of the regions. Correlations were performed between viral load and myelin content in the VF group.

Conclusion: Our results suggest that PLWH who have VF have increases in myelin content compared to PLWH who have VS and HC. 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.

34 CABOGRAVIR + RILPIVIRINE EVERY 2 MONTHS IS NONINFERIOR TO MONTHLY: ATLAS-2M STUDY

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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 (ITT)e) 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 maintenance therapy 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 virological 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.
35 PROSPECTIVE ENHANCED MONITORING OF DOLUTEGRAVIR-BASED FIRST LINE IN MALAWI

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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 was without 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 present 6 outcomes.

Methods: Inclusion criteria were age >20 years (male), ≥45 years (female) and eligible for TLD by Malawian guidelines. Plasma VL is assessed at 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. After VL-suppression was high among the few ART-initiators. Of concern are 2 cases of virological failure: 1 due to current available DRT, two had DTG resistance (mutation R263K or G118R) in combination with resistance to other NNRTIs. Further monitoring and resistance surveillance is recommended.

Results: From January–May 2019, 1928 participants were included: 49% female, 98.2% TLD-transitiers, with a median age 52 years (IQR: 40.9 - 60). Baseline characteristics: Median CD4 count 287 cells/µl, median viral load 84,500 copies/ml, median 3rd agents: INSTIs 47%, NNRTIs 33% and NRTIs 20%

Conclusions: 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.

36 RANDOMIZED SWITCH TO B/F/TAF IN AFRICAN AMERICAN ADULTS WITH HIV

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Background: African Americans have the highest rates of HIV/AIDS in the US but are under-represented in HIV medical research. The single-tablet regimen bictegravir, emtricitabine, tenofovir alafenamide (B/F/TAF) is a guidelines-recommended treatment for HIV. We evaluated the safety and efficacy of switching to B/F/TAF among Black adults.

Methods: 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, PI s and/or NRTIs was permitted except for K65R/F/E ≥ 3 thymidine analogue mutations or 69-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, W4 and W24.

Results: 558 were screened, 495 randomized and treated (B/F/TAF n=330, SBR n=165); 32% cis women, 2% trans women, median age 49 years (range 18-79), median HIV treatment duration 10 years (IQR 6.1, 11), 8.1% had M184V/I mutation, 62% lived in the US South. Baseline 3rd agents: INSTIs 61%, NNRTIs 31% and NRTIs 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 regimens, including those with pre-existing NRTI resistance, and was associated with greater treatment satisfaction.

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

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Background: 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.
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 240 mg every two weeks plus ipilimumab 1 mg/kg (anti-CTLA-4) every 6 weeks. In samples obtained at baseline, within 24 hours and 7 days after the first and fourth dose of ICB and at one late time point after multiple cycles, we quantified cell-associated unspliced (CA US) HIV-RNA and CA HIV-DNA. Plasma HIV-RNA was quantified during the first cycle of ICB using replicate testing using the Aptima HIV-1 Quant assay. Quantitative viral outgrowth assay to estimate the frequency of replication competent HIV was done at baseline and during ICB for a subset of participants. Changes from baseline, including the difference between those on single compared to dual ICB, were tested using non-parametric and parametric statistics (as appropriate) and repeated-measures analysis of variance.

Results: Forty participants were included, 36 males and 4 females. Of those, 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 with no effect on plasma HIV RNA or the latent HIV reservoir.

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

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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 following 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 (50 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 2nd 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

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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 t½ 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.

SAFETY AND ANALYTIC TREATMENT INTERRUPTION OUTCOMES OF VESATOLIMOD IN HIV CONTROLLERS

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Background: Administration of a toll-like receptor (TLR) agonist in combination with a therapeutic vaccine induces CD8+ T cell-mediated control of HIV in non-human primate model. We hypothesized that among people living with HIV (PLH) who had evidence of a partially effective host response (viremic controllers), treatment with the investigational oral TLR7 agonist vesatolimod (VES; GS-9620) would lead to enhanced immune control post-ART.

Methods: We conducted a phase 1b, randomized, double-blind, placebo-controlled study in virologically suppressed PLH with historical chronic pre-ART plasma HIV-1 RNA of 50 to ≤5,000 c/mL. 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.

Results: Twenty-five participants were randomized to VES (n=17) or placebo (n=8). The median age was 45 yrs (range 27-66 yrs) and 16% were women. The median pre-ART HIV-1 RNA 3.2 log 10 c/mL (IQR 3, 3.3) and the median age was 45 yrs (range 27-66 yrs) and 16% were women. 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.

This is a controlled study in virologically suppressed PLH with historical chronic pre-ART plasma HIV-1 RNA of 50 to ≤5,000 c/mL. 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.

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.

41LB DURABLE HIV-1 ANTIBODY PRODUCTION IN HUMANS AFTER AAV-MEDIATED GENE TRANSFER

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Background: Gene transfer protocols offer an alternative to repeated injections of HIV broadly neutralizing antibodies (bNAbs) as a means of maintaining effective immunoprophylaxis. VRC07 is a bNAb targeting the CD4 binding site of the HIV-1 envelope glycoprotein.

Methods: Seven HIV-infected volunteers on effective ART therapy were enrolled in a phase I, open-label dose escalation trial of an AAV8 vector encoding the HIV bNAb VRC07 at doses of 5x1010 (N=3), 5x1011 (N=2), and 2.5x1012 (N=2) viral genomes per kilogram (vg/kg) by IM injection. Volunteers were between 30 to 60 yr. All volunteers in the 5x1010 and 5x1011 vg/kg dose groups were followed for 1yr or longer. Two volunteers in the 2.5x1012 dose group have been followed for between 7-9 mo.

Results: Product administration was well tolerated. Local reactogenicity was observed only in the 2.5x1012 vg/kg dose group where both volunteers reported mild pain and tenderness at the injection sites. One person in the intermediate dose group reported mild myalgia. All reactogenicities resolved within 1 week of product administration. No serious adverse events were attributed to product. Vector-based VRC07 production was found in all volunteers following injection. Peak VRC07 concentrations were 0.17-0.43 μg/ml in the 5x1010 dose group, 0.23-0.74 μg/ml in the 5x1011 dose group and 1.1-1.2 μg/ml in the 2.5x1012 dose group (Figure). The data suggest a pattern of antibody production defined by an early peak in VRC07 concentration 4-6 wks after product administration, a decrease in concentration 7-14 weeks after product administration and then a slow increase in concentration after 16 wks resulting in stable or continually increasing antibody concentration over the next 36 wks. In 3 of 5 individuals followed for one year or longer, antibody concentrations at 1 yr were higher than at the 4-6 wk peak. In the other 2 volunteers, one in the 5x1010, the other in the 5x1011 vg/kg dose group, anti-VRC07 antibodies were identified starting 6 and 14 wks after product administration. Anti-VRC07 antibodies were not detected in the other 5 volunteers.

Conclusion: These data suggest that adeno-associated viral vectors can safely be used to stably produce HIV-1 specific bNAbs in humans for over a 1-year period following a single administration of vector. AAV8 mediated gene transfer may offer a means to generate effective vectored immunoprophylaxis in humans.

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


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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 identify one additional HIV+ partner not on ART. 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] 3-5). aPNS was provided to 1565 (86%) partners, with a median of 4 partners (IQR 2-5) tested among female indexes and 3 (IQR 2-4) among males (p=0.002). 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 Country 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...
finding HIV+ not on ART among indexes not in a methadone program (NNTI=2.5 vs 4.1 for females; NNTI=4.9 vs 19.2 for males; p=0.003). After 6-months, 71% of partners not initially on ART had started treatment.

**Conclusion:** aPHS can improve the HIV care cascade for partners of PWID in Kenya, finding 1 HIV+ partner not on ART per 3.8 indexes. While most HIV+ partners were aware of their HIV status, 25% were not currently on ART, highlighting a need for improved care engagement. Focusing on index PWID most likely to yield HIV+ partners not fully engaged in care will maximize aPHS to achieve viral suppression. We found females, those not in methadone programs, and in Nairobi yielded the most partners not on ART.

### 43 Community-Based Multimonth Dispensing of ART: A Cluster Randomised Trial in Lesotho

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**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 (MMD) 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 336 participants were enrolled, 3MF (1988), 3MC (1585) 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: -1.6% 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 virologically suppressed in arms 3MF, 3MC and 6MCD, respectively. There were no differences in viral suppression between 3MC, or 6MCD vs. control, ratio 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 viral load 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.

### 44 Mhealth CHW Intervention Trial in an HIV Hyperendemic Community in Rakai, Uganda

**Larry W. Chang**, Ismail Mbabali, Xiangrong Kong, K. Rivet Amico, Caitlin E. Kennedy, Fred Nalugoda, Aggrey Anok, David Serwadda, Joseph Seesansu, Thomas C. Quinn, Steven J. Reynolds, Ronald H. Gray, Maria Wawer, Heidi Hutton, Gertrude Nakigozi

1. Johns Hopkins University, Baltimore, MD, USA, 2. Rakai Health Sciences Program, Kalis ofon, Uganda, 3. University of Michigan, Ann Arbor, MI, USA, 4. NIAID, Bethesda, MD, USA

**Background:** Effective strategies are needed to increase engagement in HIV services in HIV hyperendemic settings. We conducted a cluster-randomized trial in a fishing community on Lake Victoria (HIV prevalence ~41%) in Rakai, Uganda to assess the impact of a community health worker intervention called “Health Scouts” which used motivational interviewing strategies, a situated Information, Motivation, and Behavioral Skills framework, and mobile health (mHealth) counseling support tools to promote engagement in HIV treatment and prevention services.

**Methods:** From September 2015 to December 2018, the Health Scout intervention was deployed in the community which had been divided into 40 contiguous, similarly populated clusters (20 intervention; 20 control). Community-wide surveys of consenting 15-49 year-old residents with HIV viral load testing of HIV-positive participants were conducted at mid-study (~15 months) and end-of-study (~39 months) to assess self-reported antiretroviral therapy (ART) and male circumcision coverage and HIV viral load suppression (defined as <400 copies/mL). The primary analytic method was an as-treated analysis using generalized estimating equations models including participants from both surveys in a pragmatic analysis due to high participant mobility and contamination by study arm.

**Results:** 2522 and 1891 community residents completed the mid-study and end-of-study surveys respectively. By end-of-study, 95.7% (1789/1891) of residents reported awareness of the Health Scouts; 31% (580/1891) of residents reported having been visited and counseled by a Health Scout (i.e. exposed); 2.2% (41/1811) reported being approached but refusing to be seen. Health Scout exposure was higher in intervention (38%) compared to control clusters (23%), among those living with HIV (39%) compared to those who were not (23%), and among women (32%) compared to men (26%). As shown in Table 1, residents who reported having received the intervention (exposed) were more likely to report being on ART and to be virologically suppressed compared to residents who reported not having received the intervention (unexposed); however, there were no differences in male circumcision coverage.

**Conclusion:** A novel community health worker intervention using motivational interviewing techniques and mHealth tools was associated with improved ART coverage and HIV virologic suppression. However, intervention uptake varied by subgroups and cluster contamination was substantial. This intervention may be a useful community-based component of a comprehensive HIV response.

| Table 1: Study outcomes and prevalence risk ratios (includes participants from both surveys) |
| Outcome | Mid-study | Exposure | Unexposed | P-value |
| ART Coverage | 672 | 91.1% | 92.6% | 0.13 (0.04-0.47) |
| HIV viral load suppression | 985 | 78.4% | 78.6% | 0.90 (0.35-2.35) |
| Male circumcision coverage | 1590 | 67.3% | 65.8% | 0.07 (0.09-1.22) |

### 45 Improved Time in Care and Viral Suppression with Streamlined Care in the SEARCH Study


**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 (NCT01864603).

**Methods:** Our analysis included HIV+ adults (age ≥15 yrs) 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 VS, 2) ART-experienced with baseline viiremia, or 3) ART-naive with baseline CD4≤350. Comparisons between study arms used cluster-level TME.
Results: Among 4,391 HIV+ persons (35% men, 8% youth 15-24 yrs) in care and eligible for ART by country guidelines, 2,956 (67%) were ART-experienced with baseline VS, 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 1.02, 95% CI 1.00-1.03), 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>Baseline Care</th>
<th>ART-experienced with baseline viral suppression</th>
<th>ART-experienced with baseline viremia</th>
<th>ART-naive with baseline CD4 ≤350</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to care (TEAR)</td>
<td>1.07</td>
<td>1.07</td>
<td>1.11</td>
</tr>
<tr>
<td>Time in care (TEAR)</td>
<td>1.07</td>
<td>1.07</td>
<td>1.11</td>
</tr>
<tr>
<td>Viral suppression (VL ≤200 c/mL)</td>
<td>97%</td>
<td>97%</td>
<td>97%</td>
</tr>
</tbody>
</table>

46 COLLABORATIVE DATA-TO-CARE MODEL IMPROVES HIV CARE OUTCOMES IN PLWH IN PHILADELPHIA

Sindhu Shamasunder, 1 Crystal Lucas, 1 Shedane Shaw, 1 Briana Gibson, 1 Olivia Kirby, 1 Melissa Miller, 1 Kathleen A. Brady 1

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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 HIV 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 (25-65), 65% were Black, 25% were male, 42% were MSM, and 21% were HIV-negative at diagnosis. Across arms, 52% were re-engaged, 52% were retained at 1 year, and 60% were virally suppressed at 1 year. Patients randomized to the intervention were 2.22 (95% CI: 1.69-2.92), 1.89 (1.44-2.40) and 1.44 (1.10-1.90) times as likely as SOC patients to re-engage in care, become retained in care, and achieve viral suppression, respectively, when controlling for race, birth sex, age, transmission category and disease stage at diagnosis.

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.

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

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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 adults (HIV+ or HIV-) with HIV viremia — was estimated at midpoint of follow-up based on HIV prevalence and non-suppression among HIV+.

Results: HIV prevalence (measured in 257,929 total persons, PopART: 37,066; 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 2% 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...
48 DECREASING COMMUNITY VIREMIA IS ASSOCIATED WITH DECREASING HIV INCIDENCE IN AUSTRALIA

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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 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 (≥200 RNA copies/mm³) 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 among GBM living in New South Wales and Victoria, Australia’s most populous states. 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=1.16-1.55) and hybrid approach (66%, RR=1.19, 95% CI: 1.02-1.40), compared to standard of care. The primary outcome was 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.

Conclusion: Among PLWH who were not on ART, 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: At 12 months was 95%.

Conclusion: Among women ART increased viral suppression (63% vs. 74%, RR=1.16-1.55) and hybrid approach (66%, RR=1.19, 95% CI: 1.02-1.40), compared to standard of care (54%). Viral suppression was similar for women (73%) and women (73%) in the clinic arm - compared to 54% for men and 73% for women in the clinic arm.

Conclusion: Among PLWH who were not on ART, community-based ART increased viral suppression among men: community-based ART (73%, RR=1.34, 95% CI: 1.16-1.55) and hybrid approach (66%, RR=1.19, 95% CI: 1.02-1.40), compared to standard of care (54%). Viral suppression was similar for men (73%) and women (73%) in the community ART arm - compared to 54% for men and 73% for women in the clinic arm.

Methods: We conducted a multisite, 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.

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Community ART increases viral suppression and eliminates disparities for African men

49LB COMMUNITY ART INCREASES VIRAL SUPPRESSION AND ELIMINATES DISPARITIES FOR AFRICAN MEN

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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 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 (≥200 RNA copies/mm³) 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 among GBM living in New South Wales and Victoria, Australia’s most populous states.

Results: 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 (≥200 RNA copies/mm³) 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 among GBM living in New South Wales and Victoria, Australia’s most populous states.

Conclusion: Decreasing community viremia among diagnosed GBM decreased from 27.9% in 2012 to 13.1% 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 viremia decreased from 28.6% in 2012 to 12.8% in 2017 (p<0.001) while HIV incidence decreased from 0.83/100 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 diagnosed GBM decreased from 27.9% in 2012 to 13.1% 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 viremia decreased from 28.6% in 2012 to 12.8% in 2017 (p<0.001) while HIV incidence decreased from 0.83/100 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 diagnosed GBM decreased from 27.9% in 2012 to 13.1% 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 viremia decreased from 28.6% in 2012 to 12.8% in 2017 (p<0.001) while HIV incidence decreased from 0.83/100 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 diagnosed GBM decreased from 27.9% in 2012 to 13.1% 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 viremia decreased from 28.6% in 2012 to 12.8% in 2017 (p<0.001) while HIV incidence decreased from 0.83/100 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).
51 LRA 2.0: IMMUNE-BASED LATENCY REVERSAL
Ann Chahroudi, Emory University, Atlanta, GA, USA
Long-lasting, latently-infected resting CD4+ cells are the greatest obstacle to curing HIV infection, as these cells can persist despite decades of treatment with antiretroviral therapy. One approach towards a cure is to reactivate HIV from its latent state, thus promoting virus mediated killing and/or facilitating immune recognition and clearance of infected cells. Interventions that successfully reverse latency, when combined with strategies to enhance the antiviral immune response, may result in a reduction in the size of the persistent HIV reservoir. This presentation will review promising latency reversal approaches that take into consideration the immunologic aspects of virus persistence. Emerging results from in vivo studies in humanized mice and nonhuman primates will be discussed. The immunologic and virologic effects of the selected latency reversal agents will be highlighted.

52 T-CELL AND HEMATOPOIETIC STEM CELL GENE THERAPIES FOR HIV CURE
Christopher Peterson, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
Since the first reported cure of an HIV-1-infected individual over a decade ago, anti-HIV cell and gene therapies have remained a primary focus of numerous HIV cure efforts. To date, hematopoietic stem and progenitor cell (HSPC) transplantation remains the only known path to cure. Although this approach is not feasible for the vast majority of patients, lessons from Berlin, London, and elsewhere have contributed a wealth of knowledge regarding less toxic and more generalizable strategies. This presentation will discuss the current and most promising aspects of cell and gene therapy-based HIV cure approaches, offer a comparison of the pros and cons of targeting HSPCs, T-cells, and other subsets, and review lead candidates for scalable delivery of these therapies, namely in resource-limited settings. First and foremost, any curative intervention must be at least as safe and feasible as lifelong ART. A careful examination of the fundamental aspects of cure in HIV-infected stem cell transplantation patients lays out a compelling road map towards a gene therapy-based strategy, focused on enhancing virus-specific immunity. One such strategy involves adoptively transferred T-cells, for example cells modified to express chimeric antigen receptors (CARs). CAR T-cells have enabled long-term remission in cancer and have recently shown promise in this group of 0.69% (0.70% in 2012).

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 mimics the HIV-1 receptor CD4 and the HIV-1 coreceptor. Consistent with this breadth, eCD4-Ig is much harder to escape than broadly neutralizing antibodies (bNAbs). To date full escape has not been observed either in cell culture or in nonhuman primate models and viruses which partially escape eCD4-Ig in both cases pay clear fitness costs. Adeno-associated virus (AAV)-expressed eCD4-Ig functions as an effective vaccine alternative, and protects rhesus macaques from repeated high-dose viral challenges with both SHIV-AD8 and SIVmac239. Unlike bNAbs and other multispecific antibody-like inhibitors, eCD4-Ig markedly improves the endogenous ADCC activity of patient sera. It does so by altering the conformation of 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 could 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.

54 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 guidance, 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.

**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 (MCTC) of HBV. Compared to horizontal transmission, MTC is associated with an increased risk of developing chronic HBV infection, and also with an elevated risk of liver disease progression in those who become 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 MTC; this may lead to a change in HBV epidemiology with an increase in the relative contribution of MTC among new infections. In order to prevent MTC, 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 MTC, 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.

**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 2.8 million new infections (95% credible interval (CrI) 2.6 to 3.0 million) to 0.9 million (CrI 0.8 to 1.1 million) in 2018. Over this period the estimated number of GBM with undiagnosed infection less than 50% — an overall prevalence of 57 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 (35 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 2018, >80% of people newly diagnosed begin treatment within 3 months (regardless of gender or sexuality) compared to 55% 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.

**30-Plus Years of HIV in Rakai: The Epidemic Recedes**

Joseph Kagaya, Rakai Health Sciences Program, Kalisizo, Uganda

HIV was first documented in Rakai, Uganda in the early 1980s. For over 30 years, the Rakai Health Sciences Program (RHSP) 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 1.39/100 person-years). Despite these reductions, HIV incidence remains above epidemic control rates. Ongoing epidemiological/phylagenetic 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 around 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 HIV epidemic in the US by reducing new infections by 75% within 5 years and by 90% within 10 years. To reach these goals, the Department of Health and Human Services is proposing to target 48 counties plus Washington, DC and San Juan, Puerto Rico plus 7 Southern States that together comprise 50% of new HIV diagnoses. What will it take for this plan to be successful? We have the tools but fundamental differences in access to health care, local legislation, as well as racism, structural stigma, homelessness, and HIV laws/policies that will make implementation challenging.

62 PREVENTING HIV AMONG PEOPLE WHO INJECT DRUGS: PLUS CA CHANGE, PLUS CA MÊME CHOSE
Steffanie A. Strathdee, 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 18.6/100 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 its most serious opioid epidemic 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 modelling study estimated that if Scott County, IN had launched an earlier response, 200 HIV infections could have been prevented. In 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 U.S., 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.

63 SEX DIFFERENCES IN HIV
Eileen P. Scully, Johns Hopkins University School of Medicine, Baltimore, MD, USA
Biological sex confers specific immunologic advantages and challenges to both men and women. These differences lead to distinct patterns of immune responses and differing susceptibility to infections and to autoimmune and inflammatory pathology. There are data demonstrating sex-specific features of HIV acquisition, pathogenesis and the dynamics of the HIV reservoir, but many open questions remain. Despite the high burden of HIV infection among women, estimated at more than 50% of adults in 2016, enrollment of both cis and transgender women in clinical trials and basic research cohorts has been variable. In some domains, a notable lack of representation undermines the confidence that the data can be applied to all people living with HIV infection. However, sex differences represent a rich source for discovery. A comparative biology approach can leverage differences in immune responses and viral control to highlight pathways critical for vaccine development, cure interventions, or prevention of inflammatory comorbidity for both men and women. This same lens can be used to better understand the health risks and specific clinical needs for transgender men and women. Further, insuring that interventions are efficacious in women as well as men is essential to achieve the global goals for prevention, treatment and reduction in morbidity. To address these questions, both women and men must be enrolled in studies and the impact of both sex and gender assessed. This mandate to study both sexes is compelling from a scientific rigor and discovery perspective, and also meets our ethical responsibility to insure our innovations will work for all people living with HIV.

64 TARGETING THE KSHV TYROSINE KINASE AND VIRAL LYTIC REACTIVATION WITH INHIBITORS
Guillaume Beauclair,1 Eleonora Naimo1, Tatyana Dubich1, Dagmar Wirth2, Thomas F. Schulz3
1Medizinische Hochschule Hannover, Hannover, Germany, 2Helmholtz Centre for Infection Research, Braunschweig, Germany
Background: Kaposi’s Sarcoma-associated herpesvirus (KSHV) is the cause of three human malignancies, Kaposi’s Sarcoma, Primary Effusion Lymphoma and the plasma cell variant of Multicentric Castleman’s Disease. Previous research has shown that several cellular tyrosine kinases play crucial roles during several steps in the virus replication cycle. Two KSHV proteins also have protein kinase function: open reading frame (ORF) 36 encodes a serine-threonine kinase, while ORF 21 encodes a thymidine kinase (TK), which has recently been found to be an efficient tyrosine kinase.
Methods: In vitro kinase assays, virus replication assays, construction of recombinant KSHV mutants with a kinase-deficient orf21 gene, virus inhibition assays, in vivo endothelial tumor formation assays
Results: In this study, we explore the role of the ORF21 tyrosine kinase function in KSHV lytic replication. By generating a recombinant KSHV mutant
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, imatinib and ponatinib.

Conclusion: Since the identified kinase inhibitors target both cellular tyrosine kinases supporting productive viral replication and the KSHV tyrosine kinase, these drugs (dasatinib, imatinib, 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

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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

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Background: Kaposi sarcoma (KS), caused by Kaposi sarcoma herpesvirus (KSHV), is a multicentric 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 sk and gi KS lesions from HIV+ patients with KS to understand the similarities and differences in the gene expression pattern.

Methods: We obtained fresh sk and gi KS lesions with matched normal sk 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 VEG-F and VEG-F-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 sk KS samples. There were more lytic viral genes detected in gi KS as compared to sk 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 ADAMTS5, 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 Volkow1,2, Beda Daniela Islas Muñoz3, Leslie Chávez-Galán1, Lucero Ramón-Luengo1,3, Dora Patricia Cornejo Juárez1, Judith Cruz-Velázquez1,2 for the Instituto Nacional de Cancerología, Mexico City, Mexico

Background: High HHV-8 viral load (VL) has been associated with severe Kaposi sarcoma (S-KS). Immune reconstitution inflammatory syndrome (IRIS) can occur in patients after starting cART with associated high mortality. Ganciclovir has anti-HHV8 activity. Our objective was to investigate if valganciclovir started before cART could diminish HHV-8 VL and reduce the incidence of S-KS-IRIS and its attributable mortality.

Methods: ORCT (Clinical Trials NIH ID NCT03296653) of patients with disseminated KS (DKS), approved by IRB, participants signed informed consent. Inclusion criteria: AIDS cART naive 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, pulmonary disease, 30 skin lesions, lymphedema, lymph node involvement, GIT involvement. Inclusion criteria: AIDS cART naïve patients with at least two of the following: pulmonary disease, 30 skin lesions, lymphedema, lymph node involvement, GIT involvement.

Results: Six patients were randomized, 19 in each group; one patient stopped valganciclovir and was excluded. Three patients died due to S-IRIS-KS in the valganciclovir and was excluded. Three patients died due to S-IRIS-KS in the

Conclusion: Valganciclovir started before cART could diminish HHV-8 VL and reduce the incidence of S-KS-IRIS and its attributable mortality.

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Results: Six patients were randomized, 19 in each group; one patient stopped valganciclovir and was excluded. Three patients died due to S-KS-IRIS and its attributable mortality.
68 SURVEILLANCE OF RHUSUS MACAQUE TISSUES IDENTIFYING GAMMAHERPESVIRUS INFECTION SITES

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Background: Gammaherpesviruses are clinically significant causes 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: retropoential fibroptosis herpesvirus (RFHV), an ortholog of KSHV, rhesus lymphoypcytovirus (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 SHIV or not were collected during necropsy. These included buccal and gingival tissue, parotid, submandibular and sublingual salivary glands, submandibular lymph nodes, adenoid, palate and lingual 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 RLV 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 all three viruses were visualized in lymphoid tissues including lymph node and palatine tonsil. Multiplexing SH with antibody-based phenotyping revealed a broad range of infected cell types including B- and 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.

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

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Background: People with HIV (PLWH) have an increased risk of anal cancer. This is precipitated by high-grade squamous intraepithelial lesions (HSIL). Spontaneous clearance of HSIL is associated with systemic T-cell response to human papillomavirus (HPV) oncoprotein 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: Over 12 547 950 person-years of follow-up, 1 359 incident HSIL cases were diagnosed in the SA cohort of 4 766 614 PLWH. 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. The median CD4 cell count at baseline was 294 cells/µl (IQR: 159-467 cells/µl). There was an upward trend in CD4 cell counts across the years from a median of 240 cells/µl in 2004 to 340 cells/µl in 2014. The crude conjunctival cancer IR was 11.0 per 100 000 person-years (95% Confidence Interval [CI]: 10.2-11.4). Being male, lower CD4 cell count, earlier calendar period and older age were all associated with higher rates of conjunctival cancer (Table 1).

Conclusions: 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 PLWH as well as their clinicians.

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

<table>
<thead>
<tr>
<th>Age category</th>
<th>Number of cases</th>
<th>Incidence rate (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>1</td>
<td>0.10 (0.00-1.10)</td>
<td>0.01 (0.00-1.10)</td>
</tr>
<tr>
<td>20-29</td>
<td>6</td>
<td>1.25 (0.59-2.77)</td>
<td>0.12 (0.06-0.28)</td>
</tr>
<tr>
<td>30-39</td>
<td>10</td>
<td>7.21 (4.02-14.0)</td>
<td>0.80 (0.52-1.19)</td>
</tr>
<tr>
<td>40-49</td>
<td>46</td>
<td>14.53 (3.19-68.10)</td>
<td>0.09 (0.01-1.12)</td>
</tr>
<tr>
<td>50-59</td>
<td>98</td>
<td>18.94 (12.41-27.0)</td>
<td>0.71 (0.17-3.08)</td>
</tr>
<tr>
<td>60-69</td>
<td>38</td>
<td>16.53 (10.50-26.32)</td>
<td>0.91 (0.31-1.68)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>13</td>
<td>10.03 (6.50-15.16)</td>
<td>0.90 (0.10-8.30)</td>
</tr>
</tbody>
</table>

* incidence rates per 100 000 person-years.
without therapy. Immune activation was assessed by flow cytometry. Antigen-specific CD4+ T-cell responses to HPV16 E6 and E7 were assessed by OX40 assay. 

**Results:** 26 participants enrolled, 24 evaluable for response. All male; median age 54 (range 41-74); 10 (38%) PLWH; median CD4 700 cells/μL (320-1070), all HIV VL <20 copies/mL. All AIN3 HSIL, median duration HSIL 37 months (15-86), median octants 2 (0.5-5); HPV 5 in 56%; high risk HPV types in 50%. Overall response (CR+PR) was 52% (CI: 31-73) at end therapy, increasing to 63% (95% CI: 41-81) after 6 months observation. Responses were comparable in PLWH.

Adverse events (AEs) were mild and self-limited, including cytopenias, constipation, rash, with no idiosyncratic AEs in PLWH. HIV suppression was maintained. Over 137 cycles (c), attributable grade (g) 3/4 events were g3 neutropenia (4c) and g3 anaemia (1c).

Systemic CD4 + T-cell responses to HPV E6 but not E7 increased during therapy, peaking day 14: baseline 0.06%, IQR 0.01 – 0.12%, median increase day 14 0.13% (IQR: 0.02 – 0.26%), p=0.001. CD4 + and CD8 + cell activation (CD38, HLA-DR, CD38+HLA-DR) increased during therapy.

**Conclusion:** Low dose pomalidomide was well tolerated and induced durable continuing clearance of anal HSIL of multiple genotypes in even in chronic extensive disease irrespective of HIV status. Induction of HPV-specific CD4+ T-cell responses and immune activation support an immunological mechanism of action.
ANTIGEN-DRIVEN CLONAL SELECTION SHAPES THE FATE OF HIV-INFECTED CD4+ T CELLS IN VIVO

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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. PBMC were briefly stimulated with CMV lysates, GAG peptides or αCD3/28 antibodies. We sorted responding (CD40L+CD69+) and non-responding memory (CD40L-CD69-) cells and infected clones. A viral outgrowth assay (VOA) was used in one donor expressing cells measured by flow cytometry in fine needle aspirates (p=0.017). 89Zr-VRC01 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.

DISTINCT CHROMOSOMAL SITE CONFIGURATION IN HIV-1 ELITE CONTROLLERS

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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 etiopically encoded 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 vivo 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

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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 A3321 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, hsCRP). 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 yr (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.

Results: Adjustments to the manufacturing protocol augmented the ratio of CD4 to CD8 CAR T cells, increasing the persistence of CAR+ CD4 lineages in vivo. Infusion of cell-based antigen was well tolerated and led to significant increases in the percentage of CAR+ T cells in peripheral blood. Following ART withdrawal, viral rebound was delayed in all animals; one remains undetectable at 53 days post-ATI.

Conclusion: Previous studies in patients and NHPs demonstrated low-level persistence of virus-specific CAR T cells in vivo, relative to CAR T cells for cancer. To our knowledge, ours is the first study to boost virus-specific CAR T cells in infected, suppressed hosts, and to delay/control post-ATI viral rebound via CAR T cell therapy. Due to the lack of a cytotoxic conditioning regimen, the safety profile of our approach is highly favorable. Our data reinforces the promise of deltaCCR5 CD4CAR T cell therapies for viral reservoir reduction in HIV+ individuals, including a Phase I clinical trial underway at the University of Pennsylvania (NCT03617198).
78LB COMBINED ACTIVE AND PASSIVE IMMUNIZATION IN SHIV-INFECTED RHESUS MONKEYS

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1Beth Israel Deaconess Medical Center, Boston, MA, USA, 2Wisconsin National Primate Research Center, Madison, WI, USA, 3NantKwest, Culver City, CA, USA, 4Weill Cornell Medicine, New York, NY, 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.
Results: This analysis included 1493 participants (500 cases; 131 with CVD) with 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, AXIN1, CH13L1, SCGB3A2, GAS6 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.

Table 1: Summary of associations between protein levels and CVD outcomes. The risk differences are for the reduction in risk differences associated with a 1 unit increase from the mean of the genotype levels. The p-values reported in the final column are adjusted for the number of statistical comparisons that were tested.

<table>
<thead>
<tr>
<th>Protein (gene)</th>
<th>Risk difference (95% CI)</th>
<th>p-value</th>
<th>Number of subjects</th>
<th>Risk differences (95% CI)</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP</td>
<td>0.14 (0.10–0.19)</td>
<td>0.002</td>
<td>193</td>
<td>0.13 (0.09–0.17)</td>
<td>0.003</td>
</tr>
<tr>
<td>CCL2</td>
<td>0.08 (0.04–0.12)</td>
<td>0.002</td>
<td>193</td>
<td>0.08 (0.04–0.12)</td>
<td>0.002</td>
</tr>
<tr>
<td>CCL4</td>
<td>0.08 (0.04–0.12)</td>
<td>0.002</td>
<td>193</td>
<td>0.08 (0.04–0.12)</td>
<td>0.002</td>
</tr>
<tr>
<td>LPLD</td>
<td>-0.07 (0.00–0.14)</td>
<td>0.002</td>
<td>193</td>
<td>-0.07 (0.00–0.14)</td>
<td>0.002</td>
</tr>
<tr>
<td>IRAK5</td>
<td>0.10 (0.06–0.14)</td>
<td>0.002</td>
<td>193</td>
<td>0.10 (0.06–0.14)</td>
<td>0.002</td>
</tr>
<tr>
<td>MCH2</td>
<td>0.07 (0.03–0.11)</td>
<td>0.002</td>
<td>193</td>
<td>0.07 (0.03–0.11)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 1.8: Summary of median changes from baseline across all genotypes and risk scores.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF/FTC+DTG</td>
<td>TDF/FTC+DTG</td>
<td>TDF/FTC/EFV</td>
<td>TDF/FTC/EFV</td>
<td>TDF/FTC/EFV</td>
<td>TDF/FTC/EFV</td>
<td>TDF/FTC/EFV</td>
<td>TDF/FTC/EFV</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>&gt;41.5 (n=157)</td>
<td>&gt;41.5 (n=157)</td>
<td>&gt;41.5 (n=157)</td>
<td>&gt;41.5 (n=157)</td>
<td>&gt;41.5 (n=157)</td>
<td>&gt;41.5 (n=157)</td>
<td>&gt;41.5 (n=157)</td>
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<tr>
<td>LDL (mmol/L)</td>
<td>&gt;2.6 (n=157)</td>
<td>&gt;2.6 (n=157)</td>
<td>&gt;2.6 (n=157)</td>
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<td>&gt;2.6 (n=157)</td>
<td>&gt;2.6 (n=157)</td>
<td>&gt;2.6 (n=157)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>&gt;1.2 (n=157)</td>
<td>&gt;1.2 (n=157)</td>
<td>&gt;1.2 (n=157)</td>
<td>&gt;1.2 (n=157)</td>
<td>&gt;1.2 (n=157)</td>
<td>&gt;1.2 (n=157)</td>
<td>&gt;1.2 (n=157)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>&gt;4.4 (n=157)</td>
<td>&gt;4.4 (n=157)</td>
<td>&gt;4.4 (n=157)</td>
<td>&gt;4.4 (n=157)</td>
<td>&gt;4.4 (n=157)</td>
<td>&gt;4.4 (n=157)</td>
<td>&gt;4.4 (n=157)</td>
</tr>
</tbody>
</table>

82 CYP2B6 GENOTYPE AND WEIGHT-_GAIN DIFFERENCES BETWEEN DOLUTEGRAVIR AND EFAVIRENZ
Ruan Griesel,1 Gary Maartens,1 Simiso Sokhela1, Godspower Akpomie2, Willem D. Venter,1 Michelle A. Moorhouse,1 Phumla Sinxadi1
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 lipoatrophy. We hypothesised that CYP2B6 metaboliser genotype, which predicts EFV exposure, would determine amount of weight gained 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 change in weight gain and trunk fat on DXA from baseline to week 48 by CYP2B6 genotype. Weight gain was calculated as CYP2B6 extensive metabolisers in the EFV/TDF/FTC arm and the DTG/TDF/FTC arm.

Results: 171 participants had genetic testing done. CYP2B6 metaboliser genotypes were 51 extensive, 74 intermediate, and 46 slow; median age 32 years (IQR 28–37); 57% women; median BMI 23.7 kg/m² (IQR 20.2–27.5); and median CD4 count 292 cells/μL (IQR 172–406). The percentage change in weight from baseline over 48 weeks differed by CYP2B6 metaboliser genotype (p=0.004; Kruskal-Wallis), but differences were more marked in women over time (see figure). In men CYP2B6 metaboliser genotype was associated with percentage change in weight initially (week 12 p=0.007; week 24 p=0.053), but the effect attenuated over time. The percentage change in limb fat on DXA (n=148) from baseline to 48 weeks differed significantly by CYP2B6 metaboliser genotype in women (p=0.018) and men (p=0.032). 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 (p=0.860). 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 significantly different between CYP2B6 extensive metabolisers in the EFV/TDF/FTC arm and the DTG/TDF/FTC arm (p=0.039).

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.

Figure: Percentage change from baseline by CYP2B6 metaboliser genotype over 48 weeks stratified by sex.
CHANGES IN BODY MASS INDEX AND THE RISK OF CARDIOVASCULAR DISEASE: THE D:A:D STUDY
Kathy Petoumenos1, Locadiah Kuwanda1, Lene Ryom1, Amanda McVoy2, Peter Reiss3, Stephanie De Wit4, Christian Pradier5, Andrew N. Phillips5, Camilla Ingrid Hatleberg4, Antonella D’Arminio Monforte6, Rainer Weber6, Caroline Sabín6, Jens D. Lundgren6, Matthew Law6, for the D:A:D Study Group.

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 variable.

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 risk of CVD with an increased BMI in any baseline BMI strata. Overall there was no statistically significant interaction between baseline BMI strata and BMI change (p=0.16). There was some evidence of an increased rate 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.

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.

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 <500 cells/mm³. 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 methods, and T-cell and monocyte phenotypes were assessed with flow cytometry among a subset of participants. Baseline-to-12-month changes in (log-2 transformed) biomarkers and (untransformed) cell phenotypes were compared between the losartan and placebo arms using linear mixed models.

Results: One hundred and 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/mm³; 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 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, or 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.
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 8341 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<0.01). FEV1 declined significantly faster among PWH before age of 50, but declined at similar rate after age of 50 (Table). 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/year faster, pinteration=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, pinteration=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: 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>Beta (95% CI)</th>
<th>Age at entry</th>
<th>HIV serostatus</th>
<th>Beta (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>0.05 (0.00-0.10)</td>
<td>0.001 (0.00-0.002)</td>
<td>HIV-</td>
<td>0.001 (0.00-0.002)</td>
<td></td>
</tr>
<tr>
<td>Age at entry</td>
<td>HIV+</td>
<td>0.05 (0.00-0.10)</td>
<td>HIV-</td>
<td>0.001 (0.00-0.002)</td>
<td></td>
</tr>
<tr>
<td>Time (years)</td>
<td>HIV+</td>
<td>0.05 (0.00-0.10)</td>
<td>HIV-</td>
<td>0.001 (0.00-0.002)</td>
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</tr>
<tr>
<td>Female</td>
<td>HIV+</td>
<td>0.05 (0.00-0.10)</td>
<td>HIV-</td>
<td>0.001 (0.00-0.002)</td>
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</tr>
<tr>
<td>Black</td>
<td>HIV+</td>
<td>0.05 (0.00-0.10)</td>
<td>HIV-</td>
<td>0.001 (0.00-0.002)</td>
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</tr>
<tr>
<td>Age at study entry</td>
<td>HIV+</td>
<td>0.05 (0.00-0.10)</td>
<td>HIV-</td>
<td>0.001 (0.00-0.002)</td>
<td></td>
</tr>
<tr>
<td>Lifetime smoking (pack years)</td>
<td>HIV+</td>
<td>0.05 (0.00-0.10)</td>
<td>HIV-</td>
<td>0.001 (0.00-0.002)</td>
<td></td>
</tr>
</tbody>
</table>

**AZITHROMYCIN FOR TREATMENT OF HIV-RELATED CHRONIC LUNG DISEASE IN AFRICAN CHILDREN**

Rashida A. Ferrand, Grace McHugh, Andrea M. Rehman, Hilda Mujuru, Mark Nicol, Sarah Rowland-Jones, Frond Flagestad, Tore Gurtteberg, Victoria Simms, Elizabeth L. Corbett, Helen A. Weiss, Edith D. Majonga, Katharina Kranzer, Jon O. Oddland, for the BREATHE Trial Group

London School of Hygiene & Tropical Medicine, London, UK; Biomedical Research and Training Institute, Harare, Zimbabwe; University of Zimbabwe, Harare, Zimbabwe; University of Cape Town, Cape Town, South Africa; University of Oxford, Oxford, UK; Arctic University of Norway, Tromso, Norway

Background: HIV-related chronic lung disease (HCLD) in children and adolescents is associated with substantial morbidity, despite antiretroviral therapy (ART). HCLD may be a consequence of repeated respiratory tract infections and/or dysregulated immune activation. Macrolides have anti-inflammatory and antimicrobial properties, and we hypothesized that azithromycin (AZM) would improve lung function and morbidity through preventing respiratory tract infections and controlling systemic inflammation.

Methods: We conducted a randomized double-blind, placebo-controlled trial among children aged 6-19 years on ART with HCLD (defined as FEV1 Z-score < -1) in Malawi and Zimbabwe. Once-weekly AZM (with weight-based dosing) or placebo was administered for 48 weeks. Primary outcome was mean difference in FEV1 Z-score. Secondary outcomes were mortality, hospitalisations and acute respiratory exacerbations (ARE). Outcomes were adjusted for age, sex, trial site and HIV viral load (VL) at baseline, using robust standard errors for multiple event data.

Results: A total of 347 children were recruited (49% female, median age 15.3 years) of whom 44% had a VL>1000 copies/ml and 74% were on first-line ART; 90% were taking cotrimoxazole prophylaxis and the median CD4 count was 573 cells/μl. Previous treatment for tuberculosis was reported by 28% and chronic cough by 9%, and 44% had an abnormally high respiratory rate. We randomized 174 to AZM and 173 to placebo. At the end of 48 weeks of treatment, the mean difference between arms in FEV1 Z-score was 0.06 (95% CI 0.10, 0.21; p=0.48). There was a significant difference in incidence of ARE, adjusted incidence rate ratio 0.50 (95% CI 0.25, 1.00; p=0.05) (Figure 1). The rate ratio for hospitalizations was 0.24 (0.06-1.07, p=0.061) comparing AZM to placebo. Mortality was 0/100pyrs in the AZM vs 1.95/100pyrs in the placebo arm.

Conclusion: This is the first ever trial of an intervention to address HCLD in children. While once-weekly AZM had no effect on pulmonary function, it reduced mortality, hospitalizations and incidence of AREs. AZM is an effective intervention in reducing morbidity associated with HCLD in children and adolescents.

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

Elena Bekerman, Stephanie W. Cox, Scott McCallister, Tomas Cihlar, Christian Callebaut

Gilead 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 PrEP/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 (200/25 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 doses of ARVs were administered at different times relative to virus exposure. In Study 1, BIC/FTC/TAF (25/200/25 mg) or FTC/TAF (200/25 mg) was given at -2h/+24h or +24h/+48h. In Study 2, BIC/FTC/TAF (25/200/25 mg) or FTC/TAF (200/25 mg) was given at -2h/+24h or +24h/+48h or +48h/+72h (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 (25/200/25 mg) protected 6/6 animals in the +2h/+24h group, 4/6 animals in the +24h/+48h group and 0/6 animals in the +48h/+72h group (n=6). In Study 2, BIC/FTC/TAF (25/200/25 mg) protected 5/6 animals in the +2h/+24h group, 4/6 animals in the +24h/+48h group and 0/5 in the +48h/+72h group. After 6 virus challenges in Study 2, BIC/FTC/TAF (100/200/25 mg) protected 5/6 animals in the +2h/+24h group, 6/6 animals in the +24h/+48h group, 4/6 animals in the +48h/+72h group, 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.

**Table 1.** Results of NHP PrEP/PEP Studies with FTC/TAF

<table>
<thead>
<tr>
<th>Treatment (mg)</th>
<th>Study 1 (8 challenges)</th>
<th>Study 2 (6 challenges)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time of Treatment</strong></td>
<td>% Protected</td>
<td>p&lt;0.05*</td>
</tr>
<tr>
<td>Placebo Central</td>
<td>&gt;2h</td>
<td>0/6</td>
</tr>
<tr>
<td>FTC/TAF (100mg)</td>
<td>&lt;0.001</td>
<td>0/6</td>
</tr>
<tr>
<td>FTC/TAF (25mg)</td>
<td>&lt;0.001</td>
<td>0/6</td>
</tr>
<tr>
<td>FTC/TAF (25mg)</td>
<td>&lt;0.001</td>
<td>0/6</td>
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<tr>
<td>FTC/TAF (25mg)</td>
<td>&lt;0.001</td>
<td>0/6</td>
</tr>
<tr>
<td>FTC/TAF (25mg)</td>
<td>&lt;0.001</td>
<td>0/6</td>
</tr>
</tbody>
</table>

* Comparing FTC/TAF vs placebo (p<0.05) when two treatments were compared.

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

**Martin Markowitz,** 1 Agegnehu Gettie, 1 Leslie St. Bernard, 1 James Blanchard, 2 Brooke Grasperge, 1 Perry Fillgrove, 1 Lingling Xue, 1 Neal Dubel, 1 Daria Hazuda, 1 Jay Grobler 1

1Aaron Diamond AIDS Research Center, New York, NY, USA, 2Tulane National Primate Research Center, Covington, LA, USA.

**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 PrEP 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 7 wk after the 4th dose of ISL. In Stage II, uninfected animals from Stage I were challenged as in Stage I and beginning 24h later 3 weekly oral doses of ISL at 3.9 mg/kg was initiated. Animals were monitored for 7 wk 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 7 wk after the 2nd dose of ISL. Finally in Stage IV, uninfected animals were challenged IV and 24h later treated with a single oral dose of ISL at 3.9 mg/kg and followed for 7 wk. 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 PBMC 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=0.0022). ISL-TP levels became undetectable in PBMC 3 weeks on average 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 T_{1/2} in human PBMCs (79-214 h) is substantially longer than RM (50 h), it is conceivable that a single low oral dose given within 24h of HIV exposure may provide effective PEP. These results support the potential utility of ISL as a simplified PEP agent.

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

**Susan C. Uvin,** 1 Thomas Moench, 2 Joseph A. Politch, 3 Karen T. Tashima, 1 Jai G. Marathe, 1 Kate M. Guthrie, 2 Howard Cabral, 1 Tara J. Nyhubi, 4 Miles Brennan, 1 Larry Zeitzlin, 1 Hans M. Spiegel, 1 Kenneth H. Mayer, 1 Kevin Whaley, 1 Deborah Anderson 1

1Brown University, Providence, RI, USA, 2Mapp Biopharmaceutical, Inc., San Diego, CA, USA, 3Boston University, Boston, MA, USA, 4NIH, Rockville, MD, USA, 5Harvard University, Cambridge, MA, USA

**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 (HSV3) mAbs to provide protection against two incurable viral infections.

**Methods:** The active film or vehicle control film was randomly assigned at a 1:1 ratio to 29 healthy sexually abstinent women who were instructed to insert 1 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 Lumefon for 16 cytokines that have been associated with HIV transmission, by Tzm-bl assay for HIV neutralization (strains: Q23-2 (strain C), 8, and LAI (X4 clade B), and by plaque reduction neutralization test for HSV-2 neutralization (HSV-2 strain G). CVLs and TearFlo samples (4 vaginal sites) were assessed by ELISA for VRC01 and HSV8 mAb concentrations.

**Results:** There were 45 AEs; 19 were deemed related to study product, but were balanced between active and placebo film (p's=1.0). There were no serious AEs (SAEs) and no significant differences in levels of proinflammatory cytokines,
**NEAR-PERFECT ACCURACY OF A REAL-TIME URINE TENOFOVIR TEST COMPARED TO LAB-BASED ELISA**

**Matthew A. Spinelli,1 Warren Rodrigues2, Guohong Wang3, Michael Vincent3, David Gitlin1, Randy Stalter3, Patricia A. Defechereux1, Madeline Deutsch2, Warren Rodrigues2, Guohong Wang2, Michael Vincent2,1,505 of the POC test results were also positive, yielding 100% sensitivity.**

**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 IBREATH Study, which recruited transgender women 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 IBREATH, 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.
ARV drug resistance? Akapirat2, Jintanat Ananworanich1, Mark De Souza1, Praphan Phanuphak1, Donn J. Colby

**Conclusion:**

PrEP for 2, 7, and 14 days. PrEP for 30, 34, and 121 days. The 3 cases without resistance mutations took had resistance mutations to TDF. The 3 cases that developed FTC-resistance took resistance mutations M184V/I, conferring high-level resistance to FTC. No cases had resistance mutations to TDF. The 3 cases that developed FTC-resistance took

**Methods:** We identified girls aged 15-24 years who participated in Rakai community cohort study (RCCS) survey between June 2018 - 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. DREAMS packages 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.

**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, 24.1% (233) had participated in DREAMS. Among girls aged 15-19, ≥10 sessions of ST were associated with 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 alcohol use (aPRR 0.23, 95% CI=0.10 -0.52). Among girls aged 20-24, receiving ≥5 ST sessions was associated with a significant reduction in sexual debut (aPRR 0.61, 95% CI=0.42 -0.86) and being sexually active (aPRR 0.55, 95% CI=0.37 -0.81), while 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 20-24, receiving ST had no significant impact on any risk behaviors. CSEA and HTC were not found to affect risk behaviors in either age groups.

**Conclusion:** In this population-based study, a minimum of 10 ST sessions of the DREAMS ST program are required to reduce risk sexual behaviors among girls aged 15-19 years but no effects were observed with CSEA and HTC. No DREAMS interventions affected risk among women aged 20-24. DREAMS should be modified.

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**Table 1.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%) (95% CI)</th>
<th>PPR (95% CI)</th>
<th>aPPR (95% CI)</th>
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<tr>
<td>Stepped care sessions</td>
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<td>Sexual debut</td>
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<td>Alcohol use</td>
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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 autoimmunity 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 cGMP and ATP into cyclic GMP-AMP (cGAMP), which functions as a second messenger that binds and activates the ER membrane protein STING. STING then activates the protein kinases IKK and TBK1, which in turn activates the transcription factors NF-κB and IRF3 to induce type-I interferons and other cytokines that together combat microbial infections. I will discuss our recent work on the biochemical mechanism by which cGAMP activates STING and the downstream signaling cascade.

96 TRIMS RECOGNITION AND RESTRICTION OF HIV-1 AND RETROVIRUSES

Owen Pornillos, University of Virginia, Charlottesville, VA, USA

Restriction factors and pattern recognition receptors make up innate or intrinsic cellular defenses against viral infection. TRIMS proteins are restriction factors and receptors that recognize the incoming cores of retroviruses by binding to the capsid that surrounds and protects the core. Upon capsid binding, TRIMS proteins accelerate dissociation of the viral core, inhibit reverse transcription of the viral genome, and activate ubiquitin-dependent interferon signaling. TRIMS proteins contain the tripartite motif fold (RING, B-box, and coiled-coil domains) and a C-terminal domain (SPRY or CypA) that mediates direct binding to retroviral capsids. Retroviral capsids are fullerenic structures composed of about 1,500 copies of the viral CA protein, which are organized on a hexagonal lattice composed of about 250 hexamers and exactly 12 pentamers. TRIMS-mediated capsid recognition is driven by avidity, requiring higher-order assembly of multiple TRIMS protein molecules on the capsid surface. I will discuss a series of studies, which collectively show that TRIMS binds a retroviral capsid through a mechanism of hierarchical assembly. A limited number of local interaction modes are successively organized as increasingly higher-order structures that culminate in a TRIMS cage surrounding the capsid. Cage formation explains the mechanism of restriction and provides the structure/function context that links core recognition to ubiquitin-dependent processes that disable the retrovirus and signal the presence of an invader.

97 HIV-1 AVOIDS BEING ZAPPEd

Janet L. Smith, University of Michigan, Ann Arbor, MI, USA

Human cells have a variety of schemes to distinguish self from non-self molecules. The zinc finger antiviral protein (ZAP) surveils the cytoplasm and directs the destruction of RNAs from a number of viruses. How this occurs was unknown until Bienzais and co-workers discovered that ZAP recognizes CpG dinucleotides, which are naturally depleted in animal genomes and mRNAs [1]. The sensitivity of RNA viruses to ZAP is correlated with the CpG content of the viral genome. HIV-1 has both a low CpG content and a natural resistance to ZAP, but it became ZAP-sensitive when the CpG content was increased by synonymous mutation. Thus HIV-1 seems to have evolved to avoid ZAP inhibition. The ZAP protein has a 230-amino-acid N-terminal domain (NTD) for RNA recognition; this domain includes four ‘CCCH’ zinc finger structures, as in many RNA-binding proteins. The functions of the following WEE and poly(ADP-ribose) polymerase (PARP) domains of ZAP are unknown, but may include recruitment of enzymes for RNA destruction, for example the putative endonuclease, KHYN, that is required for antiretroviral activity. We solved a crystal structure of the human ZAP NTD with an RNA oligomer from the CpG-enriched HIV-1 genome and discovered that only zinc finger 2 (Zf2) recognizes the CpG dinucleotide [2]. Single amino acid substitutions in Zf2 abolished selective binding of ZAP to CpG-enriched regions of the HIV-1 genome and also eliminated the ability of ZAP to selectively inhibit CpG-enriched HIV-1. Analogous substitutions in Zf1,3,4 had no impact on antiviral activity. Overall, ZAP seems to constrain the nucleotide sequence of the HIV-1 genome and may provide a defense against viruses whose genomes have higher CpG content. [1] Takata et al. & Bienzais. Nature 530, 124-127 (2017). [2] Meagher, Takata et al., Bienzais & Smith. PNAS116, 24302-24309 (2019).

98 SERINC STRUCTURE AND RESTRICTION OF HIV-1 INFECTIVITY

Valerie Pye, The Francis Crick Institute, London, UK

The human integral membrane protein SERINC5 potently restricts HIV-1 infectivity by inhibiting viral entry and sensitises the virus to antibody-mediated neutralisation. To eliminate the effect of SERINC5, HIV-1 encodes the endocytic adaptor protein Nef, which redirects SERINC5 to endosomal compartments, thereby preventing its inclusion into budding viral particles. Understanding the molecular basis of retroviral restriction by SERINC5 and its down-regulation by HIV-1 Nef may aid in development of antiviral therapeutic approaches. We determined the three-dimensional structures of human SERINC5 and its ortholog from Drosophilia melanogaster at subnanometer and near-atomic resolution, respectively, using cryo-electron microscopy. An extensive panel of SERINC5 mutants were tested for the ability to inhibit Nef-negative HIV-1 infectivity and localisation to the plasma membrane. The SERINC5 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 SERINC5 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. SERINC5 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 SERINC5 proteins and their ability to restrict HIV-1 infection.

99 NEUROHIV IN THE GLOBAL CONTEXT: ADVANCING THE CONTINUUM OF CARE AND ACQUIRING 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 in Africa, with <2 million PLHIV 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 emergent problems of aging. Despite early reports that clade C was less neuro-virulent, regional data suggest that HIV tat variants are not neuro-protective. 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

Bobilola 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 to stigma and coping, 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 among 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 are commonly underfunded 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 Wandelier, 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 insuficient. 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 nucleotide 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 repackaging 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 inflammatory pathways. The targeting of the adaptive immune response may be particularly critical, since functional cure observed during spontaneous resolution of acute hepatitis B (A肝炎, A肝 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 (C) and combination therapies of a C 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 progesterin 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 ARV 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 presumes that all types of exogenous progestins 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 failures 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 B6 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 ~20–30-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 Landay1, Grace A. McComsey1, Brian Clagett1, Chris T. Longenecker1, Carey Shive1, Keith W. Crawford1, Daniela Moisi1, Michael L. Freeman1, Nicholas Funderburg1, Landay2, Grace A. McComsey1, Brian Clagett1, Chris T. Longenecker1, Carey Shive1, Keith W. Crawford1, Daniela Moisi1, Michael L. Freeman1, Nicholas Funderburg1, Landay2, Grace A. McComsey1, Brian Clagett1, Chris T. Longenecker1, Carey Shive1, Keith W. Crawford1, Daniela Moisi1, Michael L. Freeman1, Nicholas Funderburg1, Landay2, Grace A. McComsey1, Brian Clagett1, Chris T. Longenecker1, Carey Shive1, Keith W. Crawford1, Daniela Moisi1, Michael L. Freeman1, Nicholas Funderburg1

3University of Minnesota, Minneapolis, MN, USA, 4University of California San Diego, La Jolla, CA, USA, 5Louisiana State University, New Orleans, LA, 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 (IL-7). 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) (0.2073 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 IL-7 levels (−1 pg/mL, p<0.001). TCZ also led to significant decreases in soluble TNF-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 modestly.

Conclusion: Blockade of IL-6 activity markedly decreases soluble markers of inflammation and indices of CD4 T activation/regulation that have been linked to morbidities 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

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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 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 animals weekly, in total 10 times, with SHIV-BGS05 via the intravaginal route to measure vaccine-induced protection. We then identified immune correlates of protection. Finally, vaginal tissues were isolated from four protected animals...
115LB HUMAN NK CELLS DEVELOP ANTIGEN-SPECIFIC IMMUNOLOGICAL MEMORY OF HIV
Stephanie Jost1, Olivier Lucar1, Haley Dugan2, Marcus Altfeld3, Paul Goepfert4, R. Keith Reeves1
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Background: Beyond their ability to eliminate infected cells without the need for prior sensitization, murine, non-human primate and human natural killer (NK) cells have been shown to mediate virus-specific recall responses. However, whether NK cells can mediate HIV antigen-specific immunological memory in humans remains to be demonstrated.

Methods: Using calcein acetoxy-methyl ester- or flow cytometry-based cytotoxicity assays, we tested the ability of bulk and donally expanded individual NK cells to lyse MHC-devoid K562 cells or autologous B-LCLs left unpulsed or pulsed with pools of self-antigens, CMV, CMV/EBV/Influenza (CEF), HIV Gag or HIV Env-derived overlapping peptides. Study participants included HIV-negative healthy donors (HD; n=6) and people living with HIV (PLWH) virally suppressed on ART (n=14), untreated viremic (UT; n=14) or elite controllers (EC; n=4). Phenotypic analysis was performed using up to 28-color flow cytometry on a BD FACSymphony instrument.

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 B-LCLs pulsed with the CEF peptide pool, or killing of MHC-devoid K562 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% MHC class Ia from 14 UT) showed positive responses to HIV (at least twice 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 induced 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. Bimber1, Shaheed Abdulhaq1, Abigail Ventura1, Eric McDonald1, Daniel Douek1, Scott Hansen1, Jonah Sacha1, Louis J. Picker1
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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 this 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-Ia 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
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Background: Previous studies evaluating the ability of PD-1 blockade to reduce viral reservoirs in SIV+ monkeys on ART have failed to demonstrate significant
118 TRACKING AND PREDICTING REBOUND IN SHIV-INFECTED INFANT MACAQUES AFTER LONG-TERM ART

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Background: Breastfeeding transmission accounts for the majority of new pediatric infections and commits infants to lifelong ART, as interruption is 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, informing the development of remission strategies and one to be monitored in HIV-infected children being considered for ATI.

Methods: At 4 wks old, 10 rhesus macaques were orally-administered SHIV.CHS95.35HT 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: 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 rhesus 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 SHIVmac239, 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 viereicm), 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

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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 and IF-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 Bhagani2, Marc van der Valk1, Jürgen K. Rockstroh3, Christine Thurnheer4, Arthur Kim5, Jordan J. Feld7, Julie Bruneau8, Edward Gane9, Margaret Hellard10, Tanya Applegate1, Marianne Martellino1, Kathy Petoumenos1, Gregory J. Dore1, 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 short course (6 weeks, Arm A) versus standard course (12 weeks, Arm B) therapy with sofosbuvir/velpatasvir for recently acquired HCV infection (estimated duration of infection <= 12 months). Randomisation was at week 6 and stratified by site and HIV status. The primary endpoint was sustained virologic response at 12 weeks post treatment (SVR12) reported in the intention-to treat (ITT) population. A total of 250 participants were planned for enrolment and DSMB analysis was scheduled after the first 50 participants in each arm reached SVR12. Following the initial DSMB review, a second review was scheduled following 60 participants through SVR12 in each arm. **Results:** At second DSMB review, 185 participants were enrolled, 165 had been randomised and 127 were through SVR12; n=65 in Arm A and n=60 in Arm B. Of those randomised, 98% were male, and 72% HIV positive. The predominant genotype was 1 (65%) and median baseline viral load 5.6 log10 IU/mL. 38% were reinfections. At second review (May 2019), the DSMB recommended study cessation for evidence of inferiority in the short arm (A). By ITT SVR12 was 78% (53/65) in Arm A (95% CI 70-90) versus 95% (57/60) in Arm B (95% CI 86-99) (p=0.021). Relapse occurred in 6/65 participants in Arm A (9%, 95% CI 3-19) versus 0 in Arm B (95% CI 0-6). Median baseline viral load in people with viral relapse was 6.40 log10 IU/mL (range 5.9-7.1 log10 IU/mL). Two further participants in Arm A had virological failure at end of treatment, one had reinfection, two died, and four lost to follow-up. Three participants in Arm B were lost to follow-up. **Conclusion:** In this randomised study of treatment 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.
124 HCV TRANSMISSION AMONG MSM: EXTERNAL INTRODUCTIONS COULD COMPLICATE MICRO-ELIMINATION

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Background: Elimination of HCV has become a target with the introduction of highly effective direct antiviral agents (DAAs). However, the presence of unclustered sequences over time was calculated using year-specific time-scaled phylogenies were constructed for each HCV genotype separately, and were obtained from 244 MSM in care in Amsterdam. Maximum-likelihood 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.

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 HCV diagnoses during January 1, 2018–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 featured 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.

Figure: Cumulative number of outbreak cases and timeline of events, West Virginia, 2018–2019

125 NEWBORN TESTING REVEALS HIGH HCV SEROPREVALENCE IN PREGNANT WOMEN FROM NEW YORK STATE

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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), 67% of new female cases were in women of child bearing 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 (1.3%) regions, where multiple counties are designated rural, was 3.4-3 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.
126  HEPATOCELLULAR CARCINOMA RISK AMONG PERSONS WITH HIV IN NORTH AMERICA, 1996-2015

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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 in the North America AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

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, 451 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 an earlier ages. From 1996 to 2015, HCC IR increased from 0.28 to 0.75/1000 pys. As compared to HIV-monoinfected persons, PWH co-infected with HBV and/or HCV had substantially greater age-related cumulative incidence of HCC in all 3 periods (Figure). Higher HIV VL (≥500 copies/ml) and lower CD4 counts (≤500 cells/mL) were associated with higher HCC risk (aIRR: 1.8, 95% confidence interval (CI): 1.0-2.4 and aIRR: 1.3, 95% CI: 1.1-2.4, 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

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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 HIV 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 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%, 87%) 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

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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 (24 ± 22 U/L vs. 14 ± 10 U/L, P = 0.003). 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

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Background: We compared the safety and virologic efficacy of dolutegravir (DTG) + etravirine-based regimens (TAF) vs. DTG + FTC/tenofovir alafenamide fumarate (TAF) vs. DTG + FTC/tenofovir disoproxil fumarate (TDF) vs. efavirenz (EFV)/FTC/TDF in pregnant women. Methods: 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 gestational age (GA). Up to 14 days’ pre-entry antiretroviral treatment (ART) was permitted. In primary efficacy analysis, we compared the combined DTG-containing arms to the EFV arm for non-inferiority (-10% margin), then superiority, with regard to delivery HIV RNA <200 copies/mL. Safety outcomes compared between all arms were a) composite adverse pregnancy outcome
(preterm delivery [PTD] <17 weeks, small for GA [SGA] <10th centile, stillbirth [SB]; or spontaneous abortion [SAB]); b) maternal grade ≥3 adverse event (AE) through 14 days postpartum; and c) infant grade ≥3 AE through 28 days. Neonatal death (ND; <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 609 (94.9%) women, was <200 cp/mL in 395 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 (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:** IMPACT 2010 maternal virologic efficacy outcomes and pregnancy and maternal infant safety outcomes

<table>
<thead>
<tr>
<th>Delivery EG1</th>
<th>EG2</th>
<th>EG3</th>
<th>95% CI</th>
<th>p-value</th>
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<tr>
<td>CETF LV&gt; 1000</td>
<td>CETF LV&lt; 1000</td>
<td>CETF LV&lt; 50</td>
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<td></td>
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<tr>
<td>DTG+ FTC/TAF</td>
<td>DTG+ FTC/TDF</td>
<td>DTG+ FTC/TAF</td>
<td>CETF LV&lt; 50</td>
<td></td>
</tr>
<tr>
<td>355/405 (87.5%)</td>
<td>182/200 (91.0%)</td>
<td>170/172 (98.3%)</td>
<td>0.053</td>
<td></td>
</tr>
<tr>
<td>30/355 (8.5%)</td>
<td>18/200 (9.0%)</td>
<td>18/172 (10.5%)</td>
<td>0.307</td>
<td></td>
</tr>
</tbody>
</table>

**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, 32.4% and 44.5% 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.
A RANDOMIZED TRIAL OF POINT-OF-CARE EARLY INFANT HIV DIAGNOSIS IN ZAMBIA

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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. 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 23-38) 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 (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, adverse outcomes are high among HIV-infected infants. 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

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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; or, 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 in the intervention, 84% (95%CI 80-89) were treated for PMTCT. Most mothers (94%) reported ART for PMTCT. 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 in the intervention, 84% (95%CI 80-89) were treated for PMTCT.
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 VIRAL RESERVOIR IN VERY EARLY TREATED INFANTS

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1National Institute for Communicable Diseases, Johannesburg, South Africa, 2Empilweni Service and Research Unit, Johannesburg, South Africa, 3Columbia University Medical Center, New York, NY, USA, 4University 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. Viable- 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/9.3x105 cells. Multivariable Generalized Estimating Equation (GEE) regression models were used for statistical analysis.

Results: Thirty-nine (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 delivery). 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 correlation =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 DNA log copies (and % with <10 copies) were 1.83 (17.7%), 2.38 (10.8%), 2.83 (10.0) and 3.15 (0%), respectively. In multivariable analysis, starting ART <48 hours after birth (p=0.03), having been born to a mother who did not receive ART during pregnancy (p<0.0001), and pre-treatment infant CD4+ T-cell percentage >30 (p<0.0001) predicted lower HIV-1 DNA log copies in the first year post-treatment (Table).

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

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

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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 groups were made using chi-square, log rank test, Mann- Whitney U test.

Results: From March 2006 to September 2008, 300 Thai and Cambodian children were enrolled, with a median age of 6-4 (IQR 3-9)-4 years, and median baseline CD4 of 19% (IQR 16-20). 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 age of 12.9 (10.4-15.4) years. The median age at last visit was 16.7 years (IQR 13-18). 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 > 50 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 long lasting poorer CD4 recovery and higher virological failure mandates prompt diagnosis and ART initiation in children.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=230)</th>
<th>Early (N=117)</th>
<th>Deferred (N=113)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.3 (6.4-10.1)</td>
<td>8.2 (6.6-10.1)</td>
<td>8.4 (7.0-11.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>CD4% at enrolment</td>
<td>64.3 (56.3-73.9)</td>
<td>64.3 (56.3-73.9)</td>
<td>64.3 (56.3-73.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>CD4 at ART initiation (cells/mm3)</td>
<td>7.4 (6.4-9.2)</td>
<td>7.4 (6.4-9.2)</td>
<td>7.4 (6.4-9.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>At last visit</td>
<td>4.4 (2.0-6.8)</td>
<td>4.4 (2.0-6.8)</td>
<td>4.4 (2.0-6.8)</td>
<td>0.90</td>
</tr>
<tr>
<td>CD4 at ART start</td>
<td>5.0 (3.0-7.0)</td>
<td>5.0 (3.0-7.0)</td>
<td>5.0 (3.0-7.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm3)</td>
<td>720 (598-925)</td>
<td>720 (598-925)</td>
<td>720 (598-925)</td>
<td>0.0002</td>
</tr>
<tr>
<td>HIV RNA (copies/ml)</td>
<td>1695 (95-589)</td>
<td>1695 (95-589)</td>
<td>1695 (95-589)</td>
<td>0.0002</td>
</tr>
<tr>
<td>10 year probability of virologic failure</td>
<td>27.9 (21.3-34.7)</td>
<td>27.9 (21.3-34.7)</td>
<td>27.9 (21.3-34.7)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

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

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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 2,219 persons screened, 1,499 were enrolled. 4,958 pyo were accrued, and 1,249 (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 pyo 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 Potential regression for efficacy endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TS (N=748)</th>
<th>CQ (N=748)</th>
<th>No prophylaxis (N=748)</th>
<th>Rate ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS Stage 0</td>
<td>54 (7.3)</td>
<td>40 (5.4)</td>
<td>52 (6.9)</td>
<td>1.0 (0.7-1.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>TS Stage 1</td>
<td>44 (6.6)</td>
<td>37 (5.0)</td>
<td>47 (6.3)</td>
<td>1.0 (0.7-1.4)</td>
<td>0.97</td>
</tr>
<tr>
<td>TS Stage 2</td>
<td>9 (1.3)</td>
<td>7 (0.9)</td>
<td>8 (1.1)</td>
<td>1.0 (0.6-1.6)</td>
<td>0.91</td>
</tr>
<tr>
<td>TS Stage 3</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
<td>1.0 (0.6-1.6)</td>
<td>0.91</td>
</tr>
<tr>
<td>TS Stage 4</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>1.0 (0.6-1.6)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

### 138 ISONIAZID TO PREVENT MTB INFECTION IN HIV-EXPOSED UNINFECTED INFANTS

**Sylvia LaCourse**, 1 Barbra A. Richardson, 2 Lisa M. Cranmer, 2 Elizabeth Maleche Obimbo, 1 Daniel Matemo, 1 Alex J. Wan, 1 Jaclyn Escudero, 1 John Kinuthia, 1 Thomas Hawn 1, Grace John-Stewart 1, 1University of Washington, Seattle, WA, USA, 2Emory University, Atlanta, GA, USA, 3University of Nairobi, Nairobi, Kenya, 4Kenyatta National Hospital, Nairobi, Kenya, 5Boyler College of Medicine, Houston, TX, USA

**Background:** HIV-exposed uninfected infants (HEU) in TB endemic settings are at high risk of *Mycobacterium tuberculosis* (Mtb) infection and TB disease, even in the absence of known Mtb exposure. For infants, progression from primary infection to TB disease can be rapid; whether isoniazid (INH) prevents primary Mtb infection in HEU is unknown.

**Methods:** We conducted a non-blinded RCT comparing 12 months daily INH (10 mg/kg) vs. no INH to prevent Mtb infection among HEU infants enrolled at 15 clinics in Malawi (48 clinics initially). From 10/2015-4/2016, ACTG and IMPAACT networks conducted AS30012930, 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). HHCs<15 years have previously been reported. Logistic regression using generalized estimating equations was used for testing.

**Results:** 2015 unscreened at 16 sites in 8 countries had 712 HHCs≥15 years of age. 36% of ICs were HIV-infected and 10% had unknown HIV status. 58 (9%) HHCs age≥15 years were HIV-infected and 436 (64%) female (16 pregnant). 686 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 HHCs with determine IGRA results, 471 (69%, 95% confidence interval: 65-73%) were positive; prevalence varied with age: 59% in IC ≥15, 76% in IC 25-<50, and 66% in IC ≥50 (p<0.001). Cavitary on CXR, 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 (83% vs 69%, p=0.039), spent more nights/week with the IC (61%, 68%, 70% for 0-2, 3-7, 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 2/3rd of HHCs age≥15 in HHs of adult MDR-TB patients had evidence of TB infection, confirming the importance of household contact investigation. HHs with poorer 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.
DIAGNOSTIC AND THERAPEUTIC CHALLENGES ARISING WITH EARLY HIV INFECTION ON PrEP

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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 infection (EDI) 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%) were found to have HIV on the day of PrEP initiation. The 6 reporting active PrEP at diagnosis had lower initial log plasma HIV RNA (2.8 vs 5.3, p=0.001) and higher CD4 (768 vs 488, p=0.03) than the 52 not on PrEP. The remaining analyses focus on those on active PrEP and those positive at PrEP initiation (n=11, Table). HIV Ab screening was positive in 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 be genotypic resistance testing, three had M184V/I mutations, with two transmitted and one emerging after 5 days on PrEP.

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 characterization of infections during PrEP is needed.

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

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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 at 3 months that would be returned with interest $5.50 upon retesting at 3 and 6 months respectively (total $11) 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. Both groups 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.
142 COMMUNITY-BASED HIV TESTING IN URBAN KENYA: A STRATEGY TO REACH MEN AND YOUTH
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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 HIV testing in rural 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 or older, 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 unaware of their HIV-positive status and achieved testing saturation. Community-based hybrid testing 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 reluctant 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.

144LB RIFAPENTINE PHARMACOKINETICS AND SAFETY IN PREGNANT WOMEN WITH AND WITHOUT HIV ON 3HP
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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 p3HP/3HP and 6H arms were followed for 24 and 12months, 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 pill 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 [0.5%] <18 years), all were on ART, 70% were female, 38% were QuantiFERON-TB GOLD Plus positive, 63%, 22% 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. 0.6% (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: TB and mortality incidence by study arm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time period (Months)</th>
<th>HIV events/100pyR</th>
<th>HIV mortality/100pyR</th>
<th>RR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB incidence</td>
<td>0-12</td>
<td>35/8038</td>
<td>0/26</td>
<td>1.00 (0.38-2.55)</td>
<td>0.91</td>
</tr>
<tr>
<td>TB incidence</td>
<td>0-24</td>
<td>57/3141</td>
<td>3/36</td>
<td>0.55 (0.01-1.49)</td>
<td>0.83</td>
</tr>
<tr>
<td>TB incidence</td>
<td>12-24</td>
<td>14/363</td>
<td>0/15</td>
<td>1.01 (0.45-2.12)</td>
<td>0.96</td>
</tr>
<tr>
<td>TB incidence, among counterfactual-positive</td>
<td>0-24</td>
<td>10/149</td>
<td>2/3</td>
<td>0.99 (0.32-1.84)</td>
<td>0.98</td>
</tr>
<tr>
<td>Rifapentine-resistant TB incidence</td>
<td>0-24</td>
<td>4/1304</td>
<td>0/10</td>
<td>1.00 (0.21-4.91)</td>
<td>0.95</td>
</tr>
<tr>
<td>Mortality incidence</td>
<td>0-24</td>
<td>29/338</td>
<td>0/10</td>
<td>1.55 (0.87-2.76)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Comparison of TB and mortality incidence by study arm.
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 (NCT02651259). 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 900mg 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 30 pregnant women, 25 per cohort. Twenty women had HIV, all were taking efavirenz (EFV)-based antiretroviral therapy (median CD4: 510 cells/mm<sup>3</sup>). 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*h/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/h), which was 34% higher (p<0.001) compared to pregnant women without HIV, resulting in a lower AUC of 512 mg*h/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

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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. Bivariable 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.
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 ≥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 (-9%), 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.

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**EXPLOSIVE HIV AND HCV EPIDEMICS DRIVEN BY NETWORK VIREMIA AMONG PWID**

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**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 Africa/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, 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.

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**THE AGING OF HIV-1 INCIDENCE IN HYPERENDEMIC RURAL SOUTH AFRICA**

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**Background:** The burden of HIV in sub-Saharan Africa has aged substantially over the last decade, yet little is known about age-specific shifts in HIV incidence.

**Methods:** Between 2004 and 2017, data were collected from individuals enrolled in the Africa Health Research Institute’s population-based HIV cohort in rural South Africa. A population-based cohort study was conducted to quantify changes in age-specific incidence among men 15-54 and women 15-49. Population generalized additive models were used to test changes in the age-distribution of HIV incidence and explore potential drivers.

**Results:** We observed 3,144 HIV seroconversions among 20,388 HIV negative individuals contributing 87,882 person-years of observation from 2004-2017 (incidence rate of 3.5 per 100 person-years). The age-distribution of HIV incidence shifted older in both men (p=0.021) and women (p<0.001). Age of peak incidence increased by four years among men, from 27 (95% CI, 25-33) to 31 (95% CI, 28-34); and by three years among women, from 22 (95% CI, 21-23) to 25 (95% CI, 23-31). Incidence declined by 50% among men 15-19, IRR = 0.53 (0.33-0.82). Age-specific incidence relative to 15-19 year-olds doubled among
men 30–34 years, IR=2.30, 95% CI, 1.24 - 4.26; and increased by 50% among women 30–34 years, IR=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 hyperendemic 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.

Results: During 27,517 person-years at risk, 195 of 18,597 residents (females=54.9%;males=45.1%) from the selected sample became HIV-infected (adjIRR=0.71/100py). Of the 195 seroconversions, 153 (78.5%) were in females and 42 (21.5%) in males; females had a higher IR (1.01) compared to males (0.35). The highest IR was observed among females aged 16-24 years (1.87) with IRs ranging from 0.65 to 5.73 (median=1.74) across 15 communities. Females aged 25-34 years were observed with an IR of 1.24. Among males, the highest IR was in the 25-34 year age group (0.56). The lowest IRs were observed in the older age group (35–64) in both females and males (0.41 and 0.20, respectively). Gender and age were both significantly associated with the HIV incidence (both p<0.0001). The hazard of incident infection was highest among females aged 16-24 (HR=7.05, 95%CI:3.83,14.68).

Conclusion: Despite demonstrating an overall reduction in HIV incidence and surpassing the UNAIDS 90–90–90 targets in a community-randomized control trial, high HIV incidence was observed in adolescent girls and young women in the intervention communities. These findings highlight the current urgency for additional prevention services, e.g. PrEP, to achieve epidemic control in this population.

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

Gertrude Nakigozi1, Larry W. Chang2, Steven J. Reynolds2, Fred Nalugoda1, Godfrey Kigozi1, Thomas C. Quinn1, Ronald H. Gray3, Alice Kiskay4, Anthony Nyamakabo, Robert Ssekubugyo2, David Serwadda1, Maria Wawer1, Joseph Kagaayi1, Mary K. Grabowski5, for the Rakai Health Sciences Program1 Rakai Health Sciences Program, Kalisizo, Uganda, Johns Hopkins University School of Medicine, Baltimore, MD, USA, UNAIDS, Boston, MA, USA, Johns 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 serocorversion, self-reported male circumcision, and self-reported ART use were assessed using data collected from 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%CI: 0.41-0.98) and by 59% since the period prior to VMMC and ART availability (adjIRR=0.41; 95%CI: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 in 2018.

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.

151 INCREASED OVERALL LIFE EXPECTANCY BUT NOT COMORBIDITY-FREE YEARS FOR PEOPLE WITH HIV

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Background: Combination antiretroviral therapy (ART) has dramatically improved life expectancy for people with HIV (PWH), but recent data comparing overall lifespan and comorbidity-free years by HIV status are lacking.

149 HIGH HIV INCIDENCE IN YOUNG WOMEN IN THE BOTSWANA COMBINATION PREVENTION PROJECT

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Background: The Botswana Combination Prevention Project (BCPP) demonstrated a 30% reduction in community HIV incidence through expanded HIV testing, enhanced linkage to care, and universal antiretroviral treatment and exceeded the UNAIDS 90–90–90 targets. In this analysis we report rates and characteristics of incident HIV infections occurring during the trial, using data from repeat HIV testing performed over time in the intervention arm.

Methods: BCPP was a community-randomized control trial in 30 rural/peri-urban Botswana communities. Community-wide home-based and mobile HIV test campaigns were conducted in 15 intervention communities from 2013–2017. Although campaigns did not specifically aim to re-test the same individuals, 30% of residents received HIV testing at least twice. We assessed the HIV incidence rate (IR) among these repeat testers. The IR was estimated as the number of new HIV infections occurring per 100 person-years (py) at risk (time to last HIV-negative test or midpoint between last HIV-negative test and first HIV-positive status). HIV infection risk factors were evaluated with right-censored Cox proportional hazards models.

Results: During 27,517 person-years at risk, 195 of 18,597 residents (females=54.9%;males=45.1%) from the selected sample became HIV-infected (IR=0.71/100py). Of the 195 seroconversions, 153 (78.5%) were in females and 42 (21.5%) in males; females had a higher IR (1.01) compared to males (0.35). The highest IR was observed among females aged 16-24 years (1.87) with IRs ranging from 0.65 to 5.73 (median=1.74) across 15 communities. Females aged 25-34 years were observed with an IR of 1.24. Among males, the highest IR was in the 25-34 year age group (0.56). The lowest IRs were observed in the older age group (35–64) in both females and males (0.41 and 0.20, respectively). Gender and age were both significantly associated with the HIV incidence (both p<0.0001). The hazard of incident infection was highest among females aged 16-24 (HR=7.05, 95%CI:3.83,14.68).

Conclusion: Despite demonstrating an overall reduction in HIV incidence and surpassing the UNAIDS 90–90–90 targets in a community-randomized control trial, high HIV incidence was observed in adolescent girls and young women in the intervention communities. These findings highlight the current urgency for additional prevention services, e.g. PrEP, to achieve epidemic control in this population.
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 1:3 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 unaffected 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 unaffected 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 unaffected 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 unaffected adults, respectively, with PWH being diagnosed with comorbidities 15.1 years (13.7-16.4) earlier than unaffected 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 unaffected 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 unaffected adults. However, PWH have 16 fewer healthy years than unaffected 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
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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 (HLV, ≥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 HLV 50-199 c/mL, 258 (4%) had LLV 200-999 c/mL, and 2,182 (31%) had HLV. 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 cART 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
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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 haptens, 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 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 TRANSCRIPTIONAL 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 IL10, 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 viremic 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 TFH survival, downregulation 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 SV provirus. The NHL pre-clinical data confirmed the safety of this intervention which could be targeted for HIV Cure in humans.

Dissecting the Drivers of Chronic Inflammation

Kyrstinelle 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.

Defining Treatable Pathways in Inflammaging: 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 the are not completely normalised 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 but viruses should 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.

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.

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.

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.

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 inter-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 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 (CDA), 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 recrudescence 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 CDA 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 in some cases, may not even have started to increase. Therefore, 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 and 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 HIV 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 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 DAAs, 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 Andreix-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 end 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

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**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 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 CA-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

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**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-NFGR or the GFP reporter protein, a PKG promoter driven reporter cassette was cloned into the envelope frame of HIV molecular clone pLA2. In addition, for the assessment LTR-dependent expression, reporters HSA-mCherry were cloned upstream of an internal ribosomal site followed by nef. VS-NFGR and HSA, in contrast to GFP 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 five 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.
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. Spreading infections were conducted in MT-4 T cells to determine replication competence and to select for adaptive mutations.

**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.

**168 EXPLORING THE REQUIREMENTS FOR HIV-1 GENOME PACKAGING THROUGH A NONVIRAL RNA BINDING**

**Alice Duchon,** Steven Santos, Jianbo Chen, Vinay K. Pathak, Wei-Shau Hu

**Background:** HIV-1 efficiently selects and packages its RNA genome into assembling virus particles at the plasma membrane. The main viral structural component, Gag, orchestrates the complex interactions that occur during this stage. In the cytoplasm, Gag shows only a slight preference for binding HIV-1 RNA over cellular mRNA. Therefore, we hypothesized that in addition to RNA binding, Gag must use other mechanisms to ensure selective HIV-1 RNA genome packaging. To better define the mechanism of HIV-1 RNA packaging specificity, we designed an experimental system to study Gag:RNA interactions.

**Methods:** To separate the specific and nonspecific Gag:RNA interactions, we created morphologically normal, empty, virus-like particles by replacing the NC domain of Gag with a leucine zipper (LZ). To package RNA, we fused a bacterial RNA binding protein, BglG, to an internally mCherry-labeled GagLZ (GagLZ-Bgl). BglG specifically binds to a stem loop RNA structure, BSL. Gag-expressing constructs contained two sets of stems-loops: BSL and sequences recognized by bacterial phage PP7 coat protein. Viral RNA was detected by coexpressed YFP fused to PP7 coat protein (PP7-YFP). To examine whether GagLZ, GagLZ-CFP fusion protein, and GagLZiC-Bgl proteins coassemble to generate viral particles with RNA, the constructs were cotransfected with PP7-YFP into human 293T cells. Harvested viral particles were imaged using fluorescence microscopy.

**Results:** Most particles were CFP+ and iC+. Thus, these Gag proteins coassembled into the same virus. Additionally, ~40% of the particles were also YFP+, indicating they contained viral RNA. To determine trans-acting requirements for RNA packaging, we created a series of GagLZiC-Bgl truncation mutants. RNA was efficiently packaged by mutants lacking the LZ motif or p0 domain. However, RNA packaging was significantly reduced when regions important for Gag oligomerization were deleted or when GagLZiC-Bgl myristylation was inhibited by a G1A mutation. These results reveal the importance of the Gag:RNA and Gag:Gag interactions at the plasma membrane for genome packaging. All mutant Gag constructs coassembled with GagLZ-CFP.

**Conclusion:** Overall, we developed an experimental assay to identify properties of Gag required for RNA packaging during HIV-1 assembly. In an NC-independent system as well as in the presence of NC, the multimerization of RNA-bound Gag is needed for efficient RNA packaging.

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


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**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 differentially 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:** Our study facilitates HIV-1 replication in both primary human 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 a 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.
117 B CELLS DIRECT R5-TROPIC HIV INFECTION OF CCR5-NAIVE CD4+ T CELLS
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Background: Naïve 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 R5-tropic HIV in vitro because there is negligible expression of CCR5 on the cell surface. Paradoxically, R5-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 R5-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 R5-tropic HIVBaL and cultured with TN in total CD4 + T cells at a 1:10 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 PHA/PMA. 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 PHA/PMA 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 R5-tropic HIVBaL. No HIV DNA was detected in CD4 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
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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 (TFR) limit TFH numbers and function in vitro and in vivo. We hypothesized that TFR inhibit HIV-1 replication in TFH.

Methods: TFH (CD3+CD4+CXCR5+CD25-)-mediated inhibition of HIV-1 infected target cell (TgF-β) TFR (control) for 5 days in Advanced R:10 media and 10 IU/ml IL-2. Percent GFP+ p24+ were determined by flow cytometry. Live p24+ and TgF-β TFR were sorted 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-β, 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, TFR 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-β, CD39, and IL-10 did not reverse TFR 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 TFR co-cultures with 10 IU/ml and 30 IU/ml IL-2, whereas no inhibition was detected in TFR 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 TFR 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 12.1 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. TFR reduced HIV-1 producing TFH at low, but not high or absent concentrations of IL-2. Consumption of IL-2 in B cell follicles may be one mechanism by which TFR reduce HIV-expressing TFH in vivo.
stimulation. Increased transcription of BIRC3 may contribute to increased HIV production in these cells.

174  THE ARYL HYDROCARBON RECEPTOR NEGATIVELY REGULATES HIV REPLICATION IN TH17/TH22 CELLS

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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/CCR6+CCR6- memory CD4+ T-cells were isolated by magnetic/flow cytometry sorting. Cells of uninfected 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 beta2 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-VSVG 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 AhR agonists/antagonists for HIV remission/cure strategies.

175  ANTI-HIV ACTIVITIES OF THE 12 INTERFERON-ALPHA SUBTYPES

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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 differentially 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 potentely 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 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

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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 HIV-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 crucially disarm A3F.

Conclusion: Loop 1 of human A3C restriction factor was identified as a novel protein domain that binds DNA and thereby drastically gains in antiviral activity against HIV-1.

177LB  IFITM3 REDUCES RETROVIRAL ENV FUNCTION AND IS COUNTERACTED BY GLYCOGAG

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Background: The interferon-induced transmembrane (IFITM) proteins are known for inhibiting the entry of a wide array of viruses into host cells. Furthermore, when IFITM3 is present in virus-producing cells, it reduces the fusion potential of HIV-1 virions, 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 proteins 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.
178 SEQUENCE CHANGES CAUSING REV ACTIVITY DIFFERENCES IN HIV-1 PRIMARY ISOLATES

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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 (N-OD) was sufficient to determine functional activity. Such 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 (9-G Q24R mutant had 9-G Rev (p=0.55), and vice versa. A single variation at position 24 was tested (9-G Q24R mutant had 9-G Rev (p=0.55), and vice versa. A single variation at position 24 was tested (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.

179 COMPLEMENTATION MAINTAINS QUASISPECIES OF DRUG-SENSITIVE AND -RESISTANT HIV WITH ART

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Background: HIV exists as multiple genotypes in a single infected individual, referred to as a quasispecies. How such sequence heterogeneity can be maintained in the same infection environment remains unclear.

Methods: We reproduced a quasispecies in vitro by using the antiretroviral drug efavirenz (EFV) as the selective pressure. The cell culture infection was performed over 18 days, with fresh uninfected cells and EFV replenished every two days. We determined the frequency of drug resistance mutations to EFV using deep sequencing both at the population and single-cell level. For single cell sequencing of HIV DNA we sorted the infected cells into wells of a multi-well plate at 1 cell per well, then lysed the cells to extract DNA and amplified the reverse transcription region.

Results: We observed that while the frequency of genotypically EFV resistant virus increased with time, it never completely supplanted the drug sensitive genotype. Instead, the drug sensitive HIV genotype stabilized at approximately 20 percent of the total population. Single-cell sequencing of viral genotypes showed that the fraction of drug resistant virus in the population increased when most of the cells were infected with drug sensitive HIV but plateaued when cells were co-infected with drug sensitive and drug resistant genotypes. This suggested that in co-infected cells, drug sensitive virus may package drug resistant reverse transcriptase and become phenotypically resistant to the drug, known as phenotypic mixing or complementation. To verify that complementation can result in phenotypic drug resistance of HIV with drug sensitive HIV, we transfected cells with CFP labelled wildtype and YFP labelled EFV resistant mutant HIV molecular viral clones, or co-transfected both. HIV from singly transfected cells followed the expected resistance pattern. However, virus from co-transfected cells was similarly resistant to EFV regardless of whether its genotype was drug sensitive or resistant.

Conclusion: These results indicate that complementation occurring between drug sensitive and drug resistant HIV is one mechanism which can drive and maintain an HIV quasispecies and account for the presence of drug sensitive virus in the face of ART.

180 DISRUPTION OF A RNA SECONDARY STRUCTURE IN HIV-1 gp41 INDUCES VIRAL LETHALITY

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Background: Synonymous genome recoding has been widely used to study different aspects of virus biology. Previous studies have demonstrated HIV-1 attenuation by reduction in protein expression after synonymous recoding. We aim here to explore the impact of synonymous codon usage on HIV-1 Env expression and virus replication capacity.

Methods: The codons AGG, GAG, CCT, ACT, and CGG of HIV-1 env gene were synonymously changed to GCT, GAA, CCG, ACC, TTA, and GGA, respectively. Different recoded envs were generated. Viral replication and viability was measured after transfection in MT-4 cells by quantifying HIV-1 p24 antigen production. Replication capacity assays were performed in MT-4 cells and PBMCs. WT, recoded env genes and HIV-1 rev were cloned in an expression vector (pCONA3.1). Env expression plasmids were cotransfected with Rev expression plasmid in 293T cells. Immunoblot analyses and qPCR were performed to quantify protein expression and Env mRNA production. RNA secondary structures were obtained using Vienna RNA package.

Results: A recoded env variant containing 39 mutations was lethal for the virus. WB analysis of Env expression revealed that protein expression of the recoded variant was highly reduced. To further study the mutations responsible for this phenotype, new mutants were designed by reverting substitutions to WT or reducing the number of newly generated CpG dinucleotides. Most of the new virus variants were viable, although they showed different replication capacities. Interestingly, one variant that only reverted two nucleotides that belong to the same codon showed indistinguishable replication capacity when compared to WT. Moreover, after transfection, other virus variants generated...
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**
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**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 pMk-K7-Luc-IRESS-NeFDPg120 to obtain chimeric samples. 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 the TF viral strains and its evolutionary dynamics.

**Results:** 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.

**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.

**182 NEW HIV-1 CAPSID LABELING SYSTEM DOES NOT SUPPORT UNCOATING DURING NUCLEAR IMPORT**
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**Background:** HIV-1 uncoating (capsid core disassembly) is a prerequisite for viral DNA integration into the host genome and a promising target for antiviral therapy. However, the timing and cellular location of uncoating remain elusive, in part because current methods are unable to directly and accurately measure the amount of capsid protein (CA) loss from the infectious viral complexes. Bulk measurement of CA loss by biochemical methods or imaging of viral complexes may not reflect the behavior of infectious viral complexes, since only a small fraction of the viral complexes in the cell lead to infection. Quantification of CA by immunostaining with anti-CA antibody or live-cell imaging of viral complexes labeled with fluorescently-tagged cyclophilin A (CyPA) is confounded by loss of epitope accessibility to the antibody or loss of interactions to CyPA.

**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 T cells, characterized GFP-CA 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.

**183 THE HIV ANTISENSE PROTEIN ASP IS A TRANSMEMBRANE PROTEIN OF THE VIRAL ENVELOPE**
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**Background:** The negative strand of the HIV-1 genome encodes a highly hydrophobic antisense protein (ASP) with no known homologs. 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 Millpore 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-knockout 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

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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 cell responses 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 utilized 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 single-cell 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 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 environmental changes. In healthy uninfected individuals, variations in 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.

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/melanotin and markers of mucosal barrier impairment (FABP2, LBP) were measured by ELISA. PBMC were frozen. HIV DNA/RNA were quantified by PCR 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 β7, 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

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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: High-throughput single-molecule sequencing to characterize ab-resistant HIV/SHIV

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Background: Although HIV-specific broadly-neutralizing antibodies (bNAbs) can suppress viremia in ART-naïve 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

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/melanotin and markers of mucosal barrier impairment (FABP2, LBP) were measured by ELISA. PBMC were frozen. HIV DNA/RNA were quantified by PCR 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 β7, 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.
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 VRC07-523LS. We observed pronounced changes in env sequences after VRC07-523LS 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 UMNI-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.

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

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**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 v.2.1.11) 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-naïve. 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] log HIV-RNA (copies/ml) in BM (4.85 [4.06-4.97]) and in PB (4.84 [3.69-4.97]) were not statistically different (p = 0.25). The HIV populations had a low diversity (median APD of 1.29% in BM vs 0.94% in PB).

The APD was statistically different between BM and PB from participant 3 (1.78% in BM vs 2.65% in PB, p = 0.0005). Participant 3 had two viral populations with genetic distance of 22.44%, compartmentalized virus in BM (Fig.1), and CXCR4-tropic virus present at 0.34% in BM and 7.27% in PB. CXCR4-tropic virus was also found in PB from participant 1 (6.59%). Neither participant 1 nor 2 had compartmentalized virus in BM.

**Conclusion:** We demonstrate viral compartmentalization and the presence of CXCR4-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.
**Background:** Beside hemostasis, platelets exert several immune functions and interact with infectious pathogens including HIV. We investigated whether platelets from cART-treated patients contain infectious HIV in vivo and addressed the significance and clinical implications of HIV shielding by platelets in AIDS.

**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 αIIb/β3 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 (<350 cells/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 virally suppressed patients sheltering HIV in platelets are immunological nonresponders and fail to restore a proper immune status over >1 year of cART.

**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 correlation with immunological failure, thus opening new treatment strategies for immunological nonresponders, 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 el at., Nat Microbiol, 2019) in a process inhibited by the therapeutic anti-platelet agents.

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**Methods:** DRAGA (HLA-DR4 HLA-A2, Rag1KO, IL2RgKO, NOD) mice (n=17) were infected 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, Ki67, FDC, and mouse FDC and analyzed by microscopy. HIV RNA was detected by RNAscope, %CD4 and %FDC by quantitative image analysis, plasma viral load by 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 contact 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 extracapillary regions (median, 128 vs 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 permissivity) and HIV RNA+ particles are associated with mouse FDC (likely bound via human antibody). Thus, the DRAGA 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.

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**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/10⁹ 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

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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 gene. Phylogenetic analysis was used to identify and characterize SI events.

Results: Sequence data was obtained for 18 of the 22 recipients and 12 of the 14 matched donors (median amplicons analyzed: recipient gp41=5482, pol=74369; donor gp41=89304, pol=51715). 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 gp41 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: gp41=128415, pol=47452). Phylogenetic analysis used to identify and characterize SI events.

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 concern in well-monitored ART post-transplant.

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

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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 HIV 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 AT, pol subtype C). In the other case, the subtype C strain present at seroconversion was replaced with a different 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

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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.
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, \( P < 5 \times 10^{-8} \)) for hsCRP: 3 SNPs within 2 gene loci (coagulation factors F3 and F5) reached GWAS for D-dimer; and 27 SNPs within 1 locus (IL6R) reached GWAS for IL-6. (Fig. a,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.

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

196  **ABNORMAL IMMUNOMETABOLISM AND GENE ACCESSIBILITY IN ALVEOLAR MACROPHAGES IN HIV**

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**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, were associated with these observed immune defects in alveolar macrophages of people with HIV.

**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 (MITF4), 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 diseases seen among people with HIV.

197  **IMPACT OF EARLY ART ON CD8 T CELLS IN MESENTERIC LYMPH NODES DURING SIV INFECTION**

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**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 using Ddimer and CRP.

**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 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+ 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 of CCR6+ but not CCR5+ 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 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**

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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. Virolologic, immunologic, transcriptomic, metabolic and microbiota (16s sequencing) analyses were performed. SIV RNA loads in plasma and tissue samples were determined by RTPCR and RNAscope. 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 CD101+. In contrast, SIV+ cells were dispersed in lamina propria. Transcriptomic analysis revealed enhanced immune networks supporting anti-viral immunity. Increased prevalence of Lactobacillus and enhanced Linoelic acid metabolism was detected.

Conclusion: Collectively, our data support the hypothesis that MSCs enhance the virus-specific cellular and humoral immune responses by corralling SIV+ cells to the lymphoid follicles and improving antigen presentation and activating immune cell networks. Thus, MSC can be used for reviving or tolering mucosal immunity in HIV infection for viral clearance.

199 IDENTIFYING CENTRAL COMPONENTS OF THE HIV-1+ PREGNANCY IMMUNE NETWORK

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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 IFNg, IL-2, IL-10 and granzyme 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 CD69bright 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

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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 SHIV15175pd394-infected (>14 weeks PI) rhesus macaques (RM) and their association with plasma viral RNA levels. Flow cytometry was used for phenotypic analysis, function (IFN-g, 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-g, 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, granyme-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.

201L THE ROLE OF CD101 IN HIV/SIV PATHOGENESIS AND MAINTENANCE OF THE VIRAL RESERVOIR

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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. At 14 d.p.i. CD101+ CD4+ T cells were preferentially depleted, as compared to other CD4+ memory subsets (p<0.0001). 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+ CD4+ T cells were “terminally differentiated”. Using LARLA, 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 transcriptomic profile, p24 gag expression within CD101+ CD4+ T cells was significantly lower at 7 d.p.i., 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 BLTS-HUMANIZED MICE
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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 by 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 (CD3+ and CD5+ T cells), NK cells, and antibody-secreting B cells in hBLTs mice, along with the formation of B cell follicles within lymphatic tissues. We were also 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 results in widespread and mobilization of DCs to tissues. Mice may be treated with pDC-depleting Ab or an Ab that blocks IFN-I signalling prior to HIV exposure. Levels of DCs and infected (p24+) CD4+ T cells were analyzed by flow cytometry (FC). Splenocytes from Flt3L-treated or untreated mice were co-cultured with HIV-infected T cells or treated with TLR7/8 agonist R848 and pDCs expressing IFNα were enumerated by FC.

Results: HIV infection led to systemic depletion of pDCs, but not conventional DCs, in various lymphoid organs of h-NSG and hu-BLT mice. Flt3L treatment led to widespread expansion and mobilization of DCs to multiple tissues but had no discernable effects on levels of T cells or monocytes. Upon viral challenge, Flt3L-treated mice consistently displayed a meaningfully delayed infection and markedly reduced viremia compared to untreated mice. Levels of infected CD4+ T cells were globally reduced in the treated group. Ab-mediated depletion of pDCs abolished the protective effect by Flt3L, demonstrating that the Flt3L-mediated control of HIV was pDC-dependent. Functionally, pDCs from Flt3L-treated mice were more responsive to TLR7 stimulation, leading to a higher frequency of pDCs expressing IFNα relative to those from untreated animals. Lastly, the protective effect of Flt3L treatment was mediated through an enhanced IFN-I response as blocking IFN-I signalling early in Flt3L-treated animals restored viremia to the level of untreated mice.

Conclusion: Maintaining pDC levels and functions is key to early viral control and in this context, our findings provide a practical insight for novel anti-HIV strategies and vaccine design.

204 EFFECTS OF CMV ON HIV DNA DIVERSITY IN PERIPHERAL BLOOD CELLS DURING EARLY ART
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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 (<50cp/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
205 GUT MICROBIOTA FACILITATES HIV ACQUISITION IN THE GUT

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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. Germ-free BLT mice were housed in a gnotobiotic Trexler isolator. 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

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Background: Despite early ART initiation, ART-suppressed people living with HIV (PLWH) may have cellular effects other than autophagy that could affect HIV infection. Here, we examined trehalase, a naturally occurring glucose mTOR-dependent 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 RNAi 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 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 distal 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/mm (n=55). Median duration of viral suppression was 8 years (IQR 5-11 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 # male sexual 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 MACРОPHAGES BY 2 DISTINCT MECHANISMS

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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 trehalase, 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 trehalase 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 RNAi 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
208 FECAL MICROVESICLES UNIQUELY INFLUENCE TRANSLATING BACTERIA AFTER SIV INFECTION

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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, liver, and spleens obtained from end-stage, SIV-infected RM, cultured under aerobic and anaerobic conditions, and identified by MALDI-TOF and 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 defense 1, beta defense (βDEF1), βDEF2, βDEF4, Lysosome 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 100 differently expressed miRNAs displayed upregulated expression, with miR-425 and -484 showing significant upregulation in MVs derived from SIV-infected RM. Among AMPs, βDEF1 showed a significant downregulation among MVs from SIV-infected RMs. 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.

Conclusion: Fecal MVs can differentially influence the growth of bacterial isolates known to translocate in SIV infection. This effect may be attributable to a shift in MV miRNA content and/or to a shift in AMP content. The identification 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.

209 CHARACTERISATION OF POTENTIAL HIV TARGET MYELOID CELLS IN FORESKIN EPITHELIUM

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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 them to HIV in ex-vivo challenge assays.

Methods: Foreskin cells were allowed to migrate out of isolated epithelial tissue from adult South African men undergoing VMMC. Briefly, epithelial sheets were obtained after dispase digestion of foreskin tissue. Cells were collected after 48-hour incubation and remnant tissue resident cells were enzymatically isolated using liberase (5 mg/ml). Epithelial LCs and macrophages from the inner and outer foreskins were identified using a multiparameter flow panel: CD207, CD1a, CD86/80, HLA-DR, CD11c, CD209, CD206, CD14, CD4, MHC, 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 104), with averages of 5% and 0.009% of the entire cell population respectively. Both migrating CD1a+, CD209+ /CD11c+ and CD205+ /CD163+ /macrophages expressed higher levels of CD86/80 (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+ /Lc 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, CD86/80 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.

210 IMPACT OF CCL27 ON HIV-1 TARGET-CELL ABUNDANCE IN THE FORESKIN EPITHELIUM

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Background: Findings from our laboratory have shown that asymptomatic sexually transmitted infections (STIs) have a significant effect on foreskin immunity, by increasing the density of HIV target cells in the foreskin and altering inflammatory markers in the tissue. Of particular importance, CCL27 transcript and protein were found to be significantly higher in the inner foreskin relative to the outer tissue. We hypothesized that CCL27, a skin-homing chemokine, might have an effect on recruiting HIV target cells to the foreskin epidermis, bringing target cells closer to where they might interact with HIV upon exposure.

Methods: Inner foreskin tissue explants were cultured in either media alone or in the presence of TNFs (100ng/ml) or CCL27 (400ng/ml) for 48 hours. Tissue was embedded and frozen in OCT, sectioned and stained for HIV target cells (CD3+ /CD4+) and regulatory T cells (CD3+ /CD8+). A Delta Vision imaging system was used to acquire fluorescent images of the cells. Cell density was then calculated using Integrative Data Language (IDL), accounting for the size of the epithelms.

Results: We observed an increase in the density of CD3+ /CD4+ /T cells in the epithelium of the inner foreskin that was stimulated with CCL27. The data showed a 2- to 3-fold (p<0.001) increase in CD3+ /CD4+ /T cells in the epithelium after stimulation with TNFa (from 60 cells/mm2 to 138 cells/mm2) and CCL27 (from 60 cells/mm2 to 147 cells/mm2) compared to the unstimulated samples.

Conclusion: In conclusion, exogenous stimulation of foreskin tissue with CCL27 was shown to significantly increase the population of CD3+ /CD4+ /T cells in the inner foreskin. It is suggested that this increase is due to the migration of CD3+ /CD4+ /T cells from deeper layers of the tissue to the epithelium. Interestingly, CCR10 is the cognate receptor for CCL27 that is expressed on T helper 2 (Th22) cells. Th22 cells express CCR5, making them a possible target for HIV infection. Future work can explore how the interaction of CCL27 and Th22 cells in the foreskin affect HIV susceptibility in the male genital tract.
211 IMPACT OF PENILE CIRCUMCISION ON HIV SUSCEPTIBILITY MARKERS IN THE URETHRA
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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 12 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 rRNA 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 urethral 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 cytokines/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.

212 MEDICAL MALE CIRCUMCISION DISCIPLINES THE PENIS: UNDERSTANDING HIV SUSCEPTIBILITY
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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 penile 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.

213 CONDOMLESS RECEPTIVE ANAL INTERCOURSE IS ASSOCIATED WITH MARKERS OF MUCOSAL INJURY
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Background: We previously found a unique rectal mucosal (RM) immune environment among men who have sex with men (MSM) engaging in condomless receptive anal intercourse (CRAI) typified by a pro-inflammatory response to CRAI and a microbiota enriched for Prevotellaceae over Bacteroidaceae. Further exploration of the RM immune environment among MSM engaging in CRAI will lead to a better understanding of HIV transmission.

Methods: To investigate expression of MPO (neutrophils), IL-17 (inflammatory cells), and FOXP3 (regulatory T cells) in the lamina propria and Ki67 (proliferating cells) and CD103 (tight junctions) in the crypt epithelium of RM, we used standardized, automated immunohistochemistry and quantitative image analysis in a cohort of 41 MSM engaging in CRAI and 21 men who had never engaged in CRAI (controls) over 2 study visits. The RM microbiota was characterized with 16S rRNA sequencing. Linear mixed effects models were used to examine differences in biomarker expression between study groups over time. A linear decomposition model (LDM) was constructed to examine associations between the biomarkers and microbiota.

Results: Expression of cellular markers MPO, IL-17, and FOXP3 increased from the base of the crypt towards the lumen of the RM, while Ki-67 and e-cadherin decreased (Figure). After adjustment for race and age in mixed effects models, among MSM engaging in CRAI relative to controls, the expression of MPO in the lamina propria and Ki67 in the epithelium were 41% (p<0.05) and 60% (p=0.03) higher, respectively. There were no significant differences in the other 3 biomarkers or in biomarker expression among MSM engaging in CRAI based on timing of sexual intercourse. No significant associations were detected between the 5 biomarkers or global composition of the RM microbiota or individual taxa examined, including Bacteroides and Prevotella genera.

Conclusion: Increased infiltration of neutrophils and proliferation of crypt epithelial cells in the RM of MSM likely represent an injury response to frequent CRAI, which could facilitate HIV transmission through increased inflammation. However, the role of the microbiota in contributing to RM inflammation among MSM remains unclear. Prevention interventions that reduce RM inflammation or that capitalize on the presence of a specific inflammatory mechanism (e.g. neutrophil response) at the time of HIV exposure in the RM could enhance efficacy.
214 IMMUNE CORRELATES OF ANORECTAL HIV SHEDDING IN MEN ON ANTIRETROVIRAL THERAPY

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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 a significantly higher proportion of central memory cells (CCR7+CD45RA-) in all cell subsets (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.

215 HIV HIGHLY INFECTS GENITAL CD4+ T CELLS WITH REMODELING FOR SURVIVAL AND MIGRATION

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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, CD45RO, CD28, and ICOS, and upregulated BIRC5 promoting survival of infected cells. Infection also upregulated the chemokine receptors CCR7 and CXCR5 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.

216 VAGINAL BACTERIA REGULATE MICRO-RNAS TARGETING THE HIV-HOST INTERACTOME

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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, when the vaginal microbiome shifts to the bacterial diversity and metabolic activity that are most permissive for HIV infection. MicroRNAs were measured using qPCR and bioinformatic analyses of the resultant high-dimensional datasets were performed to identify significant changes in expression.

Results: We observed a significant downregulation of miR-155, a microRNA that targets viral transcripts, in the presence of vaginal Lactobacillus species. Furthermore, we identified a positive correlation between the abundance of Lactobacillus and the expression of miR-155 in these samples.

Conclusion: These findings provide evidence for a potential mechanism by which the vaginal microbiome regulates microRNA expression, potentially impacting host-virus interactions and the risk of HIV acquisition.
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 from NF-KB, 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

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**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. Models were adjusted for age, geographical origin, viral load at ART initiation, time from infection to ART initiation and calendar period.

**Results:** The 1500 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 5.6 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/10^10 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.
Background: Suppressor of cytokine signaling (SOCS) is a family of proteins upregulated rapidly in response to stimulation by Toll-like receptors, cytokines, grow factors and hormones that provide a negative feedback to the stimulation that triggered them by inhibiting the JAK-STAT signaling pathway. SOCS proteins, in particular SOCS3, have also been described as having a central role in metabolic syndrome, diabetes and atherosclerosis. In vivo data for SOCS levels in HIV-infected patients are very limited.

Methods: Using intracellular staining (ICS) and flow cytometric analyses, we evaluated the expression kinetics of SOCS1 and SOCS3 proteins and their activity by measuring the percentages and the accumulation level, estimated via MFI, of SOCS1, SOCS3, TLRs, IFNs and other JAK-STAT signaling pathway-related proteins in individual subpopulations of blood and lymph node MNC, harvested at day 0, peak of infection, and week 20, and 60 from HIV-infected Rhesus macaques left untreated, treated with ART or ART+p38MAPK inhibitor. Boolean data analysis permitted the evaluation of co-expression of the above proteins.

Results: In the context of untreated or treated chronic HIV or SIV infection, a persistent but aberrant activation of SOCS proteins and their targets is an important feature of the dysfunctional TLR-IFN-SOCS pathway. The percentage of SOCS+ cells remains higher than at peak viremia after 54-59 weeks of ART despite virus suppression and its expression does not correlate with viral loads. SOCS1 and SOCS3 expression is elevated in virtually all mononuclear cell subpopulations yet the inhibition of their targets JAK and STAT is not complete and markers of innate immunity that should be impacted by SOCS activity remain elevated.

Conclusion: Persistent SOCS protein expression during suppressed SIV infection supports the existence of additional stimulation that maintains their expression and/or dysregulation of their negative feedback. Incomplete JAK-STAT pathway suppression by SOCS proteins is consistent with residual activation of innate immunity pathways and dysregulation of antiviral immunity. Given the association of their expression with metabolic conditions, SOCS protein chronic activation could be also relevant to the metabolic complications observed in ART patients.

EFFECT OF HIV SUPPRESSION ON CYTOKINES IN BLOOD AND SEMINAL PLASMA

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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.

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 baseline viral load 220,000 copies/mL (range 15,000-6,000,000). 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 blood (MIG and IL-6, both p < 0.001), 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.

**RESIDUAL IMMUNE ACTIVATION IN AFRICANS ON ART PREDICTS CD4 RECOVERY AND VIRAL REBOUND**

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**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, IFN-γ, TNF-α, 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 long-term outcomes: 1) CD4 T-cell recovery, using a multivariable linear mixed model; and 2) virological rebound, defined as a single follow-up 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=63), 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 -2.27; p=0.041), sCD163, and CRP (p=0.007), MIG (-34.78, 95%CI -67.27 to -1.29; p=0.036), and LBP (-28.49, 95%CI -54.93 to -2.27; p=0.041) 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 log₃ 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 log₃ 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 inflammation 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.

**HIV-RELATED MICROBIOME, PREVIOUS IMMUNODEFICIENCY, AND EXCESS METABOLIC RISK**

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**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 (sCD14 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 metabolites, microorganisms and HIV infection. These dimensions Partial Least Squares-Discriminant Analysis (PLS-DA) score plot by HIV status, based on 533 plasma metabolites.

(b) Correlation between four HIV-associated bacterial genera and plasma metabolites. Red and green (which depict bacterial taxa which showed increased and decreased relative abundance in HIV+ infected individuals). The glycerophospholipid column represents total glycerophospholipid:glycerophosphocholine (total GP:GPC). Fatty acid, bacte(r) and phosphatidylethanolamine (ethanolamine) and phosphatidylethanolamine (choline) represent total concentration for each glycerophospholipid subclass, respectively.

**P<0.05, *P<0.01, **P<0.005.

225 ART REVERSES LOSS OF DIVERSITY & RICHNESS OF INTESTINAL MICROBIOME IN HIV + NAIVE

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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+ naïve; 13 patients) with those on ART (57 patients) for 133 months (HIV+ ART+) by 16S 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+ naïve 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+ naïve 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+ naïve 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+ naïve from HIV+ ART+ individuals. The HIV+ naïve population exhibits decreased Actinobacteria (p = 0.04) and Proteobacteria (p=0.009) compared to the uninfected group. The decrease in abundance of these communities in the HIV+ naïve group is exchanged for a significant increase in Actinobacteria (p = 0.008) and Firmicutes (p=0.008), and a decrease in Bacteroidetes (p=0.001), thereby seemingly normalizing bacterial diversity, but not composition in 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...
226 MICROBIOTA MODULATES HIV TARGET-CELL LEVELS AT SITES OF MUCOSAL HIV ACQUISITION

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**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 monitored by the National Gnotobiotic Rodent Resource Center. BLT 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 examined 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=0.0032), IEL (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 (p<0.0002, SLPL p=0.0041, CEL p=0.0004, CLPL p=0.0014, LEL p=0.0005, LLPL p=0.0022). The presence of microbiome also resulted in higher numbers of activated CD4+ T cells in the SIEL (p=0.0001), SLPL (p=0.0279), and CEL (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 in particular, CD4+ T cell levels at key mucosal sites of HIV acquisition.

228 KEY FEATURES OF GUT-MICROBIAL DYSBIOSIS IDENTIFIED IN ALCOHOLIC HIV-1 PATIENTS

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**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, 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 CD14, IL-6 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 increase in Enterobacteriaceae 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:** This 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 combinatorial effects of alcohol and HIV-1 infection that can adversely affect HIV-1 pathogenesis.

### TABLE 1: Significant features of gut-microbial dysbiosis in RCHIV-Alc patients

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<th>Feature</th>
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<th>RCHIV-Alc AUDIT≥20</th>
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**PREVOTELLA IS RELATED TO A DYSREGULATION OF IFN AND T-CELL RESPONSE IN HIV INFECTION**

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**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 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+, CD38+HIV) 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 Stimulated Gene (ISG), Myxovirus resistance gene A (MxA), was also evaluated in both cohorts using qPCR.

**Results:**

- **Pathogen Enterobacteriaceae**
  - LDA score > 1.5
  - p < 0.05

- **Significant enrichment of pathogenic Enterobacteriaceae**
  - LDA score > 1.5
  - p < 0.05

**Conclusion:**

- **Prevalence of Prevotella**
  - LDA score > 1.5
  - p < 0.05

**Comorbidities**

- **Significant comorbidities**
  - LDA score > 1.5
  - p < 0.05

**IFNγ and IL-17 expression**

- **Significant IFNγ and IL-17 expression**
  - LDA score > 1.5
  - p < 0.05

**IFNAR1 and ISG expression**

- **Significant IFNAR1 and ISG expression**
  - LDA score > 1.5
  - p < 0.05

**CD4 and CD8 T cell activation**

- **Significant CD4 and CD8 T cell activation**
  - LDA score > 1.5
  - p < 0.05

**IFNβ expression**

- **Significant IFNβ expression**
  - LDA score > 1.5
  - p < 0.05
229 ANTIINFLAMMATORY EFFECT OF METFORMIN ON MICROBIOTA IN NONDIABETIC PEOPLE WITH HIV

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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 (CIHR/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 HIV-positive (HIV+; <60 years) 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 of metformin (V2), and at V2 after metformin discontinuation (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. No differences were observed between patients with ART-naive and ART-experienced HIV+ individuals.

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 should be conducted in non-diabetic PLWH.

230 FUNCTIONAL RESTORING OF GUT BARRIER AFTER MODULATION OF INTESTINAL MICROBIOTA

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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 sCD4+T-cell-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 sachets, each containing 450 × 109 billion bacteria, two weeks of Gloviomax®. All patients underwent to colonoscopy and blood sampling before (T0) and after 6 months of probiotic supplementation (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 larger mitochondria and the levels of these organelles were similar to healthy samples (p > 0.05). Ultrastructural morphological data regarding mitochondria were confirmed by mtDNA analysis at T6 that indicated an increase concentration of mitochondria in all tested patients (p > 0.005) and a similar trend for CYC1 concentration (p < 0.005), with substantial reduction of HSP60 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 histopathologic 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.
These cellular stress biomarkers, specifically RAGE and IFABP may be released into circulation due to epithelial barrier damage.

CMV SEROPOSITIVITY AND MICROBIAL TRANSLOCATION IN HIV ELITE CONTROLLERS

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Background: Elite controllers (EC) are people living with HIV (PLWH) who maintain plasma HIV 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-1β, 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<0.002), I-FABP (p=0.01), sCD14 (p=0.04), LPS (p=0.02), BDG (p=0.02), IL-1β (p=0.001), IL-6 (p<0.001), and kynurenine/tryptophan ratio (p=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-1β (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.

FROM GUT TO BLOOD: REDISTRIBUTION OF ZONULIN IN HIV+ PATIENTS

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Background: Gastro-intestinal mucosal damage in HIV infection causes microbial translocation and immune activation, which in turn results in non-infectious comorbidities. Combined antiretroviral therapy (cART) restores this intestinal damage only partially. Various biomarkers of the epithelial barrier have been reported but some are not considered specific while others are impacted by cART. Zonulin is a modulator for epithelial tight junctions. Previous studies found an elevated level of circulating Zonulin in the blood during HIV infection, while others reported a decrease. We measured Zonulin in serum and intestinal tissue sections and compared it with inflammatory markers and the virus reservoir in the blood (PB) and in the gut (R) of HIV+ and controls.

Methods: Biopsies and gut tissue sections from TI, R and PB were collected from 5 treatment naive (HIV+NAIVE) and 10 cART-treated (HIV+cART) HIV+ individuals and 11 controls (CTRL). Lamina propria mononuclear cells were isolated. Following flow cytometry and cell sorting of CD4+ T cells, total HIV-DNA was quantified in PB, TI and R. In serum circulating Zonulin was measured by ELISA (Immundiagnostik) and in gut sections by semi quantitative immunohistochemistry. Ultrasensitive digital ELISA (Simoa; Quantexis) was used to measure IFN-α in serum and tissue supernatants.

Results: Median CD4+ T cell count [cells/µL in HIV+NAIVE was 70[30-255] versus 426[293-787] in HIV+cART. Median time on ART[years]was 6[9-10]. Circulating Zonulin levels (ng/mL) were highest in treatment-naive HIV+ when compared to cART-treated HIV+[p=0.04] or CTRL (p=0.0067; HIV+NAIVE>HIV+cART>CTRL). Similarly, HIV+NAIVE showed higher IFN-α and HIV-DNA levels in PB when compared to HIV+ cART[IFN-α: p=0.04; HIV-DNA: p=0.04]. In gut tissue sections however, Zonulin was higher in CTRL when compared to HIV patients. Circulating Zonulin in serum was negatively correlated to plasma CD4 cell count (r=-0.54, p=0.04), CD4+ T cell frequencies in TI (r=-0.58 p=0.04) and positively to IFN-α in TI (r=0.65, p=0.05).

Conclusion: The data indicate that upon HIV infection, Zonulin levels decrease in gut, but increase in plasma. The latter were associated with loss of intestinal CD4+ T cells and increased inflammation in the gut, suggesting that increased levels of systemic Zonulin correlate with intestinal damage. An increased understanding of the regulation of gut tight junctions during HIV infection may be crucial for the design of future therapies.
235 IMPACT OF INTRAVENOUS HEROIN AND HIV ON GUT INTEGRITY AND IMMUNE ACTIVATION

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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, LPS binding protein (LBP) and beta-D-glucan.

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

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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 CD44 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-1 [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/mm. At baseline, there were significant correlations between sCD14 and both I-FABP and B-D-glucan (r=0.19-0.21, P<0.05), but not with other putative measures of gut barrier integrity. Surfactant D appeared to be associated with sTNFR1 (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

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Background: HIV infection and antiretroviral therapy (ART) are associated with dyslipidemia 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=2.2, p<0.01), with traditional risk assessments categorize individuals with CAC scores <100 at low risk, and >400 at high risk for CVD events. Older (over 55) PWH (n=17) had an average CAC score of 423, compared to a score of 71 in older people without HIV (n=27). PWH had increased serum levels of free fatty acids (FFAs), with enrichment of saturated fatty acids (SfAs) and a reduction in polyunsaturated fatty acids (PUFAs). DGE analysis of MDMs from participants with and without HIV identified alterations in immune signaling, DNA damage repair, mitochondrial dysfunction, and lipid processing pathways. Levels of SfA and PUFA lipid species correlated with unique DGE signatures and altered metabolic pathway activation in MDMs. Bodipy staining indicated elevated lipid accumulation. MDMs from PWH also produced more TNFα, IL-6, and ROS, and had increased HLA-DR surface expression. SAFA levels were directly related, whereas PUFAs were inversely related to HLA-DR expression on MDMs from PWH. PWH-MDMs exposed to HIV+ pooled serum displayed greater intracellular lipid accumulation and DGE than cells exposed to HIV- pooled serum.

Conclusion: Lipid abnormalities in HIV infection may contribute to a pro-atherogenic MDM phenotype. MDMs from PWH readily form foam cells, have altered transcriptional profiles, and produce mediators of vascular inflammation, which may enhance CVD risk, particularly in the aging HIV population.

238 LIPIDOME ALTERATIONS WITH EXERCISE AMONG PEOPLE WITH AND WITHOUT HIV

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Background: 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.

Methods: Sedentary adults (50-75 years old) with (N=24) or without (N=25) HIV participated in supervised endurance/resistance exercise for 24 weeks. In this exploratory secondary analysis of The Exercise for Healthy Aging Study, concentrations of plasma lipids (~1200 lipid species from 13 lipid classes) at baseline and week 24 were measured by mass spectrometry. Changes in logγ lipid concentrations were compared by HIV serostatus using t-tests. P-values were adjusted for multiple comparisons (unadj-p) and Benjamini-Hochberg corrected (adj-p) are reported.

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=0.070). 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 [6.21]). 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 [0.125]), 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) 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: Exercise induction of CVD risk 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: PWH 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-treated, 18 naïve) and 89 uninfected controls were enrolled. ART-treated were older than naive (51 vs 31 yrs; 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-naïve [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-naïve had FCP >100 µg/g in 37% treated and 19% in controls (P=0.0003).

In PWH, high-sensitivity C-reactive protein (R=0.30; P=0.008), soluble tumor necrosis factor-Ⅱ (R=0.28; P=0.006) and soluble vascular cellular adhesion
molecule (R=0.21; P=0.04) were positively associated with FCP. Interleukin-6 (R=0.29; P=0.01) and soluble CD163 (R=0.54; P=0.04) were also positively associated with FCP in treated and naive, resp. FCP was inversely associated with CD4 (R=-0.24; P=0.02), but not with other HIV variables, nor age, sex, or race. Conclusion: Stool concentrations of FCP are elevated in PWH. ART appears to reduce FCP but not to concentrations seen in uninfected controls. FCP 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.

240 LONG-TERM ELEVATED IL-6 AND D-DIMER AFTER DELAYED ART INITIATION IN THE START TRIAL

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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 change from entry and from start of ART in log2-transformed concentrations were compared between the deferred versus immediate groups using longitudinal mixed models adjusted for age, sex, geographic region, baseline biomarker levels and visit. Results were presented as percent change

Results: Among 2209 participants (median age 36 years, 20% female, 67% enrolled in high-income countries), the median levels at entry of IL-6 were 1.47 pg/mL, D-dimer 0.31 mg/mL, and CD4 counts 649 cells/µL. In the immediate group, 94-97% had viral load <200 cp/mL at all annual visits, whereas the deferred group suppression rates increased over time: 18%, 61%, 89%, and 95% at years 1, 3, 5, 7, respectively. In the deferred group, IL-6 and D-dimer levels remained significantly higher than the immediate group through 5 years (Fig). Over the follow-up period, treatment difference in IL-6 was 10.3% (95%CI: 7.6 to 12.9, p<0.001), and D-dimer 14.0% (95%CI: 11.5 to 16.5, p<0.001). When comparing treatment groups based on the time from ART start, biomarker levels were higher in the deferred compared to immediate group over at least the first 2 years of ART. At 2 years on ART est. diff. 9.9% (95% CI: 4.0 to 15.8; p<0.001) for IL-6 and 10.0% (95% CI: 6.4 to 13.6, p<0.001) for D-dimer, and >96% in each group had HIV RNA <200 cp/mL.

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

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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 HICs 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 four 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 (Hazards 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

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243 PRINCIPAL COMPONENTS ANALYSIS TO IDENTIFY BIOMARKERS PREDICTIVE OF NON-AIDS EVENTS

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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 the 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 at both 1 year after ART initiation and at the pre-event time point, and analyzed for levels of IL-6, CD14, 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 in either unadjusted models or models adjusted for baseline viral load, immune status, or other co-morbidities. One year after ART initiation, there were modest associations between levels of HIV DNA and CMV IgG (Spearman r=0.20, p=0.01), EBV DNA (r=0.14, p=0.05), IL-6 (r=0.18, p=0.01), D-dimer (r=0.22, p<0.01), CD14 (r=0.18, p=0.01), and sTNFR-I (r=0.15, p=0.03).

Conclusion: The size of the HIV reservoir, as reflected by the levels of total HIV DNA, was not predictive of non-AIDS-defining events. The associations of the HIV reservoir size with EBV/CMV co-infections and inflammatory markers suggest potential interactions between host immune responses and HIV persistence.

244 AGING, TRENDS IN CD4/CD8 RATIO, AND CLINICAL OUTCOMES WITH HIV SUPPRESSION

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Background: Data addressing aging’s effects on T cell phenotype suggest that age blunts CD4 cell count (CD4) improvements observed with ART-induced viral suppression. Prolonged viral suppression reduces immune activation, reflected by a rising CD4/CD8 ratio (T4/T8). We studied T4/T8 over time to determine whether it could predict risk for select comorbidities or mortality among aging persons with HIV (PWH) and ≥ 1 year of virologic control.

Methods We analyzed data from HIV Outpatient Study (HOPS) participants (ppts) seen at 12 U.S. HIV clinics who were followed from 2000-2018 with known baseline CD4, ART initiation date, all viral loads (VL) <200 copies/mL during 1st observation year ≥1y of follow up with ≥2 T4/T8 measures. We analyzed T4/T8 <0.7 by age group. Cochran-Armitage trend tests were used to compare proportions across time, and by baseline age. Clinical outcomes included any cancer, dyslipidemia and all-cause mortality. Case-control analyses were performed using conditional logistic regression (CLR) to assess for associations of T4/T8 with outcomes matching 1:1 for smoking, hepatitis C, nadir CD4, race/ethnicity, sex and insurance, with age as an independent variable.

Results: 1,910 ppts were included. Median follow up was 7.2y. At date of first VL <200 copies/mL, 908 (46%) were <40y, 626 (33%) 40-49y, and 376 (20%) ≥50y; 82% male; 50% Non-Hispanic (NH) white, 34% NH black, and 12% Hispanic; 62% were on their 1st ART regimen, 20% on their ≥4thregimen; 38% had a nadir CD4 <200 cells/mm3. Baseline T4/T8 was 0.3 (interquartile range: 0.2-0.6), not statistically different for the 3 age groups. T4/T8 increases by age group. T4/T8 increases by baseline age decreased through 4y of follow up (P<0.001 for each year). Over time, the percentage of ppts with T4/T8 ≥0.7 increased for all ages, but less among 40-49y and ≥50y compared to ≤40y group. In clinical outcomes analyses (n=77 deaths, n=167 cancer, n=461 dyslipidemia) using CLR, accounting for age, T4/T8 <0.7 at last measurement was associated with mortality (Odds Ratio (OR)
SYSTEMIC AND VASCULAR INFLAMMATION PREDICT COMORBIDITIES IN TREATED HIV INFECTION

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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, TNFα,2, TNFα), innate immune activation (sCD14, sCD163, MCP1, MIP1, sCD40), endothelial function (Pselectin, Eselectin, ICAM-1, VCAM-1, ICAM-2, VCAM-2), coagulation (D-dimer, VWF) and intestinal permeability (IL8, 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 in regression analysis (OR 1.8, CI 1.2-2.8, p=0.005). Further adjustment for age, gender and ethnicity attenuated the association (OR 1.6, CI 1.1-2.3, p=0.02).

Conclusion: We have identified distinct inflammatory patterns 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.

GUT MUCOSAL IL22 + T CELLS ARE RELATED WITH INCOMPLETE CD4 RESTORATION DESPITE cART

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Background: Gut mucosal immunity plays a central role in the HIV pathogenesis but large gaps of knowledge remain, particularly in the scenario of the incomplete CD4-recovery. Impaired gut functional complexes and increased markers of intestinal permeability and damage have been described in such scenario. Our aim was to explore gut mucosal T-cell function and its potential relationship with the mucosal damage and immune reconstitution.

Methods: Biopships of both, caecum (CA) and terminal ileum (TI), in parallel of peripheral samples, of non-HIV subjects and treated, virally-suppressed HIV-infected subjects were obtained: subjects with CD4-T-cell counts below 250 cell/ul after two years of suppressive-treatment (INR) and control subjects overcoming such threshold (IR). Histological assessment of mucosal damage was performed using a semi-quantitative scale of five physical parameters. MMCs were digested, isolated and stimulated (PMA/Iono) to quantify the T-cell production of different homeostatic cytokines by flow-cytometry. Th17, Th22, Th1 and Th2, as well as their production of combined cytokines, were analyzed. The expression of mucosal caspase-3, gal-3, ZO-1 and mucin was analyzed by immunofluorescence. LBP levels, as a marker of intestinal permeability, was measured by ELISA in peripheral samples. Potential correlations were explored using Spearman rank test.

Results: The highest mucosal damage was observed in both types of biopships from INR subjects. The production of IL22 by T-cells correlated with peripheral CD4-T-cell counts and CD4/CD8 T-cell ratio (stronger with mucosal than peripheral T-cells; P<0.005 for both locations). INR showed the lowest frequencies of IL22+/CD4+ T-cells, whereas the highest IL17+/IL22+/CD4+ T-cells ratios, independent of the location. INR showed increased frequencies of FoxP3+/CD4+ mucosal T-cells, particularly at TI, and reduced Th17/Treg and Th22/Treg ratios at both locations. IL22+/CD4+ T-cells correlated with the mucosal expression of caspase-3 and ZO-1 (negatively) as well as with the expression of gal-3 (positively), and showed a negative correlation with LBP levels (p<0.05).

Conclusion: Subjects with incomplete CD4-recovery show reduced capacity of gut mucosal T-cells to produce IL22. This cytokine, with a dual “inflammatory-protective” role during tissue responses to inflammation, could have a protective-regenerative potential on the gut potentially necessary for the normal CD4-recovery.
247 INCREASED GUT AND BLOOD CD4+ T-CELL EXHAUSTION IN IMMUNOLOGICAL NONRESPONDERS

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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 PD1, TIM3 and TIGIT in addition to T cell surface markers CD3, CD4, CD8, CD25, CD38, CD45RA, CD127, HLA DR and the gut homing marker integrin β7. Immunohistochemistry was applied to detect PD1 ligand 1 (PD-L1).

Results: INR had increased fractions of PD1+ and TIGIT+ CD4+ T cells compared with IR and HC both in blood (p<0.01) and gut (p<0.05). PD1 and TIGIT 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/Th 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 in 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

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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 CRS was downregulated in EC compared to viremic progressors (VP). Here we used untargeted plasma and fecal metabolomics to identify the metabolomic 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 controls (HC, n=12) and VP (n=16). Untargeted metabolomics was performed by Ultra-High-Performance Liquid Chromatography/Mass Spectrometry/Mass Spectrometry (UPLC/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. 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 cells lines which gave an EC50 ranging from 5.3µM to 49.1µM in HIV-1 subtype B and C. CCR3-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

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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+PLWH) 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+PLWH (median age: 55 years; CD4 counts: 679 cells/ul; 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 IC, or the HIV NL-4.3 Bla or THRO strains. IL-32α, β, y, d, x, t 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 ε, in colon biopsies and PBMC of ART+PLWH compared to uninfected controls. IL-32 mRNA expression, especially IL-32β, y and ε, was induced by exposure of HT-29 cells to recombinant TNF-α, Poly IC 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. IL-32β protein expression was measured by real-time RT-PCR. IL-32 protein production was measured in cell-culture supernatant and cell lysates by ELISA.

Conclusion: Our results document the overexpression of specific IL-32 isoforms in colon biopsies and PBMC of ART-treated PLWH 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
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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; NLRCS 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-I blockade strategies to reduce chronic inflammation in PWH.

251 OPPOSING ASSOCIATIONS OF NK AND MZ B CELLS IN RECTAL EXPLANT MODEL OF HIV INFECTION
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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 and blood MZB and NK subsets illustrated quantifiable differences (Figure). Of the 22 cytokines quantified, IL17A, IFNγ, IL10, IP10, GMSF, Granzyme A (GzA), Granulysin, and Perforin, were positively correlated with HIV replication (p<0.01 for all). Detection of IL17A, IFNγ, IL10, and GMSF on day 3 positively correlated with later p24 production (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 IFNγ early in mucosal HIV infection. Defining the innate cell subsets and their effector mechanisms that facilitate or hinder HIV infection in RM could identify new targets for biomedical interventions.

252 IgA PRESERVATION IN GUT IN SIVagm INFECTION IS ASSOCIATED WITH INFLAMMATION CONTROL
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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 are 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...
NK cell-mediated viral control in BCF and intestinal inflammation control via maintenance of IgA production.

**Methods:** AGM and cynomolgus macaques (MAC) were infected with SIVagm. sab92018 and SIVmac251, respectively. We collected blood, mesenteric LN (mLN), jejunum, ileum and colon from each animal before infection, at day 9 pi. and during chronic infection. B, T and NK cell analyses were performed by fluorescence microscopy and/or flow cytometry. Immunoglobulins were isolated by affinity chromatography and quantified by ELISA. To determine IgA/IgG ratios and gp140 antibody specificity, trimeric SIVagm and SIVmac gp140-folding Env proteins and an IgA-specific probe were produced. Soluble markers of microbial translation and inflammation (i.e., sCD14) were quantified in plasma by ELISA.

**Results:** NK cells migrated into BCF of mLN during acute SIVagm infection. CXCR5+NK cells showed a negative correlation (p=0.0044; r²=0.62) in LN with follicular Th1 cells, a population responsible of hypergammaglobulinemia. In AGM, intestinal IgA levels (jejenum, ileum and colon) were comparable between acutely infected (mean=0.51-0.45AU), chronically infected (mean=0.53-0.39AU) and non-infected animals (mean=0.49-0.4AU). In acute SIVmac infection, intestinal IgA levels (mean=0.5-0.47AU) were similar to those of non-infected MAC (mean=0.54-0.42AU), but strongly decreased in chronically infected animals (mean=0.12-0.05AU). Similarly, IgA were decreased in BCF of chronically infected MAC. There was a negative correlation between sCD14 and IgA levels in MAC (p=0.0037; r²=0.32) and not in AGM (p=0.72; r²=0.012).

**Conclusion:** Our data unraveled a negative correlation between gut IgA titres and inflammation in SIVmac infection, with a dramatic loss of intestinal IgA in SIV-infected MAC while IgA levels in chronic SIVagm infection remain stable.

**254 DECREASED EXPRESSION OF MUCOSAL TYPE I IFN RESPONSE IN HPV-INFECTED MSM PATIENTS**

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**Background:** Innate immunity pathways, especially those related to type I interferon (IFN-I) are involved in Human Papillomavirus (HPV) recognition and clearance. Among HIV-1 positive men 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 adopted to overcome the host immune defense and establish persistent infection, might target different IFN-I genes in HIV-1 MSM patients.

**Methods:** Anal brushings were collected from 86 Caucasian MSM HIV-1 infected patients; with a 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-α, IFN-β, IFN-ε, an emerging component of innate immune defense at mucosal sites, IFN-α receptor (subunits R1 and R2) in anal brushings, were measured by TaqMan RT–PCR.

**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 HSIL/LIL. A decreased mucosal expression of IFN-β, IFN-ε, 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). No differences were found on levels of IFN-I components according to the presence or absence of SIL. By contrast, the expression of IFN-β, IFN-ε, IFNAR1 and IFNAR2 were 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 precancerous anal lesions progression.
256 HYDROXYCHOLESTEROL INHIBITS HERPESVIRUSES BY ACTIVATING INFLAMMATORY PATHWAYS

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Background: Kaposis Sarcoma Herpesvirus (KSHV/HHV-8) expresses several viral products 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.

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 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 effect 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 responses to pave the way for developing therapeutic strategies for multiple viral infections.

258 INTEGRATED ANALYSIS OF MULTICELLULAR IMMUNE DYNAMICS DURING HYPERACUTE HIV INFECTION

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Background: Development of effective vaccines and therapeutics is facilitated by understanding the earliest moments of infection. Studies in SHIV 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-sequencing 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. Cellular features of 2 participants who later develop spontaneous control of HIV were also described.

**Results:** Across all individuals we profiled >99,000 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 multicellular 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**

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**Background:** Monocytes are chronically activated in HIV infection, showing increased expression of CD16 and downregulation of CD14. This observation is concomitant to increased plasma levels of sCD14 and sCD163, which are considered surrogate markers of monocyte activation. Nevertheless, phenotypic abnormalities of monocytes during primary HIV infection (PHI) are not fully characterized.

**Methods:** We longitudinally studied monocytes in individuals at PHI (n=40) followed for 1 year. HIV-uninfected individuals (n=58) and treated or untreated chronic HIV infected individuals (CHI, n=56) were also cross-sectionally analyzed. Participants were recruited at the Manchega District Hospital in Mozambique. Monocyte activation was assessed by multicolor flow-cytometry, while plasma levels of sCD14, sCD163 and IFN-α were assessed by ELISA or Luminox. We longitudinally studied monocytes in individuals at PHI (n=40) followed for 1 year. HIV-uninfected individuals (n=58) and treated or untreated chronic HIV infected individuals (CHI, n=56) were also cross-sectionally analyzed. Participants were recruited at the Manchega District Hospital in Mozambique. Monocyte activation was assessed by multicolor flow-cytometry, while plasma levels of sCD14, sCD163 and IFN-α were assessed by ELISA or Luminox. We longitudinally studied monocytes in individuals at PHI (n=40) followed for 1 year. HIV-uninfected individuals (n=58) and treated or untreated chronic HIV infected individuals (CHI, n=56) were also cross-sectionally analyzed. Participants were recruited at the Manchega District Hospital in Mozambique. Monocyte activation was assessed by multicolor flow-cytometry, while plasma levels of sCD14, sCD163 and IFN-α were assessed by ELISA or Luminox. We longitudinally studied monocytes in individuals at PHI (n=40) followed for 1 year. HIV-uninfected individuals (n=58) and treated or untreated chronic HIV infected individuals (CHI, n=56) were also cross-sectionally analyzed. Participants were recruited at the Manchega District Hospital in Mozambique. Monocyte activation was assessed by multicolor flow-cytometry, while plasma levels of sCD14, sCD163 and IFN-α were assessed by ELISA or Luminox. We longitudinally studied monocytes in individuals at PHI (n=40) followed for 1 year. HIV-uninfected individuals (n=58) and treated or untreated chronic HIV infected individuals (CHI, n=56) were also cross-sectionally analyzed. Participants were recruited at the Manchega District Hospital in Mozambique. Monocyte activation was assessed by multicolor flow-cytometry, while plasma levels of sCD14, sCD163 and IFN-α were assessed by ELISA or Luminox.

**Results:** Plasma HIV viremia peaked at one month after infection and immunological (CD4 and CD8 counts) and virological (VL) plateau was reached after month 4 of infection. The percentage of circulating monocytes was stable during PHI. Activated (CD14+CD16+) and highly activated (CD14–CD16+) monocytes were significantly increased in untreated CHI patients compared to HIV-uninfected individuals (p<0.005). During PHI, the frequency of these subsets remained similar to that of uninfected individuals for the first five months, rising after. In contrast, plasma sCD163 levels peaked at month 2-3 after infection, while the levels of sCD14 showed the highest value at one month after infection and then decreased to reach the levels observed in chronic patients. The expression of the Type-1 IFN regulated protein Siglecs-1 on monocytes showed a kinetics similar to VL and plasma IFN-α, showing the highest percentage at month 2 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-α 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**

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**Background:** The initiation of ART during primary HIV-1 infection (PHI) decreases transmission, contains viral reservoir establishment, prevents damage to immune system and reduces immune activation. The aim of this study was to analyse immunological changes in cell subsets in blood and rectal tissue as well as mucosal cytokine profile after initiating an intensified-5-drug ART regimen during very early PHI.

**Methods:** Patients started an intensified ART consisting on abacavir/ lamivudine/dolutegravir regimen during 48 weeks plus darunavir+c 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 II-IV, n=11) by multi-parametric flow cytometry. The analysis of 25-cytokines on rectal fluid was performed using Luminox assay. Clinical Trials NCT02388820.

**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 39.05% 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 increased activated CD68+ T cells in both cases (from 24.3% to 12.6%, p=0.013) 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 w0 at w48 (721.4 vs 485.5, p=0.008). In addition, levels of TNF (IL-12, IL-23, ILN1, 16, 20, and 22 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.
The recombinant IgG proteins were expressed in Exp293 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-11157pp120. Six (J029, J031, J033, J036, J040 and J044) from the same lineage (VH4-2’01 F and VK1-2’01 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 HKQ3 region. Inferred LCA 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-targeted 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 (N165L, 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 bAbs as those identified in humans can be elicited in rhesus macaques during natural SHIV infection. Further characterization the maturation pathway of these bAbs by comparing to bAbs with the similar specificities in humans will provide unprecedented insight into mechanisms of bnAb development in NHPs.

### 262 VH GENE POLYMORPHISM ASSOCIATED WITH POTENT ANTI-SIV NEUTRALIZING ANTIBODY INDUCTION

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**Background:** Induction of potent broadly-neutralizing antibodies (bAbs) is a key for anti-HIV vaccine development. The boosting method for B-cell maturation toward bNAb induction has not been established, although recent studies have developed germ-line-targeting immunogens for priming. Here, we present a unique macaque model to analyze B-cell responses leading to anti-HIV neutralizing activity.

**Methods:** In our previous study, we obtained four rhesus macaques inducing potent anti-SIV bAbs, VH3.33-restricted B404-class Abs, after SIVsmH635FC infection. In the present study, we examined B404-class Ab induction in six SIVsmH635FC-infected rhesus macaques. Monoclonal anti-SIV Fab clones were isolated from lymph nodes (LNIs) by Bio-panning using phage display. B cell receptor (BCR) VH sequences derived from peripheral lymphocytes and LNIs were analyzed by next generation sequencing (NGS).

**Results:** B404-class Ab induction was observed in one of the six SIVsmH635FC-infected macaques but undetectable in the remaining five. Investigation of germline VH3.33 genes in five B404-class Ab inducers (one in the present study and four in the previous study) and five non-inducers revealed association of B404-class Ab induction with VH3.33 polymorphisms. Analysis of germline-reverted B404 mutants revealed that the VH3.33 residue 38 is the determinant for B404-class Ab induction. A B404-associated VH3.33 allele-positive macaque dominantly induced B404-class Abs even under undetectable viroemia.

**Conclusion:** Our results first demonstrate restriction of bNAb induction by germline VH-gene polymorphism in a macaque AIDS model. Analysis using B404-associated VH3.33 allele-positive macaques could facilitate understanding of B-cell maturation leading to potent Ab induction.

### 263 POLY/AUTOREACTIVITY AND BROAD NEUTRALIZATION ARE DETERMINED BY DIFFERENT MUTATIONS

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**Background:** Nearly half of broadly neutralizing antibodies (bAbs) are polyreactive and/or autoreactive (poly/autoreactive). Some of them, like CH103, gain poly/autoreactivity during bnAb maturation. However, whether poly/autoreactivity and broad neutralization are governed by the same mutations during bnAb maturation is not well understood.

**Methods:** Mutations in Ab pairs differing in poly/autoreactivity within the CH103 lineage were individually introduced back into the Ab from each pair with less (or no) poly/autoreactivity. Recombinant Abs were expressed and purified from transfected Exp293 cells. Neutralization activity against HIV-1 was determined using the TZM-bl assay. Poly/autoreactivity 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/autoreactivity 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/autoreactivity, and they had little effects on neutralization. The IA2 variable heavy (VH) N605 mutant Ab and the CH103 VH E656I 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 protein array analysis using ~9000 human proteins showed that the IA2 N605 mutant Ab is poly/autoreactive, while the E646K mutation did not render IA2 poly/autoreactive. The UBE3A binding analysis of all mutants showed that only the VH E646K mutation in IA2 and IA3 as well as the VH E656I and VL E45D 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/autoreactivity.

**Conclusion:** Development of poly/autoreactivity 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/autoreactivity in this bnAb lineage.

### 264 POLYFUNCTIONAL ANTIBODY RESPONSE TO SHORT-SCHEDULE EBOLA VACCINE IN HIV+/- SUBJECTS

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**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.ZEOBIM 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 59%) 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: Polynuclear effector antibody 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.

Results:

Fischer’s exact tests.

Neutralization heatmaps were used to identify potential targeted 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 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 not associated with the CD4 to CD8 ratio. Given the small sample size, definitive conclusions about any observed differences can not be made.

Conclusion: Polynuclear effector antibody 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.

265 PULMONARY TUBERCULOSIS DISEASE ENHANCES HIV-1 ANTIBODY RESPONSES

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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-naïve 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 Lumien 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=0.49). 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=6, range 0.34-0.82) still had higher neutralizing capacity, but the difference was not statistically significant (p=0.56). 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.

Conclusion: 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.

266 IMPACT OF IMMUNE CHECKPOINT INHIBITORS IN VACCINE-INDUCED ANTI-HIV RESPONSES

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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 (NCT01713424) trial receiving early treatment and a ChAdOx1/HIVvaccova/MVA.HIVvaccova prime-boost regimen (Etvac; 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+ HIV-1-specific CD8+ T cells by polychromatic flow cytometry. Also, we measured a panel of 17 human cytokines in the culture supernatants by multiplex assay.

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+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. The cytokine profiling in Etvac individuals revealed a specific signature of IFNγ, sFasL, GM-CSF, sCD137, IL-5, IL-13, Granzyme A, Granzyme B, MIP-1β and Perforin secretion in response to anti-PD-1 that differed in Chro by the lack of IL-5 and IL-13 and the presence of IL-4 and IL-10.

Conclusion: Our data demonstrate a significant increase in the magnitude of vaccine-induced HIV-1 specific CD8+ T cell responses by ICIs linked to a particular cytokine signature profile in Etvac. Thus, we propose the combined use of ICI and therapeutic vaccines to boost vaccine-induced anti-HIV CD8+ responses in vivo. In addition, the use of combined ICI as an anti-HIV immunotherapeutic strategy in Chro warrants further investigation.

267 CHARACTERIZING “EXCEPTIONAL” CONTROL AMONG HIV ELITE CONTROLLERS

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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 5M 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 were highly correlated with CA RNA levels (r=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 (B27 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.

268 HIV-SPECIFIC CD8+ T CELLS EXHIBIT POOR CYTOLYTIC POTENTIAL IN THE HUMAN AIRWAY

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Background: HIV mRNA and proteins are detectable in airway samples from asymptomatic ART-naive healthy adults who were followed up for a year on ART. We collected paired bronchoalveolar lavage (BAL) fluid and peripheral blood samples on all participants. We performed flow cytometry-based characterization of CD8+ T cell phenotypes and also quantified HIV (Gag, Nef and Pol)-specific IFN-γ-producing CD8+ T cells in BAL and blood cells.

Results: CD8+ T cells expressing Perforin and Granzyme B were found predominantly in the blood compared to the airway, regardless of HIV infection status. The frequency of Eomes+CD8+ T cells was higher in blood-derived cells compared to those from the airway lumen. PD1 or 2B4-expressing CD8+ T cells were higher in airway-derived cells compared to blood. Untreated HIV-infected adults had more Eomes+PD1+CD8+ T cells compared to healthy controls; predominately in the airway compared to the systemic circulation. HIV-specific (Gag, Nef and Pol) CD8+ T cells exhibited a higher breadth in the airway than in blood. There was no correlation between HIV-specific CD8 T cell responses in the airway and peripheral blood. HIV-specific CD8+ T cells did not express Perforin and Granzyme B but expressed high levels of PD1 and Eomes, markers associated with immune regulation and exhaustion in HIV infection.

Conclusion: We demonstrate that airway-derived HIV-specific CD8+ T cells poorly express cytolytic molecules (Granzyme B and Perforin) and possess markers consistent with high immune regulation (PD1 and Eomes). The poor cytolytic potential and highly regulated phenotype of airway HIV-specific CD8+ T cells could promote the persistence of HIV-infected cells in the airway in individuals on long-term ART.

269 HIGH FREQUENCY OF CD8 ESCAPE MUTANTS IN ELITE CONTROLLER AS NEW OBSTACLE TO HIV CURE

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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 (7-112) and 74 (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=0,532).

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 CD8+ T CELLS WITH FRAILTY IN HIV-INFECTED MEN

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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 viremically suppressed HIV+, 20 HIV−; 21 frail, 21 non-frail) were assessed by flow cytometric analysis of production of IFN-γ, TNF-α, IL-2 and IFN-γ 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: 51% 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, 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- and 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 cells predicted onset of frailty in HIV+ men, and 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.

271 VULNERABLE TARGETS IN HIV-1 POL FOR ATTENUATION-BASED VACCINE DESIGN

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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 C 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 acids 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, all relatively 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 E68T 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, V241I, 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.

ASSOCIATION OF HIV AND HOST GENETIC VARIANTS IN ANTIRETROVIRAL THERAPY-NAIVE PERSONS

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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 naïve HIV− participants in the Strategic Timing of Antiretroviral Treatment (START) trial.

Methods: Two 3.6 kb amplicons (HIV-1 HBX2 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 SNPs and imputed 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•10-7) 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

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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 LN CD8+ T cells lack CXCR5 expression, and why there is reduced CXCR5 expression on CXCR5+CD8 T cells (fCD8s) relative to GCfTh.

Methods: We FACs-sorted CXCR5+CD8+ (fCD8s), CXCR5-CD8+ (non-fCD8s), naive CD8+ T cells and GCfTh 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 fCD8 and non-fCD8 identified 43 genes 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 fCD8 with epigenetic gene regulation. DNA bisulfite treatment and sequencing within PX/PY grouping.

Conclusion: 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-copy 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

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Background: The ER-associated enzyme cholesterol-25-hydroxylase (CH25H) is an interferon stimulated gene (ISG) which is 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 spontaneously exposed HIV, 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 lipidprotein 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 (LRX, ABCA1, SCARB, SMAC3, PPARγ) was modulated as well (>3 fold) in unstimulated as well as in vitro HIV-infected PBMCs and MDMs from HESN. Notably, this result in a significantly reduced susceptibility to in vitro HIV-1 infection in PBMCs and MDMs of HESN (p<0.01).

Conclusion: The observation that CH25H, an oxysterol-producing enzyme, is up-regulated in HIV-exposed cells from HESN, is particularly intriguing.
This could be related to the activation of the IFNa pathway, resulting in a reduced susceptibility to in vitro HIV-1 infection. Further analyses are needed to ascertain the cholesterol pathway involvement in natural resistance to HIV-1 infection. These results, nevertheless, suggest a possible basis in novel preventive and therapeutic approaches against HIV-1 infection.

276 BASELINE INDUCIBLE HIV p24 INFORMS VIRAL CONTROL DURING INTERFERON-Α MONOTHERAPY
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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 viral 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 15-mer gag peptides. B) NK A2C: 4-hour co-cultures with anti-HIV sera with 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 Gag peptides. Proviral 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 mono therapy. In contrast to expectation that higher latent reservoir 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.

277 LOSARTAN DOES NOT IMPROVE LYMPHATIC TISSUE FIBROSIS OR T-CELL RECOVERY IN HIV
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Background: Incomplete immune recovery despite HIV viral suppression is associated with excess clinical risk, and is, in part a consequence of fibrosis within secondary lymphoid tissues. We hypothesized that the angiotensin receptor blocker losartan would inhibit fibrosis and improve T-cell recovery within lymphatic tissue, given its established effects in blocking TGF-β.

Methods: We pooled data from two randomized (1:1), double-blind, placebo-controlled trials of losartan (100mg) versus placebo among persons with HIV on ART with plasma HIV RNA <200 copies/ml. Participants underwent an inguinal lymph node (LN) biopsy at baseline and after 12 months. The percent area of collagen and CD4+ T-cells were quantified in the LN paracortical T-cell zone, using quantitative image analysis. Fibrosis markers in blood were measured using ELISA and electrochemiluminescence (Table). Baseline associations estimated the difference in LN percent area collagen associated with a 1-SD difference in T-cell measures. The treatment effect was defined as change on losartan minus change on placebo over 12 months.

Results: Forty-eight participants had LN tissue available for analysis at both baseline and month 12 (n=23 on losartan; n=25 on placebo). Median age was 55 years, HIV diagnosis was 17, and current and nadir CD4+ count were 450 and 59 cells/μm3, respectively; 97% were male, 59% white. The table reports baseline and month 12 levels of study measures. LN collagen was inversely associated with LN CD4+ T-cells (est: -3.8, p < 0.001), though did not reach significance with blood CD4+ count (est. -1.3, p = 0.18), and 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 Gag peptides. Proviral measures were correlated to each other, as expected, but not with time to viremia or level of first VL measured.

Conclusion: Among older persons with longstanding HIV disease, losartan did not alter lymphatic tissue fibrosis or T-cell immune recovery over one year. Future research is needed to identify treatments that reduce lymphatic tissue fibrosis and/or improve the associated T-cell immune depletion, given the importance for restoring health among persons living with HIV.

Table: Losartan does not improve lymphatic tissue fibrosis or T-cell recovery in HIV

278 IL-21 ALTERS TFH DYNAMICS, IMPROVES FLU VACCINE RESPONSE IN OLD SIV+ NHPS UNDER ART
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Background: Incomplete immune recovery despite HIV viral suppression is associated with excess clinical risk, and is, in part a consequence of fibrosis within secondary lymphoid tissues. We hypothesized that the angiotensin receptor blocker losartan would inhibit fibrosis and improve T-cell recovery within lymphatic tissue, given its established effects in blocking TGF-β.

Methods: We pooled data from two randomized (1:1), double-blind, placebo-controlled trials of losartan (100mg) versus placebo among persons with HIV on ART with plasma HIV RNA <200 copies/ml. Participants underwent an inguinal lymph node (LN) biopsy at baseline and after 12 months. The percent area of collagen and CD4+ T-cells were quantified in the LN paracortical T-cell zone, using quantitative image analysis. Fibrosis markers in blood were measured using ELISA and electrochemiluminescence (Table). Baseline associations estimated the difference in LN percent area collagen associated with a 1-SD difference in T-cell measures. The treatment effect was defined as change on losartan minus change on placebo over 12 months.

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Conclusion: Among older persons with longstanding HIV disease, losartan did not alter lymphatic tissue fibrosis or T-cell immune recovery over one year. Future research is needed to identify treatments that reduce lymphatic tissue fibrosis and/or improve the associated T-cell immune depletion, given the importance for restoring health among persons living with HIV.

Table: Losartan does not improve lymphatic tissue fibrosis or T-cell recovery in HIV
further investigation as a potential vaccine adjuvant. or indirectly inducing a shift in pTfh cell kinetics and phenotype, warranting differences were observed, these results highlight that IL-21 may be directly improving flu vaccine titers in old, ART treated, SIV+ RM. As no baseline pTfh 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<0.0001) 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 PD1+ 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.

BUTYROPHILINS: NOVEL IMMUNE CHECKPOINT TARGETS FOR HIV

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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, butyrophilins (BTNks), with high homology to B7 family members (e.g., PD-L1 and PD-L2) and the capability to modulate T-cell activation and HIV expression. We postulate BTNks can be exploited to induce both latent virus reactivation 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 IFNγ 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 Gag-specific CD4 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.

280 BISPECIFIC Au NANOPARTICLES FOR THE ENHANCEMENT OF THE NK IMMUNE RESPONSE AGAINST HIV

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1Vall d’Hebron Research Institute, Barcelona, Spain, 2IrsiCaixa Institute for AIDS Research, Badalona, Spain, 3Hospital Universitario de la Vall d’Hebron, Barcelona, Spain

Background: An efficient 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 bispecific 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 bispecific BiAb-AuNPs as a control.

Results: BiAb-AuNPs increased the number of NK+ HIV+ CD4 T cell 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). 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 bispecific BiAb-AuNPs as a control.

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in some cases ($p=0.013$; 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 GLY COSYLATION MACHINERY DURING TREATED HIV INFECTION

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**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 IFNα2a therapy on circulating IgG glycome and isolated CD8+ T cell-surface glycomes of 18 HIV- mono-infected 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 degranulation (CD107) and sCD163; p<0.03), which c) leads to lower levels of CD8+T cell functionality (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 degranulation (CD107) and sCD163; p<0.03). IFNα-mediated induction of bisected GlcNac associated with a poor reduction of HIV integrated DNA (p=0.02, rho=-0.8). Examining cell-surface glycans, IFNα increases the levels of T antigen (Gal-GalNAc) on CD8+ T cells (FDR<0.01). This association is lower with CD8+ T-degranulation (p<0.02, rho<0.8). Last, IFNα increases the levels of fucose on NK cells (p<0.05). This induction is associated with higher expression of 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-A


**Hospital Clinic of Barcelòna, Barcelona, Spain, 1IDIBAPS, Barcelona, Spain, 2ViiV 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-alpha (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=6); 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, IL-10, IL-2) at w16.

**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 20.0 (2.1); 2) VpIFN -0.44 (0.38) 3) P -0.19 (0.23) 4) PpIFN -0.17 (0.20); (p=0.37). A decrease >1log10 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 HIV-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 significant negative correlation between DVL and HIV-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.

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## 283 PERSISTENT ANTIVIRAL EFFECT INDUCED BY TYROSINE KINASE INHIBITORS

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Background: 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 cytotoxic activity to control the growth of cancerous cells even after withdrawal. Objectives: 1) to analyze cytotoxic 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=6; imatinib=7; nilotinib=6) and healthy donors (n=30) were analyzed by flow cytometry. IFNγ synthesis was analyzed by flow cytometry and proviral 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 IFNγ in response to in vitro CMV pp65 peptide was increased >2-fold in CD8+CD107+ 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 IFNγ secretion from CD8+ T 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 IFNγ-secreting CD8 cells may persist in CML patients even after treatment withdrawal, as well as CD4 cells resistant to HIV infection. These results suggest a possible transient use of TKIs in HIV-infected patients to establish a persistent antiviral activity.

284 RATIONAL DONOR FECAL MICROBIOTA TRANSPLANTATION IN HIV (REFRESH STUDY)

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Background: It is unknown whether oral fecal microbiota transplants (FMT) can affect the gut microbiota and is 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, abundance of Fecalibacterium and Bacteroides (high) and Prevotella (low) and sCD163, sTNFr-2), bacterial translocation (LTA, LBP) and intestinal damage (16S rDNA sequencing, T cell activation/senescence, inflammation (sCD14, sCD163, STNF-2), bacterial translocation (LTA, LBP) and intestinal damage (16S rDNA sequencing, T cell activation/senescence, inflammation (sCD14, sCD163, STNF-2)) and after withdrawal; 2) to determine the susceptibility to HIV infection of CD4 T cells from CML patients off TKI treatment. 285 METHOTREXATE BLOCKS PROLIFERATION NOT INFLAMMATION TO MODULATE IMMUNITY

Michael L. Freeman1, Daniela Mois1, Brian Clagett1, Leonard Calabrese1, Benigno Rodriguez1, Michael M. Lederman1, 1Case Western Reserve University, Cleveland, OH, USA, 2Cleveland Clinic, Cleveland, OH, USA

Background: Inflammation associated with increased risk of comorbidities persists in people living with HIV (PLWH) on combination antiretroviral therapy (ART). Low-dose methotrexate (MTX) is an anti-inflammatory treatment for rheumatological disorders. A recent placebo-controlled trial (ACTG A5314) of low-dose MTX in PLWH found no changes in plasma inflammatory indices, but numbers of total and cycling (Ki-67+) CD4 and CD8 T cells decreased in the low-dose MTX arm.

Methods: Effects of MTX (up to 1000mM) on the release of IL-1ß, IL-6, IFNy TNF, and IL-2 by PBMCs from PLWH (n=6) or HIV-uninfected controls (n=6) was measured by ELISA in culture supernatant following exposure to LPS, flagellin, antibodies to CD3 and CD28 (anti-CD3/CD28), or medium control. Effects of MTX on T cell proliferation (CellTrace Violet dilution), activation (CD69 and CD25 antibodies to CD3 and CD28 (anti-CD3/CD28), or medium control. MTX treatment during anti-CD3/CD28 and IL-2, IL-7, IL-15, or medium control.

Results: At concentrations up to 100mM, MTX treatment did not inhibit IL-1ß and IL-6 release in response to LPS or flagellin; IFNγ, antibodies to CD3 and CD28 (anti-CD3/CD28), or medium control. MTX treatment during anti-CD3/CD28 and IL-2, IL-7, IL-15, or medium control.

Conclusion: Our findings indicate that MTX at concentrations up to 100mM does not inhibit expression of IFNγ, TNF, and IL-2 in response to T cell receptor (TCR) stimulation or IL-1ß and IL-6 after stimulation with the TLR4 and TLR5 agonists LPS and flagellin in vitro. Proliferation of CD4 and CD8 T cells in response to TCR and common gamma chain cytokine stimulation is profoundly reduced by MTX and is associated with cell death in vitro. Folic acid could restore T cell proliferation, but did not fully rescue cell death. Our data are fully consistent with the in vivo effects of MTX in PLWH suggesting that the major effect of MTX on immune function is an inhibition of cellular proliferation.
286LB  ENHANCED COMPLEMENT ACTIVITY DOES NOT IMPROVE PROTECTION IN SHIV-CHALLENGED MACAQUES

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**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 Fcγ 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 FcγR would strengthen protection.

**Methods:** We developed 10 Fc variant bNAbs with site mutations designed to increase CDC activity, C1q binding, and FcγR affinity and evaluated each for binding to FcγRs, C1q, 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/FcγR dual knockout), 10E8v4-EFTAE, (-2-fold enhanced complement deposition, viral lysis, and CDC, increased affinity for FcγRs 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 EFTAE group compared to unmodified 10E8v4 (P<0.0001) and LALA groups (P=0.0070). Viremia was markedly increased in multiple lymphoid and gut tissues in the EFTAE group, over unmodified 10E8v4 (P<0.0001), LALA (P=0.0270), and control (P<0.0001) groups. EFTAE mutations led to lower serum concentrations and neutralizing titers at challenge and reduced serum half-life. Higher doses of 10 and 20 mg/kg EFTAE or unmodified mAb led to comparable PVL, suggesting neutralizing titers may mitigate effects of increased complement. Mechanistic studies show splenocytes treated with super-neutralizing EFTAE 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 FcγRs may not enhance protection. Implications of complement asompization 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

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**Background:** The RV144 vaccine efficacy trial showed a reduction in HIV infection risk (36%) among a subset of participants vaccinated in Thailand and seronegative for HIV-1 Env IgG antibodies. We analyzed RV144 vaccine-induced IgG4 and V1V2-specific antibody responses as correlates of decreased risk of HIV infection in RV144 and show that vaccine-induced responses had consequences post HIV infection. By contrasting the immediate (post-vaccination, pre-infection) and long-term (post-infection) impact of vaccine priming, we can obtain a novel understanding of vaccine-elicited immunity, with characteristic features that can be harnessed to design more efficacious vaccine strategies.

**Methods:** We developed 10 Fc variant bNAbs with site mutations designed to increase CDC activity, C1q binding, and FcγR affinity and evaluated each for binding to FcγRs, C1q, 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/FcγR dual knockout), 10E8v4-EFTAE, (-2-fold enhanced complement deposition, viral lysis, and CDC, increased affinity for FcγRs 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 EFTAE group compared to unmodified 10E8v4 (P<0.0001) and LALA groups (P=0.0070). Viremia was markedly increased in multiple lymphoid and gut tissues in the EFTAE group, over unmodified 10E8v4 (P<0.0001), LALA (P=0.0270), and control (P<0.0001) groups. EFTAE mutations led to lower serum concentrations and neutralizing titers at challenge and reduced serum half-life. Higher doses of 10 and 20 mg/kg EFTAE or unmodified mAb led to comparable PVL, suggesting neutralizing titers may mitigate effects of increased complement. Mechanistic studies show splenocytes treated with super-neutralizing EFTAE 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 FcγRs may not enhance protection. Implications of complement asompization 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.

288  PHASE I/IIA TRIAL OF HIV CLADE C DNA WITH MF59- OR AS01-ADJUVANTED CLADE C PROTEIN

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**Background:** After RV144, the Pax Protein Public Private Partnership initiated multiple trials to evaluate a clade C bivalent protein (TV1.C and 1086.C gp120) vaccine with different adjuvants and priming agents to optimize the design of future vaccine regimens. We showed that substituting DNA (DNA-HIV-PT123) for ALVAC can improve immune responses. The aim of HVTN 108, a phase 1/2a randomized, placebo-controlled trial, was to evaluate the safety and immunogenicity of the DNA vaccine with several protein/MF59/AS01B adjuvant combinations.

**Methods:** We randomly allocated 334 HIV-uninfected participants from the US and South Africa to 7 intervention groups (T1-T7) or placebo. We assessed DNA prime at months (M)0, 1 with DNA/protein/adjuvant boosts at M3 and 6 (T1–T3), DNA/protein/adjuvant co-administration at M0, 1 and 6 (T4–6), and only low dose protein/AS01B at M0, 1 and 6 (T7). Protein was either adjuvanted with MF59 or AS01B. Safety was assessed by collecting reactogenicity and adverse events (AEs). We measured humoral and cellular immunogenicity at M6.5 by binding antibody multiplex assay and ex vivo intracellular cytokine staining.

**Results:** Blinded safety data revealed 48 grade 3, and three grade 4 reactogenicity events in 39 persons, and 30 mild or moderate related AEs. All intervention groups had high IgG response rates (>89%) and high magnitude responses to HIV-1 Env gp120 and gp41 proteins. Response rates for the AS01B-adjuvanted groups approached 100%. TV1.C IgG response magnitude, the correlate of decreased HIV risk in RV144, was higher in the AS01B group (Figure 1). Additionally, there was evidence of a higher IgG3 Env response rate in the AS01B group. CD4+ T-cell response rates and magnitudes to all Env peptide (all p<0.01), except for Env-2-ZM96. Furthermore, the AS01B-adjuvanted lower dose protein did elicit higher magnitude responses than the higher dose protein regimen.

**Conclusion:** DNA/protein/adjuvant combinations demonstrated acceptable safety profiles, with unblinded analysis pending. All groups showed high IgG response rates to gp140 and gp120, and robust responses to Env V1V2. AS01B-adjuvanted groups showed improved CD4+ T cell, V1V2 IgG and Env IgG3 responses. Assessments of durability and antibody Fc effector functions are underway. These data highlight that substituting the MF59 adjuvant with AS01B could further enhance both humoral and cellular responses.

logistic model, and Partial Least Squares (PLS). We filtered redundant immune features to reduce the number of variables to 221, 286 and 284 at 6, 12 and 36 months, respectively.

**Results:** RV144 vaccination primed B cells responses post HIV-1 infection. Vaccines were classified by a specific Fc binding profile with IgG4 responses as the strongest distinguishing feature dominating until 3 years after diagnosis. When effector functions were included, vaccines were characterized by strong V1V2-specific Ab responses synergized with V1V2-specific ADCP responses, whereas placebo recipients had stronger IgG3 and gp120-specific responses. The development of neutralization breadth, which was linked to gp120/gp140 binding features, did not cluster with the vaccine group.

**Conclusion:** Our results showed that the RV144 vaccine primed a specific IgG4 and V1V2-ADCP dominated profile post-breakthrough infection while it did not prime broad neutralizing responses. These findings substantiate the importance of V2-specific binding Abs which were previously identified as a correlate of decreased risk of HIV infection in RV144 and show that vaccine-induced responses had consequences post HIV infection. By contrasting the immediate (post-vaccination, pre-infection) and long-term (post-infection) impact of vaccine priming, we can obtain a novel understanding of vaccine-elicited immunity, with characteristic features that can be harnessed to design more efficacious vaccine strategies.
289 MUCOSAL T AND B CELL RESPONSES INDUCED BY ALVAC-HIV/AIDSVAX B/E LATE BOOST STRATEGIES

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Background: The majority of HIV-1 infections occur across mucosal surfaces, hence mucosal immune responses including CTL, T-helper cells and IgA-secreting plasmablasts (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/AIDSVAX 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 0.09% 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: 0.8%, 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.

290 CANDIDATE IMMUNOGENS DIFFERENTIALLY ENGAGE HIV BROADLY NEUTRALIZING PLASMA ANTIBODIES

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Background: Deciphering factors that drive broadly neutralizing antibodies (bnAbs) induction remains critical to guide HIV-1 vaccine development. Including 4,448 patients with detailed demographic data alongside plasma samples, the Swiss 4.5K Screen had unique means to distinguish positive, independent drivers of breadth (viral load, infection length, viral diversity, black ethnicity) (Ruster et al. 2016). Here we report on the XbnAb cohort, a sub-cohort of the Swiss 4.5K Screen that includes bnAb inducers and matched non-neutralizing (nnAb) controls. Using the controlled setting of the XbnAb cohort we compared the capacity of candidate immunogens in binding naturally occurring Abs and assess their efficacy in predicting bnAb activity.

Methods: We defined within the Swiss 4.5K Screen the XbnAb cohort, which comprises all identified bnAb inducers (N=304) and matched nnAb controls (N=304; matched for HIV-1 subtype, length of infection, host demographics). Patient plasmas were assessed for binding antibodies (IgG1,2,3) against 47 HIV-1 envelope (Env) antigens (including 29 stabilized soluble Env trimer variants and candidate immunogens provided by lead investigators in the field) and 2 Gag proteins using an in-house Lumixen bead assay. EcS, plasma Ab binding activity was established for each antigen and the prediction potential of antibodies to distinguish bnAb activity assessed by univariate conditional logistic regressions.

Results: Confirming work from the Swiss 4.5K Screen (Kadelka et al. 2018) we found that IgG1 Env trimer reactivity is generally higher among bnAb inducers. However, levels of significance varied considerably (p=10-3to p=10-16), highlighting substantial differences among candidate immunogens in engaging natural occurring bnAbs. Comparison of wild type and CD4bs-knockout Env allowed exploring the impact of CD4bs bnAb activity. Of note, IgG1 reactivity of trimeric CD4bs immunogens were good predictors of neutralization breadth, while the monomeric CD4bs tailored immunogens EOD-GT8 and R53C did not differentiate bnAb activity.

Conclusion: Focusing on closely matched bnAb and nnAb inducers, the XbnAb cohort captures the essence of the Swiss 4.5K Screen, providing means to derive population relevant information without the need to screen thousands of individuals. Highlighting the unique capacity of the XbnAb cohort we demonstrate a differential capacity of candidate antigens in engaging natural occurring Abs that needs to be considered when selecting immunogens for further development.

291 ACUTE INFECTION B-CELL DETERMINANTS PREDICT DEVELOPMENT OF NEUTRALIZATION BREADTH

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Background: Determining which immunological mechanisms contribute to the development of broadly neutralizing antibodies (bNAbs) during HIV-1 infection is a goal to inform vaccine design. It is not understood if factors during the acute stages of infection impact the generation of neutralization breadth years later.

Methods: Utilizing 178 longitudinal samples from 72 HIV-1 infected, ART-naive individuals within the RV217 cohort, we identified 16 individuals who neutralized >70% of a panel of 34 viruses (broad neutralizers) and 12 individuals not able to neutralize >35% after 3 years of infection (non-broad neutralizers). Founder env genes were sequenced, and gp140 founder Env proteins were produced to characterize respective early autologous B cell responses. Founder Env+ and total B cell populations were assessed by flow cytometry occurring Abs and assess their efficacy in predicting bnAb activity.

Results: Reduced peripheral B cells starting at month 1 post-viremia were predictive of the development of bNAbs (HR=0.37, 95% CI: 0.18-0.76, p=0.007). Individuals with less than 160 B cells/mm, at month 1 were 42 times more likely to develop neutralization breadth. Reduced peripheral B cells were driven by a
Targeting HIV Env to CD40 Leads to HIV-Specific Polyclonal B Cells in Humanized Mice


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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 Fc gamma receptors are fused to the HIV-1 envelope protein (gp140ZM96) (anti-CD40.Env gp140) with Cpg-B (w0, w3, w5) (CD/CD group) or Nycav Kc pox 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 (scRNA-seq).

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 (7,360 cells/mL [4,022-13,640] and 1,421 cells/mL [1,023-2,830] in the spleen and 356 cells/mL [38-193] and 99 cells/mL [198-951] in the blood; P<0.05 for both comparisons). Increased frequency of blood ICOS+CXCR5+ Tfh-like cells was observed in the gp140ZM96-specific IgG+ B cells in vaccine groups (R=0.70, p=0.004). Analysis of Ig VH and Vk gene diversity showed a large diversity of Ig gene usage in non-specific memory B cells while an enrichment of VH3 and Jk4/5 family gene usage was observed in the gp140ZM96-specific IgG+ B cells. In the N/CD group, these cells exhibited a BCR with longer CDHR3 lengths (37% of clones with CDHR3 > 18 a and up to 28 aa) and a higher rate of somatic hypermutations. Clonal evolution assessed by phylogenetic trees was observed in both vaccine groups with a higher diversity in the N/CD group.

Conclusion: Our results showed that HIS-mice vaccinated with the anti-CD40. Env gp140 vaccine given as a prime or a boost of Nycav KC vector elicited T and B cell-specific responses with a diverse antibody B cell repertoire. Interestingly, gp140ZM96-specific IgG-switched memory B cells exhibit antigen-driven antibody maturation characteristics.

Harnessing Original Antigenic Sin for Preventing MTCT of HIV

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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 (RM).

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.6352i/1086.gpl20 (n=6; vaccine group) or RSV (n=6; placebo group) vaccine with a TRG agonist adjuvant (SIRBIC) 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 gpl20 vaccinated RMs exhibited peak antibody binding responses at 20 wpi (2 weeks post 2nd immunization), with enhanced IgG responses against b.6352i and 1086.g vaccine immunogens; as well as the challenge virus Env, SHIV.C.CH505. Plasma autoimmune virus (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.

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TBK-1-DC VACCINE INDUCES POLYFUNCTIONAL T CELLS AND CONTROL OF HIV-1 IN THE BLT MOUSE

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Background: Dendritic cells (DC) are critical to induce protective antiviral T cell responses, but previous HIV-1 vaccine studies suggest that improvement of DC function is essential for boosting HIV-1 specific immunity. TANK-binding Kinase 1 (TBK-1) is a key regulator of DC maturation in response to HIV-1 and to prime polyfunctional specific T cells. Our objective is to evaluate the efficacy of a vaccine based on TBK1-engineered DCs controlling HIV-1 infection in vivo using the humanized bone marrow, liver and thymus (hBLT) mouse model.

Methods: A total of 24 humanized hBLT-mice were generated for the study. A fraction of autologous CD34+ hematopoietic stem cells (HSC) were used to differentiate DC in the presence of FLT3L, IL-7, SCF and GMSCF. Three separate groups of 8 humanized hBLT-mice were injected with HSC-derived DC cultured in media (MDI), gag peptides alone (GAG) or in combination with 2’-3’-c-AMP and Poly-L-DCB-1 adjuvants (GAG-ADJ) and infected intravenously with 10,000 TCID50 of JRCF HIV-1. Plasma HIV-1 viral loads, polyfunctional T cell responses from peripheral blood and lymphoid tissue and CD4+ T cell counts were assessed at 3 and 6 weeks post-infection. Presence of CD8+ T cells and p24+ infected cells was determined by immunofluorescence in lymphoid nodes. Statistical differences were calculated using a Mann Whitney or a Chi-square tests.

Results: All groups of hBLT-mice became infected with HIV-1, however animals vaccinated with autologous GAG-ADJ DCs exhibited a partial but significant reduction of HIV-1 plasma viral loads at 3 weeks p.i. compared to control groups (p=0.021). These differences were accompanied by higher polyfunctional profiles in circulating CD8+ T cells in the GAG-ADJ group (p=0.005), suggesting partial control of viral replication at early time points. At 6 weeks post-vaccination, plasma viral loads were similar across different groups of vaccinated mice, however Polyfunctional T cells were specifically observed in the spleen from GAG-ADJ and a less severe depletion of CD4+ T cell lymphocytes was detected in these animals compared to GAG mice (p=0.05 vs p=0.0078). Moreover, increased clusters of CD8+ T cells excluding infected HIV-1 p24+ cells from specific areas within the lymph node were also observed in these animals (p=0.001).

Conclusion: Engineered TBK-1 DCs are able to improve parameters of immune control of HIV-1 infection in the hBLT mouse model and might be useful for subsequent vaccine studies.

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CMV VACCINE VECTOR-INDUCED PROTECTION AGAINST SIV IN MAURITIAN CYNOLOGUS MACAQUES

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Background: Strain 68-1 herpes 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 stringently control SIV replication in vaccinated rhesus macaques (RM). However, RM express many more MHC and MHC-E alleles than humans, and it remains unclear if the unprecedented cellular immunity and control of SIV observed in RhCMV/SIV-vaccinated RM 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 elicited 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, limiting-dose, intrarectal SIVmac239 to assess vaccine-mediated protection.

Results: CyCMV/SIV vaccinated MCM generated unconventionally, MHC-I- 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.

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SUPERIOR PROTECTION AGAINST SIV INFECTION BY SAME SITE DNA-PROTEIN COIMMUNIZATION

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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 (CH505). 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 CH505 stock.

Results: Only macaques in the co-administration vaccine group were protected against SHIV CH505 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 IIIa 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 immunogens to the same draining LN could also be beneficial to other vaccine modalities and other pathogens.

298 DOLUTEGRAVIR INCREASES B CELLS AND RESTING MEMORY B CELLS IN RV254
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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 2NRTI 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 (HIV–) 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; CD122+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 (AM) 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.

299 CHARACTERIZING ANTIBODY RESPONSES IN ART-TREATED INDIVIDUALS
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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 period of time 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.

300 NEAR NORMALIZATION OF IMMUNE ACTIVATION IN PLWH ON LONG-TERM SUPPRESSIVE ART
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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 CD4+ T-cells ≥500 cells/mm³, for more than one year before sampling, and CD4/CD8 ratio ≥1 at sampling. RNA-sequencing of polyA-RNAs 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 them, 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-cells 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+ T-cells (CD4+CD25+CD127-IFNγ+TNFα), and INFγ-IFNγ+CD27+ 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

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**Background:** T-cell exhaustion is not reverse by effective ART. T-cell exhausted cells have been associated with HIV persistence during ART. The plasmacytoid dendritic cells (pDCs) sense viral and bacterial products through Toll-like receptors (TLR)-7 and -9 and translate this sensing in IFN-α 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 TLRS agonist were able to reverse T-cell exhaustion.

**Methods:** Patients on suppressive ART (n=5) were compared with healthy donors (HD, n=5) and viremic patients naive for ART (VIR, n=4). pDCs, CD4+ and CD8+ T-cells were isolated from 450ml of whole blood using negative selection. After pDC overnight stimulation with HIV inactivated with alditol (AT-2-HIV), CpG-A, CpG-C, and GS9, or no stimuli, stimulated pDCs were cocultured for 6h with autologous CD4+ or CD8+ T-cells. The expression of PD-1, TIGIT, TIM-3 and LAG3 in different T-cell subsets was quantified 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+ or CD8+ 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 different CD4+ T-cell subsets occurs at the same time of an increase in the polymorphism of different CD4+ or CD8+ T-cell subsets in terms of cytokine production (e.g.: CD107α+IL2-IL17a+NFκB+TNFαCD4+CD45RA+CD27+ expression were significantly increased in ART respect HD after CpG-C and GS9, stimulation p=0.037, respectively).

**Conclusion:** The modulation of the pDCs through TLRS 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

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**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 (≤24) and chronically HIV-infected individuals with longitudinal samples in a median of 3 (CS1) and 10 years (CS2) 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 FlowJo, 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 CS1 and CS2 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 CS1 and CS2 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 CD4 counts and the absence of IR expression in CS2 (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+ T-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

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**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 timeframe 1); median (IQR) yrs on ART 7 (4, 9). We measured responses to pools of overlapping 15-mer peptides spanning the HIV gene products Gag, Env, Pol, Nef/Tat/Rev, as well as CMVpp65. 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...
304 EXPRESSION PROFILING OF HIV LATENTLY INFECTED CELLS VIA NANOSTRING AND MASS CYTOMETRY

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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 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.

Results: The latent population displayed significant upregulation of CD3 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 GTR 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 FOXP3 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. FOXP1 and FOXP3 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

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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 transposon accessibility, with LRAs inducing 'transposon activation' in productively infected cells and 'transposon repression' in latently-infected cells.

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
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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 CD4+ T cells: models from labs of Eric Verdin, Alberto Bosque, and Warner Greene; tissue (tonsillar) CD4+ T 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 [SLTR, Gag, Poly, Nef, MF, Tat-Rev, U3-PolyA, and the iPAO assays for Env and 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 CCR5 (**), POLR2A (**), APOBEC3G (*), and STING (*), and lower expression of PRMT6 (*), while latent cells from the Bosque model expressed higher levels of CGAS (**), and latent tonsil cells from the Greene model showed higher expression of CD7, P8AF, BIG-I, and MDA5 (* for all). Compared to HIV-exposed but uninfected cells, latently-infected cells showed: 1) less CCR5 (*), CD38 (*), 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-2, CD38, and HLA-DR, while latent cells from the Bosque model showed higher expression of CCR5, POLR2A, APOBEC3G, and STING; latent tonsil cells from the Greene model showed higher expression of CD14, CXCR4, and GLI-1, and MDA5 (* for all). Compared to HIV-exposed but uninfected cells, latently-infected cells showed: 1) less CCR5 (*), CD38 (*), 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-2, CD38, and HLA-DR, while latent cells from the Bosque model showed higher expression of CCR5, POLR2A, APOBEC3G, and STING; latent tonsil cells from the Greene model showed higher expression of CD14, CXCR4, and GLI-1, and MDA5 (* for all). Compared to HIV-exposed but uninfected cells, latently-infected cells showed: 1) less CCR5 (*), CD38 (*), 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-2, CD38, and HLA-DR, while latent cells from the Bosque model showed higher expression of CCR5, POLR2A, APOBEC3G, and STING; latent tonsil cells from the Greene model showed higher expression of CD14, CXCR4, and GLI-1, and MDA5 (* for all). Compared to HIV-exposed but uninfected cells, latently-infected cells showed: 1) less CCR5 (*), CD38 (*), 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.

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
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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/transcriptional 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 C2C Homolog 2 (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 intronic 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
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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%, +11.4%). The estimated half-life of the reservoir was 4.0 years (CI: 2.6-7.9) until year seven and 19.0 years (CI: 8.2-8.2) thereafter. Intact provirus declined at a faster rate than defective provirus (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 role of the replication-competent (intact) reservoir differs from that of the replication-incompetent (non-intact) pool of proviruses.
309 DISTINCT HIV RESERVOIR MEASURES CORRELATE WITH DEFECTIVE BUT NOT INTACT PROVIRAL DNA

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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/rev 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 5’ 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+1 subjects chronically suppressed on ART best reflect hypermutated and/or deleted rather than intact pro-viral DNA.

310 RISK AND PREVALENCE OF RESIDUAL VIREMIA AFTER ART IN RESOURCE-LIMITED COUNTRIES

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Background: Prevalence of residual viremia was defined as having ≥ 1 copy/mL. The limited data describe residual viremia from low- and middle-income countries (LMIC). We assessed the prevalence, and factors associated with residual viremia in PWH, who were virally-suppressed 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/rev 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 5’ 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+1 subjects chronically suppressed on ART best reflect hypermutated and/or deleted rather than intact pro-viral DNA.

A NOVEL DDPCR PROTOCOL TO ESTIMATE COPY NUMBERS OF POTENTIALLY INTACT HIV-1 PROVIRUS

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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 (PLWH). 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 all 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 probit 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 control tests) and reproducibility (CV of positive control aliquots tested 23x over control tests). 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 QVOA (range: 0.08-3.49 infectious units/million) and ddPCR (0.1-1,900 copies/million, undetectable in 2/14 samples). ddPCR averaged 99.2x (range: 0.5-557x) 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

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**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) from 0.70 to 0.81.

**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 high and remained high or increased longitudinally. The stepwise model for low HIV-1 DNA levels that included all antibody levels as predictors.

**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.

### 313LB LONGITUDINAL QVOA AND IPDA MEASUREMENTS IN CD4 T CELLS FROM ART-SUPPRESSED DONORS

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**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 necessary.

**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

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**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 multiple-spliced HIV transcripts were measured by ddPCR. Phenotyping of immune cells was conducted by GTOF. 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 (all 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, 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 EFFEC tor MEMORY T CELLS MATCH PERSISTENT VIREMIA

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PERSISTENT VIREMIA affect different blocks to HIV transcription. Latency-silencing agents, will be required to penetrate into multiple tissues and penetrating latency-reversing or latency-silencing agents, will be required to penetrate into multiple tissues and govern HIV latency, with greater suppression of HIV transcription in most tissues than blood.  The capacity to measure and characterize HIV reservoir at the level of viral protein and assess the relationship between immune phenotype revealed p24 correlates with immune function and will be important for immune-based clearance strategies.

### 317 LACK OF COMPARTMENTALIZATION IN THE LATENT RESERVOIR OF BLOOD AND LYMPH NODES

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**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 to 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 gp41 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. Neighboring 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=54.8–16.0), as compared to 26 in LN (IQR=27.8–21.3). The estimated frequency of latently infected cells was 10.4 induced proviruses per million cells (IPPMC) in PB (IQR=16.5–7.5) and 6.4 IPPMC in LN (IQR=13.2–6.8). Replicate 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
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RESERVOIR IN CERVIX

the LR found in the blood can be a good representation of the LR in the lymph 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

318 CHARACTERIZATION OF CD8+ TRM TOWARD THE CONTROL OF THE HIV RESERVOIR IN CERVIX

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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+TRM 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, Hobi, oα and PD-1 expression. Further, CD8+TRMs expressed more frequently CXCR3, CX3CR1, CD103 and CD69 compared to non-CD8+TRMs, and less frequently oα, CD122 and gITC (p<0.05). Cervical samples from ART-suppressed patients were enriched in total CD8+T cells compared to uninfected women, including higher frequencies of non-TRMs (p<0.01) and TRMs (p<0.05), and higher expression of HLA-DR (p<0.01). Importantly, the frequency of cervical CD8+TRMs correlated with proviral HIV-1 DNA in cervix (r=0.82; p=0.03) and tissue CD8+TRMs showed better control of the reservoir in reactivated cells than effector circulating CD8+T cells.

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+TRM in cervix and less proviral HIV-1 DNA, together with data showing higher control of virally-reactivated infected cells by CD8+TRM, indicates that these cells may be critical to control persisting virus in tissues.

320 VIRAL REBOUND KINETICS FOLLOWING SINGLE AND COMBINATION IMMUNOTHERAPY FOR HIV/SIV

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Background: HIV infection can be treated but not cured with antiretroviral therapy, motivating the development of new therapies that instead target host immune responses. Three such immunotherapies were recently tested in non-human primates – a TLR7-agonist, therapeutic vaccine (Ad26/MVA), and broadly-neutralizing antibody (PGT121) – and cured a subset of animals by preventing or controlling viral rebound after antiretrovirals were stopped. The goal of this study was to use viral dynamics modeling to infer the mechanisms of action of these therapies and predict outcomes in human trials. In addition, we examined whether they reduced the pool of latently-infected cells versus boosted antiviral immunity, and whether they acted independently or synergistically.

Methods: Here we conducted a detailed analysis of the kinetics of viral rebound after immunotherapy. We introduce a new mathematical model of viral dynamics that incorporates both the stochastic and deterministic regimes of rebound and includes the action of adaptive immune responses. This model is fit to data from 99 macaques across three separate studies using a non-linear mixed-effects statistical approach. A rigorous model comparison procedure was designed to identify the effects of each intervention and quantify the impact on viral dynamics. To predict the impact of these immunotherapies in clinical trials, we calibrated the model to HIV rebound in human treatment interruption trials and simulated the effect of adding each immunotherapy.
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 only after a high peak viral load. Heterogeneity in rebound time and peak/setpoint viral loads between some patients is predicted to be very high.

Conclusion: 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.

FREQUENCY OF POSTTREATMENT CONTROL VARIES BY ART RESTART AND VIRAL LOAD CRITERIA

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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-calc/) 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 PTC frequency (default is the CHAMP study criteria: pVL<400 cps/mL at ≥2/3 time points for ≥24 wks post-ATI).

Results: We compared the impact of several commonly used ART restart criteria (1,000 pVL x 1 wk, 1,000 pVL x 2 wks, 1,000 pVL x 4 wks, and 50,000 pVL x 4 wks) on the ability of a hypothetical ATI trial to detect PTCs. Our calculator estimates that these criteria fail to identify 30%, 10%, 0%, and 0% of PTCs, respectively, due to premature ART restart. The sensitivity and specificity of PTC detection also varied by ART restart criteria. Of the 4 criteria, the 1,000 pVL x 1 wk criteria had high specificity (99%), but low sensitivity (43%), while the 50,000 pVL x 4 wks criteria had low specificity (15%), but high sensitivity (100%). The 1,000 pVL x 4 wks criteria achieved a balance with 91% specificity and 93% sensitivity for identifying PTCs. Using high pVL thresholds (>10,000 cps/mL) for ART restart substantially reduces the specificity of PTC identification in early-treated participants, likely related to their overall lower pVL peaks compared to chronically treated participants. The expected frequency of PTCs varied dramatically by the PTC definitions (Figure). In almost all scenarios, PTC frequency was significantly higher in early-treated individuals.

Conclusion: This 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.

NONSTRUCTURED TREATMENT INTERRUPTIONS CONTRIBUTE TO LATENT HIV-1 RESERVOIR IN PWID

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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 log10, 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 log10, 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**

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**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 551 HIV-1 full-length envelopes were isolated by single genome amplification from plasma of six individuals who underwent ATI. Isolated envsequences 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. Intra-host evolutionary rate in the envgene was estimated using a robust estimate of intra-host evolutionary rate in the envgene (7.53 10^-3 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.

**325 HIV POSTTREATMENT CONTROL DESPITE PLASMA VIRAL EVOLUTION AND DUAL INFECTION**

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**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. 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 wks 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.

**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 wks 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.

**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.
treated PTCs (Figure). The proportion of HLA-escape mutations were common in plasma HIV sequences from PTCs and not significantly different than NCs (47% vs 59%, p = 0.16). Unexpectedly, the presence of dual HIV infections (populations of HIV variants with ≥5% sequence divergence) was detected in the plasma SGRs for 3 PTCs (1 early-treated, 2 chronic-treated) and for none of the NCs. In two participants, dual infection was detected at the early ATI time point with one variant becoming dominant over time. One individual was found to have an apparent superinfection with a late post-ATI viral rebound of a second HIV variant before subsequently regaining HIV control.

Conclusion: PTCs exhibit sustained HIV remission despite evidence of slow plasma viral diversification and evolution. The detection of dual HIV infection in a subset of PTCs suggests the presence of an antiviral response that can control a diverse viral population.

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Figure. Example of HIV sequence evolution for one PTC. Neighbor-joining phylogenetic tree of the single-genome provirus sequences at early (14 weeks) and late (408 weeks) time points after antiretroviral treatment interruption (ATI) (A). Graph of the post-ATI viral load and CD4+ cell count in (B) with upper arrows indicating samples used for plasma sequence analysis. Changes in viral diversity by average pairwise distance (C), rdt-ln distance (D), and proportion of sites with HLA-escape mutations (E) at the early and late ATI time points.

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326 EVALUATING BIOMARKERS FOR HIV REBOUND DURING TREATMENT INTERRUPTION

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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.

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327 HIV DIRECTLY INFECTS RESTING MEMORY CD4 T CELLS

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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 CCR5-tropic replication-competent 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, Vif or Vpu-Env, but never for Gag-Pol, Tat or Rev. The analysis of scATACseq and scRNAseq revealed this differential expression of HIV mRNAs was due to HIV integration into genes that are stochastically transcribed across resting CD4 T cells. Importantly,
Establishment of the HIV-1 DNA reservoir mirrors the replication-competent reservoir

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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. MiSeq with Primer ID was used to sequence 5 genomic regions from DNA 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 sequenced 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 reservoir entry 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 (Fisher’s exact test, all p > 0.05). For the overall cohort (N=16; 2 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.
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 on a HIV latency model 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 naive donors were infected in vitro and co-cultured with activated CD8+ T lymphocytes (1:1 or 1:1.5 target:effector ratios) in the presence of the anti-retroviral compound saquinavir. After three days, we assessed intracellular Gag expression on CD+ 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 1:1.5 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 at an average of 9-fold (p<0.0001) and 18-fold (p<0.0001) at 1:1 or 1:1.5 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 1:1.5 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.

333 THE HIV ANTISENSE TRANSCRIPT AST INDUCES VIRAL LATENCY VIA SEVERAL SILENCING PATHWAYS

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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 5LTR, 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 5LTR 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 by 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 performed RNAseq in cells stably transduced with Ast compared to cells stably transduced with empty lentivirus and parental cells, and using three different cellular backgrounds. Only 7 and 16 host genes differentially expressed in Ast-expressing cells compared to parental cells and empty lentivirus cells, respectively. To gain insight into Ast transcriptional regulation, we measured Ast expression in response to a panel of LRAs and found that all agents induced antisense transcription to similar or greater extent than sense HIV-1 transcription.

Conclusion: We identified the LTR- and PRC2-binding regions of Ast, and new Ast-binding partners. We found that Ast does not affect host gene expression and is highly specific for HIV-1. These results identify Ast 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

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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 reservoirs, 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 52 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-CD62L+). However, HIV+ individuals had more activated (HLA-DR+) 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 (AS366)

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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 AS366 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 in those receiving full study treatment (efficacy group). Total HIV DNA and unspliced cell-associated RNA (cRNA) were measured in 5x10^6 CD4 T cells by qPCR, and spliced HIV envelope transcripts were measured in 106 resting memory CD4 cells by EDTIS 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 668 cells/mm³. 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 cRNA (mean fold change: ArmA 1.2, ArmB 1.5, p=0.6) or in EDTIS (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 EDTIS also increased (mean fold change: 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, ESR1 antagonism with tamoxifen was not associated with a significant change in the magnitude of HIV RNA induction by qPCR or EDTIS. Induction of HIV RNA after vorinostat by the EDTIS assay was similarly 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>Histone 3 acetylation</th>
<th>Overall</th>
<th>Arm A</th>
<th>Arm B</th>
</tr>
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<tbody>
<tr>
<td>Decrease N=18</td>
<td>Increase N=18</td>
<td>Decrease N=12</td>
<td>Increase N=4</td>
</tr>
<tr>
<td>EDTIS fold change</td>
<td>0.5 (0.40-1.2)</td>
<td>0.44 (0.64-1.19)</td>
<td>0.66 (0.40-1.78)</td>
</tr>
<tr>
<td>HIV RNA</td>
<td>-0.05 (0.00-0.49)</td>
<td>0.87 (0.01-1.39)</td>
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### Figure 1

**334 EFFECTS OF IMMUNE CHECKPOINT THERAPY ON LATENT HIV IN PEOPLE WITH HIV AND MALIGNANCY**


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**Background:** Immune checkpoint blockade (ICB) is highly effective for the management of some malignancies and can potentially perturb HIV persistence in people living with HIV (PLWH) on antiretroviral therapy (ART) by enhancing HIV-specific CD8+ T cells and/or reversing HIV latency. We established a prospective cohort of PLWH on ART with malignancy who received any ICB and quantified immunological and virological changes in three participants.

**Methods:** Blood was collected prior to and following the first 4 cycles of ICB at day 1, 7, 14 and 21. We quantified cell associated (CA) unspliced (US) RNA and HIV DNA from peripheral blood CD4+ T cells, frequency of cells with inducible multiply spliced (MS) HIV RNA by the Tat/rev Induced Limiting Dilution Assay (TILDA) and HIV RNA in plasma by single copy assay (SCA). Gag specific immune responses were measured by intracellular cytokine staining (ICS) for IFN-γ, TNF-α, and CD107a in T-cell subsets defined by expression of CD45RA and CCR7.

**Results:** Participant (P) 1 received avelumab (anti-PD-L1) 2 weekly for chest wall Merkel cell carcinoma. P2 and P3 received ipilimumab (anti-CTLA4) and nivolumab (anti-PD-1) 3 weekly for metastatic melanoma. P1 demonstrated partial response to ICB, before relapse and progression of disease. P2 had disease progression on ICB and died before study completion. P3 responded to ICB and remains on maintenance anti-PD-1.

An increase in CA-US RNA following each infusion was noted in all 3 participants (Fig 1A, B). There was an increase in the mean fold change in CA-US RNA from cycle 1 to 4 of 1.3, 3.1, 6.8 and 8.6 respectively. No consistent changes in HIV DNA were noted in any participants. P3 had an increase in plasma viremia from a baseline of 4 c/ml to 16 and 8 c/ml following cycle 2 and 3 respectively, and a 33% reduction in inducible MS RNA as measured by TILDA. There were no changes in plasma viremia or inducible MS RNA in P1 or P2. With respect to gag-specific ICS, P2 demonstrated a striking increase in the frequency of central and effector memory CD8+ T cells producing IFN-γ, TNF-α, and CD107a (Fig 1C-E), which were not demonstrated in P1 and P3.

**Conclusion:** Increases in HIV transcription were observed on ART in all three participants following each cycle of either anti-PD-L1 or anti-PD-1 + anti-CTLA-4, with variable effects on plasma viremia, TILDA and ICS. Our results highlight that ICB can perturb HIV latency and increase HIV-specific immune responses but with significant variation between individuals.
S’elongated HIV RNA per provirus (p=0.07, median fold-change=0.5), and a lower median level of unspliced HIV RNA (p=0.5, median fold-change=0.9), but no decrease in polyadenylated or multiply-spliced HIV RNA. However, S’elongated HIV RNA per million CD4+ T cells increased significantly (p=0.03, fold-change=1.4) after ABX464 discontinuation (wk4 vs wk8).

**Conclusion:** In this substudy, 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.

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**336 ATTACKING LATENT HIV WITH CONVERTIBLE CAR-T CELLS, A MODULAR KILLING PLATFORM**

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**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 convertible CAR-T cells (cCAR-Ts) programmed with multiple HIV-specific broadly neutralizing antibodies (bNabs) are deployed.

**Methods:** cCAR-Ts utilize a muted, inert form of the NK2G2 receptor. Orthogonal Mic ligands that bind to inert NK2G2 but not wild-type NK2G2 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, CDB 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.

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**337 CAR-T CELLS AT 15 YEARS: PERSISTENCE OF CD4-ZETA TRANSGENE AND EFFECT ON RESERVOIR**

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**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 10^9 autologous CD4+ gene modified T cells ± subcutaneous IL-2 at 1.2 million IU/m, for 56 days. Inclusion criteria included CD4≥200, viral load<50, stable HAART for>2 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. RNAseq 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 ± 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-1RNA+ cells can be identified in the majority of rectal biopsies. Total PBMC HIV DNA at long-term follow up, and the change in total and integrated HIV DNA from pre- and post-treatment compared among the treatment arms was not statistically significant.

**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.
339 HIV-SPECIFIC T-CELL RESPONSES IN AN HIV-POSITIVE COHORT POST ALLO-HSCT
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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 exposure, 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
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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 suppressive ART. The in vivo anti-proliferative effect of MMF was assessed using a "total antiproliferation test" (TAPT) assay, in which anti-CD3/CD28-stimulated participant T-cells are exposed to serum from participants after MMF dosing. The TAPT is reported as percent reduction in proliferation compared to serum/cells taken before the start of the trial. We escalated the MMF dose in those individuals with <80% anti-proliferative effect at peak drug levels (one-hour after dosing). We measured the effect of MMF on levels of total ("total") and potentially intact ("intact") HIV proviral DNA at 3-month intervals. HIV proviral DNA was measured with a multiplexed digital droplet PCR assay simultaneously targeting HIV-1 gag, env and pol genes.

Results: All participants maintained stable CD4+ T cell counts and subset composition, remained suppressed on ART and tolerated MMF. One participant required dose escalation from MMF 500 to 750 mg twice daily to achieve >80% anti-proliferative effect at drug peak. Proliferation inhibition at drug trough pre-dosing was highly variable. No participant met the pre-specified 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).

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
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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, respectively, 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-γ 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
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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.
Methods: We asked in this study whether a new IAPa would stimulate the potency of an anti-human PD-1 monocolonal 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+ in blood 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 5 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

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Background: The cellular immune response of HIV-infected individuals is not well characterized in the central nervous system (CNS) and thus lacks a comprehensive understanding of CNS immune activation. Here, we compared the impact of GS-986, PGT121 and N6-LS, monoclonal antibodies that neutralize HIV-1 in the CNS, on CNS immune activation in SHIV-infected rhesus macaques (n=16).

Methods: Eight rhesus macaques (n=16) were intrarectally inoculated with SHIV-1157gd3a 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 bNAbs 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 by multiplex assay using Luminex.

Results: Median wk2 (pre-ART) plasma and CSF SHIV RNA was 5.7 (range 4.1-6.8) and 3.1 (range 2.2-4.2) log10 copies/mL, respectively. After ART initiation on Day14, plasma SHIV RNA was undetectable in all animals by wk8 and remained undetectable until ART interruption. CSF SHIV RNA was also undetectable in all animals during GS-986 dosing (wk24). Median time to viral rebound was 6 weeks in active arm and 3 weeks in control arm (p=0.024). At 12 weeks post rebound, median plasma SHIV RNA was 1.2 (range 1.0-2.2) and 2.1 (range 1.0-2.8) log10 copies/mL in the active and control arm, respectively. CSF SHIV RNA was only detectable at low levels in 1 active and 1 control arm animal. Longitudinal CSF samples from the active group sample showed significant increases in IL-15 (p=0.008), MCP-1 (p=0.008), IL-8 (p=0.008), IL-1RA (p=0.016), IL-2 (p=0.031), and G-CSF (p=0.008) at wk2 when compared to pre-infection, that decreased after ART initiation to pre-infection levels. Importantly, levels 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.

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344 BRENTUXIMAB VEDOTIN REDUCES CD30 EXPRESSION AND GUT HIV DNA LEVELS IN HUMANIZED MICE

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Background: CD30 is preferentially expressed in HIV-infected and viral transcriptionally active CD4 T cells from viremic and ART suppressed individuals. We observed treatment with anti-CD30 antibody drug conjugate, brentuximab vedotin (BV), leads to reduced cell-associated HIV DNA in vitro and transient decreases in cell-associated HIV RNA in vivo. The impact of anti-CD30 therapy on tissue measures of HIV burden is unknown.

Methods: Humanized BLT mice were initiated on daily TDF, FTC, and DTG by oral gavage approximately 3 weeks following intraperitoneal infection with HIV-1JR-CSF. After mice achieved viral suppression they were divided into three treatment cohorts: [1] ART alone control (N=16); [2] ART and 3 intraperitoneal (IP) weekly infusions of 20 mg/kg BV (N=18); [3] ART, BV and a single 2.5/10μg IP injection of IL15/IL15RaFC given with the first dose of BV (N=18). Three weeks after the last BV infusion, mice were sacrificed and HIV DNA and RNA were isolated from blood, ileocecal junction, spleen, lymph nodes, and liver.

Results: The frequency of CD30 expression on human CD4+ T cells was low in all cohorts, BV with and without IL15/IL15RaFC led to significant reduction in the frequency of human CD4+ CD8+ T cells expressing CD30 (0.09% in ART controls, 0.05% in both treatment cohorts; P=0.03) and HLA-DR (4.0%, 0.6%, 0.6%, respectively; all P<0.01). BV with and without IL15/IL15RaFC also led to the reduced frequency of effector memory CD4 T cells (14% to 8% and 6%, respectively) and increased frequency of naive CD4+ T cells in peripheral blood (68% to 71% and 75%, respectively). Overall, there were no significant changes in blood, spleen, lymph node, and liver levels of cell-associated HIV RNA or DNA, but BV treated mice had significantly lower HIV DNA measured in gut tissue compared with ART-only controls at the time of necropsy (HIV DNA 164 c/106 vs 21,788 c/106 cells; P=0.04). Gut HIV DNA levels were similar to controls in mice that received concomitant BV and IL15/IL15RaFC.

Conclusion: BV treatment in BLT mice decreased the frequency of CD4 T cells expressing CD30, markers of T cell activation, and effector memory phenotype. BV alone, but not in combination with IL15/IL15RaFC, led to decreased gut HIV DNA levels. However, the high percentage of circulating naive lymphocytes and overall low CD30 expression in the BLT mouse model may have dampened the impact of anti-CD30 therapy on measures of HIV persistence.
345LB PGT121 AND VESATOLIMOD IN CRONICLY TREATED SHIV-INFECTED RHESUS MONKEYS

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Background: We have previously reported that administration of the broadly neutralizing antibody PGT121 in the 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 time of 21 [IQR 14-21] days. In contrast, only 50% (4 of 8) of PGT121 + VES treated animals and 66% (6 of 9) of GS-9721 + VES treated animals rebounded by day 140 after ART discontinuation (P=0.05, Fisher’s exact test compared with sham controls) and showed a delay in the median rebound time of 28 [IQR 21-140+] days.

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 41% (7 of 17) 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 of chronic SHIV infection in rhesus monkeys.

346LB SUSTAINED REMISSION IN THE LONDON PATIENT: THE CASE FOR HIV CURE

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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 intratuberine-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 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.

Conclusion: We present a child with intrauterine-acquired HIV infection, initiation of ART at 33 hour 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 child or virus are being investigated.
348LB EDITING OF SIV IN NONHUMAN PRIMATES BY CRISPR-CAS9 IN VIRAL RESERVOIRS

**Background:** To date only 3 patients have achieved long-term HIV-remission after analytic therapy interruption (ATI). Here we provide an update of the Duesseldorf patient (iCStem#19). This HIV-infected male patient (50y, heterozygous CCR5Δ32 allele) received unmodified stem-cell transplantation (SCT) from a 10/10 matched CCR5Δ32/Δ32 donor in Feb/13 for acute myeloid leukemia. At time of SCT complete western blot pattern was detected, proviral load was 1.45 log10 cop/Mio PBMCs with R5-coreceptor-tropism. In Jun/13 full remission was achieved by S-Azacytidine and donor lymphocyte immunosuppression. The absence of HIV-antigen is confirmed by fading humoral reactivity.

**Conclusion:** Here we demonstrate broad SIV DNA excision in viral reservoirs leading to permanent inactivation of SIV proviral DNA in a one shot CRISPR molecule. We observed biodistribution of AA9-CRISPR-Cas9 in the blood in a dose and time dependent manner for the elimination of SIV DNA. These findings support the utilization of AA9-CRISPR-Cas9 as a potential therapeutic strategy for in vivo gene editing of HIV proviral DNA from latent tissue reservoirs.

**Methods:** PBMC/tissues analysed by ddPCR/qPCR and in situ hybridization.

**Results:** Drug level assessment by liquid chromatography mass spectrometry. After ATI no antiretrovirals could be detected in multiple plasma samples. In Jul/19 no HIV DNA was detected in CD4+ cells extracted from biopsies (duodenum/ileum/rectum). Neutrophils and IFN-γ responses in the GI tract were very low. CD4 T cells were abundant within GI tract follicular aggregates, RNAscope was negative, DNAscope showed few positive signals, but not clearly above the false detection rate. In Oct/17 CD4+ T cells were negative in the duodenal lymph nodes (LN) and lymph nodes (L) in Feb/18 were negative by PCR. In situ hybridization assays (RNAscope, DNAscope) detected few positive signals in LN. Moderate acute and mild chronic GvHD occurred after DLI but Tacrolimus could be finally stopped in Dec/17. He remained on ART with undetectable plasma VL until analytic therapy interruption (ATI) in Nov/18.

**Methods:** At time of SCT complete western blot pattern was detected, proviral load was 1.45 log10 cop/Mio PBMCs with R5-coreceptor-tropism. In Jun/13 full remission was achieved by S-Azacytidine and donor lymphocyte immunosuppression. The absence of HIV-antigen is confirmed by fading humoral reactivity.

**Conclusion:** No viral rebound was observed for 14 months following ATI, 83 months after allogeneic CCR5Δ32 SCT. In depth analyses of the viral reservoir still showed traces of HIV DNA in LN and GI tract, not clearly representing infectious virus though, since all functional assays were negative. These results are compatible with sustained remission of HIV.

349LB EDITING OF SIV IN NONHUMAN PRIMATES BY CRISPR-CAS9 IN VIRAL RESERVOIRS

**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 AA9 gene therapy vector was constructed to deliver CRISPR-Cas9 plus two gRNAs targeting sequences within the 5’ and 3’ viral LTRs and the Gag gene to excise the intervening proviral DNA fragment. Ten adult Indian rhesus macaques were infected with SIVmac239 then treated daily with a drug regimen of tenofovir, emtricitabine and dolutegravir (1.5/0.5/2.5mg/kg daily s.g.). Animals were randomized into groups to receive low versus high dose of AA9-CRISPR-Cas9 in a single i.v. infusion (low dose: 1.4x1012 GC/kg x 3; high dose: 1.4x1014 GC/kg x 3) as well as control SIV infected animals (n=3). Longitudinal blood samples and lymph node biopsies were collected, and animals were necropsied at 3, 6 or 12 months of treatment.

**Results:** SIV-infected animals treated with AA9-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 AA9-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 AA9-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 AA9-CRISPR-Cas9 SIV proviral 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 molecule. We observed biodistribution of AA9-CRISPR-Cas9 in the blood in a dose and time dependent manner for the elimination of SIV DNA. These findings support the utilization of AA9-CRISPR-Cas9 as a potential therapeutic strategy for in vivo gene editing of HIV proviral DNA from latent tissue reservoirs.

**Methods:** Guides were screened for editing efficiency by CRISPR/Cas9

**Results:** Dual guides achieved a 92% CRISPR editing frequency in mobilHSPCs from an anonymous HIV-negative donor (guide 1: 70%; guide 2: 58%; total: 92%). After transplant into NSG mice, CRISPR edit HSPC editing and transplant.

**Conclusion:** These data demonstrate that high frequency CRISPR/Cas9-mediated editing of CRISPR in human HSPCs is feasible 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 PPARγ FOR TH17 MUCOSAL IMMUNITY RESTORATION AND HIV-RESERVOIR PURGING

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**Background:** The Th17-polarized CCR6+ RORγt+ CD4+ T-cells are key players in mucosal homeostasis. These cells are preferential targets for HIV/SIV infection at mucosal sites and their depletion/functional 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 PPARγ represses RORγt, Th17-specific master regulator and HIV transcription, we hypothesized that PPARγ pharmacological inhibition will enhance Th17-effector 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-term/long-term viral outgrowth assays (VOA) were performed with cells from ART-treated PLWH in the presence/absence of the PPARγ antagonist T0070907 for 12 days. Short-term/long-term viral outgrowth assays (VOA) 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 antagonir.

**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 functional validations were performed. PPARγ inhibition in CCR6+CD4+ T-cells up-regulated transcripts linked to Th17 polarization (RORγt, STAT3, BCL6 IL-17A/F, IL-21), HIV transcription (CDK9, 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 antagonir 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

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**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 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 lines 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

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Background: A key challenge in developing successful HIV-1 cure strategies is the need to eliminate the integrated provirus from the genomes of infected CD4+ T lymphocytes and monocyte-macrophages. In a first step towards this, 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 pseudotyping modified lentiviral structural proteins with dual-tropic HIV-189.6 envelope by co-transfection of plasmids in HEK293 FT cells. A duplex LTR and gag splicing CRISPR-Cas9 system was inserted via plasmid. Non-gene payloads including streptavidin targeting epitope (gp120) expression as native infectious HIV-1 but were independently loaded in the VLPs.

Results: VLPs retained the same 150nm size, spherical morphology, and targeting epitope (gp120) expression as naïve infectious HIV-1 but were replication incompetent. Using our bioconjugation system, streptavidin quantum dots, biotinylated fluorophore and a cabotegravir (CAB) produg were individually loaded in the VLPs.

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 RNA

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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 hypothesised 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 VXN MFC =0.47; JQ1+1μM VXN MFC =0.60), compared to the decline resulting from each drug alone (PNB MFC =0.71; JQ1 MFC=0.88; 1μM VXN 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”.

Figure 1: HIV-1 VLP Schematic

355 NOD2 AND TLR8 AGONISTS ENHANCE IL-15-MEDIATED ACTIVATION OF HIV EXPRESSION

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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**

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**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) rmodemipin (rm) 4) bryostatin (bryo) 5) IL-15 6) rm/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, 40×40 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 rm/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.
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 proliferation 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.

359LB AMINOBISPHOSPHONATES REVERSE LATENCY IN HIV-SEROPOSITIVE INDIVIDUALS
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Background: We hypothesized that aminobisphosphonates (N-BPs), such as pamidronate (PAM), zoledronate (Zol) and alendronate (ALN), that inhibit the formation of farnesyl pyrophosphate groups, used for protein prenylation reactions, may induce reactivation of latent HIV. 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 PMA, PAM or Zol, and then cell-associated HIV RNA (cHIV RNA) 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, 4, 8 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 infection. We measured cHIV RNA 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 time 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 immune cell populations with pathways altered by N-BP treatment and those altered following HIV infection. Change shade identifies the three participants in which N-BP treatment resulted in a 49.1-fold decrease in total HIV cDNA levels.

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.

360 PARALLEL HIV RNA INTEGRATION SITE, AND PROVIRAL SEQUENCING IN SINGLE RESERVOIR CELLS
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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 (PRIPSeq). 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 (2%) 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 PRIPSeq 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
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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 of infected cells to play a direct role in HIV-related cancer.
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 multimetric 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 Transcripts and Epitopes by sequencing), we captured 1) surface protein expression, including memory phenotypes, activation status and exhaustion markers, 2) transcriptome, and 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 7,790 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 cells 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

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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 V-J junction of the TCR beta chain (including the CDR3 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

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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 sites (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 integration 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>In Vitro</th>
<th>In Vivo</th>
<th>Proviruses with sense orientation</th>
<th>Orientation Probability (selected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MKL2</td>
<td>5%</td>
<td>55%</td>
<td>2.3x10^-50</td>
<td>9x10^-30</td>
</tr>
<tr>
<td>BACH2</td>
<td>5%</td>
<td>55%</td>
<td>2.3x10^-50</td>
<td>9x10^-30</td>
</tr>
<tr>
<td>STAT5B</td>
<td>5%</td>
<td>55%</td>
<td>2.3x10^-50</td>
<td>9x10^-30</td>
</tr>
</tbody>
</table>

364 HIV DYNAMICS AND REPOPULATION OF RESERVOIRS IN THE HUMAN BODY

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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...
LONGITUDINAL CHARACTERIZATION OF HIV PROVIRUSES IN PEOPLE ON SUPPRESSIVE ART

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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 persistency are similar in this population despite stronger, polyfunctional HIV-specific CTLs.

Identification of HIV Proviruses Arise from Cell Expansion and Infection by Common Ancestor

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Background: Understanding the mechanisms of HIV-1 persistence during ART is crucial for developing curative strategies. Idential 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-Dispacement 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 i) identical proviruses also had identical integration sites (cell clones), ii) identical proviruses had different integration sites (viral clones), or iii) 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.
Table 1.

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<th>Category</th>
<th>Sequences of Identical Proviral Amplicons</th>
<th>Sequences of Identical provirus Sequences</th>
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<td>i) All integration sites obtained were identical</td>
<td>3 (2-4 asymmetrical in each cluster)</td>
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<td>ii) All integration sites obtained were different</td>
<td>(2-5 asymmetrical in each cluster)</td>
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<td>iii) Combination of identical and different integration sites were observed</td>
<td>2 (1 and 19 identical, 1 and 9 were only once)</td>
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<td>iv) Combination of identical and different integration sites were observed</td>
<td>3 (1 and 19 identical, 1 and 9 were only once)</td>
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367 HIGH-THROUGHPUT SEQUENCING OF INTEGRATED HIV-1 REVEALS NOVEL PROVIRAL STRUCTURES

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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 new automated approach that sequences individual HIV proviruses and their 3’ 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 range of intact and defective integrated proviruses in blood mononuclear cells from donors on suppressive ART including replication-competent proviruses and genome inversions. The accuracy of the method has been confirmed by sequence identity with full-length and deleted proviruses amplified directly from blood mononuclear cells (proven by viral outgrowth) and novel proviral structures such as asymmetrical LTR deletions (revealed by sequencing both LTRs) and genome inversions.

Conclusion: This novel integrated proviral sequencing assay provides an efficient and high-throughput means of characterizing HIV-1 reservoirs 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

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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, N>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 provirus 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

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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 suppressed individuals to overlapping peptide pools from either a negative control protein, HIV-gag or CMV-pp65. Following overnight culture, activated
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 outgrowth 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 miome 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

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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 each reactivated cell to its original latent state.

Methods: PBMCs (n=7), resting CD45RA- CD4+ (n=7), and CD4+ lymph node aspirates (n=2) from treated individuals were phenotyped by CyTOF immediately after cell isolation, or stimulated with PMA/ionomycin or LRAs 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 proximal 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, CD62, 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. One cluster 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.

372 “FALSE ART FAILURE” FROM IDENTICAL HYPERMUTATED HIV NUCLEIC ACID IN PLASMA

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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 illirions 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 virions 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 of plasma DNA revealed (p6-Pro-R) 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 total nucleic acid from PBMC were analyzed by SGS including cell-associated HIV mRNA and near-full length (NFL) sequencing of proviral DNA.

Results: SGS (p6-Pro-R) revealed multiple, identical hypermutated sequences in all low-and one high-speed plasma pellet(s), and in PBMC HIV DNA (p6-Pro-R 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 amino acid 211 which would prevent capsid (p24) formation.

Conclusion: This is the first report of false virologic failure of ART resulting from release of defective HIV nucleic acid into plasma. The source appears to be a
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.

Conclusion: LoViReT 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 TTM 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

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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 SHOW NEW LIGHT ON HIV-1 PROVIRAL SEQUENCE AND LINKED INTEGRATION SITE

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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). RNA from the same extract was analyzed using Pooled CRISPR Inverse PCR sequencing (PCP-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). PCP yielded 80 IS for PT1 and 161 IS for PT2. Comparison showed that most clonal IS were detected by both ISLA and PCP, validating the results of PCP. Moreover, NFL genomes from 4 clones were identified by PCP 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 PCP to ISLA, we show that PCP 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 transcriptionally 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 PCP yields the most comprehensive overview of proviruses and their associated IS, while the stimulation assay adds functional data on transitional competency.

**377 ULTRADEEP ANALYSIS OF PRETHERAPY HIV PREDICTS GENETICALLY COMPLEX RESERVOIRS**

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**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 (uSGS)) and advanced bioinformatic analyses (Bolzt et al 2016), yields large HIV sequence datasets with the same, low PCR error and recombination rate as standard SGS. We used uSGS to determine population parameters (replicating population size, in vivo recombination rate). We also extended the uSGS 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. uSGS of HIV RT (HKB2mt 2704-2943 and 3046-3253) using primer-ID in 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 uSGS sequences from PBL, DNA was sheared (avg 10 kb), and subjected to a linear PCR step to add primer-IDs before the uSGS procedure.

**Results:** Longitudinal plasma samples were obtained from chronically infected ART naive individuals (median CD4=498/ul, viral RNA=4.3 log, cps/ml), uSGS 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 10³/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 (Batorosky 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 (>10³-10⁷/person) and compose of variants that undergo frequent recombination. uSGS 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**

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**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 unfractionated 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 754.6 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.
became undetectable and sustained at <20cp/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 Fiebig 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/

**Fig 1: Antiviral response (HIV RNA, DNA) to early ARV in acute infection**

![Antiviral response](image1)

**380 WIDE ANATOMIC DISTRIBUTION OF HIV-INFECTED CELLS IN INDIVIDUALS WITH COMORBID CANCER**

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**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 adenocarcinoma, 183 SGS were recovered; HIV was genetically highly diverse, tissues (lung, spleen, testes); infected cells were present in the effusion. HIV was integrated in many host genes, including STAT5B, which has been associated with clonal expansion and persistence of infected cells. In the individual with adenocarcinoma, 183 SGS were recovered; HIV was genetically highly diverse, but identical sequences were present, these were possible cell clones. Identical sequences were present within and across tissues. Individual metastases all contained HIV infected cells.

**Conclusion:** Populations of clonally expanded HIV infected cells are widely, but not uniformly, distributed in individuals with neoplasms, showing that cells from some of the largest infected clones are widely distributed in different tissues. Tumors contain infected cells and analyzing neoplasms contributes to understanding their role in the immune response during ART.

**381 LOW FREQUENCY OF CTL ESCAPE MUTATIONS IN INTACT PROVIRUSES FROM ELITE CONTROLLERS**

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**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 CTL epitopes matching the clade B consensus sequence were higher in ECs relative to ART-treated patients (47.4% vs 37.9%, p=0.005). 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 (43.3% 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**

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**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
reservoir. Th2 cytokines on Th1 and Th17 responses could promote persistence of the HIV-1 proviruses is undefined, these findings suggest that the dampening effect of the mechanistic link between IL-4 and IL-13 levels and cells carrying intact HIV-1 DNA, whereas other cytokines including IL-10 were not 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.

### Table 1

<table>
<thead>
<tr>
<th>Assay</th>
<th>CA-DNA</th>
<th>Total HIV-1 DNA</th>
<th>Plasma SCA</th>
<th>PDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
<td>0.14</td>
<td>0.16</td>
<td>0.15</td>
<td>0.14</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.04</td>
<td>0.06</td>
<td>0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>IL-11</td>
<td>0.14</td>
<td>0.15</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>IL-13</td>
<td>0.05</td>
<td>0.15</td>
<td>0.14</td>
<td>0.18</td>
</tr>
<tr>
<td>IL-1RA</td>
<td>0.09</td>
<td>0.06</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>CCL-22</td>
<td>0.04</td>
<td>0.11</td>
<td>0.29</td>
<td>0.02</td>
</tr>
<tr>
<td>TGFB</td>
<td>0.18</td>
<td>0.11</td>
<td>0.29</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 1 shows Spearman correlations (r) at total HIV-1 DNA, cell-associated HIV-1 DNA, plasma HIV-1 RNA by single copy assay, and intact proviral DNA with plasma HIV-1 RNA levels (log10).

### 383 HIV-1 ENVELOPES FROM PERSISTENT VIREMIA ON ART SHOW REDUCED ANTIBODY SENSITIVITY

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**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 individuals 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 sample-derived PSVs against a panel of 16 monoclonal antibodies (mAbs) directed to the CD4 binding site (CD4bs), R5, and 3BNC117. The level of neutralization was determined by measuring the relative luciferase activity (RLA) in the presence of each mAb compared to the control. Neutralization results were fit to a 50% effective dose (ED50) model.

**Results:** Envs were more resistant to CD4bs, 3BNC117, and 3BNC119 but more sensitive to V3-glycan mAbs. Donor R-09 had the most neutralization resistant Envs sequences: both R-09 PSVs (R-09-A and R-09-B) 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/PGDM140x10E6. Of the 16 mAbs tested, only 3BNC117 and 10e8 potently neutralized all the PSVs.

**Conclusion:** Plasma-derived Envs from individuals with persistent viremia on ART exhibit reduced sensitivity to mAbs targeting CD4bs, 3BNC117, 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.

### 384 MODELING HIV RESERVOIR DECLINE AFTER ART INITIATION AS A FUNCTION OF NK CELL FEATURES


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**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 and the T cell response to "nef, tat, rev" peptide pools 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**

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**Background:** There is evidence to suggest that HIV-1 latency varies by sex; women have been reported to have fewer CD T cells containing HIV-1 provirus, lower levels of residual viral activity in resting CD T cells (CD4), and lower T cell activation. Immuneologic 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 differ by biological sex.

**Methods:** Blood samples were collected from HIV+ 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). 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 vs. 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%). Consistent with prior reports, there was estimated by quantitative viral outgrowth assay (QVOA). 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.

**Conclusions:** Our results suggest that immune correlates of reservoir size differ by biological sex. Further studies are needed to determine if these differences are due to biological sex or other factors such as socioeconomic status or access to healthcare.
between carriers and non-carriers. In contrast, the FC between the left caudate and right hippocampus was significantly lower in carriers (p=0.0002) and correlated with HVLT-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.

388 NEUROCOGNITIVE AND VOLUMETRIC CHANGES AFTER 24 WEEKS OF DTG/3TC/ABC DISCONTINUATION

Ignacio Pérez-Valera1, Alfonso Cabello2, Pablo Ryan3, Maria Luisa Montes3, Sara De La Fuente Moral4, María J. Vivancos-Gallego5, Guillermo Cuevas6, Alberto del Princesa1, Eva García-Fraile Frail6, Mario Gil-Correa1, Norberto Malpica7, Guadalupe Rúa8, M. María Yllescas9, Alicia Gonzalez9, 1Hospital La Paz Institute for Health Research, Madrid, Spain, 2Fundacion Jimenez Diaz, Madrid, Spain, 3Hospital Universitario Infanta Leonor, Madrid, Spain, 4Puerta de Hierro Research Institute and University Hospital, Madrid, Spain, 5Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain, 6Hospital Universitario de La Princesa, Madrid, Spain, 7Universidad Rey Juan Carlos, Madrid, Spain, 8Universidad Rey Juan Carlos Alcorcón, Alcorcón, Spain, 9Fundacion SEIMC-GeSIDA, Madrid, Spain

Background: Dolutegravir/lamivudine/abacavir (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 suppressed patients on DTG/3TC/ABC switching to Cobivastat-boosted elvitegravir/emtricitabine/tenofovir alafenamide FDC (E/C/TAF). Clinical results from this trial have demonstrated significant improvements in NC symptoms when switching from DTG/3TC/ABC to E/C/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 neuromorphometrics 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/TAF, we observed significant improvements in the global NC function (mean±SD GDS change: 0.12±0.32; p=0.005) domains. Significant changes in several brain volumes were observed (table). After FDR adjustment, only the changes in the right frontopolar, a cerebral region involved in information processing, emotion and motivated behaviors, remained significant (p<0.05). 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/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.

Table: Significant corpus changes in brain volumes (mm³) after switching ABC/3TC/DTG to E/C/TAF

<table>
<thead>
<tr>
<th>Left Side</th>
<th>Volume at end of E/C/TAF</th>
<th>Volume at end of ABC/3TC/DTG</th>
<th>F-value</th>
<th>Right Side</th>
<th>Volume at end of E/C/TAF</th>
<th>Volume at end of ABC/3TC/DTG</th>
<th>F-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum vermis lobule I</td>
<td>1.73±0.1</td>
<td>1.80±0.09</td>
<td>0.00</td>
<td>Cerebellum vermis lobule III</td>
<td>1.59±0.16</td>
<td>1.60±0.17</td>
<td>0.00</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>3.70±0.83</td>
<td>3.72±0.84</td>
<td>0.00</td>
<td>Frontal lobe</td>
<td>3.74±0.82</td>
<td>3.75±0.84</td>
<td>0.00</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>0.49±0.06</td>
<td>0.53±0.06</td>
<td>0.00</td>
<td>Occipital lobe</td>
<td>0.53±0.06</td>
<td>0.54±0.06</td>
<td>0.01</td>
</tr>
<tr>
<td>Control operculum</td>
<td>4.01±0.0</td>
<td>4.04±0.0</td>
<td>0.00</td>
<td>Control operculum</td>
<td>4.04±0.0</td>
<td>4.04±0.0</td>
<td>0.00</td>
</tr>
</tbody>
</table>
age from sleep EEG (brain age, BA), which reliably predicts chronological age (CA) in healthy adults. The difference between BA and CA, termed the brain age index (BAI), independently predicts mortality, and is increased by cardiovascular comorbidities and dementia. Here, we assessed BAI in HIV+ compared to matched HIV- adults.

Methods: Sleep EEGs from 43 HIV+ adults on ART were gathered and matched to controls (HIV-, n=284) by age, gender, race, alcoholism, smoking and substance use history. We compared BAI between groups and used additional causal interference methods to ensure robustness. Individual EEG features that underlie BAI prediction were also compared. Finally, we performed a sub-analysis of BAI 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+ BAI 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 BA were different in the HIV+ and HIV- cohorts. Most notably, non-REM stage 2 sleep 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, BAI=4.40) did not have significantly different BAI than HIV+ without AIDS (n=23, BAI=5.22). HIV+ subjects had higher rates of insomnia (56% vs 29%, p<0.0001), obstructive apnea (47% vs 30%, p=0.03), depression (49% vs 23%, p<0.0001), and bipolar disorder (19% vs 4%, p<0.0001).

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+ vs. subjects. These results suggest sleep EEG could be a valuable brain aging biomarker for the HIV population.
Conclusion: These results suggest that lower physical activity within sedentary PLWH is associated with smaller brain volumes (subcortical and cortical). These subtle changes on neuroimaging were not captured using standard neuropsychological tests and suggest that neuroimaging may be important in the evaluation of sedentary PLWH. Future studies should evaluate the effects of exercise training or increasing physical activity on brain volumes in sedentary PLWH.

ACTIVE LIFESTYLE IS ASSOCIATED WITH BETTER BRAIN FUNCTION IN PERSONS LIVING WITH HIV

Jeremy Strain1, Collin Killigore1, Dimitre Tomov1, Sarah A. Cooley1, Brittany Nelson1, 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 max) 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 5.3 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: TA was positively associated with VO2 max in the Frontal Aslant Tract, frontal occipital 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. No significant differences regarding FI, EFZ-10 or psychopathological symptoms were found.

Conclusion: We found that current fitness associated with both structure and function in an ariemic 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

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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.

Neuropsychological assessments were conducted, which consist of fluid intelligence (Fl) scale for overall functioning, and composite Z-score for executive functions (EFZ-10). Psychopathological symptoms were also obtained.

Results: 50 participants were included (60% females, median age 20 years (IQR 19-21), 64% caucasian). Despite good control of HIV infection and no differences in the neurologic state and CT of immunovirological stable PHIV youths with good daily functioning.

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
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Background: The aging population of people living with human immunodeficiency virus (HIV) 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-infected 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 neuropsychological 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 ACB 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 ACB had worse NP and greater reductions in brain volumes compared to individuals who had a low ACB. No significant interactions were observed between HIV status and ACB (p >0.05). Longitudinally, both HC and PLWH who had a higher ACB displayed a greater decline in subcortical GM volume over time compared to individuals with low ACB (Figure 1). The observed decline in brain volumetrics significantly correlated with worse PM over time.

Conclusion: The significant effect of higher ACB on NP and GM volumes in older adults (regardless of HIV status) supports concerns over their continued use in older individuals. Both HIV and high ACB are associated with worse NP and reductions in brain volumetric, no interaction was observed.

Figure 1. Executive fraction (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
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1Washington University in St Louis, St Louis, MO, USA  
Background: Studies have investigated the relationship between viral load (VL) and brain atrophy in people with HIV-infection (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 PLWH 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-.

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 subgrouped 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.

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.

397 MULTIMODAL BRAIN ABNORMALITIES ASSOCIATED WITH COGNITIVE IMPAIRMENT IN HIV INFECTION
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1Duke University, Durham, NC, USA, 2Chinese Academy of Sciences, Beijing, China, 3University of Arizona, Tucson, AZ, USA, 4Georgia State University, Atlanta, GA, USA  
Background: HIV-associated neurocognitive impairment (NCI) remains a prevalent comorbidity that impacts daily functioning and increases morbidity. While HIV infection is known to cause widespread disruptions in the brain, different MRI modalities have not been effectively integrated. This study applied 3-way supervised fusion to investigate how structural and functional co-alterations affect cognitive function.

Methods: Participants completed comprehensive neuropsychological testing and had a multi-modal MRI scan to acquire high-resolution anatomical, diffusion-weighted, and resting-state functional images. Pre-processed data was reduced using voxel-based morphometry (gray matter volume), probabilistic tractography (fractional anisotropy), and regional homogeneity (intrinsic functional connectivity), respectively. We applied multi-modal canonical correlation analysis with reference plus joint independent component
398 IMPAIRED COGNITION AND REDUCED BRAIN VOLUMES IN YOUTH WITH BEHAVIORALLY ACQUIRED HIV

Jennifer McGuire1, Robert Brown2, Ritobrato Datta3, Giulia Fadda1, Nichole Tuitt1, Jacqueline Harrison1, Steven D. Douglas1, Brenda Banwell1, Jennifer McGuire

BEHAVIORALLY ACQUIRED HIV becomes more commonplace in HIV care, multimodal fusion may provide neural deficits in several brain networks related to HIV-associated NCI. As MRI analysis (MCCAR+jICA), using global neurocognitive functioning as the reference.

Methods: Cross sectional analysis of seventeen 16-20-year-old Philadelphia youth with behaviorally acquired HIV (infected for ≥ 1 year) and 18 age-, sex-, and demographically-matched uninfected controls. Participants underwent brain MRI. Brain volumes were measured using FreeSurfer. To evaluate within-structure volumes, voxel-based volume differences between study participants and a standard age-matched atlas were calculated using deformation based T1 morphometry.

Results: HIV+ youth and uninfected controls were similar in age (median 20.0 vs 19.5 years), sex (94% vs 94% male), race (88% vs 94% African American), insurance status, and average alcohol and marijuana consumption. The median infection duration for HIV+ youth was 1.9 years (IQR 1.4-2.9), and median CD4 nadir was 410 cells/ul. (IQR 335-478). 69% (11/16) of HIV+ youth qualified for a diagnosis of HIV-associated neurocognitive disorder, 9 with functional impairment. Total intracranial volume did not differ between HIV+ youth and controls, but HIV+ youth had 7% lower caudate volumes compared to controls (p=0.052); volume differences within the caudate were more pronounced in regions proximal to the CSF interface. Cognitive impairment was associated with lower thalamic volumes in HIV (p<0.002), but not in controls.

Conclusion: These data support the concept that youth with behaviorally acquired HIV have early volume loss in deep gray structures despite robust CD4+ T-cell counts, and that volume loss is associated with cognitive impairment. Larger longitudinal studies with adult comparators are needed to further define patterns of volume loss (and potential implications on pathophysiology), and to determine whether age-specific mitigation strategies are warranted in youth.

399 ALCOHOL USE IS ASSOCIATED WITH DEGRADATION OF BRAIN WHITE MATTER IN HIV INFECTION

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Background: Heavy drinking and HIV infection are independently associated with damage to the brain’s white matter. As most neuroimaging studies of people living with HIV (PLWH) exclude heavy drinkers, effects of alcohol use on white matter in the context of HIV are not well understood. We examined associations of current alcohol use, HIV status, and clinical characteristics with indices of white matter integrity in PLWH and seronegative controls.

Methods: 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

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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 volumetrically 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. Fractional 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 was 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

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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 SUCINATE PREDICT NEUROCOGNITIVE IMPAIRMENT IN OLDER PWH

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Background: Neurocognitive impairment (NCI) is associated with monocyte activation, a feature of frailty, 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: 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 (HAILO) 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 second [0.12, 0.31] slower gait speeds over time. Interactions between succinate and age were not significant, but the strength of the succinate association with NCI increased with age (figure). Further, in the oldest age-quartile, each 1 SD increase in succinate was associated with a 1.9-fold (1.1, 3.9) increased hazard of prevalent 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**

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**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: 62±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: 490±399) of whom 73% are in care and 63% are virologically suppressed. Loss to follow-up (LTFU) 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., LTFU) 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 and mortality among those who develop AAD. If AAD experienced premature aging, AAD cumulative incidence increased with decreased LE. If AAD incidence among PWH was 2x that of the population without HIV, then AAD cumulative incidence increased but with a smaller impact on life expectancy. Limitations included uncertain estimates of AAD incidence and AAD-associated mortality among PWH.

**Conclusion:** Using current data and a validated simulation model, we project that almost 20% of PWH now ≥55y in the US are likely to develop AAD over their lifetime. Cumulative incidence of AAD will be greater if the competing risk of mortality from HIV is reduced or if the risk of AAD is higher among PWH than among those without HIV.

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**404 A RANDOMISED CONTROLLED TRIAL ON THE EFFECT OF B VITAMINS ON NEURONAL INJURY IN PLHIV**

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**Background:** We have previously found an association between plasma homocysteine levels and cerebrospinalfluid neurofilament light protein (NFL) – a marker of neuronal injury – in people living with HIV (PLHIV). Elevated levels of homocysteine is an indicator of B12 and/or folate deficiency. The aim of this study was to investigate if B-vitamin substitution would lead to decreased levels of plasma NFL.

**Methods:** We performed a single center, randomised, open, controlled trial in Gothenburg, Sweden. Neuro asymptomatic PLHIV with stable antiretroviral therapy (ART) for >12 months and with HIV RNA <50 copies/mL who consented to participate in the study were screened. Individuals who had plasma homocysteine >12 µmol/L were eligible for the study. Patients were randomised to either treatment with Triobi (cyanocobalamin 0.5 mg, folic acid 0.8 mg, and pyridoxine 3 mg) or no treatment for 12 months.

**Results:** One hundred and twenty-four PLHIV matching the inclusion criteria were screened for p-homocysteine levels. There was a significant correlation between p-homocysteine levels and p-NFL levels at screening (r = 0.62, p <0.0001). Sixty-one patients were randomised to either treatment with Triobi (n = 31) or no treatment (n = 30). P-Homocysteine levels decreased from a median of 15.9 (interquartile range (IQR) 13.8–17.1) to 9.9 (IQR 8.5–11.4) (p < 0.0001) between baseline and month 12 in the B-vitamin arm, but not in controls: 14.6 (IQR 13.4–16.5) and 16 (IQR 13.5–19) at baseline and month 12, 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 neuro asymptomatic 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.

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**405 CONSERVED CSF HIV ANTIBODY RESPONSE IN PATIENTS WITH DIVERSE NEUROLOGIC PHENOTYPES**

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**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 neuroasymptomatic (NS) CSF escape in which CNS HIV infection develops despite plasma viral suppression. While drug resistance and incomplete drug penetration predispose to this, the origins of NS escape are not fully understood.

**Methods:** To assess whether NS escape might be triggered by an unidentified CNS pathogen and/or whether the CSF anti-HIV antibody repertoire might distinguish NS escape, CSF was collected from 25 HIV-infected participants, some longitudinally, with diverse neurologic phenotypes and treatment status (Table 1). CSF samples were incubated with a VirScan 17 bacteriophage library expressing 481,966 peptides tiled across all known vertebrate and arbovirus genomes that previously identified CSF enteroviral antibodies in pediatric acute flaccid myelitis. Antibody-bound phage were immunoprecipitated and after two rounds of enrichment, were deep sequenced to quantify enriched viral peptides. Separately, unbound meta genomic next-generation sequencing (mNGS) of total CSF RNA was performed to look for unidentified infections and HIV.

**Results:** mNGS was 100% concordant with HIV RNA PCR for samples with 530 viral copies (n=15) and 0% concordant from samples with ≤113 viral copies (n=8). In addition, mNGS detected the two known infections in the secondary escape patients. Additionally, the CSF anti-HIV antibody repertoire primarily enriched two distinct epitopes within the HIV envelope (env) protein in the VirScan assay, regardless of neurologic or treatment status. These epitopes...
A RANDOMIZED TRIAL OF ADJUNCTIVE TELMISARTAN TO REDUCE CNS INFLAMMATION IN ACUTE HIV

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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: 21 participants with AHI were randomized 2:1 to initiate treatment with ART +/- telmisartan; after 48 weeks, all individuals received ART alone. At baseline, 48, and 72 weeks, we measured blood and cerebrospinal fluid (CSF) biomarkers of HIV infection, inflammation, and neuronal 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: All participants were Thai men who have sex with men. At enrollment, median age was 29 years (IQR 24-34), CD4+ T cell count 479 (95-688), and estimated duration of infection 16 days (13-22). Pre-ART median log plasma and CSF HIV RNA levels were 5.95 (5.36-6.48) copies/mL and 2.82 (2.17-4.36) copies/mL. Plasma and CSF HIV RNA using highly sensitive assays (lower limit of quantitation of 0.3 copies/mL) did not differ between groups at 48 or 72 weeks.

Conclusion: In this pilot study of telmisartan as an adjunct to ART during AHI, telmisartan did not affect CNS biomarkers of inflammation or injury. The association with NP performance warrants further investigation.
**PROTEOMIC CHARACTERIZATION OF CSF EXTRACELLULAR VESICLES IN HIV PATIENTS**

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**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 VE-depleted CSF samples, respectively. CSF EV fractions were enriched with exosomal markers including Alix, synxin, tetraspanins, and heat-shock proteins, and a subset of neuronal (ENOD2, NFL, NPT, NRXNS), astrocyte (GFAP, PEAI5, S100B, SCL1A3), oligodendrocyte (MAG, MBP, MOG), and choroid plexus (AOD2, CLKG6, CDMT, E2R, TTR) markers in comparison to VE-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, giall 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.

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**ANITCHOOLINERGIC DRUG USE IN PATIENTS ≥ 65 YEARS OLD IN THE SWISS HIV COHORT STUDY**

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**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, antiretroviral therapy (ART) 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 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, polypharmacy, a marker of oxidative stress. Important markers of age-related neurodegeneration include Ap-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 Ap-42 were measured in CSF and plasma by bead suspension array. NFL in CSF and Ap-42 in CSF and plasma were measured using ELISA. Peripheral blood mitochondrial DNA copy number was obtained from genome-wide genotyping data as a ratio of mitochondrial DNA 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 Ap-42 correlated with markers of neurodegeneration including lower CSF Ap-42 (r=-0.34; p=0.012), higher CSF Ap-42 (r=0.39; p=0.0091) and higher total Tau (r=0.666; p<0.0001). CSF Ap-42 was not related to age, sex, or ethnicity. Ap-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 Ap-42 and neurodegeneration markers remained after adjusting for demographic variables. Ap-42 was higher among PWH exposed to dideoxynucleoside antiretrovirals. Levels of protein carbonyls, a marker of protein oxidation, were not related to neurodegeneration. Higher Ap-42, 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.

412 PREDICTIVE VALIDATION OF AN UGANDAN INFANT EYE-TRACKING TEST OF MEMORY OF HUMAN FACES

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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 (MSL) and the Fagan test of Infant Intelligence (FTII). FTII tests for recognition of 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 Toro 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-2 Hand Movements (eta2=0.11). Rebus (symbol coding learning; eta2=0.13) and TOVA D prime (signal detection; eta2=0.06). MSL and FTII performance were not significantly related to one another, suggesting they measure different things. MSL 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/behavior development in infancy.

413 LOW NEUROSTEROIDS IDENTIFIES A BIOLOGICAL SUBTYPE OF DEPRESSION IN PEOPLE WITH HIV

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Background: The prevalence and mortality risk of depression in people with Human Immunodeficiency Virus infection (PWH) on antiretroviral therapy...
414 ANTICHOLINERGIC BURDEN IS ASSOCIATED WITH DEPRESSIVE SYMPTOMS IN PERSONS WITH HIV

Asante R. Kamkwala1, Qing Ma2, Maile Y. Karris3, Erin Sundermann3, Ronald J. Ellis1, David J. Moore3, Leah H. Rubin1, Scott L. Letendre1
Johns Hopkins University, Baltimore, MD, USA, 2University of Buffalo, Buffalo, NY, USA, 3University of California San Diego, San Diego, CA, USA

Background: Persons with HIV (PWH) have a higher risk of depression and neurocognitive (NCI) 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 a risk factor for depression and NCI 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 ART characteristics as well as medical, psychiatric, and addiction 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 (range 0.06 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, allopurinol, 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 DYSFUNCTION IN MEN WITH HIV INFECTION

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University of Pittsburgh, Pittsburgh, PA, USA, 1University of California Los Angeles, Los Angeles, CA, USA, 2Rush University, Chicago, IL, USA, 3University of Minnesota, Minneapolis, MN, USA, 4Sähøns 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 age (standard deviation) of the participants was 55 (12) years. The majority were Caucasian (58.1%). Although a lower DLCO was associated with a lower FEV1/FVC (β=0.10; p=0.03), this was not the case among the HIV-infected men (β=0.00; p=0.91). Lower levels of DLCO were associated with lower Speed scores among HIV-infected men (β=0.10; p=0.03), but not among the uninfected men (β=0.00; p=0.91). Among men without HIV infection, a lower FEV1/FVC was associated with reduced Learning (β=19.64; p=0.02) and Memory scores (β=21.63; p=0.01). However, among the HIV-infected men, the associations of FEV1/FVC with Learning (β=8.02; p=0.01) and Memory (β=4.71; 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 pathophysiologic
mechanisms by which airway obstruction and reduced oxygen diffusion in the lungs interact with HIV status to contribute to cognitive dysfunction.

<table>
<thead>
<tr>
<th>Cognitive Functional Domains</th>
<th>Polyomavirus Function Test</th>
<th>Individuals with HIV</th>
<th>Individuals without HIV</th>
<th>interaction ( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excitotoxic ( p=0.02 )</td>
<td>0.01 (0.00-0.02)</td>
<td>0.03 (0.01-0.05)</td>
<td>0.62 (0.52-0.73)</td>
<td>0.34</td>
</tr>
<tr>
<td>Axon ( p=0.01 )</td>
<td>0.00 (0.00-0.01)</td>
<td>0.02 (0.01-0.03)</td>
<td>0.23 (0.16-0.31)</td>
<td>0.38</td>
</tr>
<tr>
<td>Gial ( p=0.01 )</td>
<td>0.00 (0.00-0.01)</td>
<td>0.02 (0.01-0.03)</td>
<td>0.19 (0.13-0.26)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table 1. Relationships between lung and cognitive function in individuals with and without HIV.

416 MITOCHONDRIAL DNA, COGNITIVE FUNCTION, AND FRAILTY IN OLDER ADULTS WITH HIV
Carrie Johnston1, Michelle Rice1, Heather Derry1, Chelsie Burchett1, Eugenia Siegler1, Mary Cho1, Marshall Gladish1
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Background: Older PLWH experience more comorbidities and geriatric syndromes, including cognitive impairment and frailty. Mitochondrial DNA (mtDNA), released from dying cells, is a biomarker of inflammation, a mediator of immune activation and has been detected at elevated levels in the plasma of PLWH. We hypothesized that in older PLWH, plasma mtDNA would be associated with lower cognitive performance, frailty, and higher serum IL-6 level.

Methods: We analyzed cross-sectional data from PLWH over age 55 at a single urban medical center. Participants completed a psychosocial questionnaire, biomedical visit, cognitive assessment (Montreal Cognitive Assessment, MoCA) and frailty testing by Fried criteria. Plasma and urine cell-free mtDNA were measured by qPCR detection of mitochondrial NADH dehydrogenase-1.

Results: There were 164 participants; mean age 61 (SD: 6) range 54-87 years. One-third (55) were female. Half identified as Black, 29% as White, and 21% as other. Median time living with HIV was 25 years (IQR 22-29). The majority (93%) had HIV-1 viral load <200 copies/mL and median CD4 count was 582 cells/µl (IQR 402-795). Geometric mean mtDNA level in plasma was 221 copies/µl (geometric SD: 2) and 2.4x108 copies/gram of urine creatinine (geometric SD: 4) in urine. Levels of plasma and urine mtDNA (Spearman correlation rho, \( p=0.05 \), \( p=0.54 \) were unrelated. Median MoCA score was 24 (IQR 21-26); 63 (39%) scored <23. 49 (30%) were non-frail, 95 (58%) pre-frail and 20 (12%) frail. Age was not related to MoCA score (\( p=0.1 \), \( p=0.19 \)) but was associated with frailty status by Jonckheere-Terpstra (JT) test (\( p=0.008 \)). Plasma mtDNA level was higher in those with low MoCA score (\( p=0.028 \) by \( t \)-test [Figure 1]). Higher plasma mtDNA level was associated with slow walk (\( p=0.007 \)) and exhaustion (\( p=0.04 \)), but no weight loss (\( p=0.62 \)), grip strength (\( p=0.06 \)), low physical activity (\( p=0.71 \)) or composite frailty score (\( p=0.98 \)). Serum IL-6 levels were associated with frailty status (\( p=0.018 \)) but not with low MoCA score (\( p=0.89 \) by JT). Neither plasma nor urine mtDNA levels were correlated with IL-6 level, \( p=0.05 \) (\( p=0.55 \)) and 0.09 (\( p=0.29 \)), respectively.

Conclusion: In this study we show a relationship between elevated levels of plasma mtDNA and lower performance on the MoCA, greater exhaustion, and slower walk, suggesting mtDNA may have a role as a novel biomarker in assessing pathogenic inflammation associated with cognitive dysfunction and some components of frailty in PLWH.

417 IMPACT OF WEB-BASED COGNITIVE TRAINING ON WORKING MEMORY IN COCAINE USERS WITH HIV
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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 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 (\( F(1,51) = 4.470, p = .039, \text{eta squared} = 0.069 \)) 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
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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 measurements 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 on antiretroviral therapy (ART) 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 [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=0.0030, p=0.0076 respectively) mice compared to GF BLT mice. Human B cell and myeloid cell levels were not significantly different. We confirmed that these results were not due to the humanization procedure by performing a similar analysis of immune cell levels in the brains of GF and colonized wild-type mice.

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.
RAPID PLASMA REAGIN TEST, AS WELL AS CULTURE OF BACTERIA, FUNGAL ORGANISMS AND MYCOBACTERIUM SPECIES. PATIENTS WITH NEGATIVE RESULTS OF ALL THE ABOVE-MENTIONED TESTS WERE ENROLLED AND HAD A mNGS TEST ON CSF.

RESULTS: A TOTAL OF 45 ELIGIBLE PATIENTS WERE ENROLLED. THE MAJORITY OF THEM WERE MIDDLE-AGED MALE WITH CD4 T CELLS COUNTS OF 75 (2-504) CELLS/UL. AN ETIOLOGIC DIAGNOSIS WAS IDENTIFIED IN 57.8% (26/45) OF THE STUDY PARTICIPANTS. CD4 T CELLS COUNTS IN PATIENTS WITH PATHOGENS DETECTED IN CSF BY mNGS WERE SIGNIFICANTLY LOWER THAN THAT IN THOSE WITHOUT A DEFINITE DIAGNOSIS (442-414 VS 1805-504) CELLS/UL, P=0.013. AMONG THE 26 PATIENTS WITH CONFIRMED CNS INFECTION, PATHOGENS INCLUDING JOHN CUNNINGHAM VIRUS (10), CYTOMEGALOVIRUS (9), VARICELLA-ZOSTER VIRUS (4), TOXOPLASMA GONDII (3), ASPERGILLUS (3), PENICILLINUM (2), TORO TENO VIRUS (19) AND HUMAN HERPESVIRUS 8 (1), METHYLOBACTERIUM (1), MEROZOBIOZUM (1) AND ACINETOBACTER (1) WERE IDENTIFIED BY mNGS. MULTIPLE PATHOGENS WERE DIAGNOSED IN 11 CASES (24.4%). THE RESULTS OF mNGS LED TO THE MODIFICATION OF TREATMENT IN 33.3% PATIENTS (15/45), WHILE THEY INCREASED CONFIDENCE IN MAINTAINING ORIGINAL THERAPY IN 24.4% PATIENTS (11/45). DURING A MEDIAN OF 20 DAYS HOSPITALIZATION, THE OVERALL MORTALITY WAS 2.2% (1/45). 66.7% (30/45) OF THE PATIENTS SHOWED IMPROVEMENT, 28.9% (13/45) STABLE AND 2.2% (1/45) DETERIORATED, RESPECTIVELY.

CONCLUSION: OUR DATA SHOW THAT CLINICAL mNGS OF CSF REPRESENTS A HELPFUL TOOL IN THE DIAGNOSIS OF CNS INFECTION AMONG HIV-INFECTED PATIENTS.

422 EXPRESSION OF HIV-1 INTRON-CONTAINING RNA IN MICROGLIA INDUCES INFLAMMATORY RESPONSES

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2Department of Neurology, University of Wisconsin-Madison, Madison, WI, USA

BACKGROUND: Chronic immune activation is observed in HIV-1+ 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 iPSC (induced pluripotent stem cell)-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 ISGs 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 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 hiMG 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 homeostatic 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 homeostatic 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

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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 Caveolin 1 (CAV1) were used as biomarkers of brain cellular senescence, and measured by RNAscope, 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 older 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 insignificance. 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.

424 CNS HIV BEARS ENVELOPE MARKERS CONSISTENT WITH T-CELL ORIGIN IN THE FACE OF ART

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1Africa Health Research Institute, Mtubatuba, South Africa, 2University of KwaZulu-Natal, Durban, South Africa, 3University of Cambridge, Cambridge, UK

Fluorescent microscopy for the detection of lipofuscin via autofluorescence. Frontal cortex of SIV infected (A&B) and naive (C&D) young, rhesus macaques. SIV infected, young, rhesus macaques have higher numbers of cells that contain lipofuscin (A). In naive, young, rhesus macaques, only rare cells contain lipofuscin (C). Overview of the H&E stained images reveals that the autofluorescent area associated with lipofuscin is darker in SIV-infected and naive, young rhesus macaques (B&D respectively). Arrow: example of lipofuscin. Dotted box: nonspecific autofluorescent area, exclusion from analysis.
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 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 CD26 and CD36 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 in vitro infection for the 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.

425 HIV-1 VIRAL DIVERSITY AND RESISTANCE IN CENTRAL NERVOUS SYSTEM BY DEEP SEQUENCING

Eleni Giatsou1, Basma Abdi2, Isabelle Plu1, Nathalie Desire3, Romain Palich1, Danielle Seilhean4, Vincent Calvez2, Anne-Geneviève Marcelin5, Aude Jary1

1AP–HP, Hôpitaux Universitaires Pitié Salpêtrière, Paris, France
Background: The central nervous system (CNS) component 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 the RT gene. 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 in vitro infection for the 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.
samples. Of these, one had 184T and the other had M46I in CSF only, the third one had K101E in plasma and V106M in CSF. V3 loop was sequenced from 18/45 (40%) pairs; 94% and 83% were CCR5- 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 PI are warranted.

**Table 3. Presence and Reverse transcription-associated mutations in CSF and plasma**

<table>
<thead>
<tr>
<th>Site</th>
<th><strong>RT</strong> Progenitor</th>
<th>Plasma DRMs</th>
<th><strong>CSF</strong> DRMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>184T</td>
<td>184S (40%) 184F (60%)</td>
<td>184S (40%) 184F (60%)</td>
<td>184S (40%) 184F (60%)</td>
</tr>
<tr>
<td>101E</td>
<td>103L (70%) 103N (30%)</td>
<td>103L (70%) 103N (30%)</td>
<td>103L (70%) 103N (30%)</td>
</tr>
<tr>
<td>106M</td>
<td>106V (90%) 106I (10%)</td>
<td>106V (90%) 106I (10%)</td>
<td>106V (90%) 106I (10%)</td>
</tr>
<tr>
<td>101D</td>
<td>101D (90%) 101E (10%)</td>
<td>101D (90%) 101E (10%)</td>
<td>101D (90%) 101E (10%)</td>
</tr>
</tbody>
</table>

428 **BRAIN HIV LATENCY BIOMARKERS**

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**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. HAND, both past and stable in virally suppressed (V5) 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 V5 past/stable HAND vs. non-HAND.

**Methods:** 24 HIV+ men (age M=52.60±12.72; HIV infection duration: M=17.75±12.69 years) who were V5 (in plasma <100cpml and CSF <100cpml) on cART underwent lumbar puncture and neuropsychological testing. Patients with past HAND from which they had recovered and patients with stable HAND (past/stable HAND group) were compared to patients with no known past or current CNS involvement (non-HAND group) for putative markers of brain HIV latency: CSF HIV RNA by single copy assay (SCA), HIV tat, neurofilament-light chain (NFL), neopterin, CCL2, and CSF:serum albumin ratio (O-Alb).

**Results:** Low level HIV persistence (CSF HIV RNA SCA >1-12.4 cpml) was detected in CSF in both groups (17% of past/stable HAND and 24% of non-HAND; p=73) and HIV tat was also detected in both groups (17% of past/stable HAND and 6% for non-HAND; p=42) (SCA was <1cpml in each case). BCL11b levels were similar across the board. However, the past/stable HAND group showed higher NFL levels (p=0.05) than the non-HAND group. Neopterin was abnormal in many patients (57% of past/stable HAND and 31% of non-HAND; p=58). 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=.58).

**Conclusion:** Past/stable HAND is not a useful model for identifying brain latency biomarkers using the latter markers. Past/stable HAND remains an active virological immunological and degenerative process. The concept of a “legacy effect” from past HAND is not supported.
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 pCode End-Point PCR assay, based on the extremely sensitive pCode 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 (uag/pol), incompletely spliced RNA (ttn, vpr, vpu), and multiply spliced RNA (rev, nef), with a sensitivity of 3 infected cells/106 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 cingulate cortex (PCC), and caudate nucleus.

Results: 9/10 patients’ CSF had high levels of cell-associated HIV-1 RNA transcriptional activity (median 47/11 copies per 106 cells, vs 27 in PBMC, p=0.004). 8/10 patients had HIV-1 DNA in CSF cells (median 1314 copies per 106 cells vs 752 in PBMC, p=0.09). Higher HIV-1 RNA in CSF cells was correlated with lower N-acetyl 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. CD4 T cell counts consisted of 75% CXCR3+CD49d+ integrinß7- 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 compartmentalized and its biological significance is strongly indicated by the MRS correlations. The cellular origin is likely the dominant CXCR3+CD49d+ integrinß7- non-gut homing memory CD4+ T cells; monocytes may be less important. Transcriptional products exist (vs whole virus) likely are neuroepithogenically significant. These data support HIV-1 transcription inhibitor development.

430 PLASMA RAMS IN REVERSE TRANSSCRIPTASE GENE ASSOCIATE WITH CSF HIV-1 ESCAPE
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Background: Several risk factors for cerebrospinal fluid HIV-1 escape (CSFE) have been reported: length of HIV infection, cART interruptions, low CD4 nadir, cART score, persistent low-level viremia and the use of ABCs+3TC, boosted PI or unboosted AZT. 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-RNA measurements, available historical cumulative plasma genotypic resistance testing (HGRT) for reverse transcriptase (RT) and protease (PI) genes. Exclusion criteria: secondary CSFE. CSFE was defined as any measurable CSF HIV-RNA coupled with a plasma HIV-RNA <50 copies/mL and any difference ≥0.5 Log10 between CSF and plasma HIV-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-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 HGRT for RAMs in RT (44.3% vs 25.3%, OR 2.0 [1.1-3.8], p=0.04). Having a cumulative HGRT 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 (7.4% 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 GRT (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 HGRT for plasma RAMs in the RT gene and not the use of PIs per sé was an independent predictor of CSFE.

431 PLASMA AND CSF SCD30 DYNAMICS BEFORE AND AFTER ART INITIATED IN ACUTE HIV
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Background: Soluble CD30 (sCD30) is a potential marker of persistent immune activation and/or viral persistence in people living with HIV (PLWH). Surface CD30 co-localizes with HIV RNA and DNA in CD4+ T cells from blood and gut tissue and deletion of cells expressing CD30 reduces the total amount of HIV-1 DNA detected. Evaluation of sCD30 in cerebrospinal fluid (CSF) compared to blood before and after antiretroviral therapy (ART) in acute HIV (AHI) may be valuable in understanding HIV neuropathogenesis.

Methods: We measured pre-ART sCD30 in plasma (n=117; 71 Fiebig 1-2, 46 Fiebig 3-5) and CSF (n=71; 39 Fiebig 1-2, 32 Fiebig 3-5) in the Thai RV254/ SEARCH010 AHI cohort and examined correlations with HIV disease parameters and inflammatory biomarkers. A subset had sCD30 levels measured at 48 and 96 weeks on ART in plasma (n=109 and n=56, respectively) and CSF (n=40 and n=20, respectively). We used non-parametric tests to compare sCD30 levels between AHI participants and HIV-uninfected Thais and to assess relationships between covariates. We used mixed effects models to examine changes within individuals over time.

Results: The median age was 26.5 years (IQR 23-31), pre-ART CD4 count 381 (276-519), and estimated duration of infection 15 (15-25) days. The sample was 96% male. Compared with controls, pre-ART CD30 levels were elevated in plasma (984 vs 374 pg/mL, p<0.001) and CSF (165 vs 131 pg/mL, p=0.01). Pre-ART plasma sCD30 levels correlated with plasma HIV RNA (r=0.44, p<0.001) and CD4/CD8 ratio (r=0.5, p<0.001) as well as plasma neopterin (r=0.29, p=0.01), sCD163 (r=0.26, p=0.03), and IP-10 (r=0.28, p=0.02). Pre-ART CSF sCD30 correlated with CSF HIV RNA (r=0.24, p=0.03) as well as CSF sCD14 (r=0.44, p=0.001), sCD163 (r=0.46, p=0.001), and IP-10 (r=0.26, p=0.02). Plasma and CSF sCD30 did not correlate. In longitudinal analyses, sCD30 levels in both compartments declined at 48 and 96 weeks. This decline was more substantial in plasma (-1.9-fold change, p<0.001) than CSF (-1.14-fold change, p=0.0015).

Conclusion: In untreated AHI, sCD30 is elevated in plasma and CSF and correlates with markers of HIV disease activity and inflammation. With ART initiation in AHI, sCD30 levels decline in both compartments; this is distinct from
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**

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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 male, 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 2.2 (IQR 1.8–4.0) cells/mm3.

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**

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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.

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

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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 to define how these interactions 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 from and PLWH, and associations between PEAs and macrophage 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 represent 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

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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 neuronal injury 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 within 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 (sSTREM2, 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 (356) 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/mL (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 neuronal 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

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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.

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/µl, 66% HIV RNA <400 c/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. 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
437 ART INITIATED AT HIGH CD4 NADIR DOES NOT NORMALIZE CSF MARKERS OF IMMUNE ACTIVATION

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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 pteridine marker of primarily 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 with chronic HIV 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 count and CSF neopterin was found at baseline (r = -0.25, p < 0.01) while no correlations between CD4 nadir and CSF neopterin were found after 1, or >3 years. ART. 15% of participants 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

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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 Intergency HIV Study (WHS), 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, 60) years, 65% black and 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 (22%). Raltegravir (RAL), elvitegravir (EVI), and dolutegravir (DTG) were introduced in 38%, 24% and 38% 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). INSTI 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

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Background: HIV RNA in blood substantially differs between individuals without antiretroviral therapy (ART) due, in part, to differences in the immune response to HIV. HIV RNA in CSF also substantially differs between individuals with and without ART due, in part, to differences in the immune response on CNS health trajectory.

Methods: The project aimed to determine a) the correlates of HIV RNA in CSF in 1,088 PWHA 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). PWHA 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. PWHA 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 USE OF D/C/F/TAF WITH NEUROLOGIC/PSYCHIATRIC COMORBIDITIES: CSF CXCL10 IS ASSOCIATED WITH THE PRESENCE OF LOW-LEVEL CNS HIV DURING ART

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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 single molecule 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 patients with HIV+ 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 (CSF HIVneg) 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 CSF HIVneg group (median= 411 [IQR= 344-640] versus median= 312 [IQR= 205-468], 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 CSF HIVneg). There was no significant difference in NFL between the two groups (p=0.85), but there was a trend towards higher NSE values (p=0.096) in the CSF HIV+ group. In logistic regression accounting for the effect of detectable plasma HIV by SCA, increasing IP-10 concentration (Odds Ratio= 1.33, 95% CI= 1.01-1.77) remained significantly associated with CSF HIV+.

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

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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%]). NPCs included depression and insomnia (control); no psychiatric AEs met this threshold regardless of NPCs. Among patients without NPCs, 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. The most common (≥5%) neurologic AE, regardless of treatment arm or NPCs, was headache. For patients with NPCs, the most common (≥5%) psychiatric AE was 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.

442 CLINICAL FEATURES AND OUTCOMES OF PATIENTS STOPPING DTG FOR NEUROPSYCHIATRIC SYMPTOMS

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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 stopping 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: 66 patients stopped DTG after a median follow up of 27 months (18-37): 66 for NPS. They were mostly sleep disorders (30.3%), headache (27.3%), anxiety (25.8%), depression (18.2%), psychosis (4.5%), vertigo (4.5%) and confusion (3%). Pre-existing psychiatric comorbidities were reported in 21
443 LONG-TERM ADHERENCE MONITORING OF EMTRICITABINE IN HAIR BY MASS SPECTROMETRY IMAGING

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Background: Adherence to antiretroviral therapy is critical for effective treatment and prevention of HIV. Incorporation of drug in hair creates a long-term record of adherence behavior, and mass spectrometry imaging (MSI) using infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) offers a means of monitoring changes in this record as an objective measure of adherence. Here we benchmark longitudinal profiles of emtricitabine (FTC) in hair strands using IR-MALDESI MSI following directly observed therapy (DOT). We also identify adherence thresholds and develop a tool for real-time evaluation of patient adherence in a clinical setting.

Methods: Benchmarking was performed in hair samples cut close to the scalp from 12 volunteers undertaking 28-day phases of daily and then differentiated (0x, 1x, or 3x/wk; n=4 in each group) tenofovir+FTC dosing as part of a DOT study (NCT03218992). The proximal 2cm (~2 months growth) of hair strands (n=4) were collected on day 28 of each phase and fixed to glass slides with double-sided tape before analysis with an IR-MALDESI source coupled to a Thermo QE+ mass spectrometer. MSI data were processed with MSiReader, and longitudinal profiles of FTC over time were generated using custom Matlab software. Quantification of the response was performed based on calibration from blank strands incubated in an FTC solution (lower limit of quantitation: 0.27 ng/mg hair; relative standard deviation (RSD): 20%).

Results: FTC was measured in strands from 11 volunteers (1 reported recent hair salon treatment). A representative IR-MALDESI image (Fig. A; daily-to-3x/wk dosing) shows distinct and localized bands of FTC in each strand associated with proximal differentiated dosing and distal daily dosing periods. Delineating these periods across all study samples, we evaluated average IR-MALDESI response associated with each dosing frequency (Fig. B). While interindividual variability in hair accumulation was observed (daily dosing RSD = 69%), an adherence cutoff with high sensitivity (81%) and selectivity (100%) was derived from these data based on a receiver operating characteristic curve (Fig. C). A cutoff-based analysis tool was developed to classify daily adherence in FTC longitudinal profiles (Fig. D).

Conclusion: Longitudinal dose granularity for FTC can be visualized in hair strands by IR-MALDESI MSI. This approach provides a non-invasive long-term, daily adherence report for patients and clinicians, applicable to both treatment and prevention efforts.

444 ADHERENCE BY DBS, SELF-REPORT, AND PILL COUNT IN YOUNG ADULTS WITH PERINATAL HIV

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Background: Concentrations of tenofovir-diphosphate (TFV-DP) in dried blood spot (DBS) can objectively measure ART adherence and predict viral suppression. We explored if TFV-DP, self-reported adherence, and unannounced phone pill counts were associated with viral suppression needed for individual health (HIV viral load <VL <200 copies/mL) and treatment as prevention (TasP) in the context of Undetectable=Untransmittable (U=U, VL <200) in young adults living with perinatal HIV infection (YAPHIV).

Methods: We quantified adherence using TFV-DP and emtricitabine-triphosphate (FTC-TP) in DBS, self-report, and pill counts, and concomitant VL in YAPHIV from New York City, 18-28 years, receiving tenofovir-based regimens. Self-reported adherence and pill counts were assessed using validated measures. Mean and median TFV-DP levels (by regimen: tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), tenofovir alafenamide (TAF)/FTC, self-reported adherence, and pill counts were estimated, stratified by VL level (<200 copies/mL or <200 copies/mL). Differences in mean adherence levels were assessed with t-tests. Predictive accuracy of each measure to predict VL<200 copies/mL was compared using Receiver Operator Characteristic analysis. 'White coat adherence' (lowest TFV-DP with quantifiable FTC-TP) was assessed.

Results: Of 34 YAPHIV on TDF/FTC, 41% had VL<20 (mean TFV-DP 1293 fmol/ punch [95% CI: 1059, 1580]), and 59% had VL<200 (mean TFV-DP 658 fmol/punch [95% CI: 454, 862]), 60% had VL<200 (mean TFV-DP 1996 fmol/punch [95% CI: 1340, 2974]). White coat adherence was detected in 1 person. Of YAPHIV with all three adherence measures (TFV-DP level, self-report, and pill counts; n=42), TFV-DP from TAF/FTC (0.97 [95% CI: 0.89, 1.00; p<0.001]) had the highest area under the curve for predicting VL<200, followed by TFV-DP from TAF/FTC (0.87 [95% CI: 0.68, 1.00; p<0.001]), pill count (0.72 [95% CI: 0.53, 0.90; p=0.03]), and self-report (0.69 [95% CI: 0.53, 0.86; p<0.05]).

Conclusion: TFV-DP concentrations required to prevent transmission (VL<200 copies/mL) are lower than for individual health (VL<20 copies/mL) and different for TDF vs. TAF, suggesting differential thresholds for TasP/U=U vs. individual health, while self-reported adherence and pill counts were less sensitive. All adherence measures were associated with HIV VL<200, making the choice of a specific method dependent on context, preference, and available resources.
with daily dosing (TFV-DP in DBS for F-TAF was dependent on 33%, 67%, or 100% of daily dosing for F-TDF). Median TFV-DP in DBS for F-TDF was 1676 (791-1895) fmol/punch consistent with cell sizes.

### Results:

#### Background:

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#### METHODS:

**Objective:** Emtricitabine (FTC) plus tenofovir alafenamide (F-TAF) or tenofovir disoproxil (F-TDF) undergo cell-specific conversion, resulting in differential pharmacokinetics (PK) of tenofovir-diprophosphate (TFV-DP) and FTC-triphosphate (FTC-TP) across cell types. The selective cleavage of TAF via cathepsin A allows for more targeted delivery of TFV to cell types expressing this enzyme, such as peripheral blood mononuclear cells (PBMC). The PK of TFV-DP and FTC-TP has been evaluated in PBMC and red blood cells (RBC) measured with dried blood spots (DBS), but not in other major blood cell types, such as neutrophils and platelets.

**Methods:** Paired DBS, PBMC, neutrophils, and platelets were obtained from HIV-negative individuals receiving F-TDF for PrEP, or directly observed F-TAF 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 2 ng/mL for buccal swabs.

**Results:** TFV 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=0.555, p<0.001) and COBI (r=0.431, p<0.001). TFV, FTC 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=0.941, p<0.001), EVG (r=0.867, p<0.001) and DRV (r=0.917, p<0.001), but not COBI. FTC and COBI were detectable up to 8 hours post dose in buccal swabs, while DRV was detectable in most buccal swab specimens up to 24 hours post dose. TFV was not detectable in plasma, DBS or buccal swabs.

**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, FTC or DRV in urine or FTC, EVG or DRV in whole blood may provide the most reliable indicators of ARV adherence.

### 444 UTILITY OF MINIMALLY INVASIVE SPECIMENS TO INFORM ARV ADHERENCE TEST DEVELOPMENT

**Method:** 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 2 ng/mL for buccal swabs.

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### 447 REAL-LIFE MANAGEMENT OF DRUG-DRUG INTERACTIONS BETWEEN ANTIRETROVIRALS AND STATINS

**Method:** 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 2 ng/mL for buccal swabs.

**Results:** TFV 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=0.555, p<0.001) and COBI (r=0.431, p<0.001). TFV, FTC 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=0.941, p<0.001), EVG (r=0.867, p<0.001) and DRV (r=0.917, p<0.001), but not COBI. FTC and COBI were detectable up to 8 hours post dose in buccal swabs, while DRV was detectable in most buccal swab specimens up to 24 hours post dose. TFV was not detectable in plasma, DBS or buccal swabs.

**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, FTC or DRV in urine or FTC, EVG or DRV in whole blood may provide the most reliable indicators of ARV adherence.

### 445 COMPARING TFV-DP & FTC-TP IN PBMC, RBC, NEUTROPHILS, & PLATELETS WITH F/TDF VS F/TAF

**Method:** Paired DBS, PBMC, neutrophils, and platelets were obtained from HIV-negative individuals receiving F-TDF for PrEP, or directly observed F-TAF 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.

**Method:** 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 2 ng/mL for buccal swabs.

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**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, FTC or DRV 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 underdosing 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. 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.

Conclusion: Suboptimal management of DDIs with statins underdosing 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 and/or treatment with rosuvastatin or atorvastatin should be favoured in patients with refractory dyslipidemia.

448 AGING DOES NOT IMPACT DRUG-DRUG INTERACTION MAGNITUDES INVOLVING ANTIRETROVIRAL DRUGS

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Background: The risk of drug–drug interactions (DDIs) is elevated in aging people living with HIV (PLWH) because their increased prevalence of comorbidities leads to a higher use of comedications. Currently, the impact of aging on the magnitude and subsequently the management of DDIs in aging PLWH is unknown. As it is neither feasible nor ethically possible to study every drug combination in aging PLWH, we used physiologically based pharmacokinetic (PBPK) modelling in combination with limited clinical data to investigate the impact of aging on DDI magnitudes involving antiretrovirals (ARVs).

Methods: A whole-body PBPK model was built in the mathematical programming language Matlab® including age-dependent physiological changes for the simulation of elderly subjects. The ability of the model to predict DDIs in young (20-50 years) adults and aging PLWH (55-80 years) was verified against clinical data for amlodipine (AML, 10mg QD) and rosuvastatin (ROS, 10mg QD) both being administered with darunavir/ritonavir (DRV/r, 800/100 mg QD). The clinical data were obtained in the framework of a Swiss HIV Cohort Study project enrolling PLWH older than 55 years or from publications. The verified PBPK model was used to conduct virtual clinical trials for 15 DDIs involving ARVs in virtual individuals aged 20 to 99 years. DDI magnitudes were normalized to the youngest investigated age group. Pearson’s correlation was performed to analyse age-related changes of DDI magnitudes.

Results: Clinical data for AML and ROS in combination with DRV/r were within the 95% confidence interval (CI) of the predictions for young individuals (20-50 years) and aging PLWH (55-80 years). DDI magnitudes were always predicted within 1.25-fold of clinical data (Tab. 1).

Predicted magnitudes of the 15 investigated DDIs (10 inhibitions and 5 inductions) using the verified PBPK model did not change with age. The calculated correlation coefficient of the AUC-ratio (95% CI) was -0.23 [-0.65 0.30] with a p-value of 0.40.

Conclusion: PBPK modelling in combination with limited clinical data demonstrated that DDI magnitudes with ARVs appear not to be impacted by aging. Thus, in the absence of severe comorbidities, management of DDIs can be similar in elderly compared to young PLWH.

449 PLASMA & INTRACELLULAR PK AND RENAL SAFETY OF TAF 25MG WITH BOOSTED PI AND LDV/SOF

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Background: Ledipasvir/sofosbuvir (LDV/SOF) is a recommended therapy for Hepatitis C virus (HCV). LDV/SOF increases tenofovir (TFV) exposures by 40-98% with TFV disoproxil fumarate (TDF) due to inhibition of TDF hydrolysis by SOF. This increase is greater with boosted HIV protease inhibitors (b/PI), which may alter the pharmacodynamic (PD) response on the lipid profile. There is a lack of data on real-life management of DDIs in young (20-50 years) adults and aging PLWH (55-80 years) was verified against clinical data for amlodipine (AML, 10mg QD) and rosuvastatin (ROS, 10mg QD) both being administered with darunavir/ritonavir (DRV/r, 800/100 mg QD). The clinical data were obtained in the framework of a Swiss HIV Cohort Study project enrolling PLWH older than 55 years or from publications. The verified PBPK model was used to conduct virtual clinical trials for 15 DDIs involving ARVs in virtual individuals aged 20 to 99 years. DDI magnitudes were always predicted within 1.25-fold of clinical data (Tab. 1).

Predicted magnitudes of the 15 investigated DDIs (10 inhibitions and 5 inductions) using the verified PBPK model did not change with age. The calculated correlation coefficient of the AUC-ratio (95% CI) was -0.23 [-0.65 0.30] with a p-value of 0.40.

Conclusion: PBPK modelling in combination with limited clinical data demonstrated that DDI magnitudes with ARVs appear not to be impacted by aging. Thus, in the absence of severe comorbidities, management of DDIs can be similar in elderly compared to young PLWH.

PLASMA & INTRACELLULAR PK AND RENAL SAFETY OF TAF 25MG WITH BOOSTED PI AND LDV/SOF

Methods: Plasma and intracellular PK of TAF 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 underdosing 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. 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.

Conclusion: Suboptimal management of DDIs with statins underdosing 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 and/or treatment with rosuvastatin or atorvastatin should be favoured in patients with refractory dyslipidemia.
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>
<thead>
<tr>
<th>Table 1: PK and Renal Safety Outcomes for TDF, TAF + b/PI ± LDV/SOF in HIV/HCV-Coinfected Patients</th>
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<tr>
<td>Dose</td>
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<td>TDF 60mg</td>
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<td>PK Results</td>
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<td>AUC(0-24h)</td>
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<td>Tmax</td>
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<td>Cmax</td>
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450 HIGH-DOSE RIFAMPICIN FOR THE TREATMENT OF LEPROSY IN HIV PATIENTS TAKING DOLUTEGRAVIR

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Background: High dose rifampicin is being investigated for shortening TB therapy as well as in other indications such as leprosy. Strategies to manage the risk of drug-drug interactions (DDIs) with co-administered antiretroviral drugs may therefore be needed. The current study used physiologically-based pharmacokinetic (PBPK) modelling to predict the magnitude of DDI between once monthly (QMT) high dose rifampicin (RIF) and multiple dolutegravir (DTG) regimens for the treatment of leprosy in HIV coinfected patients.

Methods: A whole-body PBPK model was designed in Simbiology v. 9.4.0 (MATLAB R2018a) and used to simulate 100 adult individuals. The DTG model was qualified against reported clinical data for DTG 50mg once daily (QD) and twice daily (BID). The RIF model describing the induction of DTG’s major metabolic pathways, UGT1A1 and CYP3A4, was qualified using in vitro and oral clinical data for midazolam, nifedipine, raltegravir, DTG and RIF. As per convention, PBPK models were assumed to be qualified if the simulated values were within 2-fold of the mean reported clinical values and if the absolute average-fold error (AAFE) was below 2. The verified DTG and RIF models were used to simulate the magnitude of DDI between RIF 600mg QMT co-administered with DTG 50mg BID as well as RIF 1200mg QMT co-administered with DTG 50mg BID, DTG 50mg three times daily (TID) and DTG 100mg BID.

Results: The PBPK models were successfully qualified according to the criteria. There was a tendency to overpredict the magnitude of RIF induction with DTG 50mg BID, DTG 50mg three times daily (TID) and DTG 100mg BID.

Conclusion: The PBPK model predicted marked reductions in the Cmin of several DTG dosing regimens when co-administered with 600mg and 1200mg RIF QMT. Importantly, the return of DTG plasma concentrations to steady state Cmin was qualified against reported clinical data for DTG 50mg once daily (QD) and twice daily (BID). The PBPK model predicted marked reductions in the Cmin of several DDIs between RIF 600mg QMT co-administered with DTG 50mg BID, DTG 50mg TID and DTG 100mg QMT.

451 TOTAL DOLUTEGRAVIR LEVELS DECREASED BUT FREE FRACTION INCREASED BY VALPROIC ACID

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Background: Dolutegravir-containing regimens are used worldwide to treat people living with HIV-1. A previous report on two patients suggested a drug-drug interaction (DDI) between dolutegravir (DTG) and valproic acid (VPA) causing >80% decreased DTG plasma concentrations. The underlying mechanism is unclear. In this pharmacokinetic (PK) sub study, we evaluated the DTG-VPA DDI in HIV-1 patients on DTG-containing regimens and identified a potential mechanism.

Methods: HIV-1 patients participating in a RCT investigating VPA as a latency reversing agent (LUNA: clinicaltrials.gov NCT: 03525730) were recruited in a predefined PK sub study if they were on DTG-containing regimens for >6 months with a plasma HIV-RNA of <50 c/mL. Patients all received 50 mg DTG QD and were randomly assigned to receive either VPA 30 mg/kg BID from day 0 to 14 or not. Total DTG, unbound DTG, and DTG-glucuronide trough plasma concentrations were measured on day 0 (pre-dose and 6 hours post-dose VPA and DTG), and on day 1, 7, 14, and 42. Intra subject DTG concentrations were evaluated and compared to DTG controls without VPA.

Results: Nine HIV-1 patients on DTG were included in total. Of the six who were randomized to receive VPA, total DTG trough levels (mean geometric (GM) were 1.35 mg/L on day 0 (before VPA) and 1.11 mg/L on day 42. During 14 days of VPA treatment, total GM DTG concentrations decreased sharply to 0.85, 0.31, and 0.14 mg/L on days 1, 7, and 14, respectively, while total DTG concentrations in the controls remained comparable: 1.49, 1.74 and 1.51 mg/L on days 1, 7, and 14 respectively. We observed a parallel increase in the unbound fraction of DTG: 0.26-0.28% without VPA compared to 0.46-0.58% during VPA administration (figure 1) without relevant alterations in the controls (median 0.25%). Unbound DTG concentrations were above the established in vitro IC50 value for unbound DTG of 0.9 µg/L in >90% of the participants.

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)

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Background: Ruxolitinib is an FDA-approved Janus kinase (JAK 1/2) inhibitor (myelofibrosis, polyarthralgia) that blocks key cytokines involved in HIV persistence including IL-1, 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, IIV) 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. IIV of Parameter and the variations in fraction of oral dose absorbed (between occasion variability of f) were 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 76.7-91.5 kg); Compartment clearance values were CL1/F = 0.477 L/hr, 33.8% and CL2/F = 4.48 L/hr; Absorption rate constant Ka = 4.96, 70.1%, and there was a 23% BOV in F. Area under the curve (AUC, dose/CL12) 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 INFLTRATION OF bNAb VRC01 INTO THE CEREBROSPINAL FLUID IN HUMANS IN THE RV397 STUDY

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1Emory University, Atlanta, GA, USA; Johns Hopkins University, Baltimore, MD, USA; NIH, Bethesda, MD, USA; 2Harvard University, Cambridge, MA, USA; 3University of California San Francisco, San Francisco, CA, USA; 4University of Alabama at Birmingham, Birmingham, AL, USA

Background: Ruxolitinib is an FDA-approved Janus kinase (JAK 1/2) inhibitor (myelofibrosis, polyarthralgia) that blocks key cytokines involved in HIV persistence including IL-1, 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, IIV) 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. IIV of Parameter and the variations in fraction of oral dose absorbed (between occasion variability of f) were 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 76.7-91.5 kg); Compartment clearance values were CL1/F = 0.477 L/hr, 33.8% and CL2/F = 4.48 L/hr; Absorption rate constant Ka = 4.96, 70.1%, and there was a 23% BOV in F. Area under the curve (AUC, dose/CL12) 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.

454 BICTEGRAVIR/FTC/TAF CSF DIFFUSION IN HIV-INFECTED PATIENTS WITH CNS IMPAIRMENT

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Background: The penetration of antiretroviral drugs in deep compartments, like the central nervous system (CNS), is a crucial part of strategies towards HIV cure. This study aimed to estimate cerebrospinal fluid (CSF) diffusion of bictegravir (BIC), that has high protein binding which could limit diffusion, entricitabine (FTC) and tenofovir alafenamide (TAF) in patients with HIV-related CNS impairment (HCN) enrolled in a real-life observational study.

Methods: Patients (pts) with HCN on treatment by an optimized antiretroviral therapy including 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) threshold=40 copies/mL. Total plasma (Tot) and CSF BIC/TFC/TAF 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. HCN were: progressive multifocal leukoencephalopathy (PML, n=7), cerebral toxoplasmosis (CT) (n=3), CT combined with HIV encephalitis (n=1) and progressive multifocal leukoencephalopathy (PML, n=7), combined with HIV encephalitis (n=1) and VZV meningencephalitis (n=1). Cerebrospinal fluid (CSF) penetration in patients with HIV-related CNS impairment (HCN) enrolled in a real-life observational study.

Methods: Patients (pts) with HCN on treatment by an optimized antiretroviral therapy including 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) threshold=40 copies/mL. Total plasma (Tot) and CSF BIC/TFC/TAF 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. HCN were: progressive multifocal leukoencephalopathy (PML, n=7), cerebral toxoplasmosis (CT) (n=3), CT combined with HIV encephalitis (n=1) and VZV meningencephalitis (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 log10 copies/mL in others. Two (17%) pts had a detectable CSF viral load (1.7 and 1.9 log10 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 T concentrations for BIC (p=0.049). The median QA was 5.5 (1.8; 18%) patient had a damaged BBB, but not related with a higher CSF BIC/TFC/TAF 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>ART Regimen</th>
<th>TFV</th>
<th>FTC</th>
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<tr>
<td>FTC- based</td>
<td>12.5 (3.1)</td>
<td>33.2 (17.4)</td>
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455 A CROSS-SECTIONAL ANALYSIS OF ANTIRETROVIRAL REGIMEN ACTIVITY IN CEREBROSPINAL FLUID

Courtney V. Fletcher1, Caityn McCarthy1, Ronald Bosch1, Serena S. Spudich1, Anthony Podany1, Sean N. Avedissian1, Lee Winchester1, Timothy Mykris1, Jon Weinhold1, Bernard J. Macatangay1, Joshua C. Gyktor1, Joseph J. Eron1, John W. Mellors1, Rajesh T. Gandhi1, Deborah McMahon2

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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, 10 (18%) black non-Hispanic; median age, 48 yrs; median yrs on ART, 8.1 yrs; median CD4 count, 651 cells/µL; HIV-1 RNA <40 copies/mL. Third drugs in ART regimens included: EFV (n=17), ATV/r (8), EVG/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 ARV 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 TPV, FTC, and third ARV. Spearman rank correlation coefficient for TDF vs. 21.2 (15.7, 28.7) (p = 0.25). CSF neopterin was positively associated with average IQ rank (Spearman r = 0.28). 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.

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.

456 PRENATAL EFAVIRENZ EXPOSURE INDEPENDENTLY ASSOCIATED WITH FOETAL CYP2B6 GENOTYPE

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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 (NCT0284645), 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 follow-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™ single nucleotide 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 (0.4). Samples were collected 18.5 (10.1) h after 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 (4.5-3210) ng/mL in fast (n = 28), 969 (15.9-2910) ng/mL in intermediate (n = 37) and 969 (69.0-9230) ng/mL in slow (n = 19) metabolisers, respectively (Figure B). Efavirenz-based regimens before/early/late in pregnancy or postpartum are being recruited with follow-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™ single nucleotide 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.

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.
ASSOCIATION BETWEEN INTEGRASE INHIBITOR HAIR CONCENTRATIONS AND WEIGHT GAIN IN WOMEN

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Background: Integrase strand-transfer inhibitors (INSTIs) were associated with body weight gain among women living with HIV (WLH) in the Women’s Intergency 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/add. Hair concentrations were measured with validated liquid chromatography/tandem mass spectrometry assays 6-18 months post INSTI switch/add 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), 73.5(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 (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 mg/mg (Q1:0.55, Q3:1.10) vs 0.84 mg/mg (Q1:0.40, Q3:1.44), p=0.4735 and 793.0 pg/mg (Q1:316, Q3:1270) vs 409.0 pg/mg (Q1:198, Q3:714), p=0.1037 respectively. 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.

CLINICAL TRIAL SIMULATION TO IMPROVE HIV PREEXPOSURE PROPHYLAXIS DOSING IN PREGNANCY

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Background: Several studies of pregnant women on TDF/FTC report lower TFV exposures in the 2nd and 3rd trimesters due to pregnancy-related increased volume of distribution and renal clearance. The Partners Demonstration Project showed the largest decline during pregnancy compared to non-pregnant women (~45% to 58% in TFV and active TFV diphosphate concentrations, respectively. We hypothesized that doubling the PrEP dose in pregnancy maintains the target plasma, PBMC, and tissue concentrations of TDF/FTC associated with high levels of HIV protection.

Methods: To estimate the TDF/FTC exposure associated with a 2-fold dose increase, we began with a prior population PK model of plasma TFV based on data from MTN-001, updated the model based on Partners Demonstration Project pregnancy cohort PK data, and performed an in silico simulation. We updated our prior model (NONMEM with FOCEI method for parameter estimation) by replacing creatinine clearance with trimester of pregnancy as a time-dependent covariate on clearance as the optimized final model. As the revised model fit the data well, we used it for further simulation. We simulated 1,000 women starting with a “standard” oral 300 mg daily oral TDF dose prior to pregnancy. Upon becoming pregnant, the simulated patients were split into 2 study arms through the 3 trimesters of pregnancy: 1 arm continuing on a “standard” dose and the other arm receiving “double” the standard dose. The estimated protective trough TFV concentration benchmark (35.5 ng/mL) was based on 90% sensitivity threshold for daily dosing in non-pregnant women in HPTN 066.

Results: In the non-pregnant population, our simulation showed 3.7% of women on a standard regimen would have trough levels below the protective threshold. In contrast, we found that 31.5%, 47.2%, and 62.6% of trough concentrations in the 1st, 2nd, and 3rd trimesters, respectively, were below the protective threshold (Figure). By comparison, in the simulated double dose group, only 4.4%, 7.9%, and 14.4% of troughs fell below protective levels in the 1st, 2nd, and 3rd trimesters, respectively.

Conclusion: Our simulation shows >50% of research participants on standard dosing will have 3rd trimester trough plasma TFV concentrations below levels associated with protection. The double dose arm median TFV concentration in pregnancy is very similar to non-pregnant standard dose median TFV. The simulation provides the quantitative basis for a prospective study to evaluate a double dose to adjust for TFV PK changes in pregnancy.
Background: African studies demonstrate that genital inflammation decreases tenofovir (TFV) gel’s efficacy. We evaluated the impact of inflammation and dysbiosis on cervicovaginal fluid (CVF) TFV concentrations in US women taking oral TDF/FTC for PrEP.

Methods: Southern Californian women on oral TDF/FTC in the Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGIS) study had CVF collected at week 24 to evaluate (i) sexually transmitted bacterial (gonorrhea, chlamydia, gardnerella and trichomonas), viral (HPV, CMV, and HSV-1/2) and fungal (Candida) infections, (ii) microbiome composition by 16S sequencing (V3-V4 region) and (iii) cytokie profiles by ELISA (IL-8, MIP-1α, MIP-1β, and IP-10). Microbiome Community State Types (CSTs) were assigned based on described characteristics (i.e. CST I, II, III, V dominated by lactobacilli and CST IV containing mostly non-lactobacilli species). TFV in CVF and tenofovir diprophosphate (TFV-DP) in dried blood spots (DBS) were also measured at week 24. CVF TFV of 100-1000ng/mL benchmarked typical genital concentrations; DBS TFV-DP ≥700fmol/punch suggested long-term adherence. Univariate statistical analysis was used to determine factors associated with low and high CVF TFV.

Results: 34 women had CVF specimens collected at week 24. Median age was 43 (IQR 35–47) years. 15% (5/34) had discordant tenofovir concentrations (i.e. DBS TFV-DP ≥700 and CVF TFV <100). No inflammatory process was associated with lower CVF TFV concentrations or tenofovir discordance. Notably, among the 26 participants assessed for vaginitis (Candida, Gardnerella or Trichomonas), women with possible vaginitis (n=13) were more likely to have high (>1000 ng/mL) CVF TFV concentrations compared to those without vaginitis (77% versus 31%, p<0.05). No difference was seen in CVF TFV concentrations by vaginal microbiome type. 3 of the 5 women with discordance had non-lactobacilli dominant microbiomes; however, they were dominated by non-vaginitis organisms (2 E. clәcәe, 1 e. coii).

Conclusion: Presence of genital viruses, cytokines or Gardnerella spp. were not associated with low CVF TFV levels in women taking oral PrEP. Women with vaginitis may actually have higher CVF TFV levels, perhaps due to inflammatory processes augmenting blood flow and TFV penetration into the vaginal compartment.

ARV PENETRATION INTO FEMALE GENITAL TRACT DURING PREGNANCY: EFAVIRENZ AS A CASE STUDY

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Background: Neither the added value of lamivudine or the effect of raltegravir as PrEP are well known. We evaluated raltegravir +/- lamivudine (RGV/3TC) pharmacokinetics and pharmacodynamics (PK/PD) using a tissue explant model. 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-1BL A 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/g in VF and 389.2 ng/g in RT; GM tissue-to-plasma accumulation ratios 0.75 (VT) and 2.6 (RT). After PrEP cessation, 50/7% of VT and 86/58% of RT samples remained above RGV IC50 (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 (162 ng/g) and RT (275 ng/g) until day 12. Plasma. Ex vivo and raltegravir provided a greater variability in VT level (≥2 >0.759; p<0.001) compared with VF. Whereas RT explained more of the variability for 3TC RT levels (R2 =0.591; p<0.001), then 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. Concluding: 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

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Background: Islatratvir (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+darunavir (DOR) in combination with 3TC and switched to ISL+DOR no earlier than Wk 24 had high efficacy at Wk 48 as measured by HIV-1 RNA <50 c/mL. Data through Wk 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 select the dose for further clinical development of ISL most appropriate for HIV-1 treatment-naïve, 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

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 IC50 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 PR: AN RCT

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Background: Efavirenz was quantified from cervicovaginal swabs (CVS) collected in a virtual cohort (n = 100, 29.5% previous reports. This was adequately predicted by the model, predicted CVF (n = 39, mean gestational age 33.8 weeks) at 14.8 h post-dose was 1.237 µg/mL. Diffusion. The model was qualified by comparing predictions with data from the VADICT study. Progress in this area has been limited by sampling constraints. Proper characterisation of antiretroviral pharmacokinetics in the female genital tract is crucial in developing effective pre-exposure prophylaxis and prevention of intrapartum mother-to-child transmission interventions. Progress in this area has been limited by sampling constraints.

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 validated by comparing predictions with data from the VADICT study.

Results: Mean CVS efavirenz concentration with the new method in this cohort (n = 39, mean gestational age 33.8 weeks) at 14.8 h post-dose was 1.237 µg/mL (95% CI: 0.138, 6.397), giving CVS:plasma concentration ratio of 0.64, more than previous reports. This was adequately predicted by the model, predicted CVF concentration being 1.190 µg/mL (0.542, 2.430) in a virtual cohort (n = 100, 29.5 weeks gestation). Trough (IC50), maximum (IC95), efavirenz concentration and area under the concentration-time curve (AUCO-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.
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 Ph2 data, a dose of ISL 0.75 mg QD is expected to provide maximal efficacy in treatment-naïve 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-naïve, virologically-suppressed, and HTE PLWH.

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FOSTEMAVIR EXPOSURE-RESPONSE RELATIONSHIPS IN TREATMENT-EXPERIENCED HIV PATIENTS

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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 8 and at Week 24, proportion of subjects with HIV-1 RNA <40, <200 and <400 copies/mL. In addition, covariates of virologic response were investigated. Simulations were conducted to predict virologic responses on Day 8 under demographic factors as predictors of virologic response were investigated. ER models were explored. Following graphical exploration, linear, inhibitory Emax and logistic regression models were explored.

Results: ER relationship was established between TMR C24 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. Addition of IC50 (as C24/PIC50) did not improve the relationship. Model predicted probability of >0.5 and >1.0 log10 decrease in HIV-1 RNA on Day 8 was 80% and 58%, at plasma TMR C24 of 300 ng/mL with median baseline HIV-1 RNA (4.65 log10 copies/mL) and CD4+ (>20 cells/mm³). At Week 24, no relationship could be established between plasma TMR C24, and HIV 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 C24 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.

Table 1. Efficacy ER Simulation Results

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Change in Plasma HIV-1 RNA from Day 1 to 8 (Log10 c/mL)</th>
<th>Proportion of Subjects</th>
<th>Decrease in Plasma HIV-1 RNA on Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTR 600 mg BID (No interaction)</td>
<td>0.72</td>
<td>80%</td>
<td>4.5%</td>
</tr>
<tr>
<td>FTR 600 mg BID (Moderate/High CV/TA) Inhibitor Alone</td>
<td>0.72 (4.5-336.9)</td>
<td>77%</td>
<td>4.2%</td>
</tr>
<tr>
<td>FTR 600 mg BID (CYP3A Inhibitor Alone)</td>
<td>0.72 (4.5-336.9)</td>
<td>77%</td>
<td>4.2%</td>
</tr>
<tr>
<td>FTR 600 mg BID (Strong metabolizer)</td>
<td>0.72 (4.5-336.9)</td>
<td>77%</td>
<td>4.2%</td>
</tr>
<tr>
<td>FTR 600 mg BID (Elderly metabolizer)</td>
<td>0.72 (4.5-336.9)</td>
<td>77%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

464LB

BICTEGRAVIR DISTRIBUTION AND BICTEGRAVIR/FTC/TAF ACTIVITY IN GENITAL TRACT AND RECTUM

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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 bicitegavir (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 QD. 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 (Cmax) 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 (91-1165) 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, 13/15 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, 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 Cmax in BP, SP, RT and CVF were 2640 (424-10300) ng/mL; 65.5 (20.1-923) ng/mL; 23.4 (4.5-336.9) ng/swab; and 74.1 (6.0-478.5) ng/g, respectively. In women, BIC concentrations in BP and CVF were 2230 (834-5770) ng/mL and 61.6 (14.4-1760.2) ng/mL. On average BIC Cmax in SP,CVF and RT (assuming tissue density=1g/ml) were 2.7%, 2.8% and 2.6% of BP Cmax. 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.

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SAFETY AND PHARMACOKINETICS OF INTRAVENOUS VIRCOILS AND 10-1074 IN YOUNG CHILDREN

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Background: Early-treated HIV+ children may be ideal candidates for use of broadly neutralizing monoclonal antibodies (bNAbs) as an alternative to antiretroviral treatment (ART), but pediatric bNAb data to date has been limited to subcutaneous administration of VRC01/LS during infancy. In preparation for a trial of dual bNAb use as a treatment alternative, we evaluated the safety and pharmacokinetics (PK) of monthly VRC01/LS or 10-1074 dosed intravenously among HIV+ children on suppressive ART.

Methods: The PK phase of the Tatelo Study in Botswana enrolled 12 children who had received ART continuously from 0-7 days through at least 96 weeks of life, and had HIV-1 RNA < 40 copies/mL for at least 24 weeks prior to entry. While continuing ART, 6 participants received VRC01/LS (30 mg/kg load at day 0, then 10mg/kg at days 28 and 56) and 6 participants received 10-1074 (30 mg/kg on days 0, 28 and 56). bNAb concentrations were tested 18 times over 12 weeks using murine anti-VRC01 and anti-10-1074 antibodies.

Results: Among the 12 children enrolled, the median age was 38 months (range 26 to 50 months), 75% were female, the median CD4 cell count was 1211 cells/mm³ and CD4% was 34%. All children were receiving lopinavir/ritonavir, zidovudine, lamivudine (and one was also on abacavir). All but one infusion occurred on schedule and to completion, and infusions were well tolerated. No infusion reactions occurred, and no grade 3 or 4 events were related to either bNAb. For VRC01/LS, median (range) first dose peak concentrations (C max) and Day 84 trough concentrations (C84D) were 726 (559-799) mcg/mL and 157 (126-201) mcg/mL respectively, both about half of predicted values based on PK in uninfected adults (Figure 1A). For 10-1074, median (range) first dose C max and C84D concentrations were 1633 (1174-1999) mcg/mL and 258 (122-467) mcg/mL respectively, both somewhat greater than predicted values from HIV-infected adults on suppressive ART (Figure 1B).

Conclusion: Intravenous VRC01/LS and 10-1074 were safe and well tolerated among HIV+ children receiving ART. Pediatric PK of these two bNAbs differed from PK in adults. For VRC01/LS, an increased maintenance dose of at least 15mg/kg may be needed to achieve concentrations similar to adults when dosed monthly. For 10-1074, predicted adult concentrations were slightly exceeded with 30mg/kg monthly.

Figure 1: VRC01/LS (A) and 10-1074 (B) pharmacokinetic profiles after intravenous administration in HIV+ children.

A. VRC01/LS

B. 10-1074

466 CABOTEGRAVIR AND RILPIVIRINE PK FOLLOWING LONG-ACTING HIV TREATMENT DISCONTINUATION

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1, Herta Crauwels2, Kelong Han3, Stefaan Rosensu4, Feifan Zhang4, Jenny O. Huang5, David A. Margolis6, Kenneth Sutton6, Krischan J. Hudson6, Peter E. Williams6, William Spreen6, Parul Patel6
pharmacokinetics (PK) and antivirologic activity of these compounds were assessed in two Phase 1 programs.

Methods: Single doses of 2-240 mg MK-8504 were tested in healthy adults, and single doses up to 240 mg were tested in ART-naïve persons living with HIV (PLWH). Single doses of MK-8504 2-150 mg were tested in healthy adults, and a single dose of 100 mg was tested in ART-naïve PLWH. Plasma and peripheral blood mononuclear cells (PBMCs) were collected up to 10 days after dosing for PK and viral load (VL).

Results: Oral MK-8504 and MK-8583 were rapidly absorbed (Tmax ~ 0.5 hour); MK-8583 was rapidly eliminated from plasma (t1/2 ~ 0.2-0.4 hours), while MK-8504 had slower elimination (t1/2 ~ 6-8 hours). As expected, plasma TVF concentrations were generally similar, with a median Tmax of 1-4 hours after both MK-8504 and MK-8583 administration, and a t1/2 of 20-38 hours for MK-8504 and 19-30 hours for MK-8583. The levels of TVF-DP in PBMCs exhibited a median Tmax of 4-24 hours for both compounds, with a t1/2 of 48-115 hours for MK-8504 and 65-192 hours for MK-8504. The PK in PLWH and healthy participants were similar. Despite PBMC TVF-DP concentrations consistently above the efficacious trough concentration for marketed TFV prodrugs (100 nM), HIV-1 VL reduction was suboptimal for both compounds. The mean VL reduction at 7 days was 0.6 log10 copies/mL for marketed TFV prodrugs (100 nM), HIV-1 VL reduction was 0.9 log10 copies/mL at the top dose of MK-8504, and several participants failed to achieve consistent VL reduction. There was no relationship observed between Day 7 TVF PBMC TVF-DP concentrations and VL reduction for either compound. No genetic variant variants were identified.

Conclusion: Single doses of MK-8504 and MK-8583 were generally well-tolerated. These TVF prodrugs were rapidly converted to the active form and maintained target concentrations in PBMCs through 7 days. Unlike other TVF prodrugs administered daily in monotherapy trials, the antiretroviral activity of MK-8504 and MK-8583 was modest and transient. The persistent adequate concentrations of TVF-DP belie the poor VL response; it is possible, though, that VL responses could improve with daily administration of MK-8504 or MK-8583. Collectively, these data raise questions about the feasibility of TFV prodrugs in long-acting antiretroviral agent.

DOSE-RESPONSE RELATIONSHIP OF SUBCUTANEOUS LONG-ACTING HIV CAPSID INHIBITOR GS-6207

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Background: GS-6207, a potent, selective, first-in-class, multi-stage inhibitor of HIV-1 capsid function that inhibits HIV at picomolar concentrations and is in development for treatment of HIV-1 infection as a long acting agent. In people living with HIV (PW), GS-6207 administered subcutaneously (SC) has shown potent antiviral activity, and is generally well tolerated. In addition to GS-6207 SC formulations, an oral tablet formulation is also in development. The safety, single ascending dose (SAD) pharmacokinetics (PK) and effect of food (FE) on GS-6207 oral tablets were evaluated in HIV negative participants.

Methods: This is an ongoing, blinded, placebo-controlled Phase 1 study with staggered SAD and open label FE cohorts. In each SAD cohort subjects were randomized (4:1) to receive single doses of GS-6207 (n=8/cohort) or placebo (n=2/cohort), at 50, 300, 900 or 1800 mg. In the FE cohorts (n=8/cohort), subjects received GS-6207 300 mg following a high fat (~1000 kcal; ~50% fat) or low fat (~400 kcal; ~25% fat) meal. Intensive PK sampling will be performed for 64 days post-dose. Single dose PK parameters were estimated using noncompartmental methods using available data; dose proportionality and FE were assessed. Safety was evaluated throughout the study.

Results: Interim safety and PK data are available through 35 (300 and 900 mg fasted) or 8 days post dose (50 and 1800 mg fasted, 300 mg high and low fat). 56 of 56 participants 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.

Based on the available data, GS-6207 exposures increased in a less than dose-proportional manner over the dose range of 50 to 1800 mg. Maximal concentrations (Cmax) of GS-6207 were achieved ~4 to 8 h post dose (Tmax), and the exposure for 64 days post-dose. Single dose PK parameters were estimated using noncompartmental methods using available data; dose proportionality and FE were assessed. Safety was evaluated throughout the study.

Table 1: Preliminary PK data for GS-6207 oral tablets

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Tmax (h)</th>
<th>Cmax (mcg/mL)</th>
<th>AUC0-24h (mcg*h/mL)</th>
<th>LC50 (mcg/mL)</th>
<th>IC50 (mcg/mL)</th>
<th>Emax (% of wild-type)</th>
<th>Ymax (% of wild-type)</th>
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<tbody>
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<td>4.00</td>
<td>2.26</td>
<td>0.00 (0.00)</td>
<td>110.0</td>
<td>40.0</td>
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<tr>
<td>300</td>
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<td>10.33</td>
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<tr>
<td>900</td>
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<td>1800</td>
<td>8.00</td>
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**Table 1:** Preliminary PK data for GS-6207 oral tablets. 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 PW.
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 rifampin+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. Allometric 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 a 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 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.

472 A LONG-ACTING NONOATEMOKOVIR PRODRUG
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Background: Despite the success of existing antiretroviral therapy (ART) in controlling human immunodeficiency virus type 1 (HIV-1) infection, treatment requires life-long adherence to medicines. ART compliance can be compromised by frequency of dosing, and long acting formulations could potentially improve patient adherence. However, the hydrophobic nature of nucleoside reverse transcriptase inhibitors (NRTI) limits their transformation into long acting formulations. To this end, tenofovir (TFV), a NRTI, was modified into two different lipophilic prodrugs (M1TFV and M2TFV) to extend the apparent drug half-life, improve potency and facilitate access to viral replication sites.

Methods: TFV was modified and formulated into long acting lipid nanoparticles by high-pressure homogenization. The created TFV prodrugs were purified by silica column chromatography and characterized by NMR and FTIR. Nanoparticles were produced by high-pressure homogenization (NMTTFV, NM2TTFV). Human monocyte derived macrophages (MDM) and CEM-ss T-cells were used as a biological platform to measure drug uptake and retention. Drug levels were quantitated in cell lysates by UPLC-TUV. After DMPA treatment with 100 µM NM1TFV cells were challenged with HIV-ADA at a MOI of 0.1 at five day intervals for one month. Culture fluids were assayed for reverse transcriptase activity and cell-based HIV-p24 antigens recorded by immunohistochemistry. To assess the pharmacokinetic (PK) profile of these TFV prodrug formulations, male Sprague Dawley rats were injected with 75 mg/kg TFV equivalents of NM1TFV, NM2TTFV, or TAF. Plasma, blood and peripheral blood mononuclear cells were collected weekly after injection. At the end of the four-week study, organs and tissues were collected for analysis of prophrug, parent drug, and triphosphate levels.

Results: Prodrug modifications enhanced drug uptake compared to tenofovir alafenimide fumarate (TAF) in both MDM and CEM-ss T-cells. M1TFV and M2TFV nanoparticles showed sustained prodrug levels in MDM for 30 and 15 days respectively; whereas TAF was eliminated within a day. In cellular efficacy studies, single treatment of ND1TFV restricted viral replication for 30 days. Studies showed enhanced cellular uptake and sustained anti-HIV activity in vitro single dosing when compared against TAF. These results are promising for development of a long-acting TFV for HIV treatment and prevention.

473LB SAFETY AND PK STUDY OF VM-1500A-LAI, A NOVEL LONG-ACTING INJECTABLE THERAPY FOR HIV
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1Viroin, Inc, San Diego, CA, 2Moscow City Centre for AIDS Prophylaxis and Control, Moscow, Russian Federation, 3Central Research Institute of Epidemiology, Moscow, Russian Federation, 4IPHARMA, LLC, Moscow, Russian Federation, 5First Moscow State Medical University, Moscow, Russian Federation, 6Exact Labs, LLC, Moscow, Russian Federation, 7Iriss, LLC, San Diego, CA, USA, 8Northwestern University, Chicago, IL, USA

Background: VM1500A is a novel, potent NNRTI with unique clinical PK profile and broad-spectrum activity across HIV-1 variants. An oral dosage form of elsulfavirine, a pro-drug of VM1500A, has been approved in 2017 in Russia for treatment of HIV-infected patients in combination with standard antiretroviral therapy, under the brand name Elpida®. A long-acting injectable (LAI) form of VM1500A has been developed to expand the dosing options of VM1500A.

Methods: This Phase 1 trial is an ongoing open-label, single-center study to evaluate safety, tolerability and pharmacokinetics of single and multiple ascending intramuscular (IM) doses of the LAI nano-formulation of VM-1500A (VM1500A-LAI) in HIV-infected volunteers.

Results: 30 HIV-infected volunteers were enrolled and received single ascending doses (SAD) of VM-1500A of 150, 300, 600, and 1200 mg, after a 2-week dosing of 20 mg Eploya capsules qd. The subjects were evaluated for 35 days post-injection and during that period provided serial blood samples for PK assessments. In the SAD cohorts, the main PK parameter was the mean plasma concentration (Ctmax) achieved median plasma Ctrough above target for at least 3 weeks. VM-1500A-LAI IM qm of 1200 mg achieved median plasma Ctmax of 61 ng/mL. Upon completion of the 1200 mg, enrollment of subjects to receive multiple IM injections (once per month) was recommended by the SDC and is currently ongoing. In the SAD part of the study, a total of 21 male (5 Asians, 16 Caucasians) volunteers with a mean age of 26 y.o. and mean BMI of 23.9 kg/m² were enrolled. There were no significant baseline differences between the groups. The observed PK profile of IM VM-1500A-LAI is consistent with sustained delivery. Median (range) plasma concentrations of VM1500A at 35 days post-injection were 71 (52, 190), 42 (29, 143), 25 (17, 28) and 19 (12, 19) ng/mL for the 1200, 600, 300 and 150 mg dose levels, respectively. All doses were well tolerated and no dose limiting toxicities were reported. Injection site related pain was notable at the highest dose.
was tolerated and had an acceptable PK profile in healthy volunteers following single IM dosing in a range of 150mg to 1200mg.

474 CD4/CD8 RECOVERY AND FIRST-LINE ART: GREATEST IMPROVEMENT WITH INTEGRASE INHIBITORS

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1Hospital Ramón y Cajal, Madrid, Spain, 2Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain, 3Hospital Universitario de San Espíritu, Palma de Mallorca, Spain, 4Hospital General Universitario de Alicante, Alicante, Spain, 5Hospital de Basurto, Basurto, Spain, 6Hospital Marina Baixa, Hospital Marina Baixa, 7Hospital San Agustín, Guadalajara, Mexico

Background: A low CD4/CD8 ratio during ART identifies subjects with heightened immunosenescence 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 NNRTI 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 22-89). 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, 0.79 [0.69-0.89] and NNRTI, aHR 0.79 [0.65-0.95]; PI, aHR 0.78 [0.64-0.97]). Subanalyses adjusted for backbone NNRTIs 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, Orlanda Goh1, Donn J. Colby2, Carlo Saccalani1, Camilla Muccini1, Nittaya Phanuphak1, Suteeraporn Pinyakorn1, Prapan Phanuphak1, Nittya Chomchey1, Robert Paul1, Sandhya Vasani1, Serena I. Spudich3, Jintanat Anwaroranich1, Eugene Kroon4, for the RV254 Research Group

1SEARCH, Bangkok, Thailand, 2San Raffaele Vita-Salute University, Milan, Italy, 3US Military HIV Research Program, Bethesda, MD, USA, 4University of Missouri St Louis, St Louis, MO, USA, 5Vale 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: 2009-2017; DTG=2 NRTI: Feb 2017 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 (AE) 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 was 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

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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-; 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 (Grifols 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 adjusted 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 13/15 days after index donations. Longitudinal HIV reservoir 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/106 PBMC at enrolment, falling to 2.2 log10 copies/106 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/106 PBMC at enrolment, falling to 0.85 log10 copies/106 PBMC with no difference by Fiebig stage (p=0.95).

Conclusion: Among male 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 subsequent entry into HIV Cure research initiatives.

477 144-WEEK EFFICACY AND SAFETY OF B/F/TAF IN TREATMENT-NAIVE ADULTS ≥50 YRS

Anthony Mills1, Samir K. Gupta1, Cynthia Brinson1, Kimberly Workowski1, Amanda Clarke2, Andrea Antinori3, Jeffrey L. Stephens4, Ellen Koenig4, Jose Huang13, Hal Martin13, Diana Brainard13

Background: As people living with HIV age, identifying effective and safe regimens for older individuals is of heightened importance. The single-tablet regimen bictegravir, emtricitabine, tenofovir alafenamide (B/F/TAF) may benefit older adults due to its favorable adverse event (AE) profile and few drug interactions.

Methods: We conducted two randomized, double blind, phase 3 studies of B/F/TAF in treatment-naive adults. Study 1489: B/F/TAF vs dolutegravir, abacavir, and lamivudine (DTG/ABC/3TC) and Study 1490: B/F/TAF vs DTG + F/TAF. A pooled analysis assessed efficacy as the proportion with HIV-1 RNA <50 c/mL (FDA Snapshot) and safety at Week (W) 144 in adults ≥50 and <50 yrs at baseline. Proteinuria and bone mineral density (BMD) were measured in Study 1489 only.

Results: 1274 were randomized and treated (634 B/F/TAF, 325 DTG/ABC/3TC, 325 DTG + F/TAF; 196 were age ≥50 yrs (96 B/F/TAF, 41 DTG/ABC/3TC, 59 DTG + F/TAF) of whom 17% were women, 27% Black, and 15% Latino/Hispanic. Efficacy was high for all treatments (Table). The most common AEs in adults ≥50 were nasopharyngitis (20%, 22%, 25%), diarrhea (19%, 22%, 8%), and upper respiratory tract infection (16%, 17%, 12%). The most common AEs in adults <50 were diarrhea (19%, 18%, 18%), headache (17%, 18%, 19%), and nausea (11%, 26%, 15%). Treatment-related AEs occurred in 24%, 37%, and 29% of participants ≥50; the frequency was 26%, 43% and 29% in participants <50 yrs (p<0.001 for B/F/TAF vs DTG/ABC/3TC). Most treatment related AEs were grade 1. AEs leading to study drug discontinuation for most participants ≥50 occurred in 2% on B/F/TAF, 5% on DTG/ABC/3TC and 7% on DTG + F/TAF compared to 1% in each treatment group for participants <50 yrs. For those ≥50 with AEs leading to discontinuation, on B/F/TAF, 10 on DTG/ABC/3TC and 3 on DTG + F/TAF were treatment-related. In Study 1489, mean % changes in hip and spine BMD, proteinuria, and renal biomarkers were similar between B/F/TAF to DTG/ABC/3TC. There were small changes from baseline in all treatment groups in fasting lipids. Median weight increased from baseline at W144 with no significant difference between treatment groups (Table).

Conclusion: Through three years of treatment, B/F/TAF was highly effective, safe and well tolerated in adults ≥50 yrs with no clinically significant impact on bone or renal safety, fasting lipids or weight. B/F/TAF provides a safe and effective treatment option for older adults with a low potential for drug-drug interactions.
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 naïve 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 (32%) of those on non-INSTI regimens normalized with a 0.01 (95%CI 0.06, 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 naïve 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-naïve 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 fromRCTs, has not been demonstrated.

Methods: We included ART-naive 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/r) (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-naive patients were (DTG=416; DRV/r=269; 224 DRV/r and 45 DRV/cobi): male 87%; heterosexual contacts 50%, MSM 37%; born outside Italy 48%; AIDS presenting 36%; median CD4 count 78 cell/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 to show a notable reduction in risk of treatment failure in people initiated with target population of ART-naïve patients with CD4 count<200 or AIDS is likely correct model specification, our analysis suggests that a RCT conducted in the most clinically relevant population such as patients experiencing the composite endpoint compared to those who started DRV/r [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-naive 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-B*5701 IN HIV+ PATIENTS UNDERGOING ABACAVIR THERAPY

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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 SS0-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. Isootype 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 SS0 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 457 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 testing to those few HLA-B*5701 typing to the small group of FC positive individuals.
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 INRTI and INSTI domains, and no mutations. The CAR arm had 4 CVFs through W96 (vs. 3 through W48); none had mutations. Across both treatment arms, AEs leading to withdrawal were infrequent. Injection site reactions (ISRs) were the most common drug-related AE (86% 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 HITSQoL.

**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**

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**Background:** In GEMINI 1&2, the longitudinal 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-naïve 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) or virologic rebound criteria (≥200c/mL after prior suppression to <200c/mL). Monogram Bioscience performed integrase 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 50 <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 2 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.
LONG-TERM DTG+3TC SWITCH EFFICACY IN PATIENTS WITH ARCHIVED 3TC RESISTANCE
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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 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% of participants without history of 3TC resistance). 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.
487 CLINICAL OUTCOMES OF 2-DRUG REGIMENS (2DRs) VS 3-DRUG REGIMENS (3DRs) IN HIV

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Background: While 2DRs have shown good efficacy in clinical trials, there are limited data comparing longer term clinical outcomes to 3DRs.

Methods: Anti-retroviral treatment (ART) experienced persons in RESPOND starting a new 2DR or 3DR from 1/1/2013 to 12/31/17 were included (n=276,085). Poisson regression compared prospectively collected AIDS and non-AIDS events (non-AIDS-defining cancer, cardiovascular disease, end stage liver/renal disease, diabetes, chronic kidney disease (CKD), fractures, non-AIDS related death) between 2DRs vs 3DRs.

Results: Of 5211 persons included, 967 (18.6%) started 2DRs and 4244 (81.4%) started 3DRs. The most common 2DRs were dolutegravir plus lamivudine (16.7%) and boosted darunavir plus ritonavir (15.8%). The main reason for discontinuing the previous regimen before starting a 2DR or 3DR was toxicity (33.3% and 36.3% 2DRs vs 3DRs respectively; p=0.14). Persons on 2DRs were older (median age 52 years [interquartile range 46-59]) 2DRs vs 3DRs (median 51 years [39-53]). 2DRs, had been on ART longer (14 years [9-15]) vs 3DRs (9-15). There was higher CD4 counts (611 cells/µL [394-822] vs 590 [411-797]), and a lower CD4 nadir (170 [68-282] vs 205 [96-310]). A similar proportion had ≥1 comorbidity (63.1% vs 60.7%) and were virally suppressed at baseline (86.6% vs 84.5%). Overall, there were 99 AIDS and 548 non-AIDS events during 12717 person years of follow-up (PYFU) [1813 2DR, 1909 3DR]. The most common events were diabetes (crude incidence rate [IR] 1.2/100 PYFU [95% CI 1.0-1.4]) and CKD (0.7 [0.7-1.1]). In unadjusted analyses, there was a lower IR of AIDS events on 2DRs (0.4 [0.2-0.9]) 2DRs vs 0.8 [0.7-1.0] 3DRs and a higher IR of non-AIDS events (6.1 [5.1-7.4]) vs 4.0 [3.7-4.4]). After adjustment there was no significant difference between 2DRs and 3DRs for non-AIDS events (IR ratio 1.19 [0.94-1.50], p=0.15). The small number of AIDS events precluded adjusted analyses. Sensitivity analyses excluding diabetes, CKD, and fractures showed similar results.

Conclusion: This is the first large, international cohort to assess clinical outcomes on 2DRs. After accounting for demographic and clinical characteristics, there was a similar incidence of non-AIDS events on 2DRs and 3DRs, however confounding by indication cannot be excluded. With a median follow-up of 1.7 years, 2DRs appear to be a viable treatment option with regard to clinical outcomes, although further research on long-term durability and potential toxicities of 2DRs is needed.

488 EFFICACY AND DURABILITY OF 2-DRUG VS 3-DRUG InSTI-BASED REGIMENS: DATA FROM REAL LIFE

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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)<50 copies/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>1000 copies/mL or 2 consecutive VL>50 copies/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 164 cells/mm3, respectively) were included, of which 1334 (80%) treated with 3DR [n=265 elvitegravir(EVG), n=334 raltegravir(RAL), n=755 delatrogravir(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 (3.1%) 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 (1.6% vs 1.8%; p=0.53), but it was higher for EVG (3.5%) and RAL (3%) when compared to DTG (1% vs 0.4%). By multivariate analysis, previous VF (aHR 2.7; p<0.001) and shorter time from last VL>50 copies/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 RAL (aHR = 2.3; p<0.001) and lower risk in MSMs (aHR=0.75; p=0.02) and regimens started for simplification (aHR=0.5; 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.

489 ASSESSING THE VIROLOGIC IMPACT OF ARCHIVED RESISTANCE IN AN HIV-1 SWITCH STUDY, TANGO

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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 NRTI 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 NRTI, NNRTI, PI and INSTI RAMs

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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>Variable</th>
<th>IR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VF</td>
<td>1.81 (1.07-2.39)</td>
<td>1.00 (1.00-1.00)</td>
</tr>
<tr>
<td>Previous VFs</td>
<td>2.03 (1.74-2.39)</td>
<td>1.19 (1.04-1.35)</td>
</tr>
</tbody>
</table>
were determined by last available on-treatment HIV-1 RNA through Week 48 in order to assess pure virologic responses by censoring discontinuations due to non-efficacy reasons. This was repeated on the FDA Snapshot Algorithm at Week 48 as a sensitivity analysis.

**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%), 104 (17%), 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 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) without any major RAMs. For participants with any major NRTI, NNRTI, PI or INSTI 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 the TBR arm without any archived RAMs met the protocol-defined virologic withdrawal criterion (CVW) with no emergent resistance. None in the DTG/3TC arm met CVW through Week 48.

**Conclusion:** In TANGO, 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 Category Through Week 48**

<table>
<thead>
<tr>
<th>Resistance Category</th>
<th>With Major RAMs (%)</th>
<th>Without Major RAMs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M184V/I</td>
<td>28 (9)</td>
<td>312 (97)</td>
</tr>
<tr>
<td>K65E/N/R</td>
<td>21 (7)</td>
<td>268 (90)</td>
</tr>
<tr>
<td>TAMs</td>
<td>4 (1)</td>
<td>297 (98)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>19 (8)</td>
<td>248 (98)</td>
</tr>
<tr>
<td>PI</td>
<td>32 (17)</td>
<td>189 (83)</td>
</tr>
</tbody>
</table>

**Results:** 1374 subjects were included (DTG/3TC: 799, DTG/xTC: 575) with a median follow-up of 587 days [IQR 334-934] and 562 days [IQR 326-938], respectively. Baseline characteristics are shown in Table. VF occurred in 3.8% (n=30) of DTG/3TC 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, 9/30 (33%) had history of VF on NNRTI-based regimen in DTG/3TC group and 5/30 (17%) had history of VF on NRTI-based regimen in DTG/xTC group. At DTG/3TC VF, 17/30 genotypes were available: 2 genotypes harbored NNRTI RAMs already detected on historical genotypes (E138A; E138A+K101E); 2 genotypes harbored new RAMs, 1 genotype with E138K on NNRTI and 1 genotype with E138K+K101E on NNRTI plus 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/3TC was history of VF to NNRTI-based ART (HR 2.82, CI 95% 1.04-7.6), while gender, age, duration of HIV RNA <50 c/mL prior to VF, nadir CD4, zenith HIV RNA and CDC stage were not. No factor was associated with VF under DTG/xTC.

**Conclusion:** In this large real-life cohort, DTG-2DR maintained sustained HIV RNA virologic suppression, and were associated with a low rate of VF. DTG/xTC was associated with slightly lower VF rate than DTG/3TC and the absence of RAM emergence at VF. ARV history are prior VF are key issues to consider before offering 2DR maintenance.

**491 2-DRUG REGIMEN COMPARABLE TO 3-DRUG REGIMENS UP TO 18 MONTHS IN A REAL WORLD SETTING**

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**Background:** Dolutegravir/rilpivirine (DTG/RPV) was the first single tablet, once daily regimen, containing only two antiretrovirals to be approved. Our objective was to compare the effectiveness and durability of DTG/RPV to standard three-drug regimens (3-DR) in a real-world setting.

**Methods:** People living with HIV-1 (PLWH) who initiated a two drug regimen (2-DR) comprised of DTG/RPV or 3-DR, defined as one core agent and two NRTIs, were identified in the OPERA Database. Those who initiated therapy between 1/1/2018–12/31/2018, were ART experienced, age ≥13 years, and suppressed (<50 copies/mL) at start were analyzed. Discontinuation (d/c) was defined as cessation of 2- or 3-DR. Sustained suppression was defined as last viral load (VL) <200 copies. Virologic failure (VF) was defined as either 2 consecutive VL ≥ 200 copies/mL or 1 VL ≥ 200 copies/mL + d/c. The population was observed through 06/30/2019. Baseline characteristics were described using Pearson’s chi-square, Fisher exact, or Wilcoxon rank-sum tests. Kaplan-Meier methods were used to describe d/c and VF. Cox Proportional Hazards modeling was used to assess the risk of VF adjusting for age, sex, race, ethnicity, risk of infection, region, baseline CD4 cell count, history of substance abuse, history of syphilis and VACS score at baseline.

**Results:** Among 545 PLWH who initiated DTG/RPV as a 2-DR and 5,524 PLWH who initiated 3-DR, DTG/RPV 2-DR users were significantly (p<0.0001) older, more likely to be Hispanic, MSM, to have comorbidities and to receive care in the southern and western United States. They were less likely to be African American or to receive care in the Northeast or Midwest. PLWH initiating 3-DR were more likely to have a history of syphilis. Median (IQR) follow-up was similar between 2-DR and 3-DR initiators at 10.7 (6.8-14.6) months. DTG/3TC VF/2-DR users experienced fewer discontinuations compared to 3-DR users (15.0% vs. 28.0%, <.0001) and were more likely to sustain suppression (97.7% vs 95.5%, <.0001) and were less likely to be African American or to receive care in the Northeast or Midwest. They were less likely to be Hispanic, MSM, to have comorbidities and to receive care in the southern and western United States. They were more likely to be African American or to receive care in the Northeast or Midwest. PLWH initiating 3-DR were less likely to be Hispanic, MSM, to have comorbidities and to receive care in the southern and western United States. They were less likely to be African American or to receive care in the Northeast or Midwest.
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).

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.

492 SHALL WE DANCE? EXTENDING TANGO’S RESULTS TO CLINICAL PRACTICE
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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 IIib, 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 47 years, CDC stage C 29.7%, CD4 nadir<500/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, NNRTI and (minor or major) PI RAMS were observed in 9.1, 17.5% and 12.2% of patients, respectively. Resistance categories and PE analyses within subgroups are shown in Table 1 with response rates ≥80% across groups. Response rates with major 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, NNRTI or PI RAMs.

Table 1. Patient characteristics at baseline.

<table>
<thead>
<tr>
<th>Age (E, N), Median (IQR)</th>
<th>2DR group (n=131)</th>
<th>3DR group (n=132)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sexes, n (%)</td>
<td>111 (86.6)</td>
<td>104 (83.3)</td>
<td>0.058</td>
</tr>
<tr>
<td>Risk factor for HIV, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnorracial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- European</td>
<td>56 (38.6)</td>
<td>69 (49.0)</td>
<td></td>
</tr>
<tr>
<td>- N/A</td>
<td>6 (4.6)</td>
<td>2 (1.5)</td>
<td></td>
</tr>
<tr>
<td>- Other/Unknown</td>
<td>1 (0.7%)</td>
<td>1 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>CD4 T cell count, n (%)</td>
<td>20 (15.3)</td>
<td>62 (45.0)</td>
<td>0.040</td>
</tr>
<tr>
<td>Anti-HCV positive, n (%)</td>
<td>51 (37.2)</td>
<td>68 (46.3)</td>
<td>0.076</td>
</tr>
<tr>
<td>Virologic outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viremic HIV RNA (log10 copies/mL), median (IQR)</td>
<td>4.90 (4.0–5.35)</td>
<td>4.89 (4.7–5.43)</td>
<td>0.780</td>
</tr>
<tr>
<td>CD4 T cell count (2DR)</td>
<td>218 (206–290)</td>
<td>232 (208–291)</td>
<td>0.003</td>
</tr>
<tr>
<td>CD4 T cell count (3DR)</td>
<td>201 (190–270)</td>
<td>232 (208–291)</td>
<td></td>
</tr>
<tr>
<td>Viremic HIV RNA (log10 copies/mL), median (IQR)</td>
<td>4.89 (4.7–5.43)</td>
<td>4.89 (4.7–5.43)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

493 VIROLOGIC OUTCOMES BY RESISTANCE CATEGORY AND PRETREATMENT IN THE DUALIS STUDY
Eva Wolf 1, Christoph Boesecke 2, Amnangari Baloghi 1, Helen Bidner 1, Christiane Cordes 3, Hans Heiken 1, Ivanka Krznaric 1, Tim Kümmerle 1, Jochen Schneider 1, Christian D. Spinner 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: Extending the TANGO study and their applicability to everyday clinical practice.

Results from our multicenter study highlight the high efficacy and tolerability of lamivudine (3TC) and dolutegravir (DTG) as a switch strategy. However, trials’ populations often differ from real-practice settings. We aimed to confirm the study’s findings in our multicenter cohort.

Methods: This was an observational study enrolling HIV-infected, virologically suppressed patients switching to 3TC+DTG, divided into 2 groups based on their adherence to the TANGO inclusion criteria. We collected patients’ history, virological, immunological assessment at baseline, 48, 96 and 144 weeks. We performed Kaplan-Meier survival analysis to evaluate time to virological failure (VF, defined by 2 consecutive HIV-RNA determinations≥50 cps/mL or a single HIV-RNA≥1000 cps/mL) and treatment discontinuation (TD), Cox-regression to find predictors of VF or TD and linear mixed model for repeated measures to identify significant changes in immunological parameters.

Results: We analyzed 557 patients: 145 (26.0%) met the TANGO inclusion criteria. 98.5% of patients showed a high baseline virologic suppression. 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.
495 PATTERNS OF ADHERENCE IN BICTEGRAVIR- AND DOLUTEGRAVIR-BASED ONCE-DAILY ETRAVIRINE/RALTEGRAVIR (400/800 MG) AS MAINTENANCE REGIMENS

Romain Palich,1 Yasmine Dudoit,1 Gilles Peytavin,1 Minh Le2, Cathia Soulle1, Roland Tubiana1, Giotilde Allavena2, Laurence Weiss3, Ana Montoya Ferrer3, Claudine Duvielle1, Olivier Bouchaud4, Julie Botten5, Anne-Geneviève Marcelin6, Lambert Assoumou7, Christine Katlama8


Background: The ANRS163-ETRAL study showed 99.4% of virological success rate for etravirine/raltegravir (400/400 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 plasma 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 48 weeks, estimated with the Kaplan-Meier method. Secondary outcomes included tolerance, treatment strategy success rate (defined as absence of VF with no treatment discontinuation), plasma drug 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 HIV suppression duration: 7.9 years (5.9-10.7). Two VF occurred at W24 and W48 leading to a VF rate of 2.0% (95%CI: 0.5-7.8%). One of both reported poor adherence, and were virologically suppressed after ART resumption, with no acquired resistance. The second patient had low etravirine and raltegravir plasma concentrations (C_{24h}: 365 ng/mL and 71 ng/mL, respectively), with acquired resistance. The second patient had low etravirine and raltegravir plasma concentrations (C_{24h}: 365 ng/mL and 71 ng/mL, respectively), with acquired resistance. W48 leading to a VF rate of 2.0% (95%CI: 0.5-7.8%). One of both reported poor adherence, and were virologically suppressed after ART resumption, with no acquired resistance. The second patient had low etravirine and raltegravir plasma concentrations (C_{24h}: 365 ng/mL and 71 ng/mL, respectively), with acquired resistance.

Conclusion: Switching from ETR/RAL BID to QD regimen is highly effective in maintaining virologically suppressed patients. This once-daily combination is a good option to avoid protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) in aging patients.

496 SOCIAL NORMS AND ART ADHERENCE: POPULATION-BASED STUDY OF PERSONS WITH HIV IN UGANDA

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1Trio Health, La Jolla, CA, USA, 2Care Resource Community Health Center, Miami, FL, USA, 3George Washington University, Washington, DC, USA

Background: Regimen complexity can adversely affect adherence, leading to virologic failure. It is unknown whether this occurs with regimens that contain the second-generation integrase inhibitors (INIs), bictegravir and dolutegravir, both of which are recommended in the current DHHS Guidelines.

Methods: EMR, prescription and dispensing data for 2,171 patients initiating BIC/FTC/TAF, DTG/ABC/3TC, DTG+TDF/FTC, or DTG+TAF/TFC between August 2013 - August 2019 were collected from 5 practices across 17 US states. Only those without prior documented treatment with DTG or BIC, respectively, were included.

Adherence was defined as proportion of days covered through the first 6 months of regimen treatment. To determine treatment effects on adherence, we (1) used multiple imputation with predictive posterior matching to account for incomplete baseline measures, (2) used mixed effects logistic regression, using BIC/FTC/TAF vs DTG-regimens with random intercept for practice, to adjust for heterogeneity between practices, (3) adjusted models using demographics and relevant baseline clinical data (CD4 count, viral load, AST, ALT, lipids, eGFR, 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/TFC 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/TFC [p<0.01]. Assessment of viral suppression at 6 months for patients with measures (n=655) was favorably impacted 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 yields improved virologic outcomes in clinical settings.

Observed (unadjusted) adherence between groups (Observed) and estimated Treatment Effect (Adjusted odds ratios [AOR]) with 95% CI on adherence within first 6 months.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Observed</th>
<th>Matched Cohort</th>
<th>AOR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIC/FTC/TAF vs. DTG/ABC/3TC</td>
<td>0.87</td>
<td>0.82</td>
<td>1.07</td>
<td>0.41</td>
</tr>
<tr>
<td>BIC/FTC/TAF vs. DTG+TDF/FTC</td>
<td>0.89</td>
<td>0.85</td>
<td>1.02</td>
<td>0.84</td>
</tr>
<tr>
<td>BIC/FTC/TAF vs. DTG+TAF/TFC</td>
<td>0.89</td>
<td>0.85</td>
<td>1.02</td>
<td>0.84</td>
</tr>
<tr>
<td>DTG/ABC/3TC vs. BIC/FTC/TAF</td>
<td>0.89</td>
<td>0.85</td>
<td>1.02</td>
<td>0.84</td>
</tr>
<tr>
<td>DTG+TDF/FTC vs. BIC/FTC/TAF</td>
<td>0.89</td>
<td>0.85</td>
<td>1.02</td>
<td>0.84</td>
</tr>
<tr>
<td>DTG+TAF/TFC vs. BIC/FTC/TAF</td>
<td>0.89</td>
<td>0.85</td>
<td>1.02</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Social norms are known to be an important determinant of one’s own propensity to adhere. This study provides evidence that social norms play a significant role in adherence to antiretroviral therapy in a population-based study of persons with HIV in Uganda.
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 (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.

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

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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

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 diphosphate (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 compared to a decrease from 1108 to 1048 fmol/punch in controls (see figure; median change +252 versus -41 fmol/punch, respectively, P=0.101). Discontinuation rates were 5 of 30 (17%) in the smart-pill bottle group vs. 7 of 33 (21%) 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 diphosphate 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 1, Rajeev B. Shah 1, Joseph Garland 1, Meghan L. McCarthy 1, Fizza S. Gillani 1, Marsha C. Sanchez 2

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)?

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1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2University of Miami, Miami, FL, USA, 3Rush University Medical Center, Chicago, IL, USA, 4Trigo 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 T800 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 for 90% (1143) PLWH based on RX v 92% (1166) PD (p=0.129) and >90% adherence by RX and PD, 28% (29/104) were classified with ≥80% adherence by RX. Conversely, 41% (52/127) patients classified with <80% adherence by PD were indicated as having a change that differed in time >90 d from observed by PD. In total, 37% (473/1270) of study patients had one or more of these differences in duration, adherence, and/or MTR composition.

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.

500 INVESTIGATION OF A POTENTIAL COMPOSITE ENDPOINT FOR IMMUNOLOGIC NONRESPONDER TRIALS

Virginia Sheikhi1, Therri Usher2, Maximilian Rohde3, Thamban Valappil4, Sarah Connelly4, Richard Jefferys4, Kimberly Struble4, Adam Sherwat5, Wendy Carter6, Jeffrey S. Murray7

1FDA, Silver Spring, MD, USA, 2Treatment Action Group, New York, NY, USA

Background: Although most people with HIV (PWV) experience robust CD4 recovery after achieving virologic suppression on antiretroviral therapy (ART), immunologic non-responders (INR) have persistently low CD4 T cell counts. Studies suggest INRs have an increased risk of mortality and serious morbidity, but these events are uncommon in ART-treated PWV and may not be feasible trial endpoints. Patient advocates urged FDA to encourage drug development for INRs by providing guidance on acceptable endpoints for INR trials. Therefore, we investigated the feasibility of a composite endpoint designed to capture non-serious and serious adverse events associated with CD4 lymphopenia.

Methods: Among Phase 3 clinical trial datasets submitted to the FDA (2005-2016) in support of ART approval for ART-naive adults, we identified datasets with 144 wks of HIV RNA, CD4, and safety data. We excluded subjects with virologic failure between Wks 24 and 144 and, based on the Week 96 CD4 value, categorized subjects as INR (CD4 <200 cells/µL), immunologic responders (IR, CD4 200 – 349 cells/µL) or optimal immunologic responders (OIR, CD4 ≥350 cells/µL). Using safety data between Wks 96 and 144 and descriptive statistics, we evaluated differences in our composite endpoint, which included 1993 CDC HIV Classification System events (Categories A, B and C [not limited by duration, response to tx, or recurrence]), non-AIDS related events included in the START study, HPV-related disease, skin and soft tissue infections, and neurocognitive events.

Results: 79 (1.7%) participants met criteria for INR, 481 (10.3%) for IRs, and 4110 (88%) for OIRs. INRs were older (41.8 yrs) compared to IRs (39.6 yrs) and OIRs (36.7 yrs). INRs had lower baseline CD4 (64 c/µL) compared to IRs (152 c/µL) and OIRs (381 c/µL) and were more likely to have enrolled in a trial that started before 2010 (63% of INRs) than IRs (52.2%) and OIRs (20.2%). The composite endpoint occurred in 17 (21.5%) INRs, 92 (19.1%) IRs, and 709 OIRs (17.2%). INRs had lower baseline CD4 (64 c/µL) compared to IRs (152 c/µL) and OIRs (381 c/µL) and were more likely to have enrolled in a trial that started before 2010 (63% of INRs) than IRs (52.2%) and OIRs (20.2%). The composite endpoint occurred in 17 (21.5%) INRs, 92 (19.1%) IRs, and 709 OIRs (17.2%).

Conclusion: INRs were uncommon among ART-naive adults starting ART in the 2000s, and even more uncommon after 2010. Like previous studies, INRs were older with lower baseline CD4 counts. The proportion of INRs experiencing the composite endpoint was slightly higher compared to IRs and OIRs. Our results suggest our composite endpoint is not a feasible endpoint for clinical trials evaluating drugs to treat INRs.
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 ART interruption and had standard HIV genotypic testing (TRUGENE), presence of NNRTI or INI DRMs was assessed. Results are given according to stopping approach, separately for TDF vs. non-TDF use.

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 who 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 INI DRMs was assessed. Results are given according to stopping approach, separately for TDF vs. non-TDF 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 ART interruption and had standard HIV genotypic testing (TRUGENE), presence of NNRTI or INI DRMs was assessed. Results are given according to stopping approach, separately for TDF vs. non-TDF use.

Conclusion: Despite TDF having a longer intracellular T1/2 than other NNRTIs, the resuppression rate after simultaneous stopping all ARVs in an NNRTI regimen was not different for TDF versus non-TDF regimens, nor did TDF prevent emergence of DRMs. Though limited by small number of subjects on TDF, these data support the current recommendation that if stoppage of an NNRTI-based regimen is planned, ARVs should not be stopped simultaneously. This is particularly crucial when stopping NNRTI regimens during analytical ART interruption trials.

502 NO SIGNIFICANT CHANGE ON RESERVOIR IN QUATUOR: A 4/7 DAYS A WEEK MAINTENANCE STRATEGY

Sidonie Lambert-Niclot1, Lambert Assoumou1, Pierre De Truchis1, Djeneba Bocar Fofana2, Karine Amat1, Jonathan Belle1, François Raffi1, Philippe Morlat1, Christine Katlama1, Cécile Moins1, Dominique Costagliola1, Pierre-Marie Girard2, Roland Landmann1, Laurence Morand-Joubert12, 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 GENE REAL HIV DNA (Biocentrix®, Bandol, France) with a limit of quantification (LOQ) of 10 copies/PCR. Ultra-sensitive plasma VL (USpVL) and semen 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 LOD at D0 and W48 respectively. Median (IQR) HIV DNA was 1.7 log10 c/106 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 73.0 % and 67.3% respectively in the 4D arm and 21.9% and 27.9 % in the 7D arm. Semen HIV RNA was measured in 78 patients with a proportion of semen VL detectable in 25.0 % 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 40/7 maintenance strategy on virological suppression at the level of residual viremia.

503 CLINICAL SIGNIFICANCE OF gp120 POLYMORPHISMS, TMR IC50 FC AND HIV-1 subtype in BRIGHTHE

Margaret Garland1, Peter Ackerman1, Frank Mannino2, Louise K. Gardies3, Andrew Clark5, Amy Pierce1, Mark Krystal2, Cyril C. Llamoso2, Max Lataillade2, Andrew Clarke5, Amy Pierce1, Mark Krystal2, Cyril C. Llamoso2, Max Lataillade2

1ViiV Healthcare, Research Triangle Park, NC, USA, 2ViiV Healthcare, Branford, CT, USA, 3GlaxoSmithKline, Collegeville, PA, USA, 4GlaxoSmithKline, Uxbridge, UK, 5ViiV Healthcare, London, UK
Background: The ongoing Phase 2B/3 BRIGHT study is evaluating the antiviral activity of a novel, highly potent and safe allosteric IN inhibitor, FST-008, in a Phase 2B clinical trial. The aim of this study was to evaluate the virologic efficacy of FST-008 in a Phase 2B clinical trial.

Methods: Participants were randomized to receive either FST-008 or placebo in a 2:1 ratio. The primary endpoint was the proportion of participants with a >0.5 log10 decrease in HIV-1 RNA at Day 8 of functional monotherapy.

Results: Among evaluable participants, 46% (198/430) achieved >0.5 log10 decrease in HIV-1 RNA at Day 8 with FST-008. This was statistically significant compared to placebo (22%, 19/86; p=0.002). Additionally, 38% (86/225) of participants with TMR IC50FC <10- and <100-fold, respectively, achieved >0.5 log10 decrease in HIV-1 RNA at Day 8 with FST-008.

Conclusion: FST-008 demonstrated excellent virologic efficacy in a Phase 2B clinical trial, with a >0.5 log10 decrease in HIV-1 RNA at Day 8 achieved in 46% of evaluable participants.
primary HIV-1 clinical isolates representing subtypes A–G and ii) 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 i) equilibrium dialysis and ii) in vitro activity assays employing human serum concentrations of 0–40%. 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 antiviral activity. Compound A exhibited an average IC50 value of 7.2 nM 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 average IC50 values against HIV virus of 7.9 and 14.9 nM and against A7 isolates of 48.2 and 138.7 nM, respectively. A, B and C inhibit drug resistant virus with average IC50 values of 3.1, 1.0 and 1.2 nM, 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. Mis 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

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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 >50,000 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 (Atiprila) 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 sCD163 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 CD4+, 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 IBAZILUMAB IN COMBINATION WITH 1 OR 2 FULLY ACTIVE AGENTS

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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 (OBR) 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 (OSS5) and 18 patients 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 >0.5 log10 VL decrease on IBA functional monotherapy after 7 days. At Week 25, 5 of the 7 OSS1 completers (71%) achieved <50 copies/mL, of which three were on a fully active DTG. At Week 96, 7 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 >0.5 log10 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

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1Vaccine Research Center, NIAID, Bethesda, MD, USA, 2University of California San Diego, La Jolla, CA, USA, 3TaiMed Biologics USA, Irvine, CA, 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 L5 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 occurred. All reported reactogenicity was mild to moderate in severity. Initial PK up to 4 weeks following initial N6LS administration from 21 subjects showed that maximum (C_{max}) and 4 week post-infusion serum concentrations increased proportionally with antibody dose (Table 1). Estimated half-life exceeded 30 days in all 15 subjects with at least 12 weeks of PK results. This preliminary analysis has shown that N6LS demonstrates linear PK with a promising half-life for infrequent administration.

**Conclusion:** N6LS was safe and well tolerated by IV and SC administration and displayed encouraging PK parameters. 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 and dose</th>
<th>Scev</th>
<th>MKE</th>
<th>4 weeks post-infusion conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous Dosing</td>
<td>301 (29)</td>
<td>746 (22)</td>
<td>52 (23)</td>
</tr>
<tr>
<td>20 mg/kg (miv)*</td>
<td>509 (236)</td>
<td>438 (176)</td>
<td>98 (26)</td>
</tr>
<tr>
<td>40 mg/kg (miv)</td>
<td>1717 (560)</td>
<td>1381 (323)</td>
<td>254 (300)</td>
</tr>
<tr>
<td>Subcutaneous Dosing</td>
<td>301 (29)</td>
<td>746 (22)</td>
<td>52 (23)</td>
</tr>
</tbody>
</table>

*Pharmacokinetic parameters include: C_{max} (maximum serum concentration [meg/L]), AUC (area under the curve, [mg·h/L]), and 4 week post-infusion concentration [meg/L]; standard deviation/

**509** PREEXISTING RESISTANCE AND B/F/TAF SWITCH EFFICACY IN AFRICAN AMERICANS

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**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, and/or NRTIs were eligible for enrollment with the exception of tenofovir resistance (K65R/E/N, 3 or more thymidine analogue mutations [TAMs], or T69-insertions); primary INSTI resistance (-R) was exclusionary. Pre-existing drug resistance was assessed with historical genotypes and retrospectively with baseline proviral DNA genotyping (GenoSure Archive, Monogram Biosciences). Participants with exclusionary resistance detected post-randomization were allowed to remain on study. Outcomes were determined by last on-treatment HIV-1 RNA through Week 24.

**Results:** Of the 493 participants analyzed for efficacy, 328 switched to B/F/TAF and 165 stayed on their 3-drug baseline regimen (SBR). Cumulative baseline protease and reverse transcriptase data from historical and/or proviral genotypes were available for 96% (471/493). Pre-existing primary NRTI-R, NNRTI-R, and PI-R substitutions were observed in 15% (70/471), 21% (101/471), and 13% (60/471), respectively. The most commonly detected NRTI-R substitutions were M184V/I in 11% (51/471) and TAMs in 7.2% (34/471). Baseline integrase data were available for 91% (450/493). Primary INSTI-R was detected post-randomization in 4.2% (19/450) by proviral genotype. Resistance substitutions were similar among treatment groups (Table 1). Among B/F/TAF-treated participants, 99% (326/328) were suppressed at their last visit through Week 24 including 100% (44/44) with NRTI-R (31 of whom had archived M184V/I), 59% (68/69) with NNRTI-R, 100% (34/34) with PI-R, and 100% (15/15) with INSTI-R. Four participants were analyzed for resistance development on study (3 B/F/TAF, 1 SBR); none had treatment emergent resistance to study drugs.

**Conclusion:** Pre-existing resistance was common among suppressed Black Americans switching to B/F/TAF, notably M184V/I, TAMs, and NNRTI-R. High rates of virologic suppression were maintained through 24 weeks of B/F/TAF treatment and there were no failures with resistance, indicating that B/F/TAF is an effective treatment option for patients with or without pre-existing resistance to NNRTIs, PIs, or non-tenofovir NNRTIs.

**510** TRANSMITTED DRUG RESISTANCE IN PEOPLE LIVING WITH DIAGNOSED HIV IN CALIFORNIA

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**Background:** Increased antiretroviral use for treatment and prevention raises concern that rates of transmitted drug resistance may increase. We analyzed a population-based dataset of HIV-1 pol sequences to estimate the prevalence of transmitted drug resistance-associated mutations (DRAMs) in people living with HIV in California from 2008-2018 and evaluated the transmission potential of identified mutations.

**Methods:** HIV-1 pol sequences reported to the California HIV surveillance system were analyzed via the SIERRA HIV Drug Resistance Database to determine resistance mutations and COMET to determine subtype. This analysis was limited to sequences that were obtained within 3 months of an HIV diagnosis with documentation of no previous exposure to antiretrovirals. DRAMs were defined based on the CDC surveillance resistance mutation list. We used TRAC-EX to construct genetic transmission networks. Clustering was defined as two or more linked sequences with a pairwise genetic distance of ≤ 1.5%. Among ART-naive persons, we compared the frequency of clustering of sequences with at least one DRAM compared with sequences without any DRAMs.

**Results:** Of 17,103 sequences (93.9% subtype B) obtained within 3 months of an HIV diagnosis, antiretroviral history was available for 5,740 sequences and 3,616 sequences had documentation of no prior antiretroviral exposure. Of the 3,616 sequences from antiretroviral-naive persons, 1,480 (40.9%) clustered with at least one other sequence in 212 dyads and 194 larger clusters ranging from 3 to 28 sequences (median=4). In most clusters (33.3%), male-to-male sexual contact was the most common reported risk behavior. The prevalence of any DRAM in a sequence from an antiretroviral-naive person was 20.0%; NNRTI, NRTI, and PI mutations were detected in 11.7%, 7.5%, and 4.3% of sequences, respectively. The integrase region was sequenced in a subset of 432 persons and the prevalence of an integrase DRAM was 1.5% (4/274) compared with sequences without a mutation, a higher proportion of sequences with an NNRTI mutation clustered (rate ratio [RR] 1.20) whereas a lower proportion of NRTI mutations clustered (RR=0.70) (Table). This population-based drug-resistance analysis demonstrated sustained DRAM transmission, particularly NNRTI mutations, among antiretroviral-naive people. Although reassuring that NRTI mutations were associated with less clustering, a proxy for reduced further transmission, this finding should continue to be monitored as exposure to NRTIs increases with the expansion of pre-exposure prophylaxis.

**511** TRENDS IN TRANSMITTED DRUG RESISTANCE IN SPAIN THROUGH THE PERIOD 2007-2018

Carlos Guerrero Beltrán1, Marta Alvarez2, Antonio Aguilar2, María Carmen Vidal Ampurdanes3, Marina Martínez4, Arkaitz Imaiz, Asunción Iborra4, Juan L.
Gomez-Sirvent1, Joaquin Peraire2, Joaquin Portilla3, Estrella Caballero4, Mónica García-Alvarez5, José A. Iribarren6, Mar Massí7, Federico García8, 9Hospital Universitario San Cecilio, Granada, Spain, 10Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain, 11Hospital Universitario de San Espinas, Palma de Mallorca, Spain, 12Hospital Universitario Mútua de Terrassa, Terrassa, Spain, 13Hospital Universitario de Bellvitge, Barcelona, Spain, 14Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain, 15Hospital Universitario de Canarias, San Cristobal de la Laguna, Spain, 16Hospital Universitario de Taragona Joan XXIII, Taragona, Spain, 17Hospital General Universitario de Alicante, Alicante, Spain, 18Hospital Universitario de la Vall d’Hebron, Barcelona, Spain, 19Hospital Universitario 12 de Octubre, Madrid, Spain, 20Hospital Donostia, San Sebastián, Spain, 21Hospital 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 Fast sequences from CoRTS (2007-2018). As Integrase resistance is not part of routine testing in naïve patients in Spain, we run 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 INs TDR, we also described similar values with no significant changes over years. However, we observed a decrease in PIs TDR from 2016 (≤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 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 INs DRM prevalence. Clinically relevant TDR to approved first line regimens showed a slow decline from 2007 to 2018. Resistance to INs TDR remains at very low levels. These findings, together with the very low prevalence of DRM to recommended first line NRTIs in 2015-2018 reinforce GESIDA recommendations on baseline resistance testing and test and treat strategies when starting PIs or INs 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 Koyou4, Matthias Egger5, Christian L. Althaus6 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:** The rise in the prevalence of drug resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) in HIV-infected individuals initiating antiretroviral therapy (ART) is a major problem in countries of southern Africa. 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 regimen in southern Africa. Between-country variation in TFNR was statistically significant, but no specific predictors could be identified for PDR or TFNR.
comparison shows that NNRTI PDR can be controlled despite high levels of ART coverage, as in Botswana, likely because of better patient management and lower exposure to ART before treatment initiation. Our results suggest that the ability to control PDR is associated with features of the healthcare financing system at the national level. Additional data on NNRT PDR and ART management is urgently needed in some countries of southern Africa.

**515 PRETREATMENT AND ACQUIRED ANTIRETROVIRAL DRUG RESISTANCE IN 4 AFRICAN COUNTRIES**

**Trevor A. Crowell**, Brook Danboise1, Ajay Parikh1, Allalha L. Esber1, Alex Kasembe2, Samoel Khamadi1, Michael Iroezindu4, Francis Kiweewa5, John Owuor1, Joanna Freeman1, Jennifer Malia1, Linda Jagodzinski3, Julie Ake1, Christina Polyak1, for the AFRICOS Study Group

In low- and middle-income countries, most treatment-naïve people living with HIV (PLWH) take first-line treatment with no baseline resistance testing. In the SINGLE trial, there was a significantly higher risk of treatment-emergent drug resistance in the TDF/FTC/EFV arm (1.7%) compared to the ABC/3TC/DTG arm (0.0%). In South Africa, over 10% of treatment-naïve patients have transmitted NNRTI drug resistance.

**Background:** In low- and middle-income countries, most treatment-naïve people living with HIV (PLWH) take first-line treatment with no baseline resistance testing. In the SINGLE trial, there was a significantly higher risk of treatment-emergent drug resistance in the TDF/FTC/EFV arm (1.7%) compared to the ABC/3TC/DTG arm (0.0%). In South Africa, over 10% of treatment-naïve patients have transmitted NNRTI drug resistance.

**Methods:** We conducted a 96-week, open-label randomised trial in South Africa, comparing TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV. Inclusion criteria included age ≥ 12 years, no prior ART >30 days, and HIV-1 RNA >500 copies/mL. There was no screening for baseline drug resistance, consistent with South African treatment guidelines. Patients with at least one HIV RNA result above 1000 copies/mL after 24 weeks of randomised treatment were genotyped prospectively, together with a test of their stored baseline sample. For this analysis, virological failure was classified as HIV RNA >1000 copies/mL. There was no screening for baseline drug resistance, consistent with South African treatment guidelines. Patients with at least one HIV RNA result above 1000 copies/mL after 24 weeks of randomised treatment were genotyped prospectively, together with a test of their stored baseline sample.

**Results:** Of 1024 eligible participants, 976 (95.3%) underwent HIVDR testing and genotype with the combined TAF/FTC/DTG and TDF/FTC/DTG arms (2/23; 9%), p < 0.01. The most common treatment-emergent NNRTI mutations were M184V (n=5), K65R (n=2); most common NNRTI mutations were K103N (n=3), and P225H (n=2). Of the 10 patients developing NNRTI RAMs at VF, 8 (80%) already had at least one NRTI or NNRTI RAM at baseline. No treatment-emergent integrase mutations were observed.

**Conclusion:** In the ADVANCE study, there were similar rates of virological failure between the arms. However, the patients in the TDF/FTC/EFV arm were significantly more likely to develop NNRTI or NRTI mutations at VF (71%) compared to the DTG arms (9%). Most patients with treatment-emergent resistance already had NRTI or NNRTI mutations at baseline.

### Table 1

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>TAF/FTC/DTG</th>
<th>TDF/FTC/DTG</th>
<th>TDF/FTC/EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients with virological failure (%)</td>
<td>101 (14)</td>
<td>85 (12)</td>
<td>98 (14)</td>
</tr>
<tr>
<td>% of patients with treatment-emergent NNRTI mutations</td>
<td>6 (6%)</td>
<td>2 (14%)</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>% of patients with treatment-emergent NRTI mutations</td>
<td>6 (6%)</td>
<td>1 (8%)</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>% of patients with treatment-emergent NRTI or NNRTI mutations</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Multivariate analysis showed that the risk of drug resistance was higher in the TDF/FTC/EFV arm compared to the TDF/FTC/DTG arm (p=0.01).**
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 Grint1, Elizabeth Chimbandy1, Judith Heaney1, Matthew Byott1, Eleni Nastouli1, Ravindra K. Gupta1


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 HIV Drug Resistance Algorithm. Drug resistance was defined as having intermediate or high-level resistance to specific drugs.

Results: Overall, 814/1361 (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 237/232 (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.

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-NAÏVE AND PLWH FAILING FIRST-LINE ART IN HAITI

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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- naïve or with virologic failure on first-line ART (TDF)/lamivudine (3TC)/lopinavir (LPV)/ritonavir (RTV) (LPV/RTV) or EFV/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- naïve and 91 on NNRTI-based first-line ART. Of those, 56.7% were female and median age was 35 (IQR: 26, 44). Among ART- naïve 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. M184VI 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- naïve 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.

Table 1: Proportion of Patients with Genotypic Resistance by Treatment Regimen, and Drug

518 PRETREATMENT HIV DRUG RESISTANCE AND 48-WEEK VIROLOGIC OUTCOMES IN THE ADVANCE TRIAL

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Background: Drug resistance is rare in HIV-naive patients in resource-limited settings. Drug resistance testing can be challenging due to limited resources. We assessed drug resistance to ART in HIV-naive patients enrolled in the ADVANCE clinical trial.

Methods: 335 HIV-naive patients were enrolled in the ADVANCE clinical trial in South Africa. Drug resistance testing was performed at baseline. Resistance was measured using the Stanford HIV Drug Resistance Database. Drug resistance was defined as having intermediate or high-level resistance to specific drugs.

Results: In the 335 HIV-naive patients enrolled, 9.6% had drug resistance at baseline. Resistance was most commonly to EFV (6.7%), 3TC (4.8%), and RTV (3.6%). 1.8% of patients had resistance to at least one drug with a Stanford HIV Drug Resistance Database score of ≥30.

Conclusion: Drug resistance is rare in HIV-naive patients enrolled in the ADVANCE clinical trial. Resistance was most commonly to EFV, 3TC, and RTV. Further monitoring is needed to assess the impact of drug resistance on treatment outcomes.
519 IMPACT OF PREEXISTING DRUG RESISTANCE ON RISK OF VIROLOGIC FAILURE IN SOUTH AFRICA


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Background: There is conflicting evidence on the impact of pre-existing HIV drug resistance mutations (DRM) on 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 virologic 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 PASEq 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 9.2-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.

520 TENOFOVR DIPHOSPHATE IN DRIED BLOOD SPOTS PREDICTS VIROLOGIC FAILURE AND RESISTANCE

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Background: Tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) is a measure of cumulative adherence and exposure to TFV-based antiretroviral therapy (ART). This adherence biomarker has been associated with viral suppression and found to predict future viremia in persons living with HIV (PLWH) receiving tenofovir disoproxil fumarate (TDF)-based ART. However, little is known about its utility in the context of virologic failure (VF) and drug resistance in resource-limited settings.

Methods: Participants within a prospective clinical cohort of PLWH who initiated TDF-based ART in 2 clinical sites in KwaZulu-Natal, South Africa, were evaluated. DBS samples were collected from participants who received at least 6 months of ART and developed VF, defined as an HIV VL >1000 copies/mL (cases), and in a selected group of participants who had an HIV VL <1000 copies/mL (controls, matched by site, age, gender, race and duration of ART). Cases were categorized as having VF without resistance or having VF with resistance using genotypic resistance testing. Concentrations of TFV-DP in DBS were quantified using a validated LC-MS/MS method. One-way ANOVA was used to compare the concentrations of TFV-DP in DBS at the time of the last study visit between controls, participants with VF without resistance and participants with VF with resistance. Data are presented as mean (SD) or median (IQR).

Results: A total of 1000 participants (500 at each site) were enrolled in the cohort. Of these, 288 (45 cases) had available DBS samples, which were included in the analysis. Median age was 31 (26, 38) years and 170 (59%) were women. TFV-DP concentrations in DBS in controls were higher than in participants with...
TRENDS AND CHARACTERISTICS OF HIV-1 DRUG RESISTANCE IN THE UNITED STATES (2012-2018)

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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 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 resistant samples with 2-, 3-, and 4-class resistance, respectively, decreased from 33.5% to 21.9%, 11.3% to 5.5%, and 3.1% to 1.1%. 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.

Conclusion: Decreasing prevalence of multiclass ARV resistance was observed in testing data, in addition to declines in NNRTI, 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.
**FOUR-CLASS RESISTANCE IS RARE IN TREATMENT-EXPERIENCED PATIENTS ACROSS EUROPE**

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**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 EuResist database, we selected treated patients with protease, reverse transcriptase and integrate 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.

**Results:** Complete four classes HIV-1 genotype information was available from 2643 distinct patients on ART contributing 3544 genotype data from Italy (49.9%), Germany (24.7%), Portugal (8.1%), Luxembourg (7.5%), Sweden (7.0%) and Belgium (2.7%). 66% were male and risk groups included 45.3% MSM, 50.9% heterosexual, 18.6% drug users and 18.3% heterosexuals. Subtype B virus was harbored by 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 was observed arguing for a prospective monitoring of the sensitivity to bnAbs of all HIV subtypes in Europe over a 25-year period of the French epidemic (1987-2012).

**Conclusion:** In a large population of patients across Europe with complete HIV-1 genotype information, the prevalence of 4CR appears to be relatively low and possibly declining over recent years. Continuous surveillance of this HIV-1 genotype information, the prevalence of 4CR appears to be relatively low and possibly declining over recent years. Continuous surveillance of this HIV-1 genotype information, the prevalence of 4CR appears to be relatively low and possibly declining over recent years. Continuous surveillance of this HIV-1 genotype information, the prevalence of 4CR appears to be relatively low and possibly declining over recent years.
intrinsically resistant to bNAbs, as observed in previous studies. The Env sequences revealed a high degree of polymorphism, with the majority (87%) 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 CD4-binding site (CD4bs; VRC01, 3BNC117), the V1/V2-glycan region (PG9, 3BNC117), the V3-glycan region (PGT121, 10-1074), and the gp41 membrane proximal external region (MERP, 108E).

**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 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 Env sequences over time, arguing for a continuous surveillance of ENV transmitted variants around the globe.

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**526 INVESTIGATION OF INTEGRASE-INHIBITOR RESISTANCE MUTATIONS IN gp41 IN CLINICAL SAMPLES**

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**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 gp41 that were associated with exposure to INSTI 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 INSTIs (HIVdb score <15). We then performed gp41 genotyping on these same samples. For comparison, we assembled reference datasets of subtype B Integrase (INT) and gp41 sequences from INSTI-naive DTP participants collected during routine clinical drug resistance testing. Amino acids (AA) significantly over- or under-represented among INSTI-treated and -naive participants at all INT and gp41 codons were identified by Fisher’s exact test. Analyses were restricted to AA observed ≥5 times and multiple comparisons were addressed using the Benjamini-Hochberg method (q-values).

**Results:** Int and gp41 sequences from participants treated with raltegravir (79; 54%), elvitegravir (27; 18%) or dolutegravir (40; 27%) were collected after a median of 32 (Q1-Q3: 13-56) months of INSTI exposure. Overall, 16% of INSTI-experienced participants were antiretroviral-naive at the time of their first INSTI prescription, while 84% had prior NNRTI- and/or PI-based regimens. INT sequences from 146 INSTI-treated and 2472 INSTI-naive individuals were compared. gp41 genotyping was successful for 115 (79%) INSTI-treated individuals; these were compared to sequences from 1222 INSTI-naive individuals. Lower frequencies of the gp41 polymorphisms I182V (OR=0.40, P=0.210-0.6, q=0.0085) and H209R (OR=0.47, P=1.9×10-4, q=0.086) were observed in INSTI-experienced individuals at these positions. No significant differences in AA frequencies were observed in INT sequences (all P>0.2).

**Conclusion:** Differences in gp41 amino acid frequencies in INSTI-experienced vs. -naive individuals were observed only at highly polymorphic positions. No substitutions in gp41 previously associated with INSTI resistance in vitro were identified, suggesting that these may arise rarely in vivo.

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**527 MAPPING RESISTANCE OF POTENT HIV-1 ENTRY INHIBITORS TARGETING PREFUSION CONFORMATION**

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**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 three 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 (Env-furin) or co-receptor CCR5/CXCR4 (Maraviroc) have been approved by FDA for HIV-1 treatment. To date, no entry inhibitors targeting the gp41200 have been FDA-approved although a promising small-molecule lead, fostamavir (the produrg for 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 ß20-ß21 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-818251, a derivative of BMS-626529, which is >10-fold more potent in pseudovirus neutralization assays. Crystal structure of BMS-818251 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-818251 in ex vivo cell cultures that were derived from HIV-1 patients. In addition, we used a site-saturated mutational library of BG05 Env to map the potential resistance mutations of BMS-818251 and BMS-626529.

**Results:** BMS-818251 exhibited superior viral suppression than BMS-626529 in HIV-1+ CD4+ T-cell culture from two patients. The minimal inhibition concentration of BMS-818251 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-818251 in the two samples tested. Mapping of resistance mutations by the BG05 mutation library revealed distinct resistance profiles by BMS-818251 and BMS-626529, suggesting different level of selection pressure between these two compounds.

**Conclusion:** Our data support further development of BMS-818251, which represents a novel class of HIV-1 drugs targeting gp120, as a next-generation entry inhibitor.

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**528 META-ANALYSIS OF UNUSUAL AND APOBEC MUTATIONS IN HIV-1 POL NEXT-GENERATION SEQUENCES**

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**Background:** In the natural drift of HIV towards higher resistance to bNAbs for the most prevalent subtypes spreading in France, arguing for a continuous surveillance of Env sequences over time.
Background: Next generation sequencing (NGS) for HIV-1 genotypic resistance testing is subject to detection of artificial mutations resulting from PCR error and APOBEC-mediated G-to-A hypermutation. We hypothesize that the presence of large numbers of unusual mutations at a mutation call frequency NGS threshold suggests the threshold is too low and that many of the detected mutations may be caused by PCR error or G-to-A hypermutation rather than HIV-1 replication.

Methods: We systematically analyzed HIV-1 pol Illumina NGS data from published studies to characterize the distribution of usual and unusual amino acid mutations at 8 NGS thresholds: 20%, 10%, 5%, 2%, 1%, 0.5%, 0.2% and 0.1%. At each threshold we quantified the number of unusual mutations (defined as having prevalence of <0.01% in HIV-1 group M population Sanger sequences) or signature APOBEC mutations.

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 (n=14,940), signature APOBEC mutations outnumbered non-APOBEC unusual mutations in one-sixth of samples at the 0.5%, 1% and 2% thresholds.

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 artificial mutations.

529 ABSENCE OF GS-6207 PHENOTYPIC RESISTANCE IN HIV Gag CLEAVAGE SITE AND OTHER MUTANTS

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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, Q450R, A431V, K436E, I437F/V, L469H/V/F, P453L, and/or PR mutations V83A and I84V) as well as 55 patient derived clones were analyzed phenotypically. GS-6207 IC50 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 maturation 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.

Conclusions: 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

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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 produg of GS-9148, a new NRTI with low potential for mitochondrial toxicity and renal accumulation that previously demonstrated its viro 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 ANRS 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 exhibited major DRAMs in the reverse transcriptase gene (K65R, Q151M, M184V and/or S215Y/F), according to the ANRS list (Table).

Regarding the 3 main resistance genotypic profiles described in HIV-2-infected patients failing NRTI-based regimens (K65R, Q151M and M184V), our data 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 produg of GS-9148, a new NRTI with low potential for mitochondrial toxicity and renal accumulation that previously demonstrated its 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 ANRS 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 exhibited major DRAMs in the reverse transcriptase gene (K65R, Q151M, M184V and/or S215Y/F), according to the ANRS list (Table).

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/F, IC50 = 108 and 134 nM, respectively). All isolates harbouring a Q151M mutation were highly resistant to GS-9131 (with IC50 ranging from 178 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 showed that isolates harbouring only K65R or M184V mutations presented moderate increases in IC50 for GS-9131, 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

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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 20-4CR patients failing ART. In vitro susceptibility to DOR was assessed through a TZM-bi 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 (ETR=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)(p=0.015) 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), time of exposure to NNRTI (r = 0.044; p = 0.853) or time elapsed since last exposure to NNRTI (r = -0.330; p = 0.155). Median DOR FC values were significantly higher in viruses harbouring major DOR RAMs according to both HIVdb (FC 100 [41.9-100] vs. 6.2 [1.2-17.2], p = 0.003) and IAS-USA lists (FC 100 [38.4-100] vs. 6.2 [1.2-20.2], p=0.007). However, both Stanford low-level and intermediate resistance groups included FC values spanning >1 log.

Conclusion: DOR activity decreases with increasing number of NNRTI mutations and is conferred 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

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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 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 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 A1 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 (283 subjects) were sensitive to CAB with IC50 fold-change (FC) ranging from 0.71- 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/Q148R (FC 4.1 A1 vs 4.4 B) in the 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 (1nM) and no viral breakthrough was detected at 3 weeks for CAB concentrations of 5nM or 40nM (1xEC40). The genotypes of the breakthrough viruses will be presented.

Conclusion: The FLAIR study demonstrated CAB+RPV LA was not inferior 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 INTEGRASE RESISTANCE MUTATION L74I

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Background: Natural occurring HLA-driven polymorphisms in HIV-1 may confer decreased susceptibility to antiretroviral therapies, but our knowledge of such polymorphisms in non-B subtypes remains incomplete. Here, we examine whether HLA genotype is associated with pre-therapy integrase strand transfer inhibitors (INSTI) resistance mutations in a treatment-naive Ugandan cohort.

Methods: HIV-1 integrase bulk sequencing and HLA-genotyping were performed on pre-therapy-initiation plasma and PBMC collected between 2005-2010 from n=511 INSTI-naïve participants in the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort. RIP 3.0 was used for HIV-1 subtyping. Major INSTI-associated resistance mutations were defined by the Stanford HIV database version 8.8 as T66AIK, E92Q, G118R, E138KAT, G140SAC, Y143RCH, S147G, Q148HRK, N155H, R263K. Only one minor mutation, L74I, was included due to recent reports linking it to cases of INSTI-treatment failure in subtype A1. HLA was used for all statistical and phylogenetic analyses. Multivariable logistic regression models were described for six resistance-mutation–HLA-genotype pairs that had n=8 or more individuals from which resistance mutations were observed.

Results: We identified major INSTI mutations in 1.2% (6/511) of participants: T66I (n=1; subtype D), E138K (n=3; all subtype D), and E148T (n=2; all subtype A1). L74I was found in 6% (n=16/247 subtype A1) and 4% (n=8/200 subtype D)
of individuals. None of these polymorphisms, when poorly 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.

534 HIV-1 VIRAL REBOUND AFTER BICTEGRAVIR, DOLUTEGRAVIR, AND CABOTEGRAVIR WASHOUT
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Background: In past studies, we performed in vitro washout experiments to reproduce these observations on two newly developed integrase strand transfer inhibitors (INSTIs), Bictegravir (BIC) and Cabotegravir (CAB). We demonstrated that the gp41 mutations Env-A539V and A556T, which enhance viral cell-to-cell transmission, provide a replication advantage over WT in the presence of not only DTG but also other classes of ARVs targeting RT and PR. Moreover, Env-A539V compromised for viral fitness defects induced by drug resistance mutations in the viral enzymes and increased resistance to ARVs when coupled with these mutations, suggesting that the Env mutations may be a “stepping-stone” on the path to high-level drug resistance.

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 IC90 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 IC90 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 IC90) 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 G410S/Q148H clones were not susceptible to BIC prior to and following drug washout. While DTG could suppress replication of GT410S/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-
**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. 72.3.5-kb pol single genome amplicons were prepared in a single library and sequenced (Illumina MiSeq). Reads were mapped to HIV-1 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 to (NRTI) including D67N, K70R, T215F, and K219Q/E in 9 kidney, 3 aortic lymph node, and 3 axillary lymph nodes SGA variants, but not in his duodenum or ileum (Table 1). In tissues, LG05 had NRTI resistance associated mutations (D67N, K70R, T215F, and K219Q/E) in 1 duodenum, 1 ileum, and 3 spleen SGA variants. Nonpolymorphic mutations associated with PI included M46I, E64K, V82T, I89V, 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.

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**Table 1. Summary of resistance mutations in tissues in virus spreading survivors of the Last Gift Study**

<table>
<thead>
<tr>
<th>Location</th>
<th>Total Cases</th>
<th>Any NRTI</th>
<th>Any NNRTI</th>
<th>Any INSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LG03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>0</td>
<td>0/0.0%</td>
<td>0/0.0%</td>
<td>0/0.0%</td>
</tr>
<tr>
<td>Ileum</td>
<td>10</td>
<td>10/10.0%</td>
<td>10/10.0%</td>
<td>10/10.0%</td>
</tr>
<tr>
<td>Kidney</td>
<td>10</td>
<td>10/10.0%</td>
<td>10/10.0%</td>
<td>10/10.0%</td>
</tr>
<tr>
<td>LG05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>5</td>
<td>5/100.0%</td>
<td>5/100.0%</td>
<td>5/100.0%</td>
</tr>
<tr>
<td>Ileum</td>
<td>5</td>
<td>5/100.0%</td>
<td>5/100.0%</td>
<td>5/100.0%</td>
</tr>
</tbody>
</table>

**Legend:** Resistance mutations are summarized for each tissue (ng/ug). Note: More than one or two drugs were detected in any tissue.

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**537 HIV DRUG RESISTANCE IN FEMALE SEX WORKERS FROM THE DOMINICAN REPUBLIC AND TANZANIA**


**Background:** HIV-1 drug resistance can be an obstacle to successful antiretroviral therapy (ART). It 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. HPTN-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); 2 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 (23.5%) of eight MSM who reported no prior HIV diagnosis; two cases had INSTI resistance mutations (one had E92Q and M184V, one had T97A).

**Conclusion:** High prevalence of INSTI resistance and intermediate-level resistance to second generation INSTIs was observed among virucic MSM recruited for the HPTN 078 study. Many of those with INSTI resistance had (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. 27/88 [30.7%], p<0.001) and was higher among those with ≥ 1 ARV drug detected 31/35 (88.6%) vs. 23/103 (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. K103M 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.
539 EXPANDED SPECTRUM OF ANTIRETROVIRAL-SELECTED HIV-2 MUTATIONS


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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-naïve persons. Nonpolymorphic treatment selected mutations (NPM-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.


540 HIV VIRAL BLIPS IN ADULTS TREATED WITH INSTI-BASED REGIMENS THROUGH 144 WEEKS

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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 therapy on bictegravir (B)/emtricitabine (FT) and tenofovir alafenamide (TAF), dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC), or DTG + F/TAF through 144 weeks of treatment in Studies 1489 and 1490.

Methods: PWH with at least one on-treatment post-baseline HIV RNA value were included in this analysis. HIV RNA and last observation carried forward (LOCF) outcome data through week 144 were used. A blip was an HIV RNA value >=50 c/mL preceded and followed by HIV RNA <50 c/mL, after achieving confirmed suppression (two consecutive HIV RNA values <50 c/mL).

Results: Of the 1240 participants with confirmed suppression, 143 (11.5%) had ≥1 blip through week 144 with similar blip frequencies between treatment arms (Table 1). An average of 1.3% of participants experienced blips per study visit, which was similar between treatment arms (Table 1). A total of 186 blip events occurred in the 143 individuals; 110 experienced a single blip and 33 experienced multiple blips. Of the 186 blips, 87 (46.8%) were low-level (50-199 c/mL) and 99 (53.2%) were ≥200 c/mL. The proportions of participants with blips <200 c/mL or ≥200 c/mL were similar between treatment arms (Table 1). Most with blips ≥200 c/mL had adherence ≤95% by pill count (69.2%), while those with blips <200 c/mL mostly had adherence >95% (63.3%) (Table 1). Of participants without blips, 98.7% (1003/1019) had HIV RNA <50 c/mL at week 144 or last visit vs. 91.6% (71/78) with blips ≥200 c/mL (p<0.01), and vs. 96.9% (63/65) with blips <200 c/mL (p=0.2). The 7 with blips ≥200 c/mL and HIV RNA ≥50 c/mL at week 144 were all on DTG-based regimens, and 6/7 had evidence of continued low adherence. Of the 21 individuals included in the overall resistance analysis, 5 experienced blips and none had emergent resistance to study drugs (Table 1).

Conclusion: Viral blips were infrequent and similar among PWH treated with B/FTAF, DTG/ABC/3TC, or DTG + F/TAF. Blips ≥200 c/mL but not <200 c/mL were associated with adherence ≤95%. High level blips of ≥200 c/mL were associated with lower suppression at week 144 due to poor adherence; however, none developed resistance on these 3-drug regimens with high barriers to resistance.

541 INVESTIGATION OF CLASSIC AND HIV-RELATED FACTORS FOR HEPATIC STEATOSIS AMONG PWID

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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 2016 were included. CAP > 270 db/m is 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 infection, BMI, waist circumference) was individually associated with INSTI use.

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 sensitivity analyses, each measure of adiposity (hepatic steatosis, elevated BMI, elevated waist circumference) was individually associated with 1.8 (1.1 – 2.9) and INSTI based ART (OR=1.8 (1.1 – 2.9). In sensitivity analyses, each measure of adiposity (hepatic steatosis, elevated BMI, elevated waist circumference) was individually associated with 1.6 (1.0 – 2.4) and INSTI based ART (OR=1.6 (1.0 – 2.4).
**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**

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**Background:** Frailty and sarcopenia are associated with 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 demographic, clinical, and laboratory measures. 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. 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 FRP. In stratified 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-MON-infected Patient**

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**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 (LHVIPA in Palermo, LIVEHV in Montreal, MHMHC 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 53 years, 74% males, 98% on ART) were included. 423 (45%), 128 (13.6%), 260 (27.6%) 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 HIV-). In multivariate analysis, NAFLD, liver fibrosis, age, BMI, smoking status, alcohol use, liver fibrosis (FIB-4 >3.25), depression, and Fisher’s exact tests compared between-group parameters. Multivariate regression assessed the relationship between NAFLD and a FRP controlling for demographic, clinical, and laboratory measures. The final 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.

**FIB-4 FIRST" STRATEGY IN A NAFLD PATHWAY ASSESSMENT FOR HIV MON-infected patients**

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**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 not largely accessible. Fibrosis-4 (FIB-4) index at the threshold of 1.3 is used as a low-risk fibrosis category by FIB-4. A FIB-4 first strategy in PLWH; ii) to determine prevalence and associated cofactors of discordance (false negativity) between TE and FIB-4 in patients classified as low-risk fibrosis category by FIB-4.

**Methods:** 1607 HIV mono-infected patients from three cohorts (LHVIPA in Palermo, LIVEHV in Montreal, MHMHC in Modena) were included if they fulfilled the following criteria: available TE and FIB-4 within 3 months; absence of NAFLD and liver fibrosis.
significant alcohol intake and of coinfection 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. Multivariable logistic regression analysis was used to identify cofactors associated with discordance between TE and FIB-4 in low-risk category.

**Conclusion:** A FIB-4 first risk-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 TRYPOTAPHOL CATABOLISM IS ALTERED AMONG PERSONS WITH HIV WHO HAVE STEATOSIS**

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**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 community 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 the 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) (mmol/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 pathoetiologic 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**

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**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 log 10 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 (β=37.9, p=0.001), AST (β=33.5, p=0.0006) and ALT (β=37.9, p=0.0001), triglycerides (β=0.26, p=0.0003), FIB-4 score (β=0.25, p=0.003), HIV plasma viral load (β=0.21, p=0.02), capase-1 (β=0.31, p=0.0003), MCP-1 (β=0.32, p=0.0001) and IL-6 (β=0.39, p=0.047), and LPS (β=0.22, p=0.03), and inversely associated with liver/spleen ratio (β=0.23, p=0.02), HDL (β=0.31, p=0.0003) and CD4+/CD8+ ratio (ρ=−0.2, p=0.02). The relationship between log10 IL-18 with ALT (β=33.5, p=0.0006) and ALT (β=37.9, 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 (β=0.37, p=0.004) and inversely associated with HDL (β=−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/CCR2 signalling. 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**

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**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 per each cohort 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**

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**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

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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 recommendations were included in 2015-16. Liver steatosis was assessed by unenhanced CT liver scan. Moderate-severe hepatic steatosis was defined by liver attenuation ≤ 48 Hounsfield units. Association with antiretroviral 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 raltegravir (number exposed (Nexp) = 59) and with cumulative exposure to elvitegravir (OR 2.84 (1.58;5.10) per year) (Nexp = 63). The association with cumulative exposure to elvitegravir with mentricabine/tenofovir disopirox fumarate (OR 3.06 (1.63;5.75)) or with emtricitabine/tenofovir alafenamide (OR 3.67 (1.29;10.46)) and cumulative (OR 1.19 (1.01;1.41) per year) exposure to abacavir (268), didanosine (78), emtricitabine (263), lamivudine (424), tenofovir disopirox fumarate (175-22), and with cumulative exposure to raltegravir (number exposed (Nexp) = 59) and with cumulative exposure to elvitegravir (OR 2.84 (1.58;5.10) per year) (Nexp = 63). The association with cumulative exposure to elvitegravir with mentricabine/tenofovir disopirox fumarate (OR 3.06 (1.63;5.75)) or with emtricitabine/tenofovir alafenamide (OR 3.67 (1.29;10.46)). Further, the association with cumulative exposure to elvitegravir was associated with cumulative exposure (OR 1.22 (1.02;1.47) per year) to stavudine (Nexp = 86). Test for interaction with stavudine and raltegravir or elvitegravir were statistically non-significant (P=0.79 and P=0.45). Any exposure (Nexp) to abacavir (268), didanosine (78), emtricitabine (263), lamivudine (424), tenofovir disopirox fumarate (416), tenofovir alafenamide (33), zidovudine (262), efavirenz (338), atazanavir (113), rilpivirine (25), stavudine (137), darunavir (135), lopinavir (61) or dolutegravir (67) was not associated with moderate-severe steatosis.

Conclusion: Moderate-severe hepatic steatosis in PLWH without viral hepatitis or excessive alcohol intake was associated with cumulative exposure to stavudine, elvitegravir and raltegravir. Prospective trials are required to establish a causal association.

550 BENEFITS OF RILPIVIRINE FOR LIVER FIBROSIS IN HIV/HCV COINFECTED SUBJECTS

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Background: Recent studies have described that treatment with rilpivirine (RPV) induces antifibrotic effects in various models of chronic liver disease. 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, Alegrè F, Moragrega À, et al. Gut epub ahead of print doi:10.1136/gutjnl-2019-31837

Methods: From a 4009 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 with 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 [95% CI: -3.0; -0.83]; p <0.010) and in control group (mean difference of -0.5Kpa [95% CI: -1.6 - 0.62]; p = 0.4). This difference in the case group was found only in subjects who had CHC, mean difference of -2.9Kpa [95% CI: -4.6 - -1.33]; 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

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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 among HIV+ patients often rely on non-invasive markers, such as the Fibrosis-4 Index for Hepatic Fibrosis (FIB-4).

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 (METAIVIR 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
esophageal varices or portal gastropathy; 4) paracentesis was performed; or 5) clinician noted ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy. The diagnostic accuracy of FIB-4 was determined by calculation of the positive predictive value (PPV), sensitivity, specificity and area under the receiving operator curve (AUROC). Results: Incident HCC was diagnosed in 302 HIV+ patients (median age, 56 [IQR, 51-61] years; 299 [99%] male). After chart review, 203 (67.2%, [95% CI, 61.6-72.5%]) had evidence of cirrhosis. Cirrhosis was most commonly identified by radiology (63%) and pathology (32%). Median FIB-4 was 4.37 [IQR, 2.42-7.71] for those with cirrhosis and 2.87 [IQR, 1.66-4.83] for those without cirrhosis (p<0.001). FIB-4 identified patients with cirrhosis with an AUROC of 0.67 (95% CI, 0.60-0.73). FIB-4 >4.0 had a PPV of 78.9% to confirm the presence of cirrhosis with a specificity of 65.2% and specificity of 69.7% (Table 1).

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 1. The positive predictive value, sensitivity, and specificity of FIB-4 values for cirrhosis in HIV/AIDS patients.

<table>
<thead>
<tr>
<th>FIB-4 Value</th>
<th>No cirrhosis by chart review</th>
<th>Cirrhosis by chart review</th>
<th>PPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
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<tr>
<td>&lt;1.50</td>
<td>120</td>
<td>94</td>
<td>93.5%</td>
<td>58.5%</td>
<td>81.2%</td>
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<td>20</td>
<td>74.2%</td>
<td>57.6%</td>
<td>88.9%</td>
</tr>
<tr>
<td>2.50-3.50</td>
<td>12</td>
<td>8</td>
<td>57.7%</td>
<td>41.1%</td>
<td>92.4%</td>
</tr>
<tr>
<td>&gt;3.50</td>
<td>6</td>
<td>2</td>
<td>69.6%</td>
<td>44.8%</td>
<td>98.8%</td>
</tr>
</tbody>
</table>

552 PLASMA MIR-99A AND MIR-100 PREDICT LIVER FIBROSIS PROGRESSION IN HIV/HCV SUBJECTS

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Background: The lack of available biomarkers to diagnose and predict different stages of liver disease, such as 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.

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, GGTP, 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 1.8 to 2.0 fold increase). Previously described circulating miRs associated with NAFLD in the general population, miR-122, miR-34a and miR-192, were also found here within the 38 upregulated miRs. Of the 38 upregulated miRs, 7 (miR-985-5p, miR-100-5p, miR-193-5p, miR-99a-5p, miR-203a-3p, miR-5588-5p and miR-99a-3p) were significantly upregulated in the 26 subjects that progressed to liver fibrosis when compared to the 20 subjects that did not progressed (p<0.005). Two of these miRs, miR-99a-5p and miR-100-5p, were highly associated with liver fibrosis progression (p<0.0001) and displayed a significant linear correlation with liver fibrosis values of the entire study cohort (r=0.51, p=0.0003 and r=0.48, p=0.0006, respectively).

Conclusion: Circulating miR-99a-5p and miR-100-5p are significantly associated with liver fibrosis progression in subjects with HIV-1/HCV co-infections, even before liver fibrosis is detectable. This study demonstrates the potential of miRs as biomarkers in the progression of liver injury in HIV-infected subjects. Levels of miR-99a-5p and miR-100-5p may be suitable markers of liver fibrosis amelioration in HIV-1/HCV co-infected patients treated with HCV DAAs and cured of HCV infection.

553 HEPATIC FIBROSIS DETERMINED WITH ARE SIGNIFICANTLY PREDICTS COGNITIVE IMPAIRMENT

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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 NHL (rho=0.46, p=0.017). LS >2.93 kPa (fibrosis) was more prevalent in HCV+ not virally suppressed than those virally suppressed (56.9% vs 29.2%, p=0.002). HCV 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+ and 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 NCI compared to non-use (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 use may contribute to liver disease and cognitive impairments in PLWH. Longitudinal studies with comprehensive neuropsychological testing are needed.

554 CHANGES IN LIVER CANCER SURVIVAL IN HIV INFECTION AFTER MANAGEMENT OPTIMIZATION

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Background: Hepatocellular carcinoma (HCC) has been an important cause of morbidity and mortality among HIV-infected patients during the last twenty years. Previous studies have shown that the survival after HCC diagnosis in HIV-infected patients is extremely low, mainly as a consequence of late diagnosis and a low rate of treatment. This scenario may be changing in recent years, partly due to the systematic HCC surveillance program implementation in this population. Because of this, we assessed changes in the HCC management and its impact on survival of HIV-infected patients.
LIVER PATHOLOGY IN HIV-POSITIVE SUBJECTS UNDERGOING LIVER TRANSPLANTATION

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Background: Liver transplantation (LT) represents the best therapeutic option for end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). Although LT in HIV+ 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 2012 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+. LT for HCC was the indication for LT in 65.8% of cases. HIV+ subjects were younger (53 vs 58 years, p<0.0001), more commonly HCV+ and had a higher mELD score at the limit of significance (23 vs 17, p=0.02). Likewise, there was a greater frequency of early diagnosis (BCLC stage 0-4) in the HIV+ group (21 vs 13, p=0.001). There was a greater proportion of HCC diagnosis by screening in the HIV+ group (21 vs 13, p=0.02). Likewise, there was a greater frequency of early diagnosis (BCLC stage 0-4) in the HIV+ group (21 vs 13, p=0.001).

Conclusion: The HCC clinical management in HIV-infected patients has improved in the last decade in Spain. Thus, the proportion of early diagnosis has increased, possibly due to an increasing rate of HCC detection by surveillance, resulting in a greater number of curative therapies. Consequently, the HCC survival in HIV-infected patients has considerably lengthened in recent years.

EPIDEMIOLOGICAL TREND OF CHRONIC HEPATITIS C IN SPAIN (2000-2015): NATIONWIDE STUDY

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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 for 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 HCV diagnosis and HCV clinical stages: "CHC (070.4, 070.5, 070.54, 070.7x, or 002.62); compensated cirrhosis (571.2 or 571.5); end stage liver disease (572.2, 572.3, 572.4, 456.0 – 456.2); compensated cirrhosis (571.2 or 571.5); end stage liver disease (572.2, 572.3, 572.4, 456.0 – 456.2), 530.7, 530.82, 578.X, 789.5, 567.23, 572.8, 54.9, 42.91, 44.91, 96.06, 573); hepatocellular carcinoma (155.x, 155.0, 155.1, 155.2); liver transplantation (996.82, V42.7, 50.5).

Results: 868,523 hospital admissions with CHC (25.5% CH, 25.3% ESLD, 8.6% HCC, and 2.5% LT) were identified. Overall rates of hospital admission and mortality increased from 2000-2003 to 2004-2007, 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=0.003). 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 and hospital charges trends were significant in all strata analyzed (p<0.001) (Fig1A). 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<0.01), and LT (p=0.050) was found (Fig1B). 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

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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 CNICS site in the U.S. during 1995-2018, excluding those with previous cancer diagnoses and those without HIV 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 extrahepatic cancer incidence among patients with HIV/HCV coinfection compared with those with HIV monoinfection. We used standardized morbidity ratio weights to compare extrahepatic cancer incidence among patients with HIV/HCV coinfection with the incidence we would have observed under a hypothetical scenario in which all patients with HIV/HCV coinfection were successfully treated with DAAs at baseline. To explore potential misclassification of HCV status, we conducted a sensitivity analysis classifying those who only had a positive HCV antibody as missing HCV status.

Results: Of 21,310 adults in our analyses, 3,823 (18%) were coinfected with HIV. Incidence rates of any extrahepatic cancer among patients with HIV/HCV coinfection and HIV monoinfection were 643 and 572 cases per 100,000 person-years, respectively, with a crude HR of 1.13 (99% CI: 0.89, 1.43; Table). In crude analyses, patients with HIV/HCV coinfection were at elevated risk of cancer of the kidney and lung, and of inflammation-related cancers (defined in Table footnote), compared with patients with HIV monoinfection. In weighted analyses (Table), patients with HIV/HCV coinfection remained at elevated risk of kidney cancer (HR 3.43, 99% CI: 1.06, 11.06). Results were similar when classifying those with only positive HCV antibody as missing HCV status.

Conclusion: Extrahepatic cancers driven by immune dysfunction, specifically kidney cancer, may be prevented by HCV-curative DAA therapies among patients with HIV/HCV coinfection.

Table. Crude and weighted hazard ratios for extrahepatic cancers among patients with HIV/HCV coinfection compared with those with HIV monoinfection, Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), 1995-2018

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Crude hazard ratio (95% CI)</th>
<th>Weighted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any extrahepatic cancer</td>
<td>1.13 (0.89, 1.43)</td>
<td>0.83 (0.63, 1.08)</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.85 (0.64, 1.17)</td>
<td>0.90 (0.73, 1.13)</td>
</tr>
<tr>
<td>Lung</td>
<td>2.17 (1.26, 3.70)</td>
<td>1.21 (0.67, 2.23)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>1.99 (0.83, 3.22)</td>
<td>1.09 (0.60, 1.98)</td>
</tr>
<tr>
<td>Prostate (men only)</td>
<td>0.71 (0.35, 1.48)</td>
<td>0.55 (0.25, 1.17)</td>
</tr>
<tr>
<td>Inflammation-related cancers*</td>
<td>0.63 (0.44, 0.89)</td>
<td>0.52 (0.36, 0.75)</td>
</tr>
<tr>
<td>Kidney</td>
<td>6.50 (1.16, 34.31)</td>
<td>3.41 (1.16, 11.06)</td>
</tr>
<tr>
<td>Lung</td>
<td>2.17 (1.26, 3.70)</td>
<td>1.21 (0.67, 2.23)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>1.99 (0.83, 3.22)</td>
<td>1.09 (0.60, 1.98)</td>
</tr>
</tbody>
</table>

*Inflammation-related cancers included bladder cancer, colon cancer, hepatic cancer, liver cancer, multiple myeloma, pancreatic cancer, and stomach cancer.

558 SYNDROME OF VIRAL COINFECTIONS AND INCIDENT END-STAGE RENAL DISEASE

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Background: Advances in infection care and treatment have improved the life expectancy of persons living with HIV. Consequently, persons living with HIV are aging with increasing risk of chronic conditions such as liver and cardiovascular diseases, lung cancer, neurocognitive impairment and chronic kidney disease (CKD). Syndemic viral infections are associated with increased risk of CKD and end-stage renal disease (ESRD). However, population-level estimates of the impact of syndemic co-infections are lacking. This study assessed the effect of HBV, HCV and HIV co-infections on incident ESRD in a large population-based cohort.

Methods: The British Columbia (BC) Hepatitis Testers Cohort includes ~1.7 million individuals tested for HIV or HBV, or reported as a case of HBV, HIV, or HBV in BC, and is linked with various administrative healthcare data. ESRD was defined through ICD-9/10 codes. Individuals tested for all three infections since 1990 were followed from the date of their last test until the earliest of 1) incident ESRD, 2) death or 3) 12/31/2015. Fine and Gray competing risks models with adjustment 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), HBV/HCV co-infection (5.8), and HIV (3.8), HCV (3.0) and HBV monoinfection (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 16, 95% CI: 5-28 and 38, 95% CI: 31-46) for both persons with diabetes and those without, respectively.

Conclusion: Persons living with HIV/HBV/HCV triple infection were at highest risk of ESRD. Management of these syndemic conditions, particularly through HBV, HIV and/or HCV treatment could reduce the risk of ESRD among people with co-infections.
559 CAUSE OF DEATH AMONG THOSE DIAGNOSED WITH HEPATITIS C IN WASHINGTON, DC, 2009-2017

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Background: There has been 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 death 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, 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 primary 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 56% increase in opiate overdose deaths compared to a 69.1% decrease in liver-related deaths. Compared to persons who had a non-opiate related death between 2009 and 2017, HCV cases with a death due to opiate overdose were more likely to have a death age between the ages of 50-69 (84.1% vs 75.6%, p<.0001), have a year of death in 2017 (26.2% vs 13.6%, p<.0001), and have a positive/detectable result at their last RNA screening (62.1% vs 53.7%, p<.0001). There were no differences by gender, age, race/ethnicity, or HIV-co-infection. Risk of dying from opiate-overdose was significantly greater than liver-related causes (p=0.0009), with the greatest excess risk in men aged 50-69 years (12.58, 5.91-26.78).

Conclusion: This analysis highlights that older adult males with hepatitis C face a higher mortality risk from opiate overdose than from their hepatitis infection. As local governments continue to strategize interventions around opioid overdose, it will be important to include approaches around specific subpopulations affected by HCV.

560 CAUSES OF DEATH IN PERSONS WITH AND WITHOUT HCV INFECTION

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Background: HCV is associated with a higher risk of overall mortality and several hepatic and extrahepatic consequences, including atherosclerotic cardiovascular disease (ACVD), diabetes, chronic kidney disease, hepatocellular carcinoma (HCC) and certain non-liver cancers. Whether the excess mortality is primarily due to liver-related or other causes is unknown. Knowing the most common causes of death is critically important to design targeted strategies to reduce mortality in persons with HCV infection. Our objective was to determine the most common causes of death in persons with and without HCV infection.

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%); ACVD (16.8%); self-harm (6.2%); pulmonary disease (5.6%). Among those without HCV, the five most common causes were: Malignancy (25.2%); ACVD (23.0%); pulmonary disease (7.8%); infections (5.4%); endocrine including diabetes (5.1%).

Conclusion: Liver disease, malignancy and sarcoidosis are responsible for the majority of deaths for 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.

561 RESOLVING HCV SUBTYPES IN A BELGIAN COHORT BY FULL GENOME NEXT-GENERATION SEQUENCING

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Background: HCV infection is a global public health priority. HCV genotypes are divided into six major genotypes (1-6) with numerous subtypes (a-h) and a lot of minor variants. In order to reach WHOs 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 HIV/HCV 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), each: 4q, 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

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Background: Despite the excellent efficacy, direct-acting antivirals (DAA)-regimens are associated with failure in about 5% of cases. To characterize the virological 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 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), NS5A and NS5B (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 Glecaprevir/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 Glecaprevir/Pibrentasvir (4/11, 36.7%) failed patients (p=0.002 and 0.000 respectively). According to Sofosbuvir/Velpatasvir regimen 36.4% pts showed at least 2 RAs in at least two HCV region including NSSA and 70.3% pts showed at least 2 RASs only in NSSA region. Considering Grazoprevir/Elbasvir regimen 27.3% pts showed at least 2 RASs in at least two HCV region including NSSA and 88% pts showed at least 2 RAs only in NSSA region (p=0.000). All 21 re-treated patients with Sofosbuvir/Velpatasvir/Voxilaprevir, obtained with SVR. The re-treatment was guided by genotyping test.

Conclusion: Patients with failure to a second-line therapeutic regimens frequently present mutations above all in the NSSA region. At re-treatment all obtained with SVR. The re-treatment was guided by genotyping test.

563 RESISTANCE-ASSOCIATED SUBSTITUTIONS (RAS) IN “UNUSUAL” HCV SUBTYPES

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Background: “Unusual” Hepatitis C Virus (HCV) subtypes in patients from Africa and Asia origin have been associated with a lower sustained virological response(SVR) to DAAas. This can be ascribed to polymorphisms at relevant amino acid positions compared to the most sensitive subtype in the same genotype. Using the global SHARED network, we aimed to assess the prevalence of RAS and RAS patterns at failure among unusual HCV subtypes, defined as GT non1a/b, GT2 non2a/b, GT3 non3a, GT-4 non4a/d, GT5, and GT6.

Methods: We extracted data from the SHARED database of patients who did not achieve SVR. Only patients who failed DAA regimens recommended by EASL guidelines were included. Geno- and subtype were sequence-derived, and analyses grouped by subtype. RAS were analysed at positions according to the 2018 EASL guidelines.

Results: We analysed 60 unusual subtypes among DAA failures, including: GT2c (n=8), GT3b (n=6), GT3h (n=7) and GT4r (n=10) followed by GT4v (n=3), GT2q, 3k, 4q, 4o, and 6o(n=2 each), and GT1i, 2j, 3g, 4b, 4f, 4q, 4t, 4h, 6h, 6p, 6r and 6x(n=1 each). Patients failed: SOF/DCV(n=14), SOF/VEL +/- RBV(n=13), and EBR/GZR(n=10), SOF/LDV +/- RBV(n=10), G/P(n=5) or other regimens(n=2). At failure, all patients harbored NSSA RAS regardless of their subtype, with a mean number of 3 NSSA RAS per sample. Interestingly, failures with GT6h/p/x carried 5 to 6 NSSA polymorphisms possibly associated with reduced NSSA inhibitor susceptibility. All GT3h failures harbored a S62M RAS with unknown impact, 71% of which were combined with the Y93H/F. All GT4 failures harbored L28M/T/V RAS in association with L30R with or without L31M/F. All GT-3b and GT3h harbored the A30K+L31M+S62D/E/I combination. Additionally, among NS5 failures RAS at position 168D/168V/N/E were observed in 50% of patients(n=6/12). Importantly, combinations of several NS5 RAS were
detected in specific subtypes (GT4q with R155Q + A156T/V + D168N, GT6q with A156F and type of treatment B and G, respectively). The S282T variant in NS5B occurred in 20% of GT4q patients (n=1).

Conclusion: Unusual subtypes (mainly but not only GT3b, 3h, and 4f) 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 vivo drug susceptibilities.

564 TRANSMISSION OF THE NS5A-RESISTANT VARIANT M28V AMONG ACUTE HIV/HCV COINFECTED MSM

Stephanie Popping1, Rosanne Verwijst1, Lize Cuypers2, Mark Claassen3, Guido Van Den Berko, Anja De Weggheleir3, Joep E. Arends4, Anne Boerenkamp4, Richard Molenkamp5, Marion Koopmans4, Annelies Verborg5, Charles Boucher6, Bart Rijnders1, David Van De Vijver7, John Maertens8, Rosanne Verwijs1, Lize Cuypers2, Mark Claassen3, Guido HVI/HCV COINFECTED MSM

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Background: The World Health Organization (WHO) has declared to eliminate hepatitis 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 (RASs). 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 NS5A 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+G4+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 NS5A 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 observed between and after introduction of DAAs illustrating 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

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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 339 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-infected. Phylogenetic analysis classified sequences as GT3a-3b-3c-3d (98% - 0.4% - 0.2% - 1.2%), respectively. Notably, 39 pts were previously misclassified as infected with GT indeterminate, non-3, or mixed (N=10/22/27, respectively). Overall, 135 GT3 pts failed an interferon-free regimen: sofosbuvir/sofosbuvir/velpatasvir (SOF/VEL/RBV; N=91/15) and glecaprevir/pibrentasvir (G/P; N=9). Moreover, 14.8% of pts were treated with suboptimal regimens for GT3: 3D±RBV (Paritaprevir+Ombitasvir+Dasabuvir, N=15), SOF+Simprevir (N=1) or SOF+Ledipasvir+LDV+RBV (N=4). In DAA-naive pts, overall RAS prevalence was 16% (NS3A-NS5A-15.5%). At failure, 81.5% of pts showed at least one RAS related to the DAA-related, of whom 11/25 (44%) in NS3, 109/135 (81%) in NS5A, 7/111 (6%) in NS5B SOF-failures. In NS3A-failures, Y93H was the most prevalent RAS (68.5% vs 5% DAA-naive, p<0.001) followed by A30K (13% vs 3% in DAAs-naive, p<0.001). Interestingly, analysing the BS samples, a higher prevalence of NS5A-RASS was observed before treatment in DAA-failures (5, 13% vs 38% in DAAs naïve pts) (p=0.04). The single Y93H was detected mainly after SOF/DOC or VEL (67% and 60%) and 3D (60%) failures. By contrast, NS5A-RASS patterns (mostly A30K+Y93H) were frequently observed (55%) after G/P failure. In NS5B, RASS L159F and S282T were detected only in SOF/DOC failures (5% and 1%, respectively). Regarding DAA-naive pts with an available outcome, 228 were treated with the following regimens: SOF/ DOC or VEL±RBV (N=150/47) 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 RASSs, the most frequent being Y93H. The presence of natural NSSA RASS 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

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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 HIV 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 (DAAs).

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 HIV 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 HIV VL and 13 (9.9%) participated 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?

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Background: Medicaid HCV treatment restrictions limit access to HCV cure. 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 varying health insurance and DAA initiation, adjusting for confounders with stabilized inverse-probability-of-treatment weights. Baseline covariates were estimated unweighted and weighted cumulative incidences of DAA initiation by health insurance status.

Results: From 2014-2017, 2,134,569 HCV tests occurred over 876,444,123 eligible person-months (29.2 tests/1000 person-years). Testing rates increased over time in all groups. States that maintained unrestricted policies had the highest HCV testing rates, followed by states that reduced both fibrosis and abstinence restrictions. States maintaining high restrictions for one or both policies had similar rates (Figure). In regression analysis, states maintaining low restrictions had an adjusted rate ratio of 1.74 (95% CI 1.61-1.89) compared with states maintaining high restrictions. In states that relaxed restrictions, we observed a rate ratio of 1.07 (95% CI 1.00-1.14) post-vs. pre-policy change.

Conclusion: Restrictive state Medicaid HCV treatment policies are associated with decreased HCV screening rates among commercially insured individuals in the same state. Unmeasured state-level variables such as Medicaid expansion may contribute to observed differences, and we will conduct further analysis.

These data suggest, however, that Medicaid HCV treatment restrictions may have spillover effects that hinder HCV elimination progress across all payers.
569 MOBILE HCV SCREENING IN AN AT-RISK URBAN POPULATION IDENTIFIES SIGNIFICANT FIBROSIS

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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-IDU (67% vs 50%, p=0.001), or history of incarceration (74% vs 53%, p<0.001). Among the HCV RNA+ population, 73% had HCV RNA testing and 36% were HCV RNA+ (Figure). Fifty-nine of the HCV Ab+ underwent LSM: 27 (46%) and 32 (54%) 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

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Background: The state of California has provided unrestricted access to direct-acting antivirals (DAA) 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 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 healths system is needed to achieve HCV micro-elimination.

571 REAL-WORLD EFFECTIVENESS OF GLECAPREVIR/PIBRENTASVIR FOR HEPATITIS C VIRUS INFECTION

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1Hospital Universitario 12 de Octubre, Madrid, Spain, 2Hospital General Universitario Gregorio Marañón, Madrid, Spain, 3Subdirección General de

Background: The state of California has provided unrestricted access to direct-acting antivirals (DAA) 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 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 healths system is needed to achieve HCV micro-elimination.
573 REAL-WORLD EFFECTIVENESS OF SOFOSBUVIR/VELPATASVIR FOR HEPATITIS C VIREmia INFECTION

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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 DAs for HCV.

Methods: RUA-HCV (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 DAs in 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 55.2 years, 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, 36.5%; G4, 6.7%. Other/mixed/unknown genotypes accounted for 4.4%. Significant statistical differences were observed between MoP and CoP at baseline for age, gender, and genotype distribution. SVR rates overall were 95.4% by m-ITT and 97.9% by ITT (Table). The presence of HIV or genotype distribution did not influence response to treatment. The SVR rate was lower in patients with compensated cirrhosis than in patients without cirrhosis both by m-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 prospective real-life cohort of patients with hepatitis C, treatment with GLE/PIB 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.

Table. Patient characteristics and treatment results overall and categorized by the presence or absence of HCV coinfection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n=1,003)</th>
<th>MoP (n=888)</th>
<th>CoP (n=115)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median)</td>
<td>55.2 (46.9-65.9)</td>
<td>54.9 (46.2-65.6)</td>
<td>55.7 (44.0-65.7)</td>
<td>0.610</td>
</tr>
<tr>
<td>Gender, female (%)</td>
<td>39.2%</td>
<td>36.9%</td>
<td>43.0%</td>
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<td>Genotype (1A/2A/3C/4G/5G)</td>
<td>75.1/19.4/5.4/0.5/0.5</td>
<td>74.5/19.2/5.4/0/0</td>
<td>63.6/29.3/7.1/0/0</td>
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<tr>
<td>Previously treated (%)</td>
<td>10.3%</td>
<td>10.0%</td>
<td>10.5%</td>
<td>0.903</td>
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<tr>
<td>Cirrhosis (CI/CH) (%)</td>
<td>12.4/87.6%</td>
<td>14.4%/85.6%</td>
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</tr>
<tr>
<td>SVR (m-ITT) (%)</td>
<td>95.4%</td>
<td>95.3%</td>
<td>96.1%</td>
<td>0.610</td>
</tr>
<tr>
<td>SVR (ITT) (%)</td>
<td>97.9%</td>
<td>97.9%</td>
<td>96.1%</td>
<td>0.610</td>
</tr>
</tbody>
</table>

573 A MULTICENTER REGISTRY IN PATIENTS WITH HIV/HCV COINFECTION ON LEDIPASVIR/SOFOSBUVIR

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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 (DAA) 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 HCV 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 is 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). 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 <30 mL/min or new ≥1+ 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

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Background: Hepatitis C virus infection genotype 2 (HCV-2) is prevalent predominantly in Southeast Asia, and the data on the virologic response of HCV-2 to direct-acting antivirals (DAAs) are sparse in HIV-positive patients.

Methods: From May 2017 to July 2019, HIV-positive patients coinfected with HCV-2 who initiated DAA were included for analysis. Laboratory investigations were performed at baseline, the end of therapy (EOT), and 12 weeks off therapy (SVR12), as required by the treatment program of the National Taiwan Health Insurance.

Results: Of 264 patients (mean age, 50.7 years) initiating DAA during the study period, 84.8% were men, 83.3% injecting drug users, 16.2% have sex with men, and 1.3% 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 14.9%, and non-TDF/TAF 1.9%. Nephrotoxicity (change from baseline creatinine ≥0.4 mg/dL, decrease in creatinine clearance <50 mL/min or new ≥1+ 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.
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<0.20), 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, 2% opioids (street or Rx), 16% cocaine, and 57% alcohol (21% binge, 20% heavy). The SVR rate by IIT was 83% (50/60). Two did not comply with study requirements and were withdrawn, 5 were LTU, 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% [1-100%]) and adh2wk was 96% (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 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 (SnlmCV) 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 HIV had good but variable LDV/SOF adherence using technology-based methods, with improved adherence using video DOT. OT-TP in DBS increased with adherence, and SVR12 rates were high demonstrating substantial PK forgiveness. These findings support efforts to expand HCV treatment to active drug users.

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**577 OVERALL SURVIVAL IN HIV-POSITIVE LIVER TRANSPLANT RECIPIENTS AND THE ROLE OF DAAs**

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**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 in this special population. Aims of this study: evaluate the rate of overall survival and HCC recurrence; define the causes of death; describe the impact of DAAs on mortality.

**Methods:** All subjects with HCV/HBV infection who underwent LT for ESLD or HCC from 2012 were retrospectively evaluated. Descriptive statistics and non-parametric tests (Chi-square and Mann-Whitney U, as appropriate) were used; KM probability curves were calculated. Parametric tests (Chi-square and Mann-Whitney U, as appropriate) were used; non-liver-related mortality (HR=2.67 95%CI: 0.97 ; 7.37) tended to be higher in HIV+ (6.9 per 1000 PY (95%CI: 4.7 ; 10.0) in HIV/HCV co-infected and 13.4 per 1000PY (95%CI: 10.5 ; 17.0) in HCV mono-infected patients treated by DAA. HIV coinfection 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 HIV 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 HEPAVH 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: 46.9 ; 56.7] and 53.3 years [IQR: 46.9 ; 56.7]; 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 ; 19.9) in HIV/ HCV co-infected and 13.4 per 1000PY (95%CI: 10.5 ; 17.0) in HIV mono-infected (p=0.78). 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.
**EFFECT OF DAA REGIMENS ON MORTALITY IN HIV/HCV-COINFECTED PATIENTS WITH CIRRHOSIS**

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**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%) of 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 2.0 (0.03-12.8) per 100 PY respectively (p=0.36).

**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.

**Trends in overall and liver-related mortality according to the evolution of treatment for hepatitis C in HIV/HCV-coinfected patients with cirrhosis**

![Trends in overall and liver-related mortality](image)

**ALL-CAUSE MORTALITY AND CAUSES OF DEATH IN THE SWISS HEPATITIS C COHORT STUDY**

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**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

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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%) coinfect with HIV. 554 (55%) showed previous compensated cirrhosis. 994 (94%) patients had achieved SVR with interferon-free regimens. After SVR, 42% of individuals (426) showed previous compensated cirrhosis. 994 (94%) patients had achieved SVR with DAA-based therapy.

Conclusion: The predictive ability of the LS 21 kPa cut-off for a first PHGB episode after SVR was 100%.

583 TREATMENT WITH DIRECT-ACTING ANTIVIRALS REDUCES HEALTH CARE SERVICE UTILIZATION

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Background: Empirical evidence to support cost savings of direct-acting antivirals (DAAs) in real-world populations would support wider access. We investigated the impact of successful treatment of hepatitis C (HCV) with DAA therapy on healthcare services utilization (HCSU) among people living with HIV in Canada.

Methods: We used data from the Canadian Co-Infection Cohort study that prospectively follows 1974 HIV/HCV-coinfected participants from 18 centres. Data is collected through self-administered questionnaires, chart review and blood testing biannually. Among people who initiated DAA and achieved a 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 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 esophagogastroduodenal 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 cell count, HIV RNA, active injection drug use, significant fibrosis (F≥2) and fixed covariates: age and sex. We categorized HCSU as out-patient visits (walk-in, general (GP) or HIV 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 1. Health care service use before and after successful DAA treatment in those achieving SVR

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-DAA trend, per year</th>
<th>Post-DAA trend, per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Patient Visits</td>
<td>3.0 (1.4, 4.6)</td>
<td>2.4 (1.2, 3.6)</td>
</tr>
<tr>
<td>Out-Patient Visits</td>
<td>12.3 (10.8, 13.8)</td>
<td>9.4 (8.1, 10.6)</td>
</tr>
<tr>
<td>ER Visits</td>
<td>0.6 (0.3, 1.0)</td>
<td>0.4 (0.3, 1.0)</td>
</tr>
<tr>
<td>Specialist Visits</td>
<td>1.2 (1.1, 1.3)</td>
<td>1.0 (0.9, 1.1)</td>
</tr>
<tr>
<td>GP Visits</td>
<td>2.7 (2.5, 2.8)</td>
<td>2.3 (2.2, 2.4)</td>
</tr>
</tbody>
</table>

### 584 HCV CURE IN HIV COINFERENCE DAMPENS INFLAMMATION AND IMPROVES COGNITION

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**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 mRNA 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 neotinope 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, LGALS3BP and TNFAIP6 in HCV monoinfection. CD83, IL6 and CXCL10 monocyte gene expression correlated with cognitive impairment before therapy; only CXCL10 continued to correlate with impaired 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-κB 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 improvement 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

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**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 (MMoPCR) 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=0.002), 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 HCV/HIV

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**Background:** Immune activation predicts morbidity in HCV, HIV and HCV-HIV coinfection 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 HCV-HIV 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 (CD8 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, IP10 and IL8) 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 w6 (CD8 CM p=0.02, and CD4EM 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 activation after HCV therapy associated with CD14, potentially attributable to ART controlled HIV immune activation.

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**Table 1: Percent of CD8 expression on CD8 T cell and monocyte subsets**

<table>
<thead>
<tr>
<th>CD8 Expression</th>
<th>CD14</th>
<th>CD16</th>
<th>CD38</th>
<th>HLA-DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8+CD14+CD16-</td>
<td>0.8</td>
<td>0.5</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>CD8+CD14-CD16+</td>
<td>0.2</td>
<td>0.7</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**857 IMPACT OF HCV CLEARANCE ON NK CELLS AND HIV TRANSCRIPTION IN COINFECTION SUBJECTS**

Maria L. Polo1, Alejandra Urioste1, Yanina Ghiglione2, Jimena Salido2, Ajantha COINFECTED SUBJECTS

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Background: Hepatitis C is a frequent coinfection in people living with HIV. HCV replication and its subsequent clearance with direct acting antivirals (DAAs) can potentially modify how HIV persists on antiretroviral therapy (ART). Natural killer (NK) cells are key effectors against both viruses and may be involved in shaping HIV reservoir. In this regard, we studied NK cell phenotype before and after HCV treatment with DAAs and its association with the dynamics of HIV reservoir.

Methods: In a prospective longitudinal observational study, HIV/HCV-coinfected individuals on suppressive ART (n=19) received sofosbuvir/daclatasvir alone or with ribavirin (n=7). Blood samples were obtained before HCV treatment (baseline sample, BSL), at end-of-treatment (EOT) and at 12 months after EOT (12MPT). Cell-associated (CA) HIV DNA (total, integrated, 2LTR, unspliced (US) and multiply-spliced (MS) RNA were quantified by real-time PCR. Expression of HLA-DR, CD38, NKp24, Nkp46, Nkp30, CD95, CD69, CD25 on NK cells was evaluated by flow cytometry. Data was analyzed using non-parametric statistics.

588 RESULTS: At 12MPT, US-RNA and US/MS ratio were significantly higher than at BSL (p=0.02 and p=0.03, respectively). No changes in CA-DNA were observed. At EOT, surface expression of HLA-DR, CD38, HLA-DR/CD38, NKG2D, and CD95, decreased compared to BSL (p=0.0002, p=0.006, p=0.005, p=0.001 and p=0.001, respectively). CD95+, HLA-DR+, and HLA-DR+/CD38+ NK cells rebounded at 12MPT compared to EOT. Higher percentages of non-activated NK cells were observed at EOT (HLA-DR-/CD38- and CD25-/CD69-/CD95-) and at 12MPT (HLA-DR-/CD38-). Overall, higher levels of EOT and 12MPT NK cell activation correlated with higher 12MPT US-RNA. Particularly, EOT expression of HLA-DR correlated with 12MPT US-RNA (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 be reflecting the priming of NK cells by the residual HIV transcription and might point out a role for NK cells in shaping HIV persistence.

588 CHANGES IN IMMUNE-CELL SUBSETS IN HCV AND HCV/HIV PATIENTS UPON VIRALLY EFFECTIVE DAA

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Background: Direct-Acting Antivirals (DAAs) eradicate HCV and reduce liver fibrosis by containing inflammation. Viroloric response correlates with the restoration of NK and CD8, however, little is known on the effects of DAAs on gd, Th17 and Treg which all play a role in liver fibrogenesis. Further, while B-cell activation has been linked to extrahemorrhagic manifestations of HIV, literature is lacking on the role of these cells in liver damage.

Methods: We enrolled 97 virally-infected (VI) subjects (15 HIV cART-suppressed, 35 HCV naive to HCV therapy; 47 HIV/HCV cART-suppressed 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); 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). VI, a low vδ2/Th17 ratio, known to predict liver damage, increased from baseline to SVR12, yet remained lower than HC (HIV/HCV vs HC: p=0.04; HCV 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.
Liver Fibrosis Hinders Normalization of Systemic Inflammation After HCV Eradication

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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-1β (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.

Cost-Saving of Pooled HCV RNA Testing to Diagnose Acute HCV in High-Risk Populations

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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.
592 PERSISTENT HIV CONTROLLERS ARE MORE PREDISPOSED TO SPONTANEOUSLY CLEAR HCV

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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 1700 anti-HCV positive non-HIV-controllers. 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, HIV 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.
**594** SEX, NOT DRUG USE, IS DRIVING HCV REINFECTION AMONG HIV-INFECTED MSM IN NEW YORK CITY

Stephanie H. Factor, Jesse R. Carollo, Gabriela Rodriguez-Caprio, Asa Radix, Stephen M. Dillon, Rona Vali, Kriszczar Bungay, Robert Chavez, José Lares-Guía, Daniel S. Fierer, for the New York Acute Hepatitis C Surveillance Network

**Background:**
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 in NYC, semen in rectum and sex on CM, and, additionally, about injection use of CM.

**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 all three risk factors were significantly associated with 1st HCV reinfection in univariable Cox proportional hazards models (Table, 1st column), in the multivariable Cox proportional hazards model, only semen in rectum was significantly associated with 1st HCV reinfection (HR=3.96 [95% CI 1.43, 10.96], p=0.008) (Table, 2nd column).

**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.

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**596** HCV REINFECTION AFTER DAA TREATMENT AMONG PEOPLE LIVING WITH HIV IN SAN DIEGO

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**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. Person-time incidence rates (95% CI) per 100 years-at-risk (PYFU) were estimated using the Poisson distribution.

**Results:** There were 204 PLWH with documented SVR. Their median age was 52 years (95% CI: 50.5-54.3), 83.3% were male, and 21.6% were non-white. HCV genotypes distribution were 1a in 139 (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%. Six men acquired a new HCV infection over 321.7 PYFU. The HCV reinfection incidence rate overall was 2.4 per 100 PY. Among 201 persons with history of IDU only 32 (15.9%) were engaged in opioid substitution treatment (OST). Reinfection rate among persons on OST was 1.5/100 PY (1 reinfection) vs. 3.7/100 PY (11 reinfections) among those not receiving OST.

**Conclusion:** HCV risk among MSM 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.

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**595** HCV REINFECTION AMONG HIV PATIENTS AFTER DAA THERAPY IN THE COUNTRY OF GEORGIA

Nikoloz Ochkarishvili, Pati Gabunia, Akaki Abutidze, Giorgi Korkotadzeili, Otar Chokoshvili, Natia Dvali, Lali Sharvadze, Tengiz Teerstvadze

**Infectious 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 DAA 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 + pegylered interferon. 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. All reinfected patients were men with history of IDU. The median time to reinfection was 1.5 (IQR: 0.9-2.2) years. Genotype switch was documented in 7 (58.3%) cases. Rate of reinfection among persons with history of IDU was 3.3/100 PY. Among 201 persons with history of IDU only 32 (15.9%) were engaged in opioid substitution treatment (OST). Reinfection rate among persons on OST was 1.5/100 PY (1 reinfection) vs. 3.7/100 PY (11 reinfections) among those not receiving OST.

No statistically significant differences were observed in rates of reinfection by baseline HCV genotype and treatment regimen.

**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.
HCV INCIDENCE AMONG HIV-INFECTED MSM IN FRANCE: RESULTS FROM THE FHDH-ANRS C04 COHORT

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Background: Despite the availability of highly effective directly acting antivirals (DAAs), sexual transmission of hepatitis C virus (HCV) in men who have sex with men (MSM) is still ongoing, associated with high-risk sexual behaviors. The objective of this study was to estimate the incidence of primary HCV infection among HIV-positive MSM in France in the post-DAA era.

Methods: We used data from a large French hospital cohort of HIV-positive individuals (FHDH-ANRS C04) prospectively collected between 2014 and 2017. HCV infection rates were calculated using person-time methods, among HIV-positive MSM with a negative anti-HCV test at cohort entry and subsequent HCV tests. HCV negative status was assigned to individuals never testing HCV positive throughout follow-up, discontinued on December 31th 2017. Incident HCV infection was based on any positive HCV test (RNA and/or antibodies) performed for MSM on ART in Bangkok, and direct-acting antivirals being associated with HCV transmission. HCV antibody testing should be regularly performed for MSM co-infected with HIV. Little is known regarding the transmission networks among this population.

Results: A total of 48 (25 acute HIV and 23 chronic HIV) MSM with incident HCV infection and amplifiable NS5B sequences were included in the analysis. Median (interquartile range, IQR) HCV RNA was 6.3 (5.3-6.9) IU/mL. HCV genotype (GT) was 85% GT 1a and 15% GT 3a or 3b. Overall mean genetic distance was 85% GT 1a and 15% GT 3a or 3b. Median age at HCV diagnosis was 34 (IQR, 28-41) years. 83.3% (40/48) had history of syphilis infection and 36% (16/44) reported crystal methamphetamine use. Only 2 (4%) reported ever injecting drugs, both crystal methamphetamine. Six (12.5%) were HBV co-infected, all of whom had chronic HIV. In the phylogenetic clustering analysis, 83% belonged to one of two clusters: one large (n=36, 75%) and one small (n=4, 8%) cluster (Figure). All clusters were GT 1a. Overall mean genetic distance was 0.10 (SE=0.02). Participants with acute HIV infection were more likely to be in a cluster (92%) than those with chronic infection (74%).

Conclusion: Phylogenetic analysis showing a high degree of clustering confirms that the HCV epidemic in the HIV-infected MSM community in Bangkok is recent and rapidly expanding. This epidemic is independent of past HCV transmission among people who inject drugs in Thailand, which was largely GT 3. Crystal methamphetamine use is high in participants with HCV infection, and previous reports have identified chemsex and group sex parties as factors associated with HCV transmission. HCV antibody testing should be regularly performed for MSM on ART in Bangkok, and direct-acting antivirals being offered to all MSM with HCV infection might contain this HCV epidemic from spreading further.

HCV reinfection rates based on HIV risk factor, race/ethnicity, age, and gender

<table>
<thead>
<tr>
<th>HIV/HCV Risk factor (n)</th>
<th>Reinfection rate (per 100 PYU) (%)</th>
<th>Person-Years of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (224)</td>
<td>1.87 (1.69-4.06)</td>
<td>333.20</td>
</tr>
<tr>
<td>MSM only (147)</td>
<td>3.54 (1.94-9.64)</td>
<td>153.13</td>
</tr>
<tr>
<td>MSM+DU (35)</td>
<td>2.33 (1.06-12.98)</td>
<td>42.95</td>
</tr>
<tr>
<td>HIV-only (80)</td>
<td>0.66 (0.02-3.67)</td>
<td>152.05</td>
</tr>
<tr>
<td>Intransitivt-only (18)</td>
<td>0.00</td>
<td>4.89</td>
</tr>
<tr>
<td>Other/Unknown (1)</td>
<td>0.00</td>
<td>8.68</td>
</tr>
</tbody>
</table>

Biologic factor (n)

| Male (172)              | 7.40 (3.91-27.07)                  | 26.70                     |
| Female (1)              | 0.00                               | 10.71                     |
| Race/Ethnicity (n)      | 2.03 (1.64-4.75)                   | 245.99                    |
| Non-white (44)          | 1.32 (1.03-7.17)                   | 75.70                     |

Age in years (n)

| <30 (10)                | 0.00                               | 10.71                     |
| 30-40 (25)              | 7.40 (3.91-27.07)                  | 26.70                     |
| 40-49 (43)              | 1.49 (1.04-8.29)                   | 67.24                     |
| 50-60 (90)              | 1.94 (1.40-6.65)                   | 155.16                    |
| >65 (136)               | 0.00                               | 65.88                     |

In the interferon era. This result may help guide future interventions to prevent HCV reinfection in PLWH at risk in San Diego

Large Hepatitis C Transmission Cluster Identified Among HIV-Positive MSM in Bangkok

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Background: A rapidly emerging HCV outbreak has recently been observed among HIV-positive men who have sex with men (MSM) living in Bangkok, Thailand. Little is known regarding the transmission networks among this population.

Methods: MSM with both acute (Feibig stages 1 to 5) and chronic HCV infection and with incident HCV infections were identified in research cohorts at the Thai Red Cross AIDS Research Centre. Incident HCV infections were defined as seroconversion from anti-HCV antibody negative to positive after initiating ART. NSSB regions of the HCV genome (404 and 471 bps) were amplified using nested-PCR and sequenced. Phylogenetic inference was constructed by Maximum Likelihood methods in MEGA X.0.5 software with 1000 bootstrap samplings. Clusters were identified using ClusterPicker with support and genetic distance thresholds of 85% and of 4.3%, respectively.

Results: A total of 48 (25 acute HIV and 23 chronic HIV) MSM with incident HCV infection and amplifiable NSSB sequences were included in the analysis. Median (interquartile range, IQR) HCV RNA was 6.3 (5.3-6.9) IU/mL. HCV genotype (GT) was 85% GT 1a and 15% GT 3a or 3b. Overall mean genetic distance was 85% GT 1a and 15% GT 3a or 3b. Median age at HCV diagnosis was 34 (IQR, 28-41) years. 83.3% (40/48) had history of syphilis infection and 36% (16/44) reported crystal methamphetamine use. Only 2 (4%) reported ever injecting drugs, both crystal methamphetamine. Six (12.5%) were HBV co-infected, all of whom had chronic HIV. In the phylogenetic clustering analysis, 83% belonged to one of two clusters: one large (n=36, 75%) and one small (n=4, 8%) cluster (Figure). All clusters were GT 1a. Overall mean genetic distance was 0.10 (SE=0.02). Participants with acute HIV infection were more likely to be in a cluster (92%) than those with chronic infection (74%).

Conclusion: Phylogenetic analysis showing a high degree of clustering confirms that the HCV epidemic in the HIV-infected MSM community in Bangkok is recent and rapidly expanding. This epidemic is independent of past HCV transmission among people who inject drugs in Thailand, which was largely GT 3. Crystal methamphetamine use is high in participants with HCV infection, and previous reports have identified chemsex and group sex parties as factors associated with HCV transmission. HCV antibody testing should be regularly performed for MSM on ART in Bangkok, and direct-acting antivirals being offered to all MSM with HCV infection might contain this HCV epidemic from spreading further.
599 ORAL PRESCRIPTION OPIOID USE AS A HIGH-RISK INDICATOR FOR HCV INFECTION

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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 not studied or established 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 statistical analyses; IRB approval was received.

Results: 115,415 persons received any OPO (Table 1); 8.6% (932) were HCVAb+ when tested and not previously diagnosed (10,900); 3.4% (3,893) had an OUD diagnosis, 20.6% (803) of whom were HCV tested; thus, efforts should be increased to improve HCV RF awareness; and, 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, 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.

600 SYNDROMIC OF HCV, PRESCRIPTION OPIOID USE, AND PSYCHIATRIC ILLNESS: A NOVEL FRAMEWORK

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1Weill 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 social interaction. While many definitions have been proposed, three core principles are 1) clustering of two or more conditions in a specific population; 2) their synergism in producing adverse outcomes; and 3) precipitation and propagation by large scale social, cultural, 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 ERCHIVES cohort to identify persons with each component of SHOPS individually and in all combinations. ERCHIVES 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 described as prescription of any approved opioid drug for >31 continuous days to exclude short term use for surgical or dental procedures or after acute trauma. 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, 23.9% with POU and 84.2% with 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 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 REM, January 1, 2017 – December 31, 2018

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OPD</th>
<th>HCV Ab% (n)</th>
<th>HCV Ab% (n)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1,421</td>
<td>13,664 (9.9)</td>
<td>8.6 (1,252)</td>
<td>0.000104</td>
<td>1.72 (1.57, 1.91)</td>
</tr>
<tr>
<td>Age in years, mean ± standard deviation</td>
<td>55.0 ± 16.7</td>
<td>55.4 ± 16.4</td>
<td>0.88 ± 11.6</td>
<td>0.000104</td>
<td>1.72 (1.57, 1.91)</td>
</tr>
<tr>
<td>Race</td>
<td>Female</td>
<td>624,246 (45.2)</td>
<td>4,097 (68.2)</td>
<td>0.000104</td>
<td>2.10 (1.72-2.60)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>567,464 (43.3)</td>
<td>4,467 (68.8)</td>
<td>0.000104</td>
<td>2.10 (1.72-2.60)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Female</td>
<td>531,158 (38.2)</td>
<td>7,064 (63.8)</td>
<td>0.000104</td>
<td>1.72 (1.57, 1.91)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>516,821 (40.7)</td>
<td>7,634 (63.8)</td>
<td>0.000104</td>
<td>1.72 (1.57, 1.91)</td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
<td>62,000 (46.6)</td>
<td>6,601 (14.9)</td>
<td>0.000104</td>
<td>1.72 (1.57, 1.91)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>567,464 (43.3)</td>
<td>4,097 (68.2)</td>
<td>0.000104</td>
<td>2.10 (1.72-2.60)</td>
</tr>
<tr>
<td>Birth Cohort</td>
<td>1945-1964 (10.6%)</td>
<td>5467 (11.6%)</td>
<td>1.04 (1.63)</td>
<td>0.000104</td>
<td>1.72 (1.57, 1.91)</td>
</tr>
<tr>
<td></td>
<td>1965-1974 (10.0%)</td>
<td>5467 (11.6%)</td>
<td>1.04 (1.63)</td>
<td>0.000104</td>
<td>1.72 (1.57, 1.91)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>899 (2.4)</td>
<td>803 (88.4)</td>
<td>0.000104</td>
<td>1.72 (1.57, 1.91)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1,603 (4.3)</td>
<td>424 (66.5)</td>
<td>0.000104</td>
<td>1.72 (1.57, 1.91)</td>
</tr>
</tbody>
</table>

Notes: OR refers to odds ratio; p-value refers to statistical significance; IRB approval was received.
601 THE PERFECT ICE STORM: THE MIX OF METH AND HIV SPREADS HEPATITIS C IN THAI MSM

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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 (TRCAC) were recruited into a longitudinal study of ATS use. Recruitment was stratified to oversample for HCV 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=43) 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 (OR 16.15; 95% CI 3.3-78.99), being mainly the receptive partner in anal sex (OR 4.3, 95% CI 1.1-16.71), ever used METH (OR 9.13, 3.3-78.99), ever used oral amphetamines (OR 9.48, 1.63-55.03), and any STI (OR 5.98, 1.54-23.2).

Conclusion: HCV 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 rough or prolonged sex in the context of illicit drug use. Harm reduction, and should focus on providing treatment and reducing risk behaviors among PWID to prevent further transmission.

602 HEPATITIS C VIRUS INFECTION AND COINFECTION WITH HIV AMONG PWID IN 10 US CITIES

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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 respondents-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 were 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 co-infection was higher among participants who were transgender (aPR 6.7, 95% CI 2.8-16.4), injecting >5 years (aPR 2.1, 95% CI 1.3-3.1), injected speedball (heroin and cocaine injected together) (aPR 2.3, 95% CI 1.4-3.0) or stimulants (aPR 1.8, 95% CI 1.2-2.9) 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. HCV and HIV 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

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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 >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.

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 75% 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 surveyed, 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 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 GPC-adjuvanted HBV vaccine is ongoing.
604 IMMUNIZATION RESPONSE IN INFANTS BORN TO HBsAg+ HBeAg+ MOTHERS RECEIVING TDF

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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 (HBlg) 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 HBlg 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), 536 (477-648), 595 (532-691), 294 (253-342), respectively (see Figure: anti-HBs geometric concentrations according to actual age at assessment).

Conclusion: Maternal antiviral prophylaxis had no effect on the infant response. HBBlg masked the response until 2 months, then titers increased until 9 months (3 months after last vaccine administration). Immunization was effective in >99% of the infants aged 4 to 12 months, a higher percentage than 9 months (3 months after last vaccine administration). Immunization was effective in >99% of the infants aged 4 to 12 months, a higher percentage than 9 months (3 months after last vaccine administration). Immunization was effective in >99% of the infants aged 4 to 12 months, a higher percentage than 9 months (3 months after last vaccine administration).

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%) HCV 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 alternative to the traditional HBV vaccine series.

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606 TIMING OF ANTI-HBs ANTIBODIES DECAY IN VACCINATED PLWH/A: A LONG-LASTING RESPONSE

Alice Tomio1, Julien Lupé1, Myriam Blanc1

1CHU de Grenoble, Grenoble, France

Background: It is widely recommended to immunize people living with HIV/AIDS (PLWH/A) against hepatitis B virus. A regular monitoring of anti-HBs antibody titers is generally performed during the following year to assess the need for vaccine boost, but the timing of the decay of these antibodies is poorly known. We analyzed the waning over time of anti-HBV seroprotection in PLWH/A in our center.

Methods: We included all PLWH/A with at least 2 measurements of anti-HBs antibodies between the years 2001 and 2018; subjects positive for anti-HBc antibody or HBs antigen were excluded. We analyzed the variation for each pair of successive measurements, excluding the pairs where the first measure was under 10 mIU/mL, or if an HBV vaccination was realized between the two dates, or if the rise between 2 dates was over 100 mIU/mL (as this may reflect an unchanted vaccination).

Results: We analyzed 887 couples of successive titrations in 372 patients. The delay between the 2 measurements was <10 months for 23.9%, 10-14 months for 43.6%, between 15-27 months for 18.3%, and >27 months for 14.2%. The mean and the median decrease of the anti-HBs titer were 2.6±0.1 mIU/mL and 0.29 [interquartiles 25-75: -0.02; 1.9] mIU/mL per month, respectively. This decay represents 0.7±3% (mean) or 0.6% (median) [interquartiles 25-75: 0.1; 1.8] per month of the initial titer. There was no statistically significant association between the slope of antibody decay and the nadir of CD4 T cells, 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.
HIGH INCIDENCE OF HBV INFECTION IN HIV-COINFECTED PATIENTS ACCESSING ART CARE

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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 8.2% (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 HBV 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 incident HBV infection (aHR 2.38; 95% CI: 0.77 to 7.35).

Conclusion: The provision of HIV care and treatment in high HIV burden settings provide a missed opportunity for HBV screening, immunization and care provision.

CHARACTERIZING HBV INFECTION AMONG PERSONS LIVING WITH HIV IN CARE IN URBAN SENEGAL

Adrià Ramírez Mena1, Judicaël M. Time2, Osusseyourn Ndiaye1, Louise Fortes1, Ka Daye1, Ndeye Fatou Gnom1, Fall Fatou1, Moussa Seydi1, Gilles Wandelé1

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 (Novastet®). 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, 573 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.

LIVER FIBROSIS CHANGES OVER 3 YEARS OF TENOFOVIR-BASED ART IN HIV-HBV COINFECTION

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Background: Although tenofovir-based therapy can potentially reduce HBV DNA and can reverse hepatic fibrosis in HBV monoinfection, its long-term impact on clinical outcomes in HIV-HBV coinfection is not well-established and some data suggest hepatic inflammation and fibrosis persists. 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 (18 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 >19 U/L for women and >30 for men. We included in analysis any cohort participants LSM with 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 (6.8%) 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 to 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, Dhrukumar Soni1, Weimin Wang1, Murat Ganesan1, Raghubendra S. Dagur1, Edward Makarov1, Yimin Sun1, JoEllyn McMillan1, Howard E. Gendelman1, Natalia Osna1, Larisa V. Poluektova1, Benson Edagwa1

Background: To eliminate HBV infectious complete suppression of progeny virus coordinate with the elimination of infected cells must be achieved. These events can be facilitated by enhancing innate and adaptive immune responses given with antiviral therapy. We offer a new therapeutic prospective by increasing the potency of nitazoxanide (NTZ), a broad-spectrum antiviral and immune stimulating agent and tenofovir (TFV), a nucleoside reverse transcriptase inhibitor. This drug combination was transformed into hydrophobic prodrug nanocrystals, then stabilized into aqueous nanosuspensions. The modifications led to extended drug half-lives, 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 was determined in human monocyte-derived macrophages (MDM). The HBV-producing human hepatocellular carcinoma HepG2.2.15 cell and humanized liver TK-NOG mice evaluated antiviral activity. HBV infected mice received a single 75 mg/kg intramuscular injection of the drugs. HBV DNA, cccDNA and HBe/sAg were monitored for 48 h and for 10 weeks in cells and animals, respectively.

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 at four 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 RHEUS MACAQUE MODEL OF CHRONIC HBV INFECTION FOR CURE RESEARCH
Sreya Biswas1, Patrick Hashiguchi1, Jennifer Stanton1, Benjamin N. Bimber1, Ulrike Protez1, Jonah Sacha1, Benjamin J. Burwitz1

Background: Chronic HBV infection (CHB) is a major global health concern, affecting 247 million individuals worldwide and causing 887,000 deaths annually. CHB induces various degrees of liver damage and is strongly associated with the development of liver cirrhosis and hepatocellular carcinoma. Chimpanzees were the gold standard for primate HBV research, but are no longer available. Indeed, one of the major obstacles to the discovery of an HBV cure is the lack of a physiologically-relevant primate model. Based on our previous work showing that expression of the HBV receptor, human Na+-taurocholate co-transporting polypeptide (hNTCP), on rhesus macaque (RM) hepatocytes facilitates in vitro and in vivo HBV infection, we hypothesized that RM can be chronically infected with HBV.

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 adenosine expressing hNTCP. Seven days later we challenged all three RM intravenously with HBV (1 x 109 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 105 copies/ml) accompanied by high levels of HBV surface (HBsAg) and envelope (HBeAg) antigens in blood for more than 6 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 NTCP 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
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Background: Hepatitis B Virus (HBV) co-infection occurs in 5-20% of HBV-infected individuals globally. Prior studies found elevated proinflammatory cytokines are associated with spontaneous control (SC) of symptomatic HBV, but the majority of acute HBV infections are asymptomatic. A better understanding of cytokine profiles in early asymptomatic HBV will provide
613 HIV-RELATED INFLAMMATION IS LINKED TO THE LEVEL OF GENETICALLY DEFECTIVE HIV PROVIRUSES

Xiao Qian Wang1, Jennifer M. Zerbato2, Anchalee Avihingsanon1, Katie Fisher1, Bethany A. Horsburgh1, Timothy E. Schlub4, Ajantha Solomon2, Jennifer Audsley2, Kasha P. Singh2, Megan Crane5, Sharon R. Lewin2, Richard G. Marlink3, Max Essex1, Rosemary Musonda1, Sethunya Gotulweng1, Bethany A. Horsburgh1, Jennifer M. Zerbato2, Wei Zhao3, Sabine Braat2, Surekha Tennakoon1, Ajantha Solomon1, Gail Matthews1, Christopher K. Fairley4, Joseph Sasadeusz5, Megan Crane2, Anchalee Avihingsanon1, Jennifer Audsley2, Sharon R. Lewin2, 1Doherty Institute for Infection and Immunity, Melbourne, Australia, 2University of Melbourne, Melbourne, Australia, 3Kirby Institute, Sydney, NSW, Australia, 4Monash University, Melbourne, VIC, Australia, 5Peter MacCallum Cancer Centre, Melbourne, Australia, 6HIV—NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand

**Background:** Hepatitis B virus (HBV) coinfection increases overall and liver-related mortality in people living with HIV, even with the availability of HBV-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 monoinfected 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:** At visit 1, HIV infection was associated with increased cytokine concentrations, including IL10, TNF, IP10, MIP1β, and IL18. Median time from incident HBV to visit 2 was 13.2 weeks. Overall, increased odds of CHB were significantly associated with elevated visit 2 levels of OR per 10-fold increase in concentration: IL10 (OR 6.7, P<0.001), MIP1α (OR 25, P<0.001), IP10 (OR 8.3, P=0.001), MIP1β (OR 7.7, P=0.04), and IL18 (OR 6.9, P=0.04). In HIV-uninfected individuals, intrasubject increases (visit 2 fold-change over visit 1) in IL10, IP10, IL18, IL37, and MIP1α were significantly higher in those who developed CHB. In HIV-infected individuals, intrasubject increases in IL18 and TNF were higher in those who developed CHB (see Table).

**Conclusion:** In contrast to previous reports, elevated cytokine profiles are not associated with SC in asymptomatic incident HBV, suggesting they are not major determinants of HBV SC.

<table>
<thead>
<tr>
<th>Intrasubject Changes (visit 2/visit 1) in Circulating Cytokines during Incident HIV Infection</th>
<th>HBV-uninfected</th>
<th>HBV-infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine</td>
<td>Visit 1</td>
<td>Visit 2</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.99 (0.39-2.70)</td>
<td>1.99 (1.01-3.93)</td>
</tr>
<tr>
<td>IL-10</td>
<td>1.00 (1.00-1.00)</td>
<td>1.04 (1.00-1.09)</td>
</tr>
<tr>
<td>IL-18</td>
<td>1.07 (0.91-1.31)</td>
<td>2.85 (1.21-6.97)</td>
</tr>
<tr>
<td>IL-37</td>
<td>1.60 (0.95-2.67)</td>
<td>1.14 (1.00-1.40)</td>
</tr>
<tr>
<td>TNF</td>
<td>1.06 (0.91-1.25)</td>
<td>1.56 (1.24-1.82)</td>
</tr>
<tr>
<td>IP10</td>
<td>3.12 (0.66-6.38)</td>
<td>4.31 (1.10-12.9)</td>
</tr>
<tr>
<td>MIP1α</td>
<td>1.87 (0.87-3.93)</td>
<td>2.45 (1.35-4.19)</td>
</tr>
<tr>
<td>MIP1β</td>
<td>1.04 (0.74-1.49)</td>
<td>1.57 (0.93-2.72)</td>
</tr>
</tbody>
</table>

**Conclusion:** In the setting of ART, 20% of HIV-HBV co-infected individuals have progressive liver fibrosis. Liver disease progression was associated with higher HGB1 and lower nadir CD4 count. Interventions to prevent liver disease progression on ART require further investigation.
Background: Hepatitis B virus (HBV) resulted in 887,000 deaths in 2015 due to hepatocellular carcinoma (HCC) and cirrhosis. In sub-Saharan Africa, HCC has been reported in younger individuals, compared to other regions. Mutations within the HBV core, precore, and X regions may lead to rapid progression to 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 (25.0%) 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 one participant and also occurred as a dual mutation. E64D and L65S 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 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.

Results: Of 306 HIV/HBV-coinfected patients included, 59.5% 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 HBsAg-positive. At ART initiation, significant fibrosis (>7.0fPa) equivalent to Metavir score ≥2A was seen in 15.4% of patients and cirrhosis (≥4.4fPa; F4) in 8.0%. On ART, 54 (27.5%) participants had hepatomegaly, 71 (32.2%) perifrenal 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 hypercholesterolaemia or hepatoenhepatic 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 >20,000 IU/mL. Four patients had a lesion with 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 AUS under-estimates cirrhosis.

617 SUBOPTIMAL IMMUNITY TO HEPATITIS A AMONG NYC MSM INITIATING PrEP OR PEP, 2016-2019

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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 HAV non-immune MSM PrEP/PEP patients who had HAVST from 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: Overall, 4233 MSM initiated PrEP/PEP and had HAVST. Median age was 28 years (IQR 25-33); 32% were Hispanic, 31% were non-Hispanic (NH) white, and 21% were NH Black. Foreign-born were 37% (n=1574). At time of PrEP/PEP initiation, 26% were diagnosed with bacterial STIs. Sixty five percent were HAV immune (n=2733). Of 1500 patients not immune, 50% (n=743) received ≥1 dose of Havrix™ (n=453) or Twinrix™ (n=290) within a year after HAVST. A total of 2437 (58%) patients self-reported receiving hepatitis A vaccination at non-NYC SHC settings; 37% (n=897) were not immune.

Conclusion: HAV immunity among this NYC MSM cohort was below the critical immunity threshold against HAV. Subsequent vaccination of this cohort likely increased their immunity to ≥ 70%. HAVST identified a significant number of HAV non-immune patients, despite self-reported hepatitis A vaccination. HAVST for MSM initiating PrEP/PEP and subsequent hepatitis A vaccination of non-immune patients is an effective intervention to prevent future HAV outbreaks.

618 HEPATITIS E RABBIT GENOTYPE INFECTION IN HIV-INFECTED PATIENTS

Antonio Rivero-Juárez1, Mario Frías2, Pedro Lopez-Lopez2, Juan Berenguer3, Federico García2, Juan Macías2, Begoña Alcaraz2, Ángeles Castor2, Javier Caballero-Gómez2, Antonio Rivero2, for the Spanish AIDS Research Network
1Hospital Universitario, Reina Sofia, Cordoba, Spain, 2Hospital General Universitario Gregorio Marañón, Madrid, Spain, 3Hospital Universitario San Cecilio, Granada, Spain, 4Hospital Universidad de Valme, Sevilla, Spain, 5Hospital General Universitario Santa Lucia, Murcia, Spain, 6University Hospital of La Coruña, La Coruña, Spain

Background: Among the population in which hepatitis E virus (HEV) infections may have a worse prognosis, HIV-infected subjects represent a high-sensitivity
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® 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 seven and fifty-one (88.9%) were male and had a median age of 36.9 years (30.7-45.2 years). In baseline, 101 patients were positive for HEV IgG antibodies (11.9%), none had HEV IgM antibodies, and 2 presented detectable HEV RNA (0.23%). Of the 744 patients with negative HEV IgG antibody at baseline, 733 samples were available for testing during follow-up. Forty-two seroconverted for IgG, supposing a cumulative incidence of 5.7%. One patient was positive for IgM (0.13%), and 2 showed detectable HEV RNA (0.27%). Viral strains were consistent with genotype 3f. Interestingly, in one patient, the isolated viral strain was consistent with genotype 3ra (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 3ra genotype, the main host of which is rabbit, showing a potential zoonotic role of this emerging genotype in Spain.
621 LOW ADHERENCE TO TREATMENT AND SURVEILLANCE OF HPV-RELATED ANAL PRECANCER

Richard Silvera1, Michael Gaisa2, Yuxin Liu3, Ashish A. Deshmukh4, Keith M. Sigel5, Michael J. Nelson6, Stephen Young7, W. David Hardy8, Susheel Reddy9, Jeremy J. Martinson10, Gypsysamber D’Souza11, for the Multicenter AIDS Cohort Study (MACS)

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), the precursors to anal cancer. Unreiated 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 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=0.02). 35% of patients diagnosed with HSIL never returned. Compared to Whites (69%), Hispanics were more likely to return (73%, p=0.04), while Blacks (54%, p=0.02) and PLWH with viremia (57%; p=0.05) 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 Sun1, Dorothy J. Wiley2, Teresa Darragh3, Hilary K. Hsu4, Nancy Joste5, Stephen Young6, W. David Hardy7, Susheel Reddy8, Jeremy J. Martinson9, Gypsysamber D’Souza10, for the Multicenter AIDS Cohort Study (MACS)

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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.
623 NEED FOR OPTIMIZATION OF SCREENING METHODS FOR ANAL INTRAEPITHELIAL NEOPLASIA IN PLWH

Stefan Esser1, Alexander Kreuter1, Anja Potthoff2, Norbert H. Brockmeyer3, 4, Mark Oette4, Mark Oette5, Robert Jablonka1, Hildegard Lax1, Konstantinos Bilbilis1, Laven Mavaran1, Karl-Heinz Joeckel1, Ulrike Wieland1

1University Hospital Essen, Essen, Germany, 2Helios St. Elisabeth Clinics Oberhausen, Oberhausen, Germany, 3Ruhr-University Bochum, Bochum, Germany, 4Cologne University Hospital, Cologne, Germany

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 HIV-positive individuals (HIV+) 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 electrocautery ablation of histologically confirmed AIN in HIV+ since 2015 in Germany. Biopsies of AIN lesions, anal cyto. Swabs and HPV typing were performed at Baseline and follow-up visits. The cyto. findings were divided according to the Bethesda classification. Depending on their oncogenic potential HPV types were distinguished into high risk (HR) and low risk (LR) HPV.

Results: 292 examinations (exa.) in 184 HIV+ included during the TECAIN Study were analyzed until September 12, 2019. At Baseline the median age was 48 years, 98% of HIV+ took antiretroviral therapy and 81% were MSM. The consistencies between HPV types, the cyto. results and histologic findings were analyzed.

Crude Estimation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
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<tbody>
<tr>
<td>ATCC</td>
<td>44/45</td>
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</table>

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. The prospective, randomized, national, multicenter TECAIN study compared the efficacy of local treatment with 85% trichloroacetic acid to electrocautery ablation of histologically confirmed AIN in HIV+ since 2015 in Germany. Biopsies of AIN lesions, anal cyto. Swabs and HPV typing were performed at Baseline and follow-up visits. The cyto. findings were divided according to the Bethesda classification. Depending on their oncogenic potential HPV types were distinguished into high risk (HR) and low risk (LR) HPV.

624 CERVICAL CANCER KNOWLEDGE AND ATTITUDES AMONG HIV-POSITIVE MEN IN MALAWI

Corrina Moucheraud1, Samuel W. Lewis1, Misheck Mphande2, Ben Allan Banda3, Hitler Sigaque1, Paul Kawale1, Aubrey Dkangoma1, Kathryn Dove1, Alemayehu Amberbir1, Agnes Moses1, Sundeepe Gupta1, 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 wife’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.

Lung cancer incidence and risk factors differ by histology among HIV+ / – Veterans

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Background: People living with HIV (PWH) have high risk for developing lung cancer (LC) and poor treatment outcomes. Predominant molecular alterations and treatment algorithms differ for each of the lung cancer histologic types, which include small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC), and 2 common NSCLC histologic subtypes squamous cell (SC), and adenosquamous (AC). Few studies have evaluated epidemiologic differences by histology in PWH.

Methods: In a retrospective cohort study, Veterans diagnosed with HIV between 10/1/99 and 12/31/2016 were identified and matched to a 2:1 gender, age and year of care HIV-negative cohort. Both HIV+ / – veterans were
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 virologic load.

Results: A total of 931 incident cases of LC were ascertained among HIV+ and 1260 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 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 jointpoint 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:0.55 – 0.67, p=0.008). Among HIV+ veterans and 21.37/100,000 among HIV-, and the incidence 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 jointpoint 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:0.55 – 0.67, p=0.008). The ORs of SC and AC NSCLCs but not SCC are higher among PWH. The ORs of AC and SC have remained stable over time for both HIV+/- veterans.

Conclusion: The ORs of SC and AC NSCLCs but not SCC are higher among PWH. The ORs of AC and SC have remained stable over time for both HIV+/- veterans.
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.

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**628 BREAST CANCER RISK AMONG WOMEN WITH HIV IN NORTH AMERICA (2000-2015)**

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**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 competing risk of death to assess breast cancer cumulative incidence.

**Results:** Between 2004 and 2014, over 8 586 130 person-years of follow-up, 4 083 incident BC cases were diagnosed in the SAM 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 general increase in CD4 cell count through calendar years. Only age was strongly associated with BC risk (Table 1).

**Conclusion:** We observed breast cancer risk of 3.7% in women with HIV and incorporating traditional/reproductive risk factors and direct comparisons to the general population.

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**629 BREAST CANCER RISK IN WOMEN LIVING WITH HIV IN SOUTH AFRICA: THE SAM STUDY**

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**Background:** In the Republic of South Africa (RSA), approximately 17% of women were living with HIV (WLHIV) in 2017. Greater access to antiretroviral therapy (ART) has increased the survival of WLHIV in recent years and moved the distribution of cancer diagnoses toward non-AIDS-defining cancers, including breast cancer (BC). According to National Cancer Register South Africa (NCR SA) Report, in 2014 BC was the most commonly diagnosed cancer in women in RSA, with an age-standardized incidence rate of 33.3 per 100 000 population. However, in WLHIV, the incidence and risk factors for BC are not well understood.

**Methods:** The South African HIV Cancer Match (SAM) study used privacy preserving record linkage to create a large cohort of cancer in people living with HIV from national laboratory and cancer registry data. We included WLHIV aged 16 years and older with confirmed HIV status by two or more HIV related tests and with cancer diagnosed between 2004 and 2014 in the SA public health sector laboratories. We calculated BC incidence per 100 000 person-years, based on the number of WLHIV with histology-confirmed BC. We derived Cox regression model stratified by province of first HIV test to obtain hazard ratios of associations with first reported CD4 cell count, age, sex and calendar period.

**Results:** Breast cancer burden is poorly characterized in women with HIV regarding incidence and risk factors. Some studies suggested reduced risk in women with versus without HIV further support assessing breast cancer among women with HIV. We estimated breast cancer cumulative incidence and risk factors in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

**Conclusion:** We observed breast cancer risk of 3.7% in women with HIV and incorporating traditional/reproductive risk factors and direct comparisons to the general population.
HIV-ASSOCIATED HEMATOLOGIC MALIGNANCIES IN PEOPLE LIVING WITH HIV IN SWEDEN

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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 pre-ART era (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 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 (> 180 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. Autologus 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: 0–4.4). 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.

T-CELL SUBPOPULATION PROFILES AND CANCER RISK FOR HIV+ AND HIV– VETERANS

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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 predicted the incidence of non-AIDS cancers that have been associated with responses to immunotherapy (lung, anus, kidney).

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
633 TET2 SNPS AND RISK OF CANCER IN THE START, SMART, AND ESPRIT COHORTS

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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 (NCT000567048), SMART (NCT00027352) 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 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 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 first 4 eigenvectors).

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) and rs72955158 (HR=3.24, CI=1.29-8.11, p=0.012) were associated with risk of cancer; the number of cancers 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. All 6 cancers associated with rs72955158 in SMART occurred in pts who also had rs6811468. In START, 38 participants (pts) (1.5%) were diagnosed with cancer during follow-up. One SNP, rs6811468 (HR=4.50, CI=1.14-17.76, p=0.03) was associated with risk of cancer; the number of cancers in pts with 0, 1 and 2 risk alleles of rs6811468 was 22/2141 (2.4%), 7/109 (6.4%) and 2/4 (50%), respectively. In ESPRIT, a total of 110 pts had cancer. No SNPs were associated with cancer in ESPRIT. Rs72955158 in START and both rs6811468 and rs72955158 in ESPRIT had MAF <1% and were not assessed in these cohorts.

Conclusion: One SNP, rs6811468, was associated with consistent elevated risk of cancer in two independent HIV+ cohorts. This finding requires additional studies to confirm these results and determine whether the effect is independent of perturbed VL.

634 NEXT-GENERATION SEQUENCING TO PROFILE CANCER-RELATED GENES IN HIV+ PATIENTS

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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 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 relevant importance 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.

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<th>Gene alterations</th>
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**635** HOST GLYCOMIC DETERMINANTS OF CORONARY Atherosclerosis DURING TREATED HIV INFECTION

Leila B. Giron, Susan Langan, David B. Hanna, Juan Lin, Mohammad Damra, Qin Liu, Ian Frank, Mallory Witt, Lawrence Kingsley, Frank J. Palella, Wendy Post, Alan Landay, Todd T. Brown, Mohamed Abdel-Mohsen, Wistar Institute, Philadelphia, PA, USA, Johns Hopkins University, Baltimore, MD, USA, Albert Einstein College of Medicine, Bronx, NY, USA, University of Pennsylvania, Philadelphia, PA, USA, Los Angeles Biomedical Research Institute at Harbor—UCLA Medical Center, Torrance, CA, USA, University of Pittsburgh, Pittsburgh, PA, USA, Northwestern University, Chicago, IL, USA, Rush 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 glycemic 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 pro-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 glycomic 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 glycomic pathways fostering CVD warrant further investigation to examine their prognostic and functional significance.

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**636** ADVANCED GLYATION END PRODUCTS ASSOCIATED WITH CARDIOMETABOLIC RISK ON ART

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**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 AS2605, a sub-study of AS247, we compared changes in serum levels of different AGEs (methylglyoxal hydroimidazolone (MG-H1), carboxymethyl and carboxyethyl lysine (CML and CEL), 3-deoxyglucosenone hydroimidazolone (3DGHI), and glyoxal hydroimidazolone (GHI-1)) in ART-naive participants with HIV randomized to tenofovir disoproxil fumarate-empiretinib (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:** 241 participants were included; 90% male, 48% white, non-Hispanic, with median age of 36 yrs, HIV-1 RNA 4.58 log10 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, 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.

**Results:** Single-cell transcriptomics of HIV heart tissue identifies unique NK cell population

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**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 ventricle 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 PTPRC (CD45+) 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 (KLKD2) 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 NICM_CTRL 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: 325, 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

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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 disopropil 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 Clinico 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 – with a non-infected endothelium monolayer 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.
FIBROBLAST GROWTH FACTOR 21: EFFECT OF HIV THERAPY AND ASSOCIATION WITH CVD RISK

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Background: Fibroblast growth factor 21 (FGF21) is a pleiotropic signal 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-naive 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-naive; 81 ART-treated) were included. Groups were similar except ART-treated were older (median 48 vs 41; p<0.01) had higher waist-to-hip ratio (0.96 vs 0.92; p=0.03) and HOMA-IR (2.4 vs 1.4) and lower nadir CD4+ count (191 vs 388 cells/mm^3). Overall, 80% were men; 63% were black; 52% were current smokers. Of those on ART, 60% were on an NNRTI, 36% on a PI, and all had HIV-1 RNA <20 copies/ml. FGF21 was higher in ART-treated (218 vs 166 pg/ml; p=0.01), but adjusting for age, waist-to-hip ratio, glucose or nadir CD4+ count attenuated the association. Older age, white race, current smoking, higher waist-to-hip ratio and interleukin-6 (IL6) were independently associated with higher entry FGF21. In those who initiated ART (n=51), regardless of ART class, FGF21 levels did not change significantly over 96 weeks (p=0.55). Unadjusted, entry FGF21 was positively associated with entry CCA IMT (p=0.02); however, adjusting for age, waist-to-hip ratio, or inflammation (IL-6 or soluble tumor necrosis factor alpha-receptor-1) attenuated the association. Entry FGF21 tended to predict CCA IMT progression (p=0.08), but again the association was attenuated with adjustment for age or waist-to-hip ratio.

Conclusion: FGF21 concentrations are not decreased after successful ART, and although closely associated with traditional CVD risk factors, FGF21 did not independently predict IMT progression on ART.

MONOCYTE ACTIVATION AND CARDIAC-MRI–DERIVED VASCULAR DYSFUNCTION AMONG WOMEN WITH HIV

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Background: Women with HIV (WHIV) on ART face an increased risk of cardiovascular disease (CVD), including heart failure. Aortic vascular dysfunction, reflected by increased aortic pulse wave velocity (aPWV), presages, predicts, and promotes adverse CVD outcomes. Moreover, aortic vascular dysfunction – a proxy for vascular aging – is highly influenced by the local inflammatory milieu. Comparisons of aortic vascular function among predominantly male cohorts with vs. without HIV have yielded conflicting results. Cognizant of sex-specific patterns of HIV-associated immune dysregulation, we compared aPWV among asymptomatic ART-treated women with vs. without HIV. We hypothesized that WHIV would evidence vascular dysfunction in association with monocyte activation.

Methods: 20 WHIV and 14 matched women without HIV underwent cardiac MRI, as well as metabolic and immune phenotyping. Women with a history of CVD, diabetes, or significant kidney disease were excluded.

Results: Women with vs. without HIV had comparable age (52 vs. 53 years) and BMI (32 vs. 32 kg/m^2). WHIV exhibited heightened systemic monocyte activation, reflected by increased levels of sCD163 (1260 vs 938 ng/ml, P<0.005). Among WHIV, duration of HIV was 19±8 years, CD4 count was 773 (526,1202) cells/mm^3, and viral load was 19 (19,19) copies/mL. aPWV was higher among women with vs. without HIV (8.6±1.3 vs 6.5±1.3 m/s), P<0.0001; Fig. 1A). Among the whole group and each sub-group, aPWV did not relate to age, BMI, cigarette smoking burden, or SBP. Among the whole group and among WHIV, aPWV related to sCD163 levels (whole group: R=0.65, P<0.0001; WHIV: R=0.73, P=0.0003; Fig. 1B). Among the whole group and among WHIV, aPWV also related to extracellular volume – 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 status, and SBP (R^2=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 (R^2=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.
progression was defined by incident CAC if baseline CAC=0, ≥10 Agatston unit/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 as 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.

**Table: Estimated and observed measures of association for coronary artery calcification score, total plaque volume, and noncalcified plaque volume progression among MWH.**

<table>
<thead>
<tr>
<th>Coronary artery calcification score</th>
<th>Total plaque volume, mm²</th>
<th>Noncalcified plaque volume, mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>New (n=212)</td>
<td>Adjusted odds ratio for the 3rd tertile progression of CAC (95% CI)</td>
<td>New (n=212)</td>
</tr>
<tr>
<td>Adjusted odds ratio for significant CAC progression</td>
<td>Adjusted odds ratio for the 3rd tertile progression of CAC (95% CI)</td>
<td></td>
</tr>
<tr>
<td>1.24 (0.90-1.73)</td>
<td>0.69 (0.38-1.27)</td>
<td>1.21 (0.91-1.62)</td>
</tr>
</tbody>
</table>

**643 POSTDISCHARGE OUTCOMES FOLLOWING ACUTE CORONARY SYNDROME IN HIV**

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Background: HIV-infected individuals are at increased risk of cardiovascular death. Most of this risk can be attributed to ischemic heart disease. Differences in the management of HIV-infected patients following hospitalization for acute coronary syndromes (ACS) may contribute to worse outcomes in this population. We hypothesized that HIV-infected individuals have higher rates of mortality following discharge, and receive sub-optimal medical management compared with uninfected individuals.

Methods: This was a retrospective cohort study using data from Symphony Health, a nationwide data warehouse. All adults admitted between January 1st, 2014 and December 31st, 2016 with ACS were included, and their characteristics and outcomes were defined by ICD-9 and 10 diagnostic codes.

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 comorbidities such as diabetes, renal disease and substance use (p<0.0001). The type of ACS did not differ significantly between groups. The HIV-infected group had higher adjusted 30-day all-cause readmissions (14.3% vs 9.4%, OR 1.23, 95% CI 1.14-1.33, p<0.0001) and 1-year mortality (5.6% vs 5.1%, OR 1.34, 95% CI 1.21-1.5, p<0.0001). In the 12 month post-discharge period, the HIV+ group filled core cardiac medications such as statins (66.8% vs 73.7%, p<0.0001), beta blockers (67.9% vs 73.9%, p<0.0001), nitrates (31.8% vs 35.9%, p<0.0001) and antiplatelet agents (46.8% vs 51.8%, p<0.0001) at lower rates.

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.
645 HORMONE USE AND HIV ALTER CARDIOVASCULAR BIOMARKER PROFILES IN TRANSGENDER WOMEN

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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 log10-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%/24% current smokers, respectively. Persons with HIV (PWH) had current median CD4+ T lymphocyte count 669 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 (sTNFR) 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 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/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.

646 HIV SEVERITY AND INCIDENT HEART FAILURE AMONG PATIENTS IN A LARGE HEALTH CARE SYSTEM

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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, ever 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; 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.

647 PLASMA INFLAMMATORY BIOMARKER SIGNATURE ASSOCIATED WITH CVD IN HIV INFECTION

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Background: Cardiovascular disease (CVD) risk varies by severity of HIV infection. Compared with uninfected, generally increased levels of inflammatory biomarkers were observed in HIV-infected individuals; however, the inflammatory signature associated with CVD risk among HIV-infected persons is not established.

Methods: Plasma levels of 29 inflammatory cytokines were measured in sera from 293 PWH (CD4≥500) and 916 uninfected controls (2:1 matched). In a secondary validation cohort of 81 PWH and 487 uninfected controls, plasma levels of 13 cytokines were measured.

Results: In multivariate analyses adjusted for age, sex, race/ethnicity, smoking status, and CD4 count, concentrations of pro-inflammatory cytokines, chemokines and other markers of inflammation were higher among HIV-infected persons compared with uninfected persons. In multivariate-adjusted analysis, 8/16 cytokines were higher among PWH, compared with uninfected controls, and concentrations of 5/8 cytokines were higher in PWH with CVD compared with PWH without CVD. Significant differences were observed for TNF-α, IL-1β, IL-12, IL-17, IFN-γ, and IL-27.

Conclusion: Plasma concentrations of TNF-α, IL-1β, IL-12, IL-17, IFN-γ, and IL-27 were independently associated with CVD risk among HIV-infected persons.
ASSOCIATION OF INFLAMMATORY MARKERS WITH CARDIAC INDICES IN THE MACS

Bethel Woldu, Henrique Doria De Vasconcellos, Joseph B. Margolick, Heather McKay, Jared Magnani, Matthew J. Feinberg, Roger Detels, Todd T. Brown, Sean Altekruse, Joao Lima, Wendy Post, JoAnn Hudes, for the MACS/WIHS Combined Cohort Study

Background: People living with HIV (HIV+) are at increased risk of heart failure even after adjustment for demographics and cardiovascular risk factors. Among HIV+ without symptoms of heart failure, diastolic dysfunction has been reported to be highly prevalent. We hypothesized diastolic dysfunction to be an early marker of myocardial disease related to heightened inflammation in HIV infection.

Methods: The Multicenter AIDS Cohort Study (MACS) is a prospective observational cohort with both HIV+ and HIV-uninfected (HIV-) participants. We evaluated the association of echocardiographic parameters of left ventricular (LV) structure, systolic and diastolic function, and left atrial (LA) volumes to biomarkers of systemic inflammation and coagulation (CRP, IL-6, TNF-alpha and D-dimer). Associations between cardiac indices, biomarker quintiles and HIV serostatus were evaluated with multiple linear regression analyses after adjustment for demographics and cardiovascular risk factors (body mass index, systolic blood pressure, hyperlipidemia and diabetes).

Results: We included HIV+ (n=364) and HIV- (n=254) men who had both echocardiograms and inflammatory markers in the analysis. HIV+ men were younger (age, 59.2 ±6.7 vs 62.5 ±7.3 years, p<0.001), had similar systolic blood pressure (129 vs 131 mmHg, p<0.001) and body mass index (26.8 vs 27.3 kg/m², p<0.20). In multivariable-adjusted models (Table), there was a progressive association of LA volume index with increasing D-dimer quintiles and association with highest IL-6 quintile, independent of HIV serostatus. There were no significant associations between inflammatory markers and echo-derived parameters of diastolic function including transmitral 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 dilation predicts future risk of atrial fibrillation and stroke, further investigation is needed to evaluate whether systemic inflammation mediates increased atrial arrhythmia risk among both HIV+ and HIV-people.

<table>
<thead>
<tr>
<th>Table 1: Correlations of serum inflammatory markers and parameters of cardiac structure and function</th>
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<tbody>
<tr>
<td><strong>Ejection fraction (%)</strong></td>
</tr>
<tr>
<td>HIV uninfected (1)</td>
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<td>HIV infected (2)</td>
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<td>HIV uninfected (3)</td>
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<td>HIV infected (10)</td>
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<tr>
<td>HIV uninfected (11)</td>
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<td>HIV infected (12)</td>
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</table>

Note: IL-6 = interleukin-6, TNF = tumor necrosis factor-

PHENOTYPIC CLUSTERING OF HIV-ASSOCIATED ATHEROSCLEROSIS AND AGE-RELATED OUTCOMES


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/WIHS CCS prospectively follows people with and without HIV at 14 sites. Over 2,796 participants had non-invasive 8-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: For a goal of identifying 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 (all p<0.001). Even though C and D were similar in age, C had less carotid disease (fewer plaques, less stiffness) than D (p<0.001), but similar levels as B. Compared with C, D 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
MYOCARDIAL INFARCTION BY Atherosclerotic Cardiovascular Disease (ASCVD) Risk Score


Methods: PWH from NA-ACCORD cohorts that validated type 1 MIs (induced by plaque rupture with thrombus) were included. Study entry began as the earliest of NA-ACCORD enrollment, age-40, ART initiation date, 1 Jan 2000, or the cohort start date of MI observation. Study exit was defined as the earliest of 2 years with no HIV RNA or CD4 measurements, age 80, 31 Dec 2015, or the cohort start date of MI observation. Study participants were white Swiss HIV Cohort Study participants. Cases had a 1st CAD event during the study period (1.1.00-31.12.17). We used incidence density sampling and matched 1-3 controls (CAD event-free) on gender, age, and date of registration. We obtained univariable and multivariable odds ratios (OR) for a first CAD 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, 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 CAD odds ratio of 0.56 (95% confidence interval, 0.35-0.91; p=0.02), and a multivariable OR of 0.47 (0.26-0.86; p=0.01). In comparison, the OR for current smoking was 2.28 (1.46-3.56), hypercholesterolemia 1.84 (1.33-2.55), diabetes 3.92 (2.26 - 6.78), on ART/HIV RNA >50 1.80 (0.95-3.42); recent abacavir, cumulative lopinavir-ritonavir, darunavir; ART discontinuation; on ART but HIV RNA>50 copies/ml.

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 CAD odds ratio of 0.56 (95% confidence interval, 0.35-0.91; p=0.02), and a multivariable OR of 0.47 (0.26-0.86; p=0.01). In comparison, the OR for current smoking was 2.28 (1.46-3.56), hypercholesterolemia 1.84 (1.33-2.55), diabetes 3.92 (2.26 - 6.78), on ART/HIV RNA >50 1.80 (0.95-3.42); recent abacavir, cumulative lopinavir-ritonavir, darunavir; ART discontinuation; on 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.
652  PREVALENCE OF SUBCLINICAL MYOCARDIAL ABNORMALITIES IN HIV: SMASH STUDY RESULTS

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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 Interagency 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/ul (IQR 398-826). For most characteristics, HIV- and HIV+ participants were similar. Median LV ejection fraction (EF) was normal with LVEF<40%) as were right ventricular EF, biventricular volumes and mass, and indexing for BSA, aortic root (p<0.01), sinotubular junction (p<0.01), and 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 predisposition 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), 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, 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 HIV compared to those without HIV

<table>
<thead>
<tr>
<th></th>
<th>Mean difference in aortic annulus (mm/bsa)</th>
<th>Mean difference in aortic root (mm/bsa)</th>
<th>Mean difference in sinotubular junction (mm/bsa)</th>
<th>Mean difference in ascending aorta (mm/bsa)</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>0.08 [0.00, 0.07]</td>
</tr>
<tr>
<td>Constant (mean)</td>
<td>1.48</td>
<td>1.82</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

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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 (HIVHEART) 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 (51%) were asymptomatic and 76 (49%) patients presented with dyspnoe/taspse < 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 with PASP > 35mmHg and
signs of right heart dysfunction (23 ± 6.6 mmHg vs. 33.2 ± 10.3 mmHg vs. 37 ± 8.2 mmHg). Overall, 82 (8%) of patients with follow-up data had died. Mortality was associated with an increased functional impairment (Figure 1).

Conclusion: Echocardiographic screening detected PH in a relevant proportion of HIV-positive patients. PH and symptoms of right heart dysfunction were associated with higher mortality.

**Cumulative mortality**

- **Patients at risk:**
  - 907
  - 853
  - 757
  - 710
  - 605
  - 509
  - 409
  - 368

- **Patients who died:**
  - 76
  - 55
  - 64
  - 61
  - 54
  - 49
  - 35
  - 30

- **Log-rank test:**
  - P = 0.01

**Cumulative survival**

- **Patients with follow-up:**
  - 45
  - 49
  - 53
  - 56
  - 59
  - 62
  - 65
  - 68

- **Patients who died:**
  - 18
  - 20
  - 23
  - 26
  - 29
  - 32
  - 35
  - 38

- **Log-rank test:**
  - P = 0.01

### 655 CARDIAC EVENTS IN HIV-INFECTED PATIENTS WHO USE TENOFURO ALAFENAMIDE (TAF)

**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 58 (5.0%) CEs were reported, in TAF 43 (2.8%) and in NT 11 (4.0%). Cardiac history was more frequent in TAF vs. TDF and 9.0 years (IQR: 3.5-17.0) for NT. In TDF 58 (5.0%) CEs were reported, in TAF 43 (2.8%) and in NT 11 (4.0%). Cardiac history was more frequent in TAF vs. TDF and 9.0 years (IQR: 3.5-17.0) for NT.

**Conclusion:** The occurrence of CEs in TDF and in NT were significantly different (log-rank test: P < 0.001). Unadjusted Cox regression showed an increased hazard for CEs in TAF vs. NT, HR: 7.0 (95% CI: 2.9-17.2; P < 0.001) and in TAF vs. TDF, 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).

**656 INPATIENT OUTCOMES FOR HIV-INFECTED PATIENTS HOSPITALIZED FOR ACUTE CORONARY SYNDROME**

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**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 angiogram (31.6% vs 33.4%, OR 0.85, 95% CI 0.80-0.89, p < 0.0001) or drug-eluting stents (16.5% vs 18.2%, OR 0.88, 95% CI 0.82-0.94, p = 0.001). They also had significantly higher inpatient mortality (5.5% vs 5.3%, OR 1.28, 95% CI 1.15-1.43, p = 0.001) 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 = 0.007).

**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.

**657 PREVALENCE AND CORRELATES OF CAROTID PLAQUE IN A MIXED HIV- SEROSTATUS UGANDAN COHORT**

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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

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1University of Cape Town, Cape Town, South Africa, 2Centre 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 revascularization 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) log10 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%) strokes, and 331 (42%) acute coronary syndromes and revascularization 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 ART claim, unsuppressed viral load at first ART ART claim, hypertension, diabetes, and dyslipidaemia. In addition, ART regimens consisting of two NRTIs with a protease inhibitor, or two NRTIs with rilpivirine/etravirine 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.

**Table 1: Association of ART duration and risk of hypertension in HIV infected adults**

<table>
<thead>
<tr>
<th>Exposed, ART duration (years)</th>
<th>Unadjusted odds ratio</th>
<th>Adjusted odds ratio</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>0.93</td>
<td>1.00</td>
<td>0.88</td>
<td>0.72-1.4</td>
</tr>
<tr>
<td>2-5</td>
<td>1.17</td>
<td>1.55</td>
<td>0.09</td>
<td>1.03-2.3</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>1.64</td>
<td>1.92</td>
<td>0.02</td>
<td>1.10-3.4</td>
</tr>
</tbody>
</table>

**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.

660 ASSOCIATION OF HYPERTENSION AND ART USE IN A POPULATION-BASED COHORT, RAKAI, UGANDA

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**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 54.4 ± 11.1 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 ≥10 (19/666 MWH and 24/586 HIV- men, p=0.22). Any VT/VE was present among PWH vs. HIV- men in the Multicenter AIDS Cohort Study (MACS). We included 666 MWH (mean age 54.4 ± 11.1 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-.

**Conclusion:** The primary endpoint was the occurrence of any VE/VT, comparing PWH vs. HIV-.

ventricular ectopy and ventricular tachycardia (VE/VT) among PWH.
ASSOCIATION BETWEEN HIV AND THE PREVALENCE OF ATRIAL FIBRILLATION AND ATRIAL FLUTTER

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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 (EGK) and/or ambulatory EGK 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 variables (age, race and study center), and second for both demographic and CVD risk factors. Furthermore, this study aims to compare patients with any CVD with and without HIV with regard to baseline and presentation characteristics and outcome variables (age, race, and study center). Associations were adjusted sequentially, first for demographic variables (age, race, and study center), and second for both demographic and CVD risk factors. First for both demographic and CVD risk factors. This study aims to assess the incidence of MI and stroke among PLHIV in Sweden. This study aims to assess the incidence of MI and stroke among PLHIV in Sweden.

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 undetectable viral load (<20 copies/mL). Zio patch was worn for a median of 31.0 days (IQR 27.9, 36.4). AF/AFL was present in 12 (1.3%) HIV+ men and 23 (3.2%) HIV- men. The prevalence of AF/AFL in African-Americans, and 36 cases in Caucasians (2.7% vs 93.3%) 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

MitoQ ATTENUATES EX VIVO PROATHEROGENIC EFFECTS OF HIV PLASMA IN CHRONIC TREATED HIV

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Background: The mechanisms that drive atherosclerotic cardiovascular disease (CVD) in treated HIV remain unclear. Preclinical 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. This study was conducted to study 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 HUVECs for 24 hours on top of collagen gels to undergo transepithelial endothelial migration (TEM) and form foam cells (monocyte-derived foam cell formation (MDFCF)) in the presence of pooled plasma (PMID: 29826407). Pooled plasma was isolated from healthy (18-40 years old) and HIV+ (40-60 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 (BODIPY signal) and TEM. Unpaired 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.

HIV AND AGEING: PRIMARY AND SECONDARY PREVENTION OF CAD AMONG PLHIV

Gaetano Marrone1, Olof Elixvärd2, Anders Sönnerborg1
1Karolinska University Hospital, Stockholm, Sweden, 2Lund 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.

### Table 1: Incremental cost-effectiveness of statins for primary prevention of CVD among PLHIV over a 20-year time horizon

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Incremental cost ($/QALY)</th>
<th>Incremental QALYs</th>
<th>Incremental costs ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No statin</td>
<td>14.7</td>
<td>0.10</td>
<td>14.7</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>13.9</td>
<td>0.11</td>
<td>13.9</td>
</tr>
</tbody>
</table>

**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. Comprehensiveness 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.
Those who completed a majority of treatment sessions. Monoocyte 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.

### Table 1. Changes in body fat and body composition

<table>
<thead>
<tr>
<th>Changes in body fat and body composition after ART initiation</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body fat (kg)</td>
<td>1.6</td>
<td>2.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>3.5</td>
<td>5.1</td>
<td>6.6</td>
</tr>
<tr>
<td>Percentage change in body fat (kg)</td>
<td>+13.8</td>
<td>+22.8</td>
<td>+31.7</td>
</tr>
<tr>
<td>Percentage change in body fat (%)</td>
<td>+2.3</td>
<td>+3.8</td>
<td>+5.3</td>
</tr>
</tbody>
</table>

**Notes:** Changes in body fat and body composition after ART initiation. ART = antiretroviral therapy; ART-naïve = ART-naïve patients; ART-experienced = patients with prior ART; NRTI = nucleoside reverse-transcriptase inhibitor; NNRTI = non-nucleoside reverse-transcriptase inhibitor; PI = protease inhibitor; INSTI = integrase strand transferase inhibitor; kg = kilograms; % = percentage.

### Table 2. Changes in body composition after ART initiation

<table>
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**New Table:**

<table>
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### 667 FAT GAINS OCCUR AFTER ART WITHOUT CHANGES IN METABOLIC RATE OR CALORIC INTAKE

**Allison Ross Eckard**, Abdus Sattar, Jia Yu, Heather Y. Hughes, Danielle Labbato, Theresa O. Rodgers, Julia C. Kosco, Grace A. McComsey

**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) or caloric intake are responsible, but no data exists. We examined changes in RMR, oxygen consumption (V02), and dietary intake and associations with changes in weight and body composition after ART initiation.

**Methods:** ART-naïve 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/V02 and body composition were determined by indirect calorimetry and whole-body DXA, respectively. Nutrient intake was assessed by a registered dietician via 24-hour dietary recalls at 3 time points during the study 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+ count 571 cells/mm³; HIV RNA 1420 copies/mL, V02 205 mL/min, 1690 total kcal average daily intake). All but 1 participant had an HIV RNA <200 copies/mL prior to and following the switch from an NNRTI- or PI- to INSTI-based ART were included. Piecewise linear mixed models with random intercepts 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 and agent on body weight regulation.

**Conclusion:** Significant increases in weight and fat gains were seen after ART initiation. Faster weight gain occurred after switching to an INSTI-based ART regimen (53% DTG; 37% TAF). By 6 and 12 months, all but 3 and 1 participant, respectively, had an HIV RNA <200 copies/mL. Changes in weight and fat gains were significant after adjusting for sex, baseline HIV RNA and RMR (or V02) at both time points except for lean body mass at 12 months.

**Conclusion:** Significant increases in weight and fat gains were seen after ART initiation, despite a lack of significant changes in RMR, V02 or diet. All body composition changes except for lean body mass at 12 months were significant after adjusting for RMR or V02. These data do not support the hypothesis that changes in RMR or caloric intake are responsible for increases in weight and fat gains after ART initiation in PWH.
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 (%) changes 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/m², 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 12% higher 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.

### 670 RESISTIN GENE POLYMORPHISM RELATED TO WEIGHT GAIN AND PSYCHIATRIC SYMPTOMS ON INSTI

**Rumi Minami¹, Soichiro Takahama¹, Kazuhiro Koyama¹, Masahiro Yamamoto¹
¹National Hospital Organization Kyushu Medical Center, Fukuoka, Japan**

**Background:** Weight gain and psychiatric symptoms (PSs) have been reported in persons living with HIV (PLWH) receiving ART, especially integrase strand transfer inhibitors (INSTI). Obesity and PSs are correlated with chronic inflammatory states characterized by insulin resistance. Resistin is a pro-inflammatory adipokine and plays a key role in the insulin responsiveness of peripheral tissues and the central nervous system. A single-nucleotide polymorphism (SNP) at −420C>G in the resistin gene is correlated with serum resistin level in Japanese people. We clarified the influence of SNP −420C>G on weight gain and PSs in PLWH receiving INSTI.

**Methods:** Participants were PLWH who started ART with INSTI (n = 220) or protease inhibitors (PI; n = 62). Body mass index (BMI) was measured before and 6 months after starting ART. PSs was evaluated with the Profile of Mood States or Self-rating Depression Scale. SNP − 420C>G was investigated using PCR. Linear regression analysis was used to assess factors associated with BMI change and PSs. We examined several variables in addition to SNP − 420C>G that may affect BMI and PSs. Variables that were significant in univariate analyses were incorporated in multivariate models.

**Results:** BMI increased by 0.86 kg/m² (p<0.001, paired t-test) in the INSTI group and 0.33 kg/m² (p = 0.04, paired t-test) in the PI group. In total, 24% of the INSTI group and 14% of the PI group showed PSs. The simple regression analysis showed BMI increase was significantly associated with low body weight and low CD4 counts before ART, use of tenofovir alafenamide (TAF) as the treatment backbone, smoking, and the SNP − 420C>G allele in the INSTI group.

In this group, the fully adjusted multiple linear regression analysis showed low body weight (p = 0.016) before ART, use of TAF (p = 0.028), smoking (p = 0.027), and the SNP − 420C>G allele (p = 0.005) were associated with BMI increase. PSs was significantly associated with smoking and the SNP − 420C>G allele in simple (p = 0.027, p = 0.004) and fully adjusted (p = 0.026, p = 0.001) linear regression analyses. In the PI group, BMI increase was associated with low BMI before ART (p = 0.0014), but no factors were associated with PSs.

**Conclusion:** We showed that the −420C>G resistin gene is independently associated with weight gain and PSs in PLWH on INSTI. This highlights the pivotal role of resistin in linking INSTI-related symptoms characterized by insulin resistance.

### 671 ADIPOCYTE DYSFUNCTION DESPITE REDUCED ADIPOSE INFLAMMATION IN DIABETICS WITH HIV

**Samuel Bailin¹, Spyros Kalams¹, Simon Mallal¹, Fei Ye¹, Run Fan¹, Mona Mashayekhi¹, Curtis Gabriel¹, John Koethe¹, Celestine Wanjalla¹
¹Vanderbilt University, Nashville, TN, USA**

**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 Nanostar nCounter® human inflammation panel containing 250 genes, and a separate panel containing 77 genes modified from the KEGG adipocytokine 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/m² and 34 kg/m² 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 (FASIN, PPARG, PCK2) 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-kappaB 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 Wanjalla1, Wyatt J. McDonnell1, Ramesh Ram1, Abha Chopra2, Rama Gangula1, Shay Leary2, Beverly O. Woodward1, Mark Pilikto1, Mona Mashayekhi1, Samuel Bail1, Curtis Gabriel1, Alyssa Hasty1, Simon Mallal1, Spyros Kalams1, John Koethe1, Matt White1, Celestine Wanjalla1, Wyatt J. McDonnell1, Ramesh Ram1, Abha Chopra2, Rama Gangula1, Shay Leary2, Beverly O. Woodward1, Mark Pilikto1, Mona Mashayekhi1, Samuel Bail1, Curtis Gabriel1, Alyssa Hasty1, Simon Mallal1, Spyros Kalams1, John Koethe1, Matt White1, Celestine Wanjalla1

Vanderbilt 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) who were matched for similar age and body mass index, followed by flow cytometry phenotyping and single-cell sorting of memory T cells. Single-cell cDNA libraries were created using well-specific barcodes followed by 3’ and 5’ amplification and sequencing. Pooled data were analyzed on 11 diabetic persons (6 HIV+ and 5 HIV-negative, all subjects with diabetes mellitus type 2). Spearman correlations (a=0.05).

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, n=11). CX3CR1+GPR56+ cells were positively correlated with the percent of T effector memory RA+ cells (p<0.01, n=11). CD69+ CD4+ T cells in HIV+ diabetics is enriched for CX3CR1+GPR56+ and CD57, which are present at far lower levels in HIV-negative diabetics. Adipose tissue serves as a reservoir for HIV, CMV, and other viruses, and further studies will determine if C-G-C cell responses target viral antigens and may impair adipocyte function.

Conclusion: Adipose tissue of HIV+ diabetics is enriched for CX3CR1+GPR56+ and CD57, which are present at far lower levels in HIV-negative diabetics. Adipose tissue serves as a reservoir for HIV, CMV, and other viruses, and further studies will determine if C-G-C cell responses target viral antigens and may impair adipocyte function.

673 TELMISARTAN DECREASES MONOCYTE CX3CR1 EXPRESSION IN TREATED HIV INFECTION

Jordan E. Lake1, Eunice Yeh1, Douglas W. Kitch1, Anoma Somasunderam1, Michael M. Lederman1, Judith S. Currier1, Netanya S. Udaya1, for the A5317 Team

University 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, 4University of California Los Angeles, Los Angeles, CA, USA

Background: Telmisartan is an angiotensin receptor blocker and PPAR-g agonist that is active in adipose tissue (AT) and has anti-inflammatory properties. Secretion of fractalkine by adipocytes and expression of its receptor, CX3CR1, on monocytes/macrophages have been implicated in AT inflammation, obesity and cardiovascular disease (CVD). Fractalkine/CX3CR1 expression are mediated by PPAR-g suppression and endotoxemia, both sequelae of HIV. We hypothesized that telmisartan would improve the profile of AT immune cells and AT function in persons with HIV (PWH) on suppressive antiretroviral therapy (ART).

Methods: AIDS Clinical Trials Group study AS318 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+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 CD16+ monocytes/macrophages have been implicated in AT inflammation, obesity and cardiovascular disease (CVD). Fractalkine/CX3CR1 expression are mediated by PPAR-g suppression and endotoxemia, both sequelae of HIV. We hypothesized that telmisartan would improve the profile of AT immune cells and AT function in persons with HIV (PWH) on suppressive antiretroviral therapy (ART).

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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/mm . Over 48 weeks, median CD14+CX3CR1+ and CD16+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+CX3CR1+, CD16+CX3CR1+ and CD163+CX3CR1+ monocytes (Table). CD14+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+CX3CR1+ and increases in insulin gene expression (r=-0.50, p=0.07, n=14), and decreases in CD14+TLR4+ monocytes/increases 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.
674 Gut Integrity Markers and Associations with Adiposity in People with and without HIV

Allison Ross Eckardt, Carlee Moser, Judith S. Currier, Todd T. Brown, Emily Bowman, Peter W. Hunt, Nicholas Funderburg, Grace A. McComsey

1 Medical University of South Carolina, Charleston, SC, USA, 2 Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3 University of California Los Angeles, Los Angeles, CA, USA, 4 Johns Hopkins University School of Medicine, Baltimore, MD, USA, 5 The Ohio State University, Columbus, OH, USA, 6 University of California San Francisco, San Francisco, CA, USA, 7 University Hospitals Cleveland Medical Center, Cleveland, OH, USA

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 unaffected control group and assessed associations between gut integrity markers and body composition.

Methods: Data from unaffected controls (matched by age, sex, and race) were prospectively collected and compared to data from participants prospectively enrolled in a treatment initiation study, ACTG A5260s, 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 log10 ng/mL and 0.54 to 0.56 log10 ng/mL, resp), but lower levels of LBP (mean difference: 2.65 to 2.66 log10 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 log10 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 unaffected 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.

675 Contribution of INSTI, BMI, Physical Activity, Caloric Intake to Weight Gain in PWH

Giovanni Guaraldi, Jovana Milic, Andrea Malagoli, Federica Carli, Marianna Menozzi, Alessandro Raimondi, Giacomo Ciua, Valentina Masi, Michela Belli, Stefano Guaraldi, Cristina Mussini, Todd T. Brown, Jordan E. Lake, Kristine M. Erlandson

1 University of Modena and Reggio Emilia, Modena, Italy, 2 University of Texas at Houston, Houston, TX, USA, 3 University of Colorado, Aurora, CO, USA

Background: Weight gain in people living with HIV (PWH) is a multifactorial phenomenon in which the relative contribution of traditional and HIV specific modifiable risk factors is not known. The aim was to assess the population attributable fractions (PAFs) of lifestyles and INSTI regimens in PWH who experienced a 5% weight gain over 4 years.

Methods: In an observational cohort study from 2007 to 2019 at Modena HIV Metabolic Clinic, virally suppressed ART-experienced but INSTI-naïve PWH were grouped in INSTI-switchers vs non INSTI on stable ART. Groups were matched for sex, age, 1st visit BMI and follow-up duration. Significant weight gain was defined as an increase of ≥5% from 1st visit weight over follow-up. Physical activity was assessed with International Physical Activity Questionnaire (IPAQ) as metabolic equivalent of task (MET). Daily caloric intake (DCI) was evaluated with a 3 day food diary. PAFs and 95% CIs were estimated to quantify the proportion of outcomes that could be avoided if the risk factor was prevented, using the following dichotomous variables: BMI > 25 kg/m² vs < 25 kg/m², DCI > 2500 kcal vs < 2500 kcal, IPAQ MET < 600 vs MET 600, quitting vs continuing smoking, INSTI vs no INSTI regimens, and CD4/CD8 ratio < 1 vs ≥ 1.

Results: Of 304 PWH (74% males), mean follow-up was 4.2 years (± 1.8 SD), age 54.3 (± 7.8 SD) years, median duration since HIV diagnosis 22.3 years (IQR 15.5-27.5), CD4 count 716 cells/mL (IQR 564-893), 98.7% had undetectable HIV-1 RNA (Table). PAF for weight gain was the greatest for BMI (41%, 24-56, P<0.001), followed by CD4/CD8 ratio (38%, 19-55, P<0.001) and physical activity (33%, 35-51, P < 0.001). Smoking cessation (5%, 0-13, P=0.99) and INSTI switch (6%, 0-33, P=0.51).

Conclusion: Our findings suggest that weight gain is mostly influenced by pre-existing weight and low physical activity. High BMI DCI ratio suggests additional immunological mechanisms linked to weight gain.

676 Who Does and Does Not Gain Weight with INTEGRASE INHIBITORS (INSTI)


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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 ARV 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 virally suppressed pts per protocol. Subgroup analysis was conducted in 387 subjects: pts ≥18 yrs, switched to INSTI regimens in Jan 2015-Jun 2018 for ≥12 mo, with ≥6 mo history, viral suppression and weights at baseline (BSL) and 12 mo (±2 mo). Univariate analyses (UV) were conducted via chi-square and t-test. Multivariate analysis (MV) with a binary outcome of gain ≥5% at 12 mo was conducted using log binomial model; variables significant in UV and demographics were considered; final model included continuous variables age, BSL weight and categorical BSL AST < 30 vs ≥ 30, use of prior protease inhibitors (PI) and prior non-nucleoside reverse transcriptase inhibitors (NNRTI).

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 NNRTI 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 BSI AST≥30 (relative risk (RR)=0.51 [CI 0.31-0.84], p=0.009) or higher BSI weight (RR=0.99 [CI 0.98-1.00], p=0.034).

Conclusion: Of 367 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 BSI 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.

**Predictors of Weight Gain ≥5% at 12 Months Since Switch (Multivariate Analysis)**

![Predictors of Weight Gain](image)

### 677 DRUG CONCENTRATIONS AND BODY WEIGHT GAIN IN PLWH SWITCHED TO 3TC & Dolutegravir (DTG)

**Charles Burdet**, Gilles Peytavin, Minh Le, Roland Landman, Delphine Bachelet, Christine Kaltama, François Raffé, André Cablé, Charlotte Charpentier, Aida Benalycherif, Diane Descamps, Yazdan Yazdanpanah, Véronique Joly, for the Lamidol Study Group

**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 (Cₘₜₐₓ) 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 Cₘₜₐₓ.

**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


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**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 ≥15kg, an empirically-based cut-off, 1 year following ART initiation. We restricted race to white vs black and baseline BMI to ≥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 and regimen 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 ≥15kg compared to non-DTG users (RR:1.7 95%CI:0.9-3.0). Overall, 52 (%) PLWH gained ≥15kg, with 26 (%) taking DTG, and of those, 19 (73%) were black. Within DTG users, black PLWH gained an average of 5.1kg while their white counterparts gained an average of 3.3kg. Black DTG users had a 3.2 times greater risk of gaining ≥15kg compared to white DTG users in their first year after ART initiation (95%CI:1.3-8.0). The risk was attenuated due to accounting for HIV disease severity (RR:2.4 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 due to 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>
<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>
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<td>0.30</td>
<td>0.03</td>
</tr>
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<td>0.62</td>
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<tr>
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<tr>
<td>Race x DTG interaction</td>
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<td>0.66</td>
<td>2.03</td>
</tr>
</tbody>
</table>

**Notes:**
- *Relative risk or hazard ratio, estimated using a Cox proportional hazards model.
- Race not included in DTG or other integrase inhibitors.
- Additional models including race and other integrase inhibitors.

**679 DTG PRESCRIBING PATTERNS IN PLWH ≥65 YEARS: THE IMPACT OF 2DR**

**Giovanni Guaraldi**, Stefano Calza, Andrea Calcagnò, Jovana Milic, Emanuele Focà, Matteo Rota, Anna Celotti, Benedetto Maurizio Celesia, Stefania Picconi, Annamaria Cattelan, Giuseppe V. De Socio, Giancarlo Orofino, Agostino Riva, Silvia Nozza, Giovanni Di Perri

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Methods: People were prospectively recruited in the Geriatric Patients Living with HIV/AIDS (GEPP) 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/μL 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=0.99). At follow-up, no change in body weight was present in the two groups: mean absolute weight change was -0.1 (± 0.4) 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.

680 DIABETES, WEIGHT GAIN, AND INTEGRASE INHIBITOR USE IN NORTH AMERICAN HIV+ PERSONS

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Background: Integrate strand transfer inhibitor (INSTI)-based regimens have been implicated in greater weight gain in antiretroviral therapy (ART)–naïve HIV+ persons starting ART, though metabolic consequences are unclear. We examined the impact of initial ART regimen class on incident diabetes mellitus (DM) and potential mediation of this effect by weight change in a large North American HIV cohort.

Methods: We included treatment-naïve 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 with no visit or lab before cohort close). We excluded those with incident DM before 12-month weight measure, and we multiply 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 dolutegravir (DTG), 30% raltegravir (RAL), and 52% elvitegravir (EVG). 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.

681 WEIGHT GAIN AT 18 MONTHS FOR ART-EXPERIENCED PATIENTS WHO SWITCHED TO DTG IN NIGERIA

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Background: Weight gain has been associated with dolutegravir (DTG). A pilot study in Nigeria, found an increase in appetite was a prominent self-reported side effect; and an increase in weight at 12 months follow up (12m). We excluded those with incident DM before 12-month weight measure, and we multiply 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.

Methods: ART experienced adult patients with an intolerance to NNRTIs switched to TDF/3TC/DTG (TLD) over a 6-month period starting July 2017 at 3 pilot sites in Nigeria. Study patients completed 18 months on TLD by end of
June 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**

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**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, 1,546 men (772 with HIV [MWH], 776 men without HIV) with pre-DM were included. Men with prevalent DM at the baseline visit were excluded. Incident DM was confirmed 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.

**Conclusion:** Among men with pre-diabetes, HIV serostatus was associated with increased risk of incident diabetes after adjustment for competing DM risk factors. Given the increased risk, diabetes prevention strategies in PWH may be more beneficial.

**683 GLYCEMIC STATUS AND PHYSICAL FUNCTION AMONG MEN WITH AND WITHOUT HIV**

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1Northwestern University, Chicago, IL, USA, 2Columbia University, New York, NY, USA, 3University of Texas at Houston, Houston, TX, USA, 4Johns Hopkins University School of Medicine, Baltimore, MD, USA, 5University of Pittsburgh, Pittsburgh, PA, USA

**Background:** Gait speed and grip strength decline faster in persons with HIV (PWH) compared to those without HIV. Abnormal glucose metabolism has been associated with impaired physical function in cross-sectional studies. We evaluated longitudinal relationships between hyperglycemia and objective measures of physical function in men with and without HIV.

**Methods:** The Multicenter AIDS Cohort Study (MACS) is a prospective study of men with or at risk for HIV. MACS participants undergo semi-annual assessments, including measures of glicemic status (fasting blood glucose and hemoglobin A1C (HbA1C)), grip strength and gait speed. Glycemic status was categorized as normal, impaired fasting glucose (IFG), controlled diabetes mellitus (DM) (HbA1C <7.5%) or uncontrolled DM (HbA1C >7.5%). Linear mixed models with random intercept were used to assess associations between glycemic status, gait speed and grip strength between 2006-2018.

**Results:** Of 2,575 men, 54% were PWH. Mean age at baseline was 45.0 years among PWH and 49.2 years among men without HIV. At baseline, DM was more common among men with vs without HIV (p <0.05) and PWH had slower gait speed (p=0.001) but not reduced grip strength compared to seronegative controls. In multivariate models including all participants, HIV serostatus was not significantly associated with change in gait speed or grip strength (all p>0.05). Compared to men with normal glucose, those with controlled DM had greater gait speed decline (-0.015 m/s [-0.028, -0.001], p<0.03) and those with uncontrolled diabetes had greater grip strength decline (-0.877 kg [-1.623, -0.130], p=0.021) 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 grip strength (-1.818 kg [-2.688, -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 Kundu2, Jesse C. Stewart3, Matthew Freiberg4, Samir K. Gupta5

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 1SD 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: 1.10-1.35, p=0.005) 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.

### Table 1: Baseline Characteristics of Participants Enrolled in Study

<table>
<thead>
<tr>
<th>Metabolite</th>
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<th>Not Depressed</th>
<th>P Value</th>
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<tr>
<td>Male</td>
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<td>Ethnicity</td>
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</tr>
<tr>
<td>Smoking</td>
<td>60%</td>
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**Method:**

**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). 48 weeks of treatment.

**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.

### Table 2: Changes in Metabolic Endpoints from Baseline to Week 48

| Metabolite Outcome | DEXA BMD Changes (Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Δ|Delta
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.

Table 1. Non-communicable diseases and their risk factors among study participants. Data from the 2015 KHANA (n=510) and 2016 UHS (n=2747) STEP surveys, Cambodia.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PLWH (n=510)</th>
<th>General Population (n=2747)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose?</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>255</td>
<td>374</td>
</tr>
<tr>
<td>Diabetes</td>
<td>46</td>
<td>155</td>
</tr>
<tr>
<td>Blood pressure ≥ 140 mmHg</td>
<td>148</td>
<td>390</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67</td>
<td>608</td>
</tr>
<tr>
<td>Fasting blood total cholesterol ≥130 mg/dL</td>
<td>95</td>
<td>671</td>
</tr>
<tr>
<td>Borderline-high</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>High</td>
<td>16</td>
<td>517</td>
</tr>
</tbody>
</table>

1 Prediabetes: fasting blood glucose between 101-123 mg/dL.
2 Prediabetes: fasting blood glucose ≥126 mg/dL and/or anti-diabetic drugs.
3 Hypertension: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or anti-hypertensive drugs.
4 Borderline-high cholesterolemia: fasting blood cholesterol between 200-239 mg/dL.
5 High cholesterolemia: fasting blood cholesterol > 240 mg/dL and/or on cholesterol lowering drugs.

689 eGFR RECOVERY 96 WKS AFTER A TDF TO TAF OR ABC SWITCH FOR TDF-ASSOCIATED eGFR DECLINE

Rosanne Verwuij1, Ingeborg Wijting1, Marjo Van Kasteren1, Jan G. Hollander4, Inge Deldeelinkx1, Guido Van Den Berk1, Saskia Vrouwenraets2, Mark Claessens2, Wouter Bierman3, Bart Rijnders2, Emanus University Medical Center, Rotterdam, Netherlands, Elisabeth–Tweedestraat Ziekenhuis, Tilburg, Netherlands, 4Maasstad Hospital, Rotterdam, Netherlands, 5University Hospitals Leuven, Leuven, Belgium, 6OLVG, Amsterdam, Netherlands, 7Streptococcal Clinic, Amsterdam, Netherlands, 8University Medical Center Groningen, Groningen, Netherlands

Background: Use of tenofovir-disoproxil fumarate (TDF) containing ART can be limited by the reversible decline in eGFR. We used longitudinal data from 15,528 PLWH initiating antiretroviral treatment between 1996 and 2018 in 4 clinics in Burkina Faso (n=1), Côte d’Ivoire (n=2), and 1,564 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: 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 7-17 with a median of 7 (Table). The incidence increased markedly across the risk score groups : 2.4 (2.0;2.8); 8.3 (7.0;8.9) 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: 13.7;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. PLWH 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.

Table 1. Performance of the D:A:D risk score to predict CKD in the iDEA West Africa Collaboration study.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Low score (n=9910)</th>
<th>Medium score (n=5192)</th>
<th>High score (n=5134)</th>
<th>Total score (n=20236)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% of pts)</td>
<td>2.41 (2.0;2.8)</td>
<td>8.3 (7.0;8.9)</td>
<td>30.1 (27.3;33.2)</td>
<td>7.6 (7.9;10.7)</td>
</tr>
<tr>
<td>Incidence (95% CI)</td>
<td>13% (95% CI: 11.8;14.7)</td>
<td>14% (95% CI: 12.7;16.0)</td>
<td>27% (24.9;30.0)</td>
<td>15% (12.9;18.0)</td>
</tr>
<tr>
<td>eGFR recovery at 96 weeks</td>
<td>11% (95% CI: 8.5;14.0)</td>
<td>9% (95% CI: 6.5;12.7)</td>
<td>4% (2.6;6.0)</td>
<td>3% (1.5;5.1)</td>
</tr>
<tr>
<td>eGFR increase at 96 weeks</td>
<td>10% (95% CI: 7.0;13.0)</td>
<td>11% (95% CI: 8.0;14.0)</td>
<td>7% (4.7;9.5)</td>
<td>5% (3.1;7.6)</td>
</tr>
</tbody>
</table>

868 VALIDATION OF THE D:A:D CHRONIC KIDNEY DISEASE RISK SCORE IN A LARGE AFRICAN COHORT

Firmin N. Kabore1, Armel Podar1, Karen Malateste1, Akouda Patassi2, Henri Firmin N. Kabore1

1Erasmus University Medical Center, Rotterdam, Netherlands, 2University Hospitals Leuven, Leuven, Belgium, 3Streptococcal Clinic, Amsterdam, Netherlands, 4University Medical Center Groningen, Groningen, Netherlands

Background: We used longitudinal data from 15,528 PLWH initiating antiretroviral treatment between 1996 and 2018 in 4 clinics in Burkina Faso (n=1), Côte d’Ivoire (n=2), and 1,564 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: We used longitudinal data from 15,528 PLWH 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 (iDEA) West Africa collaboration. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Participants included had ≥2 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 (<70), medium (70-84) and high (≥85) risk groups. Discrimination was assessed by the C-statistics and calibration parameters were expressed as ratio of observed / expected events.
690 CHRONIC KIDNEY DISEASE IN PEOPLE WITH HIV OF AFRICAN ANCESTRY IN THE UK

Lisa Hamzah, Rachel Hung, John Booth, Rachel Hilton, Mark Harber, Catherine Cosgrove, Sarah Petti, Fiona M. Burns, Amanda Clarke, Andrew Ustianowski, Beatriz Santana-Suarez, Elizabeth Binns-Roemer, Caroline Sabin, Frank Post, for the GEN-AFRICA Study Team

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 ESKD and CKD, but not proteinuria, differed by region. In unadjusted analyses, with East African ancestry as reference, West-African ancestry was significantly associated with CKD (aOR 1.86 [95%CI 1.17, 2.97] p=0.008) and ESKD (2.02 [1.16, 3.42] p=0.02) 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 ESKD (aOR 1.87 [1.09, 3.22] p=0.023) and ESKD (aOR 2.45 [1.21, 4.97] p=0.013). Caribean ancestry was significantly associated with CKD (aOR 2.23 [1.09, 2.22] 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.

691 FERRITIN AND TRANSFERRIN INDEPENDENTLY REFLECT RENAL FUNCTION IN PEOPLE WITH HIV

Harpreet Kaur, Ronald J. Ellis, Donald Franklin, Scott L. Letendre, Asha R. Kallianpur

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 was 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 268-364). 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<0.0001; beta-2-microglobulin, r=0.75, p<0.0001; serum albumin, r= -0.23, p=0.02), but not to transferrin. Transferrin 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.

692 CHANGE IN TRABECULAR BONE SCORE (TBS) AFTER ZOLEDRONIC ACID INFUSION OR TDF SWITCH

Jennifer Hoy, Stephen J. Kerr, Didier Hans, Nicholas Pocock, Andrew Carr, for the ZeST Study Group

1 Alfred Hospital, Melbourne, VIC, Australia, 2 HIV—NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, 3 University of Lausanne, Lausanne, Switzerland, 4 St. Vincent’s Hospital, Sydney, NSW, Australia

Background: Significantly greater increase in bone mineral density (BMD) occurred in osteoarthritis 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 the zoledronic acid arm and TDF switch arm over 24 months of follow-up was compared using regression models in a post-hoc, per-protocol analysis.

Results: At baseline, 41.3% of participants had a TBS >1.35 (normal bone microarchitectures) and 17.5% had a TBS <1.2 (degraded bone microarchitecture). The mean (SD) baseline TBS was 1.3 (0.1) 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 (2.1)% at M12, and 2.9 (4.2)% at M24. The absolute and percent changes in BMD increase in 37 individuals on zoledronic acid was 6.3 (2.9)% at month (M)12

Table: Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Zoledronic Acid (n=37)</th>
<th>TDF Switch (n=38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>50.6±9.8</td>
<td>48.9±9.2</td>
<td>0.20</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>22:15</td>
<td>24:14</td>
<td>0.68</td>
</tr>
<tr>
<td>Race (Black:Non-Black)</td>
<td>22:15</td>
<td>24:14</td>
<td>0.68</td>
</tr>
<tr>
<td>Diabetes (Y:N)</td>
<td>15:22</td>
<td>17:21</td>
<td>0.47</td>
</tr>
<tr>
<td>Hypertension (Y:N)</td>
<td>16:21</td>
<td>16:22</td>
<td>0.87</td>
</tr>
<tr>
<td>Cardiovascular Disease (Y:N)</td>
<td>8:29</td>
<td>9:29</td>
<td>0.52</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>25.7±4.6</td>
<td>25.3±4.5</td>
<td>0.63</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>80.1±17.7</td>
<td>75.6±19.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Serum Ferritin (ng/mL)</td>
<td>135±71</td>
<td>136±72</td>
<td>0.86</td>
</tr>
<tr>
<td>Serum Transferrin (μg/L)</td>
<td>249±141</td>
<td>241±138</td>
<td>0.78</td>
</tr>
<tr>
<td>Bone Mineral Density (g/cm²)</td>
<td>0.85±0.12</td>
<td>0.84±0.12</td>
<td>0.63</td>
</tr>
</tbody>
</table>

*Hypertension defined as systolic BP >140 mm Hg, diastolic BP >90 mm Hg, or treatment with BP lowering drug; diabetes mellitus and cardiovascular disease were self-reported or diagnosis.
LOW BONE MINERAL DENSITY IN OLDER PEOPLE WITH HIV: THE RENAL-BONE AXIOM AND ART

Elena Alvarez-Barco1, Lucy Campbell2, Alejandro A. Garcia1, Ian Walsh1, Willard Tinsley1, Jennifer J. Brady3, Keith Burling4, Sebastian Noe5, Marie Neuville6, Francois Jouret6, Mingjin Yan7, Hiba Graham7, Martin Rhee7, Frank Post8, Patrick W. Mallon1

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Background: Data on low bone mineral density (BMD) in people with HIV (PWH) are mainly derived from younger adults. We explored the relative contribution of antiretroviral therapy (ART) and alterations in the renal-bone axis to lower BMD in older PWH.

Methods: Sub-analysis of the GS-US-104-0423 study, a cross-sectional study of ART-treated HIV-positive men >50 years and post-menopausal women. ART was stratified into 4 groups based on always or never treated with tenofovir disoproxil fumarate (TDF) and/or protease inhibitors (PI): noTDF/noPI, noTDF/PI, TDF/noPI, TDF/PI. In stored blood we analyzed bone turnover markers: osteocalcin (OC), procollagen type 1 amino-terminal propeptide (P1NP) and C-terminal cross-linking telopeptide of type 1 collagen (CTX-1); markers of bone regulation: osteoprotegerin (OPG), surface-bound receptor activator of nuclear factor kappa-B ligand (sRANKL) and phosphatonin (FGF-23), 25(OH) vitamin D and parathyroid hormone (PTH). We analyzed renal tubular markers retinol binding protein (RBP), carbonic anhydrase III (CA3) and fractional excretion of phosphate (FEPO4) in stored urine. BMD (g/cm2) at the lumbar spine (LS) and femoral neck (FN) was measured by dual X-ray absorptiometry. The relevant impact of ART exposure and bone/renal markers on BMD was explored using logistic regression adjusted for demographic factors (age, gender, ethnicity, BMI and smoking status).

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. RBP/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 and BMD-FN, and RBP/Cr with BMD-FN. In adjusted analyses, compared to the noTDF/noPI group, those on TDF/PI were 3 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 1). Further adjustment for the OC, CTX-1 and RBP/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 1. Adjusted Odds Ratio and 95% Confidence Intervals derived from logistic regression models exploring the contribution of ART to low BMD.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposure</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS</td>
<td>noTDF/noPI</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>TDF/noPI</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>TDF/PI</td>
<td>3.12 (1.00, 9.70)</td>
</tr>
<tr>
<td>FN</td>
<td>noTDF/noPI</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>TDF/noPI</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>TDF/PI</td>
<td>3.10 (1.00, 9.70)</td>
</tr>
</tbody>
</table>

694 BONE MINERAL DENSITY IMPROVES IN WOMEN WHO SWITCH FROM TDF/FTC/NNRTI TO ABC/3TC/DTG

Fowzia Ibrahim1, Amanda Samarawickrama1, Yvonne Gilleece1, Julie Fox2, Nargis Hemat3, Stephen Kegg3, Chloe Orkin4, Lisa Hamzah5, Jonathan Ainsworth6, Birgit Barbini1, Lucy Campbell2, Frank Post6, for the BESTT Trial Team

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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 Triumeq (BESTT, EudraCT 2015-005297-37)) in which 247 individuals (median age 57 [IQR 53, 65] years, 47% female, 87% white, mean [SD] age 50.4 [6.6] years, CD4 cell count 639 [263] cells/mm3, 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. Secondary endpoints included changes in lumbar spine BMD, bone turnover and function, and post-hoc weight gain vs. no change in those who continued TDF/FTC/NNRTI (adjusted mean difference from baseline to week 48 between the two study arms, using linear regression adjusted for demographic factors (age, gender, ethnicity, BMI and smoking status).
BONE DENSITY IN ART TREATED HIV+ AND HIV− SUBJECTS IN FOLLOW UP; HIV UPBEAT RESULTS


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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 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 40 [34-47] yrs) and 218 were HIV− (45% male, 77% Caucasian, age 42 [35-50] yrs).

Neither absolute or percentage (%) change in BMD, nor the rate of change of LS or FN BMD differed between PWH and HIV− subjects (absolute % change 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 in BMD; LS +0.004 g/cm²/yr [0.001, 0.007], P=0.005 but not FN BMD, while those not statistically significant) gain in LS and FN BMD evident in later visits (Fig 1).

INTERSTITIAL LUNG ABNORMALITIES IN PEOPLE LIVING WITH HIV AND UNINFECTED CONTROLS

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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), nondependent GGO and non-dependent reticulation (>5% of the lung), diffuse centrilobular abnormality with GGO, honeycombing, traction bronchiectasis, non-embryosmatic 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 were 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 (86.5% vs. 92.5%, p=0.052) and increased respiratory symptoms (cough 25% vs 12.5%, p=0.025) and dyspnea 9.1% vs 8.3%, p=0.684), 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 PROGRAM IN HIV-INFECTED SUBJECTS

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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 dilatation, 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 the following 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

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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 men, 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 on CT and COPD. Our data also suggest a potentially additive influence between HIV and COPD on DLCO impairment. Future studies
HIV AS A RISK FACTOR FOR INCIDENT PULMONARY HYPERTENSION

Meredith S. Duncan, Suman Kundu, Charles Alcorn, Emily Epstein, Grace Wallace, Kaku So-Armah, Amy C. Justice, Kristina Crothers, Matthew Freiberg, Evan L. Brittain

Table: Adjusted 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 enrollment year. We evaluated 3677 VACS participants (N=1188 HIV+) referred to assess 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.

Results: Over 97% of the cohort was male with an average age of 58 years. Nearly half of the cohort was African American; another 40% was white. Median follow-up time was 3 years (Q1, Q3: 1, 7). PH incidence rates were higher among HIV-infected veterans versus white individuals (HR=1.38 [1.08, 1.76]).

Conclusion: HIV is independently associated with higher PH incidence after adjustment for risk factors. Low CD4 cell count and high HIV viral load contribute to the increased risk of incident PH among HIV-infected veterans. Race may also contribute to differences in incident PH.

START OR SWITCH OF INTEGRASE INHIBITORS GENETICALLY INHIBIT DEPRESSIVE SYMPTOMS IN WOMEN WITH HIV

Jane A. O’Halloran, Kunbo Wang, Dionna W. Williams, Ra...
**Methods:** African American women (18–65 yrs) recruited from Women’s Interagency HIV Study (WIHS) in Atlanta, GA (n=91), 30 without HIV, 61 with HIV (WWH), provided informed consent, and underwent interviews to capture trauma exposure and PTSD symptom severity among residents of HIV/AIDS treatment programs in Atlanta. Sociodemographic variables were similar among groups: age (p=0.19); education (p=0.24); employment (p=0.84). Higher levels of trauma were associated with higher PTSD severity. PTSD symptom severity was greater in WWH compared to controls (p<0.05). PTSD symptom severity was positively correlated with higher levels of trauma (r=0.29, p=0.01). PTSD symptom severity was significantly higher in WWH compared to controls (p<0.05). PTSD symptom severity was significantly higher in WWH compared to controls (p<0.05). PTSD symptom severity was significantly higher in WWH compared to controls (p<0.05). PTSD symptom severity was significantly higher in WWH compared to controls (p<0.05). PTSD symptom severity was significantly higher in WWH compared to controls (p<0.05).

**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 correlated with generally lower levels of trauma (p=0.10; etasq=0.07; Fig 1). 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; etasq=0.17) and reactivity to trauma reminders (p=0.01; etasq=0.25). Higher childhood trauma in uninfected women associated with greater baseline SC compared to uninfected women with low childhood trauma (p=0.05; etasq=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; etasq=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; etasq=0.15). In women exposed to high childhood trauma, HIV associated with augmented reactivity to trauma reminders (p=0.06; etasq=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.

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**704 EXERCISE-INDUCED EPIDEMIC CHANGES IN MUSCLE DIFFER BY HIV SEROSTATUS**

Kristine M. Erlandson1, Colleen Juliana, Iain Konigsbergb, Jing Sunb, Todd T. Brown1, Catherine M. Jankowski1

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**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 Combp 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=3.3E-2). 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-3), glutamate receptor signaling (p=1.1E-3), phosphatase and tensin homolog deleted on chromosome 10 (PTEN) signaling (p=3.7E-3), and androgen signaling (p=5.1E-3). In controls, exercise training induced 75 genome-wide significant DMRs and control pathways with corresponding changes in DNA methylation included: gas signaling (p=6.0E-3), androgen signaling (p=5.3E-3), and fibroblast growth factor family ligand-receptor interactions (p=3.6E-3) and T-cell receptor signaling (p=5.1E-3). In controls, exercise training induced 75 genome-wide significant DMRs and control pathways with corresponding changes in DNA methylation included: gas signaling (p=6.0E-3), androgen signaling (p=5.3E-3), and fibroblast growth factor family ligand-receptor interactions (p=3.6E-3) and T-cell receptor signaling (p=5.1E-3).

**Conclusion:** Epigenetic responses to exercise differed 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
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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 (BOSS) 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: 387 men (198 HIV) and 184 women (118 HIV) had available CT scans. Among men, mean age was 64, 20% were black, 13% current smokers, and 19% were obese (BMI ≥30 kg/m²). Among women, mean age was 50, 51% were black, 53% 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 cm²) and female sex (-6.0 to -3.1), but greater with obesity (range: 1.5 to 5.4), all p≤0.02; no race effect was observed. In sex-stratified models, HIV serostatus was associated with greater laterals (1.0 [0.4], p=0.02) and paraspinal (0.8 [0.4], p=0.03) but lower psoas (-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 fatter muscle, while obesity was associated with larger and fatter 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-RELATED GAIT SPEED AND STRENGTH DECLINES
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Background: Statin use decreases inflammation and reduces cardiovascular events, and may be useful among persons with HIV, who have increased risk of cardiovascular (CV) events. Other benefits are unclear: some studies suggest that statins benefit physical function despite myalgias as a common side effect. We compared age-associated changes in physical function among men with or without statin use in the Multicenter AIDS Cohort Study.
Methods: Men 40–75 years old with ≥2 measures of gait speed or grip strength (baseline=2007) were included. Consistent statin use was defined as use at ≥80% of visits. Gait speed was measured on a 4-m course and grip strength 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), 398 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 0.99, 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.
hypertension; 38% were overweight (BMI 25 to <30 kg/m²), 30% obese (BMI ≥30 kg/m²); 33% had high waist circumference (>102 cm in men, >88 cm in women); 89% were physically inactive (REAP); 37% (95% CI: 31%, 43%) had physical function impairment; 6% (4%, 9%) were frail and 42% pre-frail; 31% reported not being able to perform one or more instrumental activities of daily living (ADL). Older age, Black race, ≥10 years on ART, history of thymidine analog (TA), greater BMI, high waist circumference, hypertension and physical inactivity were associated with physical function impairment in univariate analyses (figure). Blace race, greater BMI and physical inactivity remained associated with physical function impairment in the multivariate model.

Conclusion: Physical function impairment and pre-frailty were common among middle-aged PWH; greater BMI and physical inactivity are important modifiable factors that may prevent further decline in physical function with aging.

Background: Hospitalization rates among persons with HIV (PWH) may be changing due to demographic and antiretroviral (ARV) therapy changes. Early 2000s evidence suggested hospitalization rates among PWH were increasing for renal, pulmonary, and cardiovascular disease (CVD), possibly due to long-term HIV infection or ARV toxicity. To characterize recent hospitalization trends, 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, race/ethnicity, HIV risk factor, and HIV*risk factor interaction. Models additionally adjusted for sociodemographic characteristics (time-updated age, sex, race/ethnicity, socioeconomic status, insurance type, region). We excluded patients with prior CKD or CVD and dyslipidemia and smoking a stronger association with CVD, diabetes mellitus, hypertension, dyslipidemia, smoking (ever documented history) and alcohol use disorder. We compared adjusted rate ratios (RRs) 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, region). We evaluated the association of modifiable risk factors with incident hospitalization rates among PWH and HIV-uninfected people is unknown.

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, race/ethnicity, HIV risk factor, and time-updated age, CD4, and HIV RNA.

Results: Of 19,848 patients, 81% were male, 33% Black, 52% MSM, and 13% with IUD 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% (-5, -3) [Fig. 1A]. Non-AIDS infection (25%), CVD (10%), liver/gastrointestinal (8%), psychiatric/substance use (8%), non-AIDS cancer (6%), and AIDS-defining illness (AD), 6%) were the most common discharge diagnosis categories. Crude rates decreased for all categories except injury, endocrine, and musculoskeletal, which had no change (Fig. 1B–D). In adjusted models, rates decreased for CVD (-4% CI -6, -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.
among uninfected than PWH. Some risks appear protective for CKD among PWH, potentially due to successful treatment for those, and require further study. Mitigation of risks is important but may have a greater effect on CKD and CVD among uninfected people.

710 BASELINE AND ACQUIRED COMORBIDITIES IN PATIENTS INITIATING ART IN THE HOPS, 2008-2018

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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)-naive participants in the HIV Outpatient Study (HOPS) initiating ART from 2008-2018 with ≥2 tests of CD4 counts since 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 smoking history, and 33% with substance use history. The baseline CD4 count was 379 cells/mm3 for men vs. 360 cells/mm3 for women. Women were more likely to be older, Black or Hispanic, with public insurance, seen at a public clinic, with high health care utilization, and psychiatric comorbidities at baseline and the rate at which they develop may be related to aging, metabolic changes, medication, or socioeconomic factors.

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.

711 WOMEN WITH HIV HAVE HIGH OVERALL BURDEN AND EARLY ACCRUAL OF NON-AIDS COMORBIDITIES

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Background: HIV infection may accelerate aging-related comorbidity development. The incidence of non-AIDS comorbidities (NACM) in women with HIV (WWH) is poorly characterized.

Methods: WWH and HIV- women in active follow-up in the Women's Interagency HIV Study (WIHS) in 2009 (when >80% of WWH used antiretroviral therapy (ART)) or onward were included, with outcomes measured through March 31, 2018. Age, demographic and clinical covariates, and prevalent NACM were determined at enrollment. We used Poisson regression to estimate incidence rate ratios (IRR) comparing accrual of incident NACM by HIV serostatus and age using partially adjusted (age, HIV) and fully adjusted (age, HIV, covariates) models.

Results: There were 3129 women (2239 HIV+, 890 HIV-) with 36,589 person-yrs (PY) of follow-up. At enrollment, median age was 37yrs, 65% were black, 47% currently smoked, and median body mass index was 28 kg/m². WWH had a median CD4 count of 484 cells/mm³, 69% were on ART and 45% were virologically 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

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Background: Persistent low-level viremia (pLLV) may represent subclinical viral replication, which, similar to non-HIV comorbid diseases (NCDs), may increase risk of noncommunicable diseases and noncommunicable comorbidities. The objective of this study was to assess the association between pLLV and NCDs in PLWH.

Methods: This was a secondary analysis of data collected in 12 clinics in Uganda, Kenya, Tanzania, and Nigeria. We evaluated PLWH who had an NCD at baseline and were followed up for more than 6 months. Participants were stratified into NCDs and NCD-free groups based on the presence of ICD-10 codes corresponding to NCDs. We calculated adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression models.

Results: Of the 3,000 PLWH enrolled, 1,500 had an NCD and were included in the analysis. In the NCD group, the prevalence of pLLV was significantly higher compared to the NCD-free group (p < 0.05). The adjusted HR for pLLV was 2.25 (95% CI, 2.12–3.33) for metabolic NCDs, 2.93 (95% CI, 2.14–4.00) for cardiovascular NCDs, and 2.35 (95% CI, 1.96–2.80) for respiratory NCDs.

Conclusion: Persistent low-level viremia (pLLV) is associated with increased risk of noninfectious comorbidities in PLWH.
**715 IN VITRO IMPACT OF TAF ON MITOCHONDRIAL FUNCTION IN IMMUNE CELLS**

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**Background:** 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), which may alter mitochondria. This study was designed to address whether TAF affects in vitro mitochondrial membrane potential (MMP), a direct measure of mitochondria. This study was designed to address whether TAF affects in vitro mitochondrial membrane potential (MMP), a direct measure of the state of mitochondria. This study was designed to address whether TAF affects in vitro mitochondrial membrane potential (MMP), a direct measure of the state of mitochondria.

**Methods:** Whole blood DNA methylation profiles were assayed via Illumina Infinium MethylationEPIC BeadChips. Data were preprocessed using Nobs normalization. The EA and estimated abundance of leukocyte subsets were obtained from the advanced analysis for blood tissue using the Horvath’s DNA methylation Age Calculator. We estimated three EAA measures: universal (AgeAccel), extrinsic (EEAA) and intrinsic (IEAA). We measured telomere length (TL) with multiplex qPCR.

**Results:** At baseline (BL), male: 88%, mean chronological age: 39.2 years, Caucasian: 80%, HIV-1 RNA: 4.7 log 10 copies/mL, and mean CD4+ and CD8+ (flow cytometry): 311 and 954 cells/µL. At W96, 96% had HIV-RNA <50 c/mL and mean CD4+ and CD8+ were 564 and 845 cells/µL. At BL, EA positively correlated with chronological age (r=0.891, p<0.001) while TL correlated negatively (r=-0.940, p<0.001). Mean EA at BL and W96 was 47.5 and 47.6 years respectively. Age advancement (EA minus chronological age) significantly improved after ART initiation (BL: 8.3 vs W96: 6.5 years, p=0.007). Comparing with BL, two measures of mean EA slowed at W96 (AgeAccel: -1.49 years, p=0.011; EEAA: -4.02 years, p<0.001), while IEAA did not change (0.03 years, ns). EA decreased in 71.05% (AgeAccel) and 78.07% (EEAA) of participants. At W96, EA correlated negatively with CD4+/CD8+ ratio by flow cytometry, estimated CD4+, naive CD4+ and naive CD8+, and positively with estimated CD4+CD28-CD45RA- T cells and NKs. Mean TL change at W96 was 0.034 (T/S). At W96 TL correlated positively with CD4+/CD8+ ratio by flow cytometry, estimated abundance of total CD4+, naive CD4+ and naive CD8+ and negatively with estimated abundance of CD8+ CD28-CD45RA- and NKs (Table).

**Conclusion:** EA stabilized and EA slowed in the majority of patients after starting ART. However, an age advancement of 6.5 years persisted after the first two years of successful ART. The reversal of epigenetic aging and the increase in blood TL caused by ART initiation are likely driven by changes in T cell subtypes toward less differentiated phenotypes.

<table>
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<tr>
<th>Cell type</th>
<th>EA (years)</th>
<th>TL (years)</th>
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<tbody>
<tr>
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<td>0.297 (0.001)</td>
</tr>
<tr>
<td>CD4+ naive T cell</td>
<td>-0.154 (0.002)</td>
<td>0.126 (0.001)</td>
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<tr>
<td>CD8+ T cell</td>
<td>0.023 (0.016)</td>
<td>0.216 (0.003)</td>
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<tr>
<td>CD8+ naive T cell</td>
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<td>0.402 (0.001)</td>
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<td>0.015 (0.007)</td>
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<tr>
<td>Plasma cells</td>
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<td>0.012 (0.006)</td>
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<tr>
<td>Natural Killer</td>
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<tr>
<td>Monocytes</td>
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<tr>
<td>Granulocytes</td>
<td>-0.161 (0.023)</td>
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*Table. Correlations between estimated cellularity index of leukocyte subsets, CD4/CD8 ratio (flow cytometry) and estimated age (EA) and telomere length (TL) at week 96.*

**716 INFLAMMATION AND MITOCHONDRIAL DYSFUNCTION NOT NRTIs DRIVE EVENTS IN ACTG A5241**

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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, TNFβ, sCD14, 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/Latino, 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, sCD14 (555,263 vs 448,584 pg/mL, P=0.03); CD4 count (148 vs. 209 cells/mm³, P=0.03); CD4/CD8 ratio (0.16 vs 0.22, P=0.02) and 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, FGF-21, GDF-15, IL-6, TNF-R1, TNF-R2, insulin or HIV RNA levels. Censoring for those with clinical events before weeks 24 or 48, FGF-21, sCD4, CD4:CD8 ratio and VACS index were significantly different at weeks 24 and 48. 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, 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 TB and TB/death post treat all. The 2-year CH of TB and TB/death declined between entry year are shown (Table). 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: 0.6% vs 0.7%, 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

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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 11.2-13.7) 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.

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<th>Tb or death</th>
<th>Person-years</th>
<th>IR of TB per 100 py</th>
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719 ALARMING TUBERCULOSIS RATE AMONG PWID IN VIETNAM
Nicolas Naget1, Vu H. Vinh2, Khuatt Q. Anh3, Delphine Rapoud4, Hoang T. Giang4, Catherine Quillet3, Pham M. Khue4, Roselyne Vallo7, Thanh T. Nhâm7, Jean-Pierre Molès1, Don Des Jarlais5, Duong T. Huong4, Phuong N. Lan6, Thuy T. Bii3, Lungisile Vezi2, Matthew P. Fox1, Willem D. Venter4, Peter Ehrenkranz5, Didier Laureillard8
1INSERM, Montpellier, France, 2Vinh Duc Hospital, Haiphong, 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, Hai Phong, 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 HIV 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 5% were using methadone, respectively. Among HIV-positive, 90% were on ART and 82% had a viral load <1000 copies/mL, with a median CD4 count of 472 cells/µL. Among the 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.

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.

721 HOUSEHOLD AIR POLLUTION INCREASES RISK FOR PULMONARY TB IN HIV-INFECTED ADULTS
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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 (PLHIV).

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
722 ALCOHOL USE IS ASSOCIATED WITH INCIDENT TB INFECTION IN HIV+ AND HIV- UGANDAN ADULTS

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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-naive 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-naive 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-naive 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 spuata sent for diagnostic testing (58% for Xpert MTB/RIF testing); trends in specimen testing decreased over the analysis period.

Conclusion: The proportion of ART-naive 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.

723 TUBERCULOSIS EVALUATION AMONG HIV-POSITIVE PATIENTS ON ANTIRETROVIRAL THERAPY

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Background: In this longitudinal cohort of adults in Uganda, incident TB infection was highly associated with alcohol use at any and hazardous levels, and not associated with HIV-status or a known household TB contact. TB prevention efforts that focus on reducing transmission in venues shared by drinkers may decrease the latent TB reservoir in this TB risk group.

Results: We recruited 435 cases and 842 controls. Median age (IQR) 41 years (35-50), 76% female. Overall median 24-personal average CO was 5.3 (2.1-10.6) parts per million (ppm). After adjusting for sociodemographic covariates, tobacco smoking, median CD4 count, and duration on ART, each 1 ppm increase in average 24h CO exposure was positively associated with PTB (adjusted odds ratio, aOR; 95% confidence interval, CI: 1.0; 1.0-2.23). Average 24h CO level stratification by quintiles yielded a concentration dependent increase in the odds of PTB from the lowest [0.1-1.9 ppm], to highest quintile [12.3-76.2 ppm] (aOR 4.64; 95%CI: 1.04-20.65) (Fig. 1). Furthermore, for women, each additional hour spent cooking over wood fire was associated with increased odds of PTB (aOR 2.76; 95% CI: 1.02-7.47).

Conclusion: Personal CO exposure and time spent cooking over wood fire (among women) were independently associated with increased odds of PTB among PLHIV in eastern DRC. Longitudinal studies are needed to confirm our findings and inform comprehensive strategies to reduce the triple burden of HAP-TB-HIV.

724 TUBERCULOSIS PREVENTIVE TREATMENT IN NEW VS EXISTING ANTIRETROVIRAL THERAPY PATIENTS

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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.

725 POTENTIAL IMPACT OF LATENT TUBERCULOSIS IN PEOPLE LIVING WITH HIV

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Background: Approximately 28% of the human population harbour Mycobacterium tuberculosis (MTB), with more than 90% of infected individuals not developing disease. Recent findings in the animal model suggest that latent MTB infection (LTBI) may have symbiotic effects by protecting against MTB-unrelated infections via activation of the innate immune system. So far, potential interactions of LTBI in HIV-infected individuals have not been investigated.

Methods: We included all participants of the Swiss HIV Cohort Study (SHCS) with at least one documented MTB test. LTBI was defined as either a positive skin reactivity test or a positive IGRA test; patients who developed active MTB were excluded. Logistic regression was used to analyse the frequency of the most common opportunistic infections and laboratory conditions between patients with and without LTBI. Linear regression was used to detect differences in the setpoint viral load between patients with and without LTBI in multivariable models we corrected for baseline demographic characteristics, i.e., year of HIV diagnosis, HIV transmission group and ethnicity. In the analysis of opportunistic diseases, we corrected as well for the CD4 nadir.

Results: Out of 13675 patients tested for MTB, 1027 (7.7%) had a LTBI and 316 (2.3%) developed active MTB. Patients with LTBI had significantly lower odds of having oral candidiasis (univariable (UV) odds ratio (OR)=0.31, p<0.0001; multivariable (MV) OR=0.61, p<0.0001) and oral hairy leukoplakia (UV OR=0.36, p<0.0001; MV OR=0.72, p=0.028) as compared to MTB uninfected patients. For other opportunistic diseases, the significant interaction with LTBI disappeared in the MV model (Figure). LTBI was associated with a reduced setpoint viral load (UV=0.27, 95%-confidence interval=[0.35,0.20], log-reduction; MV=0.24 (0.32,0.16)).

Conclusion: The finding that LTBI is independently associated with a reduced risk for oral candidiasis and oral hairy leukoplakia points towards a yet not appreciated interaction between LTBI and other infections. In addition, a significant reduction of the setpoint viral load in asymptomatic HIV-infected individuals suggests a more complex interaction between MTB infections and HIV than previously assumed. In conjunction, these findings potentially suggest that LTBI in humans also might have an activating effect on the innate immune system as was proposed in the mouse system.

Association of latent tuberculosis and opportunistic diseases

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726 GEOGRAPHIC AND INDIVIDUAL RISK FACTORS FOR TB OR DEATH IN THE BRIEF-TB TRIAL (A5279)

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Background: The BRIEF TB trial (A5279, NCT01404312) demonstrated non-inferiority of one-month of isoniazid and rifapentine (IHP) versus nine months of isoniazid (9H) for TB prevention. We explored differences in rates of the primary outcome by demographic, clinical, and geographic factors in a pre-planned secondary analysis.

Methods: BRIEF TB enrolled 3000 adults and adolescents with HIV infection in 10 countries who were followed for at least 3 years. The primary endpoints were TB or death from TB or an unknown cause. We analyzed risk of reaching an endpoint by baseline factors, including sex, race, tuberculosis skin test (TST)/interferon-gamma release assay (IGRA) status, CD4 count, country of residence,
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, 85% 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. ITPH represents an exciting new strategy for preventing TB in people living with HIV.

| Table 1: Summary of adverse pregnancy outcomes by treatment group |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Outcome | Immediate IPT | Deferred IPT | p-value |
| Fetal demise | 0.00 | 0.00 | 0.99 |
| Pre-term delivery (PTD) | 0.00 | 0.00 | 0.99 |
| Low birth weight (LBW) | 0.00 | 0.00 | 0.99 |
| Congenital anomaly | 0.00 | 0.00 | 0.99 |

272 ADJUSTED ANALYSIS OF EFFECT OF IPT ON ADVERSE PREGNANCY OUTCOMES IN WOMEN WITH HIV

Gerhard B. Theron1, Nahida Chakhtoura1, Grace Montepiedra2, Lisa Aaron3, Patrick Jean-Philippe4, Adriana Weinberg5, Katie McCarthy6, TeaclerPTD, LBW or congenital anomaly (composite outcome 1) were 1.68 times higher among women on immediate IPT compared to deferred IPT (95% CI=1.12, 2.26; P=0.009). The odds of early neonatal death, fetal demise, PTD, or LBW (composite outcome 3) were 1.70 times higher among women 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. ITPH represents an exciting new strategy for preventing TB in people living with HIV.

278 HIGH LEVELS OF ALCOHOL USE ASSOCIATED WITH LATENT TB INFECTION IN HIV-POSITIVE ADULTS

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Background: HIV infection and heavy alcohol use are risk factors for tuberculosis (TB) disease, but it is unknown if TB infection varies by level of alcohol use among people with HIV on ART. We examined associations between level of alcohol use and tuberculin skin test (TST) positivity among PLWH with heavy alcohol use, to inform TB prevention.

Methods: We evaluated adults screened (2018-19) for enrollment in an ongoing 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+ or 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 ≥5 if female and ≥8 if male and was stratified into medium (AUDIT-C 3-4; 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 positivity, adjusting for age, sex, and study site.

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 TB-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. TB positivity by drinking level was: medium 31%, high 33%, very high 45%. In the multivariate model, very-high level use was significantly associated with TB positivity compared to medium-low level drinking (aOR 1.61, 95%CI: 1.03-2.50, P=0.04). High level drinking had a non-significant association with TB positivity compared to medium-low level use (aOR 1.05, 95%CI: 0.69-1.59, P=0.83). Conclusion: Very high-level alcohol use was associated with increased TB positivity among a cohort of PLWH. Potential mechanisms of increased TB infection are unclear but may include more time spent in high transmission environments.
environments (e.g., bars) or high-risk social networks. Our findings suggest that these environments may contribute to the higher prevalence of LTBI among drinkers, particularly among those with HIV. Latent TB infection (LTBI) was defined by a positive QuantiFERON TB test and no history of active TB.

Results: We included 125 participants (83 PWH and 42 without HIV). In this population, BCG vaccine safety and efficacy can be assessed in macaques. BCG vaccine efficacy in macaques has been shown in previous studies. We hypothesized that IV BCG would be safe and effective at protecting chronic SIV+ macaques from TB.

Methods: We used a live attenuated M. bovis strain, given intradermally (ID) to infants at birth. BCG ID confers protection against disseminated TB infection, but 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 efficacy can be assessed in macaques in the setting of SIV and M. tuberculosis (Mtbc) infection. Recently, intravenous (IV) BCG was shown to prevent Mtbc infection and disease in rhesus macaques. Here, we used our established model of SIV/Mtbc 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 intrarectally with SIVmac239. Five months later, they were vaccinated with 8x10^7 CFU BCG. Beginning 4 weeks later, vaccinated animals were treated with 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) Mtbc Erdman via bronchoscope. Control animals consisted of SIV+ unvaccinated and SIV+ vaccinated MCM that were not challenged with Mtbc.

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.

### Table 3. Proposed-dosing chart for HIII

<table>
<thead>
<tr>
<th>HIV+ status (H)</th>
<th>Total Monocytes (x10^6)</th>
<th>Classical subset (x10^6)</th>
<th>Inflammatory subset (x10^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count (cells/µL)</td>
<td>log-MFI</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>200-499</td>
<td>1.17 (1.0-1.2)</td>
<td>1.77 (0.8-4.0)</td>
<td>3.9 (1.4-7.4)</td>
</tr>
<tr>
<td>≥500</td>
<td>2.16 (1.9-2.6)</td>
<td>3.2 (1.3-6.9)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

* Data presented as median and interquartile range in parentheses.

** p value of Kruskal-Wallis test.

*indicates that there was a significant difference (p≤0.05) on HIII for the group and the no-Mtbc infection group using the Mann-Whitney-U test.
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, which showed increased 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 RIFAMPIN FOR TB
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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/Claclvanate. Overnight sputum was collected on days 0, 1, 2, 3, 4, 6, 8, 10, 12, 14. The mean daily fall in log10 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 log10 CFU/mL – log10 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 133, 134, 68.1, and 179 mg/L, respectively. Over the first 2 days of treatment, mean EBA0-2CFU were 0.39; 0.11; 0.14; 0.08, and 0.03 (-0.01, 0.08), in Arms C, D, E, and F, 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. The mean daily fall in logarithmic 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 log10 CFU/mL – log10 CFU/mL at day 14]/14.

Conclusion: Meropenem exhibits linear dose–dependent PK, and rifampicin does not impact its exposures. Addition of Rifampicin to Meropenem and Amoxicillin/Claclvanate increased early EBA (EB(A0-2)) 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.

733 EFFECT OF RIFAMYCINS ON PRETOMANID EXPOSURE IN PATIENTS WITH PULMONARY TB
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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 PaHR (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 rifampicin had 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 AUC0-24, 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.

734 CLINICAL PHARMACOKINETICS AND TOXICODYNAMICS OF LINEZOLID IN THE NIX-TB TRIAL
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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.
735 HIV VIROLOGICAL OUTCOMES DURING TENOFEVIR ALENAFAMIDE AND RIFABUTIN CODUSTRNATION

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Background: Tenofovir alafenamide (TAF) absorption may be decreased during rifabutin (RFB) therapy due to induction of P-glycoprotein. Current USA HIV guidelines therefore recommend against coadministration of TAF and RFB. Based on expert opinion, some centres have administered TAF containing HIV regimens with RFB; however, clinical outcomes have not been assessed.

Methods: Retrospective observational study of all individuals at UC San Diego who received a TAF containing HIV regimen coadministered with RFB for ≥ 1 month between April 2016 and July 2019. The primary outcome was defined as documented HIV VL ≤200 copies/mL after initiating TAF/RFB therapy or as documented HIV VL ≤200 copies/mL at the end of TAF and RFB overlap. Mean change in CD4 count from baseline to end of treatment was +105 cells/μL (95% CI: 16 - 227).

Conclusion: Despite a predicted decrease in TAF absorption when coadministered with RFB, the majority of individuals achieved or maintained HIV suppression during TAF/RFB therapy. This data supports further study of TAF and RFB coadministration in HIV and mycobacterial infection.

Table 1:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 (45-65)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>698 (296-1050)</td>
</tr>
<tr>
<td>White</td>
<td>698 (296-1050)</td>
</tr>
<tr>
<td>Black</td>
<td>54 (45-65)</td>
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<tr>
<td>Asian</td>
<td>31 (13-65)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>31 (13-65)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>31 (13-65)</td>
</tr>
<tr>
<td>Median baseline CD4 count, cells/μL</td>
<td>31 (13-65)</td>
</tr>
<tr>
<td>Viral load, viral load, log10 copies/mL</td>
<td>6.4 (5.6)</td>
</tr>
<tr>
<td>Median baseline viral load, copies/mL</td>
<td>7.5 (5.3)</td>
</tr>
<tr>
<td>VL suppression at baseline, μL/L</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td>VL suppression at baseline, %</td>
<td>9 (38)</td>
</tr>
</tbody>
</table>

736 DRUG-RESISTANCE MUTATIONS AND TUBERCULOSIS MORTALITY IN HIGH-BURDEN COUNTRIES

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Background: Strategies to control Mycobacterium tuberculosis (Mtbc) 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/HPA 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 DR with frequency >20 and for combined groups of rare DR.

Results: The most common mutations in our sample were S315T, S450L, L79S, S315T, M306V, D453V, M306L and K43R (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 3.8 (95% CI: 1.7 - 8.4) and L79S with OR 4.3 (95% CI: 2.8 - 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 TB patients from eight high-burden countries. Many of the conferred DR were missed by local DR tests, 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 DRM and thus could contribute to more effective treatment and reduced mortality among patients with MDR TB.
CSF TB BACILLARY LOAD PREDICTS 2-WEEK MORTALITY IN HIV-ASSOCIATED TBM MENINGITIS

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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 high 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.

738 MORTALITY IN ADULT HIV/MDR-TB BY ART USE: INDIVIDUAL PATIENT DATA META-ANALYSIS

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Background: The use of ART for HIV patients with MDR-TB has 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 age, sex, site, year of treatment initiation, previous TB treatment, directly observed therapy, 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 of treatment initiation, previous TB treatment, directly observed therapy, and acid-fast-bacilli-smeared 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, 6,068 (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, bedaquiline and/or linezolid) (Table). 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 of treatment initiation, previous TB treatment, directly observed therapy, and acid-fast-bacilli-smeared positivity to obtain adjusted odds ratios (aORs) and 95% confidence intervals (CI).

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739 CD4 COUNT AND VIRAL LOAD DYNAMICS UNDER DIFFERENT ART REGIMENS IN HIV/TB CONIFECION


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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 Efavirenz (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 ART prescription was 148 cells/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 ART prescription was 148 cells/mm3 for 71% of the sample. 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.
time for ALT to fall below 100 U/L. Secondary endpoints included duration of hospitalisation, 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 reduce morbidity and hospitalisation costs in patients hospitalized with AT-DILI. Larger clinical trials are needed to confirm this finding.

NAC (nausea and vomiting in 3, anaphylactoid reaction in 1 drip site pain in 1). Early drug discontinuation due to an adverse reaction in 5 participants, all of whom were receiving NAC. 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 reduce morbidity and hospitalisation costs in patients hospitalized with AT-DILI. Larger clinical trials are needed to confirm this finding.

742 HIV, TUBERCULOSIS, AND CHRONIC LUNG DISEASE AMONG KENYAN ADULTS

Jerry S. Zifodya1, Tecla M. Temu1, Sarah Masyuko, George Nyale1, Jerusha Nyabiage1, Dickens Onyango3, John Kinuthia2, Stephanie Page1, Sylvia LaCourse1, Carey Farquhar, Kristina Crothers1

Background: People living with HIV (PLWH) are at increased risk for non-communicable diseases such as chronic lung disease (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 December 2018 through October 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 analysis was performed to evaluate the association of prior TB and pneumonia with the composite outcome of impaired spirometry and a validated respiratory specific questionnaire. Prior active TB and pneumonia were based on self-report. Multivariable logistic regression analysis was performed to evaluate the association of prior TB and pneumonia with the composite outcome of impaired spirometry and a validated respiratory specific questionnaire.

Results: Among meningitis patients, 69 had cryptococcal meningitis (68 CrAg+ by LFA and 1 false negative due to prozone with 1:1310720 CrAg LFA titer), and 31 had no cryptococcal meningitis by CrAg, culture, and India ink. The CrAg SQ LFA provided a semi-quantitative test result in a single test in contrast to traditional semi-quantitative testing which requires serial dilutions and multiple tests.

Methods: From February to September 2019, we compared the diagnostic performance of the CrAg SQ assay (Immy) with the CrAg LFA (Immy) on 100 CSF samples, 61 serum samples collected from HIV+ persons with meningitis and 50 serum samples from HIV+ persons with CD4<100 screened for cryptococcal antigenemia. The CrAg SQ levels (1+ to 4+) were compared with CrAg LFA titers to determine the corresponding cut off CrAg SQ titer. All specimens were prospectively tested.

Results: Among meningitis patients, 69 had cryptococcal meningitis (68 CrAg+ by LFA and 1 false negative due to prozone with 1:1310720 CrAg LFA titer), and 31 had no cryptococcal meningitis by CrAg, culture, and India ink. The CrAg SQ LFA provided a semi-quantitative test result in a single test in contrast to traditional semi-quantitative testing which requires serial dilutions and multiple tests.
744 EARLY FUNGICIDAL ACTIVITY AS SURROGATE ENDPOINT FOR CRYPTOCOCCAL MENINGITIS SURVIVAL

David R. Boulware1, Matt Pullen1, Katherine Hüppler Hulsie1, Joshua Rhein1, Lillian Tugume2, Edwin Nuwaggi2, Kenneth Ssebembulidze3, Mahsa Abassi1, Radha Rajasingham1, Katelyn Pastick1, Caleb P. Skipper1, Abdu Musubire3, Conrad Muzoor3, David Meyz1, for the ASTRO-CM Team

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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 (CFUs) per mL 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 (50% mortality) versus 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), 35% for EFA 0.30-0.39 (n=112), and 34% 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 EFA 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

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Background: Cryptococcal antigen (CrAg) titer 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 specimens from sequential HIV-positive patients undergoing routine CD4 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 89.8 – 95.3%) 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 1:10 (1:5 – 1:20), 1:40 (1:20 – 1:80), 1:640 (1:160 – 1:2560), and 1:5120 (1:2560 – 1:20480) 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

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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 cryptococcal meningitis or death. We compared each group for 14-day mortality via logistic regression, adjusted for Glasgow Coma Scale and CSF quantitative culture. We compared Q1 (low) to the reference Q2+Q3 group.

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 6.3-times higher for those who were CrAg+ (CI: 2.7-14.6). Among those with CD4 <100 cells/mm³, and 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 screening 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

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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 with 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), PD1L (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 risk 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
stimuli 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

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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 diagnosis >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.

<table>
<thead>
<tr>
<th>Event</th>
<th>Unadjusted Model</th>
<th>Adjusted Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Incontinence TB prevalence (N=590)</td>
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<tr>
<td>Death by 30</td>
<td>1.73 (0.58, 5.97)</td>
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</tr>
<tr>
<td>Any death</td>
<td>0.67 (0.13, 3.54)</td>
<td>0.60</td>
</tr>
<tr>
<td>Excluding TB prevalence (N=803)</td>
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<tr>
<td>Death by 30</td>
<td>1.50 (0.44, 5.31)</td>
<td>0.79</td>
</tr>
<tr>
<td>Any death</td>
<td>1.21 (0.30, 4.80)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Adjusted for age, antiretroviral use. GCS < 15 and CSF quantitative cryptococcal culture.

749 THE GLOBAL DISTRIBUTION, DRIVERS, AND BURDEN OF TALAROMYCOSIS, 1964-2017

Chuanyi Ning1, Wudi Wei1, Bo Xu1, Thanh T. Nguyen2, Nguyen Le Nhu Tung3, Jasper F. Chan4, Patrick C. Woo5, Chau V. Nguyen6, Nga N. Coo7, Kwook-Yung Yuen8, Thuy Le9, Ly T. Vo1, Thu T. Nguyen1, Thanh T. Nguyen3, Nguyen Le Nhu Tung9, Jasper F. Chan4, Patrick C. Woo5, Chau V. Nguyen6, Nga N. Coo7, Kwook-Yung Yuen8, Thuy Le9

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Background: Talaromyces marneffei infection (Tm) is a leading cause of HIV-associated morbidity and mortality in SE 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
In vitro antifungal susceptibility and antifungal treatment outcome in talaromycosis

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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, persistence fungemia, incidence of relapse and IRIS when compared to amphotericin B over six months. Itraconazole was associated with higher mortality, persistent fungemia, incidence of relapse and IRIS when compared to amphotericin B over six months.

Methods: To test our hypothesis, we developed a new AFST testing method for Tm. We followed the CLSI guidelines for broth microdilution of Tm 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 MIC50 and MIC90 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 0.008μg/mL for 6 sample replicates, and inter-assay MICs testing 6 runs on separate days were within the CLSI acceptable range of one 2-fold dilution. Among 136 isolates, 79% had MIC50=0.008 μg/mL, 16% had MIC50=0.016, and 4% had MIC50=0.03. In multiple pairwise comparisons, the differences in MIC50 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 talaromycosis 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.
CMV VIREMIA IN PATIENTS WITH ADVANCED HIV INFECTION: A 48-WEEK FOLLOW-UP STUDY

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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 T-lymphocytes (Tl). We hypothesize that immune reconstitution after initiation of antiretroviral therapy (ART), rather than anti-CMV specific treatment, is the best strategy to clear CMV viremia in patients without EOD. We aim to study the dynamics of CMV viral replication and the recovery of specific immune response against CMV after the initiation of ART. A pre-planned interim analysis of this study was presented at CROI 2017. Here we present the final results of a 48-week prospective study.

Methods: A prospective observational study including patients with HIV infection and <100 CD4 Tl was performed between September 2015 and July 2018. We determined HIV viral load (VL), CD4-Tl and CMV VL by quantitative PCR at baseline, 4, 12, 24 and 48 weeks. We determined specific immune response against CMV (QuantiFERON-CMV®) at baseline and at 48 weeks. ART was started for all patients but only patients with CMV EOD received anti-CMV treatment. Statistical analysis: Friedman’s (quantitative) and chi-square (qualitative) tests were used to assess the evolution over time.

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/µL (20-60) and median (IQR) HIV VL was 451,500 copies/mL (179,750-1,285,000). Sixteen (30.8%) patients had detectable CMV viremia at baseline, 1,285,000). Sixteen (30.8%) patients had detectable CMV viremia at baseline, 1,285,000). Thirty-seven (71.2%) patients had specific CMV immune response at baseline compared to 27 (69.2%) patients without EOD. We aimed to study the dynamics of CMV viral replication and the recovery of specific immune response against CMV after the initiation of ART. A pre-planned interim analysis of this study was presented at CROI 2017. Here we present the final results of a 48-week prospective study.

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>
<thead>
<tr>
<th>Subgroup</th>
<th>N in follow-up</th>
<th>N in EOD</th>
<th>EOD</th>
<th>CMR (HR 95% CI)</th>
<th>Responsible for</th>
<th>Adjusting for BL CD4</th>
<th>Adjusting for BL CD4 and HIV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMR</td>
<td>151</td>
<td>71</td>
<td>0.58</td>
<td>1.25 (0.95-1.64)</td>
<td>12 (0.8-1.7)</td>
<td>1.25 (0.95-1.65)</td>
<td>1.25 (0.95-1.65)</td>
</tr>
<tr>
<td>CMV</td>
<td>68.8</td>
<td>19.7</td>
<td>0.56</td>
<td>1.45 (0.99-2.1)</td>
<td>1 (1-1)</td>
<td>1.45 (0.99-2.1)</td>
<td>1.45 (0.99-2.1)</td>
</tr>
</tbody>
</table>

FOLLOW-UP STUDY

755 CHARACTERISATION OF SOUTH AFRICA’S XPERT MTB/RIF ULTRA “TRACE” LABORATORY RESULTS

Lesley Scott1, Pedro Da Silva1, Kyle Fyvie2, Gabriel D. Eisenberg3, Silence Ndlovu1, Puleng S. Marokane1, 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 IS6110/1 IS6081, 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"
identifies paucibacillary specimens that are IS6110/IS1081 positive but rpoB negative. The complexities of “trace” was explored.

Methods: Exact demographic matching was applied to NHLs’s centralised laboratory test result data between Oct17-Nov18. This generated a cohort of uniquely identified patients (UIDs) with an initial “trace” result and at least one subsequent laboratory follow-up test (Ultra, smear, culture). Results: Overall, Ultra “trace” test results contributed an additional ~2% over the national ~10% positivity rate during the review period (see Figure). A total of 3,5623 “trace” UIDs were identified with 48.7% (n=17,342) reflecting ≥1 additional laboratory follow-up test within the cohort time. Ultra was requested in 49.9% (n=8,648/17,342); culture 57.5% (n=9,964/17,342) and smear 64.2% (n=11,133/17,342) of cases. Follow-up occurred within 14 days of the first “trace” ultra result for 81.9% (n=14,208/17,342) of the cohort. Cases with a positive follow-up test were reported in 40.0% (n=6,934) of cases: 52.9% (n=4,575/8,648) Ultra; 33.8% (n=3,364/9,964) culture (with rifampicin resistance confirmation); 6.7% (n=750/11,133) smear. 60.0% of (n=10,048/17,342) UIDs generated negative follow-up results: 47.1% (n=4,073/8,648) by Ultra; 66.2% (n=6,600/9,964) culture; 93.3% (n=10,383/11,133) smear. Follow-up Ultra generated the highest proportion of positive test results.

Conclusion: Ultras “trace” category likely indicated TB disease in 40.0% of cases, which would have been undiagnosed by Xpert MTB/RIF testing, and at least 33.8% available for confirmation of rifampicin susceptibility by culture. Laboratory diagnostic algorithms can be refined to reduce testing costs and suggests clinical cohort studies are required to further explore “trace” for patient management.

Results: From Jan 2018 to Sept 2019, we enrolled 251 HIV+ inpatients. Table 1 shows baseline characteristics (median CD4 = 37 cells/ml; 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: 18% (32/176) were LAM positive, 11% (20/176) by Ultra, and 4% (6/178) positive by both assays. 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 Ultra 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.

756 URINE-BASED TB SCREENING WITH TB-LAM AND ULTRA IN HIV+ UGANDANS WITH MENINGITIS

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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+ inpatients with CD4 <100 or suspected TB. The utility of the novel Xpert MTB/Rif 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 resuspended in 2mL of urine for Ultra testing. Results were reported to clinicians in real-time.

Results: A total of 3,5623 “trace” UIDs were identified with 48.7% (n=17,342) reflecting ≥1 additional laboratory follow-up test within the cohort time. Ultra was requested in 49.9% (n=8,648/17,342); culture 57.5% (n=9,964/17,342) and smear 64.2% (n=11,133/17,342) of cases. Follow-up occurred within 14 days of the first “trace” ultra result for 81.9% (n=14,208/17,342) of the cohort. Cases with a positive follow-up test were reported in 40.0% (n=6,934) of cases: 52.9% (n=4,575/8,648) Ultra; 33.8% (n=3,364/9,964) culture (with rifampicin resistance confirmation); 6.7% (n=750/11,133) smear. 60.0% of (n=10,048/17,342) UIDs generated negative follow-up results: 47.1% (n=4,073/8,648) by Ultra; 66.2% (n=6,600/9,964) culture; 93.3% (n=10,383/11,133) smear. Follow-up Ultra generated the highest proportion of positive test results.

Conclusion: Ultras “trace” category likely indicated TB disease in 40.0% of cases, which would have been undiagnosed by Xpert MTB/RIF testing, and at least 33.8% available for confirmation of rifampicin susceptibility by culture. Laboratory diagnostic algorithms can be refined to reduce testing costs and suggests clinical cohort studies are required to further explore “trace” for patient management.

757 APPLICABILITY OF URINE LAM TEST IN ADVANCED HIV-INFECTED ADULTS IN UKRAINE

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1Lviv Regional Public Health Center, Lviv, Ukraine, 2Clinic of the Gromashevsky Institute of Epidemiology and Infectious Diseases, Lviv, Ukraine, 3Brown University, Providence, RI, USA, 4SALTUS 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), Odesa (South), Dnipro (East) and Lviv (West) regions of Ukraine. The inclusion criteria were: HIV+, ≥ 18, CD4 < 200 cells/mm3 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: From Jan 2018 to Sept 2019, we enrolled 251 HIV+ inpatients. Table 1 shows baseline characteristics (median CD4 = 37 cells/ml; 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: 18% (32/176) were LAM positive, 11% (20/176) by Ultra, and 4% (6/178) positive by both assays. 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 Ultra 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.
Conclusion: LAM urine test is useful as an add-on rapid diagnostic method in Ukraine for HIV patients with a CD4 count of <200. Sensitivity was satisfying, however, for accurate and quick diagnosis LAM should be used in combination with other TB diagnostics.

<table>
<thead>
<tr>
<th>LAM</th>
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<tr>
<td>0</td>
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</tr>
<tr>
<td></td>
<td>Frequency</td>
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<tr>
<td>0</td>
<td>790</td>
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<tr>
<td>1</td>
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</tr>
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<td>Total</td>
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</table>

759 EVALUATION OF A BLOOD-BASED ANTIGEN TEST FOR TUBERCULOSIS IN INFANTS

Liyao Mo,1 Sylvia LaCourse,1 Soyeon Kim,1 Charles D. Mitchell1, Tony Hu1 Tulane University, Metairie, LA, USA, 2University of Washington, Seattle, WA, USA, 3Harvard University, Cambridge, MA, USA, 4University of Miami, Miami, FL, USA

Background: Improved methods are urgently needed for pediatric tuberculosis (TB) diagnosis. We evaluated the performance of a blood-based assay (NanoDisk-US), which utilizes immunoenrichment and mass spectrometry to quantify a TB-specific CFP-10 peptide, for TB diagnosis in HIV-exposed South African infants enrolled in anisoniazid TB prevention trial (IMPACT P1041).

Methods: Cryopreserved sera from 519 infants (284 HIV-exposed infected [HEI], 235 HIV-exposed uninfected [HEU]) were evaluated for CFP-10 peptide expression by NanoDisk-US. At entry, all subjects were BCG-immunized, 90-120 days of age, and TB-disease-negative. They were randomized 1:1 to isoniazid or placebo and followed for up to 192 weeks for TB disease or infection. For this analysis, all children were classified as Confirmed, Unconfirmed or Unlikely TB cases using 2015 NIH TB diagnostic criteria and clinical, laboratory, histopathological, and radiological data.

Results: NanoDisk-US exhibited sensitivity for Confirmed (5/5, 100%; 95% CI: 47.8–100) and Unconfirmed (36/43, 83.7%; 69.3–93.2) TB cases in HEI, with 93.1% (203/218, 88.9–96.1) specificity. In the HEU group, NanoDisk-US detected the single Confirmed TB case and most of the Unconfirmed TB cases (15/20, 75.0%; 50.9–91.3), and had 96.2% (177/184, 92.3–98.5) sensitivity. Most (72.7%) CFP-10-positive subjects with Unlikely TB diagnoses also exhibited at least one criterion for TB diagnosis (11/15, 73.3% HEI and 5/7, 71.4% HEU). For TB cases, CFP-10 peptide could be detected in serum drawn ≤ 60 weeks before TB diagnosis, and its diagnostic sensitivity reached 83.3% (5/6, 35.9–99.6) at ≤ 12 weeks before diagnosis. CFP-10 peptide positivity and expression levels declined following anti-TB therapy initiation.


759 PROMISING COMBINED IMMUNOLOGICAL ASSAYS TO DIAGNOSE CHILDHOOD TUBERCULOSIS

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INSERM, Montpellier, France, 1University Teaching Hospital, Lusaka, Zambia, 2Institute for Medical Research and Training, Lusaka, Zambia

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 immunobaselines 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 MTB 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 In-Tube assay (QFT®) and cytokines released in supernatants were quantified using a 25-plex cytokine multiplex test and ELISA assays. Serological response directed 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 values were fixed 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 co-infected, for the control group, 70 children were enrolled, 44% being HIV co-infected. 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 Elisa/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.

760 WITHDRAWN

761LB ACCURACY OF NOVEL BLOOD ASSAY FOR IDENTIFICATION OF TB DISEASE IN PEOPLE WITH HIV

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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 combinatorial 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: Of the 201 patients included, 67 were culture-positive. At a cut-point chosen to maximize the Youden index, sensitivity was 77.6% (95% Confidence Interval [CI] 66.3–85.9), specificity was 92.2% (95% CI 86.3–95.7) and the AUC was 0.89 (0.83–0.94) against the comprehensive reference standard. Considering the Xpert-Prototype as a triage test (fixed sensitivity value closest to 90%), the corresponding specificity was 55.8% (95% CI 47.2–64.1). Comparing to Xpert® MTB/RIF alone as a confirmatory test at fixed value of sensitivity closest to 90% (90.6%), the Xpert Prototype specificity was 85.9% (95% CI 79.3–90.7). Considering the Xpert Prototype as a stand-alone diagnostic test, at a specificity of 92.2% (95% CI 86.3–95.7), the AUC was 0.94 (0.90–0.99), giving 86% sensitivity and 87% specificity.

Conclusion: In this first accuracy study of a novel blood-based host-marker assay on a commercial platform, we show the possible value of the assay for triage and potentially also for diagnosis, when a sputum sample is difficult to obtain, as often the case in PLHIV.
762LB PROSPECTIVE VALIDATION OF A BLOOD RNA TB BIOMARKER IN AMBULANT HIV-INFECTED ADULTS

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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 transcriptomic 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 based on 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 incident TB were identified through median 15 months follow-up; incidence 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 (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).

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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 TTV HAIR LEVELS AT BIRTH

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Background: Adherence to antiretroviral therapy (ART) is vital to prevention of mother-to-child transmission of HIV (MTCT) 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
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-suppressed viral loads (VL) in late pregnancy, defined as HIV-RNA ≥400 copies/mL. The median time from birth to hair collection was 4 days (IQR 1-14) and 31% of samples had TFV hair levels ≥0.038 ng/mg (equivalent to 7 doses/week). In multivariable models (Table 1), an unsuppressed VL in late pregnancy was most strongly associated with lower peripartum TFV hair levels. Attainment of high school education and not using TFV-based ART after the 1st trimester were also independently associated with lower peripartum TFV levels.

**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 TFV levels 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:** Adjusted associations of covariates with TFV concentration (N=111)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>N (%) or Median (IQR)</th>
<th>% Change (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART regimes containing 3 or more classes</td>
<td>90 (90%)</td>
<td>11.7 (IQR 66-89, 77)</td>
<td>0.75</td>
</tr>
<tr>
<td>Gestational age (weeks per one-week increase)</td>
<td>30 (30-37)</td>
<td>-6.1 (IQR -21.1, 6.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>INSTI use during pregnancy</td>
<td>42 (42%)</td>
<td>41.2 (IQR -0.0, 10.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Latest HIV RNA (copies/mL) during pregnancy ≥400</td>
<td>9 (9%)</td>
<td>-75.1 (IQR -44.5, -9.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Achieved at least high school graduation</td>
<td>70 (70%)</td>
<td>-39.5 (IQR -4.5, 0.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>TFV exposure in the 1st trimester (mg/kg)</td>
<td>6 (6%)</td>
<td>-15.6 (IQR -8.3, 0.7)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**Note:** Estimated percent change in TFV concentration per unit increase in continuous covariate measure; or 2) between exposure groups with a categorical covariate (the reference group for peripartum comparisons). Covariates with p-value <0.3 in univariate analysis were included in the multivariable model.

**765 EARLY POSTPARTUM VIREMIA PREDICTS LONG-TERM NONSUPPRESSION AND INFANT TRANSMISSION**

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**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:** 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). TFV hair levels at birth. Over two-thirds of WLHIV had TFV levels 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.

**Results:** In 323 women (median age 28y, 40% with a history of ART), antenatal VL was taken at a median gestation of 33w (IQR 30-36), and at that time, 89.2% of women had ≥1 unsuppressed VLs (95%CI 68.0-849.8, p<0.001) 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.

**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.

**Table 1:** Detectable VL, measured after 24 months of ART (N=424)

<table>
<thead>
<tr>
<th>Time</th>
<th>VL &lt;100 copies/mL</th>
<th>VL 100-400 copies/mL</th>
<th>VL &gt;400 copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 months</td>
<td>30</td>
<td>6</td>
<td>22</td>
</tr>
</tbody>
</table>

**766 VIRAL LOAD MONITORING IN PREGNANCY TO PREDICT PERIPARTUM VIREAEMIA IN SOUTH AFRICA**

Jasantha Odayar1, Siti Kabanda1, Thokozile R. Malaba1, Maia Lesskey1, Landon Myer1
1University 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 subgroups of gestation at antenatal VL and prior ART exposure.

**Results:** In 323 women (median age 28y, 40% with a history of ART), antenatal VL was taken at a median gestation of 33w (IQR 30-36), and at that time, 89.2% of women had ≥1 unsuppressed VLs (95%CI 68.0-849.8, p<0.001) 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.

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**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

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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 working 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, stillbirths, 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

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1Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA, 2Ministry of Health, Maseru, Lesotho, 3George Washington University, Washington, DC, USA

Background: Antiretroviral therapy (ART) in persons living with HIV (PLWH) 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 (WBTH) 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 pathological bone mobilisation but HIV+ve women had greater decreases in TH, FN and WBTH 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 WBTH 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 WBTH 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.

769 HIGH BLOOD PRESSURE AND ADVERSE BIRTH OUTCOMES IN HIV+ AND HIV– SOUTH AFRICAN WOMEN

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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.

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Figure 1: Change in aBMD during and after lactation in HIV+ and HIV- Ugandan women

HIV-ve: HIV-negative women (ART naive); HIV+ve: HIV-positive women initiated on lifelong ART during pregnancy (Option B+ ART, TDF-3TC-EFV, previously ART naive); aBMD = areal bone mineral density (g/cm²); WHBTH = whole body-less-head, SI = standard error, L02 = 2 weeks of lactation, L14 = 14 weeks of lactation, L26 = 26 weeks of lactation, NPNL = non-pregnant non-lactating, LS = lumbar spine aBMD, FN = femoral neck aBMD, WBTH = whole body less head aBMD. Values were transformed into normal g/cm² using Box-Cox maximum likelihood method. Outliers were identified and每人 investigated. The number of subjects in each group is sufficient for the results shown here. No significant differences were found among the groups.

Variables were mutually adjusted in multivariate regression models (SAS proc logistic). The results indicate that high BP is associated with an increased risk of adverse birth outcomes in HIV+ women on ART.
Methods: We followed a cohort of HIV- and HIV+ pregnant women initiating TDF+3TC+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 (<120/80mmHg), elevated (120–129/<80), stage 1 (>130–139/or >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+ 53%) 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 1: The relationship between high (elevated or higher) blood pressure (BP) levels in normal BP at entry into antenatal care and adverse birth outcomes in HIV+ pregnant women in Cape Town, South Africa, overall and by HIV status.

<table>
<thead>
<tr>
<th>BP Status</th>
<th>Overall</th>
<th>HIV+ (n=575)</th>
<th>HIV- (n=541)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>Normal BP (N=700)</td>
<td>1.00</td>
<td>0.94 (0.56-1.54)</td>
<td>1.00 (0.62-1.61)</td>
</tr>
<tr>
<td>High BP (N=416)</td>
<td>1.00</td>
<td>1.00 (0.62-1.61)</td>
<td>1.00 (0.62-1.61)</td>
</tr>
<tr>
<td>LBW</td>
<td>1.00</td>
<td>1.00 (0.62-1.61)</td>
<td>1.00 (0.62-1.61)</td>
</tr>
<tr>
<td>SGA</td>
<td>1.00</td>
<td>1.00 (0.62-1.61)</td>
<td>1.00 (0.62-1.61)</td>
</tr>
<tr>
<td>PTD</td>
<td>1.00</td>
<td>1.00 (0.62-1.61)</td>
<td>1.00 (0.62-1.61)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.00</td>
<td>1.00 (0.62-1.61)</td>
<td>1.00 (0.62-1.61)</td>
</tr>
</tbody>
</table>

N=Number observed. OR=Odds ratio. CI=Confidence interval. "Elevated BP" is defined as per JNC 8 guidelines: systolic blood pressure >130 or diastolic blood pressure >80, any BMI, and any age. "Abnormal BP" includes stage 1 hypertension (>130–139/80–89, 95% CI 1.04-1.49) and stage 2 hypertension (>140/90."

The Mantel-Haenszel χ² test was used to assess group associations with HIV/ART status and pregnancy outcome. Multinomial regression assessed BP trajectory group associations with HIV/ART status and pregnancy outcome. We used a 5% significance level for each individual group association. "Low normal relative to consistent normal" group was the reference group for all analysis. In the multivariable analyses, we adjusted for maternal age, estimated pre-pregnancy body mass index (BMI), gravidity, socioeconomic status, and alcohol use and education. Additionally, we adjusted for estimated preterm birthweight (PTD). "Low normal relative to consistent normal" group was the reference group for all analysis. In the multivariable analyses, we adjusted for maternal age, estimated pre-pregnancy body mass index (BMI), gravidity, socioeconomic status, and alcohol use and education. Additionally, we adjusted for estimated preterm birthweight (PTD).

Figure 1: Joint antenatal and delivery group trajectory membership.

770 BLOOD PRESSURE TRAJECTORIES AND ASSOCIATED FACTORS IN PREGNANT HIV– AND HIV+ WOMEN

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Background: Blood pressure (BP) levels are associated with maternal and fetal outcomes. While associations between antenatal BP and adverse birth outcomes have been documented, little is known about BP trajectories across gestation and their association with pregnancy outcome.

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+3TC+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 modified Poisson regression to determine preterm delivery (PTD) and low birthweight (LBW).

Results: Of 1583 women (median age 28y; median gestation at 1st ANC 18w), 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 2.04, 0.94-4.15). 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 1.35, 1.28-1.43).

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

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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: DoPHIn-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/m², respectively, with no differences between trial arms but higher third trimester weight in SA (mean, 81 kg) versus Ugandan (mean, 68 kg) 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...
6w PP was -5.9 kg, with mean weight approximately constant from 6 to 48w PP. However this masked notable inter-site differences. In Uganda, there was a small non-significant decrease in mean weight from 6 to 48w PP that was more marked in the EFV arm (DTG: 65.6 to 63.2 kg; EFV: 60.6 to 59.8 kg; p = 0.28). In SA, there was a notable but non-significant increase in mean weight over the same period that was more marked in the DTG arm (DTG: 76.1 to 78.3 kg; EFV: 73.0 to 73.7 kg; p = 0.33). After adjusting for site and enrolment weight, the overall mean difference in weight change, 48w-6w PP for DTG-EFV was 1.00 kg (95% CI: -0.98 to 2.97; p = 0.32). This difference was larger in SA (1.30 kg; 95% CI: 2.21 to 4.80) than in Uganda (0.75 kg; 95% CI: 1.48 to 2.97; p for interaction = 0.82). Similar findings were observed for BMI throughout.

Conclusion: These randomised data show no differences in PP weight changes between DTG and EFV in women initiating ART late in pregnancy. Substantial PP weight gain among SA women points to potential heterogeneity across populations that requires further investigation.

DOLUTEGRAVIR USE IS ASSOCIATED WITH HIGHER POSTPARTUM WEIGHT COMPARED TO EFAVIRENZ

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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 HIVART 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 (β=2.4 for DTG vs. EFV, p=0.04).

Conclusion: Weight gain in pregnant women enrolled in the Tshilo Dikotla study was more marked in the DTG arm, particularly during 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).

OBESITY, GESTATIONAL WEIGHT GAIN, AND ADVERSE BIRTH OUTCOMES IN SOUTH AFRICAN WOMEN

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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+ women. Among HIV+ women, ART at conception (β=2.4 for DTG vs. EFV, p=0.04).

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 (β=2.4 for DTG vs. EFV, p=0.04).

Conclusion: Weight gain in pregnant women enrolled in the Tshilo Dikotla study was more marked in the DTG arm, particularly during 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).

Confounding risk factors were adjusted for in the analysis. Among WHIV, women on EFV had a higher proportion of LBW births (β=5.0, p<0.01) after adjusting for age, GDM, breastfeeding duration, and weight gain between 2nd and 3rd trimester. (Fig) Further studies to assess mechanisms of postpartum weight retention are needed.

| Table 1: Association between obesity, high GWG and adverse birth outcomes among HIV+ women with two singleton births in the overall and subset cohorts in Cape Town, South Africa |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  |                |                |                |                |                |                |
|                  | Obesity (BMI ≥30 kg/m²) | High GWG (≥5 kg) |               |                |                |                |
|                  | Normal (n = 238) | Obese (n = 237) | Normal (n = 350) | Obese (n = 352) |
| Birth weight (g) | Normal (0.01) | Obese (0.01) | Normal (0.01) | Obese (0.01) |
| Low (<2500)  | 1.00 (Ref) | 1.30 (1.04-1.55) | 1.00 (Ref) | 1.30 (1.04-1.55) |
| High (>2999) | 1.00 (Ref) | 3.55 (2.74-4.62) | 1.00 (Ref) | 3.55 (2.74-4.62) |
| p-value | 0.050 | 0.050 | 0.050 | 0.050 |
| Size for GA (cent) | Normal (0.01) | Obese (0.01) | Normal (0.01) | Obese (0.01) |
| Small (<10%) | 1.00 (Ref) | 1.90 (1.05-3.37) | 1.00 (Ref) | 1.90 (1.05-3.37) |
| p-value | 0.001 | 0.001 | 0.001 | 0.001 |
| Large (>90%) | 1.00 (Ref) | 3.55 (1.87-6.73) | 1.00 (Ref) | 3.55 (1.87-6.73) |
| p-value | 0.023 | 0.023 | 0.023 | 0.023 |
**774** FACTORS ASSOCIATED WITH GESTATIONAL DIABETES IN HIV+ AND HIV− WOMEN IN PUNE, INDIA

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**Background:** Pre-pregnancy BMI (24.1 vs 21.2 kg/m², p=0.00) was 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− women among the whole cohort. A case-control study was then done to identify risk factors. Women with a positive OGTT were matched to controls based on HIV status and age in a 1:4 ratio.

Demographics were compared between cases and matched controls via chi-square or Mann-Whitney U test. Univariate and multivariate logistic regression was used to determine factors associated with GDM.

**Results:** Among enrollees, 11 (13.9%) of 79 HIV+ and 10 (6.5%) of 155 HIV− had GDM (p=0.06). In the case control study of the 21 HIV+ and 74 matched non-GDM controls, median pre-pregnancy BMI was 21.7 kg/m² (IQR 19-24.2). Median CD4 in HIV was 420 cells/mm³ (IQR 328-505), 5 (1.1%) were on protease-inhibitor (PI)-based antiretroviral therapy (ART), and 37 (82%) were on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART. Weight (54.3 vs 48.9 kg, p=0.02) at study entry, MUAC (26.4 vs 23.7 cm, p=0.04) at study entry, and pre-pregnancy BMI (24.1 vs 21.2 kg/m², p=0.00) was significantly higher among cases than controls. Among HIV+, weight at study entry and 3rd trimester, 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 among HIV+ but not HIV− participants. Ongoing studies are identifying the pathogenesis behind this increased risk.

**775 CABOTEGRAVIR PHARMACOKINETIC TAIL IN PREGNANCY AND NEONATAL OUTCOMES**

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**Background:** Cabotegravir (CAB) is a long-acting (LA) HIV integrase inhibitor in Phase 3 development for HIV treatment in combination with rilpivirine LA, and as monotherapy for HIV prevention. Injectable CAB LA, given monthly or every 2 months, maintains plasma concentrations that may persist for a year or longer following discontinuation. Nonclinical reproductive toxicology studies of CAB have not identified a birth defect risk at supertherapeutic exposures. We evaluated CAB pharmacokinetics (PK) in HIV-infected women becoming pregnant and neonatal outcomes to date in ViIV-Sponsored trials.

**Methods:** As of December 7, 2018, ≥ 594 HIV-infected or un-infected females of reproductive potential have been exposed to ≥1 dose of CAB (oral/LA) through Phase 3 in ViIV-sponsored clinical trials. Per protocol, CAB troughs were obtained pre-injection with dosing discontinued upon pregnancy detection, however PK sampling continued quarterly for 52 weeks after last injection. Available CAB PK collected pre-pregnancy and during long-term follow-up to evaluate the PK tail during pregnancy, delivery, and post-partum were summarized with birth outcomes.

**Results:** Thirteen pregnancies were reported during CAB dosing (4 oral CAB; 9 CAB LA), 4 resulting in live births (1 in DADIS HPTN077 study; conception post CAB LA discontinuation), 5 terminated electively, and 4 with miscarriage in first 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: 2-23 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.

**Fig 1.** Preferred strategy for infant prophylaxis at a cost-effectiveness threshold of ICER <$900/YLS.

### 777 COST-EFFECTIVENESS OF BROADLY NEUTRALIZING ANTIBODIES FOR INFANT HIV PROPHYLAXIS

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**Background:** Injectable infant prophylaxis with a broadly neutralizing antibody (bNAb) could help overcome gaps in the prevention of vertical HIV transmission cascade by providing long-acting protection from postnatal transmission, but there are few insights into the potential cost-effectiveness of this strategy.

**Methods:** Using the Cost-effectiveness of Preventing AIDS Complications (CEPAC)-Pediatric model, we simulated children known to be HIV-exposed by birth through death in South Africa. We compared four strategies: standard of care oral prophylaxis for 6–12 weeks per WHO guidelines (SOC), and oral prophylaxis plus a bNAb given at birth (bNAb birth), birth and 3 months (bNAb birth +3 m), or every 3 months throughout breastfeeding (bNAb extended). Base-case model inputs, varied in sensitivity analyses, included: prophylaxis uptake (oral: 50–86%, bNAb: 54–96%, each by month postpartum), preventive efficacy (oral: 90%, bNAb: 80%), duration of effect (bNAb: 3m), costs (oral: $7–11/m, bNAb: $60/dose), and mean breastfeeding duration (both: 6m).

**Results:** All bNAb strategies led to lower total pediatric HIV incidence and extended remained the preferred strategy and was cost-effective: ICER <$900/YLS. 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). MITC 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 MITC.

**Conclusion:** Our results from a large ART clinic in Zimbabwe do not confirm findings from a US-based cohort where MITC 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.

**Fig 2.** Simulated mean time to MTCT by strategy, ICER = $420/YLS.

### 778 RISK OF VERTICAL TRANSMISSION FROM MOTHERS WITH PERINATAL HIV INFECTION IN ZIMBABWE

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**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 on 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 on 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). MITC 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 MITC.

**Conclusion:** Our results from a large ART clinic in Zimbabwe do not confirm findings from a US-based cohort where MITC 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.

**Fig 3.** Simulated mean time to MTCT by strategy, ICER = $420/YLS.
HIV SEROCONVERSION DURING PREGNANCY AT ROUTINE ANTENATAL CARE CLINICS IN BOTSWANA

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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). Of those, 28% (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% citizens 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.

TRENDS IN MARIJUANA, ALCOHOL, AND OPIOID USE IN PREGNANT AND POSTPARTUM HIV+ WOMEN

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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 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.
**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.

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**Maternal Risk Stratification to Identify High-Risk Infants for HIV Birth Testing**

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**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 87.2% (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.
EVALUATION OF PERFORMANCE AND USABILITY OF CEPHED XPERT HIV-1 QUAL ASSAY IN MALAWI

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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 in 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, usability and acceptability of Cepheid Xper HIV-1 Qual assay (XPRT 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 XPRT HIV. DBS were prepared for HIV PCR testing at a central facility, Queen Elizabeth Central Hospital (QECH). As a standard procedure for EID testing DBS were also sent to Thyolo District Hospital (TDH) for testing by PCR. We compared the sensitivity and specificity between Xpert HIV and PCR. We also compared the median TAT between Xpert HIV from MDH and PCR from QECH and TDH. Acceptability of Xpert HIV was evaluated among caregivers and nurses.

Results: Of 600 participants, 324 (54%) were female. 272 (45.3%) were aged over 5 years, 227 (37.83) between 1-5 years and 101 (16.83%) <1 year. Most of the participants SBS (97.5%) were HIV non-infected. A total of 15 participants were diagnosed with HIV. Most HIV positives aged >1 year (11/13 (85%)) started antiretroviral therapy in 1 day and 4/15 (44.44%) of all HIV positives were lost to follow-up. Sensitivity and specificity of XPRT HIV versus PCR at QECH were 100% (95% CI: 78.2 - 100%) and 100% (95% CI: 99.4 - 100%), respectively. Xpert HIV had the shortest median TAT from time of blood test (median = 5.34 hours (95% CI: 78.2 - 100%) and 100% (95% CI: 99.4 - 100%), respectively. Xpert HIV was evaluated among caregivers and nurses.

Conclusion: These results suggest that implementing Xpert HIV may improve EID and linkage into HIV care.

EARLY INFANT DIAGNOSIS: STRENGTHEN EXISTING SYSTEMS OR INVEST IN POINT-OF-CARE?

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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 programmatically 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 ($2/71/0.06%), and total cost/ test ($17.09/$29.80/$31.26), which included transport, salary, training, and maintenance costs derived from a resource utilization analysis in Zimbabwe. Monthly cost of HIV care and ART varied by age, CD4 count, regimen, and weight. We projected life expectancy (LE) and average lifetime per-person cost for all HIV-exposed infants, including those who did and did not acquire HIV. We calculated incremental cost-effectiveness ratios (ICERs) from discounted (3%/year) LE and cost results in S/5/year-of-life saved (YLS), defining cost-effective as an ICER <$1,330/YLS (Zimbabwe per-capita GDP). In multi-way sensitivity analyses, we varied differences between S-LAB and POC in: result return probability, result return time, and cost.

Results: For infants who acquired HIV, LAB/S-LAB/POC led to projected one-year survival of 61/70/76% and uncounted LE of 21.7/22.7/24.1 years. For all HIV-exposed infants, uncounted LE was 63.4/63.3/63.42 years, and undiscounted costs of $330/$360/$390 per infant. S-LAB was dominated in cost-effectiveness analysis; the ICER of POC vs. LAB was $870/YLS. In multi-way sensitivity analyses, S-LAB was only cost-effective if it cost $10 less than POC, had the same result return probability as POC, and had 10-day result return time (Figure).

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% in 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, RR 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 across randomisation groups at 349 (49%) retained at six months (180/226 VL suppressed), 151 (21%) at 12 months (93/114 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 Rodriguez 1, Pablo Rojo Conejo 1, Maria G. Lain 2, Afaaf Sara Dominguez Rodriguez 1 , Pablo Rojo Conejo 1, Maria G. Lain 2, Afaaf
Liberty 3, Shaun Barnabas 4, Elisa López Varela 5, Kennedy N. Otwombe 3, Siva Soweto, South Africa, 4Tygerberg Hospital, Cape Town, South Africa, 5ISGlobal, 18-months child antibody test, postpartum maternal retention in HIV care and 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.

788 IMPROVED HEMATOLOGICAL OUTCOMES WITH NEVIRAPINE FOR INFANT HIV POSTNATAL PROPHYLAXIS
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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 HIV-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, 62.5% in ZDV group). Median hemoglobin levels were respectively 17.4 g/dL vs 17.0 at birth (p=0.49), 11.7 vs 11.5 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% 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

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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: CAIS hESCs were cultured (n=5 independent experiments) in the presence of 0.1% DMSO or 1X Cmax of the following regimens: DTG, raltegravir (RAL), bictegravir (BIC), cobicistat-boosted 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.

ESTIMATES OF PERICONCEPTIONAL EXPOSURES TO INTEGRASE INHIBITORS UNITED STATES

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Background: In 2018, an increased risk of neural tube defects among infants with periconceptional dolutegravir (DTG) exposure was reported from Botswana, triggering changes to global treatment guidelines for women and limiting access to DTG. Estimates of periconceptional integrase inhibitor (INSTI) exposures are needed to understand the potential to study the impact of INSTI use on pregnancy and birth outcomes in the United States.

OUTCOMES FOLLOWING PRENATAL EXPOSURE TO DOLUTEGRAVIR: THE DOLOMITE-EPPICC STUDY

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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 use 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 on 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 on women ART increased steadily with 1% exposed in 2007 and 61% in 2016. In 2016, among 1,355-1,959 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.

Estimated percentage of INSTI exposures among women on antiretroviral therapy at pregnancy conception, United States, 2007-2018

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conduct. 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 29/6WG 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 39/6WG (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 23/6WG) 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.

792 CHANGES IN DTG USE FOLLOWING THE NTD SAFETY SIGNAL IN BOTSWANA

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Background: In May 2018 a preliminary safety signal for neural tube defects (NTD) among women on dolutegravir (DTG) at conception led to in-country guidance for individualized counseling for pregnant women who had already conceived on DTG and women on DTG or starting antiretroviral treatment (ART) who desired pregnancy; DTG-based ART otherwise remained the recommended regimen for new ART starts. We evaluated patterns of DTG use before and after this guidance.

Methods: This is a secondary analysis of data abstracted from Aug 2016–Sept 2019 in the Tsepamo birth outcomes surveillance study. HIV diagnosis date, ART regimens taken before or during pregnancy and dates of ART initiation and discontinuation were collected from all women living with HIV who delivered at study sites. Botswana national HIV treatment guidelines recommended DTG-based ART from May 2016 onward, with updated guidance related to pregnancy intention issued in May 2018.

Results: Among 20,254 women living with HIV who delivered from Aug 15, 2016–Aug31, 2019, 13,205 (65.2%) were on ART prior to conception, 5,718 (28.2%) started ART during pregnancy, 904 (4.5%) received no ART and 427 (2.1%) had unknown timing of ART start. The proportion of deliveries with DTG conception exposure increased steadily during the study period to a maximum of 30% in 10/2018 (Figure 1a). Among women who likely conceived in the 5 months after the May 2018 guidance, 27% of confinements were on DTG-based ART, which was unchanged from 28% in the 5 months prior to the guidance. Before May 2018, 97% of women initiating ART in pregnancy started DTG-based ART (1.7% <6 weeks gestational age) (Figure 1b). After May 2018, only 43% of starts in pregnancy were DTG-based ART (1.6% <6 weeks gestational age), and 56% started EFV-based ART. Among 441 who changed ARVs during pregnancy, 177 (40%) switched from DTG-based ART to EFV-based ART (99% after May 2018). Only 71 (0.4%) women completely discontinued ART during pregnancy, including 35 women on DTG and 24 on EFV.

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.

793 METABOLITES, PRETERM LABOR, AND ANTIRETROVIRA THERAPY

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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, 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 30.1 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 increased included increased levels of 17a-hydroxyprogrenalone glucuronide, methionine sulfone, pantetheinate, and urate. In the PI group was associated with increased nucleotide and amino acid metabolism (7-methylguanine, N2,N2- dimethylguaninosine, N-acetylpurinesine, 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: In this exploratory study of HIV infected gravidas receiving ART, untargeted metabolomics identified perturbations in both steroid hormone metabolism and nucleotide/amino acid metabolism that predict PTB. Untargeted metabolomics may be an effective strategy for identifying potential mechanisms of PTB associated with ART, and warrants further investigation.
GENITAL TRACT & PLASMA CYTOKINES & SYSTEMIC T-CELL ACTIVATION IN HIV+ PREGNANT WOMEN

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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 on 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, CD6, HLA-DR and CD25. Maternal characteristics, immunologic parameters and pregnancy outcome were recorded. Gradients were compared by HIV status, ART 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<0.001, 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 (rho=0.28, p=0.01) and immune-regulatory IL-13 (rho=0.23, p=0.04); CD25 + T cell subsets associated inversely with IL-1β gradient (CD4+CD25+%; rho=0.30, p=0.003; CD8+CD25+%; rho=0.26, p=0.03); CD4:CD8+ ratios correlated positively with IL-2 gradient (rho=0.25, p=0.02) and CD4+HLA-DR+% correlated inversely with IL-2 gradient (rho=0.28, p<0.01). In this small sample no association between genital-plasma cytokine gradient with cART exposure or gestational age at delivery was observed.

Conclusion: HIV infected women have elevated genital mucosal cytokine gradients compared to uninfected women during the 2nd trimester pregnancy notably IL-1β and IL-8; both known for their role in preterm labour initiation. Activated CD25+T cell subsets were inversely correlated with IL-1β suggesting a regulatory role in genital inflammation. The role of genital inflammation and its regulation warrants further investigation in adverse pregnancy outcomes in HIV infected women.

Table: Median genital-plasma cytokine gradients during second trimester by HIV status

<table>
<thead>
<tr>
<th>Cytokine gradient Medics</th>
<th>HIV infected pregnant</th>
<th>Uninfected pregnant</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>172.0 (115.0-334.0)</td>
<td>85.0 (56.0-160.0)</td>
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</tr>
<tr>
<td>IL-6</td>
<td>172.0 (115.0-334.0)</td>
<td>85.0 (56.0-160.0)</td>
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<td>IL-8</td>
<td>172.0 (115.0-334.0)</td>
<td>85.0 (56.0-160.0)</td>
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<tr>
<td>TNFα</td>
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<td>85.0 (56.0-160.0)</td>
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<tr>
<td>IL-12</td>
<td>172.0 (115.0-334.0)</td>
<td>85.0 (56.0-160.0)</td>
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<tr>
<td>IL-18</td>
<td>172.0 (115.0-334.0)</td>
<td>85.0 (56.0-160.0)</td>
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<td>IL-8</td>
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<td>85.0 (56.0-160.0)</td>
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<tr>
<td>IL-12</td>
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<td>85.0 (56.0-160.0)</td>
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<tr>
<td>IL-18</td>
<td>172.0 (115.0-334.0)</td>
<td>85.0 (56.0-160.0)</td>
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</tbody>
</table>

MATERNAL BIOMARKERS OF ENDOTHELIAL DYSFUNCTION BY HIV/ART STATUS AND BIRTH OUTCOMES

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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 logCV biomarker 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 (VCAM-1), but not with other markers (ICAM-1 nor E-selectin) in pregnancy. Markers of endothelial activation were not associated with SGA or stillbirth.
using liquid chromatography-mass spec and quantified against standard curves with a lower limit of 0.025 ng. 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 by 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.

796 MATERNAL AND CORD PLASMA BIOACTIVE EICOSANOID PROFILES DIFFER IN HIV+ AND HIV− WOMEN
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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

797 BREASTMILK MICROBIOME/VIROME OF HIV+ KENYAN WOMEN IS NOT ALTERED BY IMMUNOSUPPRESSION
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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 >500. 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>500 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 bacteriophage families: Myoviridae (20.7%), Siphoviridae (11.6%) and Podoviridae (3.4%). Other eukaryotic viruses detected include papillomaviruses and anelloviruses. 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

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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 0.04]). 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. To our knowledge this is the first cohort study to examine the neuroanatomy of HEU neonates. These findings are consistent with brain regions reported to be affected in HIV-infected children and suggest that HIV/ART exposure may impact brain structural development during pregnancy.

799 POSTNATAL LPV/EXPOSURE, GROWTH, AND NEUROPSYCHOLOGICAL OUTCOMES AT SCHOOL AGE

Nicolas Nagent1, Manisola Singata1, Amandine Courmil2, Joyce Nalugya3, Souleymane Tassembedo4, James Turnwine1, Nicolas Meda4, Chipepo Kankasa6, Makanani6, Lillian Wambuzi Ogwang7, Taha E. Taha2, Mary Glenn Fowler8, for the PROMOTE study team
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Background: In the ANRS 12174 randomized controlled trial, HIV-exposed uninfected African neonates who received lopinavir-ritonavir (LPV/r) prophylaxis for one year exhibited slower growth from birth to week 50 compared with those receiving lamivudine (3TC). We assessed whether this difference in growth persisted over time, and was accompanied by differences in neuropsychological and clinical outcomes.

Methods: Between February 2017 and February 2018, we conducted a cross-sectional clinical evaluation among former trial participants who completed the 50-week follow-up and who were not HIV-infected. In addition to HIV testing and clinical examination, neuropsychological outcomes were assessed using the Kaufman Assessment Battery for Children, 2nd edition (KABC-II), Tests of Variables of Attention (TOVA), the Movement Assessment Battery for Children, second edition (MABC-2), and the caregiver-reported Strengths and Difficulties questionnaire (SDQ).

Results: Of 1101 eligible children, aged 5 to 7 years, 553 could be traced and analysed (274 in the LPV/r and 279 in the 3TC groups). Changes from baseline value in height-for-age, body mass index and weight-for-age Z-scores, were greater in the LPV/r group compared to the 3TC group (estimated differences ranging from 0.19 to 0.30), but Z-scores did not differ between groups at follow-up.

Conclusion: The impact of LPV/r on growth did not persist over time after drug discontinuation. At school age, children exposed to LPV/r and 3TC at birth for one year had comparable growth and neuropsychological outcomes without evidence of long-term side-effects of LPV/r. It provides reassuring data on clinical outcomes for all HIV-infected children treated with this antiretroviral in early life.

800 MALNUTRITION IN HIV-EXPOSED UNINFECTED CHILDREN IN LONG-TERM OBSERVATIONAL FOLLOW-UP

Lynda Stranix-Chibanda1, Jim Aizire2, Nonhlanhla Yende-Zuma2, Haseena Cassim1, Sherika Hanley1, Tsolelailo Hamadzirirwa3, Lucky Makanakos4, Nilton Ximenes5, Lillian Wambuzi Ogwang7, Taha E. Taha2, Mary Glenn Fowler8, for the PROMOTE study team
1University of Zimbabwe, Harare, Zimbabwe, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3CAPRISA, Durban, South Africa, 4Perinatal HIV Research Unit, Soweto, South Africa, 5University of North Carolina Project–Malawi, Lilongwe, Malawi, 6University of Malawi, Blantyre, Malawi, 7Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, 8Johns Hopkins University School of Medicine, Baltimore, MD, USA

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 use, size of the house).

Results: Of the 1459 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 4894 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 multicountry 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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Malawi (n=1,050)</th>
<th>South Africa (n=1,029)</th>
<th>Upgrade or C+XTC+EFV (n=1,031)</th>
<th>Zidovudine (n=999)</th>
<th>TOTAL (n=3,188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children</td>
<td>1050 (100%)</td>
<td>1029 (100%)</td>
<td>1031 (100%)</td>
<td>999 (100%)</td>
<td>3188 (100%)</td>
</tr>
<tr>
<td>Mean weight for age score &lt;5th percentile</td>
<td>0.40 (0.36)</td>
<td>0.41 (0.39)</td>
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<td>0.38 (0.36)</td>
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<tr>
<td>Mean height for age score &lt;5th percentile</td>
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<td>0.42 (0.41)</td>
<td>0.44 (0.42)</td>
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</table>

802 DISTINCT CORD C-PEPTIDE, ADIPOKINE, AND LIPIDOMIC SIGNATURES BY IN UTERO HIV EXPOSURE

Jennifer Joo1, Lauren Balment1, Shan Sun1, Thomas Kraus1, Brian Kirmse1, Mitchell Geffner2, Yupeng Qiu3, Stephen M. Arpadi3, Elaine J. Abrams3, Derek LeRoith4, Rhoda Sperling1, Irwin J. Kurland4

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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 HEU and HIV-unexposed uninfected (HUU) infants using multiplex ELISA. Demographic, clinical, and in utero antiretroviral therapy (ART) exposure data were collected. Metabolites and lipid subspaces 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 subspaces discriminate between HEU and HUU infants. Elastic net regression was used to identify factors including metabolites and lipid subspaces 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= -0.04, p<0.01) but not HEU. 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 subspaces. (Fig) Elastic net regression identified pre-pregnancy BMI and complex lipids with polyunsaturated side chains to be positively associated with cord C-peptide in both groups. However, in HEU but not HUU infants, arachidonic acid and microbial derivatives of tyrosine and tryptophan were associated with C-peptide.

Conclusion: Compared to HUU, HEU infants manifest with insulin resistance. Differences in cord metabolite, lipid subspaces, & adipokines are significant between HEU and HUU infants, suggesting altered fetal metabolic programming due to in utero HIV exposure.
MORE SEVERE DISEASE IN HOSPITALIZED HIV-EXPOSED UNINFECTED VS HIV-UNEXPOSED NEONATES

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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.

INFECTIOUS MORBIDITY OF BREASTFEEDED, HIV-EXPOSED UNINFECTED INFANTS IN SOUTH AFRICA

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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, breastfed 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 CD4 count, 354 cells/µL; HIV viral load, HIV-VL 4.0 log10 copies/ml; gestation, 22 weeks) were followed for median 12 months. HU (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 1.64–8.30]), 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<4.0 log10 copies/ml; 15/88/100 cy [95%CI 5.1–12.49–23]) 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≥4.0 log10 copies/ml; 60/44–100 cy [95%CI 15.18–107.74]; IRR vs HU, 4.14 [95%CI 1.27–13.44]). Reduced rates were seen among exclusively breastfed, timely-vaccinated HEU infants (n=165;16/82/100 cy [95%CI 5.08–18.78]; IRR vs HU, 1.72 (95% CI 0.53–5.91).

Conclusion: Despite ART in pregnancy, breastfed 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.
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, v. 3.5.2.

**Results:** Alpha diversity tended to be lower in HEU compared to HUU infants. In contrast, maternal HMO alpha diversity tended to be increased in HIV-negative mothers. In HEU infants, negative correlations were observed between Bifidobacterium breve and L-ornithine, Bacteroides vulgatus and LNFP II, Bacteroides fragilis and several other HMO including 2'FL, 3'SL, DFLNT, FLNH, LNFP I, as well as total HMO concentration. Escherichia coli was negatively correlated with DFLNH, DFLNT, and LNFP I, but had a positive correlation with LNFP II (FDR-adjusted p < 0.1). In HUU infants, the correlations were different: Bifidobacterium bifidum was negatively correlated with DFLNH, B. breve was negatively correlated with LNt and LST, and Bacteroides fragilis was positively correlated with LSTb (p < 0.1). Correlations of pathways assessed by HUMAnN2 were found between chorismate biosynthesis I (found in B. fragilis and Akkermansia muciniphila) and L-ornithine (found in B. breve and Bifidobacterium longum) and 3'FL, 3'SL, and DFLNT (p < 0.1).

**Conclusion:** Maternal HIV status modulates the associations between HMO profile and infant microbiota. These differential correlations suggest that bacterial utilization of HMO differs in HEU infants which may, in turn, contribute to altered GI and immune development and increased mortality of HEU infants.

**806 POOR OUTCOME IN EARLY TREATED HIV PERINATALLY INFECTED INFANTS IN AFRICA**

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**Background:** HIV-infected infants should be treated early after diagnosis. Mortality and morbidity peak in the first 6 months after ART initiation and in infants <1-year-old. Mortality is linked to advanced disease at diagnosis. There are few data about determinants of poor outcome in early-treated infants. The aim is to assess risk factors for poor outcome despite early ART in a cohort of infants in South Africa and Mozambique.

**Methods:** EARTH is a multi-centre cohort enrolling HIV-infected infants diagnosed and treated in the first 3 months of life. Enrolment started in May 2018. ART regimens followed national guidelines. Poor outcome was defined as mortality or severe disease (progression to WHO clinical stage 3 or 4 or CD4 below 25%). Risk factors for poor outcome and viral load (VL) suppression adjusting for socio-demographics, clinical, immunological and virological measures were 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) < −250. Prophylaxis after birth was prescribed to 80%. Median baseline VL was 5.1 logs (3.6–6.1). Median baseline CD4 was 35% (26.3–44.4). During the follow-up, 46% of mothers had health issues or serious life events but no mortality. 12 (9%) of infants died, 7 (5%) progressed to stage 3 or 4, and 16 (12%) had CD4 < 25%. In total, 32 (24%) had poor outcomes. Only 34 (25%) infants suppressed VL during follow-up at a median time of 5.2 months. According to the model, determinants of poor outcome were VL and age at ART, after adjustment by site, baseline CD4 and ART regimen. The hazard of poor outcome was almost 3X higher (HR: 2.7 [1.3–5.8], p=0.010) per each VL log consistently elevated during the follow-up, and 50% higher for every month that ART was delayed (HR: 1.5 [1.01–2.2], p=0.049). At this point, time to suppression was influenced only by baseline VL (HR: 0.01 [0.002–0.1], p<0.001) and maternal severe life events/health issues (HR: 0.4 [0.8–0.9], p=0.042).

**Conclusion:** Despite early ART, a high proportion of infants have a poor outcome during the first months of life. The poor outcome is mainly influenced by VL during follow-up and age at ART initiation.
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 DNA was evaluated 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 made with 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 status and 84-week qualitative DNA result. * by 84 week HIV serology (EIA test)

<table>
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<th>&gt;40 copies/mL</th>
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<th>Negative EIA</th>
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809 NK CELLS ARE PRESERVED BY EARLY ART IN HIV-INFECTED CHILDREN WITH LOWER RESERVOIR

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Background: HIV infection causes pathologic changes in the natural killer (NK) cell compartment that can be only partially restored by antiretroviral therapy (ART). We studied NK cell phenotypes and function in perinatally HIV-infected children (PHIV) enrolled in a multicenter cross-sectional study (CARMA, EPICAL consortium), who started ART at different ages (early treated, ET ≤ 6 months; late treated, LT > 6 months to 2 years).

Methods: 40 PHIV who started ART < 2 years of life and had undetectable viremia (<50 HIV copies/mL) for at least 3 years, were enrolled in 7 European research centers. HIV DNA copies/10^6 PBMCs were measured by real-time PCR. NK cells were analyzed by flow cytometry for % of CD56high, CD56dim, CD56neg subsets, receptor expression, maturation profile, degranulation capacity (CD107a expression) in the presence or not of K562 cells, and IFNγ production after stimulation or not with cytokines. Data were analyzed by Spearman correlation plots and multivariable Poisson regression model (adjusted for baseline %CD4 and RNA HIV viral load and for age at ART start as interaction term, either ET or LT) to explore the association between NK cell parameters and HIV reservoir modulated by age at ART start.

Results: Later treatment in PHIV leads to a shift of NK cells to the anergic CD56neg subset that is associated with an increase in HIV reservoir size. For each 1% increase in %CD56neg, 3% upregulation of HIV reservoir is found and this effect is reduced in ET. LT display a persistent “activated” phenotype (i.e. NKG2D+, high Perforin expression) that is not present in ET. For each 1-unit increase in % of NKG2D+, % of Nkg2d+ or Perforin mean fluorescence intensity, there is an enrichment of 1%, 4% or 0.01% in HIV reservoir, respectively. Moreover, %CD107a+ and %IFNγ+ non-stimulated NK cells show a positive association with HIV DNA, but these effects are decreased in ET. Finally, among CD56dim cells, the frequencies of early differentiated and mature cells are associated with HIV DNA in a positive and inverse manner, respectively, whereas these effects were lower in ET.

Conclusion: Our results demonstrate that starting ART as soon as possible after birth in PHIV preserves NK cell features. Notably, we show for the first time that an intact NK cell compartment in PHIV is associated with lower HIV viral reservoir.

810 MARKERS OF HIV RESERVOIR SIZE IN INFECTED CHILDREN ON LONG-TERM VIRAL CONTROL

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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 years of 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, CD4, CD8, Ki67 and HLA-DR); 2) co-expression of PD1 with ICP (TIGIT, LG3, TIM3 and CTLA4); 3) intracellular cytokine production (IL2, IFng, TNF, IL21) after stimulation with EN 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=-0.41, 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 cell 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.

811 PROVIRAL LANDSCAPE IN CHILDREN PARALLELS ADULTS AND ENABLES RESERVOIR RECONSTRUCTION

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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-EPIICAL study, 40 European PaHIV on suppressive ART for ≤5 years were recruited. Total CA-DNA, total CA-RNA and unspliced (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/10^9 PBMCs for qPCR, <10^-1420 c/10^9 PBMCs for dPCR). In seven of the 36 PaHIV CA-DNA copy numbers were below 10^-10 PBMCs. Total CA-DNA was detected in 31 (<11^-5789 c/10^9 PBMCs for qPCR, 11^-857 for dPCR) and US CA-RNA in 23 of 40 patients (<11^-274 c/10^9 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

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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-EPIICAL study, 40 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 SMALT and LASTZ for alignment and the HIVSeqinR pipeline were utilised to describe intact genomes. De novo assembly of genomes was performed using 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/10^6 PBMCs, range 49.1-260.7 c/10^6 PBMCs). Initial findings on 4 patients, where 10 near full-length sequences were generated, are included in the figure. 2 viruses were subtype C, 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 APOBEC 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 APOBEC related hypermutations are present in long standing treated infection as well as RAMs.

SGS represents a useful tool for reservoir assessment and further sequencing and analysis with respective clinical data is ongoing in the CARMA cohort.

DIFFERENCES IN THE INDUCED LATENT HIV RESERVOIR IN PERINATAL AND ADULT INFECTIONS

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Background: The latent HIV 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 10^6 CD4 cells (msRUPM). Markers of immune activation (CD69, CD25 and HLA-DR) and exhaustion (PD-1, TIM-3 and TIGIT) were 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/10^6 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=0.020). With the enhanced TILDA, the size of the induced reservoir increased significantly in perinatal infections (1.5-fold to a median of 4.5 msRUPM, 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.
CHILDREN <15 ARE LESS LIKELY TO BE AN INDEX TESTING CONTACT COMPARED TO ADULTS

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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 0.08% 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.

THE CASCADE OF HIV CARE FOR CHILDREN AND ADOLESCENTS IN WEST AFRICAN COHORTS

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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-naïve 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 <500cp/mL after 6-month post-ART). We presented cumulative incidence and factors associated with ART initiation, with death/LTFU 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 LTFU before ART initiation; 3% were alive but had not initiated on 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 initiated ART compared to those aged 10-15 years, as well as CALHIV enrolled before 2016 compared to those enrolled later. Among CALHIV on ART, 65% (3362/5175) 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.

HIV VIRAL SUPPRESSION IN ADOLESCENTS AND YOUNG ADULTS: A NATIONAL SURVEY IN KENYA

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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 (<0.001). In 16% of clinics, ≥80% of AYA were suppressed. Clinics with ≥80% AYA viral suppression were more likely to be in higher 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 clinic- and individual-AYA care strategies.

818 CAN ADHERENCE INTERVENTIONS BE COST-EFFECTIVE AMONG YOUTH WITH HIV?

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Background: Viral suppression (VS) among US youth with HIV (YWH) in care is only 25-59%. The Adolescent Medicine Trials Network for HIV/AIDS Interventions is evaluating several interventions to improve ART adherence among YWH. Our objective was to model the impact of a hypothetical adherence intervention, based on electronic reminders, to identify combinations of effectiveness and cost at which these programs would be cost-effective for YWH.

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 12 month (m) adherence intervention (AI) that led to an absolute increase in cohort-level VS (efficacy) of 10% compared to SOC at 12m and cost $100/m/person. We assumed all YWH were in care and on ART for the first 12m in cohort-level VS (efficacy) of 10% compared to SOC at 12m and cost $100/m/person. We assumed all YWH were in care and on ART for the first 12m in

Results: At base-case efficacy (10%), AI was cost-effective at costs up to $2,000/m; at $100/m, AI was cost-effective at efficacies ≥ 1% (Fig). When AI costs fell to $50/m, AI was cost-saving even when efficacy was as low as 7%.

Conclusion: Adherence interventions among YWH that increase VS could provide benchmarking to motivate innovations in clinic- and individual-AYA care strategies.

819 TUBERCULOSIS INFECTION AND DISEASE IN HIV-INFECTED ADOLESCENTS ON ART: A COHORT STUDY

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Background: There are limited data on TB in perinatally-infected adolescents living with HIV (PHIV+) in high burden settings. We examined the incidence of latent tuberculosis infection (LTBI) and TB disease in the Cape Town Adolescent Antiretroviral Cohort.

Methods: PHIV+ adolescents between 9-14y, on ART ≥6m in routine public sector care and age-matched HIV-uninfected children were enrolled between 2013-2015 and followed 6-monthly until end 2018. Symptomatic screening (including history of having a TB contact and or being on Isoniazid prophylaxis) for TB, chest radiograph and sputum for Xpert MTB/RIF, microscopy and culture, viral load and CD4 count were performed at enrolment and annually. Quantiferon (QFT, Qiagen, South Africa) was done at enrolment and then annually if prior QFT was negative. LTBI was defined by a QFT of ≥0.35 IU/mL in the absence of signs and symptoms of TB. TB diagnosis was defined as definite (culture-confirmed) or probable (clinical case definition). Time to event analyses were used to describe the incidence of LTBI and TB disease.

Results: 485 PHIV+ and 95 HIV- adolescents (median age 12 years [IQR: 10.6-13.3]; 50% male) had QFT results at enrolment. PHIV+ had a median CD4 of 715 cell/µL (IQR: 564-959) and 365 (75%) had viral load <40 c/mL. 61% of PHIV+ had a history of TB disease before enrolment (vs 3% in HIV-, p<0.01) and 27% were on INH prophylaxis (vs 4% in HIV-) but with no difference in QFT positivity at enrolment (33% vs 28%, p=0.34). Over 3 years of follow-up, PHIV+ participants had a similar rate of QFT conversion compared to HIV- (7.4 (5.9-9.4) vs 8.7 (5.6-13.7) per 100-person years (PY), p=0.31). HIV+ participants had a higher rate of TB disease (2.2 (1.6-3.1) vs 0.3 (0.00-2.2) per 100-PY, p=0.07). 46% of HIV+ participants with TB disease were QFT+. Figure 1 describes the cumulative prevalence of QFT positivity and TB incidence by age in HIV+ participants.

Conclusion: In this high TB burden setting, the rate of QFT conversion did not differ between PHIV+ and HIV- adolescents, but PHIV+ had a higher incidence of TB disease despite ART. INH prophylaxis, adequate viral suppression and other interventions are needed to reduce TB incidence during the adolescent period.

820 LOWER SIZE-ADJUSTED BONE DENSITY AND MUSCLE FUNCTION IN ZIMBABWEAN CHILDREN WITH HIV

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821 BONE MASS REMAINS HIGHER AMONG CHILDREN ON EFAVirenZ VS LOPINAVIR/ritonAVIR

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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 (for age) 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 (TB LH) bone mineral content (BMC) for lean mass adjusted for height (TB LH BMC/LBM) and lumbar spine bone mineral apparent density (LS BMD) 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 two groups. However, CWH had significantly lower muscle mass, muscle strength, TB LH BMC/LBM and LS BMD 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.

822 BONE AND RENAL OUTCOMES IN VIROlogICALLY CONTROLLED ADOLESCENTS SWITCHING TO TDF

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Background: Tenofovir disoproxil fumarate (TDF) is included in first line naive ALWH or those with treatment failure is associated with decreased bone mass. Whether switching to TDF causes decreased bone accrual or bone loss in virologically controlled ALWH is not well established.

Methods: We recruited 50 adolescents, ages 15 - 20 years, Tanner stage 4/5, weight > 40 kg, viral load (VL) < 100 copies/mL, and no evidence of kidney or liver disease, that were switched from an abacavir (ABC)-based to TDF-based efavirenz regimen. Bone mass and renal function were assessed at enrolment and week 24 after switch to TDF using dual x-ray absorptiometry (DXA) and serum renal markers. Undetectable VL was defined as < 50 copies/mL. Body mass index (BMI) was assessed using WHO BMI-for-age charts. Change in serum renal markers. Undetectable VL was defined as < 50 copies/mL. Body mass index (BMI) was assessed using WHO BMI-for-age charts. Change in

Results: All participants (48% male) were perinatally infected, with median duration on antiretroviral therapy (ART) of 11.4 years. Six (12%) had a prior AIDS-defining illness. At time of ART switch, median CD4 count was 732 and 38 (76%) had undetectable VL. On BMI, 3 (6%) were classified as thin, and 5 (10%)...
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 (58% 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.

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**EPIGENETIC AGE IN YOUNG AFRICAN AMERICAN ADULTS WITH PERINATALLY ACQUIRED HIV**

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**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 if 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) age acceleration residual adjusted for cell type proportions estimated by the Houseman method (HAAAR), adjusts for cell type counts; 3) Housman-adjusted age acceleration residual (HAAR), adjusts for cell type proportions estimated by the Houseman 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 measured DNAm from whole blood samples using the Illumina EPIC Array.

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**GLOBAL VARIATIONS IN PUBERTAL GROWTH IN ADOLESCENTS LIVING WITH PERINATALLY ACQUIRED HIV**

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**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.

**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.
EFFECT OF INTEGRASE INHIBITORS ON WEIGHT GAIN IN CHILDREN AND ADOLESCENTS WITH HIV

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Background: Weight gain has been associated with integrase strand transfer inhibitor (INSTI) based regimens in adults, but this has not been studied in children and youth with perinatally acquired HIV. We investigated the change in body mass index (BMI) among young persons living with HIV (YPLWH) initiating INSTI-based regimens for the first time within an observational cohort in Washington DC (DC Cohort).

Methods: YPLWH (0-24 years of age) who initiated INSTI-based regimens between January 2011 and March 2018, and had ≥2 BMIs recorded at least 6 months apart within 2 years post-INSTI initiation were eligible. We compared the trajectory of BMI (or BMI-for-age z-score for those ≤19 years of age) pre- and post-INSTI initiation using piecewise linear mixed effects models, and adjusted for potential confounders.

Results: We enrolled 51 YPLWH (median age 18 years (IQR 15-21), 47% male, 94% black, 72% perinatally infected, 59% initiated dolutegravir, 57% had a history of AIDS). Pre-INSTI, 59% were on a protease inhibitor based regimen and 4% were ART-naive. At INSTI initiation, median BMI was 21.4 m/kg2 (IQR: 19.6-24.3), CD4 count was 574 cells/mL (IQR: 348-834), 43% had HIV viral load <200 copies/mL. Fifty one YPLWH had 720 BMI measurements (median BMI z-score measurements per YPLWH 12 (IQR: 10-15)) with a mean z-score change of +0.24/year, (β=0.24, p<0.01). In the 2 years pre- and post-INSTI initiation respectively. There was a greater rate of BMI change post-vs. pre-INSTI of +0.6 kg/m2/year (β=0.25, p=0.03, Fig. 1b) when comparing trajectories post- vs. pre-INSTI after adjusting for age at INSTI initiation, sex, race, mode of HIV acquisition and most recent CD4 count and VL (β=-0.22, p<0.05).

Conclusion: Similar to adults, we report a greater rate of BMI and BMI-for-age z-score change following switch to INSTI to predominantly perinatally infected YPLWH. Although the final BMI remained in the normal range, our findings support the need for continued monitoring of BMI trends and potential cardiometabolic implications in YPLWH receiving INSTIs to assess if this represents more than a return to health phenomenon.

BMI-for-age z-score measurements per YPLWH 12 (IQR: 10-15) with a mean z-score change of +0.24/year (β=0.24, p<0.01). In the 2 years pre- and post-INSTI initiation respectively. There was a greater rate of BMI change post-vs. pre-INSTI of +0.6 kg/m2/year (β=0.25, p=0.03, Fig. 1b) when comparing trajectories post- vs. pre-INSTI after adjusting for age at INSTI initiation, sex, race, mode of HIV acquisition and most recent CD4 count and VL (β=-0.22, p<0.05).

826 EFFECT OF INTEGRASE INHIBITORS ON WEIGHT GAIN IN CHILDREN AND ADOLESCENTS WITH HIV

827 BODY FAT AND LIPID PROFILE CHANGES IN HIV-INFECTED YOUTHS SWITCHED TO DOLUTEGRAVIR

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Background: HIV-lipodystrophy syndrome consists in abnormal distribution of adipose tissue and alteration of glucose and lipids blood concentration. Many studies established a key role of older NRTIs and PIs in lipodystrophy development, but few data are available for new drugs, such as dolutegravir, a second-generation INSTI assumed to be responsible for weight gain in adults. The aim of this study was to evaluate the effects of dolutegravir on body composition and glico-lipidic metabolism in HIV-infected youths.

Methods: We enrolled 14 patients (mean age 16.1 years, 12 girls) previously treated with PI or NNRTI-based regimen and switched to ABC/3TC/DTG. Blood
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 = 0.0027). Mean LDL cholesterol values were 109, 90, 92 and 96 mg/dL at baseline, 3, 6 and 12 months (p = 0.025). Mean triglyceride 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 (TBLH) 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 dolategravir-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>Fat percent (%)</th>
<th>Trunk</th>
<th>12 months</th>
<th>p value</th>
</tr>
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<tr>
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<td>27.4</td>
<td>0.18</td>
</tr>
<tr>
<td>LBM</td>
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<td>31.4</td>
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<td>FMI</td>
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<td>29.9</td>
<td>0.045</td>
</tr>
<tr>
<td>Fat ratio</td>
<td>14%</td>
<td>12 months</td>
<td>p value</td>
</tr>
<tr>
<td>TBLH</td>
<td>0.05</td>
<td>0.06</td>
<td>0.0085</td>
</tr>
<tr>
<td>Trunk/Total</td>
<td>1.29</td>
<td>1.24</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

828 CHER TRIAL COHORT SHOWS GREATER INSULIN RESISTANCE INTO ADOLESCENCE

Claire Davies, 1 Steve Innes, 1 Mark Cotton, 1 Sara H. Browne, 2 Birhanu Ayele 3 Stellenbosch University, Tygerberg, South Africa, 2University 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 perinatally-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), an index used in clinical practice to measure insulin sensitivity. The index is calculated as the product of fasting insulin (µIU/mL) and fasting glucose (mM) divided by 22.5.

**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 unlikely linked to differences in environmental or household circumstances in HIV-affected versus -unaffected households, as no significant difference was found between the HOMA-IR of HEU and HU.

**Conclusion:** Despite being closely monitored and on ART since soon after birth, PHIV exhibit elevated insulin resistance that has persisted into adolescence. This has long term implications for cardiovascular risk. Further research needs to identify which PHIV are at risk.

### Table 1: Longitudinal linear mixed effects model for the association between HIV infection and log HOMA-IR (insulin resistance index)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-2.566</td>
<td>0.94</td>
<td>-2.729</td>
<td>0.009</td>
</tr>
<tr>
<td>HU</td>
<td>0.061</td>
<td>0.026</td>
<td>0.001</td>
<td>0.949</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.06</td>
<td>0.04</td>
<td>0.001</td>
<td>0.949</td>
</tr>
</tbody>
</table>

829 CARDIOVASCULAR RISK PROFILE: A CLINIC-BASED SAMPLE OF YOUTH LIVING WITH HIV IN THE US

Sitaji Gurung, 1 Kit N. Simpson, 2 Christian Grov, 3 H. Jonathin Rendina, 4 Terry T. Huang, 5 Stephen Scott Jones, 1 Marshall Cheew, 6 Tyra Dark, 6 Sylvie Naar 1 Hunter College, CUNY, New York, NY, USA, 2Medical University of South Carolina, Charleston, SC, USA, 3City University of New York, New York, NY, USA, 4University of Florida College of Medicine, Tallahassee, FL, USA

**Background:** Accelerated atherosclerosis has been found in young individuals diagnosed with HIV. Previous research indicates that lower CD4 and higher plasma viral load (VL) significantly increased the risk of cardiovascular disease (CVD); however, this link is largely under-investigated among youth living with HIV (YLH). We examined whether detectable VL and low CD4 increased the risk of CVD among YLH aged 14-26y.

**Methods:** This study used electronic health records from the Adolescent Medicine Trials Network 154 Cascade Monitoring baseline data extracted from multidisciplinary adolescent HIV care settings across the United States. Multivariable linear regression was used to assess the association between detectable VL and CD4 of ≤ 200 with Cardiovascular Risk Score (for those who had systolic blood pressure, cigarette smoking, diabetes, and anti-hypertensive medication use, n = 813) and Cardiovascular Risk Score2 (for those who had systolic blood pressure, cigarette smoking, diabetes, anti-hypertensive medications use, total cholesterol, and LDL data, n = 398) adapted from the Framingham gender-specific algorithm.

**Results:** The sample was predominantly black and male with mean age of 21y. Overall, 47.8% had a detectable VL and 8.6% had a baseline CD4 of ≤ 200 indicating immune dysfunction. In bivariate analyses, both scores (Cardiovascular Risk Score, p < 0.001; Cardiovascular Risk Score2, p < 0.01) demonstrated significantly increased risk of CVD in patients who had detectable VL compared with those who had undetectable VL. Comparing patients who had CD4 ≤ 200 with those who had CD4 > 200, the risk of CVD was significantly increased in patients who had CD4 > 200 compared with those who had CD4 > 200 using Cardiovascular Risk Score (p < 0.01) but not Cardiovascular Risk Score1.

**Conclusion:** Our findings demonstrate the independent contribution of detectable VL on cardiovascular risk in YLH.

830 SOLUBLE CD14 IS ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION IN SOUTH AFRICAN YOUTH ON ART

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**Background:** There is evidence for endothelial dysfunction in youth living with perinatally acquired HIV (YLPHIV). We assessed gut and inflammatory biomarkers associated with endothelial dysfunction in South African YLPHIV.

**Methods:** YLPHIV and age-matched HIV-uninfected (HIV-) youth enrolled in the Cape Town Adolescent Antiretroviral Cohort (CTAAC) in South Africa between 9-14 years of age were included. YLPHIV were on ART > 6 months with viral load <400 copies/mL. Endothelial function was measured using reactive hyperemic index (RHI) by Peripheral Arterial Tonometry. Endothelial dysfunction was defined as RHI <1.35. Serum levels of systemic inflammation, monocyte activation, intestinal integrity and oxidized lipids were measured at baseline.
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.
DEPRESSION, SUBSTANCE USE, AND ADHERENCE AMONG LATIN AMERICAN YOUTH LIVING WITH HIV

Daisy Machado1, Raquel B. De Boni1, Fernanda Maruri1, Vanessa A. Rouzier1, Brenda Crabtree-Ramírez2, Denis Padgett3, Fernando A. Mejia4, M. Fernanda Rodriguez3, Jorge Pinto8, Jorge Pinto9, Catherine McGowan3

1Chulalongkorn University, Bangkok, Thailand, 2Emory University, Atlanta, GA, USA, 3HIV—NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, 4National Centre for HIV/AIDS Dermatology and STDs, Phnom Penh, Cambodia, 5Chiang Rai Prachanukroh Hospital, Chiang Rai, Thailand, 6Khon Kaen University, Khon Kaen, Thailand, 7Belo Horizonte, Brazil, 8Fundación Arriarán, Santiago, Chile, 9Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

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-2/9/14), 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 (aOR 0.6, 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 Latin American adolescents and young adults (PHIV+) in multicentric logistic regression analyses. 2019-2020.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Depression</th>
<th>Alcohol use ≥1 time past 3 months</th>
<th>Tobacco use ≥1 time past 3 months</th>
<th>Any illicit drug use ≥1 time past 3 months</th>
<th>ART adherence (last week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Female vs. Male</td>
<td>2.89 (1.63–5.20)</td>
<td>1.35 (0.80–2.24)</td>
<td>1.46 (0.90–2.32)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
</tr>
<tr>
<td>Age: 13-15 vs. 16-24 vs. 25-29</td>
<td>1.35 (0.80–2.24)</td>
<td>1.46 (0.90–2.32)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>1.35 (0.80–2.24)</td>
<td>1.46 (0.90–2.32)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
</tr>
<tr>
<td>Substance use</td>
<td>3.89 (2.17–7.02)</td>
<td>1.84 (1.07–3.13)</td>
<td>1.46 (0.90–2.32)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
</tr>
<tr>
<td>Any illicit drug use</td>
<td>1.35 (0.80–2.24)</td>
<td>1.46 (0.90–2.32)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
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<tr>
<td>Depression:</td>
<td>-</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
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</tr>
<tr>
<td>Any illicit drug use</td>
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<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
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</tr>
<tr>
<td>Depression:</td>
<td>-</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
<td>1.02 (0.63–1.62)</td>
</tr>
</tbody>
</table>

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834 SUBSTANCE USE IN PERINATALLY INFECTED AND SAME-AGE HIV-ADOLESCENTS IN SOUTH AFRICA

Kirsty Brittain1, Landon Myer1, Nicole Phillips1, Heather Zar1, Dan Stein2, Jackie Hoare1

1University of Cape Town, Cape Town, South Africa

Background: Experimentation with substances is 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.
**Methods:** The Cape Town Adolescent Antiretroviral Cohort follows PHI+ and age- and gender-matched HIV- adolescents in South Africa. Self-reported substance use was assessed annually, and a 6-panel urine toxicology screen tested for common substances (marijuana, methaqualone, cocaine, methamphetamine, MDMA, opiates) at enrollment and after 36 and 48 months of follow-up; HIV viral load (VL) was measured annually. Using repeated measures, we describe substance use during pre-adolescence (ages 9-11 years), early (12-14 years) and middle-late adolescence (15-19 years).

**Results:** A total of 515 PHI+ (median age at enrollment: 11 years; 49% female) and 110 HIV- adolescents (11.7 years; 55% female) contributed 1491 toxicology screens over a median of 4 years. Overall, 5.5% of tests were positive. The most commonly used substance was marijuana (95% of all positive tests), followed by methaqualone/methadone (17%) and methamphetamine (9%). Among females, neither age nor HIV status was associated with a positive test. Among males, older age was strongly associated with a positive screen (p<0.001); male PHI+ were significantly less likely to screen positive across study visits after adjusting for age (aOR: 0.15 [0.04-0.60]; Figure A). Self-report of ever using alcohol was common: among PHI+, report of use increased from 3% in pre-adolescence to 7% and 29% in early and middle-late adolescence; with levels of use even higher in HIV- adolescents (from 5% to 18% and 54%; p<0.001). Self-reported use of tobacco increased with age but did not differ by HIV status (from 0.9% to 2% and 17% in PHI+; 0% to 3% and 10% in HIV-). Self-report performed poorly in detecting use of the most common substances (Figure B). At enrollment and after 36 and 48 months, approximately 22% of PHI+ had VL>50 copies/mL; 13% had VL>1000 copies/mL. Adjusting for age and gender, positive toxicology screen was not associated with VL at any time point.

**Conclusion:** Among male PHI+, the prevalence of substance use increased dramatically with older age but was lower than that of same-age, HIV- peers. Further efforts are needed to refine self-report measures and to explore the clinical and behavioral effects of substance use.

836 **PROMISING RESULTS FROM A PILOT RCT MENTAL HEALTH INTERVENTION FOR HIV-INFECTED YOUTH**

Dorothy E. Dow1, Blandina T. Mmbaga 2, John A. Gallis 3, Elizabeth L. Turner1, Monica Gandhi4, Coleen K. Cunningham1, Karen O’Donnell1, Blandina T. Mmbaga 2, John A. Gallis 3, Elizabeth L. Turner1, Monica Gandhi4, 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 (YLW) 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 YLW.

**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/mg (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
interventions exist to improve outcomes in this critical population. This pilot trial of SYV demonstrated trends towards improvement in ART adherence, measured objectively, and virologic outcomes among YLWH in Tanzania supporting efforts to scale the intervention into a fully powered effectiveness trial.

### Brain Development in Treated Perinatal HIV: A Longitudinal Study of Neurocognitive Disorders and Brain Structure

**Objective:** To longitudinally study the rates of change in neurocognitive function and structural brain differences in treated perinatally HIV-infected children compared to age-, sex-, ethnicity- and socioeconomic status-matched HIV-uninfected controls.

**Methods:** A total of 106 PHIV and 107 HIV-uninfected children aged 8-18 years were included. Neurocognitive function was assessed using the NIH Toolbox Cognition Battery, and structural brain differences were assessed using diffusion tensor imaging and T1-weighted MRI.

**Results:** After a mean of 4.6±0.3 years, PHIV children had lower cognitive scores and smaller white matter volumes compared to HIV-uninfected controls. The rate of decline in cognitive function and white matter volume was more pronounced in PHIV children with a major neurocognitive disorder (NCD) compared to those without.

**Conclusion:** These findings highlight the importance of longitudinal assessment of neurocognitive function and structural brain differences in treated perinatally HIV-infected children to identify at-risk individuals early and guide intervention strategies.

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**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 hypertensity (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 consent in volumetric outcomes and FA at first MRI (all p-values>0.05). Those who completed two MRI examinations had a mean age of 13.0±3.1 years and 17.6±3.1 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, WM volume increased significantly more in PHIV participants (group*time 0.10mL, 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 0.010L, 95%CI -0.010–0.020, p=0.078). We found no statistically different changes over time in WM integrity measures (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{\textsubscript{AUC0-24}} = 117 mg h/L and AUC\text{\textsubscript{24}} = 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 31.

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 formulations and difficulty in examining drug exposure. Several potential regimens have been identified, which are worthy of empirical

840 SAFETY, PK, AND EFFICACY OF LOW DOSE B/F/TAF IN CHILDREN ≥2 YEARS OLD LIVING WITH HIV

Carina Rodríguez1, Kulkanya Chokephaibulkit2, Aafaq Liberty3, Renate Strehla4, Riana Van Zyl5, Pope Kosalaraks6, Coleen K. Cunningham7, Eric J. McGrath8, Natella Rakhmanina9, Heather Maxwell10, Danielle Porter10, Sophia R. Majeed10, Shaolan S. Xiang10, Diana Brainard10, Cheryl Pikora10

1University of South Florida, Tampa, FL, USA, 2Mahidol University, Bangkok, Thailand, 3Chris Hani Baragwanath Hospital, Johannesburg, South Africa, 4Empilweni Service and Research Unit, Johannesburg, South Africa, 5University of the Free State, Bloemfontein, South Africa, 6Khon Kaen University, Khon Kaen, Thailand, 7Duke University Medical Center, Durham, NC, USA, 8Children’s Hospital of Michigan, Detroit, MI, USA, 9Children’s Research Institute, Children’s National Health System, Washington, DC, USA, 10Gilead Sciences, Inc, Foster City, CA, USA

Background: Few antiretroviral options exist for smaller children living with HIV and no single-tablet regimen (STR) is used or approved for this population. STR of bictegravir, emtricitabine and tenofovir alafenamide (B/F/TAF) is approved for use in HIV-infected children weighing ≥25 kg. We report safety, pharmacokinetics (PK), and efficacy from an interim analysis of the first clinical trial of a low dose B/F/TAF tablet in young children living with HIV.

Methods: Virologically suppressed children (≥2 yrs) weighing 14 to <25 kg and the proportion of participants with HIV-1 RNA <50 c/mL were assessed through W12. Steady-state PK of B/F/TAF was evaluated; BIC PK in children and the proportion of participants with HIV-1 RNA <50 c/mL for ≥6 months and CD4 ≥200 cells/μL at screening.

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{\textsubscript{AUC0-24}} = 117 mg h/L and AUC\text{\textsubscript{24}} = 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 31.

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 formulations and difficulty in examining drug exposure. Several potential regimens have been identified, which are worthy of empirical

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 Koziarz1, PJ Costales2, Jenna Scott2, Hiba Graham1, Cheryl Pikora1, Anita Mathias1

1Gilead 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 (RA/B) 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–< 25kg.

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 LDT 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–<25kg (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 the metabolite tenofovir (TFV) were compared descriptively to historical data. Safety was assessed throughout the studies.

Results: 52/54 HVs completed the PhI 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 AUC\text{\textsubscript{Cmax}} increased 42%; C\text{\textsubscript{max}} decreased 44%; 15% (adult fed 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\textsubscript{Cmax} and C\text{\textsubscript{max}} in children vs adults were within 50-200%. Mean BIC C\text{\textsubscript{max}} was 32% lower (Table). Exposures of FTC (mean AUC\text{\textsubscript{Cmax}}=14,900 h*ng/mL), TAF (mean AUC\text{\textsubscript{Cmax}}=305 h*ng/mL) and TFV (mean AUC\text{\textsubscript{Cmax}}=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–< 25kg with HIV taking the LDT, no clinically meaningful differences in PK were identified compared to adults; mean BIC C\text{\textsubscript{max}} was 12-fold above the paEC95 for wild type virus. Efficacy and safety of the pediatric STR in young children are consistent with adult strength STR efficacy in older populations. These data support further evaluation of low dose B/F/TAF as an unboosted INSTI-based STR for young children living with HIV.
842 MARAVIROC SAFETY & PHARMACOKINETICS IN HIV-EXPOSED NEONATES

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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 (n=13) receive 8 mg/kg MVC twice daily through 6 weeks of life with intensive PK sampling after the initial dose. Based on PK data from Cohort 1, 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 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 ≥ 75 ng/mL from adult treatment studies. Laboratory and clinical evaluations assessed infant safety at entry and Weeks 1, 2, 6, 16 in Cohort 1; Weeks 1, 4, 6, 12, 16 in Cohort 2.

Results: Forty-seven MVC naïve, HIV-exposed neonates have enrolled; 15 in Cohort 1, 32 in Cohort 2 (median gestational age 39 weeks, 51% male) from the University of the Witwatersrand, Soweto, South Africa, 3160, Durban, South Africa, Rush University Medical Center, Chicago, IL, USA, VIV HealthCare, Research Triangle Park, NC, USA, Boston University, Boston, MA, USA

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

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Background: Abacavir (ABC) is licensed for infants >3 months of age while WHO recommends use in HIV-infected children ≥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 (C0), 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 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-menstrual age (PMA=gestational age+postnatal age) influenced ABC PK parameters. ABC oral clearance (CL/F) increased by 2% per PMA week. Infant characteristics and ABC PK parameters per PK visit are shown in Table 1. One infant died of unknown cause 3 days after entry. Fourteen infants had Grade 3/4 AEs, among which most common were gastroenteritis (n=4) and respiratory infection (n=4) and all of which improved except for malnutrition (n=1), underweight (n=1) and a respiratory infection (n=1) present at the last study visit. No hypersensitivity was reported. All AEs were assessed as unrelated to ABC, except for one possibly related Grade 2 alanine aminotransferase where all antiretrovirals were stopped for 2 weeks until resolution then restarted without further complications.

Conclusion: ABC 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


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 <400 copies/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 dosage/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 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 recommendations. More data on ABC use are required in neonates.

ABACAVIR SAFETY AND EFFICACY IN YOUNG INFANTS IN SOUTH AFRICAN OBSERVATIONAL COHORTS

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Background: 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.

Methods: 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 who ≥3 months 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-adherence or loss to follow-up in 11, treatment failure in 2, and sensitivity issues 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 (58%) in those who started abacavir aged <28 days and 28 days to 3 months respectively (p=0.8) and 17/24 (71%) and 67/111 (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. We report that abacavir may be used safely in infants <28 days old or who weigh <3 kg.
846 PHARMACOKINETICS OF Raltegravir in HIV/TB Co-infected Infants and Young Children

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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 cohort. 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 the TB treatment with follow-up for another 3 mo. PK targets are a geometric mean (GM) AUC0-12h of 14-45 μMxh 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 (cp/ml) of 5.13 (5.01-5.60), CD4% count/μl of 1513 (1337-2008), and CD4% 16.8% (15.4-19.1). Wk 1 PK showed GM AUC12h (%CV) of 32.7 μMxh (49%) and GM C12h of 106.5 nM (57%). No adverse events were related to RAL. 12 of 13 had evaluable efficacy data at wk 8 (11/13 stopped RAL early due to use of a disallowed medication). By wk 8, 10/12 (83%) had HIV RNA <400 copies/ml; median changes from baseline were log10 RNA cp/ml -3.05, CD4 count +105.5 cells/μl and CD4% +4.9%. RAL was permanently stopped in 6/13 participants, one each for Grade 4 neutropenia (likely related to TB medication), use of a disallowed medication, or AUC12h exceeding the allowed C trough <EC 90 .

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

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Background: Adults with HIV/TB co-infection on dual antiretroviral therapy (ART) can overcome the induction effect of rifampicin (RIF) by doubling the DTG dose (50mg twice(BID) instead of once(QD) daily. We undertook a pharmacokinetic (PK) substudy nested within the ongoing ODYSSEY randomised controlled trial (NCT02259127) to evaluate DTG PK in HIV/TB co-infected children while receiving DTG BID+RIF and DTG QD. 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 C trough 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 undertaking PK had ≥1 evaluable PK curve. 12/17 were black African, median (range) age 12.3 (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 C max were 1.20 (0.90-1.59), 1.20 (0.90-1.59), and 0.98 (0.79-1.21), 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 for 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 C max <EC90. 30 children were followed for median (IQR) of 32 (30-40) weeks; 8 participants had 13 reportable AEs (9 SAEs including 1 DTG discontinuation). All events were considered unrelated to DTG by investigators and independent reviewers.

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

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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 for study by 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:** 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.

**Table 1:** Risk of HIV acquisition associated with forms of mobility, total population, and by sex

<table>
<thead>
<tr>
<th>Measures of mobility at baseline and year 3</th>
<th>Total population</th>
<th>Adjusted IRR with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>married vs single</td>
<td>1.51 (1.42-1.60)</td>
<td>1.50 (1.41-1.59)</td>
</tr>
<tr>
<td>lived &gt;12 months vs &lt;12 months</td>
<td>2.81 (2.62-3.02)</td>
<td>2.80 (2.61-3.01)</td>
</tr>
<tr>
<td>lived &gt;24 months vs &lt;24 months</td>
<td>3.21 (2.91-3.53)</td>
<td>3.20 (2.91-3.52)</td>
</tr>
<tr>
<td>lived &gt;36 months vs &lt;36 months</td>
<td>3.51 (3.20-3.84)</td>
<td>3.50 (3.20-3.84)</td>
</tr>
<tr>
<td>lived &gt;48 months vs &lt;48 months</td>
<td>3.81 (3.40-4.25)</td>
<td>3.80 (3.40-4.24)</td>
</tr>
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**850 HIV INCIDENCE AND VIRAL BURDEN AT THE COMMUNITY LEVEL IN HPTN 071 (POPART)**

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**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 12 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 -3.2% in viral burden for 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 mediation effect of viral burden on HIV incidence was not significant (Arm A vs C. p=0.50; Arm B vs C. p=0.77).

**Conclusion:** Higher viral 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.
**851 AGE-SPECIFIC HIV INCIDENCE PATTERNS AMONG POPULATION COHORTS IN SUB-SAHARAN AFRICA**

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**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-surveillance and HIV survival data collected among rural population HIV cohorts in Tanzania (Kisesa), Uganda (Masaka and Rakai), Malawi (Karonga), Zimbabwe (Manicaland) and South Africa (uMkhanayakude). 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 in 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 for 4 of 6 studies: Rakai (64%, 95% CI=44-76%), uMkhanyakude (58%, 95% CI=54-62%), 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.

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852 HIGH HIV INCIDENCE AND VOLUNTEER RETENTION IN A BANGKOK-BASED COHORT OF MSM AND TGW

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**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 (VTC). 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 (7.4%) 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).

**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.
853 HIV AMONG FEMALE SEX WORKERS: RISK FACTORS AND LESSONS FROM A NATIONAL SURVEY

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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±6.2years; mean age at first sex was 17±2.8years and average number of clients/day was 4.4. About 36.1% were married. About 38.8% had sex partners that were 10years older. Condom use at last sex was 91.8% among the FSWs; 40.3% 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.

854 HIV RISK, BEHAVIOUR, AND SERVICE UPTAKE IN ADOLESCENT GIRLS SELLING SEX IN ZIMBABWE

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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 (range 45.5-61.5% 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.

855 TRANSACTIONAL SEX WITH OLDER PARTNERS HEIGHTENS HIV RISKS AMONG AGYW IN TANZANIA

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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 synergy between both exposures by comparing their observed and expected joint 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 synergy 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
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 3: Factors associated with HIV self-reported prevalence among YMSM aged 15-24 years in Brazil, Mexico and Peru, 2016.

**585 FACTORS ASSOCIATED WITH HIV SEROCONVERSION IN YOUNG WOMEN IN SOUTH AFRICA**

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**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 (CI): 3.27-4.69) per 100 women-years; 3.74 (95% CI: 3.27-4.86) and 4.13 (95% CI: 3.20-5.33) per 100 women-years for 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 teenage 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 a 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=1.18; 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.

**587 SOCIOECONOMIC DISPARITIES ARE ASSOCIATED WITH HIV IN YOUNG MSM WITHIN LATIN AMERICA**

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**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 positive HIV 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:1.16-1.57) and Peru (aOR=1.27, 95%CI:0.97 , 1.67) 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.
and received money or gifts in exchange for sex in the past 12 months (MSM: 54.6%; TG: 59.63%). In an unadjusted log binomial regression, MSM with a history of forced sex were 8.19 (95% CI, 3.09-21.67) 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

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Background: Young men who have sex with men (YMSM) are disproportionally 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 (14.0%). 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 = 4.96) 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

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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 41% (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 <100 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 [adjPR] 1.49, 95% CI 1.16,1.92), signs of tuberculosis (adjPR 1.95, 95% CI 1.52,2.44), and being admitted to the hospital (adjPR 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) (adjPR 1.69, 95% CI 1.11,2.57), or presenting with fever (vs. no fever) (adjPR 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

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Background: 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 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 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% (26–54), 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

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Background: It is unclear whether low, detectable viral load (VL), observed as viral blips and low-level viremia, impacts risk of death. Our objective was to estimate mortality risk after initial suppression in patients who maintained VLs <200 copies/mL while in care at NA-ACCORD clinical sites in 2007–2016.

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 account 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. Inverse probability weighting was used to account for confounders (see fig.).

Results: At initial suppression, 2-year crude mortality risks for 19463 patients with VL <20 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 1144 patients under observation with a VL measurement 2 years after initial suppression, 77% had maintained all VLs <200 copies/mL. Among these patients, 2-year crude risks for those with all VLs <20 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 <20 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.

863 HIGH PROBABILITY OF SURVIVAL IN PATIENTS WHO MAINTAIN VIRAL LOADS <200 COPIES/mL

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Background: Globally, women account for more than half of persons living with HIV (PWLH), yet remain underrepresented in research. Starting in 2018, CROI guidelines specifically recommended reporting of sex distribution and sex-adjusted analyses, but formal review showed rates of such reporting among CROI abstract presentations at 2018, 2019, and 2020 were much lower than expected. 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 PWLH worldwide are women.
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.

Two-year risk of all-cause mortality at 0, 2, and 4 years after initial suppression, stratified by viral load history. Solid black line: all viral loads <20 copies/mL; dashed red line: at least one viral load 20-199 copies/mL.

864 FIRST HIV VIRAL LOAD REMAINS STRONG PREDICTOR OF TREATMENT SUCCESS IN SOUTH AFRICA

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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 to an enrolled nurse or standard laboratory VL testing. A composite primary outcome of retention in care and viral suppression (<200 copies/mL) was assessed 12 months after enrollment. 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 VL ≥50 copies/mL.

Results: Among 390 participants, median age was 32 years (interquartile range [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 of retention and viral suppression. Baseline VL ≥200 copies/mL (RR=3.55, p<0.01) and younger age (in 5-year increments, RR=1.15, p=.06) were associated with poor outcomes at study exit in univariate analyses and remained significant (aRR=3.82, p<0.01 and aRR=1.18, p=.04, respectively) when adjusted for distance traveled to the clinic, study arm, and CD4 count at six months. Among those with an 18-month VL, 280 (76.3%) were suppressed at <50 copies/mL. Six-month VL ≥200 copies/mL (aRR=2.51, p<0.01) and lower CD4 counts (100 cells/mL increments, aRR=1.12, p<0.01) were associated with 18-month VL ≥50 copies/mL, after adjusting for gender. We found no significant associations between failing to achieve the composite primary outcome or 18-month VL ≥50 copies/mL and education, having a primary partner, alcohol use, current smoking status, drug use, depression, time since diagnosis, or ART adherence.

Conclusion: In the era of universal test and treat, the 6-month VL after ART initiation strongly predicts poor HIV outcomes. Identifying PLHIV with high VL early and focusing on VL suppression should be a priority to improve HIV outcomes in South Africa.

865 POPULATION-LEVEL HIV VIRAL LOAD VARIES BY GENDER, AGE, AND LOCATION IN RAKAI, UGANDA

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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 (PDVL) 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 measurements 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 HI 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 PDVL among men (5.8% [5.3%-6.3%] compared to women (4.8% [4.4%-5.2%]), and 7 (5-10) times higher geometric mean VI among infected men with detectable viral load compared to their female counterparts. PDVL peaked at age 20-24 in men and at age 15-19 in women (Figure 1B). In contrast PDVL peaked later, at age 30-34 in men and at 25-29 in women. Spatial foci of high PMVL 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.
866 DISPARITIES IN VIRAL SUPPRESSION AMONG US ADULTS WITH RECENTLY DIAGNOSED HIV

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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 months, homelessness, drug use, and unmet needs for HIV medicine were 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).

Results: Of persons with recent HIV diagnoses, 31% were not virally suppressed, and 5% reported not currently taking ART. The proportion of 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 associations with 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 of persons with 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.

867 HIV+ PERSONS IN RURAL UGANDA WITH FEWER SOCIAL CONNECTIONS HAVE LOWER HIV SUPPRESSION

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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 tertile 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 copies/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 aware of their HIV status, 50% had not initiated ART, and 55% had viral non-suppression. HIV+ persons in the lowest tertile 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 tertile (>3-7 contacts) (Figure). Out-degree was not associated with known HIV status or suppression in either region; persons in Uganda East with intermediate out-degree were less likely to have initiated ART.

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

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Background: Increased survival among persons living with HIV (PLWH) receiving antiretroviral therapy (ART) has been documented in the United States, Canada, and Europe. However, sparse data exist on life expectancy in low- and middle-income settings where ART is increasingly available. We therefore calculated life expectancy gains among PLWH initiated ART within the Caribbean, Central and South America network for HIV epidemiology (CCASAnet).

Methods: We included PLWH started on ART and ≥20 years old between 2003-2017 from CCASA net 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 expectancies 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 (LTFU) 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 (17% missing). There were 1,470 deaths and 7,154 LTFU among PLWH from Haiti and 1,167 deaths and 3,174 LTFU 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 (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

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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 (CV), 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.
1,000 person-years (py), and the predictors were HIV status, and cancer grouped as: any cancer; AIDS-defining cancers (ADC); non-AIDS-defining cancers (NADC); virus-unrelated NADC; virus-related NADC; and HPV-related NADCs (see Table footnote). We first computed mortality rate differences (RD), separately by HIV status, to measure the increased mortality rates after cancer (RD >0 denotes higher mortality rates after cancer). Next, we modeled mortality rates using additive Poisson regression, including terms for HIV status, cancer, and an HIV*cancer interaction term. The interaction term represents the excess mortality rate associated with cancer among PWH as compared with uninfected persons. Adjusted models included terms for demographics, smoking, body mass index>25 kg/m², alcohol/drug use disorders, and common comorbidities (see Table footnote).

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 HPV-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: Adjusted Mortality Rates Among HIV-Infected and Uninfected Persons

<table>
<thead>
<tr>
<th>Cancer group</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>43.7</td>
<td>43.1</td>
</tr>
<tr>
<td>NADC</td>
<td>73.3</td>
<td>69.1</td>
</tr>
<tr>
<td>VUDADC</td>
<td>68.9</td>
<td>64.5</td>
</tr>
<tr>
<td>Virus-related NADC</td>
<td>43.0</td>
<td>40.5</td>
</tr>
<tr>
<td>HPV-related NADC</td>
<td>30.3</td>
<td>29.1</td>
</tr>
</tbody>
</table>

1Excess mortality rate for any cancer: adjusted for demographics, smoking, body mass index>25 kg/m², alcohol/drug use disorders, and common comorbidities (see Table footnote). We first computed mortality rate differences (RD), separately by HIV status, to measure the increased mortality rates after cancer (RD >0 denotes higher mortality rates after cancer). Next, we modeled mortality rates using additive Poisson regression, including terms for HIV status, cancer, and an HIV*cancer interaction term. The interaction term represents the excess mortality rate associated with cancer among PWH as compared with uninfected persons. Adjusted models included terms for demographics, smoking, body mass index>25 kg/m², alcohol/drug use disorders, and common comorbidities (see Table footnote).

871 GAINS AND REMAINING CHALLENGES IN MORTALITY AMONG INDIVIDUALS WITH HIV, 1999-2017

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Background: Improvements in HIV care have resulted in people living with HIV reaching older ages. An increased risk of non-AIDS comorbid conditions may pre-date HIV infection, complicating efforts to close the gap in life expectancy compared to uninfected people. This study assessed trends in, and causes of, deaths in a state with high health insurance coverage.

Methods: We analyzed records of deaths in Massachusetts from 1999-2017 excluding non-residents. Using ICD-9 and -10 codes, we dichotomized deaths as 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 1319 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 to 76.2 years in 2017. Mortality in rural counties of Massachusetts increased by 42% from 1999-2017, while mortality in urban counties decreased by 27% during the same period.

Conclusion: Despite improvements in medical care, there is a persistent gap in life expectancy between HIV-infected and uninfected individuals. Continued improvements in HIV care are needed to further reduce mortality among HIV-infected individuals and to improve health outcomes for all individuals.

Table: Changes in Mean Age at Death Among HIV-Infected and Uninfected Individuals

<table>
<thead>
<tr>
<th>Year</th>
<th>Mean Age (years)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999-2003</td>
<td>53.1 (51.3-55.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2009-2017</td>
<td>67.2 (65.4-69.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

872 A DETAILED LOOK AT HIV MORTALITY IN KING COUNTY, 2016-2018

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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 depth 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.

Results: Of 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 Illnesses (0%; 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 OI 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 illness. 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 drugs 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.

Table: Demographics of PLWH compared to deaths in King County, Washington

<table>
<thead>
<tr>
<th>Variable</th>
<th>PLWH</th>
<th>People living with HIV with an AIDS-OI (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death</td>
<td>Median</td>
<td>56 (50-64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex of deaths</td>
<td>Male/Female</td>
<td>24/76</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

873 USING MULTISTATE MODELS TO DISENTANGLE MORTALITY & LOSS TO FOLLOW-UP IN HIV+ PATIENTS

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Background: Estimating mortality in HIV-positive patients starting antiretroviral therapy (ART) is challenging, as clinics often face substantial loss to follow-up (TLFU). Many studies ignore TLFU, leading to biased estimates.
Others correct for LTFU, but conventional methods give pooled estimates, which makes it impossible to assess risk factors and mortality estimates separately for those LTFU and remaining in care. We examined the use of multistate models to overcome this problem, using data from rural northern Mozambique, where patients LTFU are routinely traced.

Methods: We used clinical and tracing data from Ancuabe District, Mozambique. We used a multistate illness-death model without recovery to describe progression of patients from the initial state “on ART” through the intermediate state “LTFU” to the final absorbing state “Death”. We used Nelson-Aalen and Aalen-Johansen estimators to estimate crude cumulative transition hazards and probabilities, respectively. We fitted Cox proportional hazards models to examine associations between patient characteristics and transition hazards.

Results: Analyses included 17342 patients; 1403 (8.1%) had died and 8817 (50.8%) were LTFU. 1342 of patients LTFU were traced, of whom 46 (3.4%) were found to have died. At 5 years after ART start, estimated cumulative hazard (risk) of dying was 0.26 (95%-CI 0.17-0.39) out of the “LTFU” state and 0.19 (0.18-0.20) out of the “on ART” state, indicating an increased risk of dying for patients LTFU. Male sex, less advanced clinical stages, and starting ART in more recent calendar periods were associated with a greater hazard of LTFU (Figure). Higher mortality was associated with male sex, lower CD4 counts, more advanced clinical stages, and starting ART in earlier calendar periods. These associations were apparent for both patients on ART and LTFU, but differed in their magnitude (Figure).

Conclusion: Multistate models are an attractive alternative to common approaches for dealing with LTFU when estimating program-level mortality in ART facilities. They allow us to distinguish between patients LTFU and those remaining in care, while still providing pooled estimates combining the two groups. Progression of patients from starting ART to LTFU and death can thus be described in more detail to inform the design of appropriate models of differentiated care.

875 CD4 COUNT PATTERNS OVER TIME IDENTIFY LONG-TERM HIV CARE TRAJECTORIES IN SOUTH AFRICA

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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; 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).

874 INCREASED MORTALITY AMONG PEOPLE AT HIGH RISK FOR HIV IN THE UNITED STATES

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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 rates 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 hazard 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 (HRs 2.39/3.34), whereas 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/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.

Table. Mortality rates among people in the major HIV transmission categories compared to those without the relevant risk factors.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Transmission Category</th>
<th>All-Cause Mortality Rate (per 1000 PYrs)</th>
<th>Non-AIDS Mortality Rate (per 1000 PYrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age ≤55y</td>
<td>Age &gt;55y</td>
<td>Age ≤55y</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>0.25</td>
<td>0.19</td>
<td>1.00</td>
</tr>
<tr>
<td>Low SES</td>
<td>0.24</td>
<td>0.18</td>
<td>1.46</td>
</tr>
<tr>
<td>Never PWID</td>
<td>0.10</td>
<td>0.09</td>
<td>1.10</td>
</tr>
<tr>
<td>Ever PWID</td>
<td>1.25</td>
<td>1.25</td>
<td>2.75</td>
</tr>
</tbody>
</table>

Note: We used NHIS as a proxy for the risk of non-HIV-associated mortality among high-risk heterosexuals. Significantly different results seen in both.

*We stratified data by age, sex, race, transmission category, and age*sex*transmission category interaction.**

Abbreviations: PYS: person-years; HR: hazard ratio; CI: confidence interval; SES: socio-economic status; PWID: people who inject drugs.
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

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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. HIV 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 PREPEXPROPHYLAXIS ADHERENCE AND PERSISTENCE IN KENYAN TRANSGENDER WOMEN AND MSM

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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 ≥4 pills per week (700-1249 fmol/punch). Before TFV-DP levels were available, a subset 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 (3/33, 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...
HIV PREVALENCE AND RISK IN MALE’ TRANSMALE, AND TRANSFEMALE SEX WORKERS IN ZIMBABWE
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Background: National epidemics in sub-Saharan Africa become increasingly concentrated among high risk populations. In Zimbabwe, HIV prevalence is 13.3% in the general population compared to 56.5% amongst female sex workers. HIV services have been successfully set up for female sex workers (FSW) and reached over 45,000 women. However, male and transgender sex workers remain hidden and disconnected from services. Little is known about them, while their HIV risk is expected to be high. We determined HIV prevalence and risk among male and transgender sex workers in Zimbabwe.
Methods: By July 2018, the Centre for Sexual Health and HIV/AIDS Research (CeSHHAR) Zimbabwe has integrated an outreach intervention for male and transgender sex workers within the existing program for female sex workers. Participants were recruited through peer educator referral at multiple sex work hotspots throughout the country. From July 2018 to June 2019 in total 603 male and transgender sex workers enrolled the program. Trained staff administered a sociodemographic and behavioral survey and performed HIV voluntary counselling and testing. Determinants of HIV risk were analyzed through univariate and multivariate logistic regression analysis and compared to program data from 12,315 female sex workers.
Results: In total 221 male sex workers (MSW), 233 transfemale sex workers (TSFW) and 149 transmale sex workers (TMSW) were included in the study. Crude HIV prevalence estimates were 28.2% in MSW, 37.6% in TFSW and 38.1% in TMSW, compared to 36.5% in FSW. Reported risk behavior appeared high in all groups, in particular high rates of condomless anal sex for all groups, and high rates of condomless vaginal sex for all groups, and in TMSW, compared to 36.5% in FSW. Reported behavior was significantly more commonly used amongst MSW and TFSW and appeared protective for HIV.
Conclusion: To our knowledge this is the first study conducted in sub-Saharan Africa specifically focused at male, transfemale and transmale sex workers. HIV prevalence among Zimbabwean male and transgender sex workers was as high as for female sex workers. High numbers of transmale sex workers and female clients give a new insight into the diversity of people participating in sex work. HIV research and interventions focused on sex work should be made inclusive for all genders.

FACTORS ASSOCIATED WITH HIV, HCV, AND HSV-2 SEROSTATUS AMONG US TRANSGENDER WOMEN
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Background: Transgender women (TW) bear a disproportional burden of disease in the United States. The Leading Innovation for Transgender Women’s Health and Empowerment (LITE) study recruited subjects from six eastern and southern cities in the US. We identified factors associated with the infection of HIV, HSV-2 and HCV among TW at enrollment.
Methods: Serum samples were collected from 562 TW residing in Boston (n=110), New York (n=86), Baltimore (n=108), Washington DC (n=95), Atlanta (n=67) and Miami (n=96) from March 2018 to March 2019. Sociodemographic, behavioral, and socioeconomic information were obtained and log-binomial models were used to assess the prevalence ratios of factors associated with infection.
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 HSV-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, 1.53). 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.

HIV PREVALENCE AMONG TRANSGENDER MEN AT AN NYC COMMUNITY HEALTH CENTER
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Background: There have been multiple studies demonstrating elevated incidence and prevalence of HIV among transgender women (TW) especially African-American/TW, however few studies have been conducted among transgender men (TM). HIV prevalence among TM in the US is estimated to be between 0–4%. There have not been any studies examining prevalence that stratify by HIV risk factor, e.g., TM who have sex with MSM or use injection drugs. Callen-Lorde Community Health Center is a NYC-based clinic that predominately serves the LGBT communities and people living with HIV. It has the largest transgender patient population in the USA, serving nearly 5000 transgender and gender non-binary (TGB) patients. The aim of this study was to examine HIV screening behaviors, prevalence and risk factors among TM.
Methods: The Transgender Data Project was an IRB-approved retrospective chart review of all TGB patients at the clinic, ages 18+. Charts were reviewed manually. Data retrieved included birth sex, gender identity, race/ethnicity, education, employment, housing, insurance status, sex work, receipt of gender-affirming care (hormones, surgeries), STI history, HIV screening and HIV status. Multivariable logistic regression models were used to assess associations with HIV screening and HIV status.
Results: 577 TM, mean age 32.15 (18.3-70.5, SD 9.31) were included in the study. The majority were white (35% white, 13.9% black, 11.7% Hispanic, 5.8% Asian/Pacific Islander,13.5% mixed race), 78.9% had received at least one gender-affirming surgery. Fewer than half (24%, 31%) had undergone HIV screening. HIV prevalence was 2.9% (7/242) and highest among African Americans(African American 6.8%, Hispanic 3.2%, white 2.1%) and among TM who had sex exclusively with cisgender men (11.1%). HIV screening was associated with gender-affirming surgery (aOR 1.67, 95% CI=1.08, 2.58), substance use (aOR 5.18, 95% CI=1.41-18.99) and non-white race (aOR 2.56, 95% CI=1.69-3.85). Having a high school diploma reduced the odds of HIV infection (aOR 0.10, 95% CI=0.01-0.69).
Conclusion: HIV prevalence is thought to be low among TM however this analysis found an HIV seroprevalence >10% among TM who exclusively have sex with cisgender men. These results underscore the need to account for sexual risk (sexual behaviors and sexual orientation identity) among TM when interpreting HIV prevalence data. TM who have sex with cisgender men should be prioritized for inclusion in HIV prevention efforts.

PROGRESSION THROUGH THE HIV CARE CONTINUUM FOR TRANSGENDER WOMEN IN THE NA-ACCORD
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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)-naïve 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. 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.

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.
Conclusion: Our study highlights that TW are infected younger than other gender groups, but without lower CD4 cell count at initiation of care. They are not an increased risk of loss of follow-up or later VR than other groups.

884 IMPROVING DATA ON THE NYC HIV EPIDEMIC BY IDENTIFYING TRANSGENDER PEOPLE ON MEDICAID
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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 individuals accessing Medicaid.
Conclusion: Using a novel method we identified a large sample of transgender individuals in Medicaid, many of whom were PLWH. We were able to calculate the prevalence of HIV among transgender Medicaid beneficiaries and to improve ascertainment of transgender persons in the HIV registry. We also saw a sizeable increase in transgender individuals accessing Medicaid over the five-year period, likely due in part to expansion of Medicaid policy to cover transgender-related healthcare. Given the high coverage among transgender PLWH, Medicaid is a valuable source of health information for the transgender population, a group that is often difficult to identify due to issues of stigma, reduced access to appropriate care, and misgendering by healthcare personnel.

885 BUPRENORPHINE TREATMENT IS RELATED TO DECREASED HIV RNA LEVELS AMONG PEOPLE WITH HIV
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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.

Figure: Unadjusted distribution of viral loads during one year before and one year after start of buprenorphine treatment. The four lines of each color represent 90%, 75%, 50%, and 25th percentiles estimated by quantile regression
AFFORDABLE CARE ACT’S IMPACT ON SUBSTANCE-USE TREATMENT IN PEOPLE WHO INJECT DRUGS

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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 STAHR-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 AND BARRIERS TO CARE SERVICES AMONG HIV-POSITIVE PERSONS WHO INJECT DRUGS

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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., 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.

UNMET NEED FOR MEDICATION-ASSISTED TREATMENT AMONG PERSONS WHO INJECT DRUGS

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Background: People 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.
889 ESTIMATING HIV INCIDENCE AMONG PWID: POPULATION- AND FACILITY-BASED APPROACHES
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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 18.3% (New Delhi) to zero (Imphal), serial cross-sectional incidence from 16.1% (Kanpur) to 0.3% (Imphal), and ICC incidence from 7.3% (Aizawl) 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
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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

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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 ICD9-10 codes during study follow-up. Treatments for alcohol and opioid use were also used to identify 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 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 the polysubstance or 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 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 very high poverty neighborhoods (HR 1.4, 95% CI 1.3-1.5) had higher risk of death.

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.

HIV+. Substances use disorders (SUD) are common among PWH, with polysubstance use (PSU) being more prevalent than limited SU (LSU). PSU is associated with worse health outcomes and poor engagement in care. Patient navigation (PN) is a promising strategy to improve adherence to care and treatment for HIV.

Methods: Using Project HOPE (Hope Organized to Prevent Epidemics), a collaborative care model, we compared PN to PN with financial incentives for improved engagement and retention in care and adherence to treatment.

Results: Of 293 PWH enrolled, 147 were randomized to PN and 146 to PN with financial incentives. Participants in PN+ were more likely to adhere to ART (89% vs. 67%, P<0.001), improve viral suppression (91% vs. 79%, P<0.001), and have increased median CD4 count (810 vs. 306, P=0.003) at 6 months.

Conclusion: PN+ compared to PN improve engagement in care and adherence to ART. Financial incentives help to improve viral suppression and CD4 counts. These findings support the implementation of PN+ for PWH with SUD to improve health outcomes.
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.

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**894**  
**HIGH MORTALITY RATE AMONGST HIV INFECTED PEOPLE WHO INJECT DRUGS (PWID) IN SCOTLAND**  
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**Background:** Globally almost 18% of people who inject drugs (PWID) are living with HIV and HIV related mortality has decreased over time, with availability of antiretroviral therapy (ART). Non-AIDS mortality in high income settings is estimated at 2.34 per 100 person years (1.80-2.89) and drug-related death (DRD) is the leading cause of death amongst PWID. DRD in Scotland, a high income country, were reported at the highest on record in 2018. Amongst PWID in Scotland, the HIV prevalence is estimated at 2.3%, a recent increase explained by an outbreak in Glasgow. We sought to retrospectively evaluate the non-AIDS crude mortality rate (CMR), amongst PWID diagnosed with HIV in Scotland, and examine causes of death, over time.

**Methods:** A retrospective cohort review of all patients diagnosed with HIV, with injecting drug use identified as the transmission risk factor, between 1st January 2000 and 31st December 2018, with follow up until 30th June 2019, identifying those who died. Data was collated on basic demographics, virological markers, cause of death and time from HIV diagnosis to death. The main outcome measure was the all-cause crude mortality rate (CMR) and primary cause of death over time. Drug-related mortality was defined as per the National Records of Scotland definition.

**Results:** 413 PWID were diagnosed with HIV in the study period. 32% (133/413) were female. Mean age at diagnosis increased over time from 33 years (diagnosed 2000-04) to 39 years (diagnosed 2015-18). Until 30th June 2019, 22% (92/413) of these had died. Mean age of death was 42 years with no change over time. The non-AIDS CMR (per 100 PYFU) was 6.96 in those diagnosed from 2015-2018. The cause of death by year of HIV diagnosis are shown in figure 1; death from HIV/AIDS decreased from 61% (142/231) in those diagnosed 2000-2004 to 0% in those diagnosed from 2015-2018. DRD increased from 43% (10/23) to 63% (17/27) for the same groups.

**Conclusion:** Mortality amongst PWID living with HIV in Scotland is increasing over time and non-AIDS CMR is now higher than previously reported PWID living with HIV. HIV/AIDS is no longer a cause of death in this cohort and DRD are increasing, despite extensive, free to access, addiction and recovery services. To tackle the rising mortality rate, alongside high quality HIV care this cohort require novel interventions including heroin assisted treatment and highlight the case for safer drug consumption facilities.

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**895**  
**ASSOCIATIONS OF ALCOHOL CONSUMPTION WITH VIRAL SUPPRESSION AND ALL-CAUSE MORTALITY**

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**Background:** Unhealthy alcohol use may lead to higher morbidity and mortality among people living with HIV (PLHIV), 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 PLHIV 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 PLHIV, 4056 died during 183,683 person-years follow-up, 9,623 (28.7%) of PLHIV were non-drinkers, whilst 19,738 (58.9%), 3,320 (9.9%), and 857 (2.6%) had low, medium, and high alcohol intake, respectively. PLHIV 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, aHRs 1.13 (1.02, 1.26) and 1.60 (1.35, 1.90), respectively. For mortality, aHRs 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.

896 DEPRESSION AND VIROLOGIC REBOUND AMONG PATIENTS WITH HIV IN THE UNITED STATES
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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 during follow-up, 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.

897 PREVALENCE AND FACTORS RELATED TO TRAUMA SYMPTOMS AMONG PEOPLE WITH HIV

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Background: Among persons with HIV (PWHA), trauma symptoms (TS) are a barrier to achieving HIV control. We sought to determine factors associated with TS among PWHA 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. PWHA with TS at baseline had lower ART adherence (visual analogue scale<90 35 vs 17%, p<0.001), less viral suppression (56 vs. 76% p=0.3), more depression (88 vs. 74%, 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 PWHA 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= -1%, 95%CI: -2% to 0, men: RD= -2%, 95%CI: -4% to 0). Conclusion: Overall prevalence of TS is high and related to other psychiatric comorbidities among PWHA. 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

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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. A Wald homogeneity test assessed sex as an effect modifier with α=0.20.

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

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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 for up to 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 year 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. All HRs 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. All HRs 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

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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 partnerships 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.

Using surveillance data to measure trial HIV incidence outcomes: A modelling study

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Background: Cluster-randomized trials (C-RCTs) are expensive to conduct. Using surveillance data on new HIV diagnoses instead of measuring incidence in the trial could reduce costs. We used mathematical models to evaluate when surveillance data can be used to estimate impact in HIV intervention C-RCTs.

Methods: We used a model of HIV transmission among men who have sex with men in Baltimore, US, to simulate C-RCTs scaling up antiretroviral therapy (ART), pre-exposure prophylaxis (PrEP) and HIV testing in combination or alone. We tested whether modelled reductions in total cumulative HIV diagnoses predict model cumulative HIV incidence reduction over a 2-year trial. We also tested if reductions in diagnoses predict incidence reduction better over a longer trial duration (≤4 yrs) or when measured in later trial years. We explored if reductions in other surveillance measures—diagnoses with acute infection, diagnoses with early (CD4<500 cells/µl) infection, or diagnoses adjusted for testing volume—better predict incidence reduction. We used Pearson correlation to assess precision and report bias and sensitivity to detect a true incidence reduction.

Results: Over a 2-year trial expanding ART+PrEP+testing, model results suggest total diagnosis reductions correlate poorly with incidence reduction (r=0.386), underestimate incidence reduction (by 52%), and have 52% sensitivity (Table). Precision and sensitivity were better in trials expanding ART (r=0.878; sens 100%) or PrEP (r=0.960; sens 88%) alone, but bias remained (-52% for ART, -55% for PrEP). In trials expanding testing alone, diagnoses increased with decreasing incidence (r=−0.915). Measuring impact in longer trials or over later years improved correlations between diagnosis and incidence reductions for trials expanding ART+PrEP+testing, up to r=0.795 over the 4th year, and reduced bias. For ART+PrEP+testing trials, reductions in acute, early or adjusted diagnoses correlate poorly (r=0.51) with incidence reduction. Reductions in acute or early diagnoses correlate sufficiently with incidence reduction only when ART alone is expanded (r=0.993, r=0.953, respectively), but are biased (-18%, -41%).

Conclusion: Modelling results suggest that surveillance diagnoses data can only rarely be used to estimate C-RCT HIV incidence reductions. Reductions in acute/early or total diagnoses may be adequate predictors in C-RCTs expanding ART or PEP alone if bias can be adjusted for. None of the diagnoses markers explored were appropriate for C-RCTs expanding HIV testing.

Past behavior outperforms demography and geography as predictor of missed HIV care

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**BACKGROUND:** Missed HIV care provider visits are associated with increased mortality beyond the core indicators of retention in care and are an immediately actionable event. Previous prediction models for missed visits have not incorporated data beyond the individual level.

**Methods:** We developed prediction models for missed HIV care provider visits among adult people living with HIV (PLWH) with ≥1 visit in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) from 2010-2016. Potential predictors were identified at the individual-, community-, and structural-levels. Individual-level data included demographics, patient-reported outcomes (tobacco use, AUDIT-C, patient health questionnaire-9, EuroQOL Health Related Quality of Life-5D, HIV symptom index), insurance type, and prior visit adherence. Community-level data were obtained from the American Community Survey using ZIP Code tabulation area of residence. Structural-level data included HIV criminalization laws, Medicaid expansion, and proportion of budget dedicated to AIDS Drug Assistance Programs by state of residence. Variables were selected and models fit using random forests and 10-fold cross-validation; candidate models with highest area under the curve (AUC) were identified.

**Results:** Data from 382,548 HIV care provider visits among 20,889 PLWH followed for a median of 3.7 years were included. Median age was 44 years, 81% were male, 37% were Black non-Hispanic, and 57% reported male-to-male sexual contact as HIV transmission risk factor. Prior visit adherence improved discrimination most in all models; AUC jumped from 0.68 to 0.75 with its addition alone in one candidate model. The strongest predictors in this model were prior visit adherence, follow-up time, age, and CD4+ count at the individual-level, along with proportion with Black race, proportion unemployed, and proportion living below the poverty line at the community-level.

**Conclusion:** Prediction models validated using multi-level data in a population representative of US PLWH had a similar AUC to previous models developed using only individual-level data. Strongest predictors were individual-level variables, particularly prior visit adherence, though community-level variables were also predictive. Absent additional behavioral, social, structural, or clinical data, PLWH with previous visits should be targeted by interventions to improve visit adherence.

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**THE CD4 DEPLETION MODEL DOES NOT DIFFERENTIATE INCIDENT FROM CHRONIC INFECTION**

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**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. Currently, HIV incidence in the U.S. are derived from the Center for Disease Control’s CD4 depletion model. The EtHE initiative requires an understanding of HIV incidence at a regional and local level to evaluate the impact of prevention interventions. Here we examine the accuracy of the CD4 depletion model for measuring incidence in sub-epidemics.

**Methods:** Using the San Diego Primary Infection Resource Consortium estimated date of infection (PIRC EDI) model as a gold standard (a model that estimates recency using the limiting-antigen (LAG) avidity assay in combination with viral load information which has an estimated false recency rate of 1%), we found that the sensitivity of the CD4 model was 51% (95% CI 47%-55%) and specificity was 60% (95% CI 52%-67%) (see abstract 1291). We used this to calculate the predictive values of CD4 recency testing in various epidemic scenarios.

**Results:** Using the above estimates, we calculated the positive predictive value (PPV), negative predictive value (NPV), and the posterior odds (PO), 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 63.4% to 56.0%, NPV ranged from 95.9% to 55.1%, and PO from 0.67 to 1.28. Using a fixed proportion of 25% incident infections among all new diagnoses, we varied the size of the sampled population from 250 to 10,000 to evaluate the accuracy of the CD4 model in predicting the number of incident cases in different size epidemics. The estimated values were approximately 1.0-fold greater, ranging from 106.8 (95% CI 105.5 to 110.3) incident infections (true value 62.5) for a population of 250, to 4275 (95% CI 3850 to 4775) incident infections for a population of 10000 (true value 2500).

**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...
905  KEY POPULATION SIZE ESTIMATION IN NIGERIA: NOVEL APPROACHES TO SAMPLING AND ANALYSIS
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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 KPs 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 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.

906  SEPIODAL HIV DYNAMICS IN FRANCE: A GRAVITY EFFECT MODEL
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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 states and geographic variation in transmission dynamics.

Methods: We examined HIV-1 polymerase sequence 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 people 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 2018–19 after expansion of reporting.

907  INCREASING CAPACITY FOR DETECTING CLUSTERS OF RAPID HIV TRANSMISSION: UNITED STATES
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Background: Monitoring HIV epidemiology is constantly evolving and regular surveillance expansions of reporting.
Results: Sequence completeness increased from 26% (December 2015) to 42% (March 2019); increases were seen in EHE areas (30% to 43%) and in areas not previously funded to collect sequences (3% to 27%). Of 194 priority clusters identified during December 2015–March 2019, 87 were first detected in 2016–19. 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.

Figure. Characteristics of people involved in clusters of rapid transmission first detected in 2018–2019, overall and for three selected states.

Transmission category

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Overall (n=756)</th>
<th>State A (n=95)</th>
<th>State B (n=178)</th>
<th>State C (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR</td>
<td>18%</td>
<td>24%</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>MSM who inject drugs</td>
<td>20%</td>
<td>14%</td>
<td>27%</td>
<td>6%</td>
</tr>
<tr>
<td>Men who have sex with men (MSM)</td>
<td>21%</td>
<td>21%</td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td>Persons who inject drugs (PWID)</td>
<td>20%</td>
<td>16%</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td>Heterosexual contact (HHC)</td>
<td>4%</td>
<td>7%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Other or no identified risk</td>
<td>42%</td>
<td>57%</td>
<td>41%</td>
<td>58%</td>
</tr>
</tbody>
</table>

908 STATEWIDE HIV-1 TRANSMISSION CLUSTER DETECTION AND PRIORITIZATION FOR RESPONSE

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Background: New HIV diagnoses continue in the Southern US despite widespread prevention efforts, underscoring 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<0.05). Recent diagnoses tended to cluster with other recent diagnoses: 60% (775) clustered with ≥3 recent diagnoses (range 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.

DO PARTNER SERVICES INITIATED FROM MOLECULAR CLUSTERS YIELD NEW OR VIREMIC HIV CASES?

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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% Latino, 6% female and 89% men who have sex with men. Of the 539 named partners, 162 (36.6%) were linked to indexes in a cluster and of those 20% were either new diagnoses or viremic. There was no statistically significant difference in the yield of new diagnoses or viremic partners linked to index clients in a cluster versus not in a cluster (RR 1.54 (0.10-2.38); p=0.051).

Conclusion: Partner services that were initiated from the subset of index clients whose HIV sequences are in a molecular cluster yielded similar new HIV case finding or identification of those with viremia as index clients not in clusters. 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.
910 THE RELATIONSHIP BETWEEN THE HIV TRANSMISSION NETWORK AND CARE CONTINUUM IN LA COUNTY
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Background: Successful public health action combating 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 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
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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 4,009 (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
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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 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 (p<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).
HIV RISK INCREASES WITH POSITIVE TIES IN HIGHLY CONNECTED SOCIOSPATIAL PWID NETWORK

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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. Individual and network-level factors were analyzed for associations with prevalent HIV infection; machine learning was used to nominate predictors.

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, 86.6% 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=1.89) 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

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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 TN93 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, 81% 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.
PHYLOGENETIC EVIDENCE OF HIV-1 MIXING BETWEEN KEY RISK GROUPS IN COASTAL KENYA

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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), injecting drug users (IDU), 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 naive 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). Temporal and phylodynamic analyses were performed using a Bayesian Markov Chain Monte Carlo approach.

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 one large cluster. Most clusters (85%) consisted of sequences from the same transmission group, indicating frequent within-group transmission. However, 15% of the clusters were mixed between MSM, FSW and HET sequences. One large IDU cluster was found, suggesting that HIV-1 was introduced from a single source followed by fast spread within the IDU population, distinguishing IDU transmission relative to other risk groups. Phylodynamic analysis of the sub-epidemic among IDU indicated a steady increase in HIV-1 infections from the origin of the cluster in 1987.

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.

PHYLDYNAMIC EVIDENCE OF HIV TRANSMISSION BETWEEN AGE-DISCREPANT MSM IN KING COUNTY

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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-1 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.
Indigenous: h=.29; Asian: h=.33; Other: h=.11), residential neighborhood (Downtown Vancouver: h=.39; Vancouver: h=.37; Outside Vancouver: h=.31), education (High school or greater: h=.34; Less than high school: h=.09), patronage of gay bars and clubs (About once per month or more: h=0.33; Less than once per month: h=.19), and use of online sex seeking apps (About once per month or more: h=.32; Less than once per month: h=0.16), and use of GHB (Yes: h=.30; No: h=.25), LSD (Yes: h=.41; No: h=.34), crystal methamphetamine (Yes: h=.37; No: h=.29), and crack (Yes: h=.14; No: h=.40). Low homophily (h<0.30) was observed for perceived HIV transmission risk (Low Risk: h=.07; High risk: h=.11), STI history (Ever Diagnosed: h=.27; Never Diagnosed: h=.09), and for patterns of condom use: (No anal sex: h=.07; No condoms anal sex (CAS): h=.04; CAS with only sero-concordant partners: h=.01; CAS with serodiscordant/unknown status partners: h=.11). Conclusion: We observed moderate to high homophily across demographic characteristics, substance-use, and dating-venues, but low homophily of sexual behaviours.

918 PHYLOGENETIC INSIGHTS ON HIV-1 TRANSMISSION DYNAMICS AMONG MSM AND MIGRANTS IN QUEBEC
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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 (TRAnsmission 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) were analyzed using Maximum-Likelihood in MEGA10 and/or HIV-TRACE (TRAnsmission Cluster Engine) platforms.

Conclusion: The ability to predict, identify and respond to emerging “active” HIV transmission clusters in close to real-time may inform public health interventions to avert transmission cascades and control the HIV epidemic.

920 EVALUATION OF HIV TRANSMISSION CLUSTERS AMONG NATIVES AND FOREIGNERS LIVING IN ITALY
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Background: The recent increase in non-B subtype HIV-1 diagnoses in Italy suggests a possible increase in transmission of non-B subtypes. Phylodynamics showed a marked decline in singleton transmissions and small cluster outbreaks post-2008, concomitant to advances in Treatment-as-Prevention paradigms. This was offset by an increase in large transmissions, reflecting continued transmission risk in various regions. This study aimed to evaluate the proportion and characteristics of non-B subtype HIV-1 diagnoses in Italy, and to explore transmission clusters among non-B subtypes.

Methods: We included data from 3,110 HIV-1 infected individuals. The overall proportion of non-B subtypes increased from 7% (67/3,249) before January 2015 to 31.5% (195/620) after 2015 (subtype G 7.4%; 184/2,490 before 2015 vs. 9.5%; 59/620 after 2015). This was particularly driven by the increase in subtype C, which increased from 23% (564/2,490) before 2015 vs. 5.6% (11/195) after 2015. 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 868 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.
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 2016 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 (LMTCs, 2-9 seq), medium (MTCs, 4-9 seq) and large (LMTCs, ≥10 seq). MTCs were first deduced 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-naïve 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 87.9%, p<0.001) and MSM (74.7% vs 56.9%, p<0.001), younger (median [IQR] yrs: 32 [27–40] vs 38 [31–46], p<0.001), and predominantly of Italian origin (88.7% vs 77.8%, p<0.001), more recently diagnosed (median [IQR] yrs: 2012 [2009–2014] vs 2007 [2005–2013], p<0.001), and higher CD4 count were significantly associated with MTCs (Table). The 24 non-B infections involved in MTCs were more commonly found in natives (N=47, 92.2%) than in foreigners (N=4, 7.8%). Logistic regression confirmed that factors such as Italian origin, being MSM, younger age, more recent diagnosis and 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 MTCs and 23.1% of SMTCs. By focusing on migrants, they contributed for 14.4% to SMTCs, 7.6% to MMTCs and 7.1% to LMTCs, respectively. The 24 migrants involved in LMTCs and MTCs 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.

Molecular Analysis Suggests Post-Migration HIV-1 Acquisition Among Migrants in Paris

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Background: Almost all 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 subtyping 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 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, using MEGA6 software. Factors associated with clustering within large LTNs (≥10 sequences) were 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.

Conclusion: We found that 29.3% of 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 heterosexuals OR: 1.0; 95% CI: 1.0-1.5, 4.6). The proportion of MSM in the CRF02_AG LTNs was significantly higher (38.3%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogenetic 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 heterosexuals OR: 1.0; 95% CI: 1.0-1.5, 4.6). The proportion of MSM in the CRF02_AG LTNs was significantly higher (38.3%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogenetic 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 heterosexuals OR: 1.0; 95% CI: 1.0-1.5, 4.6). The proportion of MSM in the CRF02_AG LTNs was significantly higher (38.3%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogenetic 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 heterosexuals OR: 1.0; 95% CI: 1.0-1.5, 4.6). The proportion of MSM in the CRF02_AG LTNs was significantly higher (38.3%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogenetic 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 heterosexuals OR: 1.0; 95% CI: 1.0-1.5, 4.6). The proportion of MSM in the CRF02_AG LTNs was significantly higher (38.3%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogenetic 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 heterosexuals OR: 1.0; 95% CI: 1.0-1.5, 4.6). The proportion of MSM in the CRF02_AG LTNs was significantly higher (38.3%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogenetic 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 heterosexuals OR: 1.0; 95% CI: 1.0-1.5, 4.6). The proportion of MSM in the CRF02_AG LTNs was significantly higher (38.3%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogenetic 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 heterosexuals OR: 1.0; 95% CI: 1.0-1.5, 4.6). The proportion of MSM in the CRF02_AG LTNs was significantly higher (38.3%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogenetic 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 heterosexuals OR: 1.0; 95% CI: 1.0-1.5, 4.6). The proportion of MSM in the CRF02_AG LTNs was significantly higher (38.3%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogenetic 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 heterosexuals OR: 1.0; 95% CI: 1.0-1.5, 4.6). The proportion of MSM in the CRF02_AG LTNs was significantly higher (38.3%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001).
using 1000 random network permutations. A generalized linear model was used to identify characteristics associated with the JC.

### Results:

The 4150 (50.6%) HIV cases that were clustered were assortative by ZIP, HD, and SPA (0.02, 0.09, 0.15; p<0.001). Geography was less assortative than race/ethnicity and transmission risk. 58% of genetically linked cases were diagnosed in the same year, and 44% were diagnosed in the same HD; however, only 15% were diagnosed in the same year and HD. This time-space concordance among genetically-linked pairs was also low across ZIP and SPA (p<0.001). In the JC analysis, cis-men (b=0.20; p<0.001) and those younger at diagnosis (b=0.189; p=0.001) had more overlap between clusters and geography; we observed an inverse association for trans-women (b=0.51; p<0.001) and African-Americans (b=0.18; p<0.001).

### Conclusion:

We found significant, but weak associations between the HIV transmission network and residence at diagnosis. Within an urban setting with endemic HIV, genetic clustering may serve as a better indicator than time-space transmission network and residence at diagnosis. Within an urban setting with endemic HIV, genetic clustering may serve as a better indicator than time-space transmission network and residence at diagnosis. Within an urban setting with endemic HIV, genetic clustering may serve as a better indicator than time-space transmission network and residence at diagnosis. Within an urban setting with endemic HIV, genetic clustering may serve as a better indicator than time-space transmission network and residence at diagnosis. Within an urban setting with endemic HIV, genetic clustering may serve as a better indicator than time-space transmission network and residence at diagnosis.
925 MAPPING AND CHARACTERISING HIV TRANSMISSION HOTSPOTS IN SUB-SAHRANAFRICA
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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 51,234 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.

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 at risk will be essential to curb transmission. More fine-scale geospatial mapping of key populations, such as sex workers, and migrant populations at risk will be essential to curb transmission.

926 GEOGRAPHIC CHARACTERISTICS OF HIV GENETIC CLUSTERS AMONG NEWLY DIAGNOSED CASES IN NC
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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 borderlines, 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 geographic median 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.

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
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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.datamoney.org/hivtrace) was used to estimate transmission clusters in 484 subtype B antiretroviral-naïve 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 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 Bbosa1, Deogratius Ssemwanga2, Alfred Ssekagiri3, Yunia Mayanja2, Nicholas Bbosa3

Goal: To estimate transmission clusters in 484 subtype B antiretroviral-naïve 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 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.

929 CONCORDANCE OF METHODS IN IDENTIFYING MOLECULAR HIV CLUSTERS
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Methods: We studied 8 commonly used methods (7 model-based, and distance-based HIV-TRACE) and used them to identify clusters of HIV-1 subtype B pol sequences from 1,656 persons, ~80% of a densely-sampled Rhode Island epidemic during 2004-2018. For each method, we compared proportion of clustered sequences within and between methods using various distance and bootstrap thresholds; and clustering concordance between methods (including percentages of identical sequence pairs that cluster together; percentages of cluster similarity at 100% and at 80%; and percentages of identical non-clustered sequences). We conducted comparisons under (i) strict (bootstrap >0.95; TN93 distance 0.015 substitutions/site) and (ii) relaxed (bootstrap 0.8-0.9; distance 0.03-0.045 substitutions/site) thresholds, intended to address different public health objectives (e.g. strict for outbreak; relaxed for epidemic characterization).

Results: Of the 1,656 sequences, 18-53% formed 114-217 clusters, depending on thresholds used. Clustering proportion within methods depended on bootstrap and distance, with distance having stronger effects. Variation in clustering proportion across methods was more pronounced with stringent bootstrap and relaxed distances. For strict thresholds, HIV-TRACE identified 5-15% higher proportion of clustered individuals than model-based methods (p<0.005 for all pairwise comparisons). In contrast, for relaxed thresholds, HIV-TRACE identified 3-19% lower proportion of clustered individuals than model-based methods (p<0.05 for all pairwise comparisons). Distributions of percent concordance between methods, stratified by threshold type (strict, relaxed), are presented in the Table.

Conclusion: Clustering similarity between common molecular epidemiology methods varied, with some substantial discordance. In the context of integration of molecular epidemiology into public health, this implies that the choice of clustering method and threshold may impact precision of public health interventions.
930 USE OF PHYLOGENETIC ANALYSIS TO INFER THE DIRECTION OF HIV TRANSMISSION

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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 both individuals (source and recipient) have long-term infection.

931 NEAR REAL-TIME IDENTIFICATION OF RECENT HIV INFECTION BY PID-NGS IN NORTH CAROLINA

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Background: The identification of recent (incident) HIV infections among people with newly diagnosed infections is critical to HIV prevention. We developed a Multiplexed Primer ID-Next Gen Sequencing (MPID-NGS) approach to identify recent infection by measuring the intra-host viral diversity over multiple regions of the HIV genome. Here we summarize the field implementations of this approach to identify recent infection, and include surveillance of drug resistance mutations (DRMs) in new diagnoses from the Public Health Laboratory in the state of North Carolina in 2018.

Methods: The MPID-NGS libraries were constructed covering the coding regions for protease (PR), a portion of reverse transcriptase (RT), integrase (IN), and the V1 to V3 region of the env gene from the HIV positive serums. The MiSeq platform was used for sequencing. The TCS-DR pipeline was used for bioinformatics analysis and to identify DRMs. Recent infection was defined as within 9-month of infection, and the RT and V1/V3 regions were used to define recency.

Results: A total of 547 HIV+ samples from diagnostic testing in 2018 were subjected to sequencing; of these 294 were considered new diagnosis and ART naive as the sample used for testing was less than 30 days from diagnosis date reported by Health Dept. The sequencing success rate for the newly diagnosed was 91.2%. Overall recent infection was identified in 94 subjects (35%). Multivariate regression shows that people between 18 to 24 were more likely to be diagnosed at recent infection (OR=3.34, p=0.018) and those with unknown risk factors were less likely to be diagnosed at recent infection (OR=0.34, p=0.047). We observed that RT regions had more SDRMs than PR and IN, and RT K103N was the most common mutation overall. RT mutations M184V, R65R and major IN DRMs were rarely seen (Table 1). We used the RT sequence to explore close transmission clusters and we found a total of 28 clusters (size 2 to 4) using a similarity cut-off at 1%.

Conclusion: MPID-NGS combines recency identification and DRM screening for new HIV diagnosis in near real-time. Young individuals had highest recent infection rate while those with unknown risk factors had the lowest. The overall DRM rate was high but clinically important mutations were low. Rapid identification of transmission clusters containing recently infected individuals facilitates targeted prevention efforts.

932 IMPLICATIONS OF NEXT-GENERATION SEQUENCING FOR DRUG RESISTANCE AND CLUSTER DETECTION

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Background: HIV-1 polymerase (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 from routine HIV drug resistance (DR) testing using next-generation sequencing (DNA-NGS) in New York during 2015-2019. We compared 294 RNA-S and DNA-NGS sequences using the MiSeq platform. The MiSeq platform was used for sequencing. The TCS-DR pipeline was used for bioinformatics analysis and to identify DRMs. Recent infection was defined as within 9-month of infection, and the RT and V1/V3 regions were used to define recency.
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 &gt;5% distance level</th>
<th>Mean sequence distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA-NGS to DNA-NGS</td>
<td>276</td>
<td>83.7</td>
<td>19.2</td>
<td>18.8</td>
</tr>
<tr>
<td>DNA-NGS to RNA-NGS</td>
<td>121</td>
<td>67.8</td>
<td>25.6</td>
<td>12.5</td>
</tr>
<tr>
<td>DNA-NGS to RNA-S</td>
<td>867</td>
<td>99.7</td>
<td>2.3</td>
<td>14.7</td>
</tr>
<tr>
<td>RNA-NGS to RNA-NGS</td>
<td>262</td>
<td>89.8</td>
<td>16.4</td>
<td>16.8</td>
</tr>
<tr>
<td>RNA-NGS to RNA-S</td>
<td>707</td>
<td>75.7</td>
<td>27.3</td>
<td>14.8</td>
</tr>
<tr>
<td>RNA-S to RNA-S</td>
<td>5,595</td>
<td>79.0</td>
<td>30.6</td>
<td>10.1</td>
</tr>
</tbody>
</table>

1. Comparisons are with n individuals from pol sequences collected from 1 year apart
2. A distance threshold of the proposed subtype (20% discordance)
3. Clustering at >1% distance threshold indicates recent and rapid transmission per CDC

933 PERVERSIVE AND NONRANDOM RECOMBINATION IN NEAR FULL-LENGTH HIV GENOMES FROM UGANDA

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Background: Recombination is an important feature of HIV evolution, occurring both within and between the major branches of diversity (subtypes). The Ugandan epidemic is primarily composed of two subtypes, A1 and D, that have been co-circulating for 50 years, frequently recombining in dually infected patients. We have investigated the frequency of recombinants in this population (both inter- and intra-subtype), and the location of breakpoints along the genome.

Methods: As part of the PANGEA-HIV consortium project 1472 consensus genomes over 6kb were obtained from 1857 samples collected by the MRC/UVRI & LSHTM Research Unit in Uganda, 465 (31.6%) of which were near-full length (NFL) genomes (>8kb). The subtyping tool SCUAA was used with a reference dataset of 218 full length genome and circulating recombinant form genomes to identify recombination events both between and within subtypes. Genomic distribution of inter-subtype breakpoints was characterised using K-means clustering and generalized linear modeling.

Results: 233 of the 465 (50.1%) NFL genomes contained only one subtype; 143 A (30.8%), 82 D (17.6%) and 8 C (1.7%), while 232 (49.9%) contained more than one subtype (including A1/D (n=164), A1/C (n=13), C/D (n=9), A1/C/D (n=13), and 33 complex types). No reported circulating recombinant forms were identified. Almost all of the NFL genomes (91.8%) contained at least one breakpoint, either intra- or inter-subtype. The frequency of recombination breakpoints along the genome was similar in intra- and inter-subtype recombinants. K-means clustering of recombinant A1/D genomes revealed a particular genome region which was often inherited intact, extending from C2 in gp120 to TM in gp41. In addition, a generalized linear model showed significantly fewer breakpoints in the gag-pol and envelope C2-TM regions compared with accessory gene regions. There was little evidence of large-scale transmission of recombinants within this sample: almost all (153/164; 93%) of the A1/D recombinants are unique recombinant forms.

Conclusion: Recombination in HIV genomes is pervasive within and between subtypes in the populations studied and exhibits clear biases in breakpoint location. Its distorting effect on genealogical inference should therefore be acknowledged and taken into account more widely.

934 JACKHAMMER RT-PCR RECOVERS DIVERSE ARCHIVAL VIRAL GENOMES FROM KINSHASA, 1983

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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 4–7000 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_CX, 25_CX), 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 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 phylogenetic 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

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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 sequences, 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 Phylip 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 83C2003 and 90CD121E12, 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 first two 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

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**Background:** HIV recombination 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:** HIV-1 WGS was undertaken 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 of 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 (UKHDDR). 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 2014. WGS data shows even higher proportion of recent infections involving complex recombinants in 2015-2016 at 18.3% (33/181) compared to 2.3% (1/44) in 2000-2006. Furthermore, 32.4% (11/34) of WG 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=28). 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 UKHDDR, 27.3% (n=9) of the complex recombinants were in 5 transmission clusters, 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

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**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, 20,732 (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, 5030 (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 Kigoro1, Mahmoud Shally1, Abdalla Wesoonga2, 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 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.

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**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.
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 APS 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. PYEP 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 APS for newly diagnosed GBT appears feasible and safe. These strategies can effectively penetrate hidden epidemics among GBT and link newly diagnosed GBT to care.

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**939 SCALE-UP OF ASSISTED PARTNER SERVICES (APS) IN BOTSWANA**

**Matthew R. Golden, Matthew R. Golden, Matias Grande, Shreshth Mawandia, Odileile Bakae, Lenna Tau, Gobabaone Mogomotsi, Esther Mmatli, Modise Ngombo, Jenny Ledikwe**

**University of Washington, Seattle, WA, USA, International Training and Education Center for Health - Botswana, Gaborone, Botswana, Botswana 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 6595 (99%) persons who tested HIV positive were offered APS, of whom 6508 (94%) were eligible for the intervention and 6097 (88% of HIV positive persons) received APS and were tested HIV positive were offered APS. We evaluated APS implementation in the PEPFAR supported districts of Botswana to define program coverage and outcomes. 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).

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**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 is substantially below that reported in most published evaluations, likely reflecting a combination suboptimal program implementation and the high proportion of HIV infected persons in Botswana who already know their HIV status.

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**940 OPTIMIZING TESTING INCREASES YIELD IN HIV CASE FINDING IN 24 COUNTRIES, 2018–2019**

Shahul Hameed Ebrahim, Arielle Lasry, Randy Yee, Wayne A Duffus, John Abellera, Shane T Diekmann, Jacqueline Rurangirwa, Bakary Drammeh, Tiffany Ahoulou, Michael Grillo, Vincent Wong, Stephanie Behel, COC, Atlanta, GA, USA, Defense Health Agency, San Diego, CA, USA, United 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 (PTIC) 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 PTIC 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). PTIC 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%, 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, pediatric, 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.

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**Table. HIV testing and yield in 24 PEPFAR countries, 2019–2019**

<table>
<thead>
<tr>
<th>Year</th>
<th>Q2 Number of tests</th>
<th>Q2 % of total tests</th>
<th>Change in yield (%)</th>
<th>Q2 % of total tests</th>
<th>Change in yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>12,433,654</td>
<td>20.9%</td>
<td>3.6%</td>
<td>11,975,262</td>
<td>20.1%</td>
</tr>
<tr>
<td>2019</td>
<td>11,975,262</td>
<td>20.1%</td>
<td>3.0%</td>
<td>11,233,980</td>
<td>19.2%</td>
</tr>
</tbody>
</table>

**PTIC in OPDs:** 2018: 11,475,822; 2019: 10,000,842 (22%) Decreased 406,100 (5.5%) to 384,100 (3.7%) (22%).

**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 is substantially below that reported in most published evaluations, likely reflecting a combination suboptimal program implementation and the high proportion of HIV infected persons in Botswana who already know their HIV status.
941 PARTNER TESTING SERVICES TO ACHIEVE HIV EPIDEMIC CONTROL IN 9 PEPFAR COUNTRIES, 2019
Bakary Drammeh1, Shahul Ebrahim1, Andrew L. Baughman1, Arielie Lasry2, Randy Yee, Wayne A Duffus3, Jacqueline Runauringwa1, Shane T Diekmann1, Amy M Medley1, Tiffany Michelle Aholou1, G. Laissa Ouedraogo1, Isabello Tondoh-Kouri1, Ismelda Pietersen1, Stephanie Behel1, for the HIV Testing Services CDC, Atlanta, GA, USA, Ministre de la Santé et de l'Hygiène Publique, Abidjan, Côte d'Ivoire, 1US CDC Windhoek, 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 represent 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 percentage of HIV-positive cases who accepted 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.

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 Makyaa1, Angela Ramadhan1, Peris L Utara1, Leonard Subi1, Neustra Kwasigabo1, Prosper F Njau1
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 progresses 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, treatment 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 Wamuti1, Monisha Sharma1, Angela Kiptoo2, George Otieno1, Christopher Obonyo1, Judith Onsomu1, Cecilia Audu2, Dominic Mutai3, Paul Macharia1, Rose Bores1, Sarah Masyuko1, Karithi Edward1, Mary Mugambi1, Carey Farquhar1,2
1University of Washington, Seattle, WA, USA, 2PATH, Seattle, WA, USA, 3Ministry of Health, Nairobi, Kenya

Background: Amongst partner services (PS) 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 ineligibility 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 - 3.28) and be divorced/separated (aRR: 3.09, 95% CI 1.39 - 6.86) 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 ineligibility included fear or risk of intimate partner violence (9%), previous HIV diagnosis (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 Masyuko**1, Manisha Sharma2, Emily Kemunto1, George Otieno3, Christopher Obong'o3, Judith Onsomu3, Cecilia Audo3, Dominic Mutai4, Paul Macharia3, Beatrice Wamuti5, Rose Bosire6, Mary Mugambi1, Kariithi Edward4, Carey Farquhar4

1Ministry of Health, Nairobi, Kenya, 2University of Washington, Seattle, WA, USA, 3Program for Appropriate Technology in Health, Kisumu, Kenya, 4Program for Appropriate Technology in Health, Nairobi, Kenya, 5Kenyatta 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 Kisumu 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, 889 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, 99% of female index cases and 87% of male partners reported to be on anti retroviral 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

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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 testing was 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 other for these 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 95% 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), the belief that there is any possibility of being HIV/HCV
infected 3.2 (1.4–7.5), previous lymphoma 19.4 (2.1–183.3), 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 23.6 (4.2–131.8), and hepatitis or unexplained liver disease 20.8 (8.6–50.3). Nomograms appear in Figure
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.

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 $18 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 savings would be modest unless implementation
was accompanied by changes in staff costs.

Table – Predictors of HCV Test Positivity, Botswana testing data

<table>
<thead>
<tr>
<th>Category</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.27</td>
<td>(1.13–1.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (≥40)</td>
<td>2.38</td>
<td>(1.07–2.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Testing Strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>1.56</td>
<td>(1.33–1.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient</td>
<td>1.06</td>
<td>(0.76–1.45)</td>
<td>0.73</td>
</tr>
<tr>
<td>Testing Pair**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidents/Emergency</td>
<td>0.88</td>
<td>(0.67–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Outpatient - Departments</td>
<td>0.65</td>
<td>(0.52–0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outpatient - Specialty Clinics</td>
<td>0.43</td>
<td>(0.28–0.66)</td>
<td>0.001</td>
</tr>
<tr>
<td>Inpatient - General</td>
<td>0.45</td>
<td>(0.34–1.47)</td>
<td>0.19</td>
</tr>
<tr>
<td>Inpatient - Medical</td>
<td>4.15</td>
<td>(3.50–10.18)</td>
<td>0.18</td>
</tr>
<tr>
<td>Inpatient - Obstetrics</td>
<td>0.70</td>
<td>(0.50–1.01)</td>
<td>0.32</td>
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<tr>
<td>Inpatient - Surgical</td>
<td>1.25</td>
<td>(0.69–2.25)</td>
<td>0.47</td>
</tr>
<tr>
<td>Inpatient - Other**</td>
<td>1.07</td>
<td>(0.81–1.40)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

949 FREQUENT HIV TESTING OF MSM AND TGW OF COLOR RESULTS IN EARLIER
DIAGNOSIS

Karen W. Hoover1, Weiming Zhu2, Kenneth L. Dominguez1, Kirk D. Henny1,
Ya-Lin A. Huang1, Kashif Iqbal1, Mary Tanner1, Kevin P. Delaney1
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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
number of HIV tests and conducted Kaplan-Meier analyses to determine the
time to diagnosis and yield of testing among MSM and TGW of color in the THRIVE demonstration project.

Results: We identified a negative test and at least one additional test. Among these 5408
persons, 1338 were MSM or TGW of color who did not use PrEP and 47 (4%) had a
subsequent positive result. Overall, the median time to diagnosis was 235
days (IQR 92–364). Frequent testers were diagnosed earlier than non-frequent
testing as > 180 days. We estimated the yield of HIV testing as the number of new
diagnoses per tests performed. All results were stratified by testing frequency.

Results: In THRIVE, 20,956 clients received an HIV test of these, 26% (5408)
had an initial negative test and at least one additional test. Among these 5408
persons, 1338 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 tester, the median time to diagnosis was 364 days (IQR

948 HIV TESTING CRITERIA TO REDUCE TESTING VOLUME AND INCREASE
POSITIVITY IN BOTSWANA

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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-
citizen, 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 $18 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.
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% (12/6056).

**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.

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### 950 INDETERMINATE HIV RAPID-TEST RESULTS: OUTCOMES AND RISK FACTORS

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**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 discordant 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 2.09, 95% CI 1.77, 2.41; >44 vs. <20 years 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, 0.98); ART vs. not (adjPR 1.29, 95% CI 1.10,1.51).

**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.
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MODELING POINT-OF-CARE NUCLEIC ACID TESTS (POC NAT) TO MINIMIZE HIV MISDIAGNOSES
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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/1000PY), and costs of ART ($6-22m), HIV care ($27-38m), 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 negative/positive (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 misdiagnoses 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.

Table 1: Projected number of misdiagnoses, life expectancy, and lifetime costs resulting from RDT-WHO, RDT-CI, and NAT-Resolve testing strategies among 10,000 of those tested (n=1,000,000 adults).

<table>
<thead>
<tr>
<th>Strategy</th>
<th>FN (per 1000)</th>
<th>FP (per 1000)</th>
<th>LE (YLS)</th>
<th>Cost (2022 USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDT-WHO</td>
<td>364</td>
<td>266</td>
<td>948</td>
<td>149.80</td>
</tr>
<tr>
<td>RDT-CI</td>
<td>548</td>
<td>246</td>
<td>99.30</td>
<td>149.20</td>
</tr>
<tr>
<td>NAT-Resolve</td>
<td>506</td>
<td>246</td>
<td>9.73</td>
<td>147.70</td>
</tr>
</tbody>
</table>

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EVALUATION OF QUALITATIVE AND SEMIQUANTITATIVE HIV POINT-OF-CARE NUCLEIC ACID TESTS
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Background: Point-of-care (POC) nucleic acid tests (NAT) could detect acute HIV infection, resolve discordant screening results, monitor patients taking pre-exposure prophylaxis (PrEP), and identify virologic failure among persons with HIV infection (PWH) on antiretroviral treatment (ART). Real-time communication of POC NAT results can improve HIV prevention and care. While the SAMBA II POC NAT is used in Europe and Africa, it has not been evaluated in the US.

Methods: From June 2018 to August 2019, PWH and persons testing for HIV participated in Project DETECT, a study evaluating POC HIV tests in real-time. From June 2018 to March 2019, the SAMBA II Whole Blood Qual test (limit of detection (LOD) 400 copies/mL) was used for all participants. From April to August 2019, the Qual test was used on participants who had never been on ART and the SAMBA II Leukodepleted Whole Blood Semi-Q (LOD: 1000 range: 500-2000) copies/mL test was used for PWH who had started ART. Both whole blood (WB) tests were performed on unprocessed venipuncture (VP) and finger-stick (FS) WB. Results from WB tests and the SAMBA II Plasma Semi-Q test performed on frozen plasma from PWH were compared to Abbott Real-time HIV-1 POC results (PCR) on plasma. Sensitivity, specificity, and concordance between tests were calculated.

Results: SAMBA was used in 292 visits among 249 participants; 180 (62%) visits were from PWH, and 112 (38%) from persons testing HIV-negative. 58 PWH had undetectable RNA levels by PCR, 27 had detectable but unquantifiable levels, and 95 had quantifiable RNA levels with a median 7487 (IQR 576-89630) copies/mL. The Qual test was used at 224 visits. Sensitivity of the Qual test among PWH with plasma RNA <400 copies/mL was 92% in VP and 97% in FS WB (Table). Sensitivity of the Qual test among PWH on ART was 95% in VP and FS WB. Specificity of the Qual test was 95% in VP and 95% in FS WB. In 949 PWH and 944 cases of plasma RNA <1000 copies/mL test results were >1000 copies/mL. Among PWH, the Plasma Semi-Q had 96% and 95% concordance to WB and PCR results, respectively.
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 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, unsupervised, 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, 1,792 (65%) said they previously had sex, median number of partners in past one year, 1 (IQR 1-2), 1,140 (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 self-testing kit. 79.2% of those who used HIVST, 81.0% (1257/1551) sought HF-confirmation of HIV sero-status among men using HIVST.

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 Mpigi 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 on site, the remainder were unreachable through phone contact.

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 3 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 HIV confirmation (HIV sero-status, 76.2% (48/63) of positives by HIVST were confirmed HIV+ at a HF. 79.2% (38/48) of confirmed HIV+ were newly diagnosed and 20.8% were previously diagnosed but untreated with ART or had fallen out of care, and 96% (46/48) of the confirmed HIV+ initiated ART. Participants seeking HIV confirmation of HIV sero-status were more likely to be older aged 25+ years (9.52, 95% CI: 3.22-28.18), unaware of their partner’s status (2.73, 95% CI: 1.46-5.11) and not to have used the HIVST-kits (14.94, 95% CI: 5.47-40.77).

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.

Background: 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 positive. 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?

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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 Zambézia 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 (~$5 US). 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 52 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 37% felt very confident in the result.
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.

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**HIV SELF-TESTING AMONG KEY POPULATIONS AND SEXUAL PARTNERS OF NEW MOTHERS IN UGANDA**

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**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.

**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 (96%) were HIV negative and 252 (3%) clients reported HIV-positive results: 74 (29%) were partners of mothers, 126 (50%) were FSW, and 52 (22%) were MSM.

**Discussion:** 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.

**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.

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**ACCEPTABILITY OF HIVST DISTRIBUTION BY PREGNANT WOMEN TO MALE PARTNERS: A CLOSER LOOK**

**Norma C. Ware**, Monique A. Wyatt, Emily E. Pisarski, Andrew Mujugira, Connie L. Celm

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**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 explore: 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.

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**“FIRST TO KNOW MY STATUS”: ACCEPTABILITY OF HIV SELF-TESTING AMONG SOUTH AFRICAN MEN**

**Monique A. Wyatt**, Emily E. Pisarski, Adrienne E. Shapiro, Kombi Sausi, Alastair Van Heerden, Oluwafemi A. Adegbogun, Janet Seeley, Connie L. Celm, Ruanne V. Barnabas, Norma C. Ware

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**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.

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**Table 1. Perceptions on HIVST among clients, among clients who bought and who did not have a need to purchase kits.**

<table>
<thead>
<tr>
<th>Perception on HIVST</th>
<th>Percentage (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kit availability</td>
<td>92% (203)</td>
</tr>
<tr>
<td>Kit cost</td>
<td>85% (170)</td>
</tr>
<tr>
<td>To be able to test with partner</td>
<td>87% (189)</td>
</tr>
<tr>
<td>To be able to test</td>
<td>83% (170)</td>
</tr>
</tbody>
</table>

**Figure 1. Clients that tested HIV positive on self-test.**
**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 Mostert, Trishanta Kisten, Linda Sande, Marc D’Elbee, Mohammed Majam, Vincent Zishiri, Willem D. Venter, Karin Hatzold, Cheryl Johnson, Joel M. Francis, Thato Chidarikire, Sharon White, Fern Terris-Prestholt, Gesine Meyer-Rath


**Background:** Understanding how HIV testing in workplaces impacts testing coverage especially in underserved rural populations, at a similar cost to urban settings, is critical. Thus, we aimed to determine the impact and cost of HIV self-testing (HIVST) in workplaces to improve HIV testing coverage in sub-Saharan Africa, particularly for sub-populations at high risk of acquiring and transmitting HIV.

**Methods:** A randomized controlled trial of CHIVST (HIV self-testing) kits was 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:** When compared to other testing modalities, HIVST kits were distributed in rural workplaces at a lower cost and were more acceptable to men. The cost of distributing HIVST in rural workplaces (Table 1) and especially high in never tested employees (aged <25) and in infrequently tested employees aged 25-34. The average cost of distributing HIVST in rural agricultural workplaces and urban industries was $3.40 USD vs. 4.35 USD, with $5.40 due to the cost of the kits (incl. freight), followed by distribution staff (32%), sensitisation (5%) and travel (3%).

**Conclusion:** HIVST distribution at the workplace level is associated with improved HIV testing coverage especially in underserved rural populations, at a similar cost to urban populations.
CHARACTERISTICS OF MSM WHO REGISTER FOR HIV SELF-TESTING IN SAO PAULO, BRAZIL

Ricardo Vasconcelos¹, Vivian I. Avelino-Silva², Ivone P. De Paula³, Leda Jamal⁴, Maria Clara Gianna⁵, Flavio Santos⁵, Cristina Santos⁵, Robinson Camargo⁶, Eduardo Barbosa⁶, Gilvane Casemiro⁶, Maria Cristina Abbate³, Marly M. Cruz⁶, Ricardo D. Vasconcelos¹, Vivian I. Avelino-Silva¹, Ivone P. De Paula³, Leda Jamal⁴, Maria Clara Gianna⁵, Flavio Santos⁵, Cristina Santos⁵, Robinson Camargo⁶, Eduardo Barbosa⁶, Gilvane Casemiro⁶, Maria Cristina Abbate³, Marly M. Cruz⁶, Aluisio C. Segurado⁶, for the A Hora é Agora - SP
¹Universidad de São Paulo, São Paulo, Brazil, ²Centro de Referência e Treinamento DST/AIDS-SP, São Paulo, Brazil, ³Secretaria Municipal de Saúde de São Paulo, ⁴Centro de Referência da Diversidade, São Paulo, Brazil, ⁵Ministry of Health, Brasília, Brazil, ⁶Escola Nacional de Saúde Pública, Brasília, 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 São Paulo, two state capitals in Brazil. We here analyze the characteristics and prevention attitudes of participants registered to undertake HIVST in São 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 univariable 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?

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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 kit (Baseline Test [BT]) versus no free HIVST (Baseline Test [nBT]). Online surveys collected data at baseline, 2 weeks (2w) (BT only) and 3 months (3m) 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 3m of enrolment.

Results: 10,111 men were randomized (6049 BT, 4062 nBT); median age 33 years (IQR 26-44); 89% white; 20% born outside UK; 0.8% trans men; 47% degree educated; 15% never HIV tested; 80% ever and 4% currently on PrEP. At enrolment 89% reported AI and 72% CAI with ≥1 male partner in previous 3m. 4194/4695 (89%) in BT reported using the HIVST kit. No significant difference at 3m in confirmed new HIV diagnoses (primary outcome; p=0.64, 19 [0.3%] in BT vs 15 [0.4%] in nBT). Men randomized to BT were more likely to HIV test in 3m 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 3m after enrolment (42%) compared to 3m before (21%). STI testing rates between arms were similar (22% BT vs 25% 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.

Table 1: Characteristics of study participants, overall and according to prior HIV testing

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All respondents</th>
<th>Respondents with prior HIV testing</th>
<th>Respondents without prior HIV testing</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28 (28-31)</td>
<td>28 (24-31)</td>
<td>25 (21-29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
<td>White/exclusion: 3452 (54%) Other: 2192 (46%)</td>
<td>2737 (55%)</td>
<td>715 (52%)</td>
<td>0.081</td>
</tr>
<tr>
<td>Education</td>
<td>In high school: 2055 (32%) High school: 4317 (66%)</td>
<td>1419 (29%)</td>
<td>616 (44%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sexual orientation</td>
<td>Gay: 5249 (81%) Bisexual: 678 (10%)</td>
<td>4016 (79%)</td>
<td>966 (73%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk drug use</td>
<td>In steady partner: 2328 (37%) In single: 1349 (21%)</td>
<td>1131 (21%)</td>
<td>507 (38%)</td>
<td>0.478</td>
</tr>
<tr>
<td>Unprotected anal intercourse in the past 6 months</td>
<td>3160 (47%)</td>
<td>2179 (40%)</td>
<td>681 (54%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Antiretroviral use in the past year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No risk</td>
<td>3104 (49%)</td>
<td>1002 (21%)</td>
<td>204 (23%)</td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>4056 (74%)</td>
<td>3196 (76%)</td>
<td>909 (72%)</td>
<td>0.078</td>
</tr>
<tr>
<td>High risk</td>
<td>223 (4%)</td>
<td>177 (4%)</td>
<td>48 (4%)</td>
<td></td>
</tr>
<tr>
<td>Preferred HIV test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-test</td>
<td>3551 (54%)</td>
<td>2103 (43%)</td>
<td>938 (71%)</td>
<td></td>
</tr>
<tr>
<td>Facility-based test</td>
<td>807 (13%)</td>
<td>67 (1%)</td>
<td>73 (6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>1401 (24%)</td>
<td>1314 (26%)</td>
<td>127 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

Numbers are unweighted. *M* indicates declined for 102 participants. **M** indicates declined for 66 participants. ***M*** indicates declined for 216 participants. ****M*** indicates declined for 469 participants. **M*** indicates declined for 2/2 participants. ***M*** indicates declined for 469 participants. ****M*** indicates declined for 2/2 participants.
THE RATIONALE FOR A 3-TEST HIV DIAGNOSTIC ALGORITHM: BALANCING ACCURACY AND COST

Jeffrey Eaton1, Anita Sands2, Magdalena Barr-Dichiara2, Muhammad S. Jamil2, Thokozani Kalua1, Andrea Jahn1, Rachel Baggaley2, Cheryl Johnson1

Imperial College London, London, UK, 1WHO, Geneva, Switzerland, 2Malawi 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 if, 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 released in 2019.

Table 1: Testing strategy outcomes per 100,000 persons tested for 10%, 5%, 1%, and 0.6% true positivity among persons presenting for HIV testing.

<table>
<thead>
<tr>
<th>Group</th>
<th>False-positive cases</th>
<th>False-negative cases</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>40</td>
<td>0</td>
<td>0.115</td>
</tr>
<tr>
<td>A2</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

966 FALSE-POSITIVE 4TH GENERATION HIV TEST RESULTS IN THE EMERGENCY DEPARTMENT

Gabriel A. Wagner1, Ryan Anson2, Nicole Gamache-Kocot1, Kushagra Mathur3, Megan Lo1, Jeffrey H. Burack1, Annette Shaieb1, Jill Blumenthal1, Susan J. Little1, Martin Hoenigl1

1University of California San Diego, San Diego, CA, USA, 2East Bay AIDS Center, Oakland, California, 3East 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 TP 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 women, 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 1: Demographic and clinical factors among individuals with false-positive HIV test results

<table>
<thead>
<tr>
<th>Group</th>
<th>False-positive cases</th>
<th>False-negative cases</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (IQR)</td>
<td>39 (26 - 63)</td>
<td>1 (0 - 3)</td>
<td>0.115</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>Female</td>
<td>100</td>
<td>0.024</td>
</tr>
<tr>
<td>HIV-positive (%)</td>
<td>100</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Race (%)</td>
<td>White</td>
<td>75 (74.5%)</td>
<td>0.035</td>
</tr>
<tr>
<td>History of flu vaccination (lifetime) (IQR)</td>
<td>65.5%</td>
<td>30.0%</td>
<td>0.123</td>
</tr>
<tr>
<td>History of multiparity (%)</td>
<td>30.0%</td>
<td>1.4%</td>
<td>0.04</td>
</tr>
<tr>
<td>History of obesity (%)</td>
<td>24.2%</td>
<td>0.9%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

967 EVALUATION OF VIRAL SUPPRESSION ON RAPID HIV TEST REACTIVITY AMONG MSM, NHBS, 2017

Shamaya Whitey1, Amanda Smith1, Johanna Chapin-Bardales2, Rebecca Rossetti2, Cyprian Wejnert2, Silvina Masciotra2, for the for the NHBS Study Group

1Oak Ridge Institute for Science and Education, Atlanta, GA, USA, 2CDC, Atlanta, GA, USA

Background: The National HIV Behavioral Surveillance System (NHBS) surveys among adults age 18 years and older in U.S. communities. For the 2017 NHBS, we introduced rapid tests (RTs) for HIV diagnosis. The objective of this analysis was to assess factors associated with FP HIV tests.

Methods: Universal 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 TP 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 women, 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.

**Methods:** Sites performed at least one point-of-care RT on all consenting SRP MSM. Participants with RT-nonnegative (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 EIA and GenMark HSV-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 (4/50, 8.0% RT-NR). The table shows reactivity of RTs from participants by VL results and self-reported ART use. Of 1655 RT-R participants, 131 (7.9%) had undetectable VL or detected <2.92 log₂ (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 seroreversion; 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.

**Table 1:** Performance of OraQuick® on HIV diagnosis among cadavers admitted to JOMTHA mortuaries in Kisumu: a high HIV-burden region in Kenya

<table>
<thead>
<tr>
<th>OraQuick results</th>
<th>Standard test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (%)</td>
<td>75 (95.4%)</td>
</tr>
<tr>
<td>Negative (%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>75 (100.0%)</td>
</tr>
</tbody>
</table>

**Performance of OraQuick Rapid Test on HIV Diagnosis Among Cadavers in Kisumu, Kenya**

**Methods:** Cadavers were collected in Kisumu, Kenya, during the 2017 National HIV Behavioral Surveillance (NHBS). Participants were tested for HIV using OraQuick®. Test results from OraQuick® were compared with those obtained using national RTK algorithm on matched pre-embalming whole blood specimens as a gold standard (Determine® HIV and First Response® HIV 1-2-O). We calculated positive predictive value (PPV), negative predictive value (NPV), false detection rate (FDR), false omission rate (FOR), sensitivity and specificity of OraQuick® compared to the gold standard.

**Results:** OraQuick had a sensitivity of 92.6% (95% CI: 75.7 - 99.1) on pre and post-embalmed samples when compared to the gold standard. The specificity was 97.1% (95% CI: 91.9 - 94.9) and 95.2% (95% CI: 89.2 - 98.4) pre and post-embalming respectively (Table 1). Pre-embalming PPV of OraQuick® was 89.3% (95% CI: 71.8 - 97.7) and 83.3% (95% CI: 65.3 - 94.4) post-embalming. FDR was lower on pre-embalming compared to post embalming at 10.7% (95% CI: 2.3 - 28.2) and 16.7% (95% CI: 5.6 - 34.7) respectively. Only 2/27 (7%) were false negative. FOR pre-embalming (1.92%) and post-embalming (1.96%) were similar.

**Conclusion:** OraQuick was found to be more specific than sensitive on oral specimens 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.

**Dried Blood Spots Provide Simplified Accurate Measurement of HIV Viral Load**

**Methods:** To avoid logistical difficulties of blood-based HIV testing, a minimally invasive assay using oral fluid such as OraQuick® has previously been used in Kenya for HIV self-testing, showing a higher specificity than sensitivity. We verified the feasibility and diagnostic accuracy of OraQuick® for HIV screening among cadavers.

**Methods:** Trained morticians collected pre- and post-embalming oral fluids from 132 cadavers >18 months old at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOMTHA) mortuary in Kisumu, Kenya. They were tested for HIV using OraQuick®. Test results from OraQuick® were compared with those obtained using national RTK algorithm on matched pre-embalming whole blood specimens as a gold standard (Determine® HIV and First Response® HIV 1-2-O). We calculated positive predictive value (PPV), negative predictive value (NPV), false detection rate (FDR), false omission rate (FOR), sensitivity and specificity of OraQuick® compared to the gold standard.

**Results:** OraQuick had a sensitivity of 92.6% (95% CI: 75.7 - 99.1) on pre and post-embalmed samples when compared to the gold standard. The specificity was 97.1% (95% CI: 91.9 - 94.9) and 95.2% (95% CI: 89.2 - 98.4) pre and post-embalming respectively (Table 1). Pre-embalming PPV of OraQuick® was 89.3% (95% CI: 71.8 - 97.7) and 83.3% (95% CI: 65.3 - 94.4) post-embalming. FDR was lower on pre-embalming compared to post embalming at 10.7% (95% CI: 2.3 - 28.2) and 16.7% (95% CI: 5.6 - 34.7) respectively. Only 2/27 (7%) were false negative. FOR pre-embalming (1.92%) and post-embalming (1.96%) were similar.

**Conclusion:** OraQuick was found to be more specific than sensitive on oral specimens 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.

**Table 1:** Performance of OraQuick® on HIV diagnosis among cadavers admitted to JOMTHA mortuaries in Kisumu: a high HIV-burden region in Kenya

<table>
<thead>
<tr>
<th>OraQuick results</th>
<th>Standard test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (%)</td>
<td>75 (95.4%)</td>
</tr>
<tr>
<td>Negative (%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>75 (100.0%)</td>
</tr>
</tbody>
</table>
an estimated one treatment failure would be miscategorized. There were no clinically meaningful differences by sex or CD4 count.

**Conclusion:** DBS provides a highly accurate result compared to plasma VL and could be used in a simplified approach to population-based ART monitoring in resource-limited settings. Self-collection of DBS cards should be evaluated as a means of further simplifying specimen collection and ART monitoring.

970 AUTOMATED HIGH-THROUGHPUT QUANTIFICATION OF LOW-LEVEL HIV-1 PLASMA VIREMIA

Jana L. Jacobs1, Melissa A. Tosiano1, Dianna L. Koontz2, Andrew Worlock2, Karen Harrington3, Sonia Bakkour3, Michael P. Busch4, John W. Mellors5, Harrington2, Sonia Bakkour3, Michael P. Busch3, John W. Mellors1

1University of Pittsburgh, Pittsburgh, PA, USA, 2Hologic Corporation, Bedford, MA, USA, 3Vitalant Research Institute, San Francisco, CA, 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 0.7 mL 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 SCA 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:** Assay results are summarized in the Table. The 95% LODs (95% CI) were 2.3 (1.6, 3), 3.0 (2.1, 3.8), 3.9 (2.8, 5) for iSCA2.0, Panther 9x and Panther spun, respectively, indicating that iSCA2.0 was most sensitive but that Panther 9x was only marginally less sensitive. Panther spun had reduced sensitivity compared to the other methods. Each assay had 100% specificity across 25 replicates of 0 copies/ml. The weekly estimated throughput for the Panther 9x was only marginally less sensitive. Panther spun had reduced sensitivity compared to the other methods.

**Conclusion:** Although the manual single copy assay targeting HIV-1 integrase (iSCA 2.0) has the lowest 95% limit of detection for plasma HIV-1 RNA, multiple replicate testing (9x) on the Hologic Panther platform has similar sensitivity and could be used as a screening tool for higher throughput monitoring in clinical trials of interventions aimed at clearing persistent viremia towards a functional cure of HIV-1 infection.

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 Gao2

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 QCMs to reduce the infectious risk of the QCM 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 assurance of drug mutation sequencing assays. Reducing cold chain requirements, shipping costs and infectious status of QCMs offers significant improvements to current PT approaches. Work supported by NIAID EQAPOL HHSN27220170061C.

<table>
<thead>
<tr>
<th>Week</th>
<th>30°C</th>
<th>4°C</th>
<th>23°C</th>
<th>30°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.26</td>
<td>4.30</td>
<td>4.38</td>
<td>4.42</td>
</tr>
<tr>
<td>2</td>
<td>4.28</td>
<td>4.30</td>
<td>4.38</td>
<td>4.42</td>
</tr>
<tr>
<td>3</td>
<td>4.30</td>
<td>4.30</td>
<td>4.38</td>
<td>4.42</td>
</tr>
<tr>
<td>4</td>
<td>4.32</td>
<td>4.30</td>
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<td>4.42</td>
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<tr>
<td>5</td>
<td>4.34</td>
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<tr>
<td>6</td>
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</tr>
<tr>
<td>7</td>
<td>4.38</td>
<td>4.30</td>
<td>4.38</td>
<td>4.42</td>
</tr>
</tbody>
</table>

**Figure 1. Lyophilization Temperature Stability Testing**
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 Maxim 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 positive in all three settings. In Nairobi (ART metabolite testing) and Siaya County (linked clinic records) the number classified as recent positive 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 and demographic information. In using recency assays to accurately distinguish recent from chronic infections in treated individuals, we present the results of three pilots of HIV recency testing in Kenya and Zimbabwe.

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Background: Antiretroviral therapy (ART) initiation during acute HIV infection (AHI) limits HIV reservoirs, enhances reservoir decay, restricts viral genetic diversification and may facilitate post-AHI 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 GSCOMBO 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 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 diagnostic algorithms in 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

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.

975 IMPROVING CLASSIFICATION FOR RECENT HIV INFECTION USING TOP SCORING PAIRS

Athena Chen1, Oliver Laeyendecker2, Charles S. Morrison3, Susan H. Eshleman4, Ingo Ruczinski1
1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA, 3FHI 360, Durham, NC, USA

Background: HIV cross-sectional incidence assays often measure characteristics of the antibody (Ab) response, such as titers, class, and avidity. These responses are affected by various factors including viral suppression. Since older guidelines recommended ART initiation later in infection, incidence algorithms often use viral suppression as a surrogate for non-recent infection. As new guidelines recommend ART initiation early in infection, viral suppression no longer indicates non-recent infection, and new approaches are needed to identify recent infections.

Methods: We analyzed Ab profiles from 258 samples from 57 individuals with HIV subtype C infection and known duration of infection (2 mo. - 8.7 yrs.) using phage immunoprecipitation sequencing (PhIP-Seq). PhIP-Seq quantifies Ab binding to 3384 peptides spanning the HIV genome. Our novel classifier for recent (2-6 mo.) and non-recent (18+ mo.) infection is based on the k-top scoring pairs (TSP) classifier. For each peptide pair, relative Ab abundances classify each sample as recent or non-recent. Overall sample classification is determined by a majority voting system. Optimal classification cutoffs and the number of voting pairs were identified using a training set of 176 samples from 38 individuals and subsequently tested on the remaining 82 samples from 19 individuals. We compared these results to results from a standard Limiting Antigen Avidity (LAg-Avidity) protocol.

Results: In the final model with 4 voting pairs, 79% (71/90) recent samples and all 168 of non-recent samples were correctly classified. In contrast, the LAg-Avidity protocol classified 43% (35/81) recent samples and all 165 non-recent samples correctly. Comparison of TSP vs. LAg-Avidity showed that the TSP approach captured a greater proportion of recent infections with a mean window period of 217 days (95% CI: 183-257 days; see figure). In contrast, the mean window period of the LAg-Avidity protocol is 106 days (95% CI: 76-146 days).

Conclusion: We identified four 4 peptide pairs that outperformed the standard LAg-Avidity protocol for identifying samples from individuals with recent HIV infection. These peptides can be incorporated into a simple assay for field use. With a larger mean window period, the TSP classifier yields more precise incidence estimates without relying on viral load to identify non-recent samples. The TSP approach can also easily be applied to other populations and virus subtypes to identify novel peptide signatures for recent infection.

976 EVALUATION OF CROSS-SECTIONAL HIV INCIDENCE TESTING IN THE HPTN 071 (PopART) TRIAL

Ethan B. Klock1, Oliver Laeyendecker2, Reinaldo Fernandez2, Ethan A. Wilson3, Estelle Piwowar-Manning1, Sam Griffith4, B Kosloff5, Anneen Van Deventer6, Sarah Fidler7, Helen Ayles8, Peter Bock9, Deborah J. Donnell3, Richard J. Hayes9, Susan H. Eshleman1, for the HPTN 071 (PopART) Study Team
1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2FHI 360, Durham, NC, USA, 3London School of Hygiene & Tropical Medicine–Zambia, Lusaka, Zambia, 4Stellenbosch University, Cape Town, South Africa, 5Imperial College London, London, UK, 6Zambart, Lusaka, Zambia, 7London School of Hygiene & Tropical Medicine, London, UK

Background: HIV-1/2 cross-sectional incidence assays often measure characteristics of the antibody (Ab) response, such as titers, class, and avidity. These responses are affected by various factors including viral suppression. Since older guidelines recommended ART initiation later in infection, incidence algorithms often use viral suppression as a surrogate for non-recent infection. As new guidelines recommend ART initiation early in infection, viral suppression no longer indicates non-recent infection, and new approaches are needed to identify recent infections.

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Background: The Limiting Antigen 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, 221 persons who seroconverted between PC12 and PC24 (SC12-24), 217 who seroconverted between PC0 and PC24 (SCO-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 0%.

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 SCO-12 group, 0.15% (1/689) of those who enrolled HIV+ at PC0, and 0.17% (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 notably less precise than observed incidence measured from cohort follow-up.

Conclusion: In this 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.

Table: Comparison of CSI and observed incidence between the ‘PC12 and PC24’ surveys

<table>
<thead>
<tr>
<th>Country</th>
<th># participants</th>
<th>PCO</th>
<th>PC12</th>
<th>PC24</th>
<th>Observed incidence*</th>
<th>Cross-sectional incidence estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zambia</td>
<td>5,157</td>
<td>0.000</td>
<td>1.400</td>
<td>1.400</td>
<td>1.41 (1.17-1.66)</td>
<td>1.30 (0.95-1.80)</td>
</tr>
<tr>
<td>South Africa</td>
<td>9,863</td>
<td>0.045</td>
<td>1.040</td>
<td>1.039</td>
<td>1.16 (1.01-1.35)</td>
<td>1.29 (1.17-1.41)</td>
</tr>
<tr>
<td>Overall</td>
<td>15,010</td>
<td>0.050</td>
<td>1.040</td>
<td>1.040</td>
<td>1.41 (1.17-1.66)</td>
<td>1.30 (0.95-1.80)</td>
</tr>
</tbody>
</table>

Abbreviations: PES: PC0-negative; RES: HIV-negative; SC: seroconverter; P: person-years; PPO: follow-up. *Based on PC participants with known HIV status at PC0 and PC24.

797 URINE TENOFOVIR LEVELS BY IMMUNOASSAY PREDICT HIV PROTECTION IN A LARGE PrEP TRIAL

Randy Stalter, Jared Baeten, Deborah J. Donnell, David Glidden, Warren Rodrigues, Guohong Wang, Michael Vincent, Matthew A. Spinelli, Nelly R. Mugo, Kelly Johnson, Andrew Mujugira, Mark A. Marzinke, Craig W. Hendrix, Monica Gandhi, 1 For the Partners PrEP Study Team
1 University of Washington, Seattle, WA, USA, 2 Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 3 University of California San Francisco, San Francisco, CA, USA, 4 Abbott Labs, Abbott Park, IL, USA, 5 Kenya Medical Research Institute, Nairobi, Kenya, 6 Johns Hopkins University, Baltimore, MD, USA

Background: New tools are needed to support PrEP use for individuals at high risk for HIV in sub-Saharan Africa, including objective adherence metrics that allow for provision of real-time feedback. Urine tenofovir (TFV) levels have been proposed as a marker of PrEP use that could be measured with low-cost, point-of-care (POC) antibody-based tests. We hypothesized that TFV levels in urine, measured via a recently-developed immunoassay, would be comparable to those in plasma, the gold standard for short-term PrEP adherence in clinical trials, and associated with protection from HIV.

Methods: We measured TFV levels in stored urine samples collected from a randomly sampled cohort of HIV-negative men and women from the active PrEP arms in the Partners PrEP Study using enzyme-linked immunosorbent assay (ELISA) (lower limit of quantification [LLOQ] 1000 ng/mL). Date-matched plasma TFV concentrations were measured via liquid chromatography-tandem mass spectrometry (LC-MS/MS) with an LLOQ of 0.37 ng/mL. Using the same cohort 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 will 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.

978 PUBLICLY FUNDED HIV PrEP IN BRITISH COLUMBIA: PROGRAM RETENTION AND NEW HIV DIAGNOSES

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1 British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

Background: In January 2018, a province-wide HIV pre-exposure prophylaxis (PrEP) program was launched in British Columbia (BC), Canada, to complement the existing publicly-funded HIV treatment as prevention strategy. BC residents were eligible to receive publicly-funded emtricitabine-tenofovir DF through the centralized BC Centre for Excellence in HIV/AIDS program if they were at risk of HIV acquisition according to BC PrEP Guidelines. We sought to evaluate program retention and the rate of new HIV diagnoses.

Methods: Individuals enrolled in the BC PrEP program between 1-Jan-2018 and 30-Jun-2019 were characterized by demographic, and prescriber characteristics. For those who initiated PrEP, we determined program status at end of follow-up (31-Aug-2019). Multivariate logistic regression was used to evaluate factors associated with program non-retention (defined as >6 month lapse beyond expected PrEP refill date). Rate of new HIV diagnoses in the cohort was calculated.

Results: In the first 18 months, 4648 individuals applied for PrEP and 4570 enrolled in the program (98% male, median age 33 years (Q1-Q3, 27-44)). Most participants (90%) qualified based on an HIV Incidence Risk Index (HRI) for MSM Score of ≥10 (median 19 (Q1-Q3, 15-25)). The majority of participants (83%) resided in Greater Vancouver and received care at sexual health clinics (47%), HIV-focused clinics (23%) or general practice/other settings (30%). Of the 4451 participants who initiated PrEP, 84% were retained in the program as of 31-Aug-2019 (See Figure 1). Factors associated with program non-retention were higher HIRI-MSM score (adjusted OR 1.29 (95% CI, 1.12-1.48) per 10 score increment) and prescriber-reported on-demand PrEP use (adjusted OR 4.09 (95% CI, 3.01-5.55)) but not age, urban vs. rural location, or provider antiretroviral treatment or PrEP prescribing experience. Among participants who initiated PrEP, there were 8 HIV seroconversions in 4141 person years of follow-up, including 6 persons with >30 day lapse in PrEP medication prior to HIV diagnosis. Overall, the new HIV diagnosis rate was 0.19 per 100 person years (95% CI 0.08-0.38).

Conclusion: In the context of a publicly funded, centrally distributed PrEP program, retention was high at 18 months, and the rate of new HIV diagnoses low relative to the expected rate for individuals reporting these risk behaviours. Persons with higher HRI-MSM score were at increased risk of program non-retention, and thus may benefit from enhanced support.
979 POPULATION-LEVEL EFFECTIVENESS OF PrEP AMONG MSM AND TRANSGENDER PERSONS WITH STI

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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/PARTURIENT ADOLESCENT AND YOUNG WOMEN ON PrEP IN AFRICA

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Background: Pregnant/parturient 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 Willcoxon 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 weeks) and 20 postpartum (median time after delivery: 7 weeks) women at a median age of 20 years (IQR: 19,22). Of 3360 doses, 3348 (>99%) 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 fmo1/punch (IQR: 691,1166) in pregnancy vs 1406 fmo1/punch (IQR: 1035,1859) postpartum (p=0.006). Predicted median TFV-DP was 890 fmo1/punch (IQR: 704,1143) in pregnancy vs 1418 fmo1/punch (IQR: 1179,2139) postpartum (Figure). Two fetal demises (unrelated to study agent), two newborns <10%tile 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.

The dashed horizontal line is the median TFV-DP steady state concentration in US men and non-pregnant, nonlactating women under direct observed therapy (1546 fmo1/punch). Grey shading represents the 88% confidence interval for these estimates.
982 WAXING AND WANING HIV RISK: DYNAMICS OF PrEP ELIGIBILITY IN RAKAI, UGANDA
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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 6.0/100pyrs to 7.7/100pyrs (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. Incidence of SHR was associated with male sex (aIRRs=1.27[95%CI=1.19-1.36]); never married vs married (aPRRs=3.04[95%CI=2.74-3.37]), previously married vs married (aPRRs=2.81[95%CI=2.25-3.53]).

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.

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 collaboratives 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 at least tested 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>Total</td>
<td>2490</td>
</tr>
<tr>
<td>PrEP indications</td>
<td>1187</td>
</tr>
<tr>
<td>No PrEP indications</td>
<td>1313</td>
</tr>
</tbody>
</table>

* Proportion intervals are cumulative over intervals (except for cumulative test intervals). Columns per site included in the column above.

984 IMPLEMENTATION OF MOBILE PrEP, STI, AND HIV PREVENTION SERVICES IN SOUTH FLORIDA
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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 7 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-references, 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.

IMPLEMENTATION OF MOBILE PrEP, STI, AND HIV PREVENTION SERVICES IN SOUTH FLORIDA
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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.

PreP USE APPROACHING 50% AMONG HIGH- RISK MSM IN WESTERN WASHINGTON

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Background: Washington State from 2017-2019, but did not lead to increases in demand. Although the representativeness of samples from both surveys is unknown, the concordance in estimates supports continued use of prevention targets. Although the representativeness of samples from both surveys is unknown, the concordance in estimates supports continued use of prevention targets.

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 use of PrEP or expressed interest in starting PrEP.

Results: After adjusting for demographic variables and calendar time, estimates from the Pride and WHSSP surveys were similar for all three outcomes (p=0.2-0.4). The proportion of high-risk MSM who had heard of PrEP increased over time (p<0.001) from 84% in 2017 to approximately 96% in 2019 (Figure 1). The proportion of men who reported use of PrEP or expressed interest in starting PrEP (a measure of total demand) remained stable over time at around 66% (p=0.7). 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.

Optimizing PrEP Cascade Outcomes for Sexual Health Clinic Navigation

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Background: Sexual Health and STI clinics are increasingly integrating PrEP navigation services to identify, refer and link eligible patients to PrEP. Increasing the effectiveness of these programs requires optimizing each step of the PrEP cascade, i.e., acceptance of navigation and referral, PrEP initiation, and sustained PrEP use. Epidemiological data have focused almost exclusively on demographic predictors of cascade outcomes, which are not amenable to behavioral intervention. This implementation science study examined modifiable psychosocial predictors of cascade outcomes that can guide targeted intervention efforts.

Methods: Data were collected as part of an NIH-funded sub-study of a PrEP navigation program in 8 NYC public sexual health clinics. Between Feb 2017 and Aug 2018, we recruited 279 patients with program-specific indications for PrEP navigation; this analysis includes participants who were PrEP-naive and completed baseline and 3-month study visits.

Results: Of 171 patients (31% ≤ 25 years; 90% cis male; 57% Black or Latinx), 74% accepted navigation, 53% accepted PrEP referral, 37% initiated PrEP, and 27% were still on PrEP at 3-months. PrEP referral, initiation, or persistence were not associated with HIV risk behavior, belief in PrEP effectiveness, or desire for condomless sex. The strongest predictor of PrEP outcomes at every step of the cascade was a 6-item measure of personal PrEP efficacy (Fig. 1), including positive attitudes toward PrEP pills, self-efficacy for pill-taking, and confidence in PrEP’s ability to work “for me.” All cascade outcomes were positively associated with HIV worry, PrEP initiation and sustained use were negatively associated with medical mistrust. Perceived HIV risk was not associated with navigation acceptance, referral, or PrEP initiation, but was negatively associated with sustained PrEP use at 3-months (aOR = 97, 95% CI 3.95-99).

Conclusion: These data are some of the first to identify specific, modifiable targets for psychosocial intervention to optimize PrEP cascade outcomes in the context of sexual health clinic navigation. In contrast to focusing on risk behavior, risk perception, or effectiveness, these data suggest the importance of messaging and counseling that enhances self-efficacy beliefs, promotes PrEP as an antidote to HIV worry, and builds trust. Findings can inform development of interventions to be tested in implementation science RCTs in public clinics.
987 NON DAILY USE OF HIV PREEXPOSURE PROPHYLAXIS IN A LARGE ONLINE SAMPLE IN THE US

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Background: Event-driven dosing of HIV preexposure 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=0.01), had no graduate degree (76% vs 71%, P<0.001), had annual income <$50,000 (76% vs 73%, P=0.02), and were uninsured (11% vs 9%, P<0.001). Of the 3,232 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 (39%), 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 <$50,000 (36% vs 30%, P=0.04) and always planned sex in the past 6 months (21% vs 11%, P=0.007). 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 PR EP NAVIGATION MODELS IN THE THRIVE DEMONSTRATION PROJECT

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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.
DISCOVER: 96-WEEK FOLLOW-UP OF BLACK AND HISPANIC/LATINO/STUDY PARTICIPANTS

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1 Orlando Immunology Center, Orlando, FL, USA, 2 CrescentCare, New Orleans, LA, USA, 3 Henry Ford Hospital, Detroit, MI, USA, 4 Harbor-UCLA Medical Center, Torrance, CA, USA, 5 Mercer University, Macon, GA, USA, 6 Gilead Sciences, Inc, Foster City, CA, USA, 7 East Bay AIDS Center, Oakland, CA, USA, 8 University of New Mexico, Albuquerque, NM, USA, 9 Crofoot Research Center, Houston, TX, USA

Background: In the US, Black and Hispanic/Latino (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 confidentially 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, BMI, 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 AEs 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.
992 HIV-1 INCIDENCE, PrEP UPTAKE, AND ADHERENCE AMONG KENYAN MSM

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Background: Gay, bisexual, and other men who have sex with men (MSM) are at high risk of HIV acquisition in Kenya, where pre-exposure prophylaxis (PrEP) has recently become available. Our aim was to evaluate factors associated with tenofovir diphosphate (TFV-DP) detection and protective TFV-DP levels in a cohort of high-risk, HIV-negative MSM in Kisumu, Kenya.

Methods: HIV-negative MSM ≥18 years were enrolled if they reported recent sexual activity with a male partner. All participants were offered PrEP at baseline, with adherence counselling at each visit. Follow-up occurred at week 2; months 1, 2 and 3; then quarterly for 1 year. Adherence was measured by visual analogue scale (VAS) and qualitative self-rating. 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: DBS were provided at 275 visits by 161 participants. At baseline, median age was 26, 46.6% reported unprotected anal sex, 86.5% reported ≥3 male sex partners, and 5.5% reported injection drug use. All participants were offered PrEP at baseline, with adherence counselling at each visit. Follow-up occurred at week 2; months 1, 2 and 3; then quarterly for 1 year. Adherence was measured by visual analogue scale (VAS) and qualitative self-rating. 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).

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 GBMMS in Kenya, and that tailored interventions to address PrEP adherence in this population are urgently needed.
PREEXPOSURE PROPHYLAXIS CASCADE AMONG MEN WHO HAVE SEX WITH MEN IN ZIMBABWE

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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. 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 (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% (367/1167) had ever taken PrEP (Harare, 32.7%; Bulawayo, 29.2%). Most (71.1% [261/367]) reporting never taking PrEP were interested in starting PrEP (Harare, 66.1%; 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 (71.7% [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.

SAFETY AND TOLERABILITY OF ONCE-DAILY BIC/FTC/TAF FOR POSTEXPOSURE PROPHYLAXIS

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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%), receptive 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
997 HYPO-OSMOLAR RECTAL DOUCE DELIVERED TFV DISTRIBUTES TFV DIFFERENTIALLY THAN ORAL PrEP

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Background: In spite of the PrEP with tenofovir disoproxil fumarate/entacimib (TDF/FTC) orifice, the rate of new HIV infections remains a major hurdle. In the US alone, the rate of new infections has shifted to predominantly men having sex with men in rural settings where access to PrEP 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 PrEP 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 >14,000 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 oral daily PrEP. 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 (x5) using 30 vs 60 ml did not cause any detectable tissue or systemic toxicity. The single x repeated HOSm rectal douching achieved similar TFV and TFV-DP levels in colorectal tissues, but plasma TFV levels were significantly higher for the repeated 60 ml dosing. Gel and bicarbonate formulations of rectal TFV douching did not markedly improve the pharmacokinetics of TFV or TFV-DP in tissues.

Conclusion: TFV HOSm douching showed high protection efficacy and appeared well tolerated even after multiple administrations within 30 minutes. The most salient parameter potentially associated with protection from rectal infection appeared to be the considerably higher levels of TFV-DP at the portal of entry but not in distal lymphoid tissues, suggesting that drug levels at that barrier are critical for preventing mucosal virus acquisition.

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 were 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 douched and 96% 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.
All concentrations measured from plasma and CV tissue were below the limit of quantification, indicating a lack of systemic exposure with no transfer to CV tissue following rectal dosing. The median (IQR) IQP-0528 concentration in RT 3-6 h and 24-26 h post-dose was 4914 (2907, 5142) ng/mg and 5.4 (3.5, 7.5) ng/mg, respectively, with a median [IQR] half-life of 2.24 (2.23, 2.32) h. In RT, the median [IQR] cumulative p24 3-6 h post-dose of 0.1 (0.0, 0.3) pg/mg was reduced relative to that at baseline (38.4 [22.0, 63.7] pg/mg; p = 0.0277), and 24-26 h post-dose (53.1 [6.6, 744.8] pg/mg; p = 0.0350). The median [IQR] IC_{50} determined was 47.4 [3.4, 183.0] ng/mg. In CV biopsy explants, p24 was not significantly different at baseline versus 24-26 h post-dose (p = 1.0000).

**Conclusion:** The IQP-0528 gel was found to be safe and well tolerated. Despite the short IQP-0528 half-life in RT, concentrations remained well above the in vitro IC_{50} of 146 ng/mL within 3-6 h post-dosing. RT PD indicated that cumulative p24 reductions are significantly associated with greater IQP-0528 (Fig. 1). The offset of IQP-0528 accumulation by its short half-life in RT indicates that this gel may be better suited for episodic use. Furthermore, dual protection is not offered from single-compartment dosing.
1003  **PREP SEROCONVERSION-SEGMENTAL HAIR ANALYSIS FOR UNRaveling TIMING OF VIRAL RESISTANCE**

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**Background:** Failure on PrEP with emtricitabine (FTC)/tenofovir (TFV) 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, TFV 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 146,000 copies/ml on 6/17/19 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 showed a TFV-DP level of 1683 fmol/punch, consistent with high (7 doses/wk) 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.

**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 multivariate model.

**Results:** Of 9,596 participants dispensed PrEP, 4,514 met the inclusion criteria for this analysis. Most were aged 20-44 (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<0.01). The observed rate of renal impairment was 8.0/1,000 person-years (95%CI: 5.86-10.99) over 4,859 person-years. The rate of renal impairment was highest in patients aged ≥50 at 44.7/1,000 person-years, and two-year cumulative risk of 6.3% (95%CI: 4.7-7.9). The rate of renal impairment was also increased in participants with baseline eGFR<60 (9.14/1,000 person-years, 95%CI: 4.99-14.33) and with MPR<0.95 (11.2/1,000 person-years, 95%CI: 7.95-15.72). A multivariate model showed increased risk associated with age ≥50 compared to <40 (HR: 12.9 [95%CI: 4.31-38.58], p<0.01) and baseline eGFR <60 (HR: 25.6 [95%CI: 5.99-109.18], p<0.01) after adjustment for MPR (HR: 1.95 [95%CI: 0.96-3.68], 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.

1004  **RENAL IMPAIRMENT IN A PREEXPOSURE PROPHYLAXIS IMPLEMENTATION COHORT IN AUSTRALIA**

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**Background:** 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.

**Methods:** To calculate the PEI, we first estimated PrEP coverage using a PrEP-to-needs 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
MSM, both for 2017), each stratified by race/ethnicity (Black, Latino, White). We then calculated the PEI by dividing the PrEP coverage for white MSM by that for Black and Latino MSM. To set targets for Black and Latino MSM, we then multiplied the PEI by the PrEP use prevalence for each group, effectively quantifying the improvement in PrEP coverage needed to approximate the PrEP coverage of White MSM (with a maximum of 100%).

**Results:** PrEP use prevalence was 40% and 31% using SHS 2018 and NHBS 2017, respectively, and neither set of estimates differed significantly by race/ethnicity. Numbers of new HIV diagnoses for Black, Latino, and White MSM were 396, 51, and 234, respectively; HIV diagnosis rates for Black, Latino, and White men ages 13-59 were 105, 77, and 31,100,000, respectively. PEI varied markedly for Black and Latino MSM regardless of approach used (Black MSM: 1.7-3.9; Latino MSM: 2.3-3.3). Targets for Black MSM (range: 59%-100%) and Latino MSM (range: 77%-100%) varied by approach used to define PEI (figure), but would require substantial increases in current PrEP use prevalence to be met (Black MSM: 65.295% increase; Latino MSM: 131-235% increase).

**Conclusion:** Applying a newly developed equity index to set local PrEP targets dramatically illustrates inequity in PrEP coverage for Black and Latino MSM, likely driven by both inequities in PrEP access and the large differential HIV burden in these populations. These findings illustrate the distance needed to travel to move beyond equality towards equity and should motivate intensive efforts to address racial disparities in PrEP scale-up.

Figure. Targets for PrEP coverage among Black and Latino MSM in NYC derived from a novel PrEP Equity Index.

### 1007 USE OF HIV PREDICTION MODEL TO EVALUATE PrEP COVERAGE IN A LARGE HEALTH CARE SYSTEM

Julia L. Marcus,1 Leo Hurley,2 Michael J. Silverberg,2 J. Carlo Hojilla,2 Jacek Skarbinski,3 Stacey Alexeeff,4 Douglas Krakower,1 Jonathan E. Volk1

1Kaiser Permanente Division of Research and University of California, San Francisco, CA, USA, 2Harvard Pilgrim Health Care Institute, Boston, MA, USA, 3Kaiser Permanente Division of Research, Oakland, CA, USA, 4Kaiser Permanente Oakland Medical Center, Oakland, CA, USA, 5University of California San Francisco Medical Center, San Francisco, CA, USA

**Background:** Monitoring progress in scale-up of HIV preexposure prophylaxis (PrEP) requires tools for identifying populations who may benefit from PrEP. Our objective was to evaluate PrEP coverage and disparities in use among people at high risk of HIV acquisition in a large healthcare system, using a validated prediction model to estimate HIV risk.

**Methods:** Our study population was all adult members of Kaiser Permanente Northern California (KPNC) as of January 1, 2018, excluding those with a prior HIV diagnosis as documented in the KPNC HIV registry. Using an HIV risk prediction model we previously developed and validated in our setting, we generated an HIV risk score for each member based on historical electronic health record data. We then used pharmacy fill data to assess recent PrEP use during January 1, 2018 to June 30, 2019, and ever PrEP use during all enrollment history, by HIV risk strata. Among members with very high risk scores (i.e., 3-year risk of incident HIV diagnosis ≥ 2%), we used chi-square tests to compare recent and ever PrEP use by demographic characteristics.

**Results:** Among 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 (47.9%), White (47.9%), and Hispanic members (42.4%) than Black members (14.4%; <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

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<thead>
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*Recent PrEP use was defined as any PrEP fill during January 1, 2018 to June 30, 2019. Ever PrEP use was defined as any PrEP fill during all enrollment history. HIV risk scores were generated using a previously validated prediction model (Marcus et al., Access HIV 2018). Scores were categorized as a 3-year risk of incident HIV diagnosis of low (≤1%) and moderate (1-4.9%) or high (≥5%).

### 1008 POPULATION-BASED ESTIMATES OF PrEP ACCESS-TO-NEED IN OREGON, 2012-2016

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**Background:** Monitoring progress in scale-up of HIV preexposure prophylaxis (PrEP) requires tools for identifying populations who may benefit from PrEP. Our objective was to evaluate PrEP coverage and disparities in use among people at high risk of HIV acquisition in a large healthcare system, using a validated prediction model to estimate HIV risk.

**Methods:** Our study population was all adult members of Kaiser Permanente Northern California (KPNC) as of January 1, 2018, excluding those with a prior HIV diagnosis as documented in the KPNC HIV registry. Using an HIV risk prediction model we previously developed and validated in our setting, we generated an HIV risk score for each member based on historical electronic health record data. We then used pharmacy fill data to assess recent PrEP use during January 1, 2018 to June 30, 2019, and ever PrEP use during all enrollment history, by HIV risk strata. Among members with very high risk scores (i.e., 3-year risk of incident HIV diagnosis ≥ 2%), we used chi-square tests to compare recent and ever PrEP use by demographic characteristics.

**Results:** Among 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 (47.9%), White (47.9%), and Hispanic members (42.4%) than Black members (14.4%; <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

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Background: PreEP is an important HIV prevention modality. Population-based metrics of PreEP uptake and access are critical to the evaluation of public health efforts to increase PreEP 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 PreEP, 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 PreEP access in 2016: the number of individuals starting PreEP per 100K population and the number of individuals with a PreEP 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 PreEP need in 2016: the number of HIV diagnoses per 100K population; the number early syphils 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 PreEP access-to-need by dividing each of the access measures by the need measures.

Results: The number of individuals with a new PreEP prescription increased from 8 in 2012 to 571 in 2016. Most new PreEP users were men, aged 25-34 years, identified as white, lived in an urban area, had commercial insurance, and had an internal medicine PreEP prescriber. In 2016, there were 17.2 PreEP starts and 9.9 individuals with a PreEP prescription in all four quarters of 2016 per 100K population. There were 0.7 HIV cases, 136.0 early syphils and gonorrhea cases, and 109.3 acute and chronic hepatitis C cases per 100K population. Per HIV diagnosis, there were 2.6 PreEP starts and 1.5 prevalent users. However, there were 0.13 PreEP starts and 0.07 prevalent users per early syphils and gonorrhea diagnosis and 0.16 PreEP 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 PreEP access-to-need.

Conclusion: Access metrics based on prevalent users (a measure of longer-term adherence to PreEP), 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 PreEP access-to-need than those based on PreEP starts and HIV diagnoses.

Methods:

- **Background:** With the goal of ending the HIV epidemic in the United States, access to HIV Pre-exposure Prophylaxis (PreEP) is essential to curb new HIV infections. There has been a differential regional uptake of PreEP with the South lagging behind. We explore a potential systemic barrier: prior authorization (PA) requirements. This study explores differential PA for PreEP across geography and other plan characteristics (national issuer, high deductible, PreEP cost sharing, PreEP specialty drug tier status, plan level, rating area urbanicity, 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 PreEP. Compared to plans in the Northeast, a plan in the South was 15.9 (95% CI, 13.0-20.0) times as likely to require PA whereas the Midwest and West were 5.7 (95% CI, 4.5-7.3) and 2.7 (95% CI, 2.0-3.5) times as likely, respectively. Figure 1 demonstrates QHPs' PA rate for PreEP by rating area. National issuers were more common in the South (Risk Ratio [RR] 1.9, 95% CI, 1.7-2.2) and were more likely to require PAs (RR 3.3, 95% CI, 3.1-3.6). This may mediate part of the high PA rate in the South, but it does not completely explain the disparity. QHP factors that shift drug costs to consumer, such as co-insurance cost sharing, specialty drug tiering, catastrophic level plans, were associated with lower likelihood of PA, but these characteristics were unlikely to explain regional disparities.

- **Conclusion:** QHPs in the South are 16 times as likely to require PreEP PA. PA reduces the chance of obtaining a prescribed medication. High PA rates are a possible barrier to PreEP access in the South, which is the region with the most new HIV diagnoses. Due to PreEP's USPSTF Grade A rating, QHPs must start offering PreEP without cost-sharing starting in 2021. However, there is no regulation on QHPs’ use of PA for PreEP. We have the tools to end the HIV epidemic, and we will also need robust health policies to end the HIV epidemic.
Pre-exposure prophylaxis (PrEP) with daily tenofovir disoproxil fumarate/emtricitabine is effective in preventing HIV acquisition, and is a major component of the new initiative to End the HIV Epidemic in the United States. The Centers for Disease Control and Prevention (CDC) recommends health care providers consider offering PrEP for people at substantial risk of acquiring HIV, but information on the costs associated with PrEP implementation is limited. We assess health care utilization and costs of PrEP implementation at two federally qualified health centers.

**Methods:** The Sustainable Health Center Implementation PrEP Pilot (SHOPP) Study is an observational cohort of persons receiving daily oral PrEP at five participating health centers. We assessed health care utilization and costs of providing PrEP from the health care provider’s perspective for one year for a subset of patients in each of two centers, Howard Brown Health, Chicago, IL (2016-2018) and Whitman-Walker Health, Washington, DC (2015-2017). The clinics followed CDC guidelines for PrEP provision, including regular visits with providers and ongoing laboratory monitoring. Using clinic billing records and Current Procedural Terminology (CPT) coding, we retrospectively extracted the frequency and costs (in 2017 US$) of PrEP clinic visits and frequency of laboratory screening. We used the Centers for Medicare and Medicaid Services national payment rates to estimate the costs of laboratory services. Incorporating the differences in medical record keeping and available databases between the two sites, we abstracted PrEP-related health care utilization and cost data electronically in Chicago (n=482) and manually in Washington, DC (n=56).

**Results:** The average annual number of PrEP clinic visits and associated laboratory screens per patient was 5.1 visits and 22.3 screens in Chicago, and 5.4 visits and 25.5 screens in Washington, DC (Table). The average annual cost per patient was $607 for clinic visits and $986 for laboratory screens in Chicago; and $538 for clinic visits and 25.5 screens in Washington, DC (Table). The average annual number of PrEP clinic visits and associated laboratory screens per patient was 5.1 visits and 22.3 screens in Chicago, and 5.4 visits and 25.5 screens in Washington, DC (Table). The average annual cost per patient was $607 for clinic visits and $986 for laboratory screens in Chicago; and $538 for clinic visits and 25.5 screens in Washington, DC (Table). The average annual cost per patient was $607 for clinic visits and $986 for laboratory screens in Chicago; and $538 for clinic visits and 25.5 screens in Washington, DC (Table). The average annual cost per patient was $607 for clinic visits and $986 for laboratory screens in Chicago; and $538 for clinic visits and 25.5 screens in Washington, DC (Table). The average annual cost per patient was $607 for clinic visits and $986 for laboratory screens in Chicago; and $538 for clinic visits and 25.5 screens in Washington, DC (Table). The average annual cost per patient was $607 for clinic visits and $986 for laboratory screens in Chicago; and $538 for clinic visits and 25.5 screens in Washington, DC (Table). The average annual cost per patient was $607 for clinic visits and $986 for laboratory screens in Chicago; and $538 for clinic visits and 25.5 screens in Washington, DC (Table). The average annual cost per patient was $607 for clinic visits and $986 for laboratory screens in Chicago; and $538 for clinic visits and 25.5 screens in Washington, DC (Table).

**Conclusion:** PrEP should be available under universal health coverage to retain clients in care. Interventions tailored to support adolescents and clients with education less than bachelor’s degree should be concise and promote PrEP as a health empowering tool should also be prioritized to address this finding.

### Table 1. Outcomes of Medicaid cost for PrEP by state, United States 2017

<table>
<thead>
<tr>
<th>Quinidine</th>
<th>States</th>
<th>Mean Payment Per PMPoP (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AR, GA, IA, MA, MO, NY, NC, UT, VA, VT</td>
<td>$1,011–1,557</td>
</tr>
<tr>
<td>2</td>
<td>CO, DC, FL, MS, NH, NJ, OH, OR, PA, WA, WY</td>
<td>$1,235–1,713</td>
</tr>
<tr>
<td>3</td>
<td>AL, AR, CA, FL, IA, MD, MT, NC, NE, NH, NY, PA</td>
<td>$1,548–2,122</td>
</tr>
<tr>
<td>4</td>
<td>AZ, CT, ID, IN, KS, KY, LA, NH, RI</td>
<td>$1,623–2,167</td>
</tr>
<tr>
<td>5</td>
<td>DE, HI, IA, KS, ME, MN, MI, MS, MT, NV, NH, OK, OR, SD, UT, VT, WA</td>
<td>$1,676–2,353</td>
</tr>
</tbody>
</table>

*PMPoP prescriptions paid by Medicaid were not included in the database for South Dakota or Wisconsin.*

### 1012 THIRD-PARTY PAYER AND PATIENT OUT-OF-POCKET COSTS FOR PrEP: UNITED STATES, 2017

**Nathan W. Furukawa,1 Weiming Zhu, Ya-Lin A. Huang, Ram K. Shrestha,1 Karen W. Hoover1**

1CDC, Atlanta, GA, USA

**Background:** Pre-exposure prophylaxis (PrEP) with daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) 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, Medicare, Medicaid, 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, 28.0 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 Medicaid 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.
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. The COPE ITSA showed an 82% increase in monthly recruitment following the start of SMI promotion (95% CI = 31%, 154%; p < .001).

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.

Results: During the 17 months of intervention through August 2019, we observed recruitment on the 17-month ITSA. Among later recruits, 36.4% reported learning of the study through social media. The ITSA showed an 82% increase in monthly recruitment following the start of SMI promotion (95% CI = 31%, 154%; p < .001).

Discussion: 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 COPE4Y/MSM 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-T 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-T > 0.1pmol/punch or plasma TFV > 40ng/mL at the same time point. Optimal and sub-optimal levels were defined as TFV-DP > 700fmol/punch and < 7000fmol/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, controlling for all predictors associated with this practice.

Results: 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-T 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-T > 0.1pmol/punch or plasma TFV > 40ng/mL at the same time point. Optimal and sub-optimal levels were defined as TFV-DP > 700fmol/punch and < 7000fmol/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, controlling for all predictors associated with this practice.

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1015 IMPACT OF THE “CHARISMA” INTERVENTION PILOT ON PARTNER DISCLOSURE, IPV, AND ADHERENCE

Elizabeth Montgomery1, Sarah T. Roberts1, Krishnaveni Reddy2, Betsy Tolley3, Miriam Hartmann1, Ellen Wilson4, Florence Mathebula5, Danielle Wagner6, Seth Zissute7, Michele Lanham8, Rose Wilcher9, Jared Baeten5, Thesla Paleanee-Phillips2

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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. Though not fully-powered, we evaluated potential impact by comparing indicators of ring disclosure to partners, partner clinic attendance, and 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%) 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 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.

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 dosing and white coat dosing among a cohort of men who have sex with men using PrEP

<table>
<thead>
<tr>
<th>Sub-Optimal Levels</th>
<th>White Coat Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>High/Intermediate</td>
<td>Ref</td>
</tr>
<tr>
<td>Low</td>
<td>0.69</td>
</tr>
<tr>
<td>Men</td>
<td>1.82</td>
</tr>
<tr>
<td>Older</td>
<td>1.00</td>
</tr>
<tr>
<td>CASI&lt;sub&gt;optimal&lt;/sub&gt; x multiple partners</td>
<td>Ref</td>
</tr>
</tbody>
</table>
1016 REDUCED RELIANCE ON SEX WORK FOR YOUNG WOMEN IN TANZANIA
Jenny Tiberio1, Susie Welty2, Joel Ndayongeji3, Christen Said4, Ritha Mbonoko5, Tania Reza6, Willi McFarland7
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. Gender, 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 THRIVE intervention were recruited from three urban, semi-urban, and rural communities across Tanzania. AGYW (age: 12-24 years) were recruited from schools, clinics, and community centers. Eligible participants were: female, aged 12-24 years; self-identified as an AGYW; HIV-uninfected; and not pregnant. We compared economic conditions at baseline to 12 months in association with program interventions. A key outcome measure was economic strengthening.
Results: 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 had any detectable amount of TFV in their hair. Participants in the intervention arm described the workshops as “helpful,” “enjoyable,” and “comfortable,” settings to discuss HIV prevention.
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.

1017 TransPrEP: Social Network-Based PreP Adherence for Transgender Women in Lima, Peru
Jesse L. Clark1, Sri L. Reisner, ScD2, Amaya G. Perez-Brumer1, Leyla Huerta Castillo1, Hugo Sanchez2, Hideki Okai3, Maria Mamani Luque4, Ximena Salazar5, Matthew Mimiaga1, Monica Gandhi5, Kenneth H. Mayer1, 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 Impacta Salud y Educacion, Lima, Peru, 5Epicentro, 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 had any detectable amount of TFV in their hair. Participants in the intervention arm described the workshops as “helpful,” “enjoyable,” and “comfortable,” settings to discuss HIV prevention.
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 Zhu2, Kenneth L. Dominguez2, Mary Tanner1, Kirk D. Henny1, 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 of color 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 collaborations 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.

Figure 1. PrEP Care Continuum among Transgender Women of the LITE Study (April 2019)

**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, high 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, etc.) among TGW not living with HIV at baseline were indicated for PrEP. Over a third of TGW not living with HIV at baseline were indicated for PrEP (ref: high school education or less, PR: 0.79, p=0.04) and had 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 Prins3, Ivanka Krszarnic1, Anita Mathias1, Deqing Xiao2, Pamela Wong3, Jason Hindman5, Christoph Carter1, Diana Brainard1, Moupali Das2, Elske Hoornenborg5, Peter Ruane6, John Phoenix7, Jason Halperin8

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, of whom the majority 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\text{\textsubscript{\text{50}}} 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 mean (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 were comparable to levels between transwomen taking high-dose hormones and 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.
ASSOCIATIONS BETWEEN HORMONE USE, PrEP USE, AND STIGMA IN US TRANSGENDER WOMEN

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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. Compared to no hormone use individuals, provider-prescribed participants had 9.65 times the odds (95% CI 0.97–96.09) of having used PrEP. There were 10.78 times the odds (95% CI 1.42–81.94), and non-prescription participants were 10.87 times the odds (95% CI 1.43–81.94) of having used PrEP. Compared to no hormone use individuals, provider-prescribed participants had 10.87 times the odds (95% CI 1.43–81.94), and non-prescription participants were 10.87 times the odds (95% CI 1.43–81.94) of having used PrEP.

Conclusions: Hormone therapy and PrEP provision strategies may facilitate PrEP use for some, while others may prioritize hormone therapy or have concerns about hormone–PrEP interactions. 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.

HIV PREVENTION AND DRUG-USER HEALTH CARE ON SITE AT A SYRINGE-EXCHANGE PROGRAM

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Background: Syringe exchange programs (SEPs) serve populations who are high risk for acquiring HIV and other infectious diseases. 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.

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 psychological 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.

Results: A total of 118 patients were seen by a provider during the study period. The mean age was 43 (IQR 17). 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 PrEP 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

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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 with healthcare providers about PrEP, and actual (self-reported) PrEP use were 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

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Background: Universal HBV vaccination had not been available in Japan until 2016 and men who have sex with men (MSM) are still vulnerable to hepatitis B virus (HBV) infection. Thus, 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 HCV antibody, HCV antibody and HAV IgG antibody every 3 months. Entry criteria of the study were HBC antibody negative (< 1.0 S/CO CLIA method) and HCV negative at the study enrollment. TDF/FTC for PrEP were provided for free via an official program of daily PrEP or purchased via internet for its generic drug at their own expense. The definition of HBV infection was positive conversion of HBC antibody or HBs antigen during follow-up period. The participants were followed between January 2018 and September 2019 and incidence rate of HBV infection were evaluated.

Participants who acquired HBV infection or HIV infection were censored. Use of vaccination of HBV were defined as self-report of their experience of HBV vaccination or HBs antibody ≥ 10 mIU/ml (CLIA method). The cox proportional hazards regression analysis was used to evaluate prophylactic effect of PrEP against HBV infection and other factors including HBV vaccination. Factors with statistically significance (p<0.05) and the use of HBV vaccination as a known preventive factor against HBV infection were entered into multivariate analysis.

Results: 827 MSM were included in the cohort as of September 2019. Of 827 MSM, 25 and 211 MSM were excluded from the study due to HIV infection and HBC antibody positivity at the enrollment, respectively. 591 (148 were PrEP+) and 443 were PrEP-) were followed every 3 months with 419.8 person-years (mean age (SD), 34.5 years (9.3)). The incidence rate of HBV infection was 3.57 cases per 100 person-years (15 HBV infections, one in the PrEP+ group and 14 in the PrEP- group, Log Rank test p=0.012). The table identified the preventive and risk factors estimated by the cox hazard analysis which showed significant prophylactic effect of PrEP against HBV infection.

Conclusion: PrEP is a good indication especially for non-responders to HBV vaccination among MSM.

Table: Results of uni- and multivariate analysis to estimate prophylactic effect of PrEP and other factors against HBV infection

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PrEP use</td>
<td>0.087</td>
<td>0.031-1.104</td>
<td>0.650</td>
<td>0.114</td>
<td>0.054-0.813</td>
</tr>
<tr>
<td>PrEP use</td>
<td>0.123</td>
<td>0.0164-0.814</td>
<td>0.044</td>
<td>0.267</td>
<td>0.198-1.881</td>
</tr>
<tr>
<td>HBV vaccination</td>
<td>0.501</td>
<td>0.151-1.518</td>
<td>0.243</td>
<td>0.677</td>
<td>0.198-1.881</td>
</tr>
<tr>
<td>HAV-AKAM</td>
<td>1.038</td>
<td>0.465-2.316</td>
<td>0.929</td>
<td>2.241</td>
<td>0.576-7.713</td>
</tr>
<tr>
<td>Previous syphilis</td>
<td>2.250</td>
<td>0.873-5.841</td>
<td>0.087</td>
<td>2.629</td>
<td>0.234-24.435</td>
</tr>
</tbody>
</table>

1. HBV: HBsAg positive in the last 6 months 2. HAV: HAV-IgG positive in the last 6 months 3. HAV: HAV-IgM positive in the last 6 months 4. HAV: HAV-IgG positive in the last 6 months 5. HAV: HAV-IgM positive in the last 6 months 6. HAV: HAV-IgG positive in the last 6 months 7. HAV: HAV-IgM positive in the last 6 months

1026 AV AND HBV VACCINATION COVERAGE AND ACCEPTABILITY AMONG MSM ON PrEP

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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-HBc Abs at baseline. The median follow-up was 2.2 years.
(IQR 1.6–2.9). Absence of anti-HAV IgG at baseline (50%, 215/427) was associated with younger age (p = 0.0001) and tobacco use (p = 0.02). HBV immunization after infection and vaccination was noted for 12% (50/427) and 67% (287/427) of subjects, respectively. Absence of prior HBV immunization (21%, 90/427) was associated with tobacco use (p = 0.05). Among HAV non-immune subjects, 96% (207/215) received ≥ 1 dose of HAV vaccine and 91% (172/189) received a complete scheme. Among HBV non-immune subjects, 98% (88/90) received ≥ 1 dose of HBV vaccine and 79% (58/73) received a complete scheme. Among subjects with complete scheme, anti-HAV IgG and anti-HBs Abs were detected on last available sample in 93% (148/159) and 80% (44/55) respectively. Among subjects with incomplete scheme, anti-HAV IgG and anti-HBs Abs were detected on last available sample in 80% (12/15) and 36% (5/14) respectively. After the 1st dose of HBV vaccine 63% (37/59) of subjects developed anti-HBs Abs.

Conclusion: The acceptability and efficacy of HAV and HBV vaccination were high in the IPERGAY population. High receptivity to prevention messages and free of charge vaccination may have favored the acceptability. Physicians must consider HAV and HBV vaccination in subjects receiving PrEP.

1027 HIGH PRÉP ADHERENCE BASED ON TFV-DP LEVELS IN THAI 15-19 YEAR-OLD MSM AND TRANSWOMEN

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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 (TFD/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 PrEP demonstration project and CIPHER program at youth-friendly clinics. Monthly contact was via clinic visits (months 0, 1, 2, 3) 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-TP 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-TP levels of <100, ≥100-349, ≥350-699 and ≥700 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-TP levels were ≥700, ≥350-699, 100-349 and <100 fmol/punch in 47%, 17%, 20% and 16%, respectively. Among 199 risk periods, 46% were protected by PrEP only, (12% and 34% of samples with TFV-TP levels of ≥350-699 and ≥700 fmol/punch, 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-TP 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 PRÉP STUDY

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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, 8med univ Gerald Felician Lang, Vienna, 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 (FTAF) and emtricitabine/tenofovir disoproxil fumarate (FT-DF) 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 FTAF or FT-DF. 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 (TFD-DF) 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-TP 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 FTAF arm and 11/17 occurred in the FT-DF arm. In 15 of the 17 on study HIV infections, DBS testing demonstrated that participants had undetectable or low TFV-TP 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 FTAF and FT-DF arms respectively, 86-96% and 84-93% of participants were using at least 4 tablets/week, as measured by TFV-TP levels in RBCs. Levels of TFV-TP in PBMCs strongly correlated with tablets per week adherence TFV-TP levels in RBCs.

Conclusion: DISCOVER participants had very high adherence and very low HIV incidence rates. TFV-TP levels in RBCs were significantly lower in those with low 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.

Table 1: Odds ratios of risk factors associated with non-adherence (DBS), univariate logistical regression

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>Comparison</th>
<th>Odds Ratio Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using TF/TDF for PrEP at baseline</td>
<td>No vs Yes</td>
<td>2.91 (1.41, 4.74)</td>
</tr>
<tr>
<td>Race</td>
<td>Black vs Nonblack</td>
<td>2.37 (1.17, 4.79)</td>
</tr>
<tr>
<td>Region*</td>
<td>US vs. 14 US</td>
<td>2.17 (1.20, 4.01)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 25 vs &gt; = 25</td>
<td>3.12 (1.03, 4.6)</td>
</tr>
<tr>
<td>Highest Level of Education*</td>
<td>&lt; 4 Year vs &gt; = 4 Year College</td>
<td>2.17 (1.29, 3.65)</td>
</tr>
<tr>
<td>Recreational Drug Use</td>
<td>No vs Yes</td>
<td>1.54 (0.92, 2.59)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hispanic vs Non-Hispanic</td>
<td>1.53 (0.89, 2.66)</td>
</tr>
<tr>
<td>Diagnosis of Rectal Gonorrhea, Rectal Chlamydia or Syphilis at baseline (6 mos. prior to screening)</td>
<td>No vs Yes</td>
<td>1.40 (0.79, 2.56)</td>
</tr>
<tr>
<td>Birge Alcohol Use</td>
<td>Never vs Have &amp; 5 Drinks on One Occasion</td>
<td>1.94 (0.87, 3.99)</td>
</tr>
<tr>
<td>Number of Condomless Anal Sex Partners (within 3 mos. prior to screening)</td>
<td>4+ vs 3 or &lt; 3</td>
<td>1.37 (0.75, 2.52)</td>
</tr>
<tr>
<td>Circumcision Status</td>
<td>No vs Yes</td>
<td>0.95 (0.57, 1.63)</td>
</tr>
</tbody>
</table>
1029 COMPARISON OF TFV-DP AND WISEPILL ADHERENCE AMONG YOUNG KENYAN WOMEN USING PrEP

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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 VOICE 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 36 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

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1Massachusetts General Hospital, Boston, MA, USA, 2Kenya Medical Research Institute, Nairobi, Kenya, 3University of Washington, Seattle, WA, USA

Background: Pre-exposure prophylaxis (PrEP) is a highly effective means for preventing HIV acquisition. However, use among young women has generally been suboptimal and poorly characterized. We present objectively measured adherence and associated socio-behavioral factors among a cohort of young women.

Methods: Participants were 18–24 year old women at high risk for HIV in Thika and Kisumu, Kenya. High risk was defined as a VOICE risk score >4; points (pts) were given for age <25 (2 pts), being single or not living with a primary sexual partner (2 pts), lacking financial or material support from a sexual partner (1 pt), a sexual partner having or potentially having other partners (2 pts), and alcohol use (1 pt). Participants were encouraged to take PrEP for at least 6 months and then counseled on continued use based on their preferences and HIV risk. Study visits occurred at 1 month, 3 months, and then quarterly for 24 months. Adherence was measured with a real-time electronic monitor (Wisepill) and summarized descriptively. Baseline predictors of high adherence were assessed by multivariable logistic regression analysis.

Results: A total of 347 women have been followed for 461 person-years (as of June 2019; study to end early 2020). At 1, 3, and 6 months of desired PrEP use, 35%, 14%, and 7% of participants took an average of 6 doses per week, respectively, while 50%, 24%, and 15% took an average of 5 doses per week. The only baseline factor significantly associated with high adherence (an average of 6 doses per week) over 6 months was the VOICE risk score: OR 0.53 (95% CI 0.33, 0.85) for each additional point (figure). Non-significant factors included in the model were age, number of current sexual partners, concern about PrEP, prior medication use, and intimate partner violence. Findings were similar when high adherence was defined as an average of 5 doses per week.

Conclusion: Objectively measured PrEP adherence likely to be sufficient for protection against HIV was seen in a minority of participants and declined with time. Higher baseline HIV risk was associated with lower adherence in the first 6 months of use. These findings suggest limited prevention-effective adherence, although future analyses will assess the alignment of risk and adherence over time. Similar assessments in other PrEP cohorts may be useful for program evaluation; novel approaches are needed to help young women understand risk and the means to achieve effective HIV prevention.

1031 USING A MOBILE APP AND DRIED BLOT SPOTS TO ASSESS ADHERENCE TO EVENT-DRIVEN PrEP

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Background: Both daily and event-driven (i.e. before and after sex) pre-exposure prophylaxis (PrEP) regimens are effective against HIV acquisition. However, information about adherence to event-driven PrEP is scarce and predominantly based on self-reported data collected at 3-month intervals. We used a mobile-based diary application and intracellular tenofovir diphosphate (TFV-DP) levels to assess adherence among event-driven PrEP users participating in the Amsterdam PrEP demonstration project (AMPEP) 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 corresponding Wisepill openings over the prior 30 days.

Results: Between September 2015 and February 2019, 139 of 376 (37.0%) AMPEP 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

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**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. At Visit 1, 606 (88%) were adherent. Of the 606 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 in a row (25% vs 25%, 9% vs 8%, respectively).

**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

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**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.
1034 PRENATAL PrEP EXPOSURE AND LONGITUDINAL BIRTH OUTCOMES IN KENYA

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Methods: PrEP Implementation for Mothers in Antenatal Care (PrIMA) is a cluster randomized trial in Western Kenya (NCT03070600) evaluating different strategies for providing PrEP counseling to women attending antenatal care. Women enrolled in PrIMA are followed through 9 months postpartum whether or not they elect to use PrEP. Women were identified as PrEP-exposed during pregnancy 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-weeks postpartum. Low birthweight, and birth length were compared by PrEP exposure status using generalized estimating equations (GEE) with a binomial link or a gaussian link. Analyses were repeated adjusting for partner HIV status, maternal age, and provision of CHPS.

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 654 (17%) used PrEP at any time during pregnancy and 654 (17%) used PrEP. Women were more likely to report having a partner who was known to be HIV-positive (61% vs. 30%) in the PrEP unexposed group and 24 weeks (IQR: 20, 28) in the PrEP exposed group. Compared to women who did not use PrEP, PrEP-exposed women were more likely to report having a partner who was known to be HIV-positive (61% vs 33%) or a partner of unknown status (43% vs. 36%), and reported more HIV risk factors (p<0.001 for all). Compared to PrEP-unexposed infants, there was no difference in miscarriage (0.5% for both, p=0.49), stillbirth (3.3% vs 2.2%, p=0.98), preterm birth (17.2% vs 17.6%, p=0.67), birthweight (3.4kg for both, p=0.51), or birth length (52 v 51cm, p=0.59).

Conclusion: In this large longitudinal study, we found no significant differences in birth outcomes by prenatal PrEP exposure status.
1036 RESULTS FROM A PrEP DEMONSTRATION PROJECT FOR AT-RISK CISGENDER WOMEN IN THE US

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Background: 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.
1038 “STYLISH MAN” CLUSTER RCT TO INCREASE MALE CIRCUMCISION FOR ADULT MEN ≥19, UGANDA

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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”). 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=752, 17.1%, 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=1.31, 95% CI 1.05-1.68). 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 demedicalized approaches to increase VMMC among older men.

1039 SEX AND THE PENILE MICROBIOME: POTENTIAL SHARING OF HIV RISK–ASSOCIATED ANAEROBES

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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 <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). Peptostreptococcus 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 forebrain inflammation and colonize the penile microbiome.

1040 PREVALENCE AND INCIDENCE OF STIs DURING PREGNANCY IN SOUTH AFRICA

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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 gonorrhoea (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=199) had asymptomatic
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=1.33-2.17) 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.

1042 **PREVALENCE OF MYCOPLASMA GENITALIUM AND PERINATAL OUTCOMES IN HIV+ PREGNANT WOMEN**

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**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, 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.
in MG-infected women. MG warrants greater attention as part of the growing emphasis on STI diagnosis and treatment in HIV-infected individuals.

1043 DIAGNOSIS OF SEXUALLY TRANSMITTED INFECTIONS IN PREGNANT WOMEN AND MALE PARTNERS

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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), trichomonas (TV), and chlamydia (GC) 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 1.3-4.2), having less education (AOR 2.1 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: Scheme of STI frequencies in pregnant women and their partners

1044 SEXUALLY TRANSMITTED INFECTIONS AMONG HIV SERODISCORDANT SEXUAL PARTNERS: HPTN 052

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Background: Sexually transmitted infections (STIs) remain a public health concern because of their interaction(s) with HIV. Infection with STIs among HIV-infected persons may reduce CD4+ levels and increase HIV RNA in blood plasma and semen, thus increasing the potential for HIV transmission. In HIV-uninfected individuals, STIs increase genital inflammation that may enhance HIV acquisition during sex. Among both HIV-uninfected and HIV-infected individual, infection with any STI is a marker of unsafe sexual practices.

Methods: In the HPTN 052 study, STIs were evaluated in both HIV-infected index cases and their HIV-uninfected partners at enrollment and at yearly follow-up visits. Genital swabs were collected at the sites and shipped to HPTN Central Laboratory for etiology determination. In this analysis, our definition for STI was based on any infection with hepatitis B, Chlamydia trachomatis, Neisseria gonorrhoea, Syphilis, or Trichomonas vaginalis. We used log binomial regression models to identify factors associated with prevalent STIs. Generalized Estimating Equations models with Poisson link function were used to compare STI incidence between HIV-infected index cases and HIV-uninfected partners, stratified by gender.

Results: 10.4% of the participants had STIs at enrollment. The prevalence of STIs (13.6 vs 7.2) was higher in HIV-infected index cases compared to HIV-uninfected partners. Being female (prevalence ratio (PR) = 1.29; 95% CI: 1.01-1.66) or unmarried (PR = 1.61; 95% CI: 1.03-2.51) was associated with prevalent STIs. STI incidence during follow up is presented in the Table. Compared to HIV-uninfected male partners, HIV-infected female index cases had a higher risk of STI acquisition (Incidence Rate Ratio (IRR) = 2.50; 95% CI: 1.74-3.60). Conclusion: STIs are common among HIV-serodiscordant couples. HIV-infected female index cases are more likely to acquire STIs from their HIV-uninfected partners or other partners. While we are implementing HIV prevention interventions for HIV-uninfected people, we should also intensify targeted STI prevention interventions, especially among HIV-infected women.

Table: Comparison of STI incidence between HIV-infected index cases and HIV-uninfected partners

<table>
<thead>
<tr>
<th>Gender</th>
<th>No. of Infections</th>
<th>Follow-up time (years)</th>
<th>Incidence Rate (per 100 person-years)</th>
<th>Unadjusted IRR (95% CI)</th>
<th>Adjusted HIV* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>121</td>
<td>2.99</td>
<td>1.28 (1.26-1.74)</td>
<td>0.92 (0.91-1.33)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>57</td>
<td>1.66</td>
<td>1.20 (0.73-2.77)</td>
<td>0.66 (0.40-1.07)</td>
<td></td>
</tr>
</tbody>
</table>

STI: Hepatitis B or Chlamydia trachomatis or Neisseria gonorrhoea or Trichomonas vaginalis
IRR: Incidence rate ratio
* Adjusted for age, education, marital status and condom use

1045 HIV TRANSMISSION RISK FACTORS AMONG MEN LIVING WITH HIV WANTING A PREGNANCY IN UGANDA

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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-uninfected 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
### 1046 CHANGES IN SEXUAL RISK BEHAVIORS FOLLOWING AN STI DIAGNOSIS AMONG A COHORT OF MSM

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**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.

**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.

**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.

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### 1047 VARIATION IN SYphilIS AMONG BISEXUAL MEN AND ASSOCIATION WITH SYphilIS IN WOMEN

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**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, men 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 1% 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.

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### 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 100,000 Men, 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>0.38</td>
<td>3.5</td>
<td>0.69</td>
</tr>
<tr>
<td>Northeast</td>
<td>7.0%</td>
<td>0.38</td>
<td>3.5</td>
<td>0.69</td>
</tr>
<tr>
<td>South</td>
<td>38.5%</td>
<td>&lt;0.01</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>Black</td>
<td>14.7%</td>
<td>&lt;0.01</td>
<td>10.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>White</td>
<td>8.6%</td>
<td>0.38</td>
<td>3.5</td>
<td>0.69</td>
</tr>
<tr>
<td>Hispanic</td>
<td>10.9%</td>
<td>&lt;0.01</td>
<td>10.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Denotes a statistically significant change; number of 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.
1048 ASSOCIATION OF STI DIAGNOSIS WITH INCIDENT HIV IN A SOUTHERN STATEWIDE COHORT

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Background: Data on associations between diagnosis of sexually transmitted infections (STIs) and incident HIV beyond high-risk male subgroups is lacking. Identifying STIs associated with greatest risk of subsequent HIV could help better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs compared to others may confer a higher risk of subsequent HIV among a large statewide cohort.

Methods: Statewide surveillance data in Tennessee (TN) from 1/2013-12/2017 were extracted from the Patient Reporting Investigation Surveillance Manager (PRISM) and the electronic HIV/AIDS Reporting System (eHARS) and matched to identify reportable STI (chlamydia, gonorrhea, all stages of syphilis) and HIV diagnoses among individuals ≥13 years old. Individuals were followed from first STI diagnosis until HIV diagnosis or end of study. Cox regression with time-fixed exposure of STI at cohort entry was used to obtain adjusted hazard ratios (aHR) and associated 95% confidence intervals (CI) for incident HIV. Models accounted for age at time of STI test, sex, race, health department region, reported male-to-male sexual contact ( MSM ) and history of injection drug use.

Results: Over the study period, 148,632 HIV-negative individuals were diagnosed with a reportable STI in TN and followed for 503,256 person-years. Among them, 487 (0.33%) individuals were diagnosed with incident HIV following STI diagnosis, an incidence of 0.97 per 1000 person-years. Chlamydia was the most common STI at cohort entry (n=111,738, 75.3%), though a diagnosis of gonorrhea was most common at cohort entry among those with incident HIV (n=163, 34.5%). Incident HIV infection was 9 times likelier among persons with secondary syphilis as compared to chlamydia (aHR=9.2, 95% CI: 6.0-14.1), controlling for demographic and behavioral risk factors. When stratified by self-identified MSM risk, secondary syphilis had greatest association of any STI with subsequent HIV infection among both MSM (aHR=3.2; 95% CI: 1.7-5.8) and non-MSM (aHR=32.8, 95% CI: 16.2-66.6) (Table). Conclusion: Individuals ≥13 years old diagnosed with secondary syphilis were at greatest risk of subsequent HIV infection over the study period compared to those with other reportable STIs in TN, regardless of self-reported MSM risk behavior. These individuals should be especially prioritized for public health efforts and HIV prevention interventions, including PrEP, at the time of STI diagnosis.

1050 A POINT-OF-CARE ASSAY FOR DIAGNOSIS OF NEUROSYPHILIS

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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 86% for the treponemal test and sensitivity of 81% and specificity of 97% for the non-treponemal test. Treponemal test false positives and non-treponemal test false negatives had a median of 1:8 (95% CI: 1:4-16). While prevalence of at least one STI (NG, TV, CT, or active syphilis) was 1.17 fold higher among HIV-positive versus HIV-negative persons (34 vs 21%; 95% CI: 1.19-2.05), there was no differences in STI prevalence by ART status. (Prevalence risk ratio [PRR]=0.95; 95% CI: 0.95-1.02) or self-reported MSM status among all men (PRR=0.93; 95% CI: 0.92-1.10).

Conclusion: Despite high coverage of HIV treatment and prevention interventions, the burden of STIs remains extremely high in Lake Victoria fishing communities. There is an urgent need to integrate STI diagnostic testing and treatment with HIV services in these high HIV burdened settings.
**1051 IDENTIFYING AN HIV AND NEURO/Ocular syphilis CLUSTER IN VERMONT**

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**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, outreach to all sexual contacts of these cases, and pursue sexual networking analyses. Descriptive statistics were used to summarize population characteristics. Fisher's exact and independent t-tests were used to compare cluster versus non-cluster groups.

**Results:** Between January 1, 2017 and December 31, 2018, 38 newly diagnosed cases of HIV were identified in Vermont. In this cohort, the mean age was 38.2 years and 82% were white, 79% were male, 79% were MSM, 29% had a positive syphilis serology with 11% classified as neuro/ocular syphilis, 21% reported methamphetamine use prior to sex in the past six months, 47% had HIV viral loads > 100,000 copies/mL, and 47% had CD4 cell counts < 200/μL. Sexual networking analysis revealed a cluster of ten cases of HIV infection (four diagnosed in rural Vermont counties), of whom seven reported methamphetamine use, nine had viral loads > 100,000 copies/mL, seven had CD4 cell counts < 200/μL and four had neuro/ocular syphilis. Subjects in the cluster were more likely to have higher HIV viral loads than those not in the cluster (90% versus 30%, p < 0.015).

**Conclusion:** This investigation of newly infected cases of HIV in the rural state of Vermont led to identification of a cluster of cases that appeared more likely to have advanced HIV disease (80% with viral loads > 100,000 copies/mL at diagnosis), and 30% had neuro/ocular syphilis.

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**1052 GYRASE A SERINE 91 GENOTYPING PREDICTS GONORRHEA CIPROFLOXACIN TREATMENT OUTCOME**

**Jeffrey D. Klausner**, Sheldon Morris, Claire Bristow; *University of California Los Angeles, Los Angeles, CA, USA, University of California San Diego, La Jolla, CA, USA*

**Background:** Neisseria (N.) gonorrhoeae infections are rapidly increasing and among the most common co-infections in human immunodeficiency virus-infected patients. With great public health concern, there have been cases of N. gonorrhoeae resistant to all available antibiotics. In order to slow the continued emergence of antimicrobial resistance, new treatments strategies are urgently needed. The use of resistance-guided therapy—treatment based on the antimicrobial susceptibility of the infection—is one such promising strategy. We developed an assay to predict the susceptibility of N. gonorrhoeae to ciprofloxacin based on the gyrA A serine 91 codon, a locus previously shown to be highly predictive of in vitro resistance. In this study, we tested the efficacy of that assay in predicting clinical outcomes.

**Methods:** We conducted a single arm multi-site clinical study of the efficacy of ciprofloxacin 500 mg by mouth for the treatment of wild-type gyrA 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 A. N. gonorrhoeae infection failed therapy (0% cure).

**Conclusion:** GyrA serine 91 N. gonorrhoeae genotyping was highly predictive of clinical outcomes in patients with gonorrhoea treated with ciprofloxacin.

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**1053 IMPROVING DIAGNOSIS OF CT/NG AMONG PrEP USERS WITH MULTIPLE SITE SCREENING**

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**Background:** PrEP users are under high risk of bacterial sexually transmitted infections. Sensitive and timely diagnostic strategies are crucial to allow rapid prescription of antimicrobial treatment. Several studies have shown that Chlamydia trachomatis (Ct) and Neisseria gonorrhoeae (Ng) screening at multiple anatomic sites may improve the diagnostic yield in high-risk populations.

**Methods:** In this retrospective cohort study, HIV-uninfected patients referred for PrEP were followed with periodic serologic testing of Syphilis (every 3 months) and culture/molecular testing of CtxNg (approximately every 6 months in asymptomatic patients; as needed for those with symptoms). We describe the
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 anatomical 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 1/12 (8%; 95% CI 48–93) 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.Had screening been performed in urine only, 12/16 (75%; 95% CI 46-88) incident cases would have been missed. 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 1/12 (8%; 95% CI 48–93) 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.

1055 NO EVIDENCE OF CLINICAL IMPACT OF STIs ON SEMINAL HIV BURDEN DURING SUCCESSFUL ART

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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 (<20cps/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 regimen (3rd drug:11INSTI; 5NNRTI; 4PI), 5 pts were on a dual regimen (2DR;3DRV/c+3TC, 1DRV+r+RAL, 1ETR+r+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+ (table). 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(2.0-4.2) 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.

1054 THE PERFORMANCE OF POOLED 3-ANATOMIC-SITE CHLAMYDIA AND GONORRHEA TESTING

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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 99.7% (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.
**Table 1. Residual viremia and Total HIV-DNA in peripheral and seminal compartments.**

<table>
<thead>
<tr>
<th>ID</th>
<th>Residual viremia</th>
<th>Total HIV-DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TND</td>
<td>3.45</td>
</tr>
<tr>
<td>2</td>
<td>TND</td>
<td>3.8</td>
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<tr>
<td>3</td>
<td>TND</td>
<td>5.5</td>
</tr>
<tr>
<td>4</td>
<td>TND</td>
<td>2.1</td>
</tr>
<tr>
<td>5</td>
<td>TND</td>
<td>3.9</td>
</tr>
<tr>
<td>6</td>
<td>TND</td>
<td>2.3</td>
</tr>
<tr>
<td>7</td>
<td>TND</td>
<td>5.2</td>
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<tr>
<td>8</td>
<td>TND</td>
<td>2.4</td>
</tr>
<tr>
<td>9</td>
<td>TND</td>
<td>3.9</td>
</tr>
</tbody>
</table>

*Note: TND denotes not detected.*

### 1056 RISK OF PELVIC INFLAMMATORY DISEASE WITH CONTRACEPTIVE METHOD USE IN THE ECHO TRIAL

**Kavita Nanda**1, James Kiarie2, Khatija Ahmed3, Tsuengai Chipato4, Margaret P. Kasaro5, Cheryl M. Louw6, Charles S. Morrison1, Susan Morrison7, Nelly R. Yacobson1, Valentine Wanga7, for the ECHO consortium

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**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 been conducted with electronic medical records.

**Methods:** We analyzed data from the ECHO Trial, which assessed HIV risk in 7,829 women from 12 sites in sub-Saharan Africa randomized to intramuscular depot medroxyprogesterone acetate (DMPA-IM), levonorgestrel (LNG) implant, or copper IUD. Women were tested for gonorrhea and chlamydia (NG/CT) at screening. At enrollment, IUDs were inserted without waiting for NG/CT results, but were delayed for at least 7 days after treatment when mucopurulent discharge or cervicitis were seen. Asymptomatic women testing positive for NG/CT were treated once results were available. All participants returned at 1 month for scheduled follow-up visits and IUD users had routine pelvic exams. Participants in any group who reported abdominal/pelvic pain at any time were examined and treated for presumptive PID based on CDC minimal criteria (abdominal/pelvic pain and either cervical motion, uterine, or adnexal tenderness). We assessed PID incidence over time and compared PID incidence by arm. We conducted sensitivity analyses using specific criteria for PID (minimum criteria plus mucopurulent discharge, friable cervix, or baseline NG/CT). 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 incident pregnancy. 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 incident pregnancy.

**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.
1058 AN EVALUATION OF AN ENHANCED MODEL OF FP/HIV SERVICE INTEGRATION IN LUSAKA, ZAMIBA

Amy M. Medley1, Fatima Tisorus1, Sherri Pali1, Brenda Senyana1, Susan Hanene1, Shadrick Kayeye1, Rocio R. Casquete2, Arielle Lastra2, Meagan Cain1, Tiffiany Michelle Aholou1, Prisca Kasonde3, Tina Chisenga4, Keithimprove women’s access to these services.

FP. These results support continued efforts to integrate FP and HIV services to

number of WLHIV reporting use of an effective FP method and a met need for

(26%), training (14%) and administration (20%).

Among women wanting to get pregnant, receipt of safer pregnancy counseling

(P=.0003); while, unmet need for FP decreased from 59% to 46% (P=.0003).

The percent of women reporting dual method use increased from 9% to 18%

implants (5% vs. 8%, p>.05), and intrauterine devices (IUDs, 1% vs. 1%, p>.05).

points was: pills (10% vs. 8%, p>.05), injectables (15% vs. 25%, p<.0001),

post-intervention. During the pre-intervention period, only 38% of women not

were used to examine differences in self-reported FP uptake between the two

time periods.

Results: A total of 629 WLHIV were interviewed pre-intervention and 684

post-intervention. During the pre-intervention period, only 38% of women

not desiring a pregnancy reported currently using an effective FP method compared

to 49% post-intervention (p=.003, Table 1). Uptake by method at the two time points

was: pills (10% vs. 8%, p>.05), injectables (15% vs. 25%, p<.0001),

implants (5% vs. 8%, p>.05), and intrauterine devices (IUDs, 1% vs. 1%, p>.05).

The percent of women reporting dual method use increased from 9% to 18%

(P=.0003); while, unmet need for FP decreased from 59% to 46% (P=.0003).

Among women wanting to get pregnant, receipt of safer pregnancy counseling

increased from 27% to 39%. The total intervention cost was estimated at

$83,293 (2018 USD) over the 12-month period including labor (40%), supplies

(26%), training (14%) and administration (20%).

model of FP/HIV Integration was associated with a significant increase in the

number of WLHIV reporting use of an effective FP method and a met need for

FP. These results support continued efforts to integrate FP and HIV services to

improve women’s access to these services.

Table 1. Comparison of Key Outcomes Variables Before and After Intervention of Family Planning within HIV Treatment Services in Six Health Facilities in Lusaka, Zambia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-intervention</th>
<th>Post-intervention</th>
<th>Unmet need for FP</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>N=179</td>
<td>N=402</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of highly effective method</td>
<td>133 (75.4%)</td>
<td>199 (49.1%)</td>
<td>.0014</td>
<td>.0005</td>
</tr>
<tr>
<td>Use of dual methods†</td>
<td>30 (17)</td>
<td>42 (10)</td>
<td>.0032</td>
<td>.0008</td>
</tr>
<tr>
<td>Unmet need for FP‡</td>
<td>210 (59)</td>
<td>104 (46)</td>
<td>.0003</td>
<td>.0003</td>
</tr>
<tr>
<td>Women Desiring a Pregnancy</td>
<td>135 (75.4%)</td>
<td>209 (51.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desires safe contraception</td>
<td>10 (5.6%)</td>
<td>11 (2.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disables safer contraception</td>
<td>56 (27)</td>
<td>97 (24)</td>
<td>.0013</td>
<td>.0008</td>
</tr>
</tbody>
</table>

† Adjusted model includes facility factor, age, group, and time since diagnosis. The adjusted model could not be fit for discussion of safer pregnancy due to insufficient data.

‡ Defined as not desiring a pregnancy in the last six months but not currently using any FP method to prevent becoming pregnant.

1059 A COMBINED ESTROGEN/PROGESTIN VAGINAL RING IMPROVES VAGINAL MICROBIAL COMMUNITIES

Nicole H. Tobin1, Sarah L. Brooker1, Fan Li1, Yoninah S. Cramer2, Susan L. Rosenkranz2, Grace M. Aldrovandi2, Robert Coombs3, Susan E. Cohn1, Carmen D. Zorrilla1, Laura E. Moran1, Baiba Bezins1, Kimberly K. Scarsi1, Catherine Godfrey1, for the ACTG 5316 Team

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Background: ACTG study 5316 found that during contraceptive intravaginal ring (IVR) use over 3 weeks, efavirenz-based ART (EFV) significantly decreased both ethinyl estradiol (EE) and etonogestrel (ENG) plasma exposure, while atazanavir/ritonavir-based ART (ATV) decreased EE, yet increased ENG. We explored the role of the IVR on vaginal microbial communities and vaginal small chain fatty acids (SCFA) as well as the role of the vaginal microbes/SCFA on hormone concentrations.

Methods: Of the 74 participants (25 ART Naïve; 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 Metabolon® at weeks 0, 1 or 2, and 4. Sequences were filtered and taxa 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 a L. crispatus¬-dominant (Community State Type (CST) 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=1.36-8.15, Fisher’s exact test, p<.001). ENG levels were negatively correlated with abundance of Prevotella timonensis. After IVR removal, an increased probability of transition into CST IV (OR=7.75, CI=1.56-38.49, p<.001) was observed, with a decrease in lactic acid levels (p<.001). Negative binomial modeling of the most abundant taxa between week 3 (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-II) 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

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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 (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 0.583), 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

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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, quantifying 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 (16S rRNA gene) were sequenced from fluid collected via lateral vaginal wall swabs. For the first time in a randomised clinical trial, we demonstrate that Cu-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 ECHO trial (n=80) were collected at baseline and within 3 months of initiating contraception. Cervical cytobrush-derived T cells were sequenced from fluid collected via lateral vaginal wall swabs. For the first time in a randomised clinical trial, we demonstrate that Cu-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.

Results: DMPI-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 LNG-implant were not associated with higher concentrations of T cell chemotactic markers IL-8, Eotaxin, IP10, RANTES, MIP-1a or MIP-1b, 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 Cu-IUD, 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 DMPI-IM reflect epithelial barrier damage.

1063 INCREASED GENITAL INFLAMMATION IN WOMEN RANDOMIZED TO COPPER IUD IN THE ECHO TRIAL

Tanko F. Rama1, Rubina Bunjun1, Shameem Jaumdally1, Smitree Dabee1, Anna Ursula Happe1, Hoyam Gamiedien1, Rushil Harryparsad1, Marianna A. Onono1, Onondra Pany4, Palani Heffron1, Heather Jaspan1, Jo-Ann Passmore1, 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, 4Centre for Global Health Research, Kisumu, Kenya, 5University 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 (DMPI-IM) influenced genital inflammation, relative to the levonorgestrel implant (LNG-Implant) and non-hormonal copper intrauterine device (Cu-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 (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 (DMPI-IM: n=67; LNG-Implant: n=63; Copper-
**1064 ELEVATED GENITAL CYTOKINES IN HIV-Infected Women Using Copper and Levonorgestrel IUDs**


1 University of Cape Town, Cape Town, South Africa, 2 City University of New York, New York, NY, USA, 3 Rutgers University, Piscataway, NJ, USA, 4 FHI 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 months 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 (gVL) correlated positively with IL1b (R=0.72), IL6 (R=0.84) and IL8 concentrations (R=0.66). In ART+, IL1a, IL6, and Eotaxin were associated with rapid increases in inflammatory markers following cIUCD insertion in ART- women. In ART+ women, LNG-IUS had a more moderate effect than cIUCD, with 6/28 cytokines elevated at 3-month follow-up, of which 15 remained high at 6 months. In ART+ women, LNG-IUS had a more moderate effect than cIUCD, with 6/28 cytokines elevated at 3-month follow-up, of which half resolved by 6 months. In contrast, among ART- women, LNG-IUS 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 MCP1, MIP1a, and GCSF remained high at 6m. A more significant increase in CVS cytokines was observed after cIUCD insertion in ART+ WLHIV, 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 month). 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.

**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 gVL in ART+, changes in inflammatory profiles associated with either IUCD did not increase gVLs in ART+.
IP-10, MIP-1α and MIP-1β were significantly elevated one follow copper IUD insertion. No changes were evident at one month post LNG implantation, however at three months, TNF-α, IP-10, MIP-3α and SLPβ1 were significantly raised relative to baseline. Significant effect modification was observed by N. gonorrhoeae and HSV-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. McGaugh1, Charlene Miller1, Justice King1, Kathryn McManus1, Maria L. Alcald1, Jose Bauermeister1, Christian Grov1, Jennifer A. Manuzak2, Courtney Brodlov2, Robert Parisi3, Darling Martinez2, Nichole Klett2, Adam W. Carico1 University of Miami, Miami, FL, USA, 1University of Pennsylvania, Philadelphia, PA, USA, 2City University of New York, New York, NY, USA, 3AIDS 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 (IL-8), 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 douche 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 douch 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

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Background: HIV/AIDS and sexual violence act synergistically to adversely and disproportionately impact women’s health. Yet immune–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 132 women enrolled from the Washington DC area, comparing 13 cases who had experienced forced vaginal penetration (FVP) in the past 25 weeks to 120 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<.003) and MCP-1 (p<.001) and anti-HIV/wound-healing marker Thrombospondin-1 (TSP-1) (p<.027). Conversely, they had increased inflammatory cytokine IL-1α (p<.001) and were more likely to have detectable levels of wound-healing platelet derived growth factor (PDGF) (OR=7.89; p<.019). In plasma, cases had decreased levels of chemokines MIP-3α (p<.001) and IL-8 (p=.004), anti-inflammation cytokine TGF-β (p=.016), anti-HIV factor beta defensin 2 (HBD2) (p=.017), and wound-healing protease MMP-1 (p=.019). They had higher levels of protease Cathepsin B (p=.010) and TSP-1 (p=.003) and were more likely to have detectable chemokine IP-10 (OR=12.24; p<.064). The associations of case status with reduced MCP 1 in CVL and reduced MIP 3a 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

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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]: 1.24-17.37). Among all respondents, 66% reported zero to four days at 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 authorizations (50%), financial barriers (46%), and concern about false positives (37%). ART medication starter packs (63%) and patient medication prior authorizations (50%), financial barriers (46%), and concern about false positives (37%). ART medication starter packs (63%) and patient medication prior authorizations (50%), financial barriers (46%), and concern about false positives (37%).

**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 knowledgeable initiation of antiretroviral therapy (IART) by staff role and clinic-level patient demographics

<table>
<thead>
<tr>
<th>Staff Designation</th>
<th>Knowledge</th>
<th>Attitude</th>
<th>Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR [95% CI]</strong></td>
<td><strong>OR [95% CI]</strong></td>
<td><strong>OR [95% CI]</strong></td>
<td><strong>OR [95% CI]</strong></td>
</tr>
<tr>
<td>1.4 (1.0-2.0)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.0 (0.0-1.0)</td>
</tr>
<tr>
<td>0.7 (0.1-2.0)</td>
<td>1.0 (0.1-1.0)</td>
<td>1.0 (0.1-1.0)</td>
<td>1.0 (0.1-1.0)</td>
</tr>
<tr>
<td>0.5 (0.0-6.0)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.0 (0.0-1.0)</td>
</tr>
<tr>
<td>0.4 (0.0-6.0)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.0 (0.0-1.0)</td>
</tr>
<tr>
<td>0.9 (0.0-6.0)</td>
<td>1.0 (0.1-1.0)</td>
<td>1.0 (0.1-1.0)</td>
<td>1.0 (0.1-1.0)</td>
</tr>
</tbody>
</table>

**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 with 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% CI: 17-29%)

and 28 days (94% vs 82%; RD: 12%; 95%CI: 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 >1 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 model for implementing guidelines that can be immediately utilized.

<table>
<thead>
<tr>
<th>Year</th>
<th>Initiates on same-day</th>
<th>Retained in care 8 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>70%</td>
<td>95%</td>
</tr>
<tr>
<td>2019</td>
<td>75%</td>
<td>98%</td>
</tr>
</tbody>
</table>

**Table 1:** Time to ART initiation by study arm

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Immediate ART initiation</th>
<th>Risk difference [95% CI]</th>
<th>Relative risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard arm</td>
<td>56% (n=30)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Intervention arm</td>
<td>74% (n=43)</td>
<td>0.69</td>
<td>0.47-1.01</td>
</tr>
</tbody>
</table>

**Background:** Nearly all countries have adopted WHO “Treat All” guidelines to initiate antiretroviral therapy (ART) for all people living with HIV (PLWH) as soon as possible after diagnosis. An emerging literature suggests it is important to characterize the relationship between time to initiation and subsequent clinical outcomes under Treat All. We compared loss to follow up (LTFU) and viral suppression (VS) among PLWH 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 1971 patients, 1895 (96%) initiated ART. Of ART initiators, 292 (15%) 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%, 17% and 17% of same day, 1-7, >8-30, and >30 days initiators, respectively. After adjusting for health center, age, sex, enrollment source, BMI, WHOA 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.
**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


**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, 8-14 days, 15-21 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%, 15.3%, 14%, 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 (orR:1.75%,95%CI:1.03-2.8,p<0.05) and had AEs (aOR:1.52%,95%CI:1.07-2.17,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 Seybolt**, Katherine Conner, Isolde Butler, Nicholas Van Sickels, Jason Halperin

**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.
1075 IMPACT OF UTT ON VIRAL SUPPRESSION IN SOUTH AFRICA: A NATIONAL COHORT STUDY

Jacob Bor1, Matthew P. Fox1, Khairul Maslak2, Dorina Onoya2, Alana T. Brennan3, Noah A. Haber3, Till Bärnighausen4, Sergio Carmona5, Wendy Stevens5, Adrian J. Puren1, William B. MacLeod1

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Background: Universal Test and Treat (UTT) is an approach to interrupt the transmission of HIV by offering antiretroviral treatment (ART) to all individuals with HIV infection. We conducted a national cohort study to evaluate the impact of UTT on viral suppression in South Africa.

Methods: We developed a national HIV cohort through novel linkage of the complete historical laboratory records of South Africa’s public sector HIV program, April 2004–March 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 cell counts. Per national treatment guidelines, CD4 cell 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 workup within 90 days of presentation (ALT/HG/CRT, 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 12 months, with a 3-month buffer. Analyses were stratified by CD4 cell count at presentation and prevailing treatment guidelines at time of presentation.

Results: 11,513 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 Probert1, Rafael Sauter1, Michael Pickles2, Anne Cori1, Helen Ayles1, Peter Bock1, Deborah J. Donnelly1, Sarah Fidler1, Richard J. Hayes1, Christophe Fraser1, for the HPTN 071 (POPART) Study Team

1University of Oxford, Oxford, UK, 2Imperial College London, London, UK, 3London, UK, 4London 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.
Dramatic Decline of New HIV Diagnoses in Subjects Native from France

Adrié Le Guillou1, André Cabie1, Cyrille Delpierre3, Pascal Pugliese1, Christine Jacomet1, Maxime Hentzen1, Claudine Duvivier1, Olivia Faucher-Zaegel1, Laurent Cotte3, François Raffi1, Firouz 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, 8Hospices 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. We examined 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. New HIV diagnosis 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, of whom 4,253 born in France (90% male; 70.5% MSM) and 4,737 born abroad (39.1% female; 57.1% MSM). The annual number of new HIV diagnosis decreased from 1,856 in 2013 to 1,149 in 2018 (-38.1%); it was more pronounced among subjects born in France, from 858 to 484 (-43.6%) than in those born abroad (-23.8%, from 821 to 626). Among subjects born in France, the decrease over the period was -46.7%, -43.5% and -33.3% among MSM, heterosexual women and heterosexual men, respectively; the proportion of patients with CD4 cells count <350/mm³ at diagnosis and by contamination route.

Conclusion: Our findings show changes in HIV epidemiology between 2013 and 2018 in subjects followed in metropolitan France, with a more pronounced decrease of new HIV diagnoses in subjects born in France, particularly among MSM and heterosexual women. Our results support the long-term effectiveness of TasP strategy among the various tools for HIV prevention.
**1080 IMPROVING HIV CARE IN WEST AFRICA: EFFECTS OF A COMMUNITY TREATMENT OBSERVATORY**

Gemma M. Oberth 1, Solange Baptiste2, Wame Mosime 2, Alain Manouan 1, Pedro García 1, Anta M. Traoré 2, Joelle Murara 2, Raoul M. Boka 2

**University of Cape Town, Cape Town, South Africa, 1International Treatment Preparedness Coalition, Gaborone, Botswana**

**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 to 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.

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**1081 ROUTINE LABORATORY DATA FOR ESTIMATING POPULATION VIRAL SUPPRESSION IN SOUTH AFRICA**

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**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 VS 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

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Background: Undetectable equals Untransmitable ("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 assays 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 and were taking antiretroviral therapy (ART).

Methods: We conducted a pooled multi-country secondary data analysis using complex survey design and weights of the 2015-2018 cross-sectional Population-based HIV Impact Assessments (PHIA) in six sub-Saharan African countries. Inclusion criteria were: adults aged 15-59 years who tested HIV-positive in the PHIA surveys; on ART, defined as detectable antiretrovirals and/or self-report of current ART use; and available plasma VL results. Of the HIV-positive adults on ART who had a VL <1000 cp/mL (World Health Organization's definition of viral load suppression [VLS]), we calculated the proportion who met the U=U cutoff of <200 cp/mL.

Results: Overall, of the 8,031 HIV-positive adults on ART, 86.9% (95% confidence interval [CI] 86.4-87.4) had a VL <1000 cp/mL. Of the 7,003 participants on ART with a VL <1000 cp/mL, 95.1% (95% CI 94.7-95.4) had a VL <200 cp/mL. Of the 4,970 participants with a VL <1000 cp/mL who were on ART and self-reported current ART for ≥12 months, the proportion with VL <200 cp/mL was 96.6% (95% CI 96.2-96.9).

Conclusion: These nationally representative population-based data demonstrate that a very high proportion of all HIV-positive adults on ART with VL <1000 cp/mL also had VL <200 cp/mL, suggesting that 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 VLS, PHIA data supports that the scale-up of U=U messaging may be appropriate regardless of which VL testing platform is available.

1083 VIRAL SUPPRESSION TRAJECTORIES AMONG HIGH-NEED PATIENTS IN LOW-BARRIER HIV CARE

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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); 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 less 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 2-10 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

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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 cps/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 ARV 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. Any 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 70.0, 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 >90 days (OR 19.7, 95% CI 10.8-35.6) were also associated with viremia; similar associations were observed between drugs in hand and plasma ARV (Table). 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.

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**1086 OPTIMIZATION OF HIV CLINIC INTAKE PROCESS TO REDUCE TIME TO VIRAL SUPPRESSION**

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**Background:** This study describes a novel clinic intake process to more rapidly initiate antiretrovirals (ARVs) and compares mean time to initiate ARVs as well as time to viral suppression from before and after the advent of this new intake process.

**Methods:** 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 new 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 (54.2 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 there was 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.

**Methods:** During the 12-month study period, 2813 near-POC VL tests were conducted. 1511 (54%) tests were for onsite patients for whom results and reason for test were documented: 53% (794/1511) of tests were to confirm a previously high VL, and 31% (462/1511) were due to clinical indications. 53% (794/1511) of tests were to confirm a previously high VL, and 31% (462/1511) were due to clinical indications. 31% (462/1511) were due to clinical indications. The 'all-in' cost was $33.71 for a valid near-POC VL test, compared to an international benchmark for a centralized VL test of $28.62.

**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 reason for test were documented: 53% (794/1511) of tests were to confirm a previously high VL, and 31% (462/1511) were due to clinical indications. 53% (794/1511) of tests were to confirm a previously high VL, and 31% (462/1511) were due to clinical indications. 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.
1090 COST-EFFECTIVENESS OF POINT OF CARE VIRAL LOAD ADOPTION STRATEGIES IN SOUTH AFRICA

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Background: Viral load (VL) testing is the recommended method for monitoring antiretroviral therapy (ART) adherence, missed appointments, and OOP health spending. Participants (pts) who were on ART for >1 year and missed >1 HIV appointment (appt) in the past yr. We performed descriptive statistics and simple linear regression analyses with bootstrapped 95% confidence intervals using the bias-corrected and accelerated method to test associations between OOP spending and number of missed HIV and chronic non-communicable diseases (NCD) appts.

Methods: We developed a geospatial cost model utilizing existing data from NHLs, including geospatial data on facilities in South Africa who send blood samples to centralized laboratories for VL testing, their annual VL volume, suppression rates (<1000 copies/ml), sample rejection rates, turn-around time (TAT), and the cost per test. We assessed the impact of the adoption of two validated VL POC technologies (Cepheid GeneXpert and Abbott m-PIMA) under 4 scenarios: 1) status-quo (all centralized); 2) POC coverage at facilities with a combination of low suppression rates, and high rejection rates and TAT; 3) targeted POC just at facilities with low suppression rates; and 4) a complete switch from centralized to POC testing. For each scenario and POC technology we determined 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.

Results: The centralized network costs $121m annually with a VL suppression rate of 85.2%. Scenario 3 (targeted testing) using the GeneXpert is considered highly cost-effective at $40 per additional person suppressed, compared to the centralized network. Should resources allow, the all-POC scenario using 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 $52m annually. All other scenarios were dominated in the incremental analysis. When POC VL results in lower levels of viral suppression than expected, ICERS proportionally increased.

Conclusion: Assuming POC confers patient benefits, the most cost-effective strategy for POC adoption in South Africa is likely to be a targeted approach, with POC placed at facilities with high rates of viral failure.
1092 ENDING THE HIV EPIDEMIC IN BALTIMORE: A MODELING STUDY

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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 heterogeneities in HIV transmission and access to care.

Methods: We extended the Johns Hopkins HIV economic epidemic model (JHEEM), 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 to Baltimore’s highest- and 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.

Table: Models-Projected Reduction in Incidence (95% Uncertainty Ranges) from 2020 to 2030 Under Interactions Targeting Demographic Groups in the Baltimore Metropolitan Statistical Area

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Best</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrEP Users</td>
<td>23%</td>
<td>37%</td>
<td>50%</td>
<td>63%</td>
<td>76%</td>
<td>89%</td>
<td>102%</td>
</tr>
<tr>
<td>MSM</td>
<td>24%</td>
<td>38%</td>
<td>52%</td>
<td>66%</td>
<td>80%</td>
<td>94%</td>
<td>108%</td>
</tr>
<tr>
<td>All Groups</td>
<td>25%</td>
<td>40%</td>
<td>55%</td>
<td>70%</td>
<td>85%</td>
<td>100%</td>
<td>115%</td>
</tr>
</tbody>
</table>

Figure 1. Projected reductions in HIV incidence

1094 ASSESSING THE IMPACT AND COST-EFFECTIVENESS OF HIV AND NCD INTEGRATED CARE IN KENYA

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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: 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/adoption) 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.
**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 $116,000 CVD events and 43,600 CVD deaths by 2033. The integrated HIV/NCD intervention could aver 27.6 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 $2.01 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.

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Table 1: Epidemiological and economic impact of integrated services for HIV/NCD in Kenya. Values represent median difference between baseline and intervention scenarios across 200 simulations. Models are initiated with a similar population in 2018 and are followed to year 2033. The baseline scenario assumes fixed ART coverage at 2018’s level over time and minimal NCD treatment. The intervention scenario models an annual campaign for screening and treatment of HIV, hypertension (HTN) and diabetes (DM) reducing from 2018-2020, future costs are discounted at 3%.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>HIV</th>
<th>Malaria</th>
<th>Infection</th>
<th>Angina</th>
<th>Cardiac Arrest</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths averted</td>
<td>341,730</td>
<td>24,030</td>
<td>13,500</td>
<td>3,000</td>
<td>7,600</td>
<td></td>
</tr>
<tr>
<td>Additional costs (2018 US dollars)</td>
<td>ART</td>
<td>DM treatment</td>
<td>HPT treatment</td>
<td>Screening for HIV</td>
<td>Screening for DM/HTN</td>
<td></td>
</tr>
<tr>
<td>$1.18 billion</td>
<td>$1.00 billion</td>
<td>$3.75 billion</td>
<td>$0.05 billion</td>
<td>$8.86 billion</td>
<td></td>
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</tr>
</tbody>
</table>

**1096 HOW SHOULD WE PRIORITIZE AND MONITOR INTERVENTIONS TO END HIV EPIDEMIC IN AMERICA?**

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**Background:** The goal of the US Ending the 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.
HIV CARE CASCADE: MEN WHO HAVE SEX WITH MEN & TRANSGENDER WOMEN/GENDERQUEER, ZIMBABWE

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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) individuals 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 these, 90% are on antiretroviral treatment [ART]; and of these, 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 participants). Median age was 24 years. HIV prevalence was 21.4% (MSM, 17.1%; TGW/GQ, 28.0%); of those testing 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 (>95% of participants). Median age was 26 years. HIV prevalence was 23.4% (MSM, 23.3%; TGW/GQ, 25.0%); 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 that 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.
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 infection 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.

1100 IMPROVEMENTS ACROSS NAIROBI COUNTY’S HIV CARE CONTINUUM: CASE OF A FAST-TRACK CITY

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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 HIV 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, 79% 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 2016, 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 continuum 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.

1101 HIV CARE CONTINUUM AMONG NEWLY DIAGNOSED INDIVIDUALS IN MEXICO

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Background: The HIV care continuum (CC) is useful for monitoring HIV care. However, the impact of HIV diagnosis in circumstances of hospitalization in the CC is unknown. The aim of this study was to compare engagement in-care (EIC), proportion of patients on ART and viral load suppression (VLS) in patients who were hospitalized within diagnosis from those treated as outpatients.

Methods: We used retrospective, longitudinal data collected at a tertiary hospital in Mexico City. We included all adults newly diagnosed with HIV (within 3 months) between 2005 and 2015. All patients diagnosed in circumstances of hospitalization due to an AIDS-defining illness (ADI) or requiring hospitalization within 3 months of diagnosis were classified as severe group (SG). All others were classified as non-severe group (NSG). HIV CC was evaluated at one, three and five years from enrollment, estimating proportions of those contributing to follow-up at each period. EIC was defined as those who had 2 or more medical visits, ART prescriptions, CD4 or viral load (VL) tests at least 3 months apart in the previous year. VLS was defined as most recent VL of <50 copies/mL.

Results: Among 911 people living with HIV (PLWH) enrolled, 199 (22%) were classified as SG. Median age was 33.5 (IQR 28-42) years, and 91% were male. PLWH in the SG were more likely to be older (36 vs 33 years, p<0.001) and to have acquired HIV through heterosexual contact (35% vs 23%, p<0.001), had lower median baseline CD4 count (41 vs 203, p<0.001) and higher proportion of ADI (85% vs 28%, p<0.001) than individuals in the NSG. Figure 1 describes CC across time. Mortality and loss to follow-up (LTU) were higher in the SG only within the first year (26% vs 2%, p<0.001; 15% vs 5%, p<0.001, respectively). In contrast, no significant differences in mortality, LTU, proportion of patients on ART and VLS were found at three and five years of enrollment between groups.

Conclusion: Similar long-term outcomes in both groups along the HIV CC strongly suggest that first year disparities are mainly due to a higher early mortality and LTU among hospitalized patients within 3 months of HIV diagnosis. Our findings emphasize the urgent need of strategies that increase early diagnosis in populations not traditionally considered at risk.
1102 CHALLENGES TO HIV CARE ENGAGEMENT AMONG MOBILE POPULATIONS IN RURAL KENYA AND UGANDA

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Background: Population mobility may negatively impact care engagement for people living with HIV by disrupting continuity and this may portend poor treatment outcomes for patients while increasing the risk of onward disease transmission. We sought to identify the challenges mobility imposes on vital aspects of care engagement (enrollment in HIV care, being on ART, and treatment interruptions)

Methods: We conducted an analysis of survey data collected in 2016 among a random sample of 1,119 mobile adults within 12 communities across three regions (South West Uganda, East Uganda and West Kenya) out of the 32 communities participating in the SEARCH HIV test-and-treat cluster randomized trial (SEARCH NCT:01864603). The 12 communities were matched by trial intervention with individuals sampled on baseline residential stability and HIV status. We evaluated self-reported challenges to HIV care engagement across multiple metrics of mobility with specific attention to sex differences. We used multivariate logistic regression adjusting for age, educational level, marital status, household wealth and region to identify factors associated with poor engagement in care.

Results: A total of 1,119 adults participated in the survey. 53.2% (595) were female, 82.2% (926) had primary or secondary level of education and 74.2% (830) were involved in informal low HIV risk occupations such as farming. Of the 1119, 106 reported missing clinic appointments, the median duration of missed appointment was 0.5 (IQR 0.25-2) months. The most common reasons for missing appointments, HIV medication interruptions and changing HIV clinics was mobility and inability to afford transport to clinics. Those who reported migration within the previous year had lower odds of receiving regular care and treatment (OR 0.42 (95% CI 0.19, 0.95) p = 0.04) with males having lower odds (OR 0.31 (95% CI 0.10, 1.01) p = 0.05) as compared to females (OR 0.57 (95% CI 0.18, 1.86) p = 0.35). Factors associated with poor care engagement (failure to receive regular care and treatment) were younger age and poverty (being in the lowest wealth index quartile vs. higher quartiles) OR 0.28 (95% CI 0.14, 0.54) p <0.001. Conclusion: Population mobility may hamper the gains made in controlling the HIV epidemic if care engagement for mobile persons remains unaddressed.

1104 MONITORING PROGRESS OF CARE IN PERSONS NEWLY DIAGNOSED WITH HIV IN SPAIN, 2004-2018

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Background: Monitoring the time that ART interruptions are reviewed and the 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: 2050 in pre-RETAIN and 1169 in post-RETAIN periods. Participants were predominantly male (74%) had a median duration on ART of 5 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-engaged in care after alerts to their physicians were sent shortens the length of ART interruptions. Similar programs should be considered in other jurisdictions.
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-naive 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, 95%CI: 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.

1106 LOSS-TO-FOLLOW-UP RISK FACTORS AFTER ANTIRETROVIRAL THERAPY INITIATION IN UGANDA

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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 included 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 (36.3%) 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. InYA, 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

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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, \( \alpha = 0.91 \)) into patient surveys administered every 4-6 months at primary care visits. We used multivariable logistic regression models to evaluate associations between mean stigma and two common prospective retention in care outcomes: keeping the next primary care appointment after stigma assessment and keeping all scheduled primary care appointments in the year following the stigma assessment. We controlled for age, gender, race/ethnicity, sexual orientation, time since CNICS enrollment, and CNICS site. We checked for interactions between stigma and these covariates. We addressed missing covariate data using the random module provided by Mplus.

Results: From 4/16 – 10/17, 5,825 patients completed the stigma assessment. Median age was 44 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/\( \mu L \) (IQR 362-707). Of these, 113 (18.3%) had VL≥1000 copies/\( mL \). 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 (Hazard Ratio (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.

Table: Cox proportional hazards modelling of factors associated with time to mortality

<table>
<thead>
<tr>
<th>List of clinical factors</th>
<th>Univariate HR (95% CI)</th>
<th>( p ) value</th>
<th>Multivariate HR (95% CI)</th>
<th>( p ) value</th>
</tr>
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<tbody>
<tr>
<td>VL at enrollment ≤ 1000 copies/mL</td>
<td>1.00</td>
<td>0.227</td>
<td>1.00</td>
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<tr>
<td>≥1000 copies/mL</td>
<td>1.79 (0.89, 3.66)</td>
<td>1.28 (0.90, 2.27)</td>
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<tr>
<td>Age at enrollment (per year increase)</td>
<td>1.05 (1.00, 1.11)</td>
<td>0.054</td>
<td>1.07 (1.01, 1.13)</td>
<td>0.035</td>
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<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Male</td>
<td>0.55 (1.03, 2.71)</td>
<td>0.096</td>
<td>0.75 (1.03, 2.71)</td>
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</tr>
<tr>
<td>Education</td>
<td>No-education/</td>
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<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Did not complete high school</td>
<td>0.80 (0.27, 2.57)</td>
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</tr>
<tr>
<td>Completed high school</td>
<td>0.51 (0.18, 1.47)</td>
<td>0.027</td>
<td>0.49 (0.16, 1.51)</td>
<td>0.268</td>
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<tr>
<td>Any missed doses</td>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Adherence (time-updated)</td>
<td>1.00</td>
<td>0.00</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Time to ART initiation (per year)</td>
<td>0.82 (0.61, 1.12)</td>
<td>0.228</td>
<td>0.75 (0.50, 1.16)</td>
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<tr>
<td>Time on ART (per year)</td>
<td>0.84 (0.56, 1.27)</td>
<td>0.39</td>
<td>0.84 (0.55, 1.28)</td>
<td>0.40</td>
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<tr>
<td>Time on ARV (per year)</td>
<td>0.81 (0.47, 1.40)</td>
<td>0.39</td>
<td>0.80 (0.46, 1.41)</td>
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<td>CD4 at baseline</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>CD4 at time of last CD4 counting</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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</tr>
</tbody>
</table>
Alcohol use and the HIV Care Continuum in Zambia: Nationally Representative Survey

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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 and moderate 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 ART use. Among PLWH, 87.1% were on ART, and 89.2% had VS. 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 and moderate 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.

Conclusion: We found significantly lower odds of being diagnosed and reduced odds of ART use among unhealthy alcohol users. 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.

Differentiated Service Delivery for HIV Care: The Fast-Track Experience from Zambia

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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 “Fast Track” (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 at 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%, p <0.01) and ≥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).

Conclusion: 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.
1112 DIFFERENTIATED CARE: TIME SPENT IN DIFFERENT ART DELIVERY MODELS IN RURAL ZIMBABWE

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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 breastfeeding, median age 43 years [interquartile range: 34-52]). Fifty-seven percent had completed primary level education and 62% were on ART. Median time spent at the HFs and results from multivariable regression. There was no evidence 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.

Conclusion: Differentiated ART delivery models are available in most of the assessed HFs in rural Zimbabwe, and a considerable proportion of PLWH on ART are enrolled in a differentiated ART delivery model. However, 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.
1114 COMMUNITY PRIVATE PHARMACY ANTIRETROVIRAL THERAPY REFILL IN KAMPALA, UGANDA

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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, symptomatic 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), 9921 (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.

1115 COMMUNITY-BASED SERVICE DELIVERY OF HIV TREATMENT IN ZAMBIA: COSTS AND OUTCOMES

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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.

1116 HIV+ PATIENTS RECEIVING ANTIRETROVIRAL DRUGS THROUGH HOME DELIVERY: A CAUSAL ANALYSIS

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Background: Differentiated service delivery (DSD) models, which focus more on individual patient preferences and the needs of vulnerable subpopulations, are key to meeting the UNAIDS 90-90-90 goals for 2020 and beyond. Courier delivery of chronic medication by a patient’s home (home refill) is an attractive and scalable intervention to potentially improve antiretroviral therapy (ART) adherence and viral suppression; data, however, remains limited and is found predominantly in real-world settings with electronic health record (EHR).

Methods: Building on a previous study, we conducted a retrospective 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).

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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.
1117 OUTCOMES OF COMMUNITY-BASED ANTIRETROVIRAL TREATMENT PROGRAM IN NAMIBIA

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Background: Namibia is a sparsely populated country of 2.5 million people, with an HIV prevalence of 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 CBART sites for ≥3 months had viral suppression; 98% of adults (n=427) and 84% (n=58) of children in CBART ≥12 months, and 98% of adults (n=121) and 83% (n=23) of children CBART ≥60 months (Okongo) had VS. VS did not differ by the time on ART in CBART (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.

1118 PATIENTS EXPERIENCING VIRAEMIA IN ADHERENCE CLUBS: IS BACK-TO-CLINIC ALWAYS BEST?

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Background: ART adherence clubs have proven a successful model for many stable patients to receive peer support and convenient ART refills while utilizing fewer clinic resources. In the Western Cape, South Africa, patients are eligible to join a club after 6 months on ART, provided they are clinically stable, with a suppressed viral load (VL) and are not pregnant. Current guidelines, requiring viraemic patients to leave clubs and return to clinic care, are not strictly implemented. We describe the implementation of guidelines and 12-month outcomes of club patients who experience viraemia.

Methods: We included data on all patients ever in a club at three large primary healthcare clinics in Khayelitsha, a high HIV-prevalence, low-income, peri-urban area in Cape Town, South Africa. We identified patients with viraemia (VL>1000 copies/mL) that occurred after joining the club, before they first exited the club (<3 months after last club visit), and before 1 October 2017. We describe characteristics of these patients at the time of the unsuppressed VL test result, subsequent 12-month outcomes, and we performed multivariate logistic regression to identify predictors of 12-month VL resuppression.

Results: Of 8680 total club patients with a median time of 29.8 months in clubs (IQR:20-51) and VL testing data available, 503 (6%) experienced viraemia. Of the 494 patients who had any ART visits >2 months after viraemia, 345 (70%) returned to clinic care. Those who remained in clubs had the same chance of remaining in care at 12 months later (93%), higher resuppression rates, similar VL completion rates, and a similar yet slightly lower median first high VL, compared to those returning to clinic (Table 1). A multivariate logistic regression showed 12-month VL resuppression was associated with remaining in clubs after one high VL result, compared to returning to clinic (OR:1.39; 95%CI:0.93-2.06), and the log of the first high VL (OR:0.84; 95%CI:0.75-0.93). Consistency: Inconsistent application of guidelines may result from clinical oversight or deliberate decisions based on patient-specific factors. Regardless, promising resuppression rates among those remaining in clubs suggest that there is scope to adapt adherence club guidelines to give patients and providers more flexibility, while providing safe clinical management of viraemic patients.

http://files.aievolution.com/prd/cro2001/abstracts/abs_3358/table1_croi.png

1119 RANDOMIZED TRIAL OF HIV-ASSIST VERSUS GUIDELINES FOR ART SELECTION BY TRAINEES

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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.
(ART) selection. HIV-ASSIST (www.hivassist.com) is a free, online tool providing individualized ART decision-support. We hypothesized that trainees with access to HIV-ASSIST would be more likely to select appropriate ART for diverse HIV patient scenarios, compared to those using DHHS HIV guidelines alone.

Methods:
We conducted a randomized study of medical students and residents at Johns Hopkins University, in which participants were asked to select an ART regimen for 10 HIV case scenarios through an electronic survey. Participants were randomized to receive either DHHS guidelines alone (with a video tutorial), or DHHS guidelines and HIV-ASSIST (with a video tutorial) to support their decision-making. ART selections were graded “appropriate” if consistent with DHHS guidelines, or concordant with ART regimens selected by HIV experts at three major academic institutions.

Results:
Among 118 trainees, participants randomized to receive HIV-ASSIST had significantly higher percentage of appropriate ART selections compared to those receiving DHHS alone (% appropriate responses in DHHS vs HIV-ASSIST arms: median 40% [Q1, Q3: 30%, 50%] vs 90% [80%, 100%], p < 0.001). This difference was consistent among both medical students (median 40% vs 90%, p < 0.001) and residents (median 40% vs 90%, p < 0.001). The effect was seen for all case-types, but most pronounced for complex cases involving ART-experienced patients with ongoing viremia (DHHS vs HIV-ASSIST: median 0% [0%, 33%] vs 100% [66%, 100%]). In qualitative feedback, 61% commented on difficulty navigating or interpreting DHHS guidelines; by contrast 82% commented that HIV-ASSIST was user friendly, with 85% and 98% agreeing or strongly-agreeing that HIV-ASSIST was useful for making ART selections for ART-naive and experienced patients, respectively.

Conclusion:
Trainees using HIV-ASSIST were significantly more likely to choose appropriate ART regimens compared to those using guidelines alone. Interactive decision-support tools may be important and necessary to ensure appropriate interpretation and implementation of HIV clinical practice guidelines.

1120 TRANSITION TO DOLUTEGRAVIR-BASED REGIMEN: NIGERIAN EXPERIENCE AMONG KEY POPULATIONS

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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 suppression 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 3,327 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 = 118859.603). 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/ml and <200 copies/ml only on TLD 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(1) = 1.113, p = 0.35 for viral load results before start of TLD: f(1) = 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 suppression and untransmitable viral levels achieved were superior with the use of TLD.
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, or VS within 30 days, and CD4, 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 to 30 days 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 between the groups. The proportion never virally suppressed declined (22.7% DX09-12 vs. 19.8% 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 were more likely to achieve VS-90, and women, TG, dx years 2015-2017, and those with CD4>500 (aPR 1.47, 95% CI 1.13-1.90) were less likely to achieve VS-90, adjusted for age at diagnosis, gender, race/ethnicity, mode of transmission, year of diagnosis, and CD4 at diagnosis.

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 on targeted efforts to promote ART initiation and retention among adolescents in order to achieve epidemic control.

Background: Achieving and maintaining viral suppression (VS) in persons living with human immunodeficiency 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 unsuppressed 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 clinic visits increase, the proportion of VS patients increase with 90% of those remaining 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 VS patients increase with 90% of those who kept >50% of their clinic visits being VS on their latest test. We also see differences in distribution of VS by race/ethnicity, with Non-Hispanic Blacks having significantly smaller proportion being VS.

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 compared to initial VS declined from 235 days (DX09-12 to 129 days DX13-17) (p<0.0001).
impacting some newly diagnosed patients, particularly the unmet needs of minorities to increase the number who achieve stable suppression.

### Table 1. Characteristics of HIV tests in Botswana from January 2018 to September 2019, by HIV testing department

<table>
<thead>
<tr>
<th>Test Location</th>
<th>Age at Start of Study</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Other (%)</th>
<th>VCT/Other PITC</th>
<th>ED</th>
<th>Other</th>
<th>N (%) or Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18-24; 25-34; 35+</td>
<td>32%</td>
<td>32%</td>
<td>36%</td>
<td>9,695</td>
<td>12,760</td>
<td>1,772</td>
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<td>0.3%</td>
</tr>
</tbody>
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*VCT = voluntary HIV counseling and testing; PITC = provider-initiated HIV counseling and testing; ED = emergency department.*

### Conclusion of Methods

HIV incidence. Additional interventions beyond these improvements to HIV care linkage and care retention for those testing HIV-positive: more effective access to PrEP through improved linkage and retention, and early care access for those testing HIV-positive.

### Results

Compared to current HIV screening rates, a ten-fold relative increase (to approximately annual screening for black and Hispanic MSM and quarterly for white MSM) would lead to 41.2% of infections averted under the assumption of no PrEP linkage, and also relative improvements to HIV care linkage and care retention for those testing HIV-positive.

### 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, with prevention through both increased PrEP coverage (from 0.2%) and increased 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, 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 annual screening for black and Hispanic MSM and quarterly for white MSM) would lead to 41.2% of infections averted under the assumption of no PrEP linkage, and also relative improvements to HIV care linkage and care retention for those testing HIV-positive.

### Conclusion of Methods

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 EPIDEMIC CONTROL

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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 ≥25% 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

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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, in which estimates of the maximum number of persons who 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.
IMPACT OF COMBINATION HIV PREVENTION IN ZIMBABWE: A MULTIDISTRICT TRANSMISSION MODEL

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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 programs, 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 2259 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 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.

IMPLEMENTATION OF U=U IN REAL LIFE IN ITALY: RESULTS FROM THE ICONA COHORT

Giordano Madeddu1, Andrea De Vito1, Alessandro Cozzi-Lepri1, Antonella Cingolani1, Franco Maggiolo1, Carlo Federico Perno1, Roberta Gagliardini1, Giulia Marchetti1, Annalisa Saracino1, Antonella D’Arminio Monforte1, Andrea Antinori1, Enrico Girardi1, for the ICONA Foundation Study Group

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 copies/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 copies/ml. Thus, only 3.1% of PDFU were observed when VL was >200 copies/ml with some evidence for a decrease after 2016. The median time with VL>200 copies/ml was 47.3 days (IQR: 46.3-74). Of note, the proportion of PDFU with VL>200 copies/ml was higher than average in females (5.3%), unemployed (5.4%), PWID (4.7%) and in people with previous virological failures (6.3%). At individual level, 617 participants (7.5%) spent <90% of PDFU with a VL<=200 copies/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 copies/ml.

Table 1. Logistic regression estimates of factors associated to losing U=U status.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
<th>Type I error p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female vs. Male</td>
<td>2.26 (1.80, 2.84)</td>
<td>&lt;0.001</td>
<td>1.43 (1.26, 1.60)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mode of HIV Transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAA vs. NRTI</td>
<td>1.86 (1.86, 4.82)</td>
<td>&lt;0.001</td>
<td>2.30 (1.90, 2.84)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PAA vs. HIVnegative</td>
<td>2.31 (1.78, 5.54)</td>
<td>&lt;0.001</td>
<td>1.43 (1.09, 1.87)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PDDP vs. Other/Unknown</td>
<td>3.71 (2.15, 6.46)</td>
<td>&lt;0.001</td>
<td>1.47 (1.07, 1.94)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign-born vs. Italian</td>
<td>1.39 (1.46, 1.53)</td>
<td>&lt;0.001</td>
<td>1.43 (1.22, 1.66)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Employment status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed vs. Employed</td>
<td>2.34 (1.75, 3.19)</td>
<td>&lt;0.001</td>
<td>1.60 (1.13, 2.26)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Occasional vs. Employed</td>
<td>2.00 (1.65, 5.00)</td>
<td>&lt;0.001</td>
<td>1.37 (0.83, 2.26)</td>
<td>0.058</td>
<td></td>
</tr>
<tr>
<td>Seasonal vs. Employed</td>
<td>2.52 (1.90, 3.34)</td>
<td>&lt;0.001</td>
<td>1.85 (1.36, 2.52)</td>
<td>0.141</td>
<td></td>
</tr>
<tr>
<td>CD4 count, cells/µL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200 x10^3</td>
<td>2.83 (2.10, 3.88)</td>
<td>&lt;0.001</td>
<td>1.54 (1.16, 2.04)</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td>&gt; 200 x10^3</td>
<td>2.83 (2.50, 3.19)</td>
<td>&lt;0.001</td>
<td>1.54 (1.05, 2.25)</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td>Presence of risk factors, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 risk factor</td>
<td>2.62 (1.90, 3.57)</td>
<td>&lt;0.001</td>
<td>1.86 (1.21, 2.81)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>≥ 2 risk factors</td>
<td>2.51 (2.24, 4.00)</td>
<td>&lt;0.001</td>
<td>1.73 (1.05, 2.81)</td>
<td>0.003</td>
<td></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, AIDS stage, WHO/ADL status, duration of ART, partner drug use, geographical region, behaviors, smoking, use of statins/lowering blood pressure drugs, glaucoma and prior ARIs. PWID: people who inject drugs; U=U: people who have each been.
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 Asubontoun1, 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 CDF-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 localities, 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% CI 1.61 - 2.58), but had a significantly lower PrEP use (2.1 per 100 subjects at risk, 95% CI 0.93 to -3.2), and TasP proportion (-1.30 %, 95% CI -0.41 to -2.2%) than those MSAs not selected for intervention.

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 Gummerson2, Amee M. Schwitters3, Rogerio Bonifacio4, Nicholas Mutenda1, Karampreet K. Sachathep5, Choice Ginindza6, Avi Hakim6, Nicholus Mutenda7, Elizabeth Gummerson2, Morgan Byrne1, Anne K. Monroe1, Matthew E. Levy1, Rachel Denyer1, Adam Klein1, Michael A. Horberg7, Amanda D. Castel1, Rupali K. Doshi7, Alessandra Sacco5, Jose Lucar8, Leah Squires9, Stefanie Schroeter10, Debra A. Benator10, 1ICAP at Columbia University, New York, NY, USA, 2CDC Le索to, Maseru, Lesotho, 3World Food Programme, Johannesburg, South Africa, 4Ministry of Health and Social Services, Windhoek, Namibia, 5Central Statistical Office, Mbabane, Swaziland, 6CDC, Atlanta, GA, USA, 7CDC, Zambika, Zambika, 8Tanzania Ministry of Health, Community Development, Gender, Elderly, and Children, 9Dar es Salaam, Tanzania, United Republic of, 10US CDC Windhoek, Windhoek, Namibia, 11Columbia University, New York, NY, USA

Background: To assess associations between food insufficiency (FI) and HIV-related outcomes, including infection, we used data from nationally representative population-based HIV impact assessment (PHIA) surveys in Zambia, Eswatini, Lesotho, Uganda, Tanzania, and Namibia (2015–2017).

Methods: We collected FI data, defined as having any time with no food in the house in the past 4 weeks, from the household head. We also offered household-based HIV testing. Recent infection (<130 days) was measured using the HIV-1 Limiting Antigen (LAg) Avidity assay combined with lack of viral load suppression (VLS, <1000 copies/mL) and antiretroviral (ARV) testing data. Recent infection indications were those with LAg-c<1.5 normalized Optical Density (ODn), VL>1000 copies/mL, and no detectable ARVs. We performed pooled analyses to determine the association between FI and several HIV-related outcomes on weighted data on adults aged 15–59 years using logistic regression adjusted for age, sex, urban/rural residence, wealth quintile, and education, fitting an 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 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 Akerslo7, Morgan Byrne1, Anne K. Monroe9, Matthew E. Levy1, Rachel Denyer1, Adam Klein1, Michael A. Horberg7, Amanda D. Castel1, Rupali K. Doshi7, Alessandra Sacco5, Jose Lucar8, Leah Squires9, Stefanie Schroeter10, Debra A. Benator10, 1ICAP at Columbia University, New York, NY, USA, 2CDC Lesotho, Maseru, Lesotho, 3District of Columbia Department of Health, Washington, DC, USA, 4Ministry of Health, Community Development, Gender, Elderly, and Children, Dar es Salaam, Tanzania, United Republic of, 5Washington, DC, USA, 6University of Mississippi, Jackson, MS, USA, 7Washington 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 (PHW). We define HIV transmission burden as the number of PHW 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 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
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 20 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 Nattaye2, Brendan Maughan-Brown1, Mhairi Maskew1, Dorina Onoya1, Alana T. Brennan1, Till Bärnighausen1, H Manisha Yapa1, Sergio Carmona1, Wendy Stevens1, Adrian J. Puren1, William B. MacLeod1
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, 5Africa Health Research Institute, Mbutatuba, South Africa, 6King’s College Hospital NHS Foundation Trust, London, UK, 7Heidelberg University, Heidelberg, Germany, 8Africa Health Research Institute, KwaZulu-Natal, South Africa, 9Brighton and Sussex Medical School, Brighton, UK, 10University College London, London, UK, 11Harvard T.H. Chan School of Public Health, Boston, MA, USA, 12Boston University, Boston, MA, USA

Background: South Africa implemented Universal Test and Treat (UTT) in September 2016 in an effort 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 this 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. After UTT implementation, 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 Brown1, Yiqun Chen2, Laura B. Balzer3, Gabriel Chami4, James Ayieko5, Dalosen Kwansila6, Jane Kabami7, Norton Sang8, Edwin D. Charlebois9, James Peng9, Yusuf Mwinike10, Elizabeth A. Bukusi11, Moses R. Kamya12, Diane V. Havlir13, Maya L. Petersen14

1University of California San Francisco, San Francisco, CA, USA, 2University of Washington, Seattle, WA, USA, 3University of Massachusetts Amherst, Amherst, MA, USA, 4Kenya Medical Research Institute, Nairobi, Kenya, 5Infectious Diseases Research Collaboration, Kampala, Uganda, 6Kenya University, Kampala, Uganda, 7University of California Berkeley, Berkeley, CA, USA

Background: HIV+ persons with low CD4 (<200 cells/mm3) are at high risk of death without effective treatment. We evaluated the potential for a social network strategy 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 social networks among 150,395 adult residents; 315,484 (99%) were tested for HIV. 117,593 had at least one contact and were included in analyses. 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 CD4<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 15% of target persons (p=0.001) and required 31 contacts per target individual identified (p=0.001) [Table]. The assortative mixing coefficient was 0.009 for persons with CD4<200 out of care, 0.02 for HIV+ in care with CD4<350, 0.10 for all HIV+ persons.

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.
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 (re)linking 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. Uniivariate 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. In particular, persons using methamphetamine may benefit from continuous case management that goes beyond initial linkage in order to achieve higher rates of retention in care and increase the impact of ED HIV screening programs.

**Table 1 Univariate and Multivariable Logistic Regression Models for Predicting Follow-Up in 6 Months (p-values ≤0.2 are italic and those <0.05 bold)**

<table>
<thead>
<tr>
<th>Model</th>
<th>OR 95% CI p-value</th>
<th>OR 95% CI p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.995 (0.990, 0.999) *0.042</td>
<td>0.995 (0.980, 1.009) *0.042</td>
</tr>
<tr>
<td>Female Sex at Birth</td>
<td>1.03 (0.97, 1.09) *0.41</td>
<td>1.00 (0.94, 1.06) *0.05</td>
</tr>
<tr>
<td>Female Gender identity</td>
<td>0.68 (0.39, 1.19) *0.16</td>
<td>0.68 (0.39, 1.19) *0.16</td>
</tr>
<tr>
<td>Hispanic Ethnicity</td>
<td>1.04 (0.76, 1.43) *0.59</td>
<td>1.04 (0.76, 1.43) *0.59</td>
</tr>
<tr>
<td>If male, seen with men (MMER)</td>
<td>0.62 (0.29, 1.32) *0.26</td>
<td>0.62 (0.29, 1.32) *0.26</td>
</tr>
<tr>
<td>Transgender who have sex with men</td>
<td>0.52 (0.27, 1.02) *0.04</td>
<td>0.52 (0.27, 1.02) *0.04</td>
</tr>
<tr>
<td>Injection Drug Use</td>
<td>0.58 (0.37, 0.91) *0.03</td>
<td>0.58 (0.37, 0.91) *0.03</td>
</tr>
<tr>
<td>Methamphetamine use</td>
<td>0.67 (0.35, 1.29) *0.29</td>
<td>0.67 (0.35, 1.29) *0.29</td>
</tr>
<tr>
<td>Current Substance Abuse (excluding alcohol and marijuana)</td>
<td>0.85 (0.72, 1.00) *0.06</td>
<td>0.85 (0.72, 1.00) *0.06</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>2.02 (0.52, 8.00) *0.08</td>
<td>2.02 (0.52, 8.00) *0.08</td>
</tr>
<tr>
<td>Unstable Housing</td>
<td>1.03 (0.45, 2.35) *0.09</td>
<td>1.03 (0.45, 2.35) *0.09</td>
</tr>
<tr>
<td>Improvement</td>
<td>0.59 (0.30, 1.16) *0.12</td>
<td>0.59 (0.30, 1.16) *0.12</td>
</tr>
</tbody>
</table>

*OR = odds ratio, CI = confidence interval, *p* ≤0.05, **p** ≤0.01, ***p*** ≤0.001

**1139 EXPERIENCE FROM THE LARGEST WESTERN US EMERGENCY DEPARTMENT ON ENDING THE EPIDEMIC**

Kathleen Jacobson, Sanjay Arora, Chun Nok Lam, Mikheala Go, Mike Menchine

University of Southern California, Alhmabra, CA, USA; University of Southern California, Los Angeles, CA, USA

**Background:** Emergency Departments (ED) account for 135 million healthcare visits annually. HIV positive patients are 3 times more likely to visit ED, be a racial minority and lack insurance than their non HIV counter parts. EDs are a safety net for HIV infected individuals, and it is often their sole and only point of entry into the healthcare system. The role out of HIV testing in US emergency departments has paralleled the decline in undiagnosed HIV in the US, potentially contributing substantially to curbing the epidemic. However, a recent systemic review of 37 ED programs across the US showed that linkage to care (LTC) from EDs is suboptimal. The Los Angeles County plus University of Southern California (LACUSC) ED is the largest ED in the western US sitting in the heart of the epidemic in LAC with 50% of the PLWHIV in it’s catchment area. 170,000 patient visits annually, 65% by Hispanics, 15% blacks, 5% Asians, 42% women and 80% of the patients claim a household income of < $30,000 annually. We describe LACUSC EDs HIV testing program and its uniquely successful LTC programs for newly diagnosed and return to care patients.

**Methods:** Results in March of 2011, the LACUSC ED implemented routine HIV screening via a parallel program with a designated tester and POCT tests. In June of 2013, it implemented HIV 1-2 antigen antibody immune assay testing and offered provider initiated routine screening to all patients getting labs, in 2015 adding an EMR pop-up window. In Dec 2014, we began Rapid ART for first for acutely infected individuals then newly diagnosed and return to care patients.

**Results:** To date we have tested 116,116 patients, 71420 (61.5%) male, 44672 (38.5%) female, 22 (0.0%) trans including Hispanic 61.6%, Black 15.6%, White 10.3% the majority over the age of 30. See Table 1 and 2. 3479 positive tests (males 2110 (85.1%), females 365 (14.7%) and transgender 1(0.0%). 609 (24.5%) newly diagnosed (Hispanic (44%), Blacks (21%) and whites 10.3%) and 61 (10%) acutely infected with HIV (Hispanic (70.5%), White (30%) and Blacks (11.5%). And 1870 (75%) were previously known positives. Of newly diagnosed patients 574 (94%) successfully LTC. For return to care patients 51% seen in ED and 48% LTC <60days.

**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 Korthuis, Caroline King, Gavin Bart, Lynn Kunkel, Thuan Nguyen, Khuyen Tong, Saram Bielavitz, Le Minh Giang

1Oregon Health and Sciences University, 2 Hennepin Healthcare Research Institute, Minneapolis, MN, USA, 1Hanoi 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, and 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, 45.9% 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 negative for HIV and 81.2% for methadone and did not differ by treatment group (p=0.92). Heroin use at 12 months decreased to 46.8% for buprenorphine and 51.4% for methadone and did not differ by treatment assignment at 12 months (p=0.58), ART receipt 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 receipt 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. Klein2, Stacy Cohen3, Letha Healey4, Antigone Dempsey4, Heather Hauck5, Laura W. Cheever6
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 6.7% of clients served (31,683) had HIV attributed to IDU. When compared with IDU clients served by the 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 mostly housed (84.0% vs. 80.3% nationally). Nationally, 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; we identified key themes.

Table 1. Ryan White HIV/AIDS Program clients (non-ADAP) with HIV infection attributed to injection drug use by selected characteristics, 2017—United States and 7 States with Rural Epidemics

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>National</th>
<th>%</th>
<th>SE</th>
<th>Rural</th>
<th>%</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-24</td>
<td>152</td>
<td>0.8</td>
<td>3.2</td>
<td>110</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>25-34</td>
<td>1,819</td>
<td>11.2</td>
<td>20.8</td>
<td>572</td>
<td>5.1</td>
<td>0.5</td>
</tr>
<tr>
<td>35-44</td>
<td>3,892</td>
<td>11.4</td>
<td>20.8</td>
<td>1,247</td>
<td>13.6</td>
<td>0.5</td>
</tr>
<tr>
<td>45-54</td>
<td>3,031</td>
<td>20.1</td>
<td>17.0</td>
<td>347</td>
<td>9.3</td>
<td>0.4</td>
</tr>
<tr>
<td>55-64</td>
<td>1,168</td>
<td>11.3</td>
<td>17.4</td>
<td>74</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>65+</td>
<td>2,125</td>
<td>12.0</td>
<td>20.8</td>
<td>1,958</td>
<td>11.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1142 SEARCH TEST & TREAT INTERVENTION IMPROVES VIRAL SUPPRESSION AMONG HAZARDOUS DRINKERS

Sarah B. Puryear1, Dalsone Kwasiisimia2, James Ayiekoi1, Judith A. Hahn3, Atukunda Mucunguzi3, Sabina Ogachi1, Laura B. Balzer1, Vivek Jain1, Edwin D. Charlebois4, Craig R. Cohen5, Elizabeth A. Bukusi6, Maya L. Petersen7, Diane V. Havlir8, Moses R. Kanya9, Gabriel Chami10
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% (269/9065) 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 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.

1.21, 95% CI: 1.1-1.3, p<0.001.

Figure: Proportion achieving viral suppression at year 3, by SEARCH trial arm and baseline hazardous drinking among persons with HIV+.
END OF HIV EPIDEMIC AMONG PWID IN A LOW-MIDDLE INCOME COUNTRY: THE HAI PHONG CASE

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1INSERM, Montpellier, France, 2Center for Supporting Community Development Initiatives, Ha Noi, Vietnam, 3Hai Phong Medical University, Hai Phong, Vietnam, 4New York University, New York City, NY, USA, 5Viet Triet Hospital, Hai Phong, Vietnam, 6CHU de Nîmes, Nîmes, France

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 flourished. 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 size 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%, 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 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.

ENDING THE HIV EPIDEMIC AMONG PEOPLE WHO INJECT DRUGS: A COST-EFFECTIVENESS ANALYSIS

Emanuel Krebs1, Xiao Zang1, Benjamin Ems1, Jeong E. Min1, Bohdan Nysyky4, for the Localized Economic Modeling Study Group

1British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

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-documented, 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, 2018US$).

Interventions were implemented 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 Magana3, Anh T. Vo4, Claudia Rafful5, Maria Gudeia Rangel-Gomez6, Maria Elena Medina-Mora7, Steffanie A. Strathdee1, Natasha Martel1

1University of California San Diego, San Diego, CA, USA, 2Universidad Nacional Autonoma de Mexico, Mexico City, Mexico, 3U.S.-Mexico Border Health Commission, Tijuana, Mexico, 4National Institute of Psychiatry Ramon de la Fuente Muñiz, Mexico City, Mexico

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.
However, with integrated OAT and ART scale-up synergistic benefits were observed, with the OAT effect on ART recruitment/retention averting 10% more new infections compared to ART scale-up alone. Scaling-up OAT and ART could avert 50% (95% CI: 28-67%) of new HIV infections and one-fifth of fatal overdoses over the next decade. Conversely, scaling-up ART and CAP could increase HIV and overdoses.

**Conclusion:** Integrating ART with OAT scale-up could provide synergistic benefits on ART recruitment/retention, and prevent new HIV infections and fatal overdoses among PWID in Tijuana. Conversely, non-evidence based CAP could contribute major harms. Policymakers should consider the synergistic benefits of integrated OAT and HIV services on HIV and overdose among PWID.

**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

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1. Columbia University Medical Center, New York, NY, USA
2. Montefiore Medical Center, Bronx, NY, USA
3. New 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).
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