Special Issue: Abstracts From the 2019 Conference on Retroviruses and Opportunistic Infections

Abstracts

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About This Issue

This issue of Topics in Antiviral Medicine is a special issue that includes the abstracts from the 2019 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 2019 Resources

Webcasts and electronic posters from CROI 2019 and information about CROI 2020, to be held in Boston, Massachusetts, from March 8 to March 11, 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 2019.

In addition to the Special Issue of Topics in Antiviral Medicine™, abstracts from CROI 2019 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 2019.
UPCOMING ACTIVITIES

Annual Full-Day HIV Courses
These live, full-day CME courses continue to feature cutting-edge, scientifically rigorous topics presented by leading experts in the field of HIV medicine. Visit the IAS–USA website for up-to-date information and podcasts of prior courses. This spring, IAS–USA courses focusing on the management of HIV infection will be held in:

Los Angeles, California—Monday, May 6, 2019
Chairs: Constance A. Benson, MD; Ronald T. Mitsuyasu, MD

Chicago, Illinois—Thursday, May 23, 2019
Chairs: Paul A. Volberding, MD; John P. Phair, MD

Interactive Webinars
Live, interactive continuing medical education (CME) in the comfort of your home or office, free of charge. Participants can ask questions and receive responses in real time. Visit the IAS–USA website for details. Upcoming webinars will cover the following topics:

Medical Management of HIV Among Transgender Adults—May 7, 2019
Presenter: Tonia C. Poteat, PhD, MPH, PA-C

Updates From CROI 2019: Treatment of HIV and Its Complications—May 21, 2019
Presenter: Timothy J. Wilkin, MD, MPH

HIV 101: Fundamentals of HIV Infection and Applications of Antiretroviral Therapy—June 18, 2019
Presenters: Michael S. Saag, MD, David H. Spach, MD

PrEP 2.0: TDF/FTC and Beyond – State of the Science and the Product and Delivery System Pipeline—June 25, 2019
Presenter: Raphael J. Landovitz, MD

Update on HIV Cure Strategies—July 16, 2019
Presenter: Katharine J. Bar, MD

Prior webinars are available for CME credit for up to 1 year after the live broadcast. Visit the IAS-USA website for a full list of archived webinars.

NEW: Sexual Health, HIV Prevention, and Primary Care in 2019
This new, full-day, live CME course will address the shift in primary responsibility for managing PrEP and STIs from HIV and infectious disease clinicians to primary care and internal medicine practitioners, and the best practices for maintaining the sexual health of those with or at risk for HIV infection. Information will be presented by an expert faculty of STI and HIV/AIDS clinicians and researchers. Visit the IAS-USA website to register:

New York, New York—September 12, 2019
Chairs: Roy M. Gulick, MD, MPH; Jeanne M. Marrazzo, MD, MPH, FACP, FIDSA

Cases on the Web
A series of web-based, case-driven CME activities, created to offer convenient online access to top-quality professional education. Visit the IAS–USA website for a full list of Cases on the Web activities. Recent activities address the following topics:

HIV-2: Clinical Features, Diagnosis, and Management
Author(s): Jacqueline T. Chu, MD; Rajesh T. Gandhi, MD
Date of Last Review: February 11, 2019
Expires: February 11, 2020
1.25 AMA PRA Category 1 Credits™ Available

Dates above may be subject to change. IAS–USA announcements are paperless, so please watch for email updates or visit www.iasusa.org for course information, agendas, and online registration, or to access archives of educational resources from past activities.
ABSTRACTS

How to cite the abstracts:

1 PROGRAM COMMITTEE WORKSHOP FOR NEW INVESTIGATORS AND TRAINEES
John W. Mellors¹, Serena S. Spudich ²
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Each year, the Program Committee for the Conference for Retroviruses and Opportunistic Infections (CROI) presents a half-day workshop geared toward new investigators and trainees. The goal of the workshop is to provide a broad introduction to key topics in basic, clinical and public health research, summarizing recent advances, areas of controversy and important knowledge gaps, along with a road map to relevant abstracts and presentations at CROI 2019. Presentations at the workshop are given by members of the CROI Program Committee. This year, the program will begin with a talk by Dr. Paul Bieniasz who will review aspects of the HIV-1 replication cycle, in particular recent developments in the understanding of virus entry, capsid function and RNA turnover. Following this, Dr. Penny Moore will describe advances in eliciting protective HIV-1 antibodies by vaccination, highlight emerging insights at the interface between innate and adaptive immunity, and summarize new immunological findings relevant to HIV-1 to be presented at the conference. Dr. Sharon Hillier will then describe the current landscape of biomedical HIV-1 prevention research including vaccines, broadly neutralizing antibodies, oral and injectable pre-exposure prophylaxis, vaginal and rectal microbicides, and combination approaches for prevention of HIV-1. Dr. Constance Benson will next briefly summarize the current state-of-the-art for tuberculosis treatment and prevention, highlight recent developments in the field, including new data to be presented at CROI, and identify current knowledge gaps that need to be addressed. Finally, Dr. Katharine Bar will review the current understanding of HIV-1 persistence, highlight major obstacles to achieving a cure for HIV-1, and discuss pre-clinical and clinical developments in HIV-1 cure research. Workshop participants are encouraged to interact with speakers during the moderated discussion after each talk. By the completion of the workshop, attendees will have achieved a head start toward maximizing the knowledge gained and research ideas arising from CROI 2019.

2 DISCOVERING THE ART IN SCIENCE (AND MEDICINE): THE HUMAN CONNECTION
Dawn Averitt, The Well Project, Women’s Research Initiative on HIV/AIDS, South Strafford, VT, USA
The scientific frontier is vast and our ongoing exploration continues to unveil stunning revelations impacting technology, medicine, and human health. However, the complexity of a person (not just a patient) introduces both an opportunity and a challenge to translate our knowledge of science into the art of medicine. Recognizing, if not understanding, the nuanced biologic, physiologic, emotional, and societal influences impacting people of different ages, races, sex, or gender provides boundless opportunities in research and medicine to uncover possibility and challenge long held assumptions.

3 ENGINEERING THE LATENT RESERVOIR
Paula Cannon, University of Southern California, Los Angeles, CA, USA
HIV persists in infected individuals despite antiretroviral therapy (ART). This is because the virus inserts itself into the genomes of infected cells where it can, under certain conditions, become transcriptionally silent or latent. These latent viruses are not impacted by ART but retain the potential to be reactivated at a later timepoint. In this way, latent HIV shares many of the features of a genetic locus, including sensitivity to the cell’s transcriptional or activation state. The recent development of sequence-specific genome editing tools such as CRISPR/Cas9, is suggesting new ways to consider depleting or mitigating the effects of the latent reservoir. Current genetic approaches against HIV infection include: (1) strategies to create HIV resistant cells, for example by disabling the non-essential CCR5 co-receptor gene in CD4+ T cells or their precursor hematopoietic stem cells; (2) strategies to boost or artificially redirect immune responses to recognize infected cells; and (3) strategies to target integrated HIV genomes themselves for disruption, suppression or activation. The first two approaches have the advantage of being amenable to ex vivo cell engineering, the capabilities for which have greatly advanced in recent years. Strategies targeting the HIV genome itself, however, will require the development of in vivo delivery methods that can find the needle in the haystack of an integrated latent HIV genome represents.

4 NOVEL IMAGING APPROACHES TO CHARACTERIZE AND QUANTIFY VIRAL RESERVOIRS
Jake D. Estes, Oregon Health and Sciences University, Portland, OR, USA
Effective combination antiretroviral therapy (cART) for HIV has led to vastly improved survival when treatment is available and affordable, an outcome that relies on uninterrupted adherence to cART for life. In the quest for sustained viral remission in the absence of cART (i.e. functional cure) or the complete eradication of HIV from infected individuals, it is necessary to understand the sizes, locations and characteristics of the reservoirs throughout the body from which infection can rebound after treatment is suspended. In addition, understanding HIV reservoirs in the context of their resident immune “neighborhoods” and surrounding inflammatory “landscapes” will likely be important to determine key mechanisms of viral persistence and potentially identify opportunities or pathways to exploit for future viral remission and eradication strategies. In this talk, I will discuss advances in approaches to image viral reservoirs at the tissue and cellular level in the infected host that have provided key insights on the phenotype, size, and characteristics of viral reservoirs and their local tissue microenvironments. Integration of unique, but complementary, imaging platforms that provide critical contextual insights into HIV reservoir biology with sensitive molecular and single cell approaches should prove instrumental in further promoting the development of new therapeutic strategies for sustained viral remission or elimination needed for an ‘HIV cure’ to be realized.

5 MORE COLORFUL IMMUNOLOGY: TARGETED ISOLATION OF MONOCLONAL ANTIBODIES
Mario Roedder, NIH, Bethesda, MD, USA
Monoclonal antibody (mAb) interventions for the prevention or treatment of HIV-1 infection have galvanized the field in the past five years. Broadly HIV-neutralizing mAbs are now being evaluated in clinical trials as therapeutics, “cure” strategies, and prophylaxis. The primary method of identification and isolation of these antibodies has been flow cytometric sorting of single cells, either based on antibody binding characteristics, or in bulk, from B cells of individuals infected or immunized with the antigens of interest. Optimization of this process has been undertaken on a wide range of fronts: probes (used to identify the B cells), immunophenotyping panels (to define particular subsets of interest), sorting speed and viability, post-sort culture or sequence identification (from single cells), highly sensitive micro-scale assays to define useful antibodies, cloning to express the antibody, and post-isolation improvements in affinity, solubility, manufacturability, and off-target effects. At the VRC, we built upon the successful isolation, optimization, and clinical development of VRC01 (now in Phase IIb testing HIV prophylaxis in 4,500 adults) to expand the repertoire of clinically-relevant antibodies for HIV, flu, malaria,
and RSV, as well as testing interventions in preclinical primate models using SHIV or SIV. In this talk, I will review some of the types of screening technologies that we use to efficiently isolate novel, potentially clinical useful monoclonal antibodies.

6 FELLOW TRAVELERS: INTERPRETING THE IMPACT OF THE MICROBIOME IN CLINICAL INTERVENTION
Adam Burgener, Public Health Agency of Canada, Winnipeg, MB, Canada
The microbiome represents the composition of bacteria, fungi, viruses, and their products that exist within the human body. It helps us digest food, shapes our immune system, and provides essential functions for human health. Many human diseases, including diabetes, inflammatory bowel disease, and cancer have been linked to alterations in the microbiome. There are currently >1,000 registered clinical trials examining microbiome-based interventions to promote human health and its role in disease, underscoring this expanding field of research. In HIV, the microbiome has been associated with HIV transmission and infection, mucosal inflammation, immune responses to vaccines, and efficacy of topical antiretroviral-based microbicides. Therefore, integrating microbiome sub-studies in future clinical trials will be an important component for HIV prevention and treatment strategies. In this seminar, I will provide an overview of the basics of the microbiome, methods to measure its different components, how to interpret data, examples of how this can be integrated into clinical studies and provide highlights on the microbiome in HIV and human disease.

7 MISSING U: HANDLING AND AVOIDING MISSING DATA IN CLINICAL TRIALS
Heather Ribaudo, Harvard T.H. Chan School of Public Health, Boston, MA, USA
Randomized clinical trials are the gold standard for evaluation of interventions. However, the presence of missing data can compromise their benefits, and lead to biased and inappropriate study conclusions. While methods exist to handle missing data in analysis, these may appear intimidating to the statistician and non-statistician alike, and are generally underutilized. Even when used, handling of missing data in analysis can only do so much, and it has long been advocated that considerations for minimizing missing data must start at trial design. At the request of the FDA, the National Research Council (NRC) recently convened a panel of experts to consider current state-of-the-art for handling missing data in clinical trials. The panel recommendations reinforced previous considerations and introduced some new ideas and concepts to be considered in the design and analysis of clinical trials to mitigate the impact of missing data. This talk will demonstrate the issues associated with inappropriate handling of missing data and attempt to demystify the associated analysis methodology. The recommendations of the NRC panel will be presented, including an introduction to the definition of estimands in study design and a discussion of appropriate sensitivity analyses. Examples from HIV clinical trials for both treatment and prevention will be used throughout to help demonstrate and solidify concepts. By the end of the talk, the audience will be familiar with terminology associated with missing data and have an understanding of the appropriate points to consider, and tools to implement, in clinical trial planning, analysis, and reporting to minimize the impact of missing data.

8 DESIGNING AND INTERPRETING HIV PREVENTION TRIALS IN THE ERA OF EFFECTIVE INTERVENTIONS
David Dunn, University College London, London, UK
Until recently, the design and analysis of clinical trials to evaluate HIV prevention interventions was relatively straightforward. Participants would be randomised to receive the intervention of interest or to receive no intervention (placebo under the most robust design). The analysis would compare HIV incidence rates between the groups, yielding an estimate of the effectiveness — the proportionate reduction in incidence — achieved by the intervention. This model of experimental simplicity was ended with the discovery of the remarkable effectiveness of oral pre-exposure prophylaxis (PrEP) using TDF-FTC. This meant it became ethically unacceptable to include a no-intervention group in most study populations. Current studies of novel PrEP agents have instead been designed as non-inferiority trials in which the experimental arm is compared with an active-control TDF-FTC arm. The challenges in analysing and interpreting such trials will be discussed, pointing out the need to collect additional contextual information. A different perspective is required for the evaluation of other prevention interventions, including vaccines. Here, the primary interest may lie in estimating biological efficacy rather than a direct comparison with oral PrEP. Nevertheless, the ethical requirement to offer PrEP complicates trial design and interpretation, as well as potentially requiring much larger studies. This session will attempt to illuminate key, basic concepts, keeping statistical detail to a bare minimum.

9 INTERACTIVE CASE-BASED WORKSHOP ON LIVER DISEASE
Marion G. Peters, Andri Rauch
1University of California San Francisco, San Francisco, CA, USA, 2University Hospital Bern, Bern Switzerland
This interactive case-based session is geared toward clinicians who are involved in treatment of HIV-infected patients with various liver diseases. Despite major recent breakthroughs in the treatment of viral hepatitis, there are important remaining challenges in the clinical care of those with liver diseases. This workshop will address difficult to treat HCV-infected patients who have failed direct-acting antiviral (DAA) therapies, highlight the important but often ignored hepatitis D and E viruses, and address the epidemiology and management of nonalcoholic fatty liver disease (NAFLD). Dr. Pischke (University Hospital Hamburg-Eppendorf) will discuss issues in diagnosis, clinical features, and treatment of Hepatitis E. He will highlight geographic differences in epidemiology and testing, and address the current management strategies. Dr. Jeffrey Glenn (Stanford University) will provide an overview of current diagnostic tests, clinical challenges and emerging new therapies for Hepatitis D, and the varied prevalence throughout the world. Dr. Giada Sebastiani (McGill University) will discuss NAFLD and its complex multifactorial pathogeneses, including frequent metabolic comorbidities and lifelong use of antiretroviral therapy and HIV itself, which is thought to drive this epidemic. She will highlight that early diagnosis, preventive and therapeutic strategies will help reduce the burden of NASH in people living with HIV. Dr. John Scott (University of Washington) will describe HCV DAA failures, the scenarios in which HCV resistance testing should be performed, and the choices of therapy for patients with end-stage liver disease.

(2010) SPECIAL PRESENTATION
ENDING THE HIV EPIDEMIC: A PLAN FOR THE UNITED STATES
Anthony S. Fauci, MD, NIAID, Bethesda, MD, USA
This presentation will describe the newly announced U.S. Department of Health and Human Services initiative targeting the ongoing HIV epidemic in the United States with the goals of decreasing the number of HIV incident infections by 75% within 5 years, and then by 90% within 10 years. This coordinated, multi-agency initiative will focus on geographic and demographic hotspots in 48 counties, Washington D.C., and Puerto Rico where the majority of new HIV cases are reported, as well as in 7 states with a disproportionate occurrence of HIV cases in rural areas. This new initiative builds on the scientific findings over the past 4 decades in HIV prevention, treatment, and care. Under the leadership of the Assistant Secretary for Health, HHS agencies including NIH, CDC, HRSA, and IHS will coordinate their programs and resources to implement with local, regional, and state partners evidence-based strategies to diagnose, treat, prevent, and rapidly detect and respond to the continuing HIV spread in the U.S. This HHS initiative will focus on interrupting or disrupting the genetics of HIV spread and provide a way forward to ending the epidemic in this country.

10 DISCOVERY AND DEVELOPMENT OF HIV BROADLY NEUTRALIZING ANTIBODIES
Michel Nussenzweig, The Rockefeller University, New York, NY, USA
Combination antiretroviral therapy (ART) has revolutionized the treatment and prevention of HIV-1 infection. Taken daily, ART prevents and suppresses the infection. However, ART interruption almost invariably leads to rebound viremia in infected individuals due to a long-lived latent reservoir of integrated proviruses. Therefore, ART must be administered on a life-long basis. The lecture will focus on emerging preclinical and clinical studies that suggest that immunotherapy may be an alternative or an adjuvant to ART because in addition to preventing new infections, anti-HIV-1 antibodies clear the virus, directly kill infected cells and produce immune complexes that can enhance host immunity to the virus.

11 THAILAND’S ACHIEVEMENTS IN HIV TREATMENT, PREVENTION, AND CURE RESEARCH
Praphan Phanuphak, Thai Red Cross AIDS Research Center, Bangkok, Thailand
To the external world, Thailand has achieved considerably on HIV treatment, prevention, and cure research but the reality could be different. For HIV
From the outset of the HIV epidemic it became clear that the virus capitalized on the immune defenses of the host to create an immune environment that would further foster availability of cellular targets and viral replication. Several studies in animal models of SIV and in humans at various stages of disease have concluded that immune activation represents an independent prognostic factor in HIV including treated disease with successful virologic suppression. Systemic inflammation and immune activation in HIV have been linked to excess risk for both AIDS and non-AIDS serious events in both untreated and treated people living with HIV (PLWH), and seem to accelerate the detrimental effect of other comorbidities such as smoking or diabetes or aging. In addition, inflammation and cellular activation can be critical in viral persistence contributing to the preservation, expansion or population shifts of the HIV viral reservoirs. The etiology of immune activation and inflammation in treated HIV is considered multifactorial encompassing residual viral replication, mucosal injury at effector sites that leads to innate immune activation and potentially dysbiosis, incomplete CD4 restoration, tissue fibrosis and confections. Inflammation and fibrosis in HIV are also accompanied by coagulopathy. Biomarkers that signify the degree of inflammation such as IL-6, CRP, sCD14 as well as D-dimer levels have been found in numerous studies to be strong independent predictors of morbidity and mortality in PLWH. It is though unclear if and to what extent, altering these biomarkers with anti-inflammatory or other therapies could alter clinical outcomes. Efforts to counteract the chronic inflammation in HIV have focused on the various facets of its etiology largely with small or moderate success. At the moment the best approach is treatment with antiretroviral therapy, preferably at diagnosis at early stages of disease when CD4 counts are still high, in combination with aggressive treatment of possible comorbidities. A better understanding of the etiologic pathways and how they intersect leading to chronic inflammation in HIV will be critical for improved, and efficacious, treatment interventions.

**HV VACCINE WITH LEEP DID NOT PREVENT RECURRENT CERVICAL HSIL IN HIV-INFECTED WOMEN**

Cindy Firnhaber, Avril Swarts1, Masangula Munologo2, Bridgette Goeieman2, Sophie Williams3, Simon Levin1, Mark Faesen1, Pamela Michelow, Timothy Wilkin1

1University of Colorado, Aurora, CO, USA, 2Clinical HIV Research Unit, Johannesburg, South Africa, 3Right to Care, Johannesburg, South Africa, 4National Health Laboratory Service, Johannesburg, South Africa, 5Weill Cornell Medicine, New York, NY, USA

**Background:** Women living with HIV are at high risk for cervical HSIL and rates are especially high in sub-Saharan Africa. These women have high HSIL recurrence rates after loop electrosurgery procedure (LEEP) requiring additional monitoring and treatment. More effective treatment for HSIL lesions in HIV infected women is needed. Some retrospective studies suggest that the Human Papillomavirus (HPV) vaccine used as adjuvant therapy with LEEP improves response to treatment of High-grade Squamous Intraepithelial lesions (HSIL) in HIV negative women. We evaluated the effectiveness of the HPV quadrivalent vaccine in preventing the recurrence of HSIL after LEEP in HIV infected women in Johannesburg South Africa.

**Methods:** We performed a double-blind, randomized clinical trial that enrolled 180 HIV infected women, between the ages of 18-65 years and cervical HSIL on histology in Johannesburg South Africa according to Consor criteria. The women were excluded if they were pregnant. Women received the quadrivalent HPV or placebo vaccine (1:1) at entry, week 4, and week 26. LEEP was performed at week 4. Colposcopy and directed biopsies and cervical cytology were performed at week 26 and 52. The primary endpoint was cervical HSIL by histology or cytology at either week 26 or 52, and this was compared between arms using Chi-square analysis.

**Results:** Participant characteristics included median age 39, median CD4 489, and 94% had HIV suppression (<200 copies/ml) on antiretroviral therapy. Of the 180 women enrolled, 179 women underwent LEEP and 174 women completed the vaccine/placebo series and had evaluable results at week 26 or 52. The proportion experiencing the primary endpoint of HSIL was similar in the vaccine and placebo groups, 53% vs. 45% (RR 1.16, 95% CI 0.87-1.6, P=.29). Similar results were seen when using only histologic results at 26 and 52 weeks (32% vs. 31%, RR 1.04, 95% CI 0.67-1.04, P=.9). HSIL recurrence was associated with a LEEP result of HSIL and positive margins on LEEP at week 4.

**Conclusion:** This randomized, double-blind clinical trial did not find evidence to support an adjuvant role for HPV vaccination for preventing recurrent HSIL.
post-LEEP in women living with HIV. Recurrent HSIL was high despite virologic suppression with antiretroviral therapy. More effective treatment strategies are needed to reduce the burden of recurrent cervical HSIL in this high risk population.

15 OPTIMAL LUNG CANCER SCREENING CRITERIA AMONG PERSONS LIVING WITH HIV

Subhashini A. Sellers1, Andrew Edmonds1, Catalina Ramirez1, Suchma Gribbs2, Igbo Ofotokun3, Laurence Huang4, Alison Morris5, Meredith C. McCormack5, Ken M. Kuniak6, Maria P. Rivera1, M. Brad Drummond1, Adaora Adimora1

1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2Emory University, Atlanta, GA, USA, 3University of California San Francisco, San Francisco, CA, USA, 4University of Pittsburgh, Pittsburgh, PA, USA, 5Johns Hopkins University, Baltimore, MD, USA, 6Minnesota VA Health Care System, Minneapolis, MN, USA

**Background:** Based on the National Lung Screening Trial (NLST), US Preventive Services Task Force (USPSTF) recommends screening with low-dose chest computed tomography scan for adults aged 55-80 with >30 pack-year smoking history who are current smokers or quit within the last 15 years. Persons living with HIV (PLWH) are at increased risk for lung cancer but were excluded from the NLST. This study evaluated the performance characteristics of NLST criteria in confirmed lung cancer cases and matched controls from observational cohorts of men and women with HIV. We also explored alternative thresholds to improve lung cancer detection rates.

**Methods:** We selected all confirmed lung cancers among PLWH who were current/former smokers and ≥40 years at diagnosis in the Women’s Intergency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS). Controls, selected from each cohort, were PLWH with no reported lung cancer during all follow-up visits, matched on 5-year age windows. Clinical and demographic characteristics, and proportions meeting NLST screening criteria, were compared. Alternative thresholds included iterative reductions in age, pack-years, and quit date.

**Results:** We identified 44 WIHS women and 17 MACS men with HIV and incident lung cancer (Table). Lung cancer incidence was 270 and 104 per 100,000 person-years in women and men, respectively (p<0.001). Race and income did not differ between cases and controls. Compared to controls, women with lung cancer had a significantly lower median CD4 count but no significant difference in median viral load. In men, there were no significant differences in these markers of HIV infection between cases and controls. Only 16% of women and 24% of men with lung cancer met USPSTF screening criteria. Optimal age and pack-year screening criteria in women (age 49-75, ≥16 pack-year history) yielded 52% sensitivity and 75% specificity. In men, optimal criteria (age 43-75, >19 pack-year history) yielded sensitivity (82%) and specificity (76%).

**Conclusion:** Current USPSTF lung cancer screening guidelines performed poorly in PLWH, as <25% of lung cancer cases met criteria. Alternative thresholds of age, smoking history, and quit date can better identify PWLH to screen for lung cancer. Among PLWH, lung cancer risk was higher in women than men. This study demonstrates the need for risk prediction modeling incorporating sex and markers of HIV infection to identify high risk individuals who would benefit from screening despite not meeting current USPSTF criteria.

16 HIV IS ASSOCIATED WITH DECREASED BREAST CANCER SURVIVAL: A PROSPECTIVE COHORT STUDY

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**Background:** Breast cancer is the second leading cause of cancer death among women living with HIV (WLHIV) with access to ART. In the context of ART coverage exceeding UNAIDS 90-90-90 targets, we sought to prospectively assess the impact of HIV on overall survival of women with breast cancer. **Methods:** As part of the Thabatse Cancer Cohort, we included women presenting (October 2010 to March 2018) for initial treatment of breast cancer at one of four oncology centers in Botswana. Consenting patients were interviewed, records abstracted, and followed for up to 5 years. The association between HIV infection and all-cause mortality was assessed using a multivariable Cox proportional hazards model including covariates selected a priori: cancer stage, curative versus palliative intent, receptor status, age, and personal income.

**Results:** A total of 430 women with breast cancer with known HIV status were enrolled (4 women with unknown HIV status excluded), including 135 (31.4%) WLHIV and 295 (68.6%) uninfected women. WLHIV were younger than uninfected women, median 47.5 and 55.5 years, respectively (p<0.001). Among WLHIV, 110 (84%) were on ART prior to cancer diagnosis (median duration 6.8 years) and median CD4 count was 513 cells/μL. Advanced cancer stage (III/IV) was common for both WLHIV (67%) and uninfected women (66%). Immunohistochemistry results were available for 250 women (58%); 154 (62%) women were ER+ and 65 (26%) were triple-negative. Receptor status was similar by HIV status (p=0.89). The majority (69%) received multimodality treatment with curative intent and the proportion did not differ by HIV status (p=0.80). After 847 patient-years of follow-up, 156 women died, including 66 (49%) WLHIV and 90 (31%) uninfected women. Three women (0.7%) were lost to follow-up. The majority of deaths (141, 90%) were attributed to cancer and none to HIV. Two-year survival for WLHIV was lower than those without HIV, 57% and 73%, respectively (see Figure, p<0.001). Findings were similar in adjusted analyses with WLHIV experiencing higher mortality (hazard ratio 1.86, 95%CI 1.33 to 2.61, p<0.001).

**Conclusion:** HIV infection is associated with substantially higher non-AIDS mortality among women with breast cancer. Improved understanding of
mechanisms underlying excess mortality could contribute to improved outcomes in the majority female and aging African HIV epidemic.

**Conclusion:** KSHV-MCD is an under diagnosed but highly treatable condition if recognized. Physicians need to identify and promptly treat concurrent diagnoses of PEL and KS that may contribute to morbidity and mortality.

**LONG-TERM OUTCOMES OF 58 PATIENTS WITH HIV AND KSHV-ASSOCIATED MULTICENTRIC CASTLEMAN DISEASE**

Ramya Ramaswami, Kathryn Lurain, Priscila H. Gonçalves, Mark Polizzotto, Anaïda Widell, Matthew Lindsay, Richard F. Little, Thomas S. Udink, Robert Yarchoan

NIH, Bethesda, MD, USA

**Background:** Multicentric Castleman disease (MCD) is a rare systemic lymphoproliferative disease caused by Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpes virus 8 (HHV-8). Patients with HIV and KSHV-MCD may also have Kaposi sarcoma (KS) and are at increased risk of developing non-Hodgkin lymphoma, especially primary effusion lymphoma (PEL). The historical overall survival was 2.5 years, but this has improved following the use of rituximab for KSHV-MCD and antiretroviral therapy for patients with HIV. Here, we present the long-term outcomes of the largest prospective study of KSHV-MCD and HIV+ patients in North America.

**Methods:** We evaluated long-term outcomes and concurrent diagnoses (KS and PEL) that influenced overall survival for patients with HIV and KSHV-MCD in a natural history study with 5 optional treatment regimens for MCD flares. This included high-dose zidovudine and ganciclovir, sirolimus, rituximab (R) with liposomal doxorubicin (R-LD) followed by interferon-α or high-dose zidovudine with valganciclovir (AZT/VGC), or rituximab plus infusional chemotherapy (R-EPOCH).

**Results:** There were 58 participants (54 male, 4 female) with a median (range) age of 44 years (26-68), HIV VL <50 copies/mL (50 – 64100) and CD4 count 180 cells/μL (3-1319) at MCD diagnosis. All patients were on combined antiretroviral therapy at study entry. 38 patients had prior therapy for KSHV-MCD (18 patients with R-based therapy), and 39 patients had a concurrent diagnosis of KS. Nine patients (15%) developed PEL after entry and 1 patient had been diagnosed with PEL prior to KSHV-MCD. Patients diagnosed with PEL were treated with R-EPOCH. The median duration of follow up was 4.1 years. Of the 61 patients treated with R-LD, usually followed by high-dose AZT/VGC. The 5-year overall survival was 80% (95% confidence interval (CI), 66% to 88%). Eleven patients died: 4 from PEL, 4 from KSHV-MCD and associated complications, 2 from KS and sepsis, and 1 died from pancreatic cancer. A concurrent diagnosis of KS was not clearly a prognostic factor (hazard ratio (HR) 2.4; 95% CI, 0.5-11.1, P=0.3). However, a concurrent diagnosis of PEL was associated with worse survival (HR 3.4; 95% CI, 0.99-11.6, P=0.05, figure 1).

**Conclusion:** KSHV-MCD is an under diagnosed but highly treatable condition if recognized. Physicians need to identify and promptly treat concurrent diagnoses of PEL and KS that may contribute to morbidity and mortality.

**REDUCTION OF KAPOSI SARCOMA–ASSOCIATED HERPESVIRUS LATENCY USING CRISPR-CAS9**

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**Background:** Kaposi sarcoma-associated herpesvirus (KSHV) is the causative agent of Kaposi sarcoma (KS), an AIDS defining cancer in HIV-1 infected individuals or immune suppressed transplant patients. The prevalence for both KSHV and KS are highest in sub-Saharan Africa where HIV-1 infection is also epidemic. Current therapies for KS are not effective, with high reoccurrence and mortality rate. Similar to other herpesviruses, KSHV’s ability to establish latency in the host presents a major challenge to KS treatment or prevention. Among KSHV genes, the latency-associated nuclear antigen (LANA) is absolutely required for latency. Hence, strategies to eliminate LANA from KSHV latently infected cells might lead to prevention or treatment of KS.

**Methods:** We designed a replication-incompetent adenovirus to deliver LANA-specific CRISPR-Cas9 system (Ad-CC9–LANA) at high efficiency into various KSHV latently infected cells and monitored over a period of 32 days. The effects of Ad-CC9–LANA had on KSHV episome in latently infected cells were then determined by droplet digital PCR. Real-time PCR was utilized to measure the mRNA expressions for LANA and Cas9. Immunohistochemistry (IHC) was performed to demonstrate the reduction of KSHV latently infected cells in Ad-CC9–LANA transduced cultures.

**Results:** Reduction in KSHV episome was evidence as early as 4 days of transduction by Ad-CC9–LANA. At 32 days post-transduction, the Ad-CC9–LANA transduced cultures demonstrated a substantial reduction in KSHV episome copy number in latently infected cells. These reductions were accompanied by decrease in the LANA mRNA expression and confirmed by IHC. These observations were not due to cell death due to adenovirus transduction as demonstrated by the similar growth kinetic between transduced and non-transduced cells. The Cas9 mRNA expression was also shown to be robust and detected throughout the study period.

**Conclusion:** Our study demonstrated the feasibility of using a KSHV LANA-targeted CRISPR-Cas9 system to disrupt KSHV latency in infected epithelial and endothelial cell lines. This approach to limit KS latency may also represent a viable strategy for against other tumorigenic viruses such as HCV, HPV and EBV. Therefore, it will have significant benefits to human health worldwide and particularly in developing countries where the viral cancer burden is high.

**THE ROLE OF WILMS’ TUMOR 1 IN KAPOSI SARCOMA HERPESVIRUS ONCOGENESIS**

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**Background:** Kaposi Sarcoma (KS), caused by HHV-8, is the most common HIV associated malignancy globally. It occurs predominantly in sub-Saharan Africa where it has a high mortality rate. Despite the burden of KS, it is unknown if KSHV causes a reactive proliferative process or a clonal malignancy due to oncogenic genetic alterations that occur in latent infection due to genetic instability. Discovery of recurrent genetic alterations would provide an improved understanding of KS pathogenesis and may allow for the development of prognostic biomarkers and improved treatment options. A promising cancer antigen is WT1 (Wilms' Tumor 1), for which WT1 therapeutic vaccines have demonstrated benefit in patients with leukemias and solid tumors, and has served as a prognostic marker in patients with myelodysplastic syndromes and leukemias. Different isoforms of WT1 are proposed in leukemias and in solid tumors to have both tumor suppressive and oncogenic roles. We propose that genetic alterations of WT1, a preliminary finding among a subset of KS patients play a role in KS tumorigenesis.

**Methods:** KS biopsy samples are obtained from Weill Cornell Medical College, Stroger Hospital in Chicago and from the HIPPOS study (Kampala, Uganda). Lentiviral transduction of WT1 shRNA of KSHV infected 293T and endothelial cells were used to explore the role of identified genetic alterations.

**Results:** We identified a deletion of WT1 in 2/11 patients with KS. Loss was confirmed by immunohistochemistry in these cases, while WT1 overexpression was seen in non-mutated cases. In an expanded cohort, we found additional cases that overexpress WT1 while others had no expression. In addition, the ‘tumorigenic’ form, cuyWT1, was upregulated in endothelial and 293T cells upon infection with KSHV. Similar to the role of the oncogenic form of WT1 in other cancers in regulation of secondary target genes, knockdown of WT1 decreased BCL-2 expression, an anti-apoptotic gene.

**Conclusion:** Kaposi sarcoma may manifest along a spectrum, as an inflammatory lesion or as a clonal malignancy, due to transformation in the setting of chronic KSHV infection leading to genomic instability. Given the finding of WT1 deletions in a subset of cases, as well as overexpression in others, WT1 isoforms may have pro-oncogenic and tumor suppressive roles in KS. Our data suggest that two types of KS exist, based on loss or overexpression of WT1. In KS cases that overexpress this protein, WT1 may be a promising target as a biomarker and immunotherapy.

**Immunohistochemistry for WT1 in KS**

**20LB QUANTIFICATION OF KSHV DNA AS A DIAGNOSTIC TEST FOR KAPOSI SARCOMA IN AFRICA**

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**Background:** Histopathologic evaluation, the gold standard for diagnosis of Kaposi sarcoma (KS), has long been limited in sub-Saharan Africa by lack of personnel and materials. Even where pathology is available, accuracy of KS diagnosis is often sub-optimal. This has led to widespread delays and inaccuracies in KS diagnosis, often resulting in late or improper treatment (e.g., unwarranted chemotherapy). As an alternative to histopathology, we hypothesized that quantification of KSHV DNA in skin lesions can diagnose KS.

**Methods:** We evaluated consecutive patients with skin lesions, suspected by their primary care providers to be KS, who were referred for a skin biopsy at 3 HIV care centers in Uganda. Traditional histopathologic evaluation of the 5 mm skin punch biopsies, including anti-LANA staining, was performed in Africa and by up to 3 pathologists in the US. Quantitative PCR (qPCR) for KSHV ORF 26 was performed on extracted DNA from the biopsy. Using the consensus of the US pathologists as the gold standard, we determined the sensitivity & specificity of PCR (both qualitative and quantitative) for KS diagnosis. A receiver operating characteristics curve was used to assess quantitative cutpoints and area under the curve (AUC).

**Results:** We tested 506 participants with skin lesions. Median age was 33 years, 38% were women, and 94% were HIV-infected; 22% of lesions were macules, 64% plaques, and 14% nodules. Consensus US pathologic testing revealed that 330 biopsies were KS, 149 not KS and 27 were indeterminate. Using US pathology as gold standard, the sensitivity of African pathology was 95% and specificity was 70%. Sensitivity of qualitative detection (presence or absence) of KSHV DNA for KS diagnosis was 99% but specificity was only 78%. Evaluation of quantitative KSHV DNA content found an AUC of 0.96, at the optimal cutoff (1412 KSHV copies per 5 µl specimen), sensitivity was 98% and specificity was 90%, with 96% of subjects correctly classified.

**Conclusion:** In the context of sub-Saharan Africa, where KSHV is endemic, quantification of KSHV DNA content in skin lesions by PCR has both high sensitivity and specificity for the diagnosis of KS when compared to gold standard pathology. In contrast, qualitative detection of KSHV DNA is non-specific. The findings suggest that a nucleic acid amplification-based diagnostic test for KS could largely replace the need for histopathology, be implemented in point-of-care format, and ultimately greatly improve access to timely and accurate KS diagnosis.

**21 TWO NOVEL POTENTIAL THERAPEUTIC TARGETS IN THE KSHV LIFE CYCLE**

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Twenty-five years after the discovery of KSHV our understanding of the molecular mechanisms governing its replication, persistence and pathogenicity has advanced to the point where it may become possible to identify novel therapeutic targets for pharmaceutical intervention. In our recent work, we have focused on the KSHV thymidine kinase and a non-structural membrane protein encoded by open reading frame (ORF) K15. Work by Gill and colleagues
(EMBO J. 2014) had suggested that the KSHV thymidine kinase (TK) homologue, encoded by ORF K15, has tyrosine kinase properties. We therefore explored if tyrosine kinase inhibitors already approved for cancer chemotherapy would show activity against KSHV TK. We found that several compounds potently inhibit KSHV TK in vitro and ex vivo kinase assays, and also strongly inhibit KSHV productive (lytic) replication in tissue culture, as well as KSHV-dependent tumorigenesis in a xenograft model. Regarding the viral non-structural membrane protein encoded by ORF K15 (pK15), we have previously shown that it is expressed in Kaposi Sarcoma tissue and that, in primary endothelial cells, it is required for KSHV-dependent angiogenic and proliferative effects, as well as for the ability of KSHV to reactivate from latency; pK15 recruits, and promotes the activation of, the cellular lipase PLCγ1 to achieve these biological properties (Bala et al., PLoS Path. 2012; Gramolelli et al., PLoS Path 2015; Abere et al. PLoS Path. 2017; Abere et al. J. Virol. 2018). We have now studied the interaction of pK15 with PLCγ1 to the molecular and structural level and identified first small molecule inhibitors that potently interfere with the activation of PLCγ1 by pK15 and KSHV lytic replication. Ongoing work aims to optimize these hits to reach a starting point for hit-to-lead development.

22 TARGETING THE NONCANONICAL NF-κB PATHWAY REVERSES SIV LATENCY

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Background: The leading approach to eradicate HIV consists of the induction of latency reversal and subsequent clearance of cells reactivating the virus. Here, we tested a novel latency reversing agent (LRA) strategy that selectively activates the non-canonical NF-κB pathway (ncNF-κB) using a mimetic of the second mitochondrial-derived activator of caspases (SMACm).

Methods: We evaluated the SMACm AZD5582 in 12 SIV-infected ART-suppressed rhesus macaques (RM) compared to 9 controls. After over a year of ART, RM received 3-10 weekly doses of AZD5582 intravenously at 100 μg/kg. Plasma viral loads (PVL) were measured longitudinally and levels of cell-associated SIV-RNA and -DNA were quantified in resting CD4+ T-cells isolated from peripheral blood, lymph nodes (LN), spleen and bone marrow (BM). We performed flow cytometric analysis of T cell activation and assessed the gene expression profile and SIV-specific T-cell responses following AZD5582 treatment.

Results: Treatment with AZD5582 resulted in efficient activation of ncNF-κB in absence of generalized T-cell activation in blood and LN. A persistent increase in PVL on ART was observed in 5/12 (42%) AZD5582-treated RM while PVL remained undetectable in 9 control animals. The episodes of viremia induced by AZD5582 started as soon as 48h after the first dose. Viremia >60 copies/ml was measured in 15/28 samples (53%) in a period of 10 weeks with levels reaching 1390 SIV-RNA copies/ml. The levels of cell-associated SIV-RNA in resting CD4+ T-cells isolated from LN were significantly higher in 10-dose AZD5582-treated animals vs. controls (p= 0.0157) and tended to also be higher in the spleen, but not blood or BM. The levels of SIV-DNA quantified in the same compartments were not significantly different between AZD5582-treated and control groups. Principal component analyses revealed a distinct impact of AZD5582 on the transcriptome of CD4+ T-cells isolated from blood and LN pre- and post-treatment. SIV-specific T-cell responses measured in blood and LN by ELISPOT were not negatively impacted by treatment with AZD5582.

Conclusion: Activating the ncNF-κB pathway in vivo with the SMACm AZD5582 resulted in high level and persistent induction of SIV-RNA expression in ART-suppressed RM in absence of generalized T-cell activation, indicative of latency reversal. Further studies will combine this promising LRA with immune switch or intensification.

Methods: Peripheral blood mononuclear cells (PBMCs) and plasma were collected at two or more time points from donors with plasma HIV RNA >20 copies/ml occurring for >6 months on combination ART. Single-genome sequencing was performed on plasma HIV RNA, cell-associated HIV DNA (CAD), and p24+ culture supernatants from quantitative viral outgrowth assays (qVOA). The clonal cellular origin of viremia was assessed by phylogenetics and integration site analysis (ISA), and confirmed by sequencing the integrated provirus and the flanking host sequences.

Results: Across the 10 individuals referred, median plasma HIV-1 RNA was 97.5 cpy/mL (range 40 to 156 cpy/mL) after a median of 10 years on ART. One donor (A-04) had phylogenetic evidence of virus evolution and accumulation of resistance mutations and was not analyzed further. Each of the other 9 donors had multiple identical single-genome HIV RNA sequences in plasma that did not change over time and lacked resistance to the current ART regimen. In 6 of 9 donors, HIV sequences from plasma matched proviral sequences in PBMC. Plasma HIV RNA and proviral sequences were identical to HIV RNA in p24+ qVOA wells for 4 donors (C02, C03, R09, T13). The integration sites for the intact proviruses producing viremia were mapped to the human genome for 3 donors (4th pending). Integrations were in introns of the MATR3, ZNF268, and ABCA1P genes for C02, C03, and R09, respectively. The provirus in MATR3 and ZNF268 were in the opposite orientation to the gene, whereas the ABCA1P integrant was in the same orientation. The intact provirus comprised 4.2-15.4% of all proviruses in PBMC with amplifiable pro/pol sequences.

Conclusion: Large cell clones carrying intact proviruses can produce clinically relevant levels of viremia and should be considered in managing patients. The mechanisms involved in clonal expansion and persistence of cells with intact proviruses that produce viremia need to be understood to effectively target the HIV reservoir.

24 EX Vivo and in Vivo Editing of the SIV Genome in Nonhuman Primates by CRISPR-Cas9

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Background: Antiretroviral therapy (ART) has increased survival, but is a non-curative approach as replication competent proviral DNA, with high risk for reactivation upon ART cessation, remains. As such, HIV is now a chronic disease with a broad range of co-morbidities and drug toxicity. Curative strategies to eradicate the infected cells or viral genome without further treatment are vital.

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Here, we develop and test the ability of the CRISPR-Cas9 gene editing method for elimination of the SIV viral genome in rhesus macaques.

**Methods:** We employed AAV-9 as a vector to deliver CRISPR-Cas9 designed to target sequences spanning the LTR and Gag genes and permanently inactivating proviral DNA by excising intervening DNA fragments. Adult Chinese rhesus macaques (n=8) were i.v. infected with SIVmac239. At 8 weeks post infection, animals were treated daily with a drug regimen of tenofovir, emtricitabine and deltavirgevar (5.1/2.5/2.5mg/kg daily by s.g.). Ex vivo gene editing was performed in PBMCs by AAV9-CRISPR-Cas9 transduction, PCR amplification and Sanger sequencing of the amplicons to assess the potency and precision of viral DNA elimination. In a proof of concept in vivo study, 4 animals, 3 were given an i.v. infusion of AAV-9-CRISPR-Cas9 (10^11GC/kg), and after three weeks, animals were necropsied, blood and tissues were harvested virologically and gene excision evaluations.

**Results:** In all SIV-infected animals, ex vivo excision of viral DNA was confirmed by the detection of distinct DNA fragments of 464bp and 358bp resulting from the removal of intervening DNA sequences between 5’LTR to Gag and 3’LTR to Gag, respectively. Results from Sanger sequencing confirmed the breakpoint of the viral DNA. Delivery was confirmed by the presence of Cas9 and expression of both gRNAs. In vivo, both 5’LTR to Gag and 3’LTR to Gag excision were confirmed in blood of animals that received AAV-9-CRISPR-Cas9 infusion. In contrast to the control animal, which displayed rapid viral outgrowth, no outgrowth was detected in PBMC/CEM co-cultures after 30 days from animals with AAV-9-CRISPR-Cas9.

**Conclusion:** We demonstrated, for the first time, high specificity and efficacy of the CRISPR technology for targeting SIV proviral LTR and Gag regions, which led to both ex vivo and in vivo editing of SIV DNA. These observations support the potential use of CRISPR/Cas9 technology as a curative strategy that warrants further investigation.

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**DELAYED VIRAL REBOUND DURING ATI AFTER INFUSION OF CCR5 ZFN-TREATED CD4 T CELLS**

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**Background:** Autologous CD4 T cells modified using CCR5 specific Zinc Finger Nucleases (ZFN) have a survival advantage in the presence of HIV, but the levels of modification are insufficient to control viremia (NCT00842634). The main goals of this study were to evaluate: 1) if delivery of ZFN using RNA-based transfection provides similar level of CCR5 disruption as the Ad5/35 vector 2) the safety and tolerability of a single dose of this product in HIV+ subjects 3) if a single dose of cyclophosphamide (CTX) increases engraftment 4) the persistence of the disrupted cells and their impact on viral rebound during an ATI and 5) if Δ32 CCR5 heterozygotes preferentially benefit from infusion of CCR5 ZFN treated T cells.

**Methods:** We conducted a 3-arm open-label pilot study of the safety and antiviral activity of a single infusion of autologous CD4 T cells modified by the CRISPR-Cas9 gene editing method for elimination of the SIV viral genome. The goals of this study were to evaluate: 1) if delivery of ZFN using RNA-based transfection provides similar level of CCR5 disruption as the Ad5/35 vector 2) the safety and tolerability of a single dose of this product in HIV+ subjects 3) if a single dose of cyclophosphamide (CTX) increases engraftment 4) the persistence of the disrupted cells and their impact on viral rebound during an ATI and 5) if Δ32 CCR5 heterozygotes preferentially benefit from infusion of CCR5 ZFN treated T cells.

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**Results:** We enrolled 14 participants; 93% male, 57% AA, 7% Hispanic, median age 44. Median baseline CD4 count was 831/µm³ (IQR 630-1030), SB-728m-T was safe and well tolerated. No related grade 3 or higher adverse events were observed. CCR5 disruption was confirmed in the product (MiSeq) was 24% vs 23% with Ad5 vector. The median CCR5-modified T cells was 7.4% at 1 week post infusion. The engraftment of the modified cells varied between groups during the 16-week ATI (KI p=0.04) with trend to greater early engraftment in the CTX groups (p=0.08) that was significant for the Δ32 group compared to the control (p=0.04). The rebound of HIV viremia (HIV RNA > 200 copies/ml) (Fig 1) was delayed when compared to ACTG historical controls (p=0.03). A subset of Δ32 CCR5 heterozygotes had low viral load in the absence of ART for up to 40 weeks.

**Conclusion:** Introduction of CCR5 ZFNs via RNA transfection led to similar levels of disruption as Ad5/35 vectors. CTX led to an increase in engraftment and the administration of the product led to a modest, significant delay in viral rebound during the ATI and maintenance of low level viremia for up to 40 w in some, suggesting that a more efficient CCR5 modification could potentially benefit more individuals from this cure strategy.
Pembrolizumab Induces HIV Latency Reversal in HIV+ Individuals on ART with Cancer

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Background: Pembrolizumab is a monoclonal antibody against PD-1 approved for several cancers. In HIV-infected individuals on suppressive antiretroviral therapy (ART), HIV is enriched in CD4 T-cells that express PD-1. Within a Cancer Immunotherapy Trials Network (CITN) study, we prospectively evaluated markers of HIV persistence to test the hypothesis that pembrolizumab administration might increase HIV transcription and viral production consistent with latency reversal.

Methods: CITN-12 is a prospective multicenter phase I study of pembrolizumab 200mg IV every 3 weeks in participants with HIV on ART and advanced cancer. Participants were enrolled in cohorts with CD4 counts of: 100-199 (C1), 200-350 (C2) and >350 cells/μl (C3). Specimens were collected at baseline, 2 hours, 1 day, 7 days (cycle 1 only) and before cycles 2 and 3. Plasma HIV RNA was measured using a single copy (sc) qRTPCR for HIV gag. Intracellular unspliced (us) HIV RNA (RNA) and viral DNA (vDNA) were measured in CD4 T-cells. Pairwise correlation between assays was assessed by Pearson’s correlation coefficient. Kinetics of HIV plasma RNA, intracellular usRNA, usDNA, and usRNA/vDNA were evaluated by negative binomial regression. P<0.01 was considered statistically significant, p<0.05 a significant trend.

Results: 29 participants (C1 N= 6, C2 N=12, C3 N=11) with a range of tumors were evaluated; median age 56 years (IQR 50-61); 28 men, 1 woman. Baseline sc HIV = 1.1 copies/ml (IQR 0.3-2.4), Median baseline CD4 272 cells/μl (IQR 210-568). After pembrolizumab, mean usRNA and usRNA/DNA ratio were significantly elevated at Day 7 compared to baseline (usRNA: 1.43 fold, 95% CI 1.12 – 1.82, P=0.004; usRNA/DNA: 1.63 fold, 95%CI 1.17-2.27, P=0.004) but not at day 21 (P=0.15, P=0.87 respectively). vDNA was decreased at 24 hours (0.82, 95%CI0.70-0.97, P=0.02) but not on Day 7 (P=0.2) (Figure). No significant changes in plasma sHIV RNA were observed over 2 cycles, sHIV RNA, usRNA, and vDNA were not correlated (p>0.05).

Conclusion: Pembrolizumab leads to a transient increase in HIV transcription in CD4+ T-cells in vivo in individuals on ART consistent with latency reversal. It did not lead to increased plasma HIV RNA after administration of 2 doses. Evaluation of the long-term effects of pembrolizumab on HIV persistence and HIV specific immunity are ongoing. Further evaluation of monoclonal antibodies against PD-1 as a strategy for HIV cure is warranted.

28LB POTENT ANTIVIRAL ACTIVITY OF TRISPECIFIC BROADLY NEUTRALIZING HIV ANTIBODIES

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Background: Broadly neutralizing antibodies (bnAbs) against HIV-1 have been suggested as a complementary immunotherapy to current combination small molecule anti-retroviral therapies (cART) for treatment of HIV-1 infection. Due to their monospecific nature, use of single bnAbs leads to rapid selection for escape variants in most HIV-1 infected patients and therefore use of a combination of 2 or more bnAbs is desirable to maintain durable suppression of HIV-1 replication.

Methods: We engineered trispecific antibodies (Abs) that allow a single molecule to interact with three independent HIV-1 envelope determinants: 1) the CD4 binding site, 2) the membrane proximal external region (MPER) and 3) the V1/V2 glycan site. Prior studies demonstrated improved neutralization compared to parental bnAbs. These trispecific Abs have an intact IgG1 backbone and were assessed forFc effector function and ability to suppress virus replication from activated HIV-1 infected donor T cells. One of the trispecific Abs was administered to viremic simian-human immunodeficiency virus (SHIV)-infected rhesus macaques to assess inhibition of viral replication.

Results: Each of the three combining sites of the trispecific Abs were actively bound with high affinity binding to the HIV envelope glycoprotein. In addition, trispecific Abs retained binding to Fcγ receptors via their Fc region and mediated antibody dependent cellular cytotoxicity (ADCC). In cultures of activated CD4+ T cells from HIV-1 infected patients, trispecific Abs durably suppressed viral replication compared to individual parental bnAbs. In viremic SHIV-infected macaques, treatment with trispecific Abs reduced plasma viremia up to 1000-fold that was maintained until the plasma trispecific Ab levels dropped below a value that was greater than 5-fold its IC50 against the SHIV.

Conclusion: Trispecific HIV antibodies demonstrate potent neutralization and ADCC in vitro, and mediate antiviral activity in vivo. Thus, trispecific Abs provide an attractive single immunotherapeutic protein for treatment of HIV-1 infection.

29LB SUSTAINED HIV-1 REMISSION FOLLOWING HOMOZYGOTE CCRS DELTA32 ALLOGENIC HSCT

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Background: The “Berlin Patient” underwent 2 consecutive HSCTs with total body irradiation. It is unclear which aspects of treatment contributed to this only known case of HIV cure. We report an HIV-infected male diagnosed
with Hodgkin’s Lymphoma (HL) who underwent autologous HSCT using a homozygous CCR5Δ32 donor. Nadir CD4 was 290 cells/mm and baseline VL 180,000 copies/ml. ART (TDF/FTC/EFV) was started in 2012. During episodes of ART interruption viral rebound and selection of NRTI resistance was seen. HL was refractory to 1st line chemotherapy and multiple salvage regimens. An unrelated CCR5Δ32 homozygous donor was identified with one allelic mismatch at HLA-B. Conditioning was initiated with Lomustine, cyclophosphamide, Ara-C and etoposide followed by 3.6 million CD34+ cells/kg. In vivo T-cell depletion employed anti–CD2 and gHVd prophylaxis was cyclosporine and methotrexate. ART was continued throughout (Rilpivirine, 3TC, dolutegravir). The patient developed mild gut gHVd. Full donor chimerism was maintained in blood. Six months post-HSCT complete remission was observed.

**Methods:** Co-receptor tropism was predicted with Geno2Pheno based on single genome sequencing (SGS). Post-HSCT PBMC were analysed by ddPCR and qPCR. Infectious virus was repeatedly analysed by qVOA. Isolated CD4 T cells were experimentally infected with X4 and R5 HIV.

**Results:** SGS from pre-transplant PBMC identified multiple envelope clones all with predicted R5 tropism. ART was stopped 17 months post-HSCT and plasma HIV VL remained undetectable (<14 copies/ml) at 33 months. ART drugs were not detectable in plasma by LC-MS. Total HIV DNA in CD4+ T-cells at 33 months showed 2 positive droplets in 1 out of 8 replicates (ddPCR HIV LTR; 10^-6 cells tested) and no signal in qPCR (<0.69 HIV-gag and <0.65 HIV-LTR copies/million cells). At 16 months post-transplant HIV- and R5-specific Western blot was positive while p24/p31 bands were absent. VITROS detuned and avidity analysis revealed low quantity and quality of HIV antibody titers. At three time points post-HSCT qVOA showed no reactivatable virus using a total of 24 million resting CD4+ T cells. Post-transplant CD4+ T cells did not express CCR5 and were susceptible in vitro to X4- but not R5-tropic virus.

**Conclusion:** Absence of viral rebound was observed for 16 months following ART interruption at 17 months after single allelic CCR5-Δ32 HSCT using a no irradiation approach with only mild gHVd. To our knowledge this is the longest adult HIV remission observed since the Berlin patient.

### 30 BREAKING BONES IS BAD: INCIDENT FRACTURE AND MORTALITY IN THE HIV OUTPATIENT STUDY

**Linda Battalora**1, Carl Armon2, Frank J. Palella3, Jun Li4, Edgar T. Overton5, John Hammer6, Jack Fuhrer7, Richard Novak8, John Speare9, Kate Buchanan10

**Background:** Persons living with HIV (PLWH) have higher rates of low bone mineral density (BMD) and fracture than those without HIV infection, but the contribution of bone fractures to mortality among aging PLWH in care in the United States (U.S.) has not been explored. We evaluated the associations of bone fracture with mortality controlling for sociodemographic, behavioral, and clinical factors.

**Methods:** We analyzed data from HIV Outpatient Study (HOPS) participants seen at nine U.S. HIV clinics from January 1, 2000 to September 30, 2017, with ≥2 HOPS encounters. Incident fracture rates and mortality after fracture were compared, adjusted by age, sex, and calendar period: 2000-2004, 2005-2008, 2009-2012, and 2013-2017. We used Cox proportional hazards analyses to determine factors associated with all-cause mortality for all participants and for the subset with incident fracture.

**Results:** Among 6,826 HOPS participants followed for a median of 6.2 years, 502 (7%) had incident fracture recorded and 729 (10%) had died. Of 502 fractures, 97 were major osteoporotic (hip, wrist, spine, shoulder) and 405 were not (47 site unknown). Median age at fracture was 48 years (interquartile range 41-55 years). Of patients, 16.5% with major osteoporotic fractures died (crude mortality 1.5 per 100 person-years [py]), while 14.6% with fractures at other sites died (crude mortality 1.3 per 100 py). Age- and sex-adjusted fracture rates per 100 py increased from 0.99 during 2000-2004 to 1.2 during 2013-2017 (p=0.037 for trend), and all-cause mortality rates per 100 py among those with incident fracture decreased from 8.5 to 1.9 (p=0.001 for trend), (Figure 1a and 1b, respectively). In multivariable analysis, incident fracture was significantly associated with all-cause mortality (Hazard Ratio 1.5, 95% confidence interval 1.2-1.9) as were multiple other factors, notably nadir CD4+ cell count < 200 cells/mm3, non-AIDS cancer, hepatitis C infection, and chronic liver, renal, and cardiovascular disease comorbidity. Among the 502 patients followed after incident fracture, chronic renal disease and hepatitis C infection remained independently associated with all-cause mortality.

**Conclusion:** Incident fracture increased the risk of all-cause mortality by 50 percent among U.S. PLWH in care, underscoring the need for BMD screening and fracture prevention among at-risk patients. Although fracture rates among PLWH increased during follow-up, death rates after fracture decreased, coincident with advances in HIV care.

**Figure 1a:** Fracture rates per 100 person-years by calendar period, adjusted by sex and age group, HIV Outpatient Study, 2000-2017, N=6,826

**Figure 1b:** Mortality rate per 100 person-years by calendar period among those with incident fracture, adjusted by sex and age group, HIV Outpatient Study, 2000-2017, N=6,826

### 31 COPD AND THE RISK FOR MYOCARDIAL INFARCTION BY TYPE IN PEOPLE LIVING WITH HIV

**Kristina Crothers**1, Barbara N. Harding1, Bridget M. Whitney1, Joseph Delaney1, Robin M. Nance1, Susan Heckbert2, Matthew Buddoff3, W. C. Mathews3, Joseph J. Eron4, Richard D. Moore5, Michael J. Mugavero6, Michael Saag6, Mari Kitahata7, Heidi M. Crane1, for the CNICS Cohort

**Background:** People living with HIV (PLWH) are at increased risk for chronic obstructive pulmonary disease (COPD) compared to uninfected persons, in whom COPD is a known risk factor for cardiovascular disease such as myocardial infarction (MI). However, the relationship between COPD and MI in PLWH is less well understood. MIs have been classified into types including type 1 (TIMI, atherothrombotic coronary plaque rupture) and type 2 (T2MI, supply-demand mismatch as with sepsis), with a much higher proportion of T2MI in PLWH than the general population. We hypothesized that COPD would be associated with increased MI risk among PLWH, particularly for T2MI.

**Methods:** We utilized data from six sites in the CFAR Network of Integrated Clinical Systems (CNICS) cohort. MIs were centrally adjudicated by two reviewers (3 if discrepancies) and also categorized by type and cause of T2MI. COPD was defined based on an algorithm we previously validated against spirometry requiring COPD diagnosis codes and ≥90-day continuous supply of long-acting COPD controller medications. Time to MI was assessed using Cox proportional hazards models. Models were adjusted for baseline age, sex, race/ethnicity, HIV viral load, nadir CD4 count, diabetes, hypertension, statin use, and CNICS site. We subsequently examined whether associations were attenuated by adjustment for smoking status (ever vs. never), as this was potentially an important confounder.

**Results:** In total, 25,509 PLWH were included, of whom 423 met our definition of moderate-to-severe COPD. There were 698 PLWH who had MIs (339 T1MI [54%], 294 T2MI [46%]). COPD was associated with a significantly increased risk of MI [adjusted hazard ratio (aHR) 2.09 (95%CI 1.50-2.91)] even after adding...
smoking [aHR 1.88 (95%CI 1.34-2.63)]. COPD was significantly associated with T1MI and T2MI in unadjusted analyses, but only T2MI in adjusted analyses, and this was only minimally attenuated by smoking (Table); this association was particularly notable for T2MI due to sepsis/bacteremia.

Conclusion: COPD is independently associated with an increased risk for MI in PLWH, particularly T2MI in the setting of sepsis/bacteremia. COPD severity, inadequate disease control and/or exacerbations can contribute to supply-demand mismatch, and COPD increases risk for pneumonia, a common cause of sepsis. Further investigation is required to understand mechanisms for this association and to optimize preventative and therapeutic strategies.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All MI</td>
<td>2.08 (1.50-2.81)</td>
</tr>
<tr>
<td>Type 1 MI</td>
<td>1.50 (0.98-2.35)</td>
</tr>
<tr>
<td>Type 2 MI</td>
<td>1.61 (0.61-2.70)</td>
</tr>
</tbody>
</table>

**HIV POST SCD STUDY: 80% HIGHER RATE OF AUTOPSY-DEFINED SUDDEN ARYTHMIC DEATH IN HIV**

Zian H. Tseng, Ellen Moffat, Eric Vittinghoff, Annie Bedigian, Joseph K. Wong, Philip Ursell, Andrew Connolly, Jeffrey Olgin, Priscilla Hse

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

**Background:** Persons living with HIV have higher rates of CVD including acute MI, heart failure, and our group first reported high rates of out-of-hospital presumed sudden cardiac death (SCD) using World Health Organization (WHO) criteria. However, the precise incidence of actual sudden arrhythmic deaths (SAD) in HIV remains unknown.

**Methods:** Between 2011 to 2016, we prospectively identified all incident deaths attributable to out-of-hospital cardiac arrest among individuals with and without HIV aged 18-90 in SF County for medical record review and comprehensive autopsy, toxicology, and histology via medical examiner surveillance of consecutive out-of-hospital deaths. Autopsy-defined SAD had no extracardiac cause of death or acute heart failure. Final cause was adjudicated by a committee of pathologists, cardiologists, HIV clinicians, and electrophysiologists.

**Results:** 126 out-of-hospital HIV-infected deaths were identified, and 47 of these met WHO SCD criteria. The mean age was 65.6 years, 94% male, and 57% white. Compared to uninfected WHO-defined (presumed) SCDs (N=50), SCDs with HIV were more likely to have a history of MI, psychiatric disorder, cigarette smoking, and substance abuse. Similar to the general population, about half of WHO-defined SCDs in HIV were autopsy-defined SADs; the remainder were non-cardiac and included 16 due to occult overdose. Presumed SCDs with HIV were more likely to be due to occult overdose (13% vs 34%, p<0.0001) and renal failure (1% vs. 6%, p=0.003) as compared to uninfected presumed SCDs. Adjusted incidence ratios for WHO (presumed) SCD and autopsy-defined SAD were both significantly higher in HIV (IRR 1.82, 95%CI 1.4-2.4, p<0.0005 and IRR 1.83, 95%CI 1.2-2.8, P=0.006, see Figure). After adjustment for age, gender, heart disease and CAD, SCDs with HIV had 60% higher interstitial fibrosis by myocardial triochrome staining compared to uninfected SCDs.

**Conclusion:** In this countywide postmortem study, 1/3 of apparent SCDs in HIV over a 5-year period were due to occult overdose. However, adjusted rates of both presumed SCDs and autopsy-defined SAD were 82% and 83% higher respectively in HIV compared to the uninfected population. Higher levels of cardiac fibrosis in HIV, a known substrate for SAD in the general population, may underlie the mechanism by which HIV increases risk for SAD. Development of criteria and evaluation for implantable defibrillators should be carefully considered in HIV as a means to prevent SAD in this high-risk population.

**SUDEN CARDIAC DEATH AMONG HIV-INFECTED AND -UNINFECTED VETERANS**

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1Vanderbilt University, Nashville, TN, USA, 2University of California San Francisco, San Francisco, CA, USA, 3Yale University, New Haven, CT, USA

**Background:** We have reported HIV infection as a risk factor for sudden cardiac death (SCD) in San Francisco County, but to date this association has not been examined in larger populations using chart-reviewed events. Here we examine the association between HIV infection and SCD in a large, national, cohort of HIV infected (HIV+) and uninfected veterans.

**Methods:** We analyzed data on 144,362 Veterans (30% HIV+) from the Veterans Aging Cohort Study, a prospective study of HIV+ veterans and age, sex, race/ethnicity and clinical site matched uninfected veterans. We followed veterans from their first clinical encounter on or after 4/1/2003 until SCD, non-SCD death, or censoring on 12/31/2014. Sudden cardiac death was determined using death certificates and manual review of the VA electronic health record (EHR). To meet our SCD definition, participants had to have cardiac cause of death on their death certificate. SCD was excluded for deaths in a hospital, hospice, or nursing home, or due to accidents, overdose, suicide, or homicide. SCD was also ruled out if in the year prior to death, EHR review revealed metastatic cancer or active treatment for cancer, use of high flow oxygen or dialysis, an AIDS defining illness, CD4<50 cells/mm3 within 6 months before death, DNR/DNI, a new significant health condition one month before death, or a life altering event within one year if this event resulted in an end stage disease or severe disability. We calculated rates of SCD by HIV status and used Cox proportional hazards regression to model the association between HIV infection and SCD, adjusting for demographics, prevalent cardiovascular disease, SCD risk factors, and possible confounders. In secondary analyses we compared SCD incidence in HIV+ subgroups defined by time-updated viral load and CD4 cell count to HIV uninfected veterans.

**Results:** Participants had a mean age of (50±10.7 years), were mostly male (97.2%) and African American (47.3%) and were followed for a median of 9.0 years. After adjustment for demographics, prevalent cardiovascular disease, SCD risk factors, and other possible confounders, HIV+ veterans had a 14% higher risk of SCD (hazard ratio=1.14, 95% confidence interval 1.04-1.25) compared to uninfected veterans. The risk was highest among those with sustained high HIV viral loads or low CD4 cell counts (Table).

**Conclusion:** HIV infected people have an increased risk of sudden cardiac death compared to uninfected people when they have sustained unsuppressed HIV viremia or low CD4 cell counts.
CABOTEGRAVIR IS NOT ASSOCIATED WITH WEIGHT GAIN IN HIV-NEGATIVE INDIVIDUALS: HPTN 077


Center, Seattle, WA, USA, 3Institute Nacional de Infectologia Evandro Chagas (INI/Fiocruz), Rio de Janeiro, Brazil, 4University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 5University of Arizona–Tucson, Durham, South Africa, 6George Washington University, Washington, DC, USA, 7San Francisco Department of Public Health, San Francisco, CA, USA, 8Chris Hani Baragwanath Hospital, Johannesburg, South Africa, 9University of North Carolina Project–Bethesda, MD, USA, 10University of Texas at Houston, Houston, TX, USA, 11NIH, Rockville, MD, USA

Background: In people living with HIV, ART treatment with regimens containing integrase inhibitors (INIs) has been associated with weight gain and increased waist circumference, raising concerns about possible future risk for metabolic and cardiovascular disease. These changes have been associated with female sex, non-white individuals, and those with higher baseline BMI.

HPTN 077, a Phase 2a randomized placebo-controlled study of two dose/dose-interval regimens of cabotegravir, enrolled HIV-uninfected participants from 3 sites in the US (4), Brazil (1), and sub-Saharan Africa (3). 199 participants were enrolled and randomized 3:1 to active CAB or placebo and received oral CAB 30mg or placebo (PBO) QD x 4 weeks, a one-week washout, and then sequential injections of CAB LA or 0.9% saline PBO from Week (W) 5 through W41.

Methods: We measured weight at study entry (W0), during oral study product administration (W2, W4), and during injectable study product administration (W5, 17, 19, 29/33, and 41). Age, race/ethnicity, sex at birth, injectable dosing schedule, smoking status, and BMI were assessed at baseline. Longitudinal models fitted via generalized estimating equations (GEE) were used to assess marginal cohort, smoking status, and BMI were assessed at baseline. Longitudinal models fitted via generalized estimating equations (GEE) were used to assess marginal effects of study arm on weight over time. Wilcoxon rank sum tests were used to compare medians of numeric variables and chi-square tests were used to compare frequencies of categorical variables.

Results: The table shows median weights at W0 and W41 overall, and changes from baseline (W0-W41) by covariates of interest. Mean changes were compared between arms with baseline & week 25/26 sCD14 measurements, remained on study product through week 26 with >50% adherence, no use of prohibited medications, and did not experience inflammatory conditions, receive vaccines, or have concurrent illness.

Table: Demographics and Weight/Height Change for HPTN 077 participants who had at least one injection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall</th>
<th>CAB</th>
<th>PBO</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35 (25, 45)</td>
<td>35.0 (25.0, 45.0)</td>
<td>35.0 (25.0, 45.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>68 (39%)</td>
<td>68 (39%)</td>
<td>39 (21%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Non-Hispanic White</td>
<td>71 (40%)</td>
<td>71 (40%)</td>
<td>39 (21%)</td>
</tr>
<tr>
<td>BMI</td>
<td>23.5 (20.5, 29.0)</td>
<td>23.5 (20.5, 29.0)</td>
<td>23.5 (20.5, 29.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>89.7 (79.3, 109.2)</td>
<td>89.7 (79.3, 109.2)</td>
<td>89.7 (79.3, 109.2)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Conclusions: In this moderately sized global cohort of 199 HIV-uninfected males and females, there was no difference in weight change for participants receiving CAB compared to PBO-treated participants. Although structurally similar to dolutegravir, CAB may have different effects on weight/weight gain, or the interaction between HIV-infection and ART treatment may be an important contributor to observed weight gain as part of ART.
these changes were not statistically different (p=0.60). Similarly, there were no significant differences in changes in D-dimer, KT ratio, CD4 cell counts, CD4/CD8 ratio between the arms. 

Conclusion: Visbiome E5 was safe and well tolerated among this cohort. No significant effect of Visbiome E5 on systemic inflammatory markers was identified. While high loss to follow up in the placebo arm limits the strength of our conclusions, these results do not support Visbiome E5 as a viable strategy to reduce systemic inflammation in suppressed PWH with preserved CD4 counts.

36 FACTOR X INHIBITION REDUCES COAGULATION BUT NOT INFLAMMATION IN PERSONS WITH HIV

Jason V. Baker1, Julian Wolfson2, Tess Peterson3, Kelly Garcia-Myers4, Jonathan Klaphake1, Micah Mbooberry1, Matthew Gissel4, Kathleen Brummel-Ziedins5, Irini Sereti1, Nigel Key1, Russell Tracy4

1Hennepin Healthcare Research Institute, Minneapolis, Minnesota, 2University of Minnesota, Minneapolis, MN, USA, 3University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 4University of Vermont, Rochester, VT, USA, 5VIRAD, Bethesda, MD, USA

Background: Activation of coagulation among persons with HIV is associated with a broad spectrum of end-organ disease risk, but the underlying pathogenesis is not well characterized. We hypothesized that hypercoagulation contributes to disease, in part, via upregulation of inflammatory pathways, in addition to direct effects from thrombogenesis.

Methods: Treatment effects of oral edoxaban (30mg), a direct factor Xa inhibitor, versus placebo were investigated in a randomized, double-blind, cross-over clinical trial, among participants with HIV receiving ART with plasma HIV RNA <200 copies/mL and D-dimer levels ≥100 ng/mL. Blood specimens were collected twice prior to receiving study drug and then monthly during each 4-month cross-over treatment period. Soluble biomarkers (Table) were measured using ELISA, electrochemiluminescence, and immunoturbidimetric methods. The treatment effect, defined as change on edoxaban versus change on placebo, was calculated with linear mixed models for biomarkers (in-transformed) and clinical labs (untransformed).

Results: Forty-four participants were randomized among 83 screened; 40 completed the first period and 37 completed the second period. Mean age was 49 years and CD4+ cell count was 739 cells/µL; 91% were male, 70% white, 36% current smokers, 34% with prior AIDS, and 70% had an integrase inhibitor-based ART regimen. Table 1 reports the treatment effect of edoxaban versus placebo on soluble biomarkers. Edoxaban treatment demonstrated a consistent reduction in coagulation activity; relative changes were -42% for D-dimer, -26% for TAT, and 7% for INR. There was no evidence of a significant treatment reduction in coagulation activity; relative changes were -42% for D-dimer, -26% for TAT, and 7% for INR. There was no evidence of a significant treatment reduction in coagulation activity; relative changes were -42% for D-dimer, -26% for TAT, and 7% for INR. There was no evidence of a significant treatment reduction in coagulation activity; relative changes were -42% for D-dimer, -26% for TAT, and 7% for INR.

Conclusion: The oral direct factor Xa inhibitor edoxaban substantially reduced coagulation activity among persons with HIV receiving ART with viral suppression. In this study, no effect on soluble systemic inflammatory markers was observed and there was an increased risk for minor bruising and bleeding events.

<table>
<thead>
<tr>
<th>Table 1:</th>
<th>Recombinant Edoxaban (P-value)</th>
<th>Recombinant Placebo (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8 (pg/mL)</td>
<td>0.08 (0.97)</td>
<td>0.08 (0.94)</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
<td>0.04 (0.07)</td>
<td>0.04 (0.08)</td>
</tr>
<tr>
<td>vWF:Ag (mg/mL)</td>
<td>130 (228)</td>
<td>137 (228)</td>
</tr>
<tr>
<td>SCID14 (ng/mL)</td>
<td>689 (426)</td>
<td>585 (247)</td>
</tr>
<tr>
<td>TAT (pM)</td>
<td>1.2 1 (2.65)</td>
<td>1.9 (1.47)</td>
</tr>
<tr>
<td>D-dimer (ng/mL)</td>
<td>17.9 (15.12)</td>
<td>11.9 (15.12)</td>
</tr>
<tr>
<td>INR</td>
<td>1.08 (0.08)</td>
<td>1.05 (0.08)</td>
</tr>
<tr>
<td>Haptoglobin (g/dL)</td>
<td>1.78 (0.06)</td>
<td>1.70 (0.06)</td>
</tr>
<tr>
<td>Platelets (10^9/µL)</td>
<td>258.9 (58.3)</td>
<td>236.0 (54.9)</td>
</tr>
</tbody>
</table>

Fold Change in IL-6 (pg/mL) | +2.5 (2.5) | +2.1 (2.1) |
Fold Change in SCID14 (pg/mL) | +3.4 (3.4) | +3.0 (3.0) |

37LB SAFETY, TOLERABILITY AND IMMUNOLOGIC ACTIVITY OF RUXOLITINIB ADDED TO SUPPRESSIVE ART

Vincent C. Marconi1, Carolee Mose1, Christina Gavegnano1, Athi Sitisri1, Amy Kantor1, Edgar O. Verteron1, Charles W. Flexner2, Peter W. Hunt3, Raif-Pierre Sekaly4, Carlos del Rio5, Michael M. Lederman6, Randall Tressler7, Steven G. Deeks1, Jeffrey J. Lennox8, Raymond F. Schinazi9

1Emory University, Atlanta, GA, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3Harvard Medical School, Boston, MA, USA, 4University of Alabama at Birmingham, Birmingham, AL, USA, 5Johns Hopkins University School of Medicine, Baltimore, MD, USA, 6University of California San Francisco, San Francisco, CA, USA, 7Case Western Reserve University, Cleveland, OH, USA, 8NHR, Bethesda, MD, USA

Background: Chronic inflammation is associated with end-organ disease and mortality for people living with HIV (PLWH). Ruxolitinib (RUX) is a Janus kinase (Jak) 1/2 inhibitor that reduced biomarkers of systemic inflammation in HIV-infected individuals, and HIV reservoir and persistence markers ex vivo. The goal of this trial was to determine the safety and efficacy of RUX in treated HIV disease.

Methods: ACTG 5336 was an open-label, multi-site, randomized controlled trial of RUX (10 mg BID) for 5 weeks plus continuing ART versus ART alone. Eligible participants were suppressed on ART for > 2 years, CD4+ T cells >350 cells/µL, and had no current diagnosis or history of significant medical comorbidities. Primary tolerability and safety outcomes were premature RUX discontinuation and occurrence of any pre-defined safety event. Mean changes in plasma levels of IL6 (primary efficacy outcome), SCID14, and circulating CD4 and CD8 counts were compared between arms with t-tests. Plasma HIV-1 RNA levels were measured by integrase single copy assay (ISCA) with a limit of detection of 0.4 cpm. GEE models for binary data compared changes between arms.

Results: Sixty participants enrolled (80% men, median age 44 yrs and CD4 count 737 cells/µL; n=40 RUX and n=20 ART alone). Primary safety events occurred in 2.5% in RUX arm and 0% in control arm (Fisher’s, p=0.67). Three participants prematurely discontinued RUX due to participant request, unrelated syncope, and a grade 3 increased AST. At week 4/5, there was a non-significant decrease in IL6 in the RUX arm compared to control arm (mean fold change (FC) 0.93 vs 1.00, p=0.18), but a significant decrease in SCID14 in the RUX vs control arm (mean FC 0.97 vs 1.10, p=0.03). Those on RUX had a similar likelihood of iSCA < 0.4 cpm compared to control (relative risk = 0.9, p=0.94). In the RUX arm, CD4 and CD8 cell counts increased significantly at week 2 (mean Δ 131 and 162 cells/µL) and compared to control arm (p=0.01); at week 5, CD4 counts returned to baseline while CD8 counts remained elevated in the RUX arm.

Conclusion: In a highly selected cohort of HIV-positive adults on suppressive ART, RUX was safe and well tolerated but did not significantly reduce IL6 levels. On RUX treatment there was a modest decrease in IL6 with an increase in circulating T cells through mechanisms undefined. This proof-of-concept trial provides a rationale for future studies of Jak inhibitors in PLWH who have residual inflammation or immune dysfunction despite long-term suppressive ART.

38LB WITHDRAWN / INTENTIONALLY UNASSIGNED

39LB RANDOMIZED TRIAL OF RALTEGRAVIR-ART VS EFAVIRENZ-ART WHEN INITIATED DURING PREGNANCY

Mark Mirochnick1, David E. Shapiro2, Leavitt Morrison1, Lisa Frenkel1, Nahida Chakhtoura3, George K. Siberry2, Brooke Best3, Maria Leticia S. Cruz4, Blandina T.
Background: There are no randomized trial data comparing the efficacy and safety of antiretroviral therapy (ART) containing an integrase inhibitor with efavirenz (EFV) when initiated during pregnancy. Methods: NICHD P1081 is a Phase IV multicenter, randomized, open-label trial comparing HIV virologic response (plasma HIV viral load <200 copies/mL near delivery), tolerability (remaining on study drug through delivery), and safety (maternal and infant adverse event (AE) grade ≥3) of ART when initiated during pregnancy. ART-naïve pregnant women with HIV were randomized to raltegravir (RAL)- or EFV-based ART through delivery. Enrollment began in Sept 2013 for women 28 to <37 weeks (wks) gestation (gest), was expanded to 20 to <37 wks gest after 22% were enrolled, and was completed in Feb 2018. Women and their infants were followed through 24 wks post-delivery. The randomization and primary statistical comparisons were stratified by gest age at entry.

Results: 408 pregnant women (206 RAL arm, 202 EFV arm) were enrolled at 19 sites in South America (n=210), Africa (n=114), Thailand (n=47) and the US (n=7), 205 (50%) at 20 to <28 wks and 203 (50%) at 28 to <37 wks. In the primary efficacy subgroup (n=307 with no HIV genotypic resistance to study ART at entry), a larger proportion of women in the RAL arm vs. EFV arm had delivery viral load <200 copies/mL (94% vs. 84%; p=0.01), mainly among those enrolled at ≥28 wks gest (interaction p=0.04); results were similar after including women with HIV genotypic resistance to study ART at entry (n=362, Table, interaction p=0.60). Viral load decline was greater in RAL arm at study wks 2, 4 and 6 (Wilcoxon p<0.05). Both regimens were well tolerated (Table). A larger proportion of RAL arm women achieved a rapid, sustained viral load reduction while staying on study drug until delivery, mainly by achieving a rapid viral load decline by study wk 2 (Table). There were no significant differences in occurrence of AE grade ≥3 among women or infants, stillbirth, or preterm birth (Table). One RAL infant and 4 EFV infants were HIV infected (Fisher exact p>0.05).

Conclusion: Both regimens were well tolerated in women initiating ART during pregnancy. Viral load reduction with RAL-ART was faster leading to more women with delivery viral load <200 copies/mL. These data from the first large randomized trial comparing an integrase inhibitor with EFV-ART initiated during pregnancy support the use of RAL-ART during pregnancy, especially for women starting ART late in gestation.

**Table**

<table>
<thead>
<tr>
<th>RAL arm</th>
<th>EFV arm</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery virologic load &lt;200 copies/mL†</td>
<td>57/123 (46%)</td>
<td>151/279 (54%)</td>
</tr>
<tr>
<td>Enrolled 20 to &lt;37 weeks</td>
<td>85/94 (90%)</td>
<td>87/98 (89%)</td>
</tr>
<tr>
<td>Enrolled 28 to &lt;37 weeks</td>
<td>36/40 (90%)</td>
<td>31/36 (86%)</td>
</tr>
<tr>
<td>Rapid, sustained virologic response (MAR) and remained on study drug through delivery (considers the next 3 wks)</td>
<td>55/99 (56%)</td>
<td>52/98 (53%)</td>
</tr>
<tr>
<td>Virologic load &lt;100 copies/mL at time points after wk 4</td>
<td>51/92 (56%)</td>
<td>49/93 (53%)</td>
</tr>
<tr>
<td>Maternal adverse event grade ≥3, any wk and 24 wk after delivery*</td>
<td>58/200 (29%)</td>
<td>66/202 (32%)</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 gestation weeks)</td>
<td>2/106 (2%)</td>
<td>1/103 (1%)</td>
</tr>
<tr>
<td>Infant adverse event grade ≥3, any wk and 24 wk after delivery*</td>
<td>1/79 (1%)</td>
<td>2/78 (2%)</td>
</tr>
</tbody>
</table>

*For all women who received at least one dose of study drug and remained on study through delivery.
†Secondary composite outcome for all women in the primary virologic response and tolerability analyses with a viral load result at study week 1 (days 22-28), 4 (days 31-37) and last visit before subsequent VL result after study week 4.
‡For all women who received at least one dose of study drug; for live-born infants delivered on-study.

**Figure**: Kaplan-Meier plots of time from randomization to virologic load <50 copies/mL (primary endpoint) and <100 copies/mL (delayed virologic rebound) for each of the major treatment groups; the median time from randomization to delivery is also shown in the top right graph.
Methods: HPTN 046 was a randomized controlled trial of HIV MTCT which evaluated 6 months of infant nevirapine vs placebo for HIV prevention. Mather-infant pairs were enrolled in sub-Saharan Africa from 2007–2010; 1579 women (78%) also received ART. Maternal samples were retrospectively tested for hepatitis B surface antigen (HBsAg) and, if positive, were tested for hepatitis B and/or antigen (HBsAg) at study entry and HBV viral load (VL) at delivery. Women who were HBsAg positive were classified as HIV–HBV co-infected (HIV–HBV). High HBV Vl was defined as \(>10^4\) IU/mL. The impact of HIV-HBV coinfection on HIV MTCT, low birth weight (LBW), infant mortality and maternal premature rupture of membranes and C-section was assessed using multivariable (MV) logistic and Cox regression.

Results: Among 2057 HIV-infected (HIV) women, 88 (4.3%) were HIV-HBV. HIV–HBV women had high HBV VL as low median CD4 T-cell count at study entry, when compared to HIV+/HBV- women or HIV–HBV women with HBV VL < \(10^4\) IU/mL (320, 490, and 434 cells/μL, respectively (p<0.007)). In MV analysis, adjusted for maternal CD4, age, and maternal ART, infants born to women with high HBV VL were more likely to be low birth weight (LBW), compared to HIV–+ HBV- and HIV low VL women: [30% (3/10) vs 10% (194/1953) vs 6% (5/78), respectively, p=0.03]). In a dose response analysis, HBV VL greater than 10^4 IU/ML was associated with LBW [RR=6.1 (95% CI 1.31 - 28.39)]. HIV MTCT occurred in 2/10, 0/78, and 53/1953 high HBV VL, low HBV VL, and HIV+/HBV – women, respectively, p=0.03). In a dose response analysis, HBV VL greater than 10^4 IU/ML was associated with LBW [RR=6.1 (95% CI 1.31 - 28.39)]. HIV MTCT occurred in 2/10, 0/78, and 53/1953 high HBV VL, low HBV VL, and HIV+/HBV – women, respectively, p=0.03). In a dose response analysis, HBV VL greater than 10^4 IU/ML was associated with LBW [RR=6.1 (95% CI 1.31 - 28.39)].

Conclusion: In HIV/HBV coinfected women, HBV replication increases the risk for poor infant outcomes including LBW and potentially HIV MTCT. Reduction of antepartum HBV viremia may have beneficial effects beyond the prevention of HIV MTCT in HIV/HBV coinfection.

42 IMPACT OF IMPROVED NUTRITION/SANITATION ON NEURODEVELOPMENT OF HIV-EXPOSED CHILDREN

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Background: HIV-exposed children may be at risk of impaired early child development (ECD), but preventive interventions are currently limited. Methods: We conducted a 2x2 factorial cluster-randomized trial of improved infant and young child feeding (IYCF) and improved water, sanitation and hygiene (WASH) in rural Zimbabwe (ClinicalTrials.gov NCT01824940). Pregnant women were eligible if they lived in study clusters randomized to standard-of-care (SOC; 52 clusters); IYCF (20g Nutributter®/day for infants from 6–18mo, complementary feeding counseling; 53 clusters); WASH (pit latrine, 2 hand-washing stations, liquid soap, chlorine, play space, hygiene counseling; 53 clusters); or (IYCF+WASH; 53 clusters). A sub-study evaluated ECD outcomes at 2 years of age among HIV-exposed children using the Malawi Developmental Assessment Tool (MDAT; assessing motor, cognitive, language and social development); MacArthur-Bates Communication Development Inventory (CDI) (assessing vocabulary and grammar); A-not-B test (assessing object permanence); and a self-control task. Masking of participants/fieldworkers was not possible. Analysis was by intention-to-treat using unadjusted and adjusted generalized estimating equations.

Results: 726 HIV-positive pregnant women were recruited. Mean (SD) CD4 count was 473 (221) cells/μL. Among 738 HIV-exposed live births (additional 12 from twin pregnancies), 323 children from 142 clusters had ECD assessments (68 from 31 SOC clusters; 68 from 40 IYCF clusters; 83 from 33 WASH clusters; 104 from 38 IYCF+WASH clusters). 300 children were HIV-exposed uninfected, 6 were HIV-positive and 17 had an unknown HIV status. Compared to SOC, children randomized to combined IYCF+WASH had higher MDAT scores (+4.6; 95%CI 1.9, 7.2), but there was no evidence of impact of IYCF or WASH alone. There was no evidence of an impact of either intervention on object permanence or self-control.

Conclusion: Combining IYCF and WASH interventions significantly improved motor and cognitive development in HIV-exposed children at 2 years of age.

43 UNIQUE IMMUNOLOGICAL AND VIROLOGICAL FEATURES OF EARLY TREATED HIV-INFECTED NEWBORNS

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Background: Studying HIV-1 infection in neonates with a developing immune system may offer unique opportunities for understanding viral reservoir establishment and exploring eradication strategies. The Early Infant Treatment (EIT) project in Botswana provides antiretroviral therapy (ART) to newborn HIV-1-infected infants, and longitudinally evaluates virological and immunological parameters.

Methods: Serial PBMCs were collected from 10 infants with neonatal HIV-1 infection who started ART within 72 hours (n=9) or 31 days (n=1), after birth, and were followed for 84–96 weeks (w). PBMCs collected cross-sectionally to 10 infants after a median of 93 w (range: 65–127) of ART started at a median of 119 days (range: 79–350) after birth were used as controls; PBMCs from HIV-1 negative infants (n=22) at 12w of life from Botswana were also analyzed. HIV-1 DNA was analyzed by near full-length single-genome sequencing, paired with corresponding chromosomal integration site analysis. Multiparametric flow cytometry was used to quantify phenotypic characteristics of innate and adaptive immune cells.

Results: Compared with control children, EIT infants had lower total (5.3 vs 9814, p<0.0001), intact (0.35 vs 2.4, p=0.006), and defective (1.9 vs 25.6, p=0.003) HIV-1 DNA copies (10^11 copies PMBCs 84-96w on ART). Intact proviral full-genomes represented an average of 54.3% of all sequences at baseline, compared with 3.9% at 84-96w on ART among EIT infants. Integration sites of 24 intact proviruses (determined at w0) were predominantly (71%) located in genes, with a preference for a configuration in the same orientation as host transcripts (65%); a similar distribution was noted for integration sites of defective proviruses. Proportions of mature CD56+CD16+ NK cells were significantly increased in EIT infants at 12w on ART relative to healthy infants (p=0.035); by contrast, the more immature CD56-CD16+ NK cells were not reduced compared to controls (p=0.0031) and healthy infants (p=0.0006).

HIV-1 specific CD8 T cells in EIT infants were weak in magnitude but displayed a polyfunctional profile. In a longitudinal analysis among EIT infants, positive correlations were found between total HIV-1 DNA copies and activated CD8+HLADR+ effector memory and terminally-differentiated CD8 T cells.

Conclusion: Immediate initiation of ART during neonatal HIV-1 infection is associated with a remarkably reduced viral reservoir, a prematurely-expanded
CD56+CD16+ NK subset and a weak but polyfunctional HIV-1-specific CD8 T cell response.

44  **NEONATAL ART < 7 DAYS VS 7-28 DAYS REDUCED TIME TO SUPPRESSION**

Alfredo Tagarro1, Sara Dominguez Rodriguez2, Thanyawee Puthanakit3, Paolo Palma4, Caroline Foster5, Thidarat Jupimai6, Nicola Cotugno7, Jintanat Ananworanich8, Santiago Jimenez de Ory9, Paola Zangari10, Maria Luisa Navarro10, Paolo Rossi10, Eleni Nastuoli11, Carlo Giaquinto12, Pablo Rojo Conejo13, for the EPIICAL Consortium

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**Background:** Early antiretroviral therapy (ART) in children is associated with better clinical and virological outcome. Few data are available about long-term outcome of children starting ART in the neonatal period. Our hypothesis is that HIV-perinatally infected neonates initiating ART within <7 days of life have a better long-term clinical and virological response than neonates treated ≥7 days and ≤28 days of life.

**Methods:** 44 children with perinatal HIV aged ≥28 days at start of ART were included from 4 cohorts (11% UK, 52% Spain, 7% Italy, and 29% Thailand). Primary endpoints were clinical - mortality, and progression to AIDS – and virological: time to suppression, time to virological failure, and proportion of time suppressed. Data were collected up to 15-years of follow-up. Those subjects who received triple postpartum prophylaxis and subsequently transitioned to ART within 15 days were considered as starting ART from date of prophylaxis initiation. A flexible spline interval censored survival model was applied adjusting for CD4 and viral load (VL) at the start of ART.

**Results:** 57% were female and 35% preterm. Median follow-up was 11.5[IQR 8.2-15.6] years. No patient died. 84% received postpartum prophylaxis. At ART initiation, children were aged 15.5 [0.00, 24.2] days, with CD4 total 2766 [2126; 3368], CD4:CD8 2.5 [1.6; 3.1], and log10VL 4.2 [2.9; 5.2] copies/mL. 82% infants were breastfed with median breastfeeding duration 440 [272; 504] days. No differences were observed in progression to AIDS, ART switches, time to suppression, proportion of time suppressed, and progression to AIDS. However, there was a trend towards a lower risk of progression to AIDS in those treated <7 days vs 7 to 28 days.

**Conclusion:** Even among children initiating ART <28 days of age, children starting ART in the first week of life suppressed earlier. There was similar long-term clinical, virological and immunological outcomes in children treated <7 days vs. 7 to 28 days.
**BICTEGRAVI/FTC/TAF SINGLE-TABLET REGIMEN IN ADOLESCENTS AND CHILDREN: WEEK 48 RESULTS**

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**Background:** B/F/TAF, approved for adults living with HIV-1, is a single-tablet regimen (STR) containing the novel integrase strand transfer inhibitor (INSTI) bictegravir (B) 50 mg, emtricitabine (FTC) 200 mg, and tenofovir alafenamide (TAF) 25 mg. B/F/TAF has a high barrier to resistance and no food restriction. Short-term safety and pharmacokinetics (PK) of B/F/TAF in children and adolescents, reported previously, support the use of the full adult strength tablet in this population. The 48-week (W) safety and efficacy data for 6- to <18-year-olds receiving B/F/TAF are reported.

**Methods:** Virologically suppressed adolescents (12 to <18 yr) weighing ≥35 kg (Cohort 1) and children (6 to <12 yr) weighing ≥25 kg (Cohort 2) with HIV-1 RNA <50 c/ml for ≥6 months before screening and CD4 ≥200 cells/μl received B/F/TAF once daily, in a prospective, 48-week, single-arm, open-label trial. Adverse events (AEs), laboratory results, and HIV-1 RNA <50 c/ml were assessed.

**Results:** Fifty adolescents and fifty children (total n=100) were enrolled. At baseline for Cohort 2, median age was 15 yrs (range 12-17 yrs), weight 44.7 kg (range 35-123 kg), 64% female, 65% Black, median CD4 count 751 cells/μl, 90% vertically infected. For Cohort 2, median age was 10 yrs (range 6-11 yrs), median weight 29 kg (range 25-69 kg), 54% female, 72% Black, median CD4 count 930 cells/μl, and 96% vertically infected. All 100 participants (100%, 100/100) had HIV-1 RNA <50 c/ml at W24 and 98% (74/75) at W48 by US FDA Snapshot Algorithm. No participant had treatment-emergent resistance. CD4 count remained stable to W48. With a 50-week (range 20-93 wk) median duration of exposure to study drug, the only study drug-related AE reported with greater than single participant incidence was abdominal discomfort (2%, 2 participants; grade 1). One participant discontinued after W16 due to AE (grade 2 insomnia). All participants reported B/F/TAF size and shape as acceptable and taste as palatable; median percent adherence (pill counts) to study drug was high at 99% (range 80-100%).

**Conclusion:** This 48-week efficacy, safety, acceptability, and palatability data, combined with the previously reported PK data, support the use of the first, unboosted, INSTI-based STR of B/F/TAF 50/200/25 mg for the treatment of adolescents and children (6 to <18 yrs of age and weighing ≥25 kg) living with HIV-1 and prompts further pediatric studies of appropriate formulations of B/F/TAF for children weighing <25 kg.

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**INCIDENT SYphilIS RATES AND PREDICTORS IN US WOMEN WITH HIV, 2005-2016**

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**Background:** This retrospective study included women enrolled in the US CFAR Clinical Network of Integrated Clinical Systems (CNICS) Cohort with at least one HIV clinic visit between 2005 and 2016. Data were extracted from the electronic medical record and patient reported outcomes (PRO) were collected every 6 months. Incident syphilis was defined as a newly positive nonpregnancy serologic test after a previously negative test or a 4-fold increase in titer, both with positive confirmatory testing. Each year in care was analyzed separately and more than one incident syphilis infection was allowed. Univariate (UV) and multivariable (MV) logistic regression with auto-regressive correlation structure and generalized estimating equations (GEE) were used to model the incident syphilis outcome. Variables were chosen for the MV model based on prior studies, statistical significance in the UV model (p<0.05), and data completeness.

**Results:** A total of 4,795 women in the CNICS cohort were included with 27,249 woman-years in care. Median age was 47, 63% of women were Black and 75% had acquired HIV from heterosexual sex. Overall, 4219 (88%) were tested for syphilis and 119 women (2.8%) had 125 incident infections (7.6 cases per 1000 person-years). In the unadjusted model, active drug abuse, prior IDV, hepatitis C (HCV Ab+), HIV viral load >1000 copies/ml, black race and later year of entry to care predicted incident syphilis. In the adjusted model, independent predictors were prior IDV (aOR 2.3, 95% CI 1.3-3.9), HCV Ab+ (aOR 2.1, CI 1.3-3.7), later year of entry to care (aOR 2.3, CI 1.4-3.9 for 2011-2016 compared to 1994-2004), and black race (aOR 2.3, CI 1.4-3.9 compared to white). Age and HIV VL were not predictors. (see Table)

**Conclusion:** In a large national cohort of US women with HIV, history of IV drug use and hepatitis C infection were the best predictors of incident syphilis infection. Further studies are needed to determine if this association is mediated via transactional sex or high-risk sex partners. Guidelines should prioritize women with HIV and IDV for syphilis screening and the prevention of congenital syphilis.

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**Table – Predictors of Incident Syphilis Infection in CNICS US Women in HIV Care; 2005-2016**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Odds Ratio (OR) (95% CI)</th>
<th>Adjusted Odds Ratio (OR) (95% CI)</th>
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<td>Age</td>
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<td>Hepatitis B infection (HIV Ab+)</td>
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**PREPARING FOR PrEP IN ENGLAND: PREVALENCE AND INCIDENCE OF HIV AND BACTERIAL STIs**

Dana Ogaraz, Ada R. Mititz, Sarika Desai, John Saunders, Andre Charlett, Owen N. Gill, Hamish Mohammed

**Background:** In England, the recent decline in new HIV diagnoses among men who have sex with men (MSM) attending sexual health clinics (SHCs) has been attributed to HIV combination prevention including HIV pre-exposure prophylaxis (PrEP). To evaluate recent trends in HIV and STI diagnoses, we determined the prevalence of bacterial sexually transmitted infections (STIs) and annual incidence of HIV in MSM attending SHCs in England.

**Methods:** Using GUMCAD, England’s national STI surveillance system, we extracted data on HIV from (2012 to 2017) and bacterial STI (from 2017: chlamydia, gonorrhoea, and primary, secondary, early latent syphilis) diagnoses in MSM aged ≥16 years attending SHCs. Period prevalence and 95% confidence intervals (CIs) for HIV among all attendees and bacterial STIs (at least one
diagnosis in calendar period) among HIV negative attendees in 2017 were calculated. Annual HIV incidence per 100 person-years (PY) and 95% CIs in MSM who tested for HIV at least twice in the same year from 2012 to 2016 were determined. As a proxy measure of high risk, HIV incidence in a subset of MSM with a history of a negative HIV test and an ano-genital bacterial STI in the preceding year was also examined.

**Results:** In the 159,368 MSM attending SHCs in 2017, HIV period prevalence was 20.6% (95% CI 19.6-20.2%). In MSM not known to be HIV positive (n=128,772), gonorrhoea, chlamydia, and syphilis period prevalence in 2017 was 12.1% (11.9-12.2%), 9.0% (8.9-9.2%), and 2.7% (2.6-2.8%), respectively. The number of MSM not known to be HIV positive (% tested for HIV at least twice) increased from 85,500 (31.0%) in 2012 to 120,606 (36.2%) in 2016. The annual incidence of HIV in MSM decreased 60.5% from 2.0 per 100 PY (95% CI: 1.8-2.2) in 2012 to 0.79 per 100 PY (0.69-0.89) in 2016; compared to the latter, MSM meeting proxy high risk criteria in 2016 had a two-fold higher HIV incidence [1.58 (1.25-1.99) per 100 PY].

**Conclusion:** While there is a high prevalence of bacterial STIs, there has been a sharp decrease in the incidence of HIV in MSM regularly attending SHCs. The fall in HIV incidence coincides with further intensification of HIV testing, especially repeat testing, and earlier initiation of HIV treatment and, more recently, the scale up of privately purchased generic PrEP in England from late 2017. The PrEP Impact trial, which aims to enroll 13,000 participants from communities most affected by HIV, is likely to have an additional effect on the incidence of HIV.

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**EXPANDING TESTING STRATEGIES IN PARIS: A FREE POSTAL COMPREHENSIVE STI TEST KIT**

**Methods:** An innovative French government-based comprehensive STI testing program, providing free postal self-sampling kits to high-risk MSM. We present here the baseline results from the Paris area, accounting for 60% of all participants.

**Inclusion criteria:** MSM aged over 18, >2 male sex partners in the last year, HIV-seronegative without PrEP. Test kits included 1 Microtainer Serum Separator Tube, lancets for the collection of 600μl capillary blood, 1 Urine collection tube, 2 PCR Dual Swab kits and pre-paid packaging to return samples. Serum was tested for HIV-1/2 EIA 4G serology, anti-HCV antibodies, HBs antigen (Architect, Abbott) and syphilis Tp and RPR (Biopred, Biodiag), urine, throat and anal swabs were tested for Chlamydiae trachomatis (CT) and Neisseria gonorrhoeae (NG) DNA (Cobas 6800, Roche). Results were provided to the participants, as they chose, by community-based workers following text, phone or e-mail contact or by their family physician.

**Results:** From April, 10th to June, 11th 2018, 4419 applicant men from the Paris area were eligible. Median age was 30 years, 13.0% had never been tested for HIV, they reported a median of 10 partners/year. 48.5% confirmed their inclusion and ordered the kit. As of August, 31st 2018, 1238 kits were returned (3.2% of all kits). Serum was tested for HIV-1/2 EIA 4G serology, anti-HCV antibodies, HBs antigen (Architect, Abbott) and syphilis (Biopred, Biodiag), urine, throat, and anal swabs were tested for Chlamydiae trachomatis (CT) and Neisseria gonorrhoeae (NG) DNA (Cobas 6800, Roche). Results were provided to the participants, as they chose, by community-based workers following text, phone or e-mail contact or by their family physician.

**Conclusion:** This is the first randomized study comparing local progestin effect (LNG IUD) to a non-hormonal method (C-IUD) indicates no increase in gVL shedding, a proxy for sexual transmission risk, or pVL between IUDs, with or without ART use. The LNG IUD had low discontinuation rates, reflecting its value in broadening the contraceptive method mix for WLHIV.

50 **RANDOMIZED CONTROLLED TRIAL OF INTRAUTERINE DEVICE SAFETY IN WOMEN LIVING WITH HIV**

**Methods:** This double-blind trial allocated consenting WLHIV to C-IUD or LNG IUD 1:1 between October 2015 and December 2016. Eligibility included screening and treatment for reproductive tract infections (RTIs) within the past 1m, not desiring pregnancy within 2y, and either viral suppression (pVL<1000 c/ml) in the last 6m (on ART) or CD4 count above ART initiation threshold (non-ART). We tested genital tract menstrual cup samples for gVL and swabs for RTIs, and pVL at enrollment and 3, 6, 12, 18, and 24m follow-up visits. We compared detectable gVL at 6m (primary outcome) and 24m by arm with intent-to-treat (ITT) and as-treated (AT) Mantel-Haenszel Odds Ratios (OR), stratified by baseline ART use. We reported serious adverse events (SAEs) related to IUD use and compared acceptability via IUD removal rates over 24 months by arm using proportional hazards models.

**Results:** We enrolled 199 WLHIV (134 on ART/65 non-ART users; median age of 31y and 95% had > 1 prior pregnancy). 62% of non-ART users and 15% of ART users had detectable gVL at enrollment with no differences by IUD arm. There were no significant differences in detectable gVL between arms adjusting for baseline gVL and ART group at 6m (OR=1.01, 95%CI 0.53-2.02, p=0.92; ART OR=1.01, 95%CI 0.51-2.01, p=0.98) and 24m (Table). Over 24m, there were 39 SAEs (18%, n=7 related to IUD). IUD continuation was 75% overall, with 3 partial and 7 complete exclusions and 34 elective and 5 non-elective (for PID, colposcopy and pregnancy) removals by 24m. Expulsion (8% vs. 2%, p<0.001) and elective discontinuation (7.1m vs. 10.9m median time to removal, Hazard Ratio=9.00, 95% CI 3.17-25.5) were higher for C-IUD users. Common elective discontinuation reasons were dysmenorrhea/pain (40%, C-IUD and 75%, LNG IUD) and heavy bleeding (33%, C-IUD).

**Conclusion:** This first randomized study comparing local progestin effect (LNG IUD) to a non-hormonal method (C-IUD) indicates no increase in gVL shedding, a proxy for sexual transmission risk, or pVL between IUDs, with or without ART use. The LNG IUD had low discontinuation rates, reflecting its value in broadening the contraceptive method mix for WLHIV.
51 DOUBLE-DOSE LEVONORGESTREL IMPLANT DOES NOT FULLY OVERCOME INTERACTION WITH EFAVIRENZ

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Background: We previously described 57% lower levonorgestrel (LNG) exposure in women receiving the LNG subdermal implant (standard dose, 150mg) with efavirenz (EFV)-based antiretroviral therapy (ART) compared to ART-naive women. Three of 20 women (15%) had an unintended pregnancy within 48 weeks of LNG-EFV combined use, with observed LNG concentrations ≤303 pg/mL at the visit prior to pregnancy. Among women receiving LNG-EFV, 18 (90%) had any LNG concentration ≤303 pg/mL during the study. We hypothesized this interaction could be overcome by doubling the LNG implant dose. Specifically, LNG 300 mg exposure over 48 weeks in women receiving EFV-based ART would be similar to ART-naive women receiving LNG 150 mg.

Methods: This was a pharmacokinetic evaluation of double-dose (300 mg) LNG implants in Ugandan women receiving EFV-based ART with an undetectable HIV-RNA (DoubleLNG group; n=28). LNG implants, one in each arm, and a copper intrauterine device were placed at entry. Historical controls were ART-naive women on LNG 150 mg implants. Relative to our prior study, this was a larger sample size after excluding participants with contraceptive failure.

Results: Of the 28 evaluable participants in DoubleLNG, 27 (96%) had both PK results. LNG concentrations were summarized as median (IQR), and compared between groups by geometric mean ratio (GMR) with 90% CI. The proportion with LNG ≤303 pg/mL were compared by Fisher's Exact test. After 48 weeks, LNG concentrations in the DoubleLNG group were similar compared to the对照 groups.

Conclusion: We observed 33-44% lower LNG concentrations over 48 weeks in women receiving EFV-based ART plus LNG 300 mg implants compared to ART-naive women on LNG 150 mg implants. Relative to our prior study, the magnitude of the interaction with EFV at week 48 was smaller with double-dose LNG (34% lower) vs standard-dose LNG (57% lower). Also, fewer women receiving EFV-based ART had an LNG ≤303 pg/mL in the double- vs standard-dose group (46% vs 90%, respectively; p=0.002). Doubling the dose of LNG implants does not fully overcome the interaction with EFV, and the contraceptive effectiveness of this approach remains uncertain.

52 PHARMACOGNOSMICS WORSENS AN ADVERSE ANTIRETROVIRAL-HORMONAL CONTRACEPTIVE INTERACTION

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Background: We previously described higher plasma efavirenz (EFV) concentrations, respectively, after 21 days of ENG/EE given as a vaginal ring (VR). Women receiving atazanavir/ritonavir (ATV/RTV)-containing ART had 79% and 59% lower etonogestrel (ENG) and ethinyl estradiol (EE) concentrations, respectively, after 21 days of ENG/EE given as a vaginal ring (VR). Women receiving atazanavir/ritonavir (ATV/RTV)-containing ART had 79% and 59% lower etonogestrel (ENG) and ethinyl estradiol (EE) concentrations, respectively, after 21 days of ENG/EE given as a vaginal ring (VR).

Methods: In ACTG A5316 women receiving efavirenz (EFV)-containing ART had 79% and 59% lower etonogestrel (ENG) and ethinyl estradiol (EE) concentrations, respectively, after 21 days of ENG/EE given as a vaginal ring (VR).

Results: All women were Black African. The DoubleLNG group had a median age of 33 years and median weight of 58 kg; the control group was 29 years and 69 kg, respectively. The Table summarizes LNG results by visit. After 48 weeks, LNG concentrations (Figure), which persisted after adjusting for weight and/or age. CYP2B6 genotype predicted lower day 21 ENG (p=1.7E-3) and EE (p=6.7E-4) concentrations, which were related to ART modulation of pathways responsible for hormone metabolism. We studied genetic associations with ART and hormone pharmacokinetics (PK) in A5316.

Methods: In ACTG A5316 women receiving efavirenz (EFV)-containing ART had 79% and 59% lower etonogestrel (ENG) and ethinyl estradiol (EE) concentrations, respectively, after 21 days of ENG/EE given as a vaginal ring (VR). Women receiving atazanavir/ritonavir (ATV/RTV)-containing ART had 79% and 59% lower etonogestrel (ENG) and ethinyl estradiol (EE) concentrations, respectively, after 21 days of ENG/EE given as a vaginal ring (VR). Women receiving atazanavir/ritonavir (ATV/RTV)-containing ART had 79% and 59% lower etonogestrel (ENG) and ethinyl estradiol (EE) concentrations, respectively, after 21 days of ENG/EE given as a vaginal ring (VR). Women receiving atazanavir/ritonavir (ATV/RTV)-containing ART had 79% and 59% lower etonogestrel (ENG) and ethinyl estradiol (EE) concentrations, respectively, after 21 days of ENG/EE given as a vaginal ring (VR).

Results: Of the 74 evaluable participants in A5316, 72 (97%) had both PK and SNP data (n=25 controls; n=24 EFV; n=23 ATV/RTV). Of these, 35 (49%) identified as Black, 26 (36%) as Hispanic, 8 (11%) as Asian/Pacific Islander and 3 (4%) as White, with 22 (31%) CYP2B6 normal, 32 (44%) intermediate and 18 (25%) slow metabolizers. On both days 0 and 21, CYP2B6 genotype predicted EFV PK (e.g., p=4.5E-5 for day 0 log10 EFV AUC0-24h). In the EFV group, CYP2B6 genotype predicted lower day 21 ENG (p=1.7E-3) and EE (p=6.7E-4) concentrations (Figure), which persisted after adjusting for weight and/or age. Compared to controls, EFV reduced median day 21 ENG concentrations by ~75% in CYP2B6 normal and intermediate metabolizers yet by at least 93% in slow metabolizers. EFV reduced median day 21 EE concentrations by 41% in CYP2B6 normal and intermediate metabolizers, but by 75% in slow metabolizers. No other SNPs were associated with hormone or ART PK after correcting for multiple testing.

Conclusion: CYP2B6 slow metabolizer genotype worsens the adverse PK interaction of EFV with ENG and EE administered by VR, likely due to enhanced cytochrome P450 induction by higher EFV concentrations. Lower EFV dosing
based on CYP2B6 genotype may reduce, but likely not eliminate, the impact of EFV on ENG and EE PK.

54LB POINT-OF-CARE VIRAL LOAD TESTING IMPROVES HIV VIRAL SUPPRESSION AND RETENTION IN CARE

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**Background:** Achieving the 90-90-90 targets will require efficient methods to monitor people living with HIV (PLHIV) on antiretroviral therapy (ART) in resource-limited settings. We compared point-of-care (POC) viral load (VL) testing to standard laboratory VL testing for achieving VL suppression and retention in care for PLHIV in Durban, South Africa.

**Methods:** We conducted an open-label, randomized controlled trial among adults (≥18 years) enrolled 6 months after ART initiation at an urban public clinic. Participants were randomized to receive either POC VL testing (Xpert® HIV-1 VL, Cepheid) and same day counseling or standard-of-care (SOC) laboratory VL testing. All participants were followed for 12 months and received HIV-1 VL, Cepheid) and same day counseling or standard-of-care (SOC) laboratory VL testing for achieving VL suppression and retention in care for PLHIV in Durban, South Africa.

**Retention in care:** The primary outcome was retained with VL suppression (<200 copies/mL) after decentralization of ART delivery at community pharmacies 1 year after ART initiation. The primary outcome was retained with VL suppression (<200 copies/mL) after decentralization of ART delivery at community pharmacies 1 year after ART initiation. The primary outcome was retained with VL suppression (<200 copies/mL) after decentralization of ART delivery at community pharmacies 1 year after ART initiation. The primary outcome was retained with VL suppression (<200 copies/mL) after decentralization of ART delivery at community pharmacies 1 year after ART initiation. The primary outcome was retained with VL suppression (<200 copies/mL) after decentralization of ART delivery at community pharmacies 1 year after ART initiation. The primary outcome was retained with VL suppression (<200 copies/mL) after decentralization of ART delivery at community pharmacies 1 year after ART initiation. 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The primary outcome was retained with VL suppression (<200 copies/mL) after decentralization of ART delivery at community pharmacies 1 year after ART initiation.

**Results:** Among 390 participants, mean age was 33 years, 235 (60%) were female, and median CD4 count at enrollment was 468 (IQR 309-666) cells/mm3. After 12 months, 175 (45%) participants in the POC arm and 148 (38%) in the SOC arm were retained with VL suppression, an increase of 13.9% (95% CI 6.4-21.2, p=0.0004) among participants who received POC VL testing compared to those who received laboratory VL testing (Table). When disaggregated, POC VL testing increased VL suppression by 10.3% from 83.1% to 93.3% (p=0.003) and increased retention by 7.7% from 84.6% to 92.3% (p=0.003). When restricted to those with a VL result at exit, the proportion with VL suppression increased by 5.3% from 91.0% to 96.3% (p=0.05) in the POC arm. During the study, 99.5% of SOC arm participants received the VL result on the same day, while 74.7% of SOC arm participants received a VL result a median of 41 [IQR 28-69] days after blood draw. Participants in the POC arm had a 3.4-fold (95% CI 2.5-4.8) higher rate of entry into decentralized ART delivery.

**Conclusion:** POC VL testing significantly improved HIV viral suppression and retention in care in South Africa, partly by ensuring rapid receipt of VL results to PLHIV and their providers. Increasing access to POC VL testing could help to achieve the 90-90-90 targets.
Conclusion: Micro-incentives significantly increased the uptake of home-based HIV testing among men in rural South Africa and should thus be considered as a policy option where HIV testing rates are low.

55 MODULATION OF HOST INNATE IMMUNITY BY KSHV
Blossom Damania, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
Host cells sense viral infection through pattern recognition receptors (PRRs), which detect pathogen-associated molecular patterns (PAMPs) and stimulate an innate immune response. PRR activation initiates signal transduction events that ultimately result in interferon and inflammatory responses. Human tumor viruses, including Kaposi sarcoma-associated herpesvirus (KSHV), are detected by several different PRRs. KSHV, also known as human herpesvirus (HHV8), is associated with three different cancers in the human population and evasion of host immunity is intimately linked to viral pathogenesis and oncogenesis. We will discuss host immune pathways that are activated upon KSHV infection and we will describe how KSHV viral genes engage a variety of mechanisms to evade the host innate immune response.

56 EBV: IMMUNOPATHOGENESIS AND THE PATH TO AN EBV VACCINE
Jeffrey Cohen, NIAID, Bethesda, MD, USA
EBV is the principal cause of infectious mononucleosis and is associated with about 2,000 new cases of cancer worldwide each year, including epithelial cell malignancies such as gastric and nasopharyngeal carcinoma, and B cell lymphomas. EBV is associated with several malignancies in patients with HIV including Burkitt lymphoma, Hodgkin’s lymphoma, diffuse large B cell lymphoma, primary CNS lymphoma, primary effusion lymphoma, plasmablastic lymphoma, and smooth muscle tumors. No vaccine has been licensed to prevent EBV infection or disease. We have developed two EBV self-assembling nanoparticle-based vaccines that present viral glycoproteins in a symmetrical array. The first contains a bacterial ferritin conjugated to a portion of EBV glycoprotein gp350, the major target for B cell neutralizing antibody in human plasma. The second nanoparticle vaccine consists of EBV gH/gL/gp42 which are viral glycoproteins important for fusion of the EBV envelope to host cell plasma membranes and entry of the virus into cells. Nanoparticles containing gp350 induced high titers of antibodies in mice and nonhuman primates that neutralized virus infection of B cells. Most of the antibody elicited in nonhuman primates targeted the host cell receptor (CD21) binding site on gp350. Nanoparticles containing gH/gL/gp42 induced potent neutralizing antibody in mice and nonhuman primates that inhibited infection of both B cells and epithelial cells. These antibodies also blocked EBV glycoprotein-mediated fusion of epithelial cells and B cells. These EBV vaccines are promising candidates to prevent EBV infection and/or disease.

57 HPV: NEW INSIGHTS INTO ONCOGENESIS AND OPPORTUNITIES FOR IMMUNE CONTROL
Denise Galloway, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
A group of ~15 high risk human papillomaviruses (HPVs) cause nearly all cervical cancers and the majority of anal, vulvar, vaginal, penile, and oropharyngeal cancers. These cancers all express the two viral oncoproteins, E6 and E7. The E6 protein binds to the ubiquitin ligase E6AP, and targets the tumor suppressor p53, the proapoptotic Bak protein and a repressor of hTERT transcription for degradation. Through a C-terminal motif E6 binds various PDZ proteins that affect epithelial polarity. The E7 proteins bind and degrade pRB and p130, as well as histone remodeling and modifying enzymes, and CDK inhibitors. Together these activities promote genetic instability. We have been investigating additional mechanisms by which E6 and E7 cause genetic instability by impairing the response to DNA damage. Both oncoproteins, but particularly E6, impair the Homology dependent repair pathway and the Fanconi Anemia/BRCA pathway. Understanding the precise mechanisms provides new mechanisms for therapies to treat HPV associated cancers.

58 HBV: FROM VIRAL INTEGRATION TO LIVER CANCER, IMPACT ON CURE STRATEGIES
Fabien Zoulim, INSERM, Strasbourg, France
Chronic HBV infections represent a major public health problem as they are the main cause of hepatocellular carcinoma (HCC) worldwide. Viral suppression is achieved in the majority of treated patients with current antiviral approaches and is associated with a decreased risk of disease progression towards cirrhosis and HCC. However, the later risk is not eliminated. The development of HBV-induced HCC relies on multiple mechanisms: i) random integration of HBV genome into host chromosomes leading to insertional mutagenesis, ii) expression of viral proteins interfering with cellular gene expression and signaling pathways, or to chronic oxidative stress, iii) chronic liver inflammation, iv) hepatocyte death and regeneration, that may lead to clonal expansion and selection of transformed hepatocytes. Deep sequencing of HBV associated tumors have shown telomer shortening, mutations in TERT promoter and TP53. It was shown in hepatocyte culture that viral genome integration can occur very early after infection. In patients, in the so called “immune tolerance” phase, major integration events occur and are associated with clonal expansion of hepatocytes. This suggests that molecular damage of the host genome occurs even in this phase that is generally recognized as clinically benign, and that hepatocyte death and turn over occurs leading to clonal expansion. This is a strong argument for early treatment intervention to prevent integration events. Integration has also other impact on the novel cure strategies. HBsAg loss is used as a clinical endpoint of functional cure. Recent studies showed that the expression of HBsAg is mainly driven by cccDNA in HBeAg(+) patients, but mainly by integrated viral sequences in HBeAg(-) patients. Thus, this endpoint might be more difficult to reach in patients where HBsAg is mainly expressed from integrated sequences. It was also shown, that siRNA approaches targeting the extreme 3’ end of the viral transcripts may be limited by truncation of these RNAs resulting from viral genome rearrangements during the integration process. It will be also important to understand the impact of integration on circulating viral RNAs, a newly described biomarker of HBV infection, that could serve to track the pool of cccDNA and/or integration events. In conclusion, HBV integration is a molecular event involved in liver oncogenesis which may have an impact on the development of novel cure strategies and monitoring of patients.

59 UPDATE ON ANTIRETROVIRAL DRUGS AND BIRTH DEFECTS
Lynne M. Mofenson, Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA
While there are >30 antiretroviral (ARV) drugs approved for HIV therapy, there are only limited data on ARVs in pregnancy. The mean lag time from ARV approval to data availability in pregnancy is 5 years; most ARVs receive regulatory approval with only animal data to evaluate potential fetal effects. For low incidence outcomes such as birth defects, data are often only collected post-approval. To determine if a birth defect is associated with a drug or simply reflects the baseline population rate of a defect, the number of required exposures will vary based on the defect population prevalence. To rule-out >2-fold increased risk in overall defects, with 3% population prevalence, 200 early pregnancy exposures are needed, but to rule out >3-fold increased risk in a rare defect like neural tube defects (NTDs), with 0.1% population prevalence, 2000 early exposures are needed. Exposure timing is critical, as teratogenic risk is highest very early in pregnancy, before most women recognize they are pregnant, but most reports do not distinguish pre-conception from first-trimester exposure. Post-pregnancy defect reports to pharmacovigilance databases have limitations including reporting bias, case duplication, and lack of denominators. Prospective reports during pregnancy, with follow-up for birth outcome, such as the Antiretroviral Pregnancy Registry, has fewer biases. In 1998, efavirenz (EFV) was approved with a warning on use in pregnancy due to animal data showing central nervous system defects with in utero exposure in primates. Retrospective reports of NTDs in humans increased concern, leading to FDA classification of “positive fetal risk” in 2005; collection of prospective cases over the subsequent 13 years has now shown no increased NTD risk. In contrast, with dolutegravir (DTG), animal data did not raise concerns, but a well-designed prospective active surveillance study in Botswana detected a potential signal of concern for NTD with preconception DTG exposure. In contrast to the delay experienced with EFV, due to active surveillance, significant numbers of already-exposed pregnancies will be collected prospectively over the next 12 months, and with coordinated global efforts to combine additional exposures with denominator data, this signal should be able to be confirmed or refuted within a year. Continuing prospective active birth outcome surveillance is required as new ARVs are introduced into populations including women of childbearing potential.
ART OPTIONS AND TREATMENT DECISIONS FOR WOMEN OF REPRODUCTIVE POTENTIAL
Monica Gandhi, University of California San Francisco, San Francisco, CA, USA
In light of recent data on the safety of antiretrovirals in pregnancy, a review of what is known and what is not known about ART options and treatment decisions for women of reproductive potential will be undertaken. This talk will summarize guidelines for the use of ART for women of childbearing potential desiring pregnancy and during pregnancy and the data (or lack of data) behind these recommendations. Pharmacokinetic, safety, tolerability, and efficacy considerations for various ART regimens during pregnancy will be covered. The importance of involving women in decision-making around treatment options pre-conception and during pregnancy will be emphasized. Moreover, the talk will touch upon ART considerations for women of reproductive potential not desiring pregnancy and on contraception. The talk will conclude with recommendations to researchers and policy-makers on how to increase the participation of women of child-bearing potential and pregnant women in clinical trials and observational cohorts.

POLICY AND PROGRAM DECISIONS FOR ART IN WOMEN OF REPRODUCTIVE POTENTIAL
Irene Mukui, Ministry of Health, Nairobi, Kenya
Women represent 51% of persons living with HIV globally. In sub-Saharan Africa, women account for close to 60% of HIV-infected persons, a large proportion of whom are in their reproductive years. Women living with HIV have changing fertility desires and reproductive health needs and frequently become pregnant particularly with increasing access to antiretroviral therapy (ART). Making programmatic, public health, and clinical management decisions for HIV infected women requires consideration of factors that influence women, maternal and fetal health safety. HIV care and treatment programs are uniquely placed to address child bearing desires of women, provide an opportunity to prevent unwanted pregnancies by availing effective contraception, make choices for use of antiretroviral agents that minimize risk of maternal transmission of HIV, and provide optimal maternal outcomes and have minimal or no possible fetal teratogenic effects. This presentation will provide insight into public health and programmatic considerations that middle and lower income countries that manage large HIV treatment programs have to make while developing policy guidance for ART use among women of reproductive potential. These considerations include safety and efficacy of ARV agents, availability of and access to comprehensive reproductive and family planning services, the need for understanding of women’s fertility desires and reproductive health choices and the balance between individualized care versus a public health approach to program implementation. Recent safety concerns on use of dolutegravir (DTG) suggesting possible increased risk of neural tube defects in infants born to women who were taking DTG at the time of conception have brought into sharp focus and reinvigorated the discussion on the need for safety data among women of reproductive potential. In addition, many large public health programs are now faced with the realities of individualized care and choice versus public policy directives, which can present significant implementation challenges based on how sophisticated health systems are. The talk will include case studies from middle and lower income countries’ adaptation of DTG following the release of the WHO interim guidance recommending use of DTG based regimes as preferred first-line with caution on DTG use at periconception period. The presentation will also explore the involvement and role of women in policy decision making and lessons learnt.

CHALLENGES IN ANTIRETROVIRAL RESEARCH IN WOMEN OF REPRODUCTIVE POTENTIAL
Anne D. Lyerly, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
The HIV research agenda has historically been characterized as having a “vessels and vectors” orientation toward women — in other words, when included in research, women have been studied primarily in terms of their capacity to infect partners and fetuses. While progress has been made, significant evidence gaps remain due to under-representation of women, including women who become pregnant while on ARVs (and their interests) in the HIV research agenda. These evidence gaps lead to uncertainty about safety and dosing of drugs in women of reproductive potential, suboptimal or adverse outcomes for women and offspring, as well as issues of access to effective treatments and preventive. Advancing the evidence base will require addressing a range of ethical, legal and cultural challenges around research with women of childbearing potential. This presentation will highlight the importance of and ethics around conducting such research, and attend to four (of several) pressing challenges facing researchers designing research with women of childbearing potential, including: 1) assessing and managing risks and benefits to a fetus that does not yet and may never exist; 2) deciding when it is appropriate to require and/or offer access to contraception; 3) managing unexpected (or incident) pregnancies, including decisions about data collection and continuation of study drug; and 4) appropriate communication of study results, including development of guidance that is responsive to the interests and priorities of those most affected. Finally, current or evolving international consensus recommendations regarding these specific challenges will be described.

CHASING THE DRAGON: OPIATES AND HIV
Ricky N. Bluthenthal, University of Southern California, Los Angeles, CA, USA
The opioid crisis is the first truly national drug epidemic in US history. Unlike prior drug use epidemics, the opioid crisis has reached all groups regardless of demographic characteristics, economic status, or geography. HIV-related consequences of the opioid crisis include increased injection drug use (still a key risk factor for HIV transmission), increased mixing of drug using subgroups (e.g., opioid and methamphetamine use), and HIV outbreaks in remote and poorly served locales (e.g., Scott County, Indiana). In addition, increases in acute HCV are also likely to lead to elevated susceptibility to HIV transmission among people who inject drugs. Research aimed at identifying “hot spot” for HIV outbreaks and consideration of policy responses for addressing the multiple consequences of the opioid crisis on HIV epidemiology, prevention, and care will be presented.

CHEMSEX AND IMPLICATIONS FOR HIV TRANSMISSION AND MANAGEMENT
Mark R. Pakianathan, St. George’s University of London, London, UK
Chemsex refers to the use of psychoactive substances in sexual settings by gay, bisexual, and other men who have sex with men (GBMSM). Chemsex is a socially constructed phenomenon and as such there is no specific case definition for it and substances used and social contexts vary between countries. Chemsex is often facilitated by smartphone geospatial networking applications and the substances linked to chemsex include methamphetamine, GHB/GBL (Gamma hydroxybutyrate/Gamma butyrolactone), mephedrone, other cathinones, cocaine, ketamine, and other amphetamines. The presentation will review published data on chemsex across the globe. In particular it will explore its relationships with STIs, shigellosis, hepatitis C and HIV. Additionally it will explore implications for PrEP use in this population. Potential drug-drug interactions between the psychoactive substances and antiretrovirals will be explored and data on antiretroviral adherence in HIV-positive men disclosing chemsex will also be presented. Finally there will be practical suggestions for clinicians on effective clinical communication around chemsex and how to address harm minimization. Implications for health policy and research gaps will also be highlighted.

HIDDEN IN PLAIN SIGHT: THE ALCOHOL EPIDEMIC
Leckness C. Simbayi, Human Sciences Research Council, Pretoria, South Africa
Alcohol is widely used for pleasure by many cultures throughout the world except in Muslim-majority countries. Although it has also been credited with having some protective effect for some health outcomes, its abuse is highly problematic as it causes a large social and economic burden, both to individuals who consume it and other people close to them such as family members, friends, co-workers and strangers. Most importantly, causal relationships have now been established between harmful alcohol drinking and the risk of HIV acquisition. Alcohol abuse also has some impact on the engagement in care and adherence with antiretroviral therapy among people living with HIV. This presentation will present an update on the global epidemic of alcohol especially harmful drinking, followed by the global epidemic of HIV, and then a brief discussion of how the two epidemics converge with each other especially in sub-Saharan Africa. It will then posit about the mechanisms that explain the link between alcohol and HIV/AIDS as well as provide some relevant research evidence in support thereof. Finally, the implications of convergence of the two epidemics for both policies and intervention programmes will be presented.
66 TOBACCO SMOKING: THE SILENT KILLER
Lene Ryom, Centre of Excellence for Health, Immunity and Infections, Copenhagen, Denmark
The smoking epidemic in people living with HIV (PLWHV) differs significantly from that in the HIV-negative general population (GP). Firstly, smoking rates in PLWHV are disproportionately high (2-3 times higher than in the GP) with a roughly even distribution of smoking men and women. Smoking further impacts the health of PLWHV much more severely than that of the GP. As such, the excess risk of mortality in smoking PLWHV is three times higher compared to the GP with up to twelve life years lost due to smoking. Tobacco smoke contains several thousand substances of which multiple are considered poisons or carcinogenic. Nicotine may enhance viral replication and several studies suggest a lower proportion of smoking PLWHV are virally suppressed. Smoking also changes the innate and adaptive immune response by causing inflammation and immune suppression—effects similar to that of HIV itself causing a state of double trouble for smoking PLWHV. Smoking further increases risks of several AIDS-defining conditions including esophageal candidiasis and tuberculosis, thereby directly counteracting the effects of antiretroviral treatment. For non-AIDS conditions the risk of bacterial pneumonia is 73% higher among smoking PLWHV compared to never-smokers. An estimated 70% of all myocardial infarctions in PLWHV are attributed to smoking, making smoking a more important individual risk factor than hypertension and HIV itself. In NA-ACCORD almost 20% of all cancers and over 90% of lung cancers were directly attributed to smoking. While smoking cessation in PLWHV may already after one-year lower risks of cardiovascular events, lung cancer risks remain elevated even several years after cessation in the DAD study. PLWHV are almost 20% less likely to quit smoking than the GP, possibly related to greater sociodemographic challenges. HIV guidelines recommend regular assessment of smoking status and motivation to quit, followed by cessation advice and combined behavioral counselling and pharmaceutical substitution therapy. As smoking is a leading cause of preventable morbidity and mortality in PLWHV it is imperative to design studies to clarify the complex needs of different groups of smoking PLWHV. Such studies should address effectiveness of different smoking cessation interventions and safety profiles of pharmaceutical substitutions. Smoking cessation should further become a top priority in the clinical management of PLWHV to break the silence of the killing smoke.

67 RAISING THE WALL IN MATERNAL/FETAL IMMUNITY
Sallie Permar, Duke Human Vaccine Institute, Durham, NC, USA
Despite the highly-successful use of antiretroviral (ART)-based prevention for reduction of mother to child transmission (MTCT), as of 2017, 180,000 children continue to become infected with HIV-1 annually. Moreover, the fetal toxicities and prematurity associated with combination ART use in pregnancy are continuing to come to light. Pregnancy and the postpartum period are high risk for acute HIV acquisition, which translates into high risk for HIV transmission to the developing fetus and breastfeeding infant. HIV variants transmitted perinatally have been demonstrated to be resistant to neutralization by concurrently circulating maternal antibodies. Thus, strategies that could synergize with ART to further reduce HIV MTCT during pregnancy may include temporary enhancement of autologous virus neutralization and targeted induction of functional antibodies that efficiently cross the placental barrier, which may be achievable with currently available HIV-1 vaccines. Furthermore, the pediatric HIV epidemic is bi-modal, with a peak in the neonatal period and a renewed high-risk period in adolescence following sexual debut. Therefore, vaccines that will eliminate the HIV epidemic will require administration during childhood. The early life immune system represents a unique immune landscape that could potentially be harnessed for qualities that are needed for the elicitation of protective immunity. In fact, recent reports have demonstrated that HIV-infected children develop broadly-neutralizing antibodies at a higher frequency and faster pace than that of HIV-infected adults. Intriguingly, the broadly-neutralizing antibodies identified in HIV-infected children have lower levels of somatic mutation than that of adults. Moreover, immunization strategies that aim for long-term development of protective immunity are well-suited for integration with the pediatric vaccine schedule, while immediate protection in the breastfeeding period can be achieved through concurrent passive administration of a potent broadly-neutralizing antibody. Therefore, enhancing and leveraging maternal and infant HIV immunity through novel passive and active immunization strategies provide renewed hope for ending the HIV-1 epidemic at the earliest stages of life.

68 HUGGING PHYLOGENETIC TREES: USE OF MOLECULAR ANALYSIS FOR PUBLIC HEALTH INTERVENTION
Alexandra M. Oster, CDC, Atlanta, GA, USA
New tools have made it possible to identify clusters of ongoing HIV transmission through the analysis of HIV molecular data. Although analysis of molecular data to understand transmission clusters has become more widespread in recent years, such analysis has typically been retrospective. Now, public health agencies are beginning to use data routinely collected through surveillance to prospectively identify clusters for public health response aimed at strengthening prevention efforts and ensuring that people with and at risk for HIV have access to the services they need. Cluster detection efforts can be used to prompt public health action, but this work must be done in a way that maximizes benefit and minimizes potential harms. This presentation will describe this new strategy and the promise it holds for HIV prevention.

69 A VIRUS-PACKAGEABLE CRISPR SCREEN IDENTIFIES HIV RESTRICTION AND DEPENDENCY FACTORS
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Fred Hutchinson Cancer Research Centre, Seattle, WA, USA
Background: HIV relies on host-encoded factors to complete its life cycle inside the host cell but also must evade recognition by host-encoded factors that have evolved to defend cells against viral invasion. We developed a powerful screening technology to identify HIV restriction and dependency factors in a system that is flexible to cell type and HIV strains.

Methods: HIV-CRISPR screening is a novel CRISPR/Cas9-mediated functional screening method to find HIV restriction factors. The HIV-CRISPR approach takes advantage of the packaging system of HIV to rescue HIV-CRISPR vectors encoding Cas9 and single-guideRNAs (sgRNAs) from cells. sgRNA-encoding HIV-CRISPR genomes are packaged in trans into budding HIV-1 particles. Release of HIV-CRISPR genomes into the supernatant is dependent on the extent of HIV replication within each cell in the population, thus revealing genes that restrict HIV replication within cells. We assembled an sgRNA library specific for Interferon Stimulated Genes (ISGs) into HIV-CRISPR to create PIKA HIV, the HIV-Packageable ISG Knockout Assembly. We then screened PIKA HIV-transduced THP-1 cells to find HIV-1 restriction and dependency factors.

Results: We find that the antiviral effects of a small panel of genes, including MxB, IFITM1, Tetherin and TRIM5, together account for the 8-fold inhibition of HIV-1AI replication by IFN in THP-1 cells. Many, but not all of these same factors were identified in a parallel screen with an RS-tropic, clade A primary isolate. However, Tetherin does restrict the primary isolate, suggesting that Vpu-mediated antagonism of Tetherin varies significantly across viral strains. Further we find that potent IFITM-mediated inhibition of VSV-G pseudotyped HIV-1 is a major block to infection and masks the effects of other antiviral effectors. We also identify novel factors, including SEG62 and TLR2/MDDBB, to be important dependency factors for replication for both viruses. Screens with viral mutants reveal additional restriction factors that may be masked by binding of host cell factors to wildtype HIV.

Conclusion: Highlighting the strength of the HIV-CRISPR approach, we have identified in one screen in one cell type with one virus, many key players in genetic resistance to HIV including TRIMs, Tetherin, IFITM, and MxB. The ability of IFN-induced restriction factors to inhibit HIV replication in human cells suggests that these human restriction factors are incompletely antagonized and that this antagonism varies from virus to virus.

70 A FUNCTIONAL MAP OF HIV-HOST INTERACTIONS IN PRIMARY HUMAN CD4+ T CELLS
Judd F. Hultquist1, Joe Hiatt2, Lara Rheinemann2, Ryan Leenay2, Andrew May2, Wesley I. Sundquist1, Alexander Marson1, Nevan J. Krogan2
1Northwestern University, Chicago, IL, USA, 2University of California San Francisco, San Francisco, CA, USA
Background: The limited coding capacity of the HIV genome necessitates a heavy reliance on the host molecular architecture for optimal replication. Attempts to biochemically identify host factors that physically interact with HIV proteins have yielded hundreds of candidates, but it is unknown which
of these are essential for virus replication. Here, we report a proteomics-to-genetics approach to assess the functional roles of HIV-human protein–protein interactions in primary CD4+ T cells.

**Methods:** Leveraging a high-throughput CRISPR-Cas9 platform for primary T cell genome engineering, we targeted 435 host factors previously identified to physically interact with HIV proteins for knock-out in CD4+ T cells from multiple donors. Each population was subject to deep sequencing to quantify editing efficiency and concurrently challenged with replication-competent HIV-1 to assess the impact on HIV infection.

**Results:** Using this platform, we achieved robust editing efficiencies with high donor-to-donor concordance, averaging 75% allelic knock-out at the population level. The repair outcomes at each edited site demonstrated remarkable predictability based on the target site sequence and surrounding chromatin structure. Of the 435 targeted genes, we identified 86 HIV host factors, 47 of which have not been previously reported. While most host factors were conserved between donors, several displayed notable donor variation. These factors were temporally separated into early and late-acting genes and physically segregated by HIV interacting protein, greatly facilitating and expediting functional analyses. Mechanistic interrogation revealed critical roles for these new HIV host factors in viral entry, transcription, budding, and maturation.

**Conclusion:** These findings reveal several new host factors underlying HIV replication in primary CD4+ T cells and model an interdisciplinary approach to systems biology as a means to streamline experimental discovery. Donor-to-donor and cell type-to-cell type variations in host factor dependency suggest the virus employs substantial functional plasticity to achieve robust infection, complicating host-based therapeutic strategies. The continued extension of this technology to resting memory T cells and for the targeted insertion of single nucleotide variants will ultimately unveil new insight into the host determinants underlying HIV replication, latency, and pathogenesis.

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**HIV-1 Complexes Traffic with Host CPSF6 on Microtubules Prior to Nuclear Entry**

Zhou Zhong1, Douglas K. Fischer1, Chris Klime6, Sooin Jang1, Alan N. Engelman2, Simon C. Watkins1, Zandrea Ambrose1

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**Background:** HIV-1 DNA nuclear entry is required for infection and is mediated by viral capsid. The host protein CPSF6 has been shown to bind HIV-1 capsid, to facilitate nuclear import of viral pre-integration complexes, and to mediate integration of viral DNA into actively transcribed genes. While CPSF6 has predominantly nuclear expression as a result of binding to host transportin TNPO3 via its RS domain, a small fraction of CPSF6 is localized outside of the nucleus, leading us to study its interaction with HIV-1 in the cytoplasm.

**Methods:** In this study, we conducted high speed live-cell confocal imaging to investigate intracellular trafficking of WT or mutant HIV-1 containing functional, fluorescently tagged integrase (IN). Infection was performed in cells with fluorescently labeled microtubules, TNPO3, and full-length or mutant CPSF6. In addition, HIV-1 capsid uncoating kinetics were measured in infected cells using an imaging-based assay.

**Results:** CPSF6 was expressed as puncta in the perinuclear region of the cytoplasm, which trafficked on microtubules with TNPO3. Upon infection, WT HIV-1 complexes associated with perinuclear CPSF6 and TNPO3, trafficking together on microtubules. However, a mutation in capsid that abolishes binding to CPSF6, N74D, rendered the virus unable to associate with cytoplasmic CPSF6. Disruption of microtubule polymerization resulted in diminished virus and CPSF6 movement. Truncation or mutation of the RS domain of CPSF6 led to reduced binding to TNPO3 and increased cytoplasmic expression at the cell periphery, resulting in restriction of HIV-1 infection. This CPSF6 mislocalization resulted in the formation of higher-order complexes around HIV-1 IN-containing complexes, premature capsid uncoating, and altered microtubule trafficking of IN complexes after infection with WT HIV-1 but not N74D HIV-1. In addition, Crispr-mediated knockout of the CPSF6 gene in cells altered microtubule-mediated trafficking towards the nucleus of WT HIV-1 but not the capsid mutant.

**Conclusion:** These data suggest that after WT HIV-1 entry into the cell, viral complexes interact with CPSF6 and TNPO3 on microtubules near the nucleus, which is required for efficient capsid uncoating and nuclear entry of pre-integration complexes.

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**HIV-1 Capsid Determinants that Influence Nuclear Envelope Docking and Nuclear Import**

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**Background:** An essential step of HIV-1 infection is to transfer the replication complex into the nucleus. An HIV-1 intact viral core is approximately 61-nm wide, must get translocated through 39-nm-diameter nuclear pores, suggesting that the viral core undergoes uncoating and/or conformational changes before entering the nucleus. While HIV-1 capsid (CA) protein plays a critical role in nuclear import, the CA determinants that influence nuclear envelope (NE) docking and viral core translocation through the nuclear pore have not been defined. To study these events, we developed a quantitative imaging assay for association of single viral complexes with the NE and for their nuclear import. Using this system, we evaluated several CA mutants in which core-surface-associated amino acids were substituted and determined their ability to dock at the NE and/or enter the nucleus.

**Methods:** HIV-1 CA mutants, including hyperstable (E45A) and hypostable (P38A) mutants, were generated in envelope-deficient genomes. VSV-G pseudotyped virions were produced and used to determine their infectivity in HeLa, CEM-SS, and MT4 cells. For imaging assays, HIV-1 virions were labeled with HIV-1 integrase-superfolder green fluorescent protein (sIgFP) and used to study NE docking and nuclear import in both fixed- and live-cell assays. A high-throughput live-cell imaging assay was developed to study NE docking and residence time of CA mutants. HIV-1 CA amounts were determined using a quantitative immunostaining assay.

**Results:** We identified CA mutants that exhibited a longer NE residence time compared to wild-type viral complexes, indicating that these CA determinants can influence the kinetics of association of viral complexes with the nuclear pore. These CA mutants did not show infectivity defects in HeLa cells, but were defective in T cell lines (CEM-SS and MT4 cells). Interestingly, viral complexes of these mutants docked at the NE exhibited lower CA signals in immunofluorescence assays, suggesting alterations in the viral core structures. Live-cell imaging experiments are being performed to determine whether the CA mutants increased the NE residence time of those viral complexes that enter the nucleus.

**Conclusion:** We have identified CA mutants that exhibit long NE residence times, indicating defects in NE association, a phenotype which has not been previously reported. Further characterization of these CA mutants may provide valuable insights into the essential steps of NE docking.

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**Single HIV-1 Virus Imaging with CA-Egfp Questions a Role of Nuclear CA in Integration**

Irena Zurnic, Lieve Dirix, Veerle Lemmens, Doortje Borrenberghs, Susana Rocha, Johan Hofkens, Frauke Christ, Jelle Hendrix, Zeger Debryser

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**Background:** The role of HIV-1 capsid protein (CA) in early HIV replication is known to extend beyond uncoating. Still, a consensus model on the relationship between HIV-1 uncoating, nuclear import and integration is lacking, mostly due to conflicting results on intracellular capsid distribution. Resolving the dynamics of capsid uncoating thus necessitates a robust method of imaging functional viruses containing labeled CA.
Methods: We fluorescently labeled CA and evaluated replication of the resulting labeled viruses. We generated dually labeled VSV-G pseudotyped particles containing eGFP-tagged CA (CA-eGFP) and mCherry-tagged Vpr, transincorporated integrase (IN-mCherry). Since CA-eGFP by itself did not allow viral particle release, we co-transfected plasmids coding for CA-eGFP with a WT CA plasmid at a 1:10 ratio during virus production. At discrete time points after infection, we analyzed the cellular localization of both CA-eGFP and IN-mCherry by confocal microscopy in the absence and the presence of inhibitors of the early HIV replication steps.

Results: We investigated the cellular distribution and intensity of fluorescent, CA and IN in HeLa P4 cells. CA and IN colocalized in 20-30% of all cytoplasmic complexes. Importantly, the intracellular distribution and fluorescence intensity of IN-mCherry complexes were unaffected by CA-eGFP labeling. CA-eGFP complexes accumulated in the perinuclear area, but only 10-15% of these also contained IN-mCherry. Using both CA-eGFP and immunocytochemistry, we confirmed the presence of CA in the nucleus, which rarely (<5%) colocalized with IN-mCherry. Under PF74 treatment, the number of nuclear complexes containing labeled IN decreased 15-fold while CA-eGFP decreased 5-fold, consistent with a PF74-mediated nuclear import block. The inhibition of CA-eGFP labeled viruses with PF74 suggests that at least some of the dually labeled particles undergo bona fide uncoating and nuclear import. When using Ral to block integration, we observe a 25% accumulation of fluorescent IN, but not CA-containing complexes in the nucleus. These data question the role of nuclear CA in integration and urge investigation of other nuclear roles of this protein.

Conclusion: Directly labeled CA allows single virus imaging of HIV-1 preintegration steps and provides insights in the cytosolic and nuclear distribution of CA. Therefore, virions carrying labeled IN and CA represent a suitable system to address HIV-1 entry following both the viral PIC and the fate of the associated capsid.

74 DISRUPTION OF HIV-1 LTR SEQUENCE BY A NUCLEOCAPSID MUTATION LEADS TO DTG RESISTANCE

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Background: Dolutegravir (DTG), a key component of ART, tightly binds to the catalytic site of integrase (IN) and to the canonical -CAOH dinucleotide sequence of the LTR at the viral DNA (vDNA) ends. Resistance to DTG is poorly understood.

Methods: DTG-resistant viruses were selected using in vitro serial passage experiments under DTG pressure. We monitored the viral dynamics of early steps of HIV-1 replication using multiplex immunofluorescent cell-based detection of viral DNA, RNA and protein (MICDDRP) and qPCR. To elucidate the resistance mechanism, we used next-generation sequencing and analyzed the sequence of the LTR termini of HIV-1 that is integrated into host DNA.

Results: Through in vitro passage experiments we discovered that a mutation at the zinc-fingers of HIV nucleocapsid (HIV NC) enhances DTG resistance, -4-fold, by itself, or -7-fold in the presence of an E157Q polymorphism in the IN region (HIV NC). We demonstrate that in the absence of DTG, both HIV NC and HIV IN replicate more slowly than wild-type HIV-1 (HIV WT) without reducing integrated vDNA. MICDDRP and qPCR revealed that HIV NC and HIV IN significantly increase the amount of vDNA during reverse transcription and subsequently integrated them into host genome even at 8h post-infection. Analysis of the virus termini sequences after integration revealed that amount of normals -CAOH dinucleotide sequences at the LTR ends was significantly affected: whereas -CAOH was present in HIV WT at 99% and 98% of the 5'- and 3'-LTRs, it was found in 97% and 43% for those of HIV NC and 79% and 46% for those of HIV IN. Notably, the virus termini sequences formed by HIV NC, contained more frequent insertions, deletions, and abnormal LTR ends, which are the substrates of IN and part of the DTG binding site.

Conclusion: We report an example of a remarkable epistatic drug resistance mechanism, whereby a mutation in the NC viral gene affects the function of 3 viral proteins, (NC, RT, and IN) resulting in resistance to DTG. We propose that NC changes to affect vDNA formation, which in turn affects the selectivity of DTG binding and its exclusion from the active sites of HIV NC and HIV IN, DTG resistance is further enhanced by an IN polymorphism, thus highlighting an important role of polymorphisms in IN drug resistance and therapies.

75 INTEGRASE (IN) TETRAMERS ARE THE AUTHENTIC TARGETS FOR ALLOSTERIC HIV-1 INHIBITORS

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Background: Allosteric HIV-1 integrase (IN) inhibitors (ALLINIs) are a new, promising class of antiretroviral agents that disrupt the proper viral maturation by inducing hyper-multimerization of IN and consequently inhibiting its binding to the viral RNA genome. Previous biochemical and crystallographic studies have emphasized the importance of IN catalytic core domain and C-terminal domain for ALLINI induced hyper-multimerization of the protein. Here, we have elucidated a crucial role of the N-terminal domain (NTD) for the ALLINI activity. Specifically, we show the importance of NTD mediated tetramerization of IN for the inhibitor induced hyper-multimerization of the protein.

Methods: The separation of different oligomeric states (tetramers, dimers and monomers) of WT IN allowed us to delineate striking selectivity of ALLINI for IN tetramers versus the lower order oligomers. In addition, trans-complementation assays, which allowed us to reconstitute IN tetramers using two dimeric IN mutants, further confirmed the selectivity of ALLINIs for IN tetramers. Based on these findings we have created molecular models of ALLINI mediated tetramer-tetramer interactions.

Results: Consistent with the experimental results, the docking scores and free energy calculations indicate that tetramers are preferred over dimers for the formation of ALLINI induced polymers. Interestingly, our lead pyridine-based ALLINI KF116 exhibited ~10-fold higher activity (EC50~0.7 nM) against a clinically relevant Dolutegravir (DTG) resistant mutant HIV-1LNL4-3 (HIV WT, HIV IN, HIV NC, HIV RT) compared to the wild-type counterpart. Complementary in vitro experiments with recombinant WT and mutant INs revealed that WT IN was a mixture of tetramers, dimers and monomers; whereas under identical conditions the DTG resistant IN (HIV WT, HIV IN, HIV NC, HIV RT) predominantly formed tetramers.

Conclusion: These observations indicate that ALLINI KF116 is highly complementary to DTG and raise possibilities for the synergistic combination of ALLINIs and INSTIs to further increase the genetic barrier to resistance by limiting HIV-1 options for drug resistant substitutions. Taken together, our biochemical findings coupled with virology experiments show that ALLINIs are highly active during virion maturation and suggests that IN tetramers are formed in virions that are selectively targeted by ALLINIs.

76B TARGETING VIRUS ENV AND CD44 IMPROVES bnAb AVAILITY AND NEUTRALIZATION POTENCY

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Background: Broadly neutralizing antibodies (bnAbs) hold great promise for the prevention and treatment of HIV infection, but this virus has evolved elaborate ways to evade effective neutralizing antibodies. One of these is the evasion of antibody avidity: Low Env density with spike distances surpassing the average “wingspan” of an IgG impedes inter-spike crosslinking and Env structural constraints hamper intra-spike crosslinking; these limitations of bivalent binding may restrain bnAb potency. Here we hypothesized that bnAb neutralizing activity could be increased through a strategy that overcomes the evasion of Ab avidity by using bispecific Abs (BiAbs) targeting both Env and a host molecule known to be present on the viral surface, CD44.

Methods: BiAbs were engineered using the CrossMAB Technology. Neutralizing activity was assessed using the TZM-bl assay for infectious viruses, including the deCamp global panel.

Results: We engineered a prototype BiAb that combines the bnAb PGDM1400 (anti-V2 apex) with the anti-CD44 Ab RG7356 and assessed its neutralizing activity against diverse HIV-1 strains, including primary isolates and the deCamp global panel. As expected, RG7356 had no neutralizing activity. PGDM1400/
RG7356 neutralized more potently than the parental bnAb, PGDM1400, for 14/16 of HIV-1 strains tested. The mean level of neutralization enhancement (defined as IC₅₀ ratio of parental and bispecific Ab) was 8.6 (range 0.6 to 75.5). Mechanistically, the potency enhancement occurred irrespective of target cell CD44 expression but was critically dependent on presence of CD44 on the virion surface. Similar enhancement of virus neutralization was observed when PGDM1400 was replaced by other bnAbs (e.g., 10-074 and N6).

Conclusion: Our data provide strong evidence that bnAbs neutralize most HIV-1 strains through predominantly monovalent binding and increasing avidity via binding to a host protein on the virion surface could substantially enhance virus neutralization.

### 77 IPT AND PREGNANCY OUTCOMES IN HIV-POSITIVE WOMEN: THE TSHEPISO COHORT

E. Chaisson1, Neil A. Martinson2, for the TSHEPISO Study Team

TB/HIV co-infection, despite appropriate therapy.

Hoffmann 3, Fildah Mashabela2, Christopher Hoffmann 1, Kelly E. Dooley1, Richard TB disease which results in poor maternal and infant outcomes. IMPAACT study P1078 found that isoniazid preventive therapy (IPT) during pregnancy resulted in a higher risk of adverse maternal and neonatal outcomes compared to IPT post-delivery, questioning the safety of IPT in pregnant women living with HIV (PWLHIV).

Methods: Tshepiso was a prospective cohort study evaluating maternal and infant outcomes among PWLHIV with and without active TB disease from January 2011 through January 2014 in Soweto, South Africa. Mother-infant pairs were followed through one year of life. Here we report the outcomes among PWLHIV without TB disease who reported initiating vs not initiating IPT during pregnancy. This was an observational study; IPT was initiated by public antenatal and HIV clinics and not by the study.

Results: The Tshepiso study enrolled 155 PWLHIV without TB disease. This analysis includes 151 women with known pregnancy outcomes; 69 (46%) reported initiating IPT during pregnancy. The median age and CD4 T-cell count at enrollment was 30 years (IQR 27 ,31) and 364 cells/mm³ (IQR 252,464) for women on IPT vs 29 years (IQR 26,32) and 372 cells/mm³ (IQR 275,477) for women not on IPT. 63 (78%) and 43 (65%) women were on cART, 52 (83%) and 37 (86%) with EFV, respectively. Viral load during pregnancy was <400 copies/mL in 60 (75%) women on IPT and 35 (52%) women not on IPT (p=0.004). The proportion of neonates born prematurely was lower in those exposed to IPT during pregnancy compared to unexposed (10% vs 22%; p=0.06). There was no difference in fetal demise (1% vs 1%; p=1.0), low birth weight (9% vs 18%; p=0.22) or maternal mortality (0% vs 1%; p=1.0). A composite of the four outcomes (16% vs 28%; p=0.08) showed fewer events among infants exposed to IPT. Stratified analyses by viral load suppression did not demonstrate differences in pregnancy outcomes.

Conclusion: In this study, IPT use during pregnancy was not associated with a higher rate of poor maternal or infant outcomes. Though this study had well characterized exposures and outcomes, it was not designed to study the effect of IPT on pregnancy outcomes. IPT exposed and non-exposed PWLHIV may differ in factors associated with adverse outcomes in PWLHIV. More research is needed to evaluate the safety of IPT for PWLHIV given their high risk of TB disease and the poor maternal and infant outcomes associated with maternal TB/HIV co-infection, despite appropriate therapy.

### 78 POTENTIAL CONCERN FOR TIMING OF DMPA INJECTION AMONG WOMEN TREATED FOR HIV AND TB

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Background: Effective contraception is of upmost importance for young women with HIV-associated TB, as unintended pregnancy among such women is associated with increased maternal and infant morbidity and mortality. Rifampicin (RIF) and Ethinyl estradiol (EEV) are both inducers of metabolizing enzymes and can reduce concentrations of contraceptive medications. Effects of these drugs on the pharmacokinetics (PK) of depot medroxyprogesterone acetate (DMPA), the most commonly used contraceptive in sub-Saharan Africa (SSA) and globally, are unknown. Safety of concurrent use of these 3 drugs is also unknown. We hypothesized that clearance of MPA would be increased when given with RIF and EFV, potentially resulting in levels of MPA <0.1 ng/mL (levels associated with escape ovulation) prior to 12 weeks post-DMPA dose.

Methods: ACTG A5338 was a multicentre, single-arm, PK study among women in SSA stable on EFV-based antiretroviral therapy (ART) and RIF-based TB treatment. We determined plasma MPA concentrations pre-dose and 2, 4, 6, 8, 10 and 12 weeks after DMPA 150 mg injection and measured plasma progestrone levels from week 2 onwards. The primary outcome measure was the proportion of women with sub-therapeutic MPA levels (<0.1 ng/mL) at week 12. MPA PK parameters were calculated using non-compartmental methods and compared with historical ART-naive controls without TB who received DMPA.

Results: Baseline characteristics of the 42 evaluable participants are shown in Table 1. Five women (11.9% [95% CI 4.0 -25.6%]) had MPA <0.1 ng/mL at week 12 with one of the five having MPA <0.1 ng/mL at week 10 compared to one of 16 (6.3%) at week 12 among the historical controls. No participant had progestrone levels >5 ng/mL (suggesting ovulation) throughout the study including at week 12. Compared to historical controls, median area under the concentration-time curve over 12 weeks (AUCO-12) was lower (7.63 vs. 12.38 ng*wk/mL, p=0.004) and apparent clearance was higher (19.681 vs. 12.177 L/wk, p=0.004). There were no grade 3 or higher adverse effects attributed to DMPA.

<table>
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<td>Composite Outcome*</td>
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<tr>
<td>Fetal Demise</td>
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<td>23 (29%)</td>
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<td>Gestational Age at Birth (weeks)</td>
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<tr>
<td>Maternal Mortality (≤42 days)</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Neonatal Deaths</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Infant Deaths</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.45</td>
</tr>
<tr>
<td>TB Mother</td>
<td>2 (3%)</td>
<td>2 (2%)</td>
<td>1.0</td>
</tr>
<tr>
<td>TB infant</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Composite outcome includes fetal demise, low birth weight, prematurity and congenital anomaly
**Conclusion:** DMPA, when given with EFV-based ART and RIF-based TB therapy, was safe and well tolerated. MPA clearance was higher than in controls, leading to sub-therapeutic concentrations of MPA in some women at 10 and 12 weeks post-dose, though progesterone levels typically associated with ovulation were not observed. It may be prudent to dose DMPA more frequently than every 12 weeks in women on EFV-with HIV-associated TB taking RIF.

<table>
<thead>
<tr>
<th>TABLE 1: PARTICIPANTS BASELINE CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Characteristics</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>20-29</td>
</tr>
<tr>
<td>30-39</td>
</tr>
<tr>
<td>40-49</td>
</tr>
<tr>
<td>African Race</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
</tr>
<tr>
<td>HIV RNA &lt; 400 copies/mL</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
</tr>
<tr>
<td>&lt;50</td>
</tr>
<tr>
<td>50-199</td>
</tr>
<tr>
<td>200-349</td>
</tr>
<tr>
<td>≥350</td>
</tr>
<tr>
<td>Enrollment by country</td>
</tr>
<tr>
<td>South Africa</td>
</tr>
<tr>
<td>Kenya</td>
</tr>
<tr>
<td>Botswana</td>
</tr>
<tr>
<td>Zimbabwe</td>
</tr>
</tbody>
</table>

**Conclusion:** The number of child contacts identified was similar across study arms, but more child contacts per adult TB case were identified and subsequently screened at CBI compared with SOC sites. However, the yield of child TB contacts requires further optimization as there are many missed opportunities to diagnose or prevent TB. Additional research is needed to enhance the definition of child household contacts and overcome barriers to CCM that impede identification and screening of child TB contacts in high TB/HIV burden settings.

**80LB SAFETY & PK OF WEEKLY RIFAPENTINE/ISONIAZID (3HP) IN ADULTS WITH HIV ON DOLUTEGRAVIR**

**Kelly E. Dooley**, Gavin Churchyard, Radojka M. Savic, Akshay Gupte, Mark A. Marzinke, Nan Zhang, Vinodh Edward, Lisa Wolf, Modulakgotla Sebe, Morongwe Likoti, Mark Fyvie, Innocent Shibambo, Trevor Beatrie, Richard E. Chaisson, for the DOLPHIN Study Team

**Background:** Short-course preventive therapy with 12 once-weekly rifapentine/isoniazid doses (3HP) could transform TB control, but drug interactions with antiretrovirals may pose implementation challenges. In a previous trial, 3HP administered with dolutegravir (DTG) resulted in serious adverse events (AE) in 2/4 healthy subjects (fever, hypotension, elevated transaminases); the study was halted. We conducted a Phase I/II study of 3HP and DTG in adults with HIV to characterize safety, drug interactions, and viral suppression.

**Methods:** HIV infected adults with undetectable viral load on efavirenz (EFV)-based regimens were recruited into 3 groups. All received DTG in place of EFV for 8 weeks, then began 3HP, after 3HP completion, all participants were followed for 4 more weeks. Viral loads were measured at baseline and weeks 11 and 24. Groups 1A (n=12) and 1B (n=18) had intensive DTG PK sampling performed at week 8 (pre-HP), then weeks 11 and 16 following the 3rd and 8th doses of HP. Group 2 (n=30) were treated with the same schedule and had sparse DTG PK sampling at weeks 8, 11 and 16. Primary endpoints were 1) grade >3 AE and 2) population PK parameters of DTG with or without HP. An independent Study Monitoring Committee recommended release of results following its second review.

**Results:** Of the 60 participants who received 3HP, 43 (70%) were female, median (IQR) age was 40 (35-48) years, all were black African, median (IQR) CD4 was 683 (447-935) cells/mm³, and median (IQR) BMI was 28.9 (24.0-32.9) kg/m². All participants received ≥6 HP doses at the time of this report. Three Grade 3 AE occurred (2 elevated creatinine, 1 hypertension). HIV viral loads at baseline, day 58 (pre-HP), day 72 (3rd HP dose) and day 168 (post-HP) were all below 50 copies/mL.
<40 c/mL. Table 1 shows Group 1A and 1B PK results. The geometric mean (GM) trough concentration of DTG on Day 58 (pre-HP) was 1003 ug/mL (5th-95th %ile: 500-2000), and during HP treatment S46 (134-1616) with all trough levels but one above DTG IC90 of 64 ug/mL (Table). Overall, HP administration decreased DTG bioavailability by 29% (RSE 13%) (+18%, -37% and -35% for week 1, 3 and 8), while clearance remained unchanged.

Conclusion: Co-administration of DTG and HP was well-tolerated, with no HP-related Grade >3 AE. Although HP decreased DTG bioavailability, which was associated with a modest decrease in trough levels, all trough levels but one were above the DTG IC90. All viral loads were suppressed. DTG may be co-administered with 3HP without dose adjustment.

<table>
<thead>
<tr>
<th>Time</th>
<th>Drug</th>
<th>GM</th>
<th>5th</th>
<th>95th</th>
<th>Co-administration</th>
<th>GM</th>
<th>5th</th>
<th>95th</th>
<th>PK parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>1</td>
<td>895</td>
<td>440-1224</td>
<td>1</td>
<td>102</td>
<td>72-152</td>
<td>0.3</td>
<td>0.26</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>3</td>
<td>900</td>
<td>423-1337</td>
<td>1</td>
<td>105</td>
<td>74-162</td>
<td>0.3</td>
<td>0.25</td>
</tr>
<tr>
<td>24</td>
<td>4</td>
<td>1</td>
<td>865</td>
<td>418-1285</td>
<td>1</td>
<td>102</td>
<td>71-153</td>
<td>0.3</td>
<td>0.25</td>
</tr>
<tr>
<td>48</td>
<td>2</td>
<td>3</td>
<td>893</td>
<td>444-1397</td>
<td>1</td>
<td>104</td>
<td>73-158</td>
<td>0.3</td>
<td>0.26</td>
</tr>
<tr>
<td>72</td>
<td>4</td>
<td>2</td>
<td>900</td>
<td>423-1337</td>
<td>1</td>
<td>105</td>
<td>74-162</td>
<td>0.3</td>
<td>0.25</td>
</tr>
<tr>
<td>96</td>
<td>3</td>
<td>1</td>
<td>915</td>
<td>461-1374</td>
<td>1</td>
<td>106</td>
<td>76-163</td>
<td>0.3</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*HP doses were given on Days 50, 60, 70, 79, 80, 90, 100, 120, 140, 180, 220, 280.

81LB PHARMACOKINETICS AND SAFETY OF ADJUSTED DARUNAVIR/РИТОНАВИР WITH RIFAMPICIN IN PLWH

Ismaeel Ebrahim, Gary Maartens, Wynand Smythe, Catherine Orrell, Lubbe Wiesner, Helen Muller

University of Cape Town, Cape Town, South Africa

Background: Darunavir (DRV)/ritonavir(r) is better tolerated than lopinavir (LPV)/r and has a higher generic barrier to resistance. Co-administration of DRV/r with rifampicin (RIF), the key component of first-line TB treatment, is currently contraindicated as significant reductions in DRV exposures are expected; this has been a barrier to the use of DRV/r in resource-limited settings where TB is endemic. We aimed to evaluate the safety and pharmacokinetics (PK) of adjusted doses of DRV/r in PLWH.

Methods: We enrolled virologically suppressed participants on a second-line DRV/r regimen without RIF. Based on data from a Physiologically-Based PK model, we selected two adjusted doses of DRV/r (1600/200 mg daily and 800/100 mg 12 hourly) with RIF for comparison to plasma exposures with DRV/r. PK was determined and RIF added for 7 days, then the dose of RIF was increased to 200 mg; 7 days later the dose of DRV was increased; after another 7 days participants were crossed over to the alternative adjusted DRV dose. DRV was measured in plasma samples after observed doses at baseline and after each dose adjustment. Non-compartmental analysis was used to estimate the PK parameters. Clinical adverse events, ALT, and bilirubin were monitored every 2 to 3 days during treatment with RIF.

Results: Eighteen of a planned 28 PLWH were enrolled and started on study treatment before the study was stopped due to high rates of hepatotoxicity. Only 4 participants completed the study. Six (35%) of the participants were withdrawn for DAIDS grade 3 (n=3) or 4 (n=3) ALT elevations developing after 9-12 days of RIF; 3 participants were symptomatic. Hepatotoxicity resolved in all cases after withdrawal of study treatment and participants were successfully re-established on their standard of care ART regimen. The PK parameters are shown in table 1. Trough concentrations were below the protein-adjusted EC50 of 200 ng/mL in 2 participants in the QD group adjusted dose group on RIF.

Conclusion: Adjusted doses of DRV/R with RIF were associated with unacceptable risk of hepatotoxicity and there was a marked reduction in DRV trough concentrations with the QD adjusted dose in our study.

Table 1. Geometric mean (range) darunavir pharmacokinetic parameters.

<table>
<thead>
<tr>
<th>DRV/r 800/100 daily</th>
<th>DRV/r 1600/200 + RIF (n=7)</th>
<th>DRV/r 800/100 bid + RIF (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>2487 (631-8560)</td>
<td>134 (55-1600)</td>
</tr>
<tr>
<td>Cmin, ng/mL</td>
<td>2716 (615-7550)</td>
<td>209 (58-1040)</td>
</tr>
<tr>
<td>AUCinf, ng*h/mL</td>
<td>261184 (48474-830798)</td>
<td>39074 (21412-89788)</td>
</tr>
<tr>
<td>GM, ng/mL</td>
<td>6856 (3610-12400)</td>
<td>4268 (2030-7720)</td>
</tr>
<tr>
<td>GM, %I</td>
<td>5 (2-4)</td>
<td>5 (2-4)</td>
</tr>
</tbody>
</table>

82 EARLY BACTERIAL ACTIVITY OF HIGH-DOSE ISONIAZID AGAINST MULTIDRUG-RESISTANT TB

Kelly E. Dooley1, Sachiko Miyahara2, Florian von Groote-Bidlingmaier1, Xin Sun1, Richard Hafner1, Susan L. Rosenkranz5, Eric Nuermberger1, Laura E. Moran4, Kathleen Donahue6, Susan Swindells7, Andreas H. Diacon1, for the ACTG A5312 Study Team

1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Harvard University, Boston, MA, USA, 3TASK Applied Science, Cape Town, South Africa, 4DAIDS, NACDI, Bethesda, MD, USA, 5Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, 6Social & Scientific Systems, Silver Spring, MD, USA, 7University of Nebraska Medical Center, Omaha, NE, USA

Background: High-dose isoniazid (INH) may be useful in treating multidrug-resistant tuberculosis (MDR-TB), particularly when INH resistance is mediated by inhA mutations. Although the World Health Organization (WHO) recommends 'high-dose' INH as part of the new shorter MDR-TB regimen, the optimal dose and its efficacy are not established.

Methods: AIDS Clinical Trials Group (ACTG) A5312 is a Phase 2A randomized, open-label trial in which individuals with smear-positive pulmonary MDR-TB with INH resistance mediated by an inhA mutation (Group 1) were randomized to receive INH doses of 5, 10 or 15 mg/kg daily for 7 days. Controls with drug-sensitive TB (Group 2) received the standard INH dose of 5 mg/kg/day. Sputum cultures were collected daily, beginning at baseline. The early bactericidal activity of INH, estimated as the average daily change in log10 colony forming units (CFU) on solid media (EBATTP-7) or average daily change in time to positivity (TTP) in hours on liquid media (EBATTP-7) over 7 days of treatment was estimated using nonlinear mixed effects models. Safety data were collected from study entry through Day 21.

Results: 59 participants (43 in Group 1, 16 in Group 2) were enrolled, all in South Africa. The majority (73%) were men, median age was 32 years, 20% were HIV co-infected, and 88% had cavitary lung disease. 58/59 (98%) completed study treatment (one withdrew consent in the 15 mg/kg arm). Eight participants had grade 3 (and no grade 4) adverse events (fever, pain, dyspnea, pneumonia, pyrexia, anemia, constipation). All unrelated or unlikely to be related to study drugs. Mean EBATTP-7 in Group 1 at doses of 5, 10 and 15 mg/kg was 0.07 (+18%, -37% and -35% for week 1, 3 and 8), while clearance remained unchanged.

Conclusion: INH had substantial EBA against Mycobacterium tuberculosis strains with inhA mutations among patients with MDR-TB, provided it was dosed at 10-15 mg/kg, supporting WHO recommendations for high-dose INH in this population. Activity at these doses was similar to the standard 5 mg/kg dose in drug-sensitive TB. Longer-term tolerability, plus efficacy of high-dose INH against strains with katG mutations require further study.
LONG-TERM MORTALITY AFTER TUBERCULOSIS CURE IN THE CIPRA HT-001 TRIAL

Yvetot Joseph1, Marc Antoine Jean Juste1, Serena Koenig2, Sean Collins3, Zhiven Yao3, Ananksha Dua4, Pierre Cremieux5, Patrice Severe1, Daniel Fitzgerald6, Jean William Pape1

1Ghesko, Port-au-Prince, Haiti, 2Brigham and Women’s Hospital, Boston, MA, USA, 3Analysis Group, Inc, Boston, MA, USA, 4Well Cornell Medicine, New York, NY, USA

Background: Although TB is a curable disease, studies from industrialized settings suggest an elevated risk of long-term mortality after TB recovery. Long-term outcomes data for individuals co-infected with TB and HIV from the developing world are limited.

Methods: We conducted a retrospective analysis of 14-year follow-up data (2005-2018) for 703 adult HIV positive patients enrolled in the CIPRA HT-001 study at Les Centres Ghesko, Haiti. Demographic and clinical data, including TB diagnosis, TB and HIV treatments were recorded in the study database and electronic medical records. The TB cohort was defined as patients with active TB at enrollment or incident TB during follow-up (cases). Time to death was estimated and cases and controls with no history of TB using Kaplan-Meier analysis and the log-rank test. We used univariate and multivariate Cox proportional hazards models to estimate hazard ratios for mortality. Time-varying ART status and CD4 count were included in the multivariate models. A period of 8-months post TB diagnosis was used to define the start of follow-up and exclude acute mortality from TB; additional sensitivity analyses using a longer period of 2-years were conducted.

Results: 703 patients were included; 151 cases, and 573 controls. Baseline characteristics were similar in cases and controls. After exclusion of acute mortality on TB treatment, TB cases had lower survival rates, 5-year 82.3% vs 93.5%; 9-year 63.5% vs 83.9%, and lower median time to death (9.2 months vs median not reached, p<0.001) compared to controls (Figure 1). In univariate Cox models, the risk of death was higher for cases than controls (HR 2.9, 95% CI 1.8, 4.8, p<0.001). After adjusting for time-varying ART status and CD4 count, the risk of mortality remained significantly higher for cases (HR 3.6, 95% CI 2.1, 6.3, p<0.0001) however, time-varying ART and CD4 values were not independent predictors of mortality in that model. Mortality trends were similar in all sensitivity analyses.

Conclusion: Patients with HIV who had TB coinfection had a higher risk for long-term mortality after TB recovery compared to patients with no history of TB. CD4 count and time of ART initiation were not independently associated with risk of mortality in this model. Long-term mortality risk after TB treatment among HIV positive patients should be thoroughly documented to elucidate the mechanisms and assess its impact on mortality.
FALL IN HCV INCIDENCE IN HIV+ MSM IN LONDON FOLLOWING WIDER ACCESS TO DAA THERAPY

Lucy J. Garvey1, Colette J. Smith2, Christof Stingone1, Indrajit Ghosh3, Alison Rodgers1, Lakshmi Jain1, Chandni Sood1, Tabitha Mahungu1, Carolyn Freeman3, Subathira Dakshina3, Filippo Ferro1, Laura Waters1, Ashley Brown1, Graham S. Cooke1, Sanjay Bhagani1


Background: Modelling of the London HCV epidemic in HIV+ MSM suggested early access to DAA treatment plus risk behaviour modification may reduce incidence. With high rates of linkage to care and treatment access, micro-elimination of HCV within HIV+ MSM may be realistic, ahead of 2030 WHO targets. Data from European cohorts have shown a reduction in HCV incidence amongst HIV+ MSM. We examine the effect of HCV treatment access (in the pre- and post-DAA era) and risk-behaviour modification upon incidence of HCV first and re-infections in HIV+ MSM in three large London clinics.

Methods: A retrospective cohort study was conducted at 3 London HIV clinics (Royal Free and St Mary’s Hospitals, Mortimer Market) between July 2013 and June 2018. During each 6-month period the following data were collected: [1] number of first acute HCV diagnoses [2] number of subsequent acute HCV diagnoses (re-infections) [3] denominator of HIV+ MSM under active follow-up [4] number of PEG IFN/RBV or DAA-based HCV treatments for acute/early HCV (<12m since diagnosis) [5] number of PEG IFN/RBV or DAA-based HCV therapies for chronic HCV (>12m since diagnosis). Incidence rates (acute HCV diagnoses/ HIV+ MSM 1000 PYFU) and re-infection rates (re-infections/all incident infections x 100) were calculated for each time-period.

Results: 293 acute HCV infections were identified (246 first infections and 47 re-infections). DAA treatment became widely available in late 2015. All centres adopted risk-reduction behaviour intervention with counselling/psychology. Incidence of first HCV episode peaked at 17.72/1000 HIV+ MSM PYFU (95% CI 12.81–22.64) in 2015. Rates fell to 4.64 (95% CI 2.53–7.78) by 2018. Re-infection rates increased from 9% to 16% during the study period. Supervised early HCV treatments (<12m of diagnosis) increased from 22% to 61% between 2013 and 2018. Supervised chronic HCV/HIV treatment rates increased from 2.8/month in pre-DAA era to 15.6/month post-DAA era. Time from diagnosis to starting any HCV treatment reduced from average of 40.9 months (2013) to 3.1 months (2018).

Conclusion: There has been a 74% reduction in incidence of first HCV infection and 62% reduction of overall HCV incidence in HIV+ MSM since the epidemic peak of 2015 which coincides with wider access to DAA-based therapy across London. However re-infection rates remain high and maybe increasing.

Further interventions to reduce ongoing transmission including access to treatment for reinfection are likely needed if micro-elimination is to be achieved.

HCV REINFECTION AMONG HIV-INFECTED MSM IN NEW YORK CITY

Jesse B. Carroll1, Stephanie H. Factor1, Gabriela Rodriguez-Caprio1, Asa Radij2, Stephen M. Dillon1, Rona Val1, Kriszcz J. Bungay3, Robert Chavez4, José Lares-Guia5, Daniel S. Fierer1, for the New York Acute Hepatitis C Surveillance Network

1Icahn School of Medicine at Mt Sinai, New York, NY, USA, 2Callen–Lorde Community Health Center, New York, NY, USA, 3Gotham Medical Group, New York, NY, USA, 4AIDS Healthcare Foundation, New York, NY, USA, 5Office of José Lares-Guia, MD, New York, NY, USA

Background: High HCV re-infection rates of 3-15% have been reported after IFN treatment in HCV-infected MSM in Europe. There are no data on HCV re-infection from similar cohorts in the United States, or among those cured with all-oral direct-acting antiviral (DAA) therapy.

Methods: We assessed all HCV-infected MSM from our cohort in New York City (NYC) for clearance of HCV. Clearance was defined as SVR 12 if by treatment, or undetectable HCV VL for ≥12 weeks if by spontaneous clearance (SC). Re-infection was defined as new HCV viremia after clearance. Clinical onset of re-infection was defined as the date of the 1st-noted ALT elevation or HCV viremia. Observation time was defined as the period between 12 weeks after completion of therapy or SC, and either the clinical onset of HCV re-infection or the last undetectable HCV VL in those not re-infected.

Results: We identified 267 HIV-infected MSM with documented clearance of primary HCV infection and ≥4 weeks follow-up. Median age was 45; 170 (64%) were white, 40 (15%) black, 55 (21%) Hispanic; genotypes (n=258) were 1a in 106 (41%), 1b in 33 (13%), and other in 75 (29%). Median CD4 count was 579 cells/µL; median HIV VL was <50 copies/mL. We found 44 re-infections among 38 (14%) men, onset between 2006 to 2018, a median of 1.5 (IQR 0.8,2.9; range 0.3-11.4) years after clearance, among 38 (14%) men, onset between 2006 to 2018, a median of 1.5 (IQR 0.8,2.9; range 0.3-11.4) years after clearance; genotypes (n=41) were 1a in 31 (76%), 1b in 3 (7%), and other in 7 (17%). Including the re-infections, follow-up was available for a total of 300 episodes of HCV clearance, with a median follow-up time of 1.8 (IQR 0.8,3.3; range 0.1-11.4) years, and a total of 734 person-years (PY). The overall re-infection rate was 5.7/100PY (95% CI 4.2,7.7), with no significant difference among the 112 (37%), 160 (53%), or 28 (9%) infections cleared with IFN, DAA, or SC, respectively (p=0.52, Fisher exact). Further, time to re-infection did not differ among the groups (p=0.82, log-rank test) (Figure).

Conclusion: The high HCV re-infection rate in our large cohort of HIV-infected MSM in NYC was independent of whether clearance was by IFN or DAA treatments, or by SC, and comparable to Europe rates. Most re-infections occurred within the first 2 years, but infections continued to occur for more than 11 years after clearance. These data suggest that long-term surveillance is warranted for all HIV-infected MSM after clearance of HCV infection. Further, strategies to reduce HCV re-infections are needed to meet the goal of eliminating HCV in these men who are at significant risk for HCV infection.
A PHASE 1 STUDY OF LEDIPASVIR/SOFOSBUVIR IN PREGNANT WOMEN WITH HEPATITIS C VIRUS

Catherine A. Chappell, Elizabeth E. Krans, Katherine Bunge, Ingrid Macio, Debra Bogen, Kimberly K. Scars, Leslie A. Meyn, Sharon L. Hillier

1Magee–Womens Research Institute, Pittsburgh, PA, USA, 2University of Nebraska Medical Center, Omaha, NE, USA

Background: Hepatitis C virus (HCV) infection is increasing among pregnant women in the United States, increasing the risk of perinatal transmission. Pregnancy is a window of opportunity for health care interventions, including HCV treatment that could improve maternal health and prevent perinatal HCV transmission. There are no published data on the safety or efficacy of HCV direct-acting antivirals in pregnancy. Therefore, the primary objective of this pilot study was to define the safety of and virologic response to ledipasvir 90mg-sofosbuvir 200mg (LDV/SOF) therapy in pregnancy.

Methods: In this open-label, phase 1 study, HIV-negative pregnant women with chronic genotype 1 HCV infection were enrolled between 23-24 weeks of gestation and began a 12-week course of LDV/SOF. Participants had to take at least 73 (87%) planned doses to be evaluable. Viral load testing was performed at 7 visits: screening, enrollment, 13-21 days and 5-6 weeks after LDV/SOF initiation, 1-7 days and 12 weeks after LDV/SOF completion, and at delivery. Maternal adverse events, delivery outcomes and the sustained virologic response 12 weeks after therapy (SVR12), defined as undetectable HCV viral load, are reported.

Results: Of 28 pregnant women with chronic HCV who screened, 20 were excluded because of genotype 2 or 3 infection (n=10), ongoing illicit drug use (n=4), declining study participation (n=3), intentions to delivery off-site (n=2), and an APRI score of >1 (n=1). Eight women were enrolled, all of whom were white, with a median age of 32 (range 25-38) years. Seven of the women were HCV infected due to intravenous drug use, 4 of whom were receiving opioid pharmacotherapy, and one was perinatally infected. Of 7 evaluable patients, the median HCV viral load at enrollment was 518,173 (range 103,457-3,757,923) copies/mL. All had a rapid response to therapy and all achieved SVR12 (Table). All adverse events related to LDV/SOF were ≤ grade 2. All seven participants delivered at term with undetectable HCV viral loads at delivery. One-year follow-up of infants is ongoing.

Conclusion: In this first study of HCV treatment in pregnant women, response to LDV/SOF was similar to the viral response observed in nonpregnant individuals without any safety concerns identified. Larger studies are needed before this strategy can be recommended. A substantial proportion of women screened out due to genotypes 2 or 3 infection, highlighting the importance of further research to expand HCV treatment options in pregnancy.

Table: HCV virologic response to LDV/SOF during pregnancy by participant (copies/mL)

<table>
<thead>
<tr>
<th>Study visit</th>
<th>1</th>
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<th>4</th>
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<td>12 weeks' response</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<td>24 weeks' response</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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</tr>
</tbody>
</table>

88 INCIDENT DIABETES AND GLUCOSE CONTROL AFTER HCV TREATMENT WITH DAA’S IN ERCHEVES

Adeel A. Butt, Samia Aslam, Peng Yan, Obaid S. Shaikh, Abdul-Badi Abou-Samra

1VA Pittsburgh Healthcare System, Pittsburgh, PA, USA, 2Weill Cornell Medicine College in Qatar, Doha, Qatar

Background: HCV is associated with an increased risk of diabetes. How treatment with newer directly acting antiviral agents (DAA) affects this risk is unknown. Our objective was to determine the effect of DAA treatment upon the risk and incidence of diabetes.

Methods: We identified chronic HCV-infected persons treated with pegylated interferon/ribavirin (PEG/RBV) or DAA regimens and propensity-score matched untreated controls. We excluded persons with prevalent diabetes, HIV or HBV coinfection, those treated with both PEG/RBV and DAA regimens. Diabetes was defined using a combination of blood glucose values, prescription of hypoglycemics and ICD-9/10 codes.

Results: We identified 4,764 PEG/RBV treated, 21,279 DAA treated, and same number of untreated controls. Diabetes incidence rate [95% CI]/1,000 person-years of follow up were 19.8[18.3,21.4] among PEG/RBV and 9.89[8.7 ,11.1] among DAA treated persons (P<0.001). Among the treated, rates were 13.3[12.2,14.5] for those with SVR and 19.2[17.4,21.1] for those without SVR (P<0.0001). Treatment was associated with a larger reduction in incident diabetes rate in persons with more advanced fibrosis/cirrhosis (absolute difference 2.9 for FIB-4<1.25; 5.7 for FIB-4 1.26-3.25; 9.8 for FIB-4>3.25). DAA treatment (HR 0.48, 95%CI 0.42,0.56) and SVR (HR 0.81, 95%CI 0.70,0.93) were associated with a significantly reduced risk of diabetes. DAA treated persons had longer diabetes free survival compared to untreated and PEG/RBV treated persons. There was no significant difference in diabetes free survival between untreated and PEG/RBV treated persons.

Conclusion: HCV treatment significantly reduces the incidence and risk of subsequent diabetes, driven largely by DAA regimens. Treatment benefit is more pronounced in persons with more advanced liver fibrosis.
90 HIV VIREMIA AND LOW CD4+ INCREASE HCC RISK IN THOSE WITHOUT ADVANCED LIVER FIBROSIS

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Background: Despite rising incidence of hepatocellular carcinoma (HCC) in HIV patients, few studies have evaluated determinants of HCC during the antiretroviral therapy era. We evaluated HIV-related and traditional risk factors for HCC in a large cohort of HIV+ patients.

Methods: We conducted a retrospective cohort study among HIV+ patients in the Veterans Aging Cohort Study from 1999-2015. Patients had HIV RNA and CD4+ cell count simultaneously assessed in the Veterans Affairs (VA) system, and follow-up began on this date. Incident HCC was determined using the VA Cancer Registry. We used multivariable Cox regression to determine adjusted hazard ratios (HR [95% confidence interval]) of HCC associated with cumulative unsuppressed HIV RNA (≥500 copies/mL), time-updated lower CD4+ count, older age, male sex, race/ethnicity, morbid obesity (body mass index ≥35 kg/m²), time-updated diabetes status, alcohol use disorder, hepatitis B virus (HBV), and hepatitis C virus (HCV) coinfection. The analysis was repeated substituting time-updated HIV RNA for cumulative unsuppressed HIV RNA. Since advanced hepatic fibrosis/cirrhosis is the strongest determinant of HCC and may overwhelm other risk factors, we stratified analyses by low and high baseline FIB-4 (<3.25 versus ≥3.25, respectively), a commonly used fibrosis index.

Results: Among 36,525 HIV+ patients, 275 (0.8%) developed incident HCC. Overall, baseline FIB-4 ≥3.25 was the strongest factor associated with HCC (HR 15.1 [9.7-23.3]). However, 36.4% of HCC events occurred among those with FIB-4 <3.25. Among these patients, older age (HR 1.4 [1.4-1.7] per 10 years), morbid obesity (HR 2.6 [1.2-5.3]), diabetes (HR 1.5 [1.3-2.1]), ≥12 months of unsuppressed HIV RNA (HR 2.0 [1.4-2.9]), lower CD4+ count (<200 cells/mm³: HR 1.6 [1.0-2.4] versus ≥500 cells/mm³), HBV coinfection (HR 2.3 [1.7-3.3]), and HCV coinfection (HR 6.1 [4.1-9.0]) were independently associated with incident HCC. The risk of HCC was also increased with higher HIV RNA level (HR 1.3 [1.1-1.4] per 1.0 log₁₀ copies/mL).

Conclusion: Among HIV+ patients without advanced liver fibrosis, higher HIV RNA and longer duration of HIV viremia, greater immunosuppression, morbid obesity, and diabetes, in addition to HBV and HCV coinfection, increased the risk of HCC. Addressing these factors before development of advanced fibrosis could help reduce the incidence of HCC in HIV+ patients.

91LB SINGLE HEPATOCYTE ANALYSIS IN HIV-HBV CONFECTION SHOWS HBV TRANSCRIPTION SILENCING

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Background: Hepatitis B virus (HBV) is a leading cause of liver failure and hepatocellular carcinoma worldwide. Due to shared modes of transmission, ~10% of people living with HIV also have chronic HBV infection. HBV cannot be cured because the long-lived covalently closed circular DNA (cccDNA) resides in hepatocytes. Here, we used single-cell laser capture microdissection (scLCM) and droplet digital PCR (ddPCR) to characterize the HBV replication landscape in situ in humans. We quantified cccDNA, total HBV DNA, and pre-genomic RNA (pgRNA) in each hepatocyte, adjusting for intracellular cytoplasmic RNA 7SL.

Methods: Here, we used single-cell laser capture microdissection (scLCM) and droplet digital PCR (ddPCR) to characterize the HBV replication landscape in situ in humans. We quantified cccDNA, total HBV DNA, and pre-genomic RNA (pgRNA) in each hepatocyte, adjusting for intracellular cytoplasmic RNA 7SL.

Results: We examined a median (range; total) 255 (52 – 290; 1100) hepatocytes that were individually isolated from five HIV/HBV co-infected persons with increasing exposure to dual- and single-activity antiretroviral therapy (DAART) against HIV and HBV (HBV-1; no exposure to >7 years of exposure). Total HBV DNA, cccDNA, and pgRNA were quantified in each cell. The proportion of infected hepatocytes (cccDNA positive) decreased with longer DAART exposure from 100% (HB1) to 33% (HB5; Table). The median (range) total HBV DNA per cell was 1 cp/cell (0-112 cp/cell); of cccDNA was 1 cp/cell, (0-31 cp/cell); and of pgRNA was 38 cp/cell, (0-199 cp/cell). The amounts of cccDNA, total HBV DNA, and pre-genomic RNA were significantly lower in infected liver than in non-infected liver.
DNA, and pgRNA significantly decreased in infected cells with longer DAART duration (p<0.005 for all targets). HBV transcription (pgRNA) did not correspond with cccDNA levels in the same cells (p=0.05). Additionally, we identified cells that contained cccDNA but not pgRNA, defined here as transcriptionally silent, that accumulated with longer DAART from 0% (HB1) to 46.1% (HB5) of infected hepatocytes (Table).

Conclusion: Our results indicate that the HBV viral landscape is highly dynamic, and that there is heterogeneity in transcription of cccDNA including complete silencing. Understanding transcriptional silencing in HBV-infected hepatocytes may be critical to emerging immunotherapy and could be exploited to develop a functional cure.

92LB IMPACT OF UNIVERSAL TESTING AND TREATMENT IN ZAMBIA AND SOUTH AFRICA: HPTN071(POPART)

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Background: Universal testing and treatment was proposed as a strategy to achieve steep reductions in HIV incidence in generalized epidemics, yet prior trials showed inconsistent results. We report the results of HPTN071(POPART), the largest HIV prevention trial ever conducted.

Methods: In this community-randomized trial (2013-18), 21 urban communities in Zambia and South Africa were arranged in 7 matched triplets and randomized within triplets to: Arm A (full POPART intervention including universal ART), B (POPART intervention with ART per local guidelines) and C (standard of care). Local guidelines adopted universal ART in 2016. The POPART combination prevention intervention comprised annual rounds of home-based HIV testing by Community HIV-care Providers (CHiPs) who supported linkage to care, ART adherence and other HIV services. Impact was measured in a Population Cohort (PC) comprising one randomly selected adult (aged 15-36s) at baseline, 12m, 24m and 36m. Intervention data on HIV testing and ART uptake were collected by CHiPs in Arm A and B communities.

Results: A total of 48,301 adults were enrolled in the PC. Baseline HIV prevalence was similar across arms (A:21.2%; B:21.1%; C:22.4%). Between 12-36m, 553 incident HIV infections were observed in 39,733 person-years (1.4/100py). The adjusted HIV incidence rate ratio for Arm A compared with C was 0.93 (95%CI:0.74-1.18; p=0.51, Table) and for Arm B compared with C was 0.70 (95%CI:0.55-0.88; p=0.006). Intervention data indicated that the first two 90s were achieved in Arms A and B after three annual rounds. Viral suppression (VL<400 copies/mL) at 24m was 72.1% in Arm A, 67.9% in Arm B and 62.5% in Arm C, with lower rates in men and younger adults (<25y).

Conclusion: The POPART intervention achieved the 90-90-90 targets and high rates of VS (~70%). The intervention, with ART delivered according to local guidelines (Arm B), reduced HIV incidence by 30%. The lack of effect in the full intervention arm (Arm A), where universal treatment was delivered prior to change in guidelines, was surprising and not explained by observed rates of VS. Phylogenetic and qualitative analyses may shed light on this dissonant finding.

93 A RANDOMIZED TRIAL ON INDEX HIV SELF-TESTING FOR PARTNERS OF ART CLINETS IN MALAWI

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Background: HIV testing of sexual partners of HIV-positive clients (index testing) is critical for case identifications and reducing transmission. Current index testing strategies have limited reach – only 20% of partners in Malawi are tested using standard partner referral slips (PRS) – a paper version of passive facility referrals for partners. Delivery of HIVST to partners at their home may address barriers to index testing. We evaluated an index HIVST intervention among partners of ART clients in Malawi.

Methods: A randomized trial was conducted at 3 district hospitals in Malawi between March28-June13, 2018. ART clients were screened during routine services. Inclusion criteria were: >15 years of age; sexual partner with unknown HIV status; no history of interpersonal violence with that partner; and partner lives in facility catchment area. Clients were randomized 1:2: (1) standard PRS or (2) HIVST (Oraquick HIV Self-Test®) demonstration and distribution and referral for confirmation by blood-based testing). Baseline and follow-up surveys were conducted with ART clients and a subset of sexual partners willing to present at facilities for a survey. Primary outcomes (partner tested, test result, confirmatory testing) were reported by ART clients. Uni- and multivariate logistic regressions were conducted.

Results: 365 ART clients enrolled in the study, with median age 37 years and 22% male. Only 3 clients refused HIVST. 91% and 92% of clients in HIVST and PRS arms respectively reported distributing the intervention to their partners (p-value=0.70; Table). However, 81% of partners in HIVST tested compared to only 29% of partners in PRS (AOR:9.6; p-value<0.001). Positivity rates did not differ by arm (19% in HIVST versus 16% in PRS; p=0.74). Among newly diagnosed HIV-positive partners in HIVST, only 20% received a confirmatory, blood-based test within 4-weeks. 99% and 97% of ART clients reported being diagnosed HIV-positive partners in HIVST, only 20% received a confirmatory, blood-based testing). Baseline and follow-up surveys were conducted with ART clients and a subset of sexual partners willing to present at facilities for a survey. Primary outcomes (partner tested, test result, confirmatory testing) were reported by ART clients. Uni- and multivariate logistic regressions were conducted.

Results: 365 ART clients enrolled in the study, with median age 37 years and 22% male. Only 3 clients refused HIVST. 91% and 92% of clients in HIVST and PRS arms respectively reported distributing the intervention to their partners (p-value=0.70; Table). However, 81% of partners in HIVST tested compared to only 29% of partners in PRS (AOR:9.6; p-value<0.001). Positivity rates did not differ by arm (19% in HIVST versus 16% in PRS; p=0.74). Among newly diagnosed HIV-positive partners in HIVST, only 20% received a confirmatory, blood-based test within 4-weeks. 99% and 97% of ART clients reported being comfortable providing HIVST and demonstrating use to partners, respectively. Among partners who used HIVST and completed a survey (n=126; median age 39 years; 67% men), 16% reported challenges understanding HIVST instructions
and 8% were unable to interpret HIVST results. Reported adverse events (psychological IPV/end of relationship) did not vary by arm (~8%).

**Conclusion:** Index HIVST greatly increased HIV testing without increased risk of adverse social events. Inadequate interpretation and test confirmation limits the impact of index HIVST and requires further study.

| Table: Participant characteristics and outcomes across arms of an index HIVST study targeting sexual partners of ART clients reported by ART clients (N=395) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| %                              | N (%)                          | P<0.05                          | p<0.05                          |
| Study Outcomes                 | Fletcher test                  | vLS test                        | Fletcher test                  |
| Partner-randomised intervention | 98 (92%)                       | 234 (91%)                      | 93.0 (0.42-1.09)               | 0.97 | 1.21 (0.48-2.95) |
| Partner tested                  | 209 (95%)                      | 155 (95%)                      | 10.0 (0.99-10.16)              | <0.001 | 0.82 (0.75-10.15) |
| Partner tested vLS-positive     | 48 (26%)                       | 30 (18%)                       | 1.21 (0.50-3.79)               | 0.74  | 0.84 (0.21-3.30) |
| Partner completed confirmatory test | 2 (10%)                       | 1 (1%)                         | 1.00 (0.70-1.43)               | 0.9   | 1.00 (0.70-1.43) |

**Conclusion:** Male circumcision uptake at study end. After accounting for baseline coverage differences, HIVST coverage was significantly higher in the intervention arm (P<0.0001; Fig.1A). ART coverage and viral suppression, we estimated risk ratios(RR) and 95% confidence intervals(CI) accounting for clustering using log-linear Poisson regression adjusted for potential baseline coverage imbalances, stratified by time and pair. MC uptake among HIV-uninfected uncircumcised men aged 16-49 years was evaluated using pair-stratified interval-censored Cox proportional hazards.

**Results:** We enrolled 8,974 HIV-negative and 3,596 HIV-positive residents in the longitudinal cohort. An additional 11,767 residents were assessed for HTC uptake at study end. After accounting for baseline differences, HTC coverage was significantly higher in the intervention arm at study end (P<0.0001; Fig.1A). ART coverage and viral suppression increased in both arms, with greater increases in the intervention arm (ART P<0.0001; viral suppression P=0.004; Fig.1B-C). At study end, 98% (95%CI: 98%-100%) of HIV-positive cohort participants in the intervention arm (ART P<0.0001; viral suppression P=0.004) were virally suppressed. A small number (348) of 1,873 HIV-negative uncircumcised men reported becoming circumcised, with higher uptake in the intervention arm (P<0.0001).

**Conclusion:** Population levels of HTC, ART, viral suppression, and MC increased in both arms over time, with significantly greater increases in the intervention arm. Remarkably, at study end, nearly all HIV-positive cohort participants in intervention communities were on ART and virally suppressed.
FACTORS ASSOCIATED WITH PERSISTENT VIREMIA WITH UNIVERSAL “TEST & TREAT” IN UGANDA

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Background: Beginning in 2013, Uganda implemented universal “test and treat” in high-risk populations, including fishing communities along Lake Victoria. Here, we use population-based data to identify characteristics associated with persistent viremia among HIV-positive individuals in hyperendemic fishing communities during “test and treat” scale-up.

Methods: Between November 2011-February 2017, five surveys were conducted in four Ugandan fishing communities (>40% HIV prevalence) as a part of an open cohort of all consenting persons aged 15-49 years. HIV viral loads were assessed among HIV-positive participants at three surveys. The unit of analysis was a person-interval (two consecutive visits). Person-intervals were categorized into four outcomes based on a viral load cutoff of 400 copies/mL: durable suppression, new/renewed viral suppression, viral rebound, and persistent viremia. Multivariate Poisson regression with generalized estimating equations and robust variance estimators was used to estimate adjusted relative risk ratios (aRRRs) and 95%CIs of persistent HIV viremia versus durable or new/renewed viral suppression.

Results: 3,404 HIV-positive individuals participated in the cohort, including 1,346 participants with viral load data at ≥2 visits (n=1,883 person-intervals). Overall, the prevalence of durable suppression was 50.4% and becoming newly suppressed was 30.3%, while the prevalences of viral rebound and persistent viremia were 2.9% and 16.4%, respectively. Over the study period, the prevalence of population-level durable suppression increased from 29.7% to 39.1%. Younger age (15-29 vs. 40-49 years; aRRR=1.93 [95%CI: 1.27-2.93]), male sex (aRRR=1.87 [95%CI: 1.32-2.65]), and being never married (vs. currently married; aRRR=1.93 [95%CI: 1.39-2.68]) were factors significantly associated with persistent viremia. Younger age and male sex were strongly correlated with high risk sexual behaviors. These findings were consistent in sensitivity analyses restricted to the most recent survey interval.

Conclusion: In hyperendemic communities with universal “test and treat”, being young (<30 years), male, and never married were associated with persistent viremia. Young people had higher levels of high-risk sexual behavior suggesting those most likely to have persistent HIV viremia are also most likely to sustain HIV transmission. Programs tailored to men and high risk youth are necessary to reduce HIV transmission in sub-Saharan Africa.

VIROLOGIC FAILURE, LOW-LEVEL VIREMIA, AND VIRAL BLIP AFTER HIV RNA SUPPRESSION

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Background: Time to HIV RNA suppression after antiretroviral therapy (ART) initiation may impact durability of viral suppression. Our objective was to estimate risks of: a) virologic failure; b) low-level viremia (LLV); and c) viral blip by time to suppression among patients enrolled in NA-ACCORD clinical cohorts in 2006–2015.

Methods: We followed 14,551 new ART initiators aged ≥18 years from suppression (2 consecutive viral loads [VLs] ≤50 copies/mL [cpm]) to unsuppressed VL, death, loss to follow-up, or administrative censoring. Time to suppression was categorized as ≤6, 6–12, or >12 months. Outcomes were: a) virologic failure: 2 consecutive (≤180 days) VLs ≥200 cpm; b) LLV: 2 consecutive (≤270 days) VLs 51–199 cpm; and c) viral blip: 1 VL 51–199 cpm preceded and followed by VL ≤50 cpm (≤270 days between VLs). For each outcome, we estimated cumulative incidence (risk) and risk differences (RD) by time to suppression over 7 years, accounting for death as a competing event. Unsuppressed VL other than the outcome of interest was censored. Inverse probability weights were used to account for informative censoring and confounding by ART regimen (NNRTI, PI, INSTI) and other factors.

Results: After starting ART, 31% (4575) of patients suppressed in ≤6 months, 41% (5912) in 6–12 months, and 28% (4064) in >12 months. Among patients who suppressed in ≤6 months, we observed 7-year weighted risks of failure, LLV, and blip of 13.7%, 5.8%, and 27.8%, respectively. Corresponding weighted risks were 15.9%, 6.6%, and 28.3% for patients who suppressed in 6–12 months, and 21.5%, 9.2%, and 26.3% for patients who suppressed in >12 months. Patients who suppressed in >12 months had a 7.8% (95% CI: 4.0%, 22.1%) higher risk of failure, 3.4% (95% CI: 1.2%, 11.1%) higher risk of LLV, and similar risk of blip (RD: -1.4% [95% CI: -8.1%, 5.7%]) compared to those who suppressed in ≤6 months. No notable differences in risks of failure, LLV, or blip were observed between patients who suppressed in 6–12 months and those who suppressed in ≤6 months.

Conclusion: Suppression >12 months after ART initiation was associated with higher long-term risks of failure and LLV compared to suppression in ≤6 months; there was no association with risk of blip. Investigating whether the relationships between time to suppression and these outcomes are modified by ART regimen is warranted. Identifying barriers to achieving rapid HIV RNA response may be needed to maximize durability of viral suppression and optimize treatment as prevention efforts.
System (CHDSS) trends in HIV incidence, and prevalence of viral load suppression (VLS, <1000 RNA copies/mL) and CBI including circumcision among men (MC), and HIV testing, diagnosis, and use of antiretroviral therapy (ART) among persons living with HIV (PLHIV). Located in Chokwe District, CHDSS includes ~95,000 residents.

**Methods:** Since 2014, HIV testing services (HTS) including referral for MC and follow-up linkage-to-care for PLHIV has been offered annually at all ~20,515 CHDSS households. HIV incidence and prevalence of HIV, VLS, and CBI were assessed with annual surveys of residents aged 15-59 years in 10% (2014-2015) or 20% (2016-2017) of randomly selected households. Dried blood spots of participating PLHIV were tested at CDC for VLS and recent infection (mean <161 days). Annualized HIV incidence was calculated with a standard formula; participants on ART or with VLS were defined as having longstanding infection. Census-weighted CHDSS HIV incidence, incidence rate ratios (IRR), and prevalence of HIV, VLS, and CBI were estimated for the first three survey rounds (R1-R3, April 2014–March 2017). District health facilities offered ART for all PLHIV beginning in mid-2016, R3.

**Results:** During R1-R3, 39,586 (72%) of 55,287 residents aged 15-59 years tested for HIV at home at least once, and 3,449 (866 men) were newly HIV diagnosed and provided linkage services. HIV prevalence decreased from 27.3% in R1 to 25.7% in R3 (p < 0.05) (Table). By R3, prevalence of MC, and prior HIV diagnosis, current ART use, and VLS among PLHIV increased 14.0%-21.6% (Table). Of 2,750 PLHIV (1.1%) had been recently infected (R1, 1.5%; R2 1.2%; R3, 0.7%), HIV incidence decreased 53% overall (p < 0.05), and 54% and 51% (p < 0.05) among men and women, respectively (Table). Among persons aged 15-24 and 25-59 years, HIV incidence fell from 1.3% (0.2-2.5%) and 2.4% (0.6-4.3%) in R1 to 0.4% (0.1-1.0%) and 1.3% (0.1-2.4%) in R3, respectively.

**Conclusion:** In a high HIV prevalence district in Mozambique, increasing population prevalence of HIV biomedical interventions was associated with increasing prevalence of VLS and an approximate 50% reduction in HIV incidence among adults. Annual home-based HTS with referral and linkage services can help achieve rapid scale up of CBI, increased VLS, and reduced HIV incidence.

**100 PROTECTION AGAINST PENILE OR INTRAVENOUS SHIV CHALLENGES BY bNAB 10-1074 OR 3BNC117**

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**Background:** Broadly neutralizing antibodies (bNabs) 10-1074 and 3BNC117 are in clinical development for HIV prevention and treatment. In macaque models, passively administered 10-1074 or 3BNC117 protects against repeated rectal or vaginal SHIV challenges; however, their efficacy against other HIV acquisition routes relevant to men (penile) or persons who inject drugs (intravenous, IV) has not been discerned. Here, we evaluated the protective efficacy of a single subcutaneous (SC) injection of 10-1074 alone, or in combination with 3BNC117, against repeated penile or IV SHIV challenges, respectively.

**Methods:** Macaques (6 rhesus, 5 cynomolgus) were injected SC once with 10-1074, or a combination of 10-1074+3BNC117, respectively (10mg each bNab/kg). Beginning one week later, macaques were challenged repeatedly once weekly with SHIVsf162P3 (rhesus) or SHIVAD8-EO (cyno) via penile (200 TCID50) into the prepuce pouch, 16 TCID50 into the distal urethra) or IV (130 TCID50) routes, respectively, until SHIV infection was confirmed via plasma viral load. Control macaques, which received no antibody, were challenged identically (10 penile, 2 IV). Longitudinal plasma samples were assayed via Tzmbl neutralization assay, using viruses pseudotyped with 10-1074-sensitive (X2088_c9) or 3BNC117-sensitive (Q769.d22) HIV Envs to determine bNAb concentrations.

**Results:** Macaques administered 10-1074 and challenged via the penes were protected against a median of 15.3 weekly challenges, as compared to controls...
Garcia-Lerma 1
George Khalil 1, Yi Pan 1, Jonathan T. Lipscomb 1, James F. Rooney 2, Darius Babusis 2, McCormick 2, James Mitchell 1, Gerardo Garcia-Lerma 1, Vivek Agrahari 2, Pardeep 1, M. Melissa Peet2, Kenji Nishiura 1, Onkar N. Singh 2, Timothy J. Charles Dobard

**Background:** On-demand topical PrEP for HIV prevention has several advantages over a daily oral PrEP regimen, including reduced costs, less drug toxicity, decreased risk of resistance, and potential to increase adherence. Inserts containing tenofovir alafenamide fumarate (TAF) in combination with elvitegravir (EVG) are being developed by CONRAD/EVMS for flexible, on-demand vaginal or rectal pericolic use. We recently found in a dose-ranging pharmacokinetic assessment in macaques that vaginal administration of inserts containing 20 and 16 mgs of TAF and EVG, respectively, resulted in rapid accumulation of EVG and durable levels of tenofovir diphosphate (TFV-DP) in mucosal tissues at concentrations associated with in vivo protection. Here we used a macaque model of vaginal SHIV transmission to investigate the protective efficacy of TAF/EVG inserts.

**Methods:** Normal cycling pigtail macaques (n=14) were exposed vaginally to SHIV162P3 once a week for up to 13 weeks. Six macaques received inserts containing a fixed-dose combination of TAF/EVG (20 mg/16 mg) and 8 received matching placebo inserts. Inserts were placed in the posterior vagina near the cervix 4 hours before each SHIV exposure. Insertion was monitored weekly by serology and RT-PCR amplification of SHIV RNA in plasma. A Kaplan-Meier survival analysis was used to compare the survival distribution between the two groups and efficacy was calculated as 1-p1/p0, where p1 and p0 denote the proportion of infections per total challenges for TAF/EVG and placebo controls, respectively.

**Results:** Of the 8 macaques that received placebo inserts, 7 became SHIV infected while 1 remained SHIV negative following 13 weekly challenges. The median number of challenges to infect macaques treated with placebo inserts was 3 (range 2-13). In contrast, 5 of 6 macaques that received TAF/EVG inserts remained protected after 13 challenges resulting in an estimated efficacy of 92%. Survival analysis demonstrate at least a 9-fold reduction in risk of infection in macaques that received TAF/EVG compared to placebo inserts (p=0.007; log-rank).

**Conclusion:** Vaginal administration of inserts containing TAF and EVG was highly effective in preventing SHIV infection in a macaque model that mimics vaginal transmission of HIV in women. The data support the clinical development and first-in-human testing of TAF/EVG inserts for on-demand topical prophylaxis against vaginally acquired HIV infection.

**101 PROTECTION AGAINST VAGINAL SHIV INFECTION WITH AN INSERT CONTAINING TAF AND EVG**

**Charles Dobard,** M. Melissa Peet, Kenji Nishiura, Onkar N. Singh, Timothy J. McCormick, James Mitchell, Gerardo Garcia-Lerma, Vivek Agrahari, Pardeep Gupta, Srinamakama Jolinalagadda, Jill Schwartz, Wald Heneine, Gustavo Doncel, Meredith Clark

**Background:** Vaginal administration of inserts containing TAF and EVG was highly effective in preventing SHIV infection in a macaque model that mimics vaginal transmission of HIV in women. The data support the clinical development and first-in-human testing of TAF/EVG inserts for on-demand topical prophylaxis against vaginally acquired HIV infection.

**Methods:** Normal cycling pigtail macaques (n=14) were exposed vaginally to SHIV162P3 once a week for up to 13 weeks. Six macaques received inserts containing a fixed-dose combination of TAF/EVG (20 mg/16 mg) and 8 received matching placebo inserts. Inserts were placed in the posterior vagina near the cervix 4 hours before each SHIV exposure. Insertion was monitored weekly by serology and RT-PCR amplification of SHIV RNA in plasma. A Kaplan-Meier survival analysis was used to compare the survival distribution between the two groups and efficacy was calculated as 1-p1/p0, where p1 and p0 denote the proportion of infections per total challenges for TAF/EVG and placebo controls, respectively.

**Results:** Of the 8 macaques that received placebo inserts, 7 became SHIV infected while 1 remained SHIV negative following 13 weekly challenges. The median number of challenges to infect macaques treated with placebo inserts was 3 (range 2-13). In contrast, 5 of 6 macaques that received TAF/EVG inserts remained protected after 13 challenges resulting in an estimated efficacy of 92%. Survival analysis demonstrate at least a 9-fold reduction in risk of infection in macaques that received TAF/EVG compared to placebo inserts (p=0.007; log-rank).

**Conclusion:** Vaginal administration of inserts containing TAF and EVG was highly effective in preventing SHIV infection in a macaque model that mimics vaginal transmission of HIV in women. The data support the clinical development and first-in-human testing of TAF/EVG inserts for on-demand topical prophylaxis against vaginally acquired HIV infection.

**102 MODERATE EFFICACY OF ORAL SINGLE-AGENT TAF AGAINST VAGINAL SHIV INFECTION IN MACAQUES**

**Ivana Massud,** Mian-er Cong, Susan Ruone, Angela Holder, Kenji Nishiura, George Khalil, Yi Pan, Jonathan T. Lipscomb, James F. Rooney, Darius Babusis, Yeojin Park, Scott McCallister, Christianelle Ballebaut, Wald Heneine, Gerardo Garcia-Lerma

**Background:** Tenofovir alafenamide (TAF) is a prodrug of TFV that is under development and first-in-human testing of TAF/EVG inserts for on-demand topical prophylaxis against vaginally acquired HIV infection. We recently showed that oral TAF in combination with FTC was highly effective in preventing vaginal simian HIV (SHIV) infection in female pigtailed macaques. Here we investigated if TAF alone is sufficient for preventing vaginal SHIV infection.

**Methods:** The efficacy of single agent TAF in preventing vaginal infection was investigated in an established model of vaginal SHIV exposures consisting of up to 15 once-weekly virus challenges with SHIV162P3. Nine pigtail macaques received a clinically equivalent dose of TAF (1.5 mg/kg) orally 24h before and 2h after each weekly virus exposure. Infection outcome was compared with 21 placebo animals (6 real-time and 15 historical controls). TFV-diphosphate (TFV-DP) and dATP levels in PBMCs were measured once a week at the time of virus challenge. Kaplan-Meier survival analysis and a log-rank test was used to compare time to infection in TAF-treated animals relative to controls. Infection rates were compared using the fisher exact test. TFV-DP levels were measured in vaginal and rectal biopsies from a separate group of 9 macaques.

**Results:** Infection rates and time to SHIV RNA detection were similar in real-time and historical controls (p=0.500 and p=0.319, respectively). Two of the 9 TAF-treated animals did not metabolize TFV (TFV-DP level of 15 and 16 mfs/106 cells) and were excluded from the analysis. Three of the remaining 7 TAF-treated and 19/21 control animals became infected (p=0.021). Infection in TAF-treated animals was also delayed relative to controls (p=0.036). TFV-DP levels in the 3 animals infected during TAF PrEP (median=351 mfs/106 cells; range=t143-1,568) were similar to those seen in the 4 uninfected macaques (median=331; range=236-584; p=0.359). dATP/TFV-DP ratios were also similar among infected and protected animals (median=0.685 and 1.045; p=0.982). After a single oral dose, TFV-DP was detected in 5/9 vaginal and 9/9 rectal biopsy specimens (5 and 7.9 mfs/mg, respectively).

**Conclusion:** A clinically equivalent dose of single agent TAF administered orally 24h before and 2h after virus exposure without FTC conferred moderate protection against vaginal SHIV infection in female macaques. These data highlight the importance of defining the PBMC TFV-DP concentrations associated with complete viral protection from single agent TAF.

**103 LYMPHOID TISSUE PHARMACOKINETICS OF TENOFOVIR-ALAFENAMIDE VS -DISOPROXIL FUMARATE**

**Courtney V. Fletcher,** Ann Thorkelson, Kayla Campbell, Lee Winchester, Timothy Mykriš, Jon Weinhold, Jodi Anderson, Jacob Zulk, Puleng Moshele, Sir Jostad, Anthony Podany, Jason V. Baker, Timothy Schacker

**Background:** The secondary lymphoid tissues (LT), lymph nodes (LN) and gut-associated lymphoid tissue (GALT), are the primary sites of HIV replication and where the latent pool of virus is maintained. In HIV-infected persons with undetectable plasma HIV-RNA, an association has been reported between low concentrations of antiretroviral drugs (ARVs) in LT and measures of persistent viral production. In animals, tenofovir alafenamide (TAF) has been found to have enhanced LT penetration compared with tenofovir disoproxil fumarate (TDF). No confirmatory or comparative human LT data, however, are available. The objective of this work was to compare the LT pharmacokinetics (PK) of TAF and TDF in HIV-infected persons.

**Methods:** Participants were HIV-infected persons enrolled in clinical studies of LT compartments and receiving TAF or TDF with other ARVs. PBMCs and mononuclear cells (MNCs) from LN, ileum and rectal tissues were obtained at steady-state. Intracellular concentrations of tenofovir-diphosphate (TFV-DP) were quantified by LC/MS/MS. Summary statistics were calculated.

**Results:** PK data were obtained from a total of 58 persons. TAF, n=13; TDF, n=45. The Table presents median and interquartile range values for TFV-DP in PBMCs (TAF, n=38; TDF, n=45), LN (TAF, n=9; TDF, n=43), ileum (TAF, n=9; TDF, n=22) and rectum (TAF, n=7; TDF, n=35). In PBMCs, median TFV-DP concentrations were 7-fold higher with TAF compared with TDF. In LN MNCs, TFV-DP concentrations were 4.7-fold higher with TAF vs. TDF.

**Conclusion:** TAF administration in HIV-infected persons produced higher TFV-DP concentrations in LN MNCs than did TDF. This finding confirms animal studies showing LN concentrations of TFV-DP were 5.7 to 15-fold higher with TAF, depending on the anatomical site of the LN. The 7-fold higher TFV-DP concentrations in PBMCs achieved with TAF vs. TDF, is consistent with other literature and known PK characteristics of TAF and TDF. TFV-DP concentrations in the ileum and rectum were lower with TAF compared with TDF; this may be due acting single agent delivered from implants.
to better bioavailability of TAF vs. TDF and thus a lower fraction of unabsorbed drug in the gastrointestinal lumen. The higher LN concentrations of TFV-DP achieved with TAF demonstrate that drug penetration into this compartment can be modified in HIV-infected persons. This finding allows pharmacodynamic evaluations to investigate whether enhanced LN concentrations elicit a different virologic response.

### Table: Baseline HIV risk, on-study STIs, HIV incidence rates in US (not on PrEP) and in DISCOVER

| Baseline HIV risk (%) | Preexposure drug use in prior 12W | Prescribed by a FG providers | Any STI | Any STI | Atezolizumab group
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</thead>
<tbody>
<tr>
<td>HIV incidence rate in (not on PrEP)</td>
<td>9.9/12/5.9</td>
<td>25.6</td>
<td>10</td>
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#### Methods

This randomized (1:1), double-blind, active-controlled study was conducted in North America and Europe at sites with high HIV prevalence in MSM. Entry required ≥2 episodes of condomless anal sex (CAS) in past 12W or rectal gonorrhea/chlamydia or syphilis in past 24W. Participants received daily blinded F/TAF (200/25 mg) or F/TDF (200/300 mg), with matching placebo; pill counts and blood levels were used to measure adherence. Primary endpoint was the HIV infection rate per 100 persons year (PY) when 50% completed 96W. Renal safety, 3 anatomic site sexually transmitted infection (STI) testing and risk behavior were assessed every 12W. Using CD4 reported HIV surveillance data we calculated the background “HIV incidence rate” in at risk individuals not on PrEP from 105 US metropolitan statistical areas (MSAs) for comparison.

#### Results

Of 3,751,740 eligible patients in 2007-2017, there were 1422 incident HIV cases. The best-performing model for predicting incident HIV was least absolute shrinkage and selection operator (Lasso), with an AUC of 0.90 in 2007-2014. The final model included 41 predictors, such as Black race, home ZIP code, and behavioral variables potentially predictive of HIV risk, we applied logistic regression and machine learning methods to predict incident HIV cases in a derivation dataset of patients entering the cohort in 2007-2014. We assessed performance of candidate models by cross-validated area under the curve (AUC, range 0-1). We evaluated how the best-performing model might perform prospectively by validating it among members entering the cohort in 2015-2017, and compared this full model with simpler models using only traditional risk factor variables (i.e., men who have sex with men [MSM] and sexually transmitted infections [STIs]).

#### Conclusion

Prediction models using EHR data can identify patients who are at high risk of HIV acquisition but uptake has not been limited. Electronic health record (EHR) data may help identify patients who are at high risk of HIV acquisition and could benefit from PrEP.

### Background

HIV preexposure prophylaxis (PrEP) prevents HIV acquisition but uptake has not been limited. Electronic health record (EHR) data may help identify patients who are at high risk of HIV acquisition and could benefit from PrEP.

### Methods

We developed and validated a prediction model to identify potential PrEP candidates in a cohort of members of Kaiser Permanente Northern California not diagnosed with HIV and having ≥2 years of enrollment and ≥1 outpatient visit during 2007-2017. Using EHR data on 68 demographic, clinical, and behavioral variables potentially predictive of HIV risk, we applied logistic regression and machine learning methods to predict incident HIV cases in a derivation dataset of patients entering the cohort in 2007-2014. We assessed performance of candidate models by cross-validated area under the curve (AUC, range 0-1). We evaluated how the best-performing model might perform prospectively by validating it among members entering the cohort in 2015-2017, and compared this full model with simpler models using only traditional risk factor variables (i.e., men who have sex with men [MSM] and sexually transmitted infections [STIs]).

#### Results

Of 3,751,740 eligible patients in 2007-2017, there were 1422 incident HIV cases. The best-performing model for predicting incident HIV was least absolute shrinkage and selection operator (Lasso), with an AUC of 0.90 in 2007-2014. The final model included 41 predictors, such as Black race, home ZIP code, and use of medications for erectile dysfunction. The full model performed well when validated prospectively using 2015-2017 data (AUC 0.89). Model performance remained high when excluding the MSM variable (AUC 0.87) or STI variables (AUC 0.90), but was reduced when including only MSM (AUC 0.74), STIs (AUC 0.61), or both (AUC 0.78; Figure). Patients in the top 1% of HIV risk scores included 45/68 (66%) male HIV cases but 0/13 (0%) female HIV cases among those entering the cohort in 2015-2017. Using the top 1% of risk scores to define potential PrEP candidates in 2015-2017, we identified 6076 candidates, of whom 5577 (92%) were not currently on PrEP.

#### Conclusion

Prediction models using EHR data can identify patients who are at high risk of HIV acquisition but not using PrEP, and should be tested as a strategy to improve PrEP use. Models using rich clinical data outperform models using only traditional risk factor variables. Additional EHR variables or other data are needed to identify females who may benefit from PrEP.
PERSISTENCE WITH HIV PREEXPOSURE PROPHYLAXIS IN THE UNITED STATES, 2012-2016

Ya-Lin A. Huang, Guoyu Tao, Dawn K. Smith, Karen W. Hoover

CDC, Atlanta, GA, USA

Background: Daily oral preexposure prophylaxis (PrEP) with Truvada is highly effective in preventing HIV infection with adherence to daily dosing and persistence with PrEP during periods of HIV risk. We estimated persistence and associated factors among a cohort of PrEP users with commercial health insurance.

Methods: Using data from the IBM® MarketScan® Research Databases, we created a cohort of PrEP users aged 18-64 years who initiated PrEP between 1/1/2012 and 12/31/2016. We restricted our analysis to persons continuously enrolled in their health plans for at least 6 months prior to and 6 months after their initial PrEP prescription. We monitored each person’s medication fill persistence, defined as time from the initial PrEP prescription fill until there was a gap in prescription fills >30 days. Patients were considered nonpersistent if they did not refill within 30 days after exhausting PrEP medications from previous fills. We used Kaplan-Meier time-to-event methods to estimate the proportion of PrEP users who persisted with PrEP at 6 and 12 months after initiation. We censored patients if they disenrolled from insurance or were diagnosed with HIV prior to nonpersistence. We conducted Cox proportional hazards models for nonpersistence adjusting for sex, age, urbanicity, and other factors.

Results: In our cohort of 7,250 commercially insured PrEP users, 98.2% were male, and 10.6% were aged 18-24 years. During the study period, after initiation 74.8% of PrEP users persisted for 6 months, and 53.7% for 12 months. The median persistence was 14.5 months (95% CI: 13.9-15.0), but was significantly shorter for female PrEP users (6.9 months; 95% CI: 4.7-11.6) and for users aged 18-24 years (8.6 months; 95% CI: 7.4-9.3). After adjusting for other factors, we found that PrEP users who were female, young, and resided in rural area were less likely to be persistent users. The Kaplan-Meier curves of PrEP persistence stratified by age group demonstrated that PrEP persistence increased with age. Only 36.6% of the users aged 18-24 years persisted for 12 months, compared to 65.3% aged 55-64 years. (Figure)

Conclusion: More than half of commercially insured persons who initiated PrEP persisted with it for 12 months. However, women and young users persisted with PrEP for shorter times than men or older adults. We were not able to assess reasons for PrEP nonpersistence. A better understanding of patient factors for nonpersistence is important to support PrEP use for persons who might benefit from it during periods of risk.

IMPACT OF PREP ON DRUG RESISTANCE AND ACUTE HIV INFECTION, NEW YORK CITY, 2015-2017

Kavita Misra, Jamie Huang, Demetre C. Daskalakis, Chi-Chi Udeagu

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Background: A major concern for PrEP use is possible induction of drug resistance by prescribing PrEP to persons with undiagnosed HIV infection. Such persons may not have been screened appropriately for HIV or may have been screened during the window period between HIV exposure and infection. However, no data are available to determine the frequency of this phenomenon.

Methods: Using data from cases assigned for partner services from November 2015 to August 2017, we examined the viral resistance profile of recently diagnosed persons (< 12 months) in New York City (NYC) with a recent history of PrEP use to determine rates of mutations to PrEP component medications: emtricitabine (3TC) (M184I/V/IV/MV) and tenofovir disoproxil fumarate (TDF) (K65R). We compared acute HIV infection (AHI), negative NAAT, and prevalence of viral resistance in pre-diagnosis PrEP users and those with no PrEP use (never-users).

Results: In this period, 95 (3%) out of 3,721 persons with a recent HIV diagnosis assigned for partner services had a report of pre-diagnosis PrEP use. Median duration of PrEP exposure before diagnosis was 3 months (IQR=7). Pre-diagnosis PrEP users were more likely than never-users to have a negative NAAT pre-diagnosis (33% vs 4%, p<0.0001), and were more likely to be diagnosed with AHI (33% vs 9%, p<0.0001). Genotypes were available for 75% of pre-diagnosis PrEP users and 62% of never-users. M184I/V/IV/MV was significantly more prevalent among pre-diagnosis PrEP users than never-users (26% vs 2%, p-value <0.0001). K65R mutations were found in 4 persons; none were pre-diagnosis PrEP users.

Conclusion: In a study of recently HIV diagnosed people from NYC, persons with a history of pre-diagnosis PrEP use were significantly more likely to have resistance mutations to 3TC. There were no signature TDF mutations (K65R) detected among pre-diagnosis PrEP users. In addition, persons with a history of PrEP were significantly more likely to have AHI leading to diagnosis. The latter may be due to an effect of the PrEP or the possibility that persons receiving PrEP are more likely to be receiving health care more regularly. Only one-third of pre-diagnosis PrEP users had evidence of a negative NAAT. Our findings stress the importance of screening regularly to reduce the likelihood of PrEP start during undetected HIV infection in order to reduce the risk of inducing drug resistance.

THE CURRENT STATUS OF LATENCY REVERSING AGENTS

Carine M. Van Lint, Université Libre de Bruxelles, Brussels, Belgium

Combination antiretroviral therapy (cART) successfully prolongs the life of HIV+ patients, prevents the development of AIDS and substantially reduces the risk of HIV-1 transmission. However, cART is not curative and patients must adhere to a life-long cART regimen, leading to a new set of complications and making of HIV a chronic disease. Indeed, cessation of cART invariably leads to a rapid rebound
of the virus in most patients. HIV-1 persistence is notably due to the existence of replication-competent, transcriptionally-silent proviruses in a latent state. Latently-infected cells, mainly resting CD4+ T cells but possibly other infected cell types, are insensitive to cART and can evade the patient immune system. However, latency is a reversible state and reactivation of HIV-1 gene expression from latently-infected cells constitutes a permanent source for virus production in cART-treated patients. One of the most explored therapeutic approach aiming at purging HIV-1 reservoirs, the shock and kill strategy, consists in reactivating HIV-1 gene expression from the latently-infected cellular reservoirs, followed by killing of the virus-producing infected cells. Several classes of latency reversing agents (LRAs), including epigenetic modifying agents, have been studied to reactivate viral gene expression, based on the understanding of the molecular mechanisms involved in HIV-1 latency. Due to the small numbers of latently-infected cells found in vivo, these molecular mechanisms have been mainly studied in vitro cell line and primary cell models for HIV-1 latency and in ex vivo models obtained with patient-derived latently-infected cells. However, many of these studies have highlighted the major contribution of epigenetic and transcriptional mechanisms to HIV-1 silencing. Clinical trials using individual LRAs have yielded variable, but sometimes encouraging results concerning their ability to induce HIV-1 transcription. However, none of these trials have caused significant and persistent reduction in the HIV-1 reservoir size. The multiplicity of the silencing mechanisms involved in HIV-1 latency, the intrinsically dynamic and heterogeneous nature of the latent HIV-1 cellular reservoirs, the variations in patient clinical history and the lack of selectivity of LRAs constitute causes of the LRA inefficacy in clinical trials. These causes will need to be understood in order to rationally improve the “shock” strategy so that it could reach clinical success.

109 DISCOVERY AND CHARACTERIZATION OF A VIRUS-INTRINSIC HIV LATENCY CIRCUIT
Leor Weinberger, Gladstone Institutes, San Francisco, CA, USA
Over the past decade, our studies found that HIV-1 latency is driven by stochastic fluctuations in Tat transcription (Weinberger et al. Cell 2005), which provided the first evidence for a classic theory that transcriptional fluctuations (a.k.a., ‘noise’) are harnessed for cell-fate decisions. We subsequently characterized a ‘hardwired’ virus-intrinsic HIV circuit that regulates latency and appears optimized by evolution (Razooky et al. Cell 2015; Rouzine et al. Cell 2015). Our studies also found FDA-approved compounds that act as noise-enhancer molecules and potentiate current LRAs, dramatically increasing their potency (Dar et al. PNAS 2012; Dar et al. Science 2014). Recently, we discovered that HIV alternative splicing is post transcriptional, thereby generating a noise-attenuating circuit that regulates HIV’s latency decision (Hansen et al. Cell 2018). Perturbing the HIV latency circuit, for example with noise-enhancer or suppressor molecules, may represent a novel strategy for HIV cure, and functional cure, approaches.

112 DYNAMICS OF ACUTE HCV IN WESTERN EUROPE
Jürgen K. Rockstroh, University of Bonn, Bonn, Germany
The Global Health Sector Strategy GHSS calls for the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%). Indeed, with the advent of highly successful and well tolerated direct acting antiviral combinations, allowing HCV cure after short durations of treatment within 8-12 weeks in more than 95% of all treated patients, HCV elimination appears to be a reachable goal. Nevertheless, the WHO report from 2016 clearly describes some significant obstacles which need to be overcome in order to approach HCV elimination. The first major obstacle clearly is underdiagnoses with only 20% of people with HCV worldwide having been diagnosed so far. Equally disturbing is that while approximately 71 million people were thought to be infected with HCV in 2015, only 1.76 million people received HCV treatment in 2016 despite all praised advances in HCV therapy. Microelimination in well targeted patient groups with regular monitoring such as hemophiliacs, dialysis patients and also HIV/HCV coinfected patients therefore, appear low-hanging fruits on the pathway to global HCV elimination. First national studies from Netherlands and Switzerland suggest that indeed by increasing treatment uptake in all HIV/HCV coinfected men who have sex with men (MSM) the incidence of newly acquired acute HCV infections has been successfully reduced by over 50%. Nevertheless, increased HCV outbreaks among HIV negative MSM using PrEP as well as the high risk of HCV reinfection in MSM in general jeopardize these first encouraging reports. Clearly, earlier HCV treatment initiation and use of HCV-RNA and HCV-antigen testing rather than HCV-serology, allowing earlier acute HCV diagnosis, will be needed to impact HCV dynamics in the long-term. Under consideration of the still significantly increasing PrEP user number in Western Europe a call for action is needed to prevent a further spread of HCV into the MSM community.
higher than new HCV infection rates. However, a recent study showed that nearly 60% of surveyed countries had the opposite—more HCV infections than cures. Therefore, control is unlikely to occur without improved focus on and success in reducing the number of new HCV infections. Risk factors for HCV infection vary globally, but together result in ~1.75 million new HCV infections annually worldwide. An effective preventative HCV vaccine could prevent transmission regardless of risk factors. While a highly effective vaccine could prevent infection altogether, a vaccine that increases the rate of HCV clearance and prevents chronic infection may be sufficient to reduce transmission and disease burden. Despite vaccine need, barriers to vaccine development remain, including limitations to HCV culture systems, viral diversity, limited models and at-risk populations for testing vaccines, and incomplete understanding of protective immune responses. On the positive side, there is evidence that protective immunity exists in populations at ongoing risk of infection. For those who have cleared initial infection and become reinfected, more rapid and effective control of viral replication with subsequent exposures compared to initial exposure supports that adaptive immunity develops and, while not sterilizing, that it protects against chronic disease. Decades of research have revealed that HCV-specific CD4+ helper T cells, CD8+ cytotoxic T cells, and antibodies are all important in mediating protection against persistent HCV infection. Vaccine strategies to induce all three adaptive immune responses are in development. Adjuvanted envelope or core protein and virally vectored non-structural antigen vaccines have advanced into healthy volunteers not at risk for HCV, with viral vectors encoding non-structural proteins the only vaccine strategy tested in at-risk individuals to date. Despite development challenges, a prophylactic vaccine is necessary for global HCV control. This talk will discuss the need for a vaccine, evidence that a vaccine to prevent chronic infection is possible, challenges to immunologic control of HCV, and the vaccine strategies tested to date.

114 CHOICES AND DILEMMAS: PREVENTING TUBERCULOSIS IN PEOPLE WITH HIV INFECTION

Amita Gupta, Johns Hopkins University, Baltimore, MD, USA

An estimated 23% of the world’s population is infected with tuberculosis infection. Notably, an estimated 300,000 people with HIV died from tuberculosis in 2017 with the vast majority of deaths occurring in low and middle income countries. Preventing tuberculosis in people living with HIV is therefore a global priority. The most common regimen used for tuberculosis preventative therapy has been Isoniazid Preventive therapy. However this regimen requires 6-9 months of daily therapy with longer therapy needed for areas with high community exposure and incidence. Recently several trials have identified newer and shorter regimens for tuberculosis prevention: a one month daily isoniazid with rifapentine regimen; a 3 month weekly isoniazid and rifapentine regimen; and a 4 month daily isoniazid and rifampin regimen. In addition special populations such as children and pregnant women have also been more formally studied in clinical trials. Phase II vaccines trials for the prevention of tuberculosis have also had some interesting results. Lastly, expert guidance statements and new clinical trials have been launched for preventing tuberculosis in those with known exposure to multi-drug tuberculosis. This talk will summarize the data from these different studies and highlight the choices and dilemmas of preventing tuberculosis in people living with HIV infection.

115 TREATING MULTIDRUG-RESISTANT TUBERCULOSIS IN THE REAL WORLD: NEW DRUGS AND REGIMENS

Jennifer Furin, Harvard Medical School, Boston, MA, USA

The treatment landscape for rifampin-resistant forms of tuberculosis (RR-TB) is rapidly changing with the introduction of new drugs and shorter treatment regimens. For the first time ever, phase III trials and rigorous operational research studies are being done to support policy on the optimal management of RR-TB. This information is being used by programs and normative public health bodies to offer radically different therapeutic options for people living with the disease, including all-oral therapy. There are, however, inherent tensions between the existing RR-TB science, the WHO treatment recommendations, and what is actually being done in countries. This is driven in part by the noxious “standard of care” regimen and the long periods of time it takes to design, execute and complete RR-TB trials. This session will present the 2018 WHO recommendations for the treatment of RR-TB and the science behind those recommendations, including the STREAM-1 and delamanid phase III trials. The status of ongoing RR-TB studies will also be reviewed, with an eye toward improving the way RR-TB clinical trials are done. Finally, the state of the field will be discussed in terms of ethics, human, rights, and an alarming lack of access to novel therapies in most regions of the world, since advances in RR-TB science mean little if they cannot reach the people who need them most.

116 THE STORY OF U=U: SCIENTIFIC UNDERPINNINGS

Pietro L. Vernazza, St Gallen Cantonal Hospital, St Gallen, Switzerland

The story of U=U began in the 1990s when it became apparent that the risk of sexual transmission of HIV varied by sexual practice. In the beginning of this century, many physicians started to question if there was in fact any risk of HIV transmission at all during fully suppressive antiretroviral therapy. The Rakai data indicated risk of transmission to HIV negative serodifferent partners was strongly correlated with the viral load of the positive partner; and while only two small observational studies prospectively evaluated this question in the setting of fully suppressive cART, the absence of any documented case of transmission with suppressive ART gained attention. In 2008 the Swiss Federal Commission on AIDS related issues published what became rapidly known as the “Swiss statement”. Based on the absence of any reported case and on additional biological data supporting the observation, the commission decided that the evidence was strong enough to claim absence of any risk of sexual transmission in the setting of optimal cART use. The statement also made reference to other similar public health messages, such as non-transmission to household contacts, where the absence of evidence was the only basis for such statements. Furthermore, the publication of the Swiss statement raised the profile of this issue and likely supported the reporting of any observed cases of transmission. The continued absence of evidence of any such cases was a further argument supporting the statement of “no-risk”. The obvious weakness of the “Swiss statement” was the assumed detection and reporting of cases of transmission. Therefore, the development of prospective, well-designed studies actively looking for cases of transmission in the setting of suppressive ART provided important scientific evidence to support the statement of “no-risk”. None of three large studies observed a single case of sexual transmission in the setting of fully suppressive cART. The increasing number of documented exposures without any signal of risk of transmission increases the certainty of the “no risk” statement.

117 CARING FOR U: CLINICAL CONUNDRUMS

Nneka Nwokolo, Chelsea and Westminster Hospital, London, UK

U=U, the concept that a person with an undetectable viral load is incapable of transmitting HIV sexually, has transformed the lives of people living with HIV worldwide and is doing much to reduce the stigma associated with this condition (although there is still a long way to go). Evidence for U=U comes from clinical trials involving thousands of couples (both homosexual and heterosexual) in serodifferent relationships in which no linked transmissions occurred from HIV-positive people with fully-suppressed viral loads. Clinically, however, the practical implementation of U=U in some circumstances may pose a significant challenge; for example, - Can a clinician discussing the risk of transmission with a patient in a resource-limited setting with poor or no access to viral load monitoring, or where structural factors and competing priorities adversely impact adherence, reassure that patient with the same certainty as they could an individual who doesn’t have these concerns? - Strictly speaking, U=U applies to the risk of sexual transmission; can we reliably apply this message in the context of breastfeeding, to a healthcare worker following a sharps injury or to an HIV negative individual who shares a syringe during intravenous drug use? - Should we offer postexposure prophylaxis to a patient with a sexually transmitted infection whose sexual partner informs him or her that they have an undetectable viral load? So, while at an individual level, U=U provides powerful motivation for adherence to treatment and retention in care, it is crucial that we continue to strive for answers to the many as yet unanswered questions that still remain.

118 ME AND U: COMMUNITY PERSPECTIVES

Carrie Foote, Indiana University, Bloomington, IN, USA

In early 2016, the Undetectable=Untransmissible (U=U) campaign began in an effort to ensure the message of U=U was shared with community; at the time there was much resistance to the science and hesitance to share the message with providers and people living with HIV. Led by people living with HIV, the campaign took off and now has become global; the U=U slogan is now universally known in the HIV arena around the world. This session provides an
overview of the global campaign today, some of the main community impacts, and remaining community challenges. Key issues covered include: the impact of U=U on dismantling HIV related stigma; importance of ‘language matters’ when communicating the U=U science; and the impact of U=U on the sexual and reproductive lives of PLWH. Community concerns discussed include the continued resistance to sharing the message, limited updates to existing resources to reflect the U=U science; questions about breastfeeding and syringe sharing; concerns with unequal access to testing, treatment and care; and concerns with stigmatizing and criminalizing people living with HIV who are not virally suppressed. Personal stories of PLWH and examples of the campaign are shared to illustrate the main points.

More Than U: Maximizing Population-Level Effects of U=U
Andrew E. Grulich, University of New South Wales, Sydney, NSW, Australia

At the population level, U=U is part of HIV treatment as prevention. HIV treatment as prevention explicitly includes the goals of increasing HIV testing, HIV treatment, and undetectable viral load. In 2014, UNAIDS released its 90/90/90 goals with the dual aims of improving the health of people living with HIV and reducing HIV transmission to lead to the end of the AIDS epidemic. The 90/90/90 goals are based in part on modelling of the preventive effects of HIV treatment as prevention in an African heterosexual epidemic. Several pragmatic population-based trials of HIV treatment as prevention are underway in sub-Saharan Africa, and observational evidence provide strong evidence that treatment roll-out has been associated with reduced HIV transmission in some settings. In epidemics where transmission among men who have sex with men (MSM) predominates, transmission dynamics are substantially different, and it is likely that achieving the 90/90/90 goals may not be enough, on its own, to end the HIV epidemic. U=U is a vital part of combination prevention, and effects are maximised where it is combined with ensuring early HIV diagnosis. The treatment as prevention.

The Challenges of HIV Treatment in an Era of Polypharmacy
David Back, University of Liverpool, Liverpool, UK

The prevalence of HIV-infected people aged 50 years or older is increasing rapidly and this population often exhibits a higher number of comorbidities and other age-related conditions at a younger age than in the general population. Numerous cohort studies (eg NA-Accord, EuroSIDA, DatAIDS, GEPP, PODIVM, MACS, US Veterans Affairs, POPPY; SHCS) have highlighted the increasing burden of co-morbidities in older PLWH with some studies describing the prevalence of polypharmacy (most often described as more than 5 co-medications) to be >40%. With polypharmacy comes the inevitable consideration of drug-drug interactions (DDIs). So we need to understand i) the mechanisms of DDIs (which are not always CYP-mediated), ii) the difference in DDI potential of the currently recommended antiretroviral agents and iii) the clinical relevance of DDIs. We always need to be aware of the unexpected! The prescribing information or label of a drug is often the primary source of DDI awareness. But the labels cover a limited number of specific DDIs and not infrequently there are differences between the US Prescribing Information and the European SmPC or country specific information which may confuse. Therefore health care professionals often rely on other sources (websites, apps) for their daily management of DDIs. With commonly used co-medications it may be necessary to: change or modify the dose of a co-medication, change the ARV, modify the dose of the ARV or take care with the timing of administration. However it is also important to take care that co-med are not under dosed. As we look to the future, we need research programs to determine the impact of eliminating medications not essential for quality of life and survival for those aging with HIV (ie de-prescribing). We also need to face the challenge of DDI studies with long acting ARVs – currently injectable and implants. However there are other emerging technologies and with all long acting medicines there will be an important role for PBPK modelling in generating DDI data in virtual patients.

NeuroHIV: What the Virus Tells Us
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HIV-1 can be detected in the brain/CNS, and more conveniently in cerebral spinal fluid (CSF), at all times after infection. Its presence reflects a number of processes ranging from the trafficking of infected T cells through the establishment of an independently replicating population (compartmentalization) where the virus has evolved to infect a host cell with a low density of CD4 (CD4<sup>+</sup> phenotype). A deeper understanding of these multiple processes has come from a clearer definition of viral entry phenotypes. A common misconception in the HIV-1 field is that all viruses that use CCR5 (RS viruses) are macrophage-tropic. In fact, macrophage-tropic/viruses, with their ability to enter cells with a low density of CD4 (as seen on macrophages), are rarely found in the blood and have not been detected among transmitted/founder viruses. The main form of HIV-1 found in the blood, and the form that enters the CNS by trafficking in infected T cells, uses CCR5 but requires a high density of CD4 (as seen on CD4<sup>+</sup> T cells) for efficient entry; this predominant form of HIV-1 is more appropriately called RS T cell-tropic. This clearer understanding of HIV-1 entry phenotypes has allowed a reassessment of when and where macrophage-tropic/CD4<sup>+</sup> viruses evolve and their role in pathogenesis. Earlier studies highlighted the detection of CD4<sup>+</sup> viruses in the CNS and their link to severe CNS disease at late stages prior to death, such as HIV-associated dementia (HAD). The evolution of macrophage-tropic viruses can be viewed as an evolutionary path the virus follows when its target CD4<sup>+</sup> T cells become limiting, a situation that is especially common behind the blood-brain barrier in the CNS. Persistent viral infection in the brain is likely to be very different from infection of CD4<sup>+</sup> T cells in tissues such as lymph nodes, spleen, and GALT. The question of viral escape in the CNS during suppressive therapy, either transient or persistent, can now be addressed in the context of viruses that are adapted to replication in this environment. Similarly, rebound virus in the CSF after treatment interruption may provide insight into the presence of compartmentalized reservoirs.

BRAIN CONNECTIVITY IN NEUROLOGICALLY ASYMPTOMATIC PEOPLE WITH HIV SWITCHING ART
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Background: Central nervous system (CNS) toxicities of antiretroviral therapies are well described. Functional MRI (fMRI) can assess brain activity and functional connectivity (FC) non-invasively, providing insights into pathogenic mechanisms. We assessed changes in fMRI patterns in neurologically asymptomatic people with HIV (PWH) participating in two studies assessing CNS parameters when switching antiretroviral therapy.

Methods: Virologically suppressed PWH switching from tenofovir DF/emtricitabine (TDF/F) with efavirenz to rilpivirine (n=10) and TDF/F with raltegravir to dolutegravir (n=12) were included. Changes in CNS parameters included patient-reported outcome measures (PROM) of sleep (PSQI) and depression (HADS). fMRI imaging was assessed at baseline and at least 120 days after switching therapy and included resting-state fMRI (RS-fMRI) and behavioral stop signal reaction times (SSRT) task fMRI. Resting state and SSRT fMRI were examined by independent component analyses (ICA) using the FSL’s MELODIC tool.

Results: Of 22 participants, all were male, median age (range) was 49 (33–71) years, median CD4<sup>+</sup> count (range) was 700 (339–1164) cells/µL and HIV RNA was less than <20 copies/mL in all. Switching from efavirenz to rilpivirine was associated with enhanced connectivity of the Dorsal Attention Network (DAN) most pronounced in the right superior parietal lobule and a reduction in stop SSRTs (response inhibition, p=0.025, see figure) which was positively correlated with the duration of time previously on efavirenz (median 5 range 1–10 years, p=0.02). Switching from raltegravir to dolutegravir was associated with increased connectivity in the DAN, sensory-motor (SM), and associative visual (VISAS) networks. There was a 4.8% decline in anxiety scores on HADS and a 2% decline in sleep symptoms on PSQI, with scores of 19 and 14, and 22 and 20 at baseline and follow-up, respectively, after switching from efavirenz to rilpivirine (p<0.005) and no significant changes in PROMs when switching from raltegravir to dolutegravir. No association between changes in fMRI and PROMs were observed.

Conclusion: In PWH switching antiretroviral therapy, changes in fMRI are evident. This was most pronounced in PWH switching from efavirenz to rilpivirine where improved attention and response inhibition on fMRI was evident. Whilst changes were evident on fMRI when switching integrase inhibitor, any clinical implications of these findings require further validation.
123 DEEP-LEARNING CEREBRAL BLOOD FLOW FOR COGNITIVE-IMPAIRMENT CLASSIFICATION IN HIV

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Background: Despite the use of combination antiretroviral therapy (cART), HIV-associated neurocognitive disorders (HAND) remain prevalent in people living with HIV (PLWH). A potential biomarker reflective of HAND is changes in cerebral blood flow (CBF) over time, which can be measured with Arterial Spin Labeling. We propose a method of approximating and classifying cognitive impairment (CI) in PLWH using longitudinal CBF data and deep neural networks (DNN).

Methods: Virologically controlled (viral load < 50 copies/mL) PLWH (n=63) participants and HIV-controls (n=33) with at least 2 separate imaging sessions were analyzed. The majority were male (54%) and the mean age was 48 years (+/-13.1). Free Surfer regions were combined to get an average CBF for 12 brain regions (cerebellum, thalamus, caudate, putamen, pallidum, amygdala, frontal, parietal, temporal, cingulate, occipital). Participants completed neuropsychological testing representing 3 cognitive domains (learning, memory, and executive). Raw scores were transformed into Z-scores using demographic-corrected norms, and Z-scores within a cognitive domain were averaged for domain Z-scores. A domain Z-score < -1 was classified as CI. Average rates of change (AROC) were calculated by subtracting the CBF of time point 1 from time point 2 and dividing by the time between the scans. A DNN was trained for each cognitive domain on the CBF and AROC using cross-validation, and evaluated based on mean squared error (MSE). A low MSE (< .2) indicates good approximation.

Results: A DNN could discriminate between PLWH and HIV-controls with AUC .94 using CBF and AROC. The best individual brain regions for discriminating these 2 groups were the thalamus, amygdala, pallidum, and hippocampus. For CI prediction in PLWH, the MSE for the DNNs across all brain regions in PLWH was .11 and AUC .86. The best predictors of impairment in the learning domain in PLWH using CBF and AROC were the caudate, thalamus, and putamen. The best predictors in the memory domain in PLWH were the putamen and amygdala. The best predictors in the executive domain in PLWH were the cerebellum cortex and cingulate. All regions showed a reduction in CBF over time in PLWH.

Conclusion: HAND persist in spite of cART. Our models indicate a decrease in CBF is associated with HIV in specific brain regions, and the rate of decrease of CBF is indicative of impairment. These changes are involved in various domains and are primarily subcortical in nature.

124 HOST GLYCOMIC DETERMINANTS OF HIV-ASSOCIATED NEUROCOGNITIVE IMPAIRMENT DURING THERAPY

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Background: A comprehensive understanding of the pathophysiological mechanisms driving HIV-associated chronic inflammation can lead to the development of strategies to delay or prevent age-associated co-morbidities that are increasingly prevalent despite suppressive antiretroviral therapy (ART). Glycans on circulating glycoproteins and immunoglobulin G (IgGs) are known to modulate systemic inflammatory responses. However, whether HIV-associated chronic inflammation, at least in part, is promoted by alterations in the host glycome remains unknown.

Methods: We profiled the glycomes of plasma and IgGs from 40 HIV+ individuals (ART-suppressed and viiremic) and 10 matched HIV- controls, including a subset of ART-suppressed individuals with variation in levels of HIV-associated cognitive impairment as measured by clinical global deficit scores (GDS). We also measured levels of 16 pro- and anti-inflammatory cytokines, and markers of T-cell activation, using Luminex and flow cytometry, respectively.

Results: HIV infection was associated with persistent alterations in plasma and IgG glycomes, including decreased levels of the anti-inflammatory highly-sialylated glycans when compared to HIV- controls (FDR < 0.05). Levels of IgGs highly-sialylated glycans were reduced with age in HIV+ ART+ individuals (rho = -0.72, p = 0.005). Levels of plasma highly-sialylated glycans (A4G4S3) correlated with higher CD4 count (rho = 0.57, p = 0.03), lower levels of CD4+ T cell activation (rho = -0.66, p = 0.004), and lower levels of the pro-inflammatory cytokine TNFa (rho = -0.8, p = 0.0009). Finally, when we compared levels of glycan structures between HIV+ ART+ individuals with and without cognitive impairment (with comparable CD4 count, nadir CD4, and age), we found that levels of seven glycan structures were statistically different between the two groups (FDR<0.05). When the levels of these seven glycan structures were correlated with GDS, we found that levels of hypo-sialylated oligosaccharides positively correlate with the degree of neurological impairment (rho = 0.74, p = 0.0001).

Conclusion: Our data show that altered glycosylation patterns persist despite suppressive ART, and suggest that lower levels of sialylated glycans, with documented anti-inflammatory roles, may contribute to immune activation, chronic inflammation, and the pathogenesis of combinatorial HIV- and age-associated co-morbidities affecting the central nervous system.
Methods: sCD30 levels were measured in banked cerebrospinal fluid (CSF) samples and matching plasma from healthy HIV-uninfected controls (n=18), HIV-infected viremic individuals (n=52), individuals on suppressive ART (n=40), HIV-controllers (n=10), and participants with CSF escape (plasma RNA <50 copies/mL, detectable CSF RNA; n=10). sCD30 levels (median, IQR) were compared across groups and correlated with CSF HIV RNA and markers of axonal injury and myeloid cell activation using nonparametric tests.

Results: Compared with uninfected controls (30 ng/mL, 23-50), plasma sCD30 levels were elevated in viremic participants (75 ng/mL, 53-116; p<0.001), but not in those on suppressive ART (35 ng/mL, 31-39). In contrast, CSF sCD30 levels remained elevated in ART-suppressed individuals (34 ng/mL, 19-46; p=0.002) and in those with CSF escape (33 ng/mL, 27-40; p=0.004) compared with controls (18 ng/mL, 11-23). Interestingly, individuals with very low level CSF HIV RNA (detectable but <40 copies/mL) had higher CSF sCD30 than those with higher RNA levels (quantifiable above the limit of detection) and to participants with undetectable CSF RNA (median 33 vs 24 vs 19 ng/mL, p=0.005). No association was observed between CSF sCD30 and plasma HIV RNA, concurrent or nadir CD4 T cell count, duration of infection, plasma sCD30, or CSF total protein. CSF sCD30 correlated with CSF neurofilament-light chain, a marker of axonal injury (r=0.36, p<0.001), but not with neopterin, a marker of myeloid cell activation.

Conclusion: Soluble CD30 levels remain elevated in the CSF but not plasma of HIV-infected individuals on ART. In addition, CSF sCD30 is correlated with neuronal injury markers and low-level residual CNS viremia, but not with markers of myeloid cell activation or general CNS inflammation. CSF sCD30 appears to be produced in the setting of very low, but not higher, levels of CSF HIV RNA, which may reflect virus release compared to the high burst size characteristic of productive viral infection.

Figure 1. Shown is median +/- IQR.
risk of neuronal harm compared to TDF, we compared plasma NFL levels in patients switching from cobi/entec/teno/efav from E/C/TDF to E/C/TAF with those who continued E/C/TDF.

**Methods:** Plasma NFL was analysed at baseline, week 24, and week 84, in stored plasma samples from 414 participants (272 switching to E/C/TAF and 142 continuing E/C/TDF) enrolled in the randomized, active-controlled, multicenter, open-label, noninferiority Gilead GS-109 trial. For quality control (QC) plasma samples with NFL concentrations of 12.1 pg/mL and 188 pg/mL, intra-assay coefficients of variation (CVs) were 7.8% and 6.7%, respectively.

**Results:** We found a small but statistical significant decrease in plasma NFL in the E/C/TAF arm after 84 weeks from 10.3 to 9.6 pg/mL, p<0.01 (Figure). The change was significantly different (p<0.01) from the E/C/TDF arm, in which plasma NFL increased from 11.1 to 11.7 pg/mL (ns). As expected, eGFR increased in the E/C/TAF arm but not in the E/C/TDF arm. Plasma NFL was significantly correlated with age and eGFR. Delta eGFR and treatment group were both found as independent predictors of plasma NFL changes from baseline to week 84 in a multiple linear regression analysis.

**Conclusion:** We found no evidence of increased risk of CNS injury when switching from TDF to TAF. It should be noted that the NFL levels in both arms were within the limits normally found in HIV-negative controls; it is unclear whether the small decrease in plasma NFL found after switch to TAF is of any clinical significance. This study indicates that switching from TDF to TAF appears safe with regard to neuronal injury.

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**128** **CARDIOVASCULAR RISK SCORES PREDICT LONGITUDINAL COGNITIVE FUNCTION IN OLDER PLWH**

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**Background:** Cardiovascular (CV) disease (CVD) and associated risk factors have been linked with neurocognitive impairment (NCI) in cross-sectional studies of persons living with HIV (PLWH), although the specific CV risk factors that correlate with NCI have varied. We examined the utility of two commonly used 10-year CV risk scores—the Atherosclerotic CVD (ASCVD) and Framingham Heart Study Global CV risk score (FRS), which combine multiple CV risk factors—to predict longitudinal cognitive function in an observational cohort of older PLWH.

**Methods:** Participants from the ongoing AIDS Clinical Trials Group AS232 study who underwent neurocognitive testing (Trailmaking A and B, Hopkins Verbal Learning Test- Revised, Digit Symbol) at entry were eligible. Raw scores are standardized using demographically-adjusted norms and combined into a summary z-score (NPZ-4). Participants undergo repeat neurocognitive testing every 48 weeks. The 10-year ASCVD risk score and FRS were calculated at entry. We first assessed how well the baseline ASCVD risk score and FRS predicted NPZ-4 at Year 4 in unadjusted linear regression models. We then performed stepwise linear regression (Table) to determine the covariate-adjusted association between baseline 10-year CV risk and NPZ-4 at Year 4.

**Results:** Of 988 participants, mean age was 52 years, 20% were women, and 90% had an undetectable viral load. Mean ASCVD risk score and FRS were 6.8% and 13.1%, respectively. Both risk scores were lower in women than men (ASCVD 4.1% vs. 7.5%, p<0.001; FRS 8.1% vs. 14.3%, p<0.001). For every 1% higher baseline ASCVD risk, NPZ-4 at Year 4 was lower by 1.4 SD (p=0.003). Baseline ASCVD risk predicted NPZ-4 at Year 4 overall and in both women and men (Table). In adjusted models, for every 1% higher baseline ASCVD risk, NPZ-4 at Year 4 was 1.1 SD lower, though this did not reach statistical significance (p=0.085). Baseline ASCVD risk significantly predicted NPZ-4 at Year 4 for women (-3.1 SD per 1% higher risk, p=0.010) but not for men (-0.4 SD per 1% higher risk, p=0.55), even after adjustment for NPZ-4 at entry. The associations between baseline FRS and NPZ-4 were comparable, although higher ASCVD risk had a greater effect on NPZ-4 than higher FRS (Table).

**Conclusion:** Higher baseline 10-year CV risk predicted worse cognitive function at Year 4 in PLWH, though this association was attenuated in men after adjusting for covariates. A higher CV risk score may help to identify PLWH who are at risk for worse cognitive function over time.

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**129** **OBESITY IS INDEPENDENTLY ASSOCIATED WITH NEUROCOGNITIVE DECLINE IN HIV**

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**Background:** Neurocognition may decline more with age among people living with HIV (PLWH) compared to uninfected persons. The factors related to this decline are not well understood in the current antiretroviral therapy (ART) era.

**Methods:** AIDS Clinical Trials Group (ACTG) AS232 (HAILO) is an observational cohort study of PLWH ≥ 40 years old, on ART. Participants undergo annual assessments for neurocognitive impairment (NCI), with NCI defined by ≥1 z-score ≥2 SD below 0 or ≥2 z-scores ≥1 SD below 0 on Trailmaking A and B and the Wechsler Adult Intelligence Scale-Revised Digit Symbol tests. Obesity was defined as body mass index (BMI) >30 kg/m², overweight as ≥25-30 kg/m², normal weight as 18.5-25 kg/m², and underweight < 18.5 kg/m². Participants who developed NCI during the first 3 years were compared to persons who maintained normal neurocognition. We used logistic regression to assess the age-adjusted associations between NCI and baseline covariates including sex, race, alcohol use, BMI, waist circumference, nadir CD4, history of AIDS defining illness, hemoglobin A1C. Only covariates with a p-value < 0.1 from age-adjusted analysis were included in the multivariable models.

**Results:** Of 929 participants, 81% were male, 31% Black, and 20% Hispanic. Median age was 51 years (IQR 46-56). Most individuals (92%) had undetectable plasma HIV RNA with median CD4 count 631 cells/mm³ (IQR 458-840) at study entry. At study entry, 16% had NCI, 29% were obese, and 40% were overweight. Over 3 years, 6% of participants developed NCI while 78% remained...
unimpaired. In multivariable models, increasing age (OR 1.04; 95% CI 1.00, 1.08; p=0.04), and having an obese (OR 2.45; 1.05, 5.70; p=0.04) or overweight BMI (OR 2.21; 1.00, 4.91; p=0.05) vs normal BMI were associated with increasing prevalence of NCI compared to those who remained unimpaired.

Conclusion: Both greater age and obesity were independently associated with worsening cognitive function. These results extend previous work demonstrating a higher risk of NCI among obese PLWH by showing that obese individuals are also at greater risk of subsequently transitioning from unimpaired to impaired neurocognition.

130 HIGH HIV VIRAL BURDEN PERSISTS IN CXCR3+ GC THP DESPITE VERY EARLY ART INITIATION

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Background: Early initiation of Combination Antiretroviral Therapy (cART) during acute HIV infection blunts peak viremia, reduces HIV viral reservoirs and preserves immune function, but treatment interruptions often result in rapid viral rebound. We studied persons identified and treated at the onset of plasma viremia, in many when viral load is less than 1000 RNA copies/ml to define the dynamics of HIV suppression in lymph node (LN) tissues. Additionally, we investigated the cell subset that remained persistently HIV infected.

Methods: We studied 16 hyperacute HIV-infected subjects who initiated therapy in Fiebig stage I, subdivided into three groups based on when the LN sample was obtained. Group 1 was sampled within 3 months, group 2 was sampled at one year and group 3 was sampled after two years on therapy. Immunofluorescence (IF) microscopy and RNAscope in situ hybridization (ISH) techniques were used to quantify Gag p24 protein and Gagpol RNA respectively. The Cobas AmpliPrep HIV-1 test was used to quantify LN and plasma viral loads and viral gag and nef and envelope sequencing were conducted using ABI 3130xl sequencing platform. Digital droplet PCR was used to quantify HIV RNA levels in FACs sorted LN cell subsets and follicular CD4+ T cells harboring HIV antigens were extensively phenotyped by flow cytometry.

Results: Despite rapid plasma viral suppression at a median of 16.5 days, Gag p24 antigen and quantifiable RNA were readily detectable in the LN in 12 out of the 16 donors sampled in all three experimental groups. Moreover, sequencing analysis revealed viral evolution in Gag, Nef and/or Envelope sequences in 4 out of 6 LNs sampled >3 months after therapy compared to the transmitted founder virus sequences obtained just before cART initiation. There was no significant reduction in Gagp24 antigen in LN samples obtained after a year on cART compared to the samples obtained within 3 months on cART (p=0.04). RNA quantification of FACs sorted THF subshets showed significantly higher levels of Gag p24 mRNA copies in CXCR3+ follicular CD4+ T cells compared to other THF subshets (p=0.01).

Conclusion: Our results highlight the huge difference in viral load decay kinetics between peripheral blood and LN, despite very early cART initiation. Importantly, we identify that CXCR3+ THF contribute significantly to viral persistence in the LN during therapy. These results underscore the need for future interventions directed at eliminating residual virus in tissue sanctuaries.

131 SIROLIMUS REDUCES T-CELL CYCLING AND IMMUNE CHECKPOINT MARKER EXPRESSION, ACTG A5337

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Background: Reversing immune dysfunction and inhibiting T-cell proliferation are critical to immune-boosted HIV cure strategies. A prior retrospective analysis of the use of sirolimus, an mTOR inhibitor, in HIV+ renal transplant recipients suggests that it may lead to lower CD4+ T-cell HIV DNA, but prospective studies are lacking. Therefore, we sought to evaluate the safety of sirolimus in ART-suppressed HIV-infected individuals and its effect on immune function and HIV-1 reservoir size.

Methods: A5337 was an open-label, single-arm, pilot study of 20 weeks of oral sirolimus treatment for HIV-infected individuals on ART with HIV RNA <40 cps/mL. Eligibility criteria included at least 24 months on ART, HIV RNA < assay limit and CD4+ cell count ≥ 350 cells/mm3. Measures of T-cell activation and cycling, immune exhaustion and CRS expression (secondary efficacy outcomes) were compared by paired t-tests prior to vs after continuous oral sirolimus.

Results: 32 participants enrolled in the study. Participants had a median age of 52 years, 28% were female and 56% were black non-Hispanic. The median baseline CD4+ cell count was 813 cells/mm3. Two participants did not start study drug. 14 completed less than 20 weeks of sirolimus, and 16 completed 20 weeks of therapy. Twenty weeks after initiating sirolimus, CD4+ cell counts declined by a mean of 118 cells/mm3 (p=0.04; n=16). Three participants had a grade 3 adverse event (stomatitis and perturbations of fasting glucose in a known diabetic) or a decrease in CD4+ cell count to <300 cells/mm3. Two participants stopped sirolimus because of asymptomatic transient Epstein Barr viremia. Other individuals discontinued because of lower grade toxicities or minor, clinically insignificant laboratory abnormalities. Twenty weeks of sirolimus was associated with significant decreases in the percentages of cycling Ki67+ CD4+ and CD8+ T cells (mean change -0.3%, p=0.031, and -0.5%, p=0.005, respectively), PD-1+ CD8+ T cells (-2.9%, p=0.008), and CCR5+ CD8+ T cells (-3.9%, p=0.001).

Conclusion: Sirolimus use was associated with significant reductions in CRS markers and T-cell markers of cell cycling and immune exhaustion. There was a relatively high rate of treatment discontinuation, in part because of protocol-defined stopping criteria.

132 PD-1 AND CTLA-4 BLOCKADE IN MACAQUES INDUCES T-CELL EXPANSION AND SIV REACTIVATION

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Background: The HIV reservoir is largely composed of resting memory CD4+ T-cells, a large fraction of which expresses the co-inhibitory receptors PD-1 and CTLA-4, and is believed to be a key determinant of viral latency and immune reconstitution. We hypothesized that dual blockade of PD-1 and CTLA-4 would increase T-cell activation and function and thereby reduce HIV reservoir size.

Methods: 32 rhesus macaques (RMs) were i.v. infected with SIVmac239 and initiated ART (TDF/FTC/DTG) at day 60, which was maintained for 1 year. RMs were divided into four groups of 8 each: control antibody (n=6); anti-PD-1 mAb (n=6); anti-CTLA-4 mAb (n=6); anti-PD-1/CTLA-4 ICB (n=6). All RMs underwent analytic ART interruption (ATI). Peripheral blood (PB), lymph node (LN), and rectal biopsy (RB) were collected at one year and group 3 was sampled after two years on therapy. PBMCs were isolated, and CD4+ and CD8+ T-cells were phenotyped by flow cytometry.

Results: Central memory CD4+ T-cells, a large fraction of which express the co-inhibitory receptors PD-1 and CTLA-4, and is believed to be a key determinant of viral latency and immune reconstitution. We hypothesized that dual blockade of PD-1 and CTLA-4 would increase T-cell activation and function and thereby reduce HIV reservoir size.

Conclusion: Both greater age and obesity were independently associated with worsening cognitive function. These results extend previous work demonstrating a higher risk of NCI among obese PLWH by showing that obese individuals are also at greater risk of subsequently transitioning from unimpaired to impaired neurocognition.
potent activity in increasing SIV RNA in plasma, suggesting checkpoint blockade may facilitate viral induction and improve T-cell function.

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plasma SIVmac239 RNA copies per mL

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133 FTY720 LIMITS T FOLLICULAR HELPER CELL INFECTION IN LYMPHOID SITES OF SIV PERSISTENCE

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Background: Lymph nodes (LN) and their resident T follicular helper CD4+ T cells (Tfh) are critical sites for HIV replication and persistence. Therefore, optimizing antiviral activity in lymphoid tissues will be needed to reduce or eliminate the HIV reservoir. In this study, we treated ART-suppressed SIV-infected rhesus macaques (RM) with the lymphosphosphingolipid sphingosine-1-phosphate receptor modulator fingolimod (FTY720). With this design, we aimed at exploring the potential utility of fingolimod, approved clinically for multiple sclerosis, in retaining cytolytic lymphocytes in lymphoid sites of SIV persistence, from which they are typically excluded during ART, and to impact on the viral reservoir.

Methods: 10 RMs infected with SIVmac239 started TDF/FTC/DTG treatment at day 42 post-infection; ART was continued for 4 months. Group 1 RMs (n=5) received FTY720 at 28 µg/kg per day and Group 2 (n=5) at 50 µg/kg per day. FTY720 was administered orally once a day starting 28 days after the last dose of ART. In this study, we treated ART-suppressed SIV-infected rhesus macaques (RM) with the lymphosphosphingolipid sphingosine-1-phosphate receptor modulator fingolimod (FTY720).

Results: FTY720 treatment was safe and well tolerated, and plasma SIV levels remained undetectable (<60 RNA copies/mL) during the entire treatment.

Conclusion: FTY720 administration has the potential to limit a critical cellular reservoir of Tfh cells. As such, FTY720 should be considered in combined immune based interventions aimed at HIV remission.

134 TRANSCRIPTIONAL SIGNATURE OF LYMPH NODE CD8+ T CELLS IN HIV ELITE CONTROLLERS

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Background: Extensive evidence has indicated that peripheral blood HIV-specific CD8+ T cell cytolytic activity and effector functions are associated with the control of HIV replication in HIV elite controllers (EC). However, the majority of HIV replication in EC likely occurs in lymphoid tissue, where CD8+ T cell immune surveillance mechanisms are undefined. Here we performed single-cell RNA sequencing (scRNAseq) analyses to determine the transcriptional signature of HIV-specific CD8+ T cells that control viral replication in lymphoid tissue of EC.

Methods: We isolated human lymph node (LN) mononuclear cells from infranigal LN of HIV-infected EC and cervical LN of chronic progressors (CP) from the SCOPE cohort at UCSF and the Center for Investigation of Infectious Diseases (INER-CIENI) in Mexico City, respectively. We index sorted single HIV-specific CD8+ T cells, as identified by MH-class I tetramers, and subjected these cells for scRNAseq using the SMARTseq-v2 platform. Functional assays were analyzed on a BD LSR II flow cytometer. The results were analyzed using RStudio, FlowJo, and GraphPad Prism.

Results: Using an unsupervised scRNAseq analysis approach, we observed distinct clustering between EC cells and CP cells driven by 2264 differentially expressed genes. Compared to CP, EC cells expressed lower levels of cytolytic genes, and upregulated expression of several secreted molecules with potential anti-HIV activity, including as CCL5, TNF, and IL32. In order to determine a gene signature that could distinguish EC cells from CP cells, next we used a supervised classification approach, yielding a list of 200 genes that were enriched for immune-related and protein translation-related genes. Within this gene signature, EC cells showed a downregulation of inhibitory receptor genes and an upregulation of specific cytokines and ribosome subunits, implying that these cells are highly functional. We functionally confirmed this signature with ex vivo peptide stimulation polyfunctional cytokine and protein translation assays, finding heightened polyfunctional and protein translation capacity in lymph node CD8+ T cells from HIV EC.

Conclusion: Our findings suggest that protective HIV-specific CD8+ T cells in lymphoid tissue of EC are defined by unique non-cytolytic functional features with a high capacity to translate mRNA into protein upon antigen encounter, and call into question known correlates of protection mediated by peripheral blood CD8+ T cells.

135 CHARACTERIZING THE PROVIRAL LANDSCAPE IN HIV-1 ELITE CONTROLLERS

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Background: HIV-1 elite controllers (EC) represent a rare group (less than 1%) of infected individuals with undetectable viral loads in the absence of antiretroviral therapy (ART). However, the dynamics and evolution of the proviral reservoir in these individuals are largely unknown.

Methods: 68 HIV-1 ECs with undetectable viral loads (viral load <50), 38 viremic controllers (VCs, viral load 50-2000), and 34 chronically ART-treated patients were included in this study. Genomic DNA was extracted from PBMCs and diluted to single genome levels for HIV-1 near full-length next generation viral sequencing. Quantitative viral outgrowth assays (QVQAs) were performed...
with autologous CD4+ T cells; outgrowing virus was subjected to HIV-1 near full-genome sequencing.

**Results:** We obtained 1066, 1385, and 1601 individual proviral sequences in ECs, VCs, and ART-treated patients, respectively. The median frequency of proviral species in ECs was significantly lower than in VCs (p=0.0009) and ART-treated patients (p<0.0001). The relative number of genome-intact sequences in ECs was also significantly lower when compared to ART-treated patients (p<0.0001), but was not different from VCs (p=0.2740). Among intact proviral genomes in ECs, 46% were clonally expanded, a proportion considerably higher than in VCs (8%) but similar to ART-treated patients (31%). Notably, we identified 2 subgroups of ECs with markedly different intact reservoir sizes: one group of ECs had high proportions of intact proviral genomes within all detected proviral species, ranging from 13% to 100%; among these intact proviral genomes, very high proportions of clonal sequences were identified by full-genome sequencing (36%-80%) that frequently were entirely identical to sequences isolated from QVOA. In contrast, we observed 3 ECs in whom no intact proviral sequences were observed after assay 52-76 million PBMCs for near full-genome sequencing and another 31-67.5 million PBMCs for QVOA, suggesting that these 3 patients may approximate a sterilizing cure of HIV-1 infection.

**Conclusion:** This detailed analysis suggests that ECs can be distinguished into 2 different subgroups. ECs with unusually high proportions of intact proviral genomes and very few defective proviral sequences, and ECs with no intact proviral genomes detectable in large numbers of cells. Exploring the reasons for differential viral reservoir dynamics in these patients may allow us to identify mechanisms enabling a drug-free remission of HIV-1 infection.

136 **INTERFERON A2B REDUCES INDUCIBLE CD4-ASSOCIATED HIV IN ART-SUPPRESSED INDIVIDUALS**

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**Background:** In prior studies, treatment of ART-suppressed individuals with pIFNα resulted in a significant decrease in levels of CD4 T cell-associated inducible HIV expression from CD4 cells isolated from chronically infected, ART-suppressed individuals receiving pIFNα-2b immunotherapy in a randomized clinical trial (NCT02272777).

**Methods:** We enrolled 54 HIV-infected individuals receiving suppressive ART (HIV VL < 50 copies/ml) and with CD4 count > 450/µL who were randomized 1:1:1 to 3 treatment arms: 1. 1 µg/kg of pIFNα-2b (Pegintron, Merck) for 20 weeks, with ART interruption (start at week 4, resume ART upon confirmed VL < 20 copies/ml); 2. 1.5 µg/kg of pIFNα-2b added to ART 3. ART only (control). All subjects were sampled at baseline and week 20. CD4 + T cells were isolated from PBMC and cultured (2-10 replicates) for 16-hour with medium (control) All subjects were sampled at baseline and week 20. CD4+ T cells were measured. Consistent with pilot trial results, a 20-week course of pIFNα-2b resulted in a significant decrease in CD4+ T cell-associated inducible HIV expression from CD4 cells isolated from chronically infected, ART-suppressed individuals receiving pIFNα-2b immunotherapy in a randomized clinical trial (NCT02272777).

**Methods:** We obtained 1066, 1385, and 1601 individual proviral sequences in ECs, VCs, and ART-treated patients, respectively. The median frequency of proviral species in ECs was significantly lower than in VCs (p=0.0009) and ART-treated patients (p<0.0001). The relative number of genome-intact sequences in ECs was also significantly lower when compared to ART-treated patients (p<0.0001), but was not different from VCs (p=0.2740). Among intact proviral genomes in ECs, 46% were clonally expanded, a proportion considerably higher than in VCs (8%) but similar to ART-treated patients (31%). Notably, we identified 2 subgroups of ECs with markedly different intact reservoir sizes: one group of ECs had high proportions of intact proviral genomes within all detected proviral species, ranging from 13% to 100%; among these intact proviral genomes, very high proportions of clonal sequences were identified by full-genome sequencing (36%-80%) that frequently were entirely identical to sequences isolated from QVOA. In contrast, we observed 3 ECs in whom no intact proviral sequences were observed after assay 52-76 million PBMCs for near full-genome sequencing and another 31-67.5 million PBMCs for QVOA, suggesting that these 3 patients may approximate a sterilizing cure of HIV-1 infection.

**Conclusion:** This detailed analysis suggests that ECs can be distinguished into 2 different subgroups - ECs with unusually high proportions of intact proviral genomes and very few defective proviral sequences, and ECs with no intact proviral genomes detectable in large numbers of cells. Exploring the reasons for differential viral reservoir dynamics in these patients may allow us to identify mechanisms enabling a drug-free remission of HIV-1 infection.

**137 NEF-STOP REPAIR DYNAMICS, BUT NOT ANTI-Α4Β7, INFLUENCE POSTTREATMENT VIRAL CONTROL**

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**Background:** In contrast to published data, we have recently reported (AIDS 2018) that treatment with an antibody to eotaxin in rhesus macaques infected with STIVmac239 having a stop codon in nef (STIVmac239nefstop) was not associated with prolonged significant post-treatment suppression of viremia. The only other clear difference was the rate of peripheral blood (PB) CD4 decline below the control groups of the two studies. The current analysis attempts to identify additional factors potentially responsible for the different outcomes observed.

**Methods:** Twenty-two Mamu-A001, 8008 and B017 negative Indian rhesus macaques were infected i.v. with 200 TCID50 STIVmac239nefstop. At 5 weeks post-infection (wpi), combination anti-retroviral therapy (cART) was started and 4 weeks later, animals received a total of 8 infusions every 3 weeks of eotaxin antibody (n=12) or control antibody (n=10); cART was stopped at 18 wpi and animals were followed for additional ~7 months (set-point average 45 and 48 wpi, PVL-sp). In addition to plasma SIV RNA viral loads (PVL) and PB CD4 counts, levels of cell-associated SIV RNA and DNA viral load (Cav/L), were measured during cART administration and ~3 months post cART interruption in LN and rectal gut (RAL) biopsy samples.

**Results:** PVL peaked at week 2-5 wpi without a significant drop in PB CD4 counts by 2 wpi (~8% decline, n., n=22). A positive correlation was found within the frequency of nef-open restored viruses (FRV) and PVL at 2 wpi (r=0.66 P<0.001) as well as between FRV at 2 wpi and LN SIV-DNA Cav/L (r=0.67, P<0.001), but not PVL or RAL SIV-DNA Cav/L, at the time of cART initiation (when FRV was 100% in all animals). PVL-sp was associated with LN SIV-DNA Cav/L (r=0.62, P=0.002), but not with rectal SIV-DNA Cav/L (r=0.07, n.s.) at the time of cART interruption. ~7 months following antiretroviral treatment completion mean PVL (~10^-4 copies/ml), PB-CD4 T cell counts (~900 cells/ul), LN or rectal SIV Cav/L were not significantly different between the two groups.

**Conclusion:** While a lack of exactly corresponding analyses from the published study precludes direct comparison, the current analysis suggests that differential rates of repair of the nef mutation may have contributed to the observed different outcomes between the two studies. Following SIV infection, faster viral dissemination in LNs appears to be facilitated by restoration of the virus to nef-open and predicts higher virologic set-point following cART interruption.

**138 SEARCH INTERVENTION REDUCES MORTALITY AT A POPULATION LEVEL IN MEN WITH LOW CD4 COUNT**

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**Background:** HIV Test-and-Treat has the potential to reduce mortality of HIV+ persons with low CD4+ counts on a population level by rapidly initiating ART among “late presenters” not previously in care and among persons disconnected from prior care. We evaluated the effect of streamlined ART delivery for HIV+ persons with CD4<350 cells/µL after population-wide HIV testing during the SEARCH study (NCT01864603).

**Methods:** At baseline (2013-2014), HIV testing at multi-disease health fairs and in homes reached 91% of 143,870 adult stable residents in 32 communities in rural Kenya and Uganda. All HIV+ persons with CD4<350 were eligible for ART. In 16 intervention communities, ART was delivered via patient-centered streamlined care including supported linkage and rapid ART start. In 16 control communities, ART was delivered via country standard of care. Mortality was ascertained after 3 years via comprehensive outreach. We evaluated (1) identification of HIV+ persons with CD4<350 at baseline, (2) among these
persons, the effect of streamlined care on ART start and mortality, and (3) gender differences in mortality. Comparisons between study arms used cluster-level TMLE; survival estimates used Kaplan–Meier; estimates of ART start among ART-naïve persons treated death as a competing risk.

**Results:** Among 13,266 baseline HIV+ residents, 22% (N=2,956) had CD4<350. Of these, 33% (988/2,956) were new diagnoses and 10% (282/2,956) were diagnosed but not ART-naïve. HIV+ women (N=4,597) were twice as likely as HIV+ women (N=8,669) to have CD4<350 and untreated (16% vs. 5%, respectively). Among persons with CD4<350, streamlined care reduced mortality by 27% vs. control (RR=0.72; 95%CI 0.57-0.93; p=0.02). Mortality was reduced substantially more among men (RR=0.60; 95%CI 0.43, 0.86; p=0.005) than women (RR=0.90; 95%CI 0.60, 1.31; p=0.56). Despite immediate ART eligibility in both arms, persons with CD4<350 started ART faster under streamlined care vs. control (76% vs. 43% by 12 months, respectively, p<0.001). Within each arm, time to ART start was similar between men and women. However, more men vs. women had baseline HIV RNA>100,000 copies/mL (29% vs. 19%, respectively), placing men at elevated risk of HIV progression/death.

**Conclusion:** After population-based HIV testing, SEARCH streamlined care accelerated ART start and reduced mortality at a population level among HIV+ persons with CD4<350, particularly among men. These interventions may play a key role in meeting the UNAIDS goal of eliminating AIDS deaths.

**139 LONG-ACTING CABOTEGRAVIR + RILPIVIRINE AS MAINTENANCE THERAPY: ATLAS 48 WEEKS RESULTS**

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**Background:** ATLAS, a phase 3, open-label, multicenter study, was designed to establish whether switching to monthly long-acting (LA) Cabotegravir (CAB) + Rilpivirine (RPV) LA is noninferior to continuing current 3-drug oral ART in adults with virologically suppressed HIV-1 infection.

**Methods:** Eligible participants had HIV-1 RNA <50 c/mL for ≥26 months without virologic failure on oral regimens comprising 2 NRTI + 1 INSTI, NRTI, or PI. Participants were randomly assigned (1:1) to continue current ART (CART) arm or to switch to the LA arm. The LA arm participants received oral CAB 30mg + RPV 25mg once daily for 4 weeks for safety monitoring, then single 3 mL loading doses of CAB LA 200 mg (200 mg/ml) and RPV LA 900 mg (300 mg/ml) by IM injection, followed by 2 mL IM injections every 4-7 weeks of CAB LA 400mg and RPV LA 600mg. The primary endpoint was HIV-1 RNA ≤50 c/mL at W48, using the FDA snapshot algorithm with a 6% noninferiority margin.

**Results:** 616 participants initiated treatment (308/arm; ITT-E). Median age was 42 yrs (26% ≥50 yrs); 33% were female and 68% white. Baseline regimens included 2 NRTI + 1 INSTI, NRTI, or PI (17%). At W48, 5 participants (1.6%) in the LA arm and 3 (1.0%) in the CART arm had HIV-1 RNA ≥50 c/mL, meeting noninferiority criteria for the primary endpoint. Similarly, the LA arm was noninferior to CART for the key secondary endpoint of HIV-1 RNA <50 c/mL (93% vs 95%). Similar to CART, LA did not differ in meeting noninferiority criteria for the primary endpoint (Table). The LA arm was noninferior to CART for the key secondary endpoint of viral load (VL) <50 c/mL at W48 by FDA snapshot algorithm (NI margin 6%). Safety, tolerability and confirmed virologic failure (CVF) were secondary endpoints.

**Conclusion:** 616 participants initiated treatment (308/arm; ITT-E). Median age was 42 yrs (26% ≥50 yrs); 33% were female and 68% white. Baseline regimens included 2 NRTI + 1 INSTI, NRTI, or PI (17%). At W48, 5 participants (1.6%) in the LA arm and 3 (1.0%) in the CART arm had HIV-1 RNA ≥50 c/mL, meeting noninferiority criteria for the primary endpoint (Table). Similarly, the LA arm was noninferior to CART for the key secondary endpoint of HIV-1 RNA <50 c/mL (93% vs 95%). Similar to CART, LA did not differ in meeting noninferiority criteria for the primary endpoint (Table). The LA arm was noninferior to CART for the key secondary endpoint of HIV-1 RNA <50 c/mL (93% vs 95%). Similar to CART, LA did not differ in meeting noninferiority criteria for the primary endpoint (Table). The LA arm was noninferior to CART for the key secondary endpoint of viral load (VL) <50 c/mL at W48 by FDA snapshot algorithm (NI margin 6%). Safety, tolerability and confirmed virologic failure (CVF) were secondary endpoints.

**References:** 1. Participant and health-care provider randomized sequence control. 2. AS (participation and health care provider randomized sequence control). 3. Methods: ART-naive participants received induction therapy with topical DTG/ABC/3TC (CART) for 20 weeks. These with HIV-1 RNA <50 c/mL at 16 weeks were able to enter the maintenance phase and were assigned (1:1) to continue CART or LA. Participants in the LA arm received an oral lead-in of CAB 30mg + RPV 25mg once daily for 4 weeks to assess tolerability before receiving CAB+RPV as intramuscular monthly LA injectable therapy. The primary endpoint was viral load (VL) ≤50 c/mL at W48 by FDA snapshot algorithm (NI margin 6%). Safety, tolerability and confirmed virologic failure (CVF) were secondary endpoints.

**Results:** S66: results of participants who initiated induction therapy were randomly assigned to the LA (N=283 or CART arm). The median age was 34 yr (11% ≥50 yr); 22% were female and 74% were white. At the induction phase start, median CD4 count was 444 cells/mm³ (7% <200 cells/mm³), median VL was 4.49 log₁₀ c/mL (20% ≥ 100,000 c/mL). Six participants in the LA arm (2.1%) and 7 in the CART arm (2.5%) had HIV-1 RNA ≥50 c/mL at W48, meeting noninferiority criteria for the primary endpoint (Table) and for the key secondary endpoint of HIV-1 RNA <50 c/mL (LA 93.6% vs CART 93.3%). Four LA recipients (1.4%) had CVF; 3 had mutations in the NNRTI + INSTI domains (K101K/E/Q + G140R, E138K + V108I); and 1 was not tested (PO only). The CAR arm had 3 CVFs with no INSTI resistance. Adverse events (AE) leading to withdrawal and serious AE were infrequent in both arms. The most common drug-related AE was injection site reactions (ISRs; 82% of participants in the LA arm); frequency decreased over time. 99% of ISRs were Grade 1 or 2; the median
SAFETY AND PK OF SUBCUTANEOUS GS-6207, A NOVEL HIV-1 CAPSID INHIBITOR

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Background: GS-6207, a selective, multi-stage inhibitor of HIV-1 capsid protein, is in development for the treatment of HIV-1 infection. GS-6207 is characterized by potent antiviral activity, low predicted human clearance, and low aqueous solubility, making it well suited for an extended-release formulation. This Phase 1 study evaluated the safety, tolerability and pharmacokinetics (PK) of a subcutaneous (SC) suspension of GS-6207 in healthy volunteers.

Methods: This is a randomized, blinded, placebo-controlled healthy volunteer study with staggered single dose escalation cohorts. Within each cohort, subjects were randomized (4:1) to receive single SC doses of GS-6207 (n=8)/placebo (N=2)/cohort) at 30, 100, 300 or 450 mg. PK parameters will be estimated and summarized by dose and dose proportionality will be assessed. Safety, tolerability and PK will be evaluated for at least 24 weeks post-dose.

Results: 40 subjects received a single SC dose of GS-6207 (N=32) or placebo (N=8). The study is ongoing with interim safety and PK data available through at least 20 weeks ( Cohort 1, 30 mg), 16 weeks (Cohort 2, 100 mg), 8 weeks (Cohort 3, 300 mg) and 4 weeks (Cohort 4, 450 mg). PK parameters for Cohorts 1 and 2 have been estimated. Analysis for Cohorts 3 and 4 is ongoing. The PK profile of SC GS-6207 is consistent with sustained delivery. T1/2 values ranged from 21 to 35 days (Cohorts 1 and 2). The median apparent terminal T1/2 was between 30 to 38 days and concentrations are measurable for at least 16 weeks, to date (Cohorts 1 and 2). The increase in exposure (Cmax and AUC) between 30 and 100 mg GS-6207 was approximately dose proportional. To date, there have been no deaths, serious adverse events, or Grade 3 or 4 adverse events (AEs). Most AEs were mild (Grade 1) and resolved.

Conclusion: Based on the interim data, GS-6207 was safe and well tolerated following single SC doses of up to 450 mg in healthy subjects. Sustained delivery supports a dosing interval of at least 3 months. The safety and PK of GS-6207 supports evaluation of its antiviral activity in HIV-infected participants.

SYSTEmATIC DETERMINATION OF IN VITRO HIV-1 INTEGRASE RESISTANCE FROM CLINICAL SAMPLES

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Background: Resistance phenotype data is relatively sparse for the newest HIV integrase inhibitors, dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB). Here, we report the phenotypic susceptibility of a large panel of oligoclonal patient-derived subtype B recombinant viruses selected to maximize in vivo sequence variation.

Methods: Using integrase sequences from the BC-CFE database (N=16,583), 27 integrase positions were identified as having amino acids that differed in prevalence between integrase-treated (primarily RAL and/or EVG) and naive individuals. All unique amino acid permutations at these positions were identified (N=288) and N=137 subtype B samples were selected as the representative samples. Extracted RNA was diluted to −500 copies/mL and amplified in 12 independent RT-PCR reactions. Amplicons with no nucleotide mixtures at these positions were used to make recombinant viruses by co-
transfection with linearized integrase-deleted pNL4.3 in CEM-GXR cells. To date, N=130 recombinant viruses were successfully harvested and sequenced to confirm the absence of mixtures at these codons and match to amplicon sequence. Titration and phenotyping were performed in MT4-LTR-EGFP cells, where infectivity data was collected using a SpectraMax i3 MiniMax 300 Imaging Cytometer. EC50s fold-change (CF) relative to a NL4.3 control were determined on day 3 or 4 post-infection.

**Results:** The 130 variants phenotyped to date represent 88% of the observed sequence variation along the clinical samples at these 27 relevant integrase codons. Of these, 15%, 13%, and 30% had >3-FC for DTG, BIC and CAB, respectively. As expected, variants with the highest CF had G140S and Q148R/H. R263K was the only single variant confering >3-FC for all three drugs. However, a variant harboring G163R/D232E also had >3-FC for all three drugs. The CF values were closely correlated across all three drug tested. The greatest exceptions were variants with N155H/G163E or L74I/T97M/F121C/V151I/E157D/G163K, where both had >75-FC for CAB. As expected, variants with the highest CF for DTG and BIC, if new mutations or permutations are identified it is straightforward to select these for future phenotyping.

**Conclusion:** Observed sequence variation can be used to efficiently generate panels of resistant viruses for phenotype analysis. We confirm broad cross-resistance between DTG, BIC, and CAB, and identify new patterns leading to decreased susceptibility to the newest integrase inhibitors. This work should be extended to non-subtype B variants.

### 144 DTG VS LPV/R (DAWNING): EFFICACY BY BASELINE NRTI RESISTANCE AND SECOND-LINE NRTI USE

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**Background:** DAWNING is a non-inferiority study comparing dolutegravir (DTG) + 2 nucleoside reverse transcriptase inhibitors (NRTIs) with lopinavir/ritonavir (LPV/r) + 2 NRTIs in HIV-1 infected adults failing first-line therapy (HIV-1 RNA ≥400 copies/ml) on 2-3 NRTIs. As part of the study, resistance testing was performed on baseline samples to determine the presence of TAMs or K65R, respectively; however, subject numbers in these subgroups were small (Table 1).

**Methods:** Subjects were randomised (1:1, stratified by screening HIV-1 RNA and number of fully active NRTIs) to 52 weeks of open-label treatment with DTG or LPV/r + 2 investigator-selected NRTIs, including at least one fully active NRTI based on screening resistance testing. The primary endpoint was the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 (Snapshot algorithm). Post-hoc efficacy analyses were performed based on baseline NRTI resistance profile and NRTI use in the second-line background regimen (BR).

**Results:** Of 624 subjects randomised and treated, 499 (80%) received <2 active NRTIs at baseline. Overall, 88% (261/312) of subjects on DTG versus 70% (219/312) on LPV/r achieved HIV-1 RNA <50 c/mL at Week 48 (Figure 1). The proportion of subjects with HIV-1 RNA <50 c/mL was 1.7 log cp/ml (1.3-2.1) by d10. These individuals showed antiviral efficacy in 5/9 participants in the high VL group compared to 1/3 in the low VL group (differences were all significant). The elimination half-life of PGT121 was ~22 days in HIV- and HIV+/ART+ participants. The first part of the study was a randomized, double blinded, dose escalation, placebo-controlled trial of PGT121 in adults who were HIV-uninfected (HIV-, N=20) and HIV-infected on ART (HIV+/ART+, N=15). PGT121 was given once at 3, 10, and 30 mg/kg IV and 3 mg/kg SC (N=5/group, 4:1 Ab/placebo). All participants were monitored for reactogenicity for 3 days and adverse events (AEs) for 56 days. PK and virologic assessments were performed through 6 months. The lower limit of quantification (LLOQ) of VL was 1.6 log cp/mL.

**Results:** PGT121 was safe and well-tolerated with no related mod/severe AEs. The elimination half-life of PGT121 was ~22 days in HIV- and HIV+/ART+ groups, with variation by dose and route. In rhesus monkeys, PGT121 showed antiviral efficacy in 5/9 participants in the high VL group with a median drop in VL of 1.7 log cp/ml (1.3-2.1) by d10. These individuals showed PGT121 sensitive virus at baseline but developed rebound by d28 with emergence of resistance. In the low VL group, PGT121 decreased VL to

### Table 1. Proportion of subjects with HIV-1 RNA <50 c/mL (Snapshot algorithm) at Week 48 by baseline resistance and NRTI use

<table>
<thead>
<tr>
<th>NRTI used</th>
<th>Baseline NRTI mutations</th>
<th>Treatment</th>
<th>N</th>
<th>Number responding</th>
<th>assessed</th>
<th>Difference in Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>M184V/I only or ≥ 1 NRTI</td>
<td>LPV/r</td>
<td>252</td>
<td>182/252 (72%)</td>
<td></td>
<td>12.1 (5.0, 19.1)</td>
</tr>
<tr>
<td>STC or FTC + other NRTI</td>
<td>M184V/I only or ≥ 1 NRTI</td>
<td>DTG</td>
<td>261</td>
<td>220/261 (84%)</td>
<td></td>
<td>12.6 (4.9, 20.3)</td>
</tr>
<tr>
<td>Any</td>
<td>K65R only or + ≥ 1 NRTI</td>
<td>LPV/r</td>
<td>92</td>
<td>65/92 (74%)</td>
<td></td>
<td>10.3 (-1.3, 21.9)</td>
</tr>
<tr>
<td>TDF + other NRTI</td>
<td>K65R only or + ≥ 1 NRTI</td>
<td>LPV/r</td>
<td>8</td>
<td>7/8 (88%)</td>
<td></td>
<td>1.8 (-36.4, 32.8)</td>
</tr>
<tr>
<td>AZT + other NRTI</td>
<td>≥ 1 TAM</td>
<td>DTG</td>
<td>36</td>
<td>30/36 (86%)</td>
<td></td>
<td>7.3 (-8.9, 23.0)</td>
</tr>
</tbody>
</table>


**145LB THERAPEUTIC ACTIVITY OF PGT121 MONOCLONAL ANTIBODY IN HIV-INFECTED ADULTS**

**Kathryn E. Stephenson**, Boris Julg, Jessica Ansel, Stephen R. Walsh, Chen S. Tan, Lori Maxfield, Peter Abbink, Huub C. Gelderblom, Frances Priddy, Allan C. deCamp, Roberto Arduino, Edwin DeJesus, Georgia Tomaras, Michael S. Seamen, Dan Barouch

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**Background:** PGT121 is a recombinant human IgG1 mAb that targets a V3 glycan-dependent epitope region of HIV Env. PGT121 is a potent neutralizing antibody in vitro and has been shown to prevent and treat simian-human immunodeficiency virus in rhesus monkeys. Here we present safety, pharmacokinetic (PK) and antiviral efficacy data from the first-in-human phase 1 clinical trial of PGT121 conducted in the United States.

**Methods:** The first part of the study was a randomized, double blinded, dose escalation, placebo-controlled trial of PGT121 in adults who were HIV-uninfected (HIV-, N=20) and HIV-infected on ART (HIV+/ART+, N=15). PGT121 was given once at 3, 10, and 30 mg/kg IV and 3 mg/kg SC (N=5/group, 4:1 Ab/placebo). The second part of the study was an open label trial of PGT121 given once at 30 mg/kg IV in HIV-infected adults not on ART with high VL (3.3-4.8 log cp/mL, N=9) and low VL (2.6-2.6 log cp/mL, N=3). All participants were monitored for reactivity for 3 days and adverse events (AEs) for 56 days. PK and virologic assessments were performed through 6 months. The lower limit of quantification (LLOQ) of VL was 1.6 log cp/mL.

**Results:** PGT121 was safe and well-tolerated with no related mod/severe AEs. The elimination half-life of PGT121 was ~22 days in HIV- and HIV+/ART+ groups, with variation by dose and route. In rhesus monkeys, PGT121 showed antiviral efficacy in 5/9 participants in the high VL group with a median drop in VL of 1.7 log cp/mL (1.3-2.1) by d10. These individuals showed PGT121 sensitive virus at baseline but developed rebound by d28 with emergence of resistance. In the low VL group, PGT121 decreased VL to
In the early years after ART introduction in Africa, there were marked declines in annual mortality, with reductions of 10-20% observed in various settings. There is limited information on the impact of the current rapidly expanding HIV treatment access on general population mortality in sub-Saharan Africa.

Methods: From 2011 to 2016, ART coverage in western Kenya increased from 34% to 60%. Data from a health and demographic surveillance system (HDSS) with HIV home-based counselling and testing (HBCT) surveys took place in 2011, 2012, 2013, and 2016. Mortality trends were assessed in a closed cohort of residents.

Results: Seventy percent of HDSS residents in Gem, western Kenya, (22,668/32,467, aged 15–64 years) participated in the 2011 survey and comprised the cohort followed over time. All-cause mortality was 10.0% (95% confidence interval (CI) 8.4-11.7) per 1000 person-years (PY) in 2011, and declined to 7.5% (95% CI 5.8-9.1) per 1000 PY in 2016. Mortality was stable over the study period, at 5.7 per 1000 PY among the non-HIV infected. Among HIV-infected persons, mortality declined from 30.5 per 1000 PY in 2011 to 15.9 per 1000 PY in 2016 (average decline 6% per year). Individuals on ART experienced higher mortality rates than non-HIV-infected individuals (rate ratio 2.8, 95% CI 2.2-3.4).

Conclusion: This study suggests mortality among HIV infected individuals declined substantially during ART expansion between 2011 and 2016, though less than the declines reported during early ART introduction. Mortality trends among HIV positive persons are critical to understanding epidemic dynamics. As ART use continues to expand, HDSS platforms offer a unique opportunity to monitor mortality alongside trends in HIV prevalence and incidence.

### Table 1. Opioid overdose death rates per 100,000 persons with diagnosed HIV infection, United States, 2011–2015

<table>
<thead>
<tr>
<th>Region of residence at death</th>
<th>Year of Death</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>% Change from 2011 to 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>2011</td>
<td>30.6</td>
<td>35.0</td>
<td>34.7</td>
<td>19.8</td>
<td>21.2</td>
<td>-23.8%</td>
</tr>
<tr>
<td>South</td>
<td>2011</td>
<td>35.2</td>
<td>30.2</td>
<td>29.8</td>
<td>16.5</td>
<td>17.6</td>
<td>-23.7%</td>
</tr>
<tr>
<td>West</td>
<td>2011</td>
<td>25.5</td>
<td>27.1</td>
<td>26.0</td>
<td>16.4</td>
<td>18.1</td>
<td>-22.7%</td>
</tr>
</tbody>
</table>

#### Footnotes
1. ICD-10 codes of X60-X64 for the underlying cause and ICD-10 codes of T40.0, T40.1, T40.2, T40.3, T40.4, and T40.8 as a multiple cause of death.
2. Data not statistically adjusted to account for unknown transmission categories.
3. Interpret rate with caution; rate calculated based on numerator less than 12.

### References

1. University of Amsterdam, Amsterdam, Netherlands, 2nd Kenya Medical Research Institute, Kisumu, Kenya, 3rd CDC, Atlanta, GA, USA, 4th US CDC Nairn, Nairobi, Kenya, 5th University of Maryland, Baltimore, MD, USA, 6th US CDC Kisumu, Kisumu, Kenya

Background: The opioid epidemic is a nationwide public health emergency. Persons with HIV might be at increased risk for drug overdose deaths, including overdoses involving an opioid. We examined characteristics of unintentional drug overdose deaths involving an opioid (hereafter, opioid overdose deaths) during 2011-2015 among persons with diagnosed HIV infection in the United States.

Methods: We used National HIV Surveillance System data reported through December 2017 to summarize opioid overdose deaths between 2011 and 2015 among persons with diagnosed HIV in the 50 states and District of Columbia. Opioid overdose deaths were selected by using the International Classification of Disease, Tenth Revision (ICD-10). Death rates were calculated per 100,000 persons with diagnosed HIV. We examined death rates by demographic, geographic, and HIV transmission categories.

Results: There were 1,363 opioid overdose deaths among persons with diagnosed HIV during 2011-2015. Although the rate of all deaths among persons with diagnosed HIV was 12.7% less in 2015 (1630.6 per 100,000) than in 2011 (1,868.8 per 100,000), the opioid overdose death rate per 100,000 people with diagnosed HIV was 42.7% greater in 2015 (33.1 per 100,000) than in 2011 (23.2 per 100,000). Rates of opioid overdose deaths were higher in 2015 than 2011 for all subgroups examined by age, sex, race/ethnicity, transmission category, and US Census region of residence at death, with the exception of the West US Census region. In 2015, the rate of opioid overdose deaths was highest among persons aged 50–59 years at death (41.9 per 100,000), females (35.2 per 100,000), whites (49.1 per 100,000), persons who inject drugs (137.4 per 100,000), and the Northeast US Census region (60.6 per 100,000), compared to their respective counterparts.

Conclusion: Opioid overdose death rates were higher in 2015 than in 2011 among nearly all demographic, transmission, and geographic categories examined despite the decreased rate of total deaths among persons with diagnosed HIV during 2011–2015. Differences in opioid overdose deaths among subgroups of persons with diagnosed HIV call for targeted prevention efforts. Intensified overdose prevention is needed for achieving optimal care of persons with diagnosed HIV and to further decrease mortality.
incidence of mortality with and without pre-therapy CD4 at 1 year was 4.54% (95% CI 3.73, 5.60) and 7.06% (95% CI 5.14, 9.98), respectively (Cox test for equality p=0.03). After adjustment for pre-therapy WHO stage, sex, age, facility type, ART initiation date, patients without a pre-therapy CD4 had 1.48 times the hazard of mortality in the first year compared to those with a pre-therapy CD4 determination (95% CI 1.00, 2.17, p=0.046). Advanced WHO stage and male sex were associated with higher probability of early mortality (WHO stage IV, HR, 7.69 (95% CI, 4.19, 14.13 p<0.001) male sex, HR, 1.62 (95% CI, 1.13, 2.32 p<0.008)).

Conclusion: Despite the possibility of unmeasured confounding, these results suggest that patients initiating ART without pre-therapy CD4 experience a higher risk of early mortality even after adjustment for demographic characteristics and disease stage. Even though pre-therapy CD4 are no longer required to determine eligibility, further research to evaluate the safety of discontinuing pre-therapy CD4 is needed before widespread discontinuation.

149 UTILITY OF CD4 CELL COUNT MONITORING IN BOTSWANA: ANALYSIS OF ROUTINE LABORATORY DATA

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1 Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 2University of Botswana, Gaborone, Botswana, 3‘Botswana—Pfizer Partnership, Gaborone, Botswana, 4Ministry of Health, Gaborone, Botswana, 5London School of Hygiene & Tropical Medicine, London, UK

Background: Botswana has an adult HIV prevalence of 21.9%. An estimated 317,945 patients (84% of HIV-infected individuals) are on treatment. National guidelines recommend both CD4 count and viral load monitoring. Since the country adopted universal test-and-treat in June 2016, an increasing burden has been placed on the health system. This study aims to assess the ongoing need for regular CD4 monitoring in Botswana.

Methods: Data from all HIV-infected patients having CD4 counts at the Gaborone clinics served by the Botswana Harvard reference laboratory during 2015, 2016, and 2017 were analysed. CD4 count and viral load data were assessed to determine the proportion of patients presenting with advanced disease (CD4<200 cells/µL), trends in CD4 cell counts over time, and the proportion of patients presenting without advanced disease experiencing a drop in CD4 count to below 200 cells/µL during follow up.

Results: 193,050 CD4 counts were performed on 60,899 patients, with a median frequency of monitoring of 1.48 CD4 measurements per patient per year. 76% (46,474) of patients were established clinic patients, while 24% (24,675) were new to care during the study period. 24.8% (3,571/14,425) of patients had a drop in CD4 count to below 200 cells/µL during follow up.

Conclusion: A significant proportion of patients in Botswana still present with advanced disease, demonstrating the ongoing importance of baseline CD4 testing to identify patients at risk of opportunistic infections and in need of interventions including cotrimoxazole prophylaxis and cryptococcal antigen screening. Very few individuals with CD4 counts above 200 cells/µL experienced a drop to below 200 cells/µL, suggesting limited utility for ongoing CD4 count monitoring in individuals without advanced disease in settings with routine viral load testing.

150 TRENDS IN CD4 AND VIRAL LOAD TESTING IN SOUTHERN AFRICA: ANALYSIS OF 6 COUNTRIES

Elizabeth Zanievski1, Cam Ha Dao Ostinelli1, Nicola Maxwell1, Mary Ann Davies1, Jonathan Euvrard2, Janneke van Dijik3, Samuel Bosomprah3, Frank Tanser1, Matthew P. Fox1, Nathan Ford1, Nosia Sipambo4, Josephine Muhairwe5, Matthias Egger6

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Background: Since 2015 the World Health Organization has recommended CD4 testing before starting antiretroviral therapy (ART) to detect advanced disease and routine viral load (VL) testing at 6 months and every 12 months thereafter to detect treatment failure. We assessed trends in CD4 and VL testing in six countries in Southern Africa.

Methods: We included adults (≥15 years old) who started ART at one of the HIV treatment programs that participate in the International epidemiology Databases to Evaluate AIDS (IeDEA) Southern Africa region between 2005 and 2017, and had ≥6 months of follow-up time from ART start. We assessed the proportion of patients with a CD4 count at ART initiation, the percent with a VL test ≥6 months after ART start and, of those, the percent with virologic failure at the first test ≥6 months after ART start. Virologic failure was defined as VL >1000 cells/mm3. The CD4 count at ART start was defined as a CD4 count within a window of 3 months before to 1 week after ART start. Analyses were stratified by sex, age and year of ART start.

Results: Our analysis included 520,175 adults from 14 programs in six countries with a median (IQR) age of 34.4 (28.7-41.3) years, of whom 65.0% were female. Median (IQR) follow-up time was 43.6 (23.2-73.0) months and similar across countries. The percent with CD4 testing at ART start has declined over the years from a high of 76.2% in 2005 to a low of 49.4% in 2017. In recent years, the frequency of CD4 testing has also decreased, most notably in Malawi, South Africa and Lesotho (Figure). Women aged 15-24 years had the least CD4 testing (62.5%) and men aged 25-49 years the most (68.3%). Young men aged 15-24 years had the least VL testing (38.4%) and women aged 25-49 years had the most (48.0%). Of those with a VL test, 11.4% had virologic failure with young men aged 15-24 years at greatest risk (19.5%) and women 50+ years at lowest risk (6.2%). Virologic failure has been decreasing in recent years, from 13.7% in 2010 to 8.6% in 2015.

Conclusion: CD4 testing at ART start has steadily declined over the years, alongside reduced CD4 testing in general. Virologic failure has been declining; however, without expanded CD4 and VL testing, many patients with advanced disease or with treatment failure may go undetected.

151 HIGH LEVELS OF DRUG RESISTANCE AMONG ART-EXPERIENCED HOSPITALIZED PATIENTS

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Background: In sub-Saharan Africa, an increasing number of patients hospitalized with advanced HIV are ART-experienced and mortality among them is extremely high during and after hospitalization. In patients on first-line ART with an elevated viral load (VL≥1000 copies/mL), WHO recommends a...
switch to 2nd line conditional on a 2nd elevated VL three months after the 1st one and enhanced adherence counseling, regardless of CD4 level and hospitalization status. To assess if patients may benefit from a faster switch to 2nd line, we measured rates of ARV drug resistance (DR) among ART-experienced hospitalized patients. There were previously no data available on HIV DR among these patients.

Methods: A cross-sectional survey was implemented between September 2017 and April 2018 in two hospitals supported by MSF in Kinshasa (KS), Democratic Republic of Congo, and Homa Bay (HB), a rural area in Kenya. Hospitalized people living with HIV (PLWH) aged 15 years and above receiving first-line ART for at least 6 months and with CD4<350 cells/µL were invited to participate. CD4 count, VL and resistance genotype were done at inclusion. Resistance was defined as any major (intermediate/high, Stanford HIVdb) NRTI or NNRTI DR. A regimen-specific genotypic sensitivity score (gSSS) was calculated (maximum score 3, fully susceptible regimen).

Results: In total, 305 participants were included after a median of 5.3 years ([IQR:2.5–10.3]) on ART in KS (77%-TDF/3TC/EFV,8%-ABC/3TC/EFV) and 4.0 years ([IQR:1.8–8.9]) in HB (71%-TDF/3TC/EFV,11%-AZT/3TC/EFV), 69% (KS) and 54% (HB) were female, and the median age was 38 (31–48) and 32 (30–42) years. The median CD4 was 69 cells/µL ([IQR:29-134] and 135 cells/µL ([IQR:46–255]) in KS and HB, respectively and 70% in KS and 37% in HB had a VL<1,000 cp/mL. Among those with CD4<50 cells/µL, 87% and 84% had a VL<1,000 cp/mL in KS and HB. Of those with VL>1000cp/mL, 73% had dual-class DR in both sites, with 73% on an ineffective regimen (gSSS=2) in KS, and 74% in HB. Age, old CD4 count and suboptimal self-reported adherence were associated with treatment failure (VL>1000cp/mL and Dual-class DR) in HB and with low CD4 (CD4<50 cells/µL) in KS.

Conclusion: A high proportion of PLWH hospitalized with advanced disease and on first-line ART were resistant to their ARV treatment in each site. A fast switch to 2nd line ART after one single elevated VL or CD4<50 cells/µL should be immediately recommended to accelerate immune reconstitution and improve outcomes among those patients.

152 HIV DR RESISTANCE IN SOUTH AFRICA: RESULTS FROM A POPULATION-BASED HOUSEHOLD SURVEY

Sizulu Mayo, Gillian Hunt, Zuma Khangelani, Nonpumelo P. Zungu, Edmore Marinida, Musa Masabo, Karidia Diallo, Cheryl Dietrich, Thomas Rehle

1Human Sciences Research Council, Pretoria, South Africa, 2National Institute for Communicable Diseases, Johannesburg, South Africa, 3US CDC Pretoria, Pretoria, South Africa, 4University of Cape Town, Cape Town, South Africa

Background: HIV treatment as prevention succeeds by reducing the duration of infectiousness (i.e., time from infection to diagnosis and from diagnosis to viral suppression). Monitoring levels of HIV drug resistance (HIVDR) is a priority activity for the country. HIVDR testing was included for the first time in the 5th national HIV household survey conducted in 2017.

Methods: Multi-stage stratified cross-sectional random sampling was used to select households for participation nationally. Dried blood spots were collected from all households in 2017. HIVDR samples were collected from all consenting adults aged 18 years and older who self-reported daily ARV use in a survey done concurrently with the house-to-house interview. HIVDR samples were tested to determine HIV status, estimated recency of infection, exposure to antiretroviral drugs (ARVs), and HIVDR in addition to behavioral data from all household members who agreed to participate. HIVDR testing was conducted on HIV-positive samples with viral load ≥1000 copies/mL using next generation sequencing methodologies.

Results: Of 1107 HIV positive samples from virally unsuppressed participants, 697 (63%) were successfully amplified by polymerase chain reaction and sequenced. Drug resistant mutations (DRM) were identified in 27.4% (95% CI 22.8-32.6) of samples: 18.9% (95% CI 14.8-23.8) had resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) only, 7.8% (95% CI 5.6-10.9) had dual resistance to NNRTIs and nucleoside reverse transcriptase inhibitors (NNRTIs), and 0.5% (95% CI 0.1-2.1) had resistance to second-line regimens that include protease inhibitors (NRTIs), and 0.5% (95% CI 0.1-2.1) had resistance to second-line regimens that include protease inhibitors (PIs). Table 1 shows HIVDR by exposure to ARVs, sex, and age. NNRTI-only resistance was found in 14.3% ARV+ve and 20.6% ARV-ve samples (p=0.311), while dual NNRTI and NRTI resistance occurred in 4.3% ARV+ve and 2.1% ARV-ve samples (p<0.001). Among those who were ARV-ve but self-reported daily ARV use (ARV defaulters; n=41), 75.6% had DRM; 56.4% with NNRTI-only resistance, 14.3% with dual NNRTI and NRTI resistance. There were no significant age and sex differences among either NNRTI-only resistant and dual NNRTI and NRTI resistant samples.

Conclusion: These findings demonstrate high proportions of DRM among virally unsuppressed HIV-infected persons in South Africa. While these results include treatment defaulters, pretreatment HIVDR levels are concerning. Programmatic implications include stronger adherence support to reduce ARV defaulting, and strengthened first line ART regimens by including integrase strand transfer inhibitors (INSTIs) as a part of first line treatment. These findings support the national transition to include Dolutegravir as part of first-line ART in South Africa.
TISSUE-RESIDENT MEMORY CD8+ CELLS

Michael R. Betts, University of Pennsylvania, Philadelphia, PA, USA

Recent studies have established that non-recirculating resident memory CD4+ and CD8+ T cells can be found in virtually every human tissue. These cells bear a transcriptional profile of tissue retention and immediate effector function, suggesting a pivotal role in protective immunity. Resident memory CD8+ T cells specific for HIV have been found in sites of HIV persistence (gut and function, suggesting a pivotal role in protective immunity. Resident memory cells bear a transcriptional profile of tissue retention and immediate effector deficiencies in blood were observed, collectively identifying determinants of ILC frequencies in MLNs. Moreover, in HIV-uninfected subjects with durable uninfected rhesus macaques. Experimental depletion of CD4+ T cells in infection with loss of CD4 T cells and/or GI barrier damage, and in healthy underlying ILC3 loss in HIV-infection we created hallmarks of progressive HIV-1 infection is characterized by depletion of ILCs with decreased integrity of GI tract epithelium. Interestingly, ILC depletion is not a generalized feature of all viral infections. There is thus considerable interest in understanding the exact mechanisms of ILC loss in HIV/SIV infections. We find that in ARV naïve, SIV-infected nonhuman primates, distinct inflammatory and type I interferon gene signatures coincide with rapid loss of ILC3s in gut-draining mesenteric lymph nodes (MLN). Pharmacologic control of viremia with antiretroviral treatment was sufficient to reconstitute ILC3s in the MLN, and MLN ILCs were preserved in infected rhesus macaques. Experimental depletion of CD4+ T cells in combination with dextran sodium sulfate was sufficient to significantly reduce ILC frequencies in MLNs. Moreover, in HIV-infected subjects with durable CD4+ T cell deficiency, deemed idiopathic CD4+ lymphopenia, similar ILC deficiencies in blood were observed, collectively identifying determinants of ILC homeostasis in primates and potential mechanisms underlying their depletion in HIV/SIV infection.

MECHANISMS UNDERLYING LOSS OF ILCs IN HIV/SIV-INFECTED INDIVIDUALS

Jason Brenchley, National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

Innate lymphoid cells (ILCs) play critical roles in mucosal barrier defense. HIV-1 infection is characterized by depletion of ILCs with decreased integrity of GI tract epithelium. Interestingly, ILC depletion is not a generalized feature of all viral infections. There is thus considerable interest in understanding the exact mechanisms of ILC loss in HIV/SIV infections. We find that in ARV naïve, SIV-infected nonhuman primates, distinct inflammatory and type I interferon gene signatures coincide with rapid loss of ILC3s in gut-draining mesenteric lymph nodes (MLN). Pharmacologic control of viremia with antiretroviral treatment was sufficient to reconstitute ILC3s in the MLN, and MLN ILCs were preserved in elite controller RMs with natural virologic control. To understand mechanisms underlying ILC3 loss in HIV-infection we created hallmarks of progressive HIV-1 infection with loss of CD4 T cells and/or GI barrier damage, and in healthy uninfected rhesus macaques. Experimental depletion of CD4+ T cells in combination with dextran sodium sulfate was sufficient to significantly reduce ILC frequencies in MLNs. Moreover, in HIV-infected subjects with durable CD4+ T cell deficiency, deemed idiopathic CD4+ lymphopenia, similar ILC deficiencies in blood were observed, collectively identifying determinants of ILC homeostasis in primates and potential mechanisms underlying their depletion in HIV/SIV infection.

MEMORY NK CELLS AS NOVEL EFFECTORS AGAINST HIV AND SIV

R. Keith Reeves, Harvard Medical School, Boston, MA, USA

Natural killer (NK) cells provide rapid early responses to viral infections and thus can contribute substantially to disease modulation and potentially vaccine efficacy. Traditionally, NK cells have been considered to be nonspecific components of innate immunity, but burgeoning evidence suggests that the functional repertoire of NK cells is far more diverse and can include adaptive features and memory recall. Some of the first evidence that NK cells respond in an antigen-specific fashion came from experiments revealing that subpopulations of murine NK cells could respond to a specific MCMV protein, and that in the absence of T and B cells, murine NK cells also mediated adaptive immune responses to a secondary challenge with specific hapten. These data have been followed by demonstrations of NK cell memory to viruses and viral antigens in mice, non-human primates, and most recently humans. Indeed recent work from our laboratory and others has shown that adaptive NK cells are mounted against both HIV and SIV antigens, both by infection and multiple vaccine vectors. These responses have proven to be robust, long-lived, and particularly enriched in tissues. Mechanistically, adaptive NK cell responses in humans and non-human primates largely depend on NKG2C expression and MHC-I-mediated presentation on target cells. In this presentation a current state of the field will be discussed, including multiple types of memory NK cells, how each type may mobilize against HIV and SIV infection, and how these novel phenomena could ultimately be harnessed in the context of effective vaccine and antiviral modalities.

HIV SUPPRESSION BY CD8+ LYMPHOCYTES

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The persistence of HIV infection under ART is due to a reservoir of latently infected cells that remain indefinitely despite full suppression of virus replication. HIV latency is triggered by several mechanisms that lead to the silencing of virus expression including epigenetic DNA modification through methylation and histone deacetylation, limited availability of critical transcription factors and inefficient elongation of the nascent viral transcripts. Defining the mechanisms responsible for the establishment and maintenance of the HIV reservoir under ART has been the focus of efforts aimed at HIV eradication. Numerous studies have demonstrated that CD8+ T cells inhibit virus replication during untreated HIV/SIV infection. However, the mechanisms responsible for this antiviral effect remain poorly understood and include the direct killing of HIV/SIV-infected cells (i.e., cytotoxic T lymphocyte activity) as well as non-cytolytic mechanisms. Several studies now have shown that depletion of CD8+ lymphocytes results in increased viremia without prolonging the average in vivo lifespan of productively infected cells, thus suggesting a key role for non-cytolytic mechanisms of virus suppression. Experiments conducted in ART-treated SIV-infected rhesus macaques have demonstrated that depletion of CD8+ lymphocytes is followed by reactivation of virus production, and increased susceptibility to the latency reversal effect of an IL-15 superagonist. These results reveal an important role of CD8+ lymphocytes in cooperating with ART to maintain virus suppression and also strongly suggest that CD8+ lymphocytes function to silence HIV expression. Indeed, our recent studies employing in vitro models of HIV latency have demonstrated a CD8+ lymphocyte mediated suppression of HIV expression in CD4+ T cells that functions to induce the establishment of latency 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 and persistence in ART-treated HIV-infected individuals may provide critical insight to support the design of new approaches for HIV eradication.

OBESITY: A GROWING PROBLEM IN ANTIRETROVIRAL THERAPY

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Over the past two decades, the prevalence of obesity (i.e., body mass index ≥30 kg/m²) among persons living with HIV (PLWH) has steadily risen, which is clinically important as obesity increases the risk of diabetes, cardiovascular disease, fatty liver disease, neurocognitive impairment, and other comorbidities. Among PLWH, traditional risk factors for obesity (e.g., food insecurity, lack of readily available healthy foods, insufficient physical activity, and limited knowledge of healthy lifestyle practices) intersect with HIV-specific factors. Many PLWH experience abrupt weight gain after starting antiretroviral therapy (ART). A retrospective analysis of more than 14,000 patients starting ART found that, after three years of treatment, 22% of normal-weight individuals became overweight and 18% of overweight individuals became obese. Weight gain on ART is multifactorial and may be due, in part, to reduced inflammation and catabolism following viral suppression; increased access to health education, social support services (e.g., food assistance), smoking cessation, and treatment of depression with entry into HIV care; and effects of specific ART medications. While weight gain appears to occur with all current ART regimens, between-class and within-class differences have emerged. AIDS Clinical Trials Group (ACTG) study A5257 found a higher incidence of severe (>10%) weight gain among ART-naïve participants after starting a regimen containing the integrase strand transfer inhibitor (INSTI) raltegravir versus the protease inhibitors (PI) darunavir or atazanavir, each boosted with ritonavir. In a large retrospective analysis, ART-naïve patients starting INSTI-based regimens...
had higher weight gain compared to those starting non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens; among INSTIs, weight gain was greater with dolutegravir and raltegravir versus elvitegravir-containing regimens. Recent smaller analyses also report weight gain among patients with virologic suppression switched from PI- or NNRTI-containing regimens to INSTI regimens, and a minor weight increase in those switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF). In summary, weight gain is common among PLWH starting ART and may occur following regimen switches. Rigorous clinical trial data is needed to confirm findings from observational cohorts, in addition to studies of potential mechanisms linking antiretroviral agents and body weight.

139 KEEP FORGETTING: HIV, AGING, AND COGNITIVE DISORDERS
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HIV infection is a leading cause of cognitive impairment in people under the age of 60, worldwide. Historically, there was little need to differentiate cognitive disorders due to HIV from that of age-associated neurodegenerative disorders, such as Alzheimer’s disease, because few patients living with HIV survived into geriatric age groups where prevalence of these neurodegenerative disorders increase exponentially. This talk will provide recent evidence of persistent clinically meaningful cognitive challenges in patients aging with HIV. We will review likely neuropathogenic mechanisms and recent data on the typical clinical presentation. We will review data captured, primarily from clinical settings, that can inform potential interactions among HIV infection, vascular central nervous system damage, and Alzheimer’s disease as we address facts and fiction around brain aging with HIV. Addressing one of the most challenging clinical geriatric neuroHIV issues of the current time, we will discuss current knowledge around differential diagnosis related to cognitive disorders in people living with HIV over the age of 60 years.

160 PrEP FAILURES: DIAGNOSIS, RESISTANCE, AND TREATMENT
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PrEP with TDF/FTC has shown in demonstration projects and real life implementation an effectiveness that was better than in clinical trials. However, despite its high effectiveness, and because of its increased use, a number of PrEP failures have been reported highlighting that, as any preventive tool, proper use will be associated with protection against HIV-infection. PrEP failures have many causes which need to be clearly diagnosed. System failures refer to the lack or limited access to PrEP because of unavailability, lack of awareness among people at risk and health care providers, and cost. Governments should endorse WHO guidelines and offer PrEP to those who need it. Doctors failures refer to insufficient knowledge of PrEP with the failure to rule out HIV-infection when starting or renewing PrEP, or reluctance to prescribe PrEP. People failures are mostly due to the deferred or improper use of PrEP since strict adherence to PrEP is critical for effectiveness. Assay failures refer to the challenges of HIV diagnosis due to the low sensitivity of HIV tests during the first days/weeks following HIV acquisition, the impact of TDF/FTC use on HIV antibody and viral load assays and also the challenge of ruling out HIV-infection in case of false positive serologic assays on PrEP. Drugs failures which are the most feared causes of PrEP failure remain rare with only a handful of breakthrough HIV-infections in people with good adherence to PrEP. These cases are potentially due to the acquisition of a virus with TDF and/or FTC resistance, exposure to a very high HIV inoculum, pharmacokinetic variability in blood and/or tissues, drug drug interactions, concomitant STIs or altered microbiota. PrEP failures can lead to drug resistance when started or maintained in a person with HIV-infection. In clinical trials, most cases of HIV-infection with resistance occurred when PrEP was started in someone with undiagnosed HIV-infection. In case of HIV-infection antiretroviral therapy including drugs with a high genetic barrier to resistance (boosted darunavir, dolutegravir, bictegravir) should be immediately initiated pending the results of a genotypic resistance test. Overall, true biomedical failures of PrEP remain rare, but these cases should be thoroughly investigated to understand the reasons of PrEP failures.

161 CAN TWO DRUGS TANGO: THE ROLE OF DUAL THERAPY
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In an era of largely well-tolerated antiretrovirals with high virologic efficacy, the new ‘battle’ is that of two vs three drug regimens (2DR vs 3DR). The majority of studied 2DR have been boosted-protease inhibitor based so, despite any possible benefit of fewer drugs, hampered by the limitations of the PI class including tolerability, long-term toxicity and extensive drug-drug interactions. Additionally, several 2DR have demonstrated suboptimal efficacy with high rates of emergency drug resistance at virological failure. Unboosted integrase inhibitors with a high barrier to resistance offer the option of non-PI-based 2DR and, to date, dolutegravir/rilpivirine and dolutegravir/lamivudine have demonstrated high efficacy in switchable and first-line therapy, respectively; these combinations, however, face the challenge of proving efficacy, but the challenge of shifting the paradigm of 3DR that has been central to practice for over 2 decades. Current guidelines still prefer 3DR – how much evidence is required for 2DR to be elevated from ‘alternative’ status? Must 2DR be better than 3DR in some way or simply similar? With injectable options on the horizon we need to consider not only how to best use 2DR, but how to deliver treatment in new way. Who will want to trade daily pills for regular injections and how can we integrate that into busy clinical practice?

Many questions about 2DR remain unanswered, including the impact of baseline resistance, efficacy in suboptimal adherence and the importance of compartment penetration. The balance between embracing progress and employing caution when 3DR has delivered so much is a tricky one, but the decisions we help our patients make should be considered within a robust ethical framework. We need to ensure that future studies fill the gaps in our knowledge so we can incorporate 2DR into our practice in the safest and most appropriate manner.

162 YOUNG TRANSGENDER INDIVIDUALS
Asa Radix, Callen-Lorde Community Health Center, New York, NY, USA

Transgender and gender diverse youth (i.e., those whose gender identity does not align with their sex assigned at birth), especially transfeminine youth of color, face high rates of verbal and physical violence, unsafe school environments, family rejection and homelessness. Stigma and discrimination against transgender people have been linked to adverse health outcomes, such as low self-esteem, depression and substance use, which are inextricably tied to HIV vulnerability. Although data on HIV incidence and prevalence are limited for transgender youth, young transgender women of color are disproportionately impacted. Few data exist for transgender men and gender diverse individuals assigned female at birth, however trans men who have sex with cisgender men and engage in sexual risk behaviors such as condomless sex, are at heightened risk for HIV infection. Transgender youth face unmet medical needs, including access to gender-affirming care and HIVSTI testing, counseling and prevention services. Research has shown underutilization of pre-exposure prophylaxis (PrEP) among those at risk for HIV. This presentation will review recent epidemiologic data related to HIV in transgender and gender diverse youth and describe current and evolving developmentally appropriate and culturally sensitive HIV prevention interventions. To be successful clinical settings should seek to engender resilience through self-acceptance and increased sense of belonging, provide navigation of legal and other structural barriers to care and offer avenues for peer support and social activism. The Callen-Lorde Community Health Center in New York City operates one of the largest and longest-running transgender clinic programs in the United States, serving over 4000 clients (including 1,215 who are aged 24 and under) through on-site and mobile health services. The clinic illustrates best practices for HIV prevention including implementation of trauma-informed medical care, multidisciplinary teams with expertise in transgender medicine, facilitated referrals to surgeons and specialists, comprehensive sexual health education and a robust PrEP program.

163 ENGAGING YOUNG WOMEN IN SUB-SAHARAN AFRICA
Sinead Delany-Moretliwe, Wits Reproductive Health and HIV Institute, Johannesburg, South Africa

Adolescent girls and young women (AGYW) in sub-Saharan Africa (SSA) are at substantial risk for HIV infection. Oral PrEP has the potential to provide HIV protection if used consistently. Two blinded efficacy trials of oral PrEP in women in SSA did not show evidence of HIV protection in AGYW because of low adherence in these trials; adherence was lowest in AGYW. These findings led to concerns that AGYW did not perceive their risk or did not want to use HIV prevention products. Recent open-label demonstration studies of oral PrEP in AGYW however have shown that young women do perceive their risk and that uptake of open-label oral PrEP is high. Challenges remain, however with taking a pill a day. This presentation will present updates on findings from open-label studies about uptake and continuation of oral PrEP in AGYW, as well as strategies that have been shown to improve PrEP continuation. Progress on
expanding national programmes and lessons learned from these will also be reviewed. The implications of these findings for the development of new PrEP products and delivery approaches will be considered.

164 MAKING PREVENTION WORK FOR YMSM: BRIDGING REAL-WORLD NEEDS THROUGH DIGITAL ENGAGEMENT
Lisa Hightow-Weidman, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
Despite evidence for the efficacy of treatment as prevention as both antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP), uptake and sustained retention in the prevention and care continuum for young men who have sex with men (YMSM) is suboptimal. Thus, both in the United States and globally, YMSM remain disproportionately impacted by HIV. The effectiveness of ART for reducing HIV transmission requires successes at multiple steps of the HIV prevention and care continuum (HIV testing, PrEP or ART treatment initiation, and treatment adherence), which may prove challenging for YMSM due to individual, structural, and societal barriers. Comprehensive, evidence-based behavioral, psychosocial, and structural interventions are needed to optimize PrEP and treatment as prevention among YMSM. Technology-delivered interventions are well-suited for YMSM given their modality, the ubiquity of technology in the population, and the platform’s suitability for delivering tailored content specific to each user’s unique needs. These interventions can be particularly useful for YMSM who, due to anticipated or actual stigma, are unable or unwilling to talk to providers about their same-sex attractions and behaviors, and yet are in need of prevention and care services. However, the strategies to “make prevention work” for YMSM must maximize the potential for digital tools to address gaps in the cascade, and ensure that engagement bridges the resources shared through the digital world with their real-world needs. The accessibility and anonymity of online spaces may provide a particularly powerful intervention modality for amplifying resilience and empowerment thus countering the stereotypes and social institutions that perpetuate HIV-related stigma, racism, and blame experienced by YMSM. A brief review on how the use of technology, specifically, mobile health (mHealth) has evolved as seen from the lens of researcher, provider and patient/participant will be provided. Use of mHealth to mitigate stigma, improve patient-provider communication and provide social support - all factors known to be important in prevention and care outcomes -- will be discussed. Practical strategies, best practices and future innovations will be presented.

165 DON’T LEAVE THEM BEHIND: HETEROSEXUAL YOUNG AFRICAN MEN
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Background: The number of young people living in Africa (15-24 years) is projected to double over the next 30 years. Africa’s ability to benefit from this population growth will depend on their health and well-being. High HIV incidence among young people may drive rises in the absolute numbers of new infections. Whilst HIV prevention initiatives are focusing on specific subgroups of young people (e.g. adolescent girls and young women, young men and women selling sex, men having sex with men), young heterosexual men are being left behind. As for adult men, adolescent and young men are less likely to seek health services than their female counterparts, with research suggesting that this is at least in part due to shame or the need to “save face”. Indeed, a well-recognized notion is that help-seeking can be seen as a threat to masculine identity in both adult and young males, due to masculinity-related cultural constructs which conflate help-seeking behavior with being “weak”. Supply-side barriers include stigmatizing attitudes of providers about sexuality and, limited youth-friendly services. Studies conducted in sub-Saharan Africa (SSA) suggest that efforts to engage and interest male youth in HIV prevention could include: offering them free or low-cost specific sexual & reproductive health and HIV services, creating separate and confidential spaces for them, intensifying efforts to sensitize health-care workers to be more “youth friendly”, in particular, respecting confidentiality, being nonjudgmental and accommodating young men’s concerns of looking “weak”. Conclusions: The population-level impact of youth-focused HIV prevention interventions being implemented in SSA will be diminished if young heterosexual men continue to be left behind. Lessons learned from innovative approaches to enhance voluntary medical male circumcision uptake, including use of HIV self-testing and harnessing female peers’ influence, could inform design and implementation of other male youth-focused HIV prevention initiatives. Setting the pattern for healthy health-seeking behavior in adolescents will likely have benefits throughout the life course.

POSTER ABSTRACTS

166 ENTRY KINETICS OF GLOBALLY REPRESENTATIVE AND VERTICALLY TRANSMITTED HIV ENVELOPES
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Background: Understanding HIV entry kinetics may reveal important dynamic properties relevant to transmission and vaccine design. To date, most entry kinetics studies are limited to either lab-adapted isolates or a limited selection of primary isolates and their mutational derivatives. We sought to determine the breadth of naturally occurring HIV-1 isolates.
Methods: An optimized time-of-addition assay with T20 was used to measure the kinetics of the transition between the prehairpin (PHI) and 6-helix bundle (6HB) states of HIV gp41 for more than 150 primary envelopes (Env). Env isolates included a globally representative panel (global) and vertically transmitted Env associated with in-utero (IUT, 5 mom/baby pairs, 37 Envs) and breast milk (BMT, 6 mom/baby pairs, 50 Envs) transmission. Normalized time-dependent infectivity data were fit to a lognormal cumulative distribution. The corresponding probability distribution (PDF) was used to derive the average time it takes to reach the PHI/6HB transition (delay, time point of greatest increase in infection) and the duration of transition (width of PDF at 75% of its maximum, in minutes).
Results: Lognormal distributions fit the data with high accuracy (R²>0.85 for 99% of experiments). The delay and duration among global Envs ranged from 3-15 minutes and 6-35 minutes, respectively. IUT Maternal/infant isolates had a uniquely confined range of delay/duration with some of the fastest kinetics (~1 min). BMT Env kinetics were highly diverse and 3/6 infants each harbored a single Env with remarkably long delays of 40–60 minutes and equally long durations. Kinetic interpretations of these metrics were supported by strong correlations to both T20 (R²=0.87) and 10E8 sensitivity (R²=0.79) across a 1000 and 100-fold range of EC50, respectively.
Conclusion: Circulating HIV Envs exhibited a broad range of PHI kinetics that reflect their diverse nature. PHI kinetics were also significant determinants of sensitivity to both T20 and 10E8, one of the broadest neutralizing antibodies known to date. Vertically transmitted BMT isolates exhibited remarkably unique kinetic extremes suggesting a functional bottleneck in this transmission route that restricts labile Envs, while IUT isolates were highly restrained in both delay and duration. The naturally occurring, kineticlly slow Envs we identify may offer unique insights into the design of highly stable and native gp41 antigens that reflect the natural diversity of Env.

Nicholas E. Webb, Nicole Tobin, Grace M. Aldrovandi
CD4-DEPENDENT MODULATION OF HIV-1 ENTRY BY LY6E
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Background: The role of IFN-induced genes (ISGs) in viral infection remains incompletely understood. While most ISGs are antiviral, some ISGs have been shown to promote viral infection, including HIV-1. Indeed, we previously showed that IFN-inducible LY6E protein promotes HIV-1 infection in human PMBCs and high CD4-expressing SupT1 cells.

Methods: We examined the effect of LY6E on low- and high-CD4 + T cells, as well as human primary cells including monocyte-derived macrophages (MDMs). We used shRNAs to knock down the endogenous LY6E in these cells and determined its influence on HIV-1 entry and replication. We performed immunofluorescence microscope imaging analysis to examine the co-localization between CD4 and LY6E. We performed lipid flotation assay to dissect the biophysical and functional interplay between CD4 and LY6E on the plasma membrane and intracellular compartments.

Results: We provide evidence that LY6E inhibits HIV-1 entry and spread in low CD4-expressing Jurkat cells and human monocyte-derived macrophages (MDMs), through downregulation of the viral receptor CD4 from the plasma membrane. We found that knockdown of LY6E in Jurkat cells increases HIV-1 entry yet overexpression of LY6E in Jurkat cells inhibits HIV-1 entry and replication. LY6E is co-localized with CD4 in Jurkat cells and MDMs and enhances the CD4 internalization from the plasma membrane. We artificially manipulated the CD4 level in Jurkat and SupT1 cells and found that overexpression of CD4 in Jurkat cells overcomes the inhibitory effect of LY6E; blocking the function of CD4 in SupT1 with a neutralizing antibody eliminates the enhancement of LY6E on HIV-1 entry. The CD4-dependent inhibitory phenotype of LY6E can be recapitulated in low CD4-expressing human MDMs.

Conclusion: Our study reveals a CD4-dependent function of LY6E that distinctly modulates HIV-1 entry and replication. Given that HIV-1 targets low CD4-expressing cells during primary infection but replicates efficiently in high CD4-expressing T cells at the late stage of diseases, our observation has implications for understanding of the diverse roles of IFN-induced proteins in different stages of HIV-1 infection and AIDS pathogenesis.

ELUCIDATING MECHANISMS BY WHICH MUTATIONS IN ENV CONTRIBUTE TO HIV-1 DRUG RESISTANCE
Rachel Van Duyne, Phuong Pham, Jonathan Spindler, Ann Wiegand, Mary F. Kearney, Eric O. Freed

Background: Despite the effectiveness of antiretroviral therapy (ART), virological failure can occur in HIV-1 infected individuals, often in the absence of recognized drug resistance mutations (DRMs). By performing in vitro selection experiments, we identified mutations within the HIV-1 envelope (Env) glycoprotein that broadly increase viral fitness by overcoming blocks to virus replication, including several selected in the presence of the antiretroviral (ARV) inhibitor Dolutegravir (DTG). The goal of this study was to determine the mechanism by which the Env mutations afford ARV escape.

Methods: Virus replication and quantification of viral spread in the presence of ARVs were measured by propagating Env mutant viruses in a spreading infection in T-cell lines and primary PBMCs. Cell-free and cell-to-cell virus transmission was measured using reporter viruses and cell lines. Finally, we measured the effective multiplicity of infection (MOI) of viral transmission events.

Results: We calculated the fold-change in IC50 of two of the DTG-insensitive Env mutants, A556T and A539V, as 4-5 fold, comparable to that of current DTG DRMs in integrase. The de novo-selected DTG-resistant Env mutant, A539V, also exhibits markedly reduced sensitivity to at least two other classes of ARVs. Using a GFP-expressing reporter virus, we determined that the A539V mutation greatly enhances the efficiency of cell-to-cell transfer and increases the effective MOI of the transmitted virus. We are currently measuring the viral DNA load per infected cell in the presence and absence of DTG. Remarkably, we selected a DTG-resistant Env mutation at the same position in a subtype C transmitter founder virus. Finally, we observed that propagation of an ARV-resistant mutant in high concentrations of DTG forced selection of additional Env mutations, which may ultimately enable the acquisition of DRMs in integrase.

Conclusion: These results provide insights into escape from ARVs and demonstrate that mutations in Env can contribute to broad HIV drug resistance in vitro. The study of Env mutants that result in a decreased sensitivity to DTG is of particular interest as resistance mutations in integrase have been challenging to characterize to date. We speculate that these Env mutations may provide a “stepping stone” on the path to high-level drug resistance in vivo. We are currently investigating the implications of these findings for HIV drug resistance in nonhuman primate models and in patients.
(p<0.001) between short sequence repeats and deletion start and stop sites, indicating that nucleotide homology at deletion sites is not due to chance. **Conclusion:** This study showed that deletions in HIV proviruses occur at non-random sites, indicating they are generated by a specific mechanism. The presence of short sequence repeats at deletion junctions (an important factor for the generation of recombinants) and the identification of a common deletion site at the cPPT (a known recombinant site) suggests deletions occur as a result of RT-mediated template switching. Understanding the mechanisms that generate defective proviruses will be important for developing future eradication methods that enhance their production.

170 HOST FACTORS INFLUENCE SIV AND HIV-1 INFECTION AND SENSITIVITY TO CAPSID INHIBITORS

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**Background:** SIVs of chimpanzees (cpz) and gorillas (gor) rarely established infections in humans in which these viruses were further transmitted from human to human. The viral capsid (CA) is the key viral determinant of primate lentiviruses that are targeted by cytoplasmic proteins such as cyclophilin A, TRIM5α, CPSF6 (mRNA processing protein cleavage and polyadenylation specificity factor 6) and MA2 that affect infection and likely regulate cross-species transmission.

**Methods:** In order to characterize the impact of different cell types and dependency pathways versus restriction pathways, luciferase reporter viruses for SIVcpz (for both SIVgp2Ptt and SIVgp2Pts), SIVgor and rare HIV-1 N, 0 and P were constructed. Infection experiments using VSV-G pseudotypes were performed in the presence and absence of host proteins and pharmacological inhibitors (e.g. cyclosporine A, PF74).

**Results:** Here we show that small inhibitors of the viral capsid (PF37, PF74) differentially affect the infection of SIVcpz and HIV-1s in human and non-human cells. While SIVgp2Ptt was sensitive to PF37 inhibition in human HOS and HeLa cells, SIVgp2Pts were only inhibited in HOS cells. No SIV gp2 were blocked in rhesus monkey cells by PF37. In contrast, HIV-1 M was sensitive to PF37 in all three cell types. We constructed a SIVgp2Ptt with the capsid of the Pts virus. The chimeric SIVGPt lost only partially the sensitivity to the capsid inhibitor.

**Conclusion:** Manipulation of the viral infection by inhibitors for capsid is strikingly dependent on the cell-type. PF37 and related capsid inhibitors can inhibit non-HIV-1 primate lentiviruses. This inhibition, however, requires unidentified cellular host factors that differentially interact with HIV-1 M, and SIVcpz. PF37/PF74-sensitivity of SIVcpz is only partially regulated by the viral capsid.

171 VPX INDUCES AN IFN-RELATED INNATE IMMUNE RESPONSE DISTINCT FROM SAMHD1 ABRATION

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**Background:** SAMHD1 is an HIV restriction factor that acts by depleting the intracellular pool of nucleotides, a process that is counteracted by the virion-packaged accessory protein Vpx, through SAMHD1 proteosomal degradation. SAMHD1 mutations lead to Aicardi-Goutieries syndrome characterized by increased IFN production. SAMHD1 depletion has also been associated to aberrant DNA production and production and innate immune activation. Here, we investigate the interplay between SAMHD1 depletion, innate immune activation and susceptibility to HIV-1 infection.

**Methods:** CD14+ human monocytes were differentiated to macrophages. Knockdown of SAMHD1 was achieved by RNA interference or by transducing macrophages with VLP-containing HIV-2 Vpx. A SAMHD1 knockout T2M-bi cell line was generated by CRISPR/Cas9. Susceptibility to HIV-1 infection was examined by flow cytometry after infection with a VSV-G pseudotyped NL4-3 GFP-expressing virus. Gene expression was assessed by quantitative PCR.

**Results:** Vpx-induced degradation of SAMHD1 significantly increased HIV-1 infection in primary macrophages. However, no significant change in infection was seen when SAMHD1 expression was inhibited by either siRNA in macrophages or in the CRISPR/Cas9 knockout cell line model. To assay the role of Vpx, whole transcriptome profiling of macrophages untreated or Vpx transduced was performed. 41 genes were differentially expressed: 14 downregulated and 27 significantly upregulated after Vpx-induced SAMHD1 degradation. Interestingly, 14 out of 27 upregulated genes (52%) were IFN-stimulated genes (ISG), including IFNB1, IRF7 and CXCL10, suggesting a relationship between Vpx and activation of the innate immune system. Identified ISG expression was confirmed and extended in additional donor cell samples. Further evaluation of the pathway underlying innate immune activation after Vpx treatment in macrophages showed enhanced expression of the RNA sensors RIG-I and MDA5 without involvement of DNA sensors. On the contrary, when SAMHD1 expression is downregulated by siRNA or by CRISPR/Cas9, increased expression of DNA sensors cGAS and STING was found, without any significant effect on RNA sensors.

**Conclusion:** Vpx-mediated degradation enhances innate immune activation that is distinct and independent of SAMHD1 expression. These differences may help explain variability in the pathogenicity and immune control of HIV infections.

172 EVOLUTION-GUIDED STUDIES TO UNDERSTAND THE ANTIVIRAL MECHANISM OF IFITM3

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**Background:** The interferon-induced transmembrane (IFITM) proteins are a group of antiviral factors that inhibit the replication of diverse viruses, including HIV-1, at two stages: restriction of incoming viruses in target cells and inhibition of virion infectivity in producer cells. Evidence points to inhibition of virus-cell fusion as the basis for both antiviral functions, but the precise molecular mechanism is unknown. Recent studies suggest that IFITM genes belong to a family of transmembrane proteins known as Dispanins, which are characterized by two transmembrane domains separated by a conserved intracellular loop (CIL). Whereas IFITM proteins inhibit viral and host membrane fusion, another member of the Dispanin family known as PRRT2 inhibits synaptic vesicle fusion in neurons. Therefore, a comparative evolutionary and biochemical analysis between IFITM proteins and other Dispanin members, such as PRRT2, will uncover the mechanistic basis behind membrane fusion regulation.

**Methods:** Multiple sequence alignments of Dispanin family members were performed to identify regions of conservation and divergence. Residues in IFITM1 that are analogous to functionally important sites in PRRT2 were mutated and tested for impact on antiviral functions. 293T cell lines stably expressing IFITM3 variants were generated and challenged with Influenza A and retroviral pseudotypes to study the inhibition of virus entry, while 293T cells co-transfected with IFITM3 variants and retroviral plasmids were used to study the inhibition of virion infectivity.

**Results:** A single residue change in the CIL of IFITM3, never before studied in the context of its function, resulted in a substantial loss of antiviral activity. Importantly, the analogous residue in PRRT2 is critical for its regulation of synaptic vesicle fusion. Western blot and Immunofluorescence analysis indicate that the single mutation disrupts protein function without affecting protein expression or turnover.

**Conclusion:** The identification of a single amino acid residue critical to the function of IFITM3 provides an important tool in the search for the molecular mechanism driving antiviral function. The finding that analogous mutations in IFITM3 in PRRT2 disrupt their respective functions suggests that both proteins similarly remodel host membranes and/or operate via the same downstream effectors. We are currently addressing whether the two proteins contain overlapping interaction partners which coordinate vesicular trafficking and fusion.

173 ERAP2 ADMINISTRATION REDUCES IN VITRO PBMC SUSCEPTIBILITY TO HIV-1 INFECTION

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**Background:** Haplootype-specific alternative splicing of the endoplasmic reticulum (ER) aminopeptidase type 2 (ERAP2) gene results in either full-length (FL, haplootype A) or alternatively spliced (AS, haplootype B) mRNA. HapA/HapA homozygous (homoA) subjects show a reduced susceptibility to HIV-1 infection,
RESULTS: As previously shown homa subjects were less susceptible to in vitro HIV-1 infection (p < 0.01). Addition of eRHAFL-2 to in vitro HIV-infected cells did not affect cell viability and resulted in a reduction of viral replication in both homa and homb individuals with a peak effect observed using 100 ng/ml of the protein (p < 0.01 in both cases). This protective effect was independent from an increase of HLA-ABC expression and/or of perforin and granzyme expression by CD8+ lymphocytes

Conclusion: The role and the targets of eRHAFL-2 in the extracellular milieu are still undisclosed and need further investigation. However, data herein suggest that once added to cell culture eRHAFL-2 preserves its protective function against HIV-1 infection, even in homosubjects who do not genetically produce it. Presumably this defensive feature is mediated through an unconventional mechanism, distinct from immune system modulation.

174 INCREASED SAMHD1 CORRELATES WITH ISGS IN HIV-1-INFECTED PATIENTS
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Background: SAMHD1 is an inducible host innate immunity restriction factor that inhibits HIV-1 replication. The underlying mechanisms of SAMHD1 transcriptional regulation remains elusive and considerable controversy exists over whether type I IFN can support SAMHD1 production. In order to gain new insights into the role played by SAMHD1 in regulating the natural course of HIV-1 infection, we evaluated SAMHD1 expression and its relationship with the IFN response in vivo.

Methods: Peripheral blood mononuclear cells (PBMCs) isolated from 335 HIV-1-infected individuals were examined. Demographical and clinical characteristics of patients are reported in Table 1. CD4+ T cells, CD14+ monocytes and gut mucosal biopsy samples were also analysed in a subgroup of HIV+ infected patients on suppressive antiretroviral therapy. Gene expression levels of SAMHD1 and ISGs (MxB, HERC5, IRF7) were evaluated by real-time RT-PCR assays.

Results: SAMHD1 levels in HIV+ positive patients were significantly increased compared to those in healthy donors (p < 0.04). Virologically suppressed treated patients exhibited higher SAMHD1 levels than healthy donors (p < 0.0008), and naive patients (p < 0.0001). SAMHD1 levels were higher in CD4+ T cells than in CD14+ monocytes paired samples (treated patients: p < 0.003; healthy donors: p < 0.0001). By comparing SAMHD1 expression in CD4+ T cells and CD14+ monocytes between HIV+ infected patients and healthy donors, an increased SAMHD1 expression in these cell subsets was recorded in treated HIV+ positive patients (patients vs healthy donors, CD4+ T cells: p < 0.0001; CD14+ monocytes: p < 0.0001). We selected a subgroup of 7 out of treated HIV+ positive patients with relatively low PBMC SAMHD1 mRNA expression in order to explore SAMHD1 levels in GALT. We found twofold higher median values of SAMHD1-mRNAs in PBMC compared to those measured in GALT paired samples (p < 0.04). Moreover, SAMHD1 was expressed more strongly than MxB, HERC5, and IRF7 in virologically suppressed HIV+ infected patients (p < 0.0001 for all the analyses), and positive correlations were found between SAMHD1, MxB, HERC5, and IRF7, levels.

Conclusion: Taken together these findings indicate that SAMHD1 is more strongly expressed than the classical IFN-related genes, increased during antiretroviral therapy and correlated with several ISGs in HIV+infected patients on HAART.
Methods: We developed a Förster resonance energy transfer (FRET) construct consisting of the mUKG and mKoK fluorescent pair, separated by a protease cleavage site and linked to the viral accessory protein Vpr that is incorporated into virions via a non-covalent interaction with the Gag p6 protein. Viruses were monitored using a FACSAria II flow cytometer.

Results: The FRET protease (PR) substrate is incorporated into viruses and undergoes cleavage in the presence of active protease, resulting in a colorimetric change that can be detected by flow cytometry. Processing of the FRET PR substrate correlated extremely well (R² = 0.93, p < 0.0001) with processing of Gag by western blot over a wide range of protease inhibitor (PI) concentrations, indicating it is an accurate surrogate of protease activity within virions. Next, we generated viruses from patient-derived infectious molecular clones (IMCs) that incorporated the FRET PR reporter. We found that processing of the FRET PR reporter varies significantly in patients, with 35.0-59.8% of viruses demonstrating processing. Importantly, the extent of processing observed by flow cytometry correlated with the infectivity of the viruses on JLTRG reporter cell lines (R² = 0.29, p < 0.0001). The FRET PR reporter also correctly identified PI drug resistance in 2 of 13 IMCs and was able to detect differences in budding efficiency for several Gag and PR mutant viruses. The assay is highly reproducible (Z-factor of 0.88) indicating it has robust sensitivity to probe mutant phenotypes or screen for drugs affecting the precursor or mature protease.

Conclusion: Flow virometry represents a powerful technique for monitoring viral heterogeneity with important implications for immunity and pathogenesis. This study is the first demonstration that flow virometry can (1) monitor functional viral activities such as protease processing, (2) detect interpatient viral heterogeneity that correlates with fitness, (3) identify drug-resistant viruses, and (4) identify mutants resulting in alterations in viral budding or maturation.

THE VIRAL ENVELOPE

The negative strand of the HIV-1 genome encodes a 189-aa, highly hydrophobic antisense protein (ASP) with no known homologs. Humoral and cellular immune responses against ASP in HIV-1 patients demonstrate that it is expressed in vivo, but its role in viral replication remains unknown. We studied ASP expression in chronically infected myeloid and lymphoid cell lines, and its impact on viral fitness.

Methods: For intracellular and nuclear staining, we used BD Cytofix/Cytoperm and eBioscience FixP3 kits. Data were acquired on Millipore Guava flow cytometer and analyzed with Flowjo, or Zeiss LSM 880 confocal microscope and analyzed with Zen Blue. Virion-capture assays used antibodies immobilized on Protein G Dynabeads. For Fluorescence Correlation Spectroscopy (FCS) we used ISS Q2 confocal microscope and ISS Vistavision.

Results: We analyzed two myeloid and seven lymphoid HIV-1 infected cell lines using a monoclonal antibody (324.6) against an epitope mapping between two putative transmembrane domains of ASP, and we detected ASP in the nucleus of all infected cell lines. Confocal microscopy evidenced a polarized nuclear distribution of ASP, preferentially in areas with low content of suppressive epigenetic marks. Reactivation of HIV-1 with PMA led to transllocation of ASP to the cytoplasm and cell membrane. Cell surface detection of ASP without cell permeabilization shows extracellular exposure of the ASP epitope recognized by 324.6. Surface staining with antibodies to ASP and gp120 showed that the two proteins co-localize (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 the binding efficiency of 324.6 to single virions in solution was ~28%. Thus, these two assays demonstrate the presence of ASP on the surface of mature HIV-1 virions. Finally, we produced HIV-1NL4-3-derived viruses with single-nucleotide mutations that introduce early stop codons in the ASP open reading frame without changing the amino acid sequence of Env on the opposite strand. ASP-deficient viruses displayed a ~50% reduction in replication rate compared to wildtype virus.

Conclusion: ASP is expressed on the surface of productively infected cells, and is a structural protein found in the envelope of mature HIV-1 virions. Further, ASP expression promotes viral replication. Thus, ASP may represent a new target for therapeutic or preventive vaccines.

UNPAIRED GUANOSINES IN THE HIV LEADER RNA DIRECT HIV GENOMIC RNA PACKAGING

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Background: HIV-1 and HIV-2, the causative agents of AIDS, package two copies of their RNA genome into one viral particle. It remains unclear how the viral protein Gag specifically selects viral RNA from a large pool of cellular mRNAs. HIV-1 Gag protein has been shown to bind exposed guanosines in the leader region of its RNA and these interactions are thought to be important for packaging. Currently, little is known about HIV-2 RNA packaging mechanisms. To test the hypothesis that exposed guanosines in the HIV-2 leader RNA play a key role in RNA packaging, we mutated guanosines predicted to be exposed in nine regions of the leader RNA and examined the effects of these mutations on genome packaging.

Methods: We visualized HIV-2 RNA in individual viral particles using single-virion analysis, an assay developed in our lab that can detect viral genomes at single RNA sensitivity. In this system, viral particles are visualized by tagging Gag proteins with cerulean fluorescent protein (CeFP), whereas RNA is visualized based on specific interactions between bacterial protein BglG tagged with yellow fluorescent protein (YFP) and RNA stem loop sequences (BSL) engineered into the HIV-2 constructs. RNA packaging efficiency is determined by quantifying the proportion of Gag particles (CeFP signal) that contain HIV RNA (YFP signal).

Results: HIV-2 RNA with wild-type sequences were packaged efficiently: ~95% of viral particles contained viral RNA. In contrast, mutating guanosines in all nine regions of the HIV-2 leader RNA resulted in loss of RNA packaging: only ~10% of viral particles contained viral RNA. Thus, exposed guanosines are critical for HIV-2 RNA packaging. To identify specific regions crucial for RNA packaging, we examined additional mutants in which individual regions or multiple regions were mutated. We identified one primary region and three secondary regions that are important for RNA packaging. Mutation of any individual region did not significantly affect genome packaging. However, mutating the primary region together with any of the secondary regions caused defects in genome packaging and we identified the specific set of guanosines that were responsible for the most severe defect.

Conclusion: Our results demonstrate that exposed guanosines in the HIV-2 RNA leader are critical for genome packaging. Furthermore, not all guanosines in the RNA leader are equal; cumulative interactions between Gag and multiple specific sites direct genome packaging.

DETECTION AND SEQUENCING OF ASP TRANSCRIPTS DURING EARLY HIV-1 INFECTION

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Identification of HIV-1 Env Mutations That Enhance Entry into Macaque Cells

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Background: Although rhesus macaques are a central animal model for HIV-1 vaccine development research, most transmission-founder (T/F) HIV-1 strains replicate poorly in macaque cells. This species-specific restriction has been attributed to the activity of host specific restriction factors, as well as a single nonsynonymous mutation in macaque CD4 that inhibits binding by HIV-1 Envelope (Env). Recent research efforts employing either laboratory evolution or structure-guided design strategies have discovered several Env mutations in envelope (Env). Recent research efforts employing either laboratory evolution or structure-guided design strategies have discovered several Env mutations in Env that enhance usage of macaque receptors.

Methods: CD4+ T cells isolated from three patients infected with subtype B were stimulated with anti-CD3/CD28. Reverse transcription was performed using the biotinylated specific antisense primer, followed by CDNA purification by streptavidin-coated magnetic beads, PCR amplification with patient-specific asp primers, cloning and sequencing.

Results: Expression of asp RNA was detected in CD4+ T cells from three HIV-infected individuals during early infection following stimulation with anti-CD3/CD28. In contrast, no expression was detected in unstimulated PBMCs, either resting or stimulated, or in unstimulated CD4+ T cells. Sequence analysis of asp transcripts from cells (26 clones) and of the corresponding env on the plus strand in serum (30 clones) indicate that the dominant length variants in the asp RNA pool in cells are the same as those found in genomic env in serum. In asp RNA transcripts from cells, the complete canonical (i.e. as in HXB2) asp ORF was identified in 20% of the clones, in two of three patients. Clones carrying shorter or longer ORFs (non-canonical stop codons) were also identified, in regions that were either hyper variable or characterized by a variability to some extent in the corresponding env sequence on the plus strand.

Conclusion: Our results show that asp RNA is easily detectable in stimulated CD4+ T cells isolated from untreated patients during early infection. Our data also represent the first nucleotide sequences obtained in patients for asp, demonstrating that it may well be expressed in those HIV-1 lineages in which the asp ORF is present. The finding of a new HIV antigen would represent an important step in our understanding of HIV pathogenesis and perhaps open new perspectives in the development of novel anti-HIV drugs and vaccines.

Mutations in the GP41 Ectodomain Can Contribute to HIV-1 Resistance to smFIs

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Background: Small-molecule fusion inhibitors (smFIs) such as IC9564 can inhibit human immunodeficiency virus type 1 (HIV-1) entry into the cells. Recently, we have developed novel IC9564-derived smFIs as a new class of HIV entry inhibitor. In the present study, we investigated HIV-1 variants selected under smFI pressure to get a better understanding of the smFI-virus interaction.

Methods: Resistant variants were induced by culture of HIV-1 89.6-infected PM1 cells in the presence of smFIs. We then constructed infectious 89.6 clones carrying mutations selected in the resistant variants. The susceptibility of the infectious clones to smFIs and other class of entry inhibitors was tested by TZM-bl assay.

Results: Selection of 89.6 variants under gradually-increased concentrations of IC9564, OKS3-019 and NIT-078 revealed the sequential selection of 4 mutations (H769P (CT), F522V (FP), M261I (SP) and H72Y (CI)), 3 mutations (R838K (CT), R588K (HR1) and V681I (CI)) and 2 mutations (G594R (DSL) and G600E (DSL)), respectively. Studies with engineered smFI-resistant env variants indicate contribution of amino acid changes in the gp41 ectodomain to smFI resistance. Unexpectedly, these variants were not only highly resistant to smFIs, but also critically dependent on smFI derivatives. It can be speculated that gp41 modification
by these mutations may induce structural rearrangements resulting in formation of the closed conformation, thereby rendering these viruses dependent on smFs. These results enhance our understanding of Env complex interactions that influence both HIV-1 entry and susceptibility to smFs.

183 HIV PROVIRAL TRANSCRIPTION RAPIDLY UPREGULATES BCL3, BIRC2, AND BIRC3 TRANSCRIPTION

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Background: ACH-2 cells usually produce low levels of HIV when unstimulated. Viral production increases dramatically with TNFα stimulation. Prior to stimulation with TNFα, surface staining of HIV Env identifies two ACH-2 populations, one which stains for Env and p24, and one which does not. With TNFα stimulation the HIV Env+ population stains more intensely for Env and produces >90% of the virus found in the supernatant; the Env- population slowly becomes Env+ but produces virus at a much lower rate. We have used the ability to separate Env+ and Env- population using flow cytometry to describe the effect of HIV proviral transcription on the ACH-2 transcriptome immediately prior to, and 3, 6, and 9 hours after TNFα stimulation in Env- and Env+ cells.

Methods: ACH-2 cells were dual stained with PGP and VRC07 and bulk sorted before and 3, 6, and 9 hours post-stimulation with 10U TNFα/ml (N=6 replicates). Cells were immediately spun down, lysed with RNAzol and then frozen. Total RNA was extracted, poly-adenylated RNA purified, fragmented and then reversed transcribed using random hexamers. Illumina ready libraries were generated and sequence by paired-end HiSeq 4000 2x75 reads.

Results: In the HIV Env- population the frequency of HIV RNA reads increased from 0.05±0.01% prior to stimulation to 0.53±0.15% 9 hour post-stimulation. In the HIV Env+ population the frequency of HIV RNA reads increased from 3.8±0.4% prior to stimulation to 12.9±2.0% 9 hours post stimulation. In both populations, similar increases between pre-stimulation and 3, 6, and 9 hours of NFkB2, NFκB1, REL B and TNFAIP3 message were consistent with similar TNFα and NFκB signaling in both populations. The Env+ population showed an 8.4x increase in BCL3 (P=7.5x10^-12), a 5.6x increase in BIRC3 (P=1.1x10^-29), and 2.4x increase in BIRC2 (P=1.1x10^-7) messages 3 hours post-stimulation. Except for BIRC2, these changes persisted 9 hours post-stimulation. These changes were not observed in the Env- population.

Conclusion: These data suggest that proviral transcription of HIV RNA results in a rapid increase in cellular anti-apoptotic message. Upregulation of these transcripts could stymie the cells innate antiviral responses, increase the longevity of infected cells and increase viral proliferation. Upregulation of BCL3 could also contribute to non-canonical activation of the NfκΒ pathway thus further increasing viral production.

184 CHARACTERIZATION OF THE EPITRANSCRIPTOMIC LANDSCAPE OF HIV-INFECTED CELLS

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Background: The study of RNA modifications, today known as epitranscriptomics, is of growing interest. The N6-methyladenosine (m6A) and 5’-methylcytosine (m5C) RNA modifications are abundantly present on mRNA molecules, and impact RNA interactions with other proteins or molecules, thereby affecting cellular processes, such as RNA splicing, export, stability and translation. Recently mA marks were found to be present on HIV transcripts and affect viral replication. However, no study has been performed to date to investigate the impact of HIV replication on the transcript methylation level in the infected cell. We used a productive HIV infection model to explore the landscape of mA and mC marks on the transcriptome of HIV-infected cells over a time period of 36 hours and compared them with mock-treated cells.

Methods: The SupT1 T cell line was infected with a high dose of VSV-G pseudotyped HIV-EF-pb vector to ensure ~80% infection efficiency. Cells were collected at 12, 24 and 36 post-infection for mRNA extraction and FACS analysis. mA RNA modifications were investigated by methylated RNA immunoprecipitation followed by sequencing (MeRIP-Seq). mC RNA modifications were investigated using a bisulfite conversion approach followed by sequencing (BS-Seq). Untouched mRNAs were used as input controls.

Results: We obtained a total of 707 million reads. Upon quality control, filtering, and genome alignment we obtained between 8.3 and 40.6 million aligned reads depending on the sample. Preliminary analyses identified transcript methylation as well as multiple genes displaying differential methylation upon HIV infection.

Conclusion: Our results highlight the presence of RNA modifications and their potential modulation by HIV, and provide a valuable resource for epitranscriptomic analyses. Therefore, RNA methylation offers a new layer of possible regulation for HIV replication, as well as an array of novel putative therapeutic opportunities to block HIV.

185LB AN HIV E-MAP REVEALS GENETIC INTERACTIONS MEDIATING HIV INFECTION

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Background: Functional genetic screens using RNAi and CRISPR-Cas9 are useful for identifying host genes mediating viral infection, however individual genes identified in conventional genetic screens are sometimes difficult to place into the cellular complexes and pathways in which they function. Pairwise genetic interaction screens offer an enhanced approach to studying gene function, permitting for the quantification of functional relationships between genetic perturbations, facilitating the characterization of protein complexes and hypothesis generation regarding gene function. In this proof-of-principle study we have applied genetic interaction mapping to investigate the genes mediating HIV infection in human cells. We present a HIV viral epistasis map (vE-MAP) constructed by pairwise knockdown of 356 human genes in human cells (>63,000 unique combinations).

Methods: We generated a combinatorial knockdown matrix of 356 HIV host-dependency factors (>63,000 unique combinations) in cultured human cells and utilized high-throughput microscopy and luminometry to quantify genetic interactions impacting HIV infection. Human genes of interest identified in the vE-MAP screen were studied in primary CD4+ T-cells utilizing Cas9-RNP single and combinatorial knockouts.

Results: Hierarchical clustering of vE-MAP data highlights known human protein complexes and resolves structural submodules of the eIF3 complex. In addition to combinatorial knockdown perturbations, we also demonstrate that gene knockdowns may be combined with small molecules and viral mutants to gain insights into their function. In a novel discovery, the vE-MAP identifies numerous negative genetic interactions between the CNOT complex and known HIV host-dependency factors, several of which we validate in primary CD4+ T-cells. Finally, we observe that HIV infection in primary CD4+ T-cells requires CNOT1, 10 and 11 for suppression of type 1 interferon response.

Conclusion: This study establishes a foundation for viral genetic interaction mapping utilizing host genetic perturbations, viral mutations and small molecule treatments. We report that the CNOT complex is required for HIV infection in primary T-cells via suppression of the innate immune response.
186 ELUCIDATING THE ROLE OF THE PPIP MOTIF IN HIV-1 CAPSID IN POSTENTRY EVENTS

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Background: The HIV-1 capsid (CA) protein plays multiple roles in the viral replication cycle. As a domain in Gag, CA drives the formation of the immature Gag lattice. Upon maturation, CA reassembles to form the conical core which encompasses the viral RNA genome. During the early stages of the viral replication cycle, CA is involved in a number of processes, including uncoating, recognition by host cellular proteins and nuclear import. Recently, we demonstrated that a highly conserved proline-rich motif (PPIP122-125) in the short loop between CA helices 6 and 7 is an important element for virion assembly. In this study, we characterize the role of the CA PPIP motif in early stages of HIV-1 infection.

Methods: We selected for compensatory mutations that rescue assembly and maturation defects of the original PPIP mutants. Replication kinetics, nuclear import efficiency, and host cell restriction factor sensitivity of mutant viruses were analyzed in different cell lines and physiologically relevant cell types. Structures of mutant CA proteins were determined by X-ray crystallography. Nuclear import kinetics were characterized by light microscopy using APOBEC3F-labeled viral complexes.

Results: A set of replication-competent viruses including T58S/T107I/P122A, V111/T58A/P122A, T58A/I124A and V111/T58A/I124A have been analyzed in this study. Although T58A/I124A and V111/T58A/I124A mutants are replication competent in PBMCs and parental Jurkat cells, they are highly replication defective in cyclolinphin A (CypA)-deficient Jurkat cells and monocye-derived macrophages (MDMs). We further demonstrated that V111/T58A/I124A virions enter the nucleus faster than WT virus and are insensitive to cyclosporine A treatment. Upon propagation in CypA-deficient Jurkat cells, the V111/T58A/I124A virus acquired a mutation, I124V, which restores its replication competence. In vitro, HIV-1 infectivity and replication were both significantly reduced for Nef dimerization (Ile 109/Leu 112/Tyr 115/Phel 121 to Asp; 4D mutant) and AP-2 binding (Asp 174/175 to Ala; DDA mutant and Arg/34 to Glu; RE mutant) based on previous X-ray crystal structures. A virus defective for Nef expression was also included (ΔNef mutant) as reference control. Effects of these mutations on viral infectivity and replication were investigated using TZM-bl reporter cells and CEM-GFP cells, respectively. BLT (bone marrow-liver-thymus) and hPBMC-NSG humanized mice were infected with each virus (2000 TCID50 equivalents/mouse), and replication measured by real-time quantitative RT-PCR targeting Gag or p24. Results showed decreased viral loads and displayed CD4+ T cell counts comparable to wild-type HIV-1 within the course of 6 weeks post infection. Nested PCR and nucleotide sequencing did not identify reversions of the 4D mutant recovered in humanized mice. Humanized BLT mice infected with ΔNef viruses showed significantly lower viral loads and reduced CD4+ T cell counts compared to wild-type HIV-1 pathogenesis.

Conclusion: Our findings demonstrate that Nef homodimerization is important for HIV-1 pathogenesis. In vitro, HIV-1 infectivity and replication were both significantly reduced with the 4D, DDA, RE and ΔNef viruses. Humanized BLT mice infected with ΔNef viruses showed significantly lower viral loads and reduced CD4+ T cell depletion compared to wild-type HIV-1 within the course of 22 weeks post infection. hPBMC-NSG humanized mice were infected with each virus (2000 TCID50 equivalents/mouse), and replication measured by real-time quantitative RT-PCR targeting Gag or p24 AlphaLISA assays in plasma and tissues. Human CD4+ T cell counts were followed in peripheral blood and tissues by flow cytometry as a surrogate for HIV-1 pathogenesis.

Results: In vitro, HIV-1 infectivity and replication were both significantly reduced with the 4D, DDA, RE and ΔNef viruses. Humanized BLT mice infected with ΔNef viruses showed significantly lower viral loads and reduced CD4+ T cell depletion compared to wild-type HIV-1 within the course of 22 weeks post infection. HPMBC-NSG mice infected with the ΔNef and 4D mutant viruses showed decreased viral loads and displayed CD4+ T cell counts comparable to uninfected mice within the course of 6 weeks post infection. Nested PCR and nucleotide sequencing did not identify reversions of the 40 mutant recovered from humanized mice. However, a possible reversion was found in one viremic mice infected with the RE mutant.

Conclusion: Our results demonstrate that Nef homodimerization is important for HIV-1 pathogenesis in humanized mouse models of HIV/AIDS. These data

187 SINGLE-CELL ANALYSIS REVEALS P2X-DEPENDENT HIV-STIMULATED CALCIUM SIGNALING


A single-cell imaging platform is a novel and effective tool for tracking both calcium influx and HIV-1 productive infection in cells. Our findings demonstrate that HIV-1 exposure can activate calcium influx through a mechanism that is sensitive to a P2X receptor antagonist. We observe that a P2X receptor antagonist reduces calcium influx and HIV-1 productive infection. These findings demonstrate that calcium signaling correlates with productive infection and indicates importance of calcium signaling in early infection events. Further development of P2X inhibitors as drugs could prove to be effective at both suppressing viral load and preventing inflammation-associated comorbidities.

Results: HPV-1 exposure was associated with an acute increase in intracellular calcium levels that corresponded to HIV-1 productive infection. Treatment with NF449 reduced HIV-stimulated calcium influx and HIV-1 productive infection. The higher magnitude of calcium influx was associated with higher levels of HIV-1 productive infection.

Conclusion: The Beacon single cell imaging platform is a novel and effective tool for tracking both calcium influx and HIV-1 productive infection in cells.
support a strategy to disrupt Nef dimerization by small molecules as a new path to antiretroviral drug discovery.

189 RESTING HIV-INFECTED CD4 T CELLS EXPRESS NEF AND VPU, WHICH DOWNREGULATE MHC AND BST2

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Background: The HIV reservoir resides in resting memory CD4 T cells. These infected cells are difficult to eradicate because of their lack of virus expression. Current eradication strategies aim to reaivate virus expression in these cells, allowing them to be recognized and killed by immune CD8 T cells specific for HIV peptide/MHC-I complexes (pMHC). In addition, broadly neutralizing antibodies may bind to cell surface Env protein and elicit antibody-mediated killing. However, HIV encodes two proteins, Nef and Vpu, which allow escape from both these eradication strategies through downregulation of pMHC and tetherin (BST2). Importantly, the timing of the expression of Nef and Vpu in HIV-infected resting CD4 T cells remains unclear.

Methods: We aimed to explore this aspect of HIV infection by direct infection of resting CD4 T cells with two CCR5-tropic replication-competent GFP reporter viruses. For one virus GFP reports the expression of the Env transcript, and for the other virus GFP reports the expression of the Env/Vpu transcript. We sorted CD4 T cells that were lacking expression of four activation markers: CD69, CD25, CD154 and HLA-DR. These resting CD4 T cells were infected with either reporter virus and examined daily for the expression of GFP, cell surface HLA-A02, HLA-B07, tetherin, CD45R0, and CCR5 by antibody staining. Env expression was monitored by staining with the broadly neutralizing antibodies PG9 or VRC01.

Results: Our data show that HIV directly infects resting memory CD4 T cells expressing CCR5. GFP expression for either virus starts to appear 3 to 4 days after infection. The GFP-positive cells infected with either virus showed downregulation of CD4, HLA-A02, HLA-B07, tetherin, CD45R0, and CCR5 by antibody staining. Env expression was monitored by staining with the broadly neutralizing antibodies PG9 or VRC01.

Conclusion: We conclude that HIV directly infects resting memory CD4 T cells to establish the reservoir. This direct infection of resting memory CD4 T cells confers a replicative advantage to HIV by expressing Nef to downregulate pMHC and Vpu to downregulate BST2 before activation for virion production. We therefore believe latently HIV-infected cells are cloaked from recognition by the immune system, thus providing a new strategy for persistence.

190 IMPAIRED NEF’S ABILITY TO COUNTERACT SERINC5 BY IMMUNE-DRIVEN MUTATIONS

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Background: The host proteins SERINC3 and 5 (SERINC3/5) are inhibitors of HIV-1 infectivity that are counteracted by Nef. Introduction of mutations to the highly conserved FPD (F120/Q125) motif in Nef resulted in disruption of Nef’s ability to counteract SERINC3 and enhance infectivity. Because this region encompasses HLA-restricted CTL epitopes, we hypothesized certain naturally arising HLA-mismatching polymorphisms in the consensus F120/Q125. In contrast, Nef functions of CD4 and HLA class I downregulation remained unchanged regardless of the Nef genotype of 120Y/125Q or 120Y/125H.

Methods: We aimed to explore this aspect of HIV infection by direct infection of resting CD4 T cells with two CCR5-tropic replication-competent GFP reporter viruses. For one virus GFP reports the expression of the Env transcript, and for the other virus GFP reports the expression of the Env/Vpu transcript. We sorted CD4 T cells that were lacking expression of four activation markers: CD69, CD25, CD154 and HLA-DR. These resting CD4 T cells were infected with either reporter virus and examined daily for the expression of GFP, cell surface HLA-A02, HLA-B07, tetherin, CD45R0, and CCR5 by antibody staining. Env expression was monitored by staining with the broadly neutralizing antibodies PG9 or VRC01.

Results: Our data show that HIV directly infects resting memory CD4 T cells expressing CCR5. GFP expression for either virus starts to appear 3 to 4 days after infection. The GFP-positive cells infected with either virus showed downregulation of CD4, HLA-A02, HLA-B07, tetherin, CD45R0, and CCR5 by antibody staining. Env expression was monitored by staining with the broadly neutralizing antibodies PG9 or VRC01.

Conclusion: We conclude that HIV directly infects resting memory CD4 T cells to establish the reservoir. This direct infection of resting memory CD4 T cells confers a replicative advantage to HIV by expressing Nef to downregulate pMHC and Vpu to downregulate BST2 before activation for virion production. We therefore believe latently HIV-infected cells are cloaked from recognition by the immune system, thus providing a new strategy for persistence.

191 SYNTHESIS AND EVALUATION OF TIGHT-BINDING HYDROXYPYRAZOLE INHIBITORS OF HIV-1 NEF

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Background: The HIV-1 Nef accessory factor is critical to the HIV life cycle in vivo and promotes immune escape of HIV-infected cells in part via downregulation of cell-surface MHC-I. Previously we discovered small molecules that bind directly to Nef and block many of its functions, including enhancement of viral infectivity and replication in T cell lines. These compounds, based on a hydroxyazepinone core, also rescue cell-surface MHC-I expression in patient-derived CD4+ T-cells, enabling recognition and killing by autologous CTLs. Nef inhibitors may provide a new approach to antiretroviral therapy that includes a path to eradication of HIV-infected cells. This study focused on medicinal chemistry optimization of hydroxyazepinone Nef inhibitors to improve potency and metabolic stability.

Methods: Nef inhibitor analogs in this study are based on a previous diphenylpyrazoloazadiazine hit compound with a hydroxyazepinone core linked to chlorophenyl, nitrophenyl, and thiouamide moieties. The thiouamide group was replaced with a variety of heterocyclic moieties, along with multiple substitutions of the other ring systems, for a total of 254 unique compounds. Analogs were screened for tight-binding interaction with recombinant Nef proteins by surface plasmon resonance (SPR), and for antiretroviral activity in TZA-bl reporter cells infected with HIV-1. Active compounds were then evaluated for antiretroviral activity in donor PBMCs and for metabolic stability against liver microsomes in vitro.

Results: Multiple analogs bound tightly to recombinant Nef proteins by SPR, with K_s values in the nM to pM range. Several of these compounds suppressed HIV-1 replication in donor PBMCs with K_s values in the 1-10 nM range without cytotoxicity, and were resistant to metabolism by mouse liver microsomes. Some analogs also reversed MHC-I downregulation in a Nef-transfected T cell line.

Conclusion: HIV-1 Nef inhibitors based on a hydroxyazepinone core are amenable to a wide range of structural modifications and retain inhibitory activity despite addition of bulky heterocyclic substituents. Several analogs displayed tight binding to recombinant Nef in vitro, potent antiretroviral activity in primary cells infected with HIV-1, and the capacity to restore cell-surface MHC-I expression. Future efforts will evaluate pharmacologic properties in vivo with the goal of identifying analogs suitable for testing in humanized mouse models of HIV-1 replication and latency.

192 ACTIVATION OF TEC KINASES BY HIV-1 NEF AT THE CELL MEMBRANE REQUIRES DIMER FORMATION

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Background: The HIV-1 Nef virulence factor supports high-titer viral replication and pathogenicity. Nef interacts with Itk and Btk, two Tec-family kinases expressed in HIV-1 target cells (CD4 T cells and macrophages). Knockdown or pharmacological inhibition of Itk suppresses HIV-1 entry, transcription and egress, suggesting that Nef-mediated Itk activation is required for efficient viral replication in vivo. Here we demonstrate that Nef activates both Itk and Btk at the cell membrane through a mechanism dependent on Nef homodimer formation.

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Results: BicF analysis showed that wild-type HIV-1 Nef interacted with both Itk and Btk at the cell membrane, resulting in enhanced kinase activation loop phosphorylation. Nef dimerization interface mutants retained interaction with both kinases, but failed to induce kinase activation, supporting a role for Nef homodimer formation in the activation mechanism. Addition of small molecule Nef inhibitors reversed Nef-dependent Itk autophosphorylation, suggesting that these compounds may interfere with Nef dimerization and Itk activation through an allosteric mechanism. HIV-1 infection upregulated endogenous Itk activity in Jurkat and SupT1 cells in a Nef-dependent manner, while HIV-1 with Nef dimerization interface mutations replicated poorly in both T cell lines and donor PBMCs.

Conclusion: Our results support a mechanism in which Nef recruits Itk and Btk to the membrane, and drives kinase activation via a dimerization-dependent mechanism. Nef dimerization interface mutants replicate poorly in T cells, and Nef inhibitors interfere with Itk activation, suggesting that suppression of the Nef-Itk pathway may account for part of their antiretroviral mechanism of action. These findings provide a strong rationale to support further antiretroviral drug development targeting Nef homodimerization and the Nef-Itk/Btk signaling pathways.

ACTIVATION OF TEC-FAMILY KINASES ITK AND BTK BY HIV-1 AND SIV NEF PROTEINS IN VITRO

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Background: The Nef proteins encoded by HIV-1 and SIV are critical for efficient viral replication and AIDS progression. In addition to downregulating cell-surface immune and viral receptors, Nef also induces constitutive activation of host-cell tyrosine kinases of the Src and Tec families. Nef-mediated activation of Itk, a Tec family member expressed in CD4 T cells, is essential for several stages of the HIV-1 life cycle. Nef also interacts with Btk, which is expressed in B cells and macrophages. Itk and Btk share a similar domain organization consisting of PH, SH3, SH2, and kinase domains. Here we tested whether interaction of recombinant purified Btk and Itk proteins with Nef was sufficient for kinase activation in vitro.

Methods: Full-length and ‘Src-like’ cores (SH3-SH2-kinase) of Itk and Btk were expressed in SF9 insect cells and purified. A kinetic kinase assay (ADP Quest; Eurofins) was used to measure the rates of autophosphorylation and peptide substrate phosphorylation in the presence and absence of recombinant purified HIV-1 and SIV Nef. Activation loop autophosphorylation was assessed by immunoblotting with phosphospecific antibodies. Surface plasmon resonance (SPR) was used to measure the interaction of Nef with recombinant purified Itk and Btk regulatory domains.

Results: Both HIV-1 and SIV Nef strongly enhanced full-length Btk autophosphorylation and kinase activity in vitro, with autophosphorylation occurring primarily on the activation loop at Tyr511. In contrast, Nef had no effect on the Btk core protein, implying that the PH domain is important for interaction with Nef and kinase activation. Nef induced modest enhancement of full-length Itk autophosphorylation on activation loop Tyr511, but did not affect the Itk core. Interestingly, a mutant of Nef lacking the conserved motif required for SH3 domain binding (PxxP) activated Btk and Itk to the same extent as wild-type Nef. This mutant failed to activate the Src-family kinase Hck, suggesting that Nef activates Tec and Src family kinases by distinct mechanisms. This conclusion is supported by SPR data, which showed that the Itk SH3 domain alone does not bind to Nef.

Conclusion: HIV-1 and SIV Nef proteins activate Btk and to a lesser extent Itk in vitro, through an SH3 domain-independent mechanism distinct from Src-family kinases. Small molecules that interfere with this Nef-dependent kinase signaling pathway may provide a new route to antiretroviral drug development.

LIPID BINDING DOMAIN IMPACT ON HIV-1 NEF AND SRC-FAMILY KINASE HCK U-SH3-SH2 COMPLEX

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Background: The HIV-1 accessory protein Nef supports high-titer viral replication, immune evasion of HIV-infected cells, and is essential for AIDS progression. Efficient replication of HIV-1 in primary human macrophages requires expression of the myeloid Src-family kinase, Hck. Nef provides a crucial link between HIV-1 and this host cell kinase, interacting with Hck through its SH3 domain and driving constitutive kinase activation. Both Nef and Hck are myristoylated at their N-termini, resulting in co-localization to the cytoplasmic face of cellular membranes. Also contributing to membrane localization are the anchor and unique domains of Nef and Hck, respectively, which are positioned N-terminal to the Nef core and Hck SH3 domain. To better understand the role of these N-terminal lipid binding domains on Nef homodimerization and Hck recruitment, we are pursuing the X-ray crystal structure of full-length Nef (FL-Nef; SF2 allele) in complex with the Hck unique-SH3-SH2 (Hck-US2) regulatory domains.

Methods: We developed an E. coli expression system for the expression and purification of soluble Hck-US2 tandem regulatory domains. Stable interaction between purified Hck-US2 and FL-Nef was then determined using analytical size-exclusion chromatography (SEC) and surface plasmon resonance (SPR). The Hck-US2 and FL-Nef expression systems were combined to co-purify the two proteins as a complex (FL-Nef:Hck-US2) by immobilized metal affinity chromatography and SEC. Crystallization trials of this purified complex are in progress using the sitting-drop vapor diffusion method.

Results: Using our expression system, the Hck-US2 protein has been successfully expressed and purified from E. coli in soluble form. Hck-US2 and FL-Nef form stable complexes in solution as demonstrated by both analytical
SEC and SPR. The SPR analysis suggests a high affinity interaction between Hck-US2 and FL-Nef with a kinetic $K_d$ value in the low $\mu$M range. In addition, the recombinant FL-Nef-Hck-US2 complex has been purified to homogeneity and is currently in crystallization trials.

**Conclusion:** The Hck-US2 protein is amenable to expression and purification in soluble form and stably interacts with FL-Nef in solution, enabling structural analysis of the complex by X-ray crystallography. This complex structure is anticipated to yield fresh insight into the role of these N-terminal lipid binding domains in the regulation of protein:protein interactions at biological membranes.

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**196 IP-10 PRODUCTION BY THE LYMPH NODE MEDIATES ENTRY OF SIV-SPECIFIC CCRX3+ CD8+ T CELLS**

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**Background:** Lymph nodes (LN) harbor cells chronically infected by HIV/SIV, especially CD4+ follicular helper lymphocytes which are located within the B cell areas. LN are characterized by low frequency of effector memory CD8 T cells that are, in general, excluded from the follicles. Using a vaccination protocol that combines intramuscular DNA delivery followed by in vivo electroporation, we have analyzed the trafficking of virus-specific CD8+ T lymphocytes.

**Methods:** Eight MamuA01+ rhesus macaques were immunized with plasmid DNA encoding p57gag. Two weeks after the fourth vaccination, the animals were sacrificed, and the dissemination of vaccine-induced T cell responses was monitored throughout the body by immunophenotyping combined with CM9gag tetramer staining, followed by flow cytometry. Chemokine production, including CXCL9, CXCL10 and CXCL11, by lymph node mononuclear cells (LNMC) from the vaccinated animals stimulated ex vivo with SEB and IFNγ was measured by ELISA, multiplex chemiluminescence detection assays (MSD) and intracellular staining.

**Results:** High magnitude (up to 15% of total CD8+ T cells) of vaccine-induced virus-specific CD8+ T cells were found in peripheral blood from all the immunized macaques. These cells were actively dividing (Ki67), expressed high levels of CCRX3 and efficiently migrated into central and peripheral LN. The CM9-specific CD8+ T cells within the LN also expressed CCRX3 and had an effector phenotype (CD95+CD28lowCD45RAlowCD127+CCR6-CCR4+) with no significant CCR7 expression, suggesting that these cells could be located outside the T cell areas. LNMC from these vaccinated macaques stimulated ex vivo with IFNγ or SEB released high levels of IP-10 (CXCL10) and CXCL11. A combination of surface and intracellular staining with anti-CCRX3 and IP-10 antibodies revealed that these chemokines were produced by HLA-DR+ B lymphocytes, CD11c+CD14- dendritic cells and a subset of cells with the phenotype (CD3-CD20-CD14-CD1cHLA-DR-CD21+) of follicular dendritic cells (FDC).

**Conclusion:** Expression of CCRX3 by the vaccine-induced virus-specific CD8+ T cells indicates that these cells can migrate into areas where the chemokines CXCL9, CXCL10 and CXCL11 are produced. Because these chemokines are produced within the LN by cells located in the B cell areas (B lymphocytes and FDC) the data suggest that a CCRX3-dependent and CCRX3-independent pathway of effector cells entry into the follicles exist.

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**197 LYMPH NODE TREG SUBSETS ARE EXPANDED IN SOME HIV+ PEOPLE ON SUPPRESSIVE ART**

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**Background:** Tregs including follicular regulatory T cells (TFR) are expanded and frequency of follicular CD8 (fCD8) T-cells within LN were presented. The more frequent CD141+ mDCs and frequency of follicular CD8 (FC8) T-cells within LN were presented. The more frequent CD141+ mDCs was present in LN, the less pDCs exhibiting an early stage of apoptosis and the less frequency of cDC8 T-cells were present ($r=0.829, p=0.042$ and $r=0.886, p=0.019$, respectively). Furthermore, we found a strong correlation between the percentage of pDCs expressing PDL1 and the levels of follicular CD8+ T-cells PD1+ (r=0.943, p=0.005). Of note, this correlation was not present neither between the levels of pDCs PD1+ and non-follicular CD8+ T-cell levels nor with other myeloid dendritic cells expressing PDL1.

**Conclusion:** We explored a pDCs crosstalk with CD141+ mDCs and FC8+ T-cells, and its relation with FC8+ T-cell exhaustion in LNs of HIV-infected patients. This pathway may be a drug target that may enhance HIV-specific response within LNs, allowing the development of HIV curative strategies.

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**198 DENDRITIC CELLS CORSWALK WITH FOLLICULAR CD8+ T CELLS IN HIV-INFECTED LYMPH NODES**


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**Background:** Plasmacytoid dendritic cells (pDCs) have been related with HIV spontaneous control. However, a deregulation mainly consisting in an aberrant IFN-1 production lead to an inflammatory environment that could enhance HIV pathogenesis. It has been communicated that HIV provokes alteration in phenotype, function of pDCs and its interaction with other cell types in lymphoid tissues in relation with HIV-disease outcomes remain largely unknown.

**Methods:** Seven inguinal LN samples prior to antiretroviral onset were obtained from HIV-infected patients. PBMCs were obtained at the same time point of LN biopsies. A comprehensive analysis of DCs, pDCs and T-cells was performed by deep immunophenotyping using multiparametric flow cytometry.

**Results:** pDCs levels were inversely correlated with viral load (VL) both in PBMCs and LNs ($r=-0.893, p=0.007$ and $r=-0.9, p=0.037$, respectively). Alternatively, VL positively correlated with exhausted pDCs in LN, assessed by PDL-1 expression ($r=0.829, p=0.042$). Indeed, we found a strong positive correlation between the frequency of pDCs in PBMCs and pDCs in LN (r=0.9, p=0.016). Interestingly, associations between pDCs survival and CD141 mDCs and frequency of follicular CD8 (FC8) T-cells within LN were presented. The more frequency of CD141+ mDCs was present in LN, the less pDCs exhibiting an early stage of apoptosis and the less frequency of cDC8 T-cells were present ($r=0.829, p=0.042$ and $r=0.886, p=0.019$, respectively). Furthermore, we found a strong correlation between the percentage of pDCs expressing PDL1 and the levels of follicular CD8+ T-cells PD1+ ($r=0.943, p=0.005$). Of note, this correlation was not present neither between the levels of pDCs PD1+ and non-follicular CD8+ T-cell levels nor with other myeloid dendritic cells expressing PDL1.

**Conclusion:** We explored a pDCs crosstalk with CD141+ mDCs and FC8+ T-cells, and its relation with FC8+ T-cell exhaustion in LNs of HIV-infected patients. This pathway may be a drug target that may enhance HIV-specific response within LNs, allowing the development of HIV curative strategies.
LONGITUDINAL DYNAMICS OF FOLLICULAR CD4+ T CELLS IN ACUTE SIV INFECTION

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Background: Follicular T helper CD4+ (Tfh) cells play a critical role in germinal center (GC) formation and B cell maturation. GCs in lymph nodes (LN), particularly within Tfh cells, are sites for preferential SIV infection and replication. Changes in Tfh phenotype and functions in early acute SIV infection may be a major determinant in the development effective antibody-mediated control of SIV infection.

Methods: Eighteen rhesus macaques were intravenously infected with SIVmac251 and underwent staggered necropsy during acute and chronic infection. Tfh cells from surface LN (sLN), mesenteric LN (mLN) and spleen were immunophenotyped. We further examined mLN to quantify and localize viral RNA (vRNA) using immunohistochemistry, and performed gene expression and pathway enrichment analyses on sorted Tfh cells from LNs in resting and stimulated conditions.

Results: The frequency of Tfh cells decreased at day 10 post-infection (p.i.) and partially rebounded after 20 days in all tissues. Using principal component analyses we found similar phenotypic profiles in Tfh from mLN and sLN; in contrast, Tfh isolated from the spleen clustered separately after 10 days p.i. Although plasma viremia (pVL) peaked day 10 p.i., vRNA in mLN was detectable as early as day 5 p.i. within follicles and the T cell zone. While pVL decreased after 20 days, tissue vRNA was increased until 90 days p.i., but was not preferentially found within the follicles during this early period. Very early following infection, transcriptional profiling of Tfh-related genes showed profound modulation of cytokine production and inflammatory pathways. Moreover, we observed a decrease in Tfh responsiveness to stimulation as early as day 5 p.i. This functional ability was partially recovered after 20 days p.i. irrespective of the increasing vRNA found the tissue. tSNE analyses showed independent clustering pre- and post-infection, and Tfh cells from day 90 p.i. had the most similar profile to pre-infection suggesting a partial recovery in responsiveness in later stages of infection.

Conclusion: SIV infection has a profound effect in Tfh frequencies, phenotypic and genetic profiles across tissues since acute infection. This effect suggests a temporal decrease in Tfh ability to provide B cell help during early stages of infection associated with high levels of viremia in blood and tissues, that may directly impact or delay the early induction of SIV-specific antibody production.

CYTOLYTIC HIV-SPECIFIC CD8+ T CELLS DO NOT RECYCLE THROUGH TISSUES

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Background: Cytolytic effector memory HIV- and SIV-specific CD8+ T cells are key correlates for natural and vaccine-induced viral control. While assumed, it remains unknown if these cells leave the blood to access HIV reservoirs in lymphoid and peripheral tissues. To directly address this question, we present for the first time a spatial map of the tissue egressing (recirculating) immune system by sampling blood, lymph node (LN) and thoracic duct lymph (TDL) in HIV-1 seronegative and seropositive individuals.

Methods: We isolated LNs and matched human blood and TDL mononuclear cells through thoracic duct cannulation of HIV-seronegative and seropositive individuals on and off antiretroviral therapy. Functional and phenotypic assays on total and HIV+ lymphocytes were performed by flow cytometry and transcriptional data was collected through RNAseq using the SMARTseq2 platform. The results were analyzed using RStudio, FlowJo, and Graphpad Prism.

Results: Through transcriptional, functional and phenotypic analysis, we show that expression of cytolytic molecules by effector memory CD8+ T cells are almost entirely confined to blood, while their phenotypic counterparts in the thoracic duct, and many tissues, represent non-cytolytic T cells with a higher regenerative capacity. Unlike their blood counterparts, HIV- and CMV-specific CD8+ T cells in TDL and LNs generally lack cytolytic molecule expression and killing ability. We further demonstrate that those HIV-specific CD8+ T cells detectable in the TDL possess an intermediate differentiation status (CCR7-CD45RA-CD27+), thereby defining the identity of HIV-specific CD8+ T cells capable of accessing HIV reservoirs in peripheral tissues.

Conclusion: Our results demonstrate that not all types of memory CD8+ T cell surveys tissues and reveal that cytolytic molecule expression is mostly confined to effector memory HIV-specific CD8+ T cells in blood during steady-state and chronic HIV disease. These data also suggest that the intermediate differentiation status of peripheral blood HIV-specific CD8+ cells is a marker of tissue recirculation rather than a dysfunctional state as previously assumed.

MICROBIAL TRANSLLOCATION MEASURED BY CONFOCAL ENDOMICROSCOPY IN HIV-INFECTED PATIENTS

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Background: The disruption of the intestinal mucosal in HIV individuals leads to an increase of bacterial translocation, immune activation and non-AIDS events in HIV infected individuals. Confocal endomicroscopy could help to assess the changes in gut mucosa. The objective of the study was to describe morphological and dynamic findings in patients with HIV infection by direct visualization of the intestinal mucosa with confocal endomicroscopy and correlate these findings with bacterial translocation markers.

Methods: Demographic and clinical characteristics, pathological changes of rectal mucosa biopsies, confocal endomicroscopy findings (amount of intramucosal bacteria, amount of fluorescein in the crypt lumen and lamina propria), microbial translocation (LBp, CD14 and EndoCAb) and inflammation (TNF-alpha, IL-6, usPCR, DD) in plasma, T-cell and monocyte subsets in rectal biopsy and peripheral blood were analyzed in 10 HIV individuals. A correlation between microbial translocation and other factors was also performed.

Results: We recruited 9 men and 1 woman with median age of 37 years, 9 homosexual and 1 heterosexual. The median CD4 nadir and current CD4 was 572 and 767 cells/mm3, respectively. Only 1 out of 10 patients showed fibrosis in rectal epithelium. In most of the biopsies analyzed, mild chronic inflammation was observed (8/10 individuals). Regarding confocal endomicroscopy, the amount of intramucosal bacteria was high and fluorescein in lamina propria was increased in most individuals, suggesting an abnormality of the mucosal barrier. Translocation markers and monocyte subsets in mucosa were associated with changes of gut mucosa assessed by confocal endomicroscopy: a) CD14+ and %CD11c+ CD14- cells vs. the amount of fluorescein in lamina propria (Rho=0.73 p=0.015 and Rho=0.81 p=0.0045, respectively); b) Endocab and %CD8+ cells vs intramucosal bacteria (Rho=0.64 p=0.04 and Rho=0.68 p=0.029, respectively). In addition, translocation markers were also correlated with markers of inflammation (EndoCAb vs TNF-alpha (Rho=0.76 p=0.01) and LBP vs TNF-alpha (Rho=0.65 p=0.041) and T-cell subsets in peripheral blood (LBP vs CD4+ (Rho=-0.75 p=0.01), LBP vs CD4+ (HLA-DR+) (Rho=-0.70 p=0.02), and LBP vs CD8+ (HLA-DR+) (Rho=-0.73 p=0.01)).

Conclusion: These data suggest that confocal endomicroscopy could be a good tool to further study gut epithelial damage and microbial translocation in HIV infected patients.

ISOLATION OF TRANSLOCATING BACTERIA IN PROGRESSIVE SIV INFECTION OF RHEUS MACAQUES

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Background: Microbial translocation is a significant contributor to chronic immune activation and inflammation in HIV-infected humans. In SIV-infected rhesus macaques (RM), translocation has been demonstrated to occur across the gastrointestinal barrier; however, translocating bacterial taxa are not representative of the gut microbiota, with Proteobacteria appearing to preferentially translocate. To fully characterize translocating bacterial populations, we isolated translocated bacteria from chronically SIV-infected macaques and identified them subsequent to live culture.

Methods: Liver, mesenteric lymph node, and spleen samples were taken during necropsy from one uninfected and twenty chronically SIV+ infected patients. Tissue samples were homogenized and plated on: a) Brain Heart Infusion, b) TSA-Tween 80, and c)
TSA+5% Sheep’s Blood media under aerobic conditions, and d) Brucella Blood and e) CDC Blood media under anaerobic conditions. Isolates were grown for 1–7 days, colonies were streaked for purity, and identified using MALDI–TOF and 16S rDNA sequencing. Shannon α–diversity was calculated for a) SIV+, b) SIV+ Vancomycin–treated and c) SIV+ or SHIV+ animals (no Vancomycin).

**Results:** Thirty-six species have been identified thus far, 5 Proteobacteria (Enterobacteriaceae), 4 Actinobacteria (50% Actinomycetaeae, 25% Corynebacteriaceae, 25% Coriobacteriaceae), 2 Bacteroidetes (50% Odoribacteriaceae, 50% Prevotellaceae) and 25 Firmicutes (32% Lactobacillaceae, 16% Streptococcaceae, 12% Enterococcaceae, 8% Aerococcaceae, 8% Eubacteriaceae, 8% Leuconostocaceae, 4% Bacillaceae, 4% Planococcaceae, 4% Staphylococcaceae, 4% Veillonellaceae). Surprisingly, although our cohort exhibited comparable microbial translocation, α-diversity between tissue sites was significantly reduced in the Vancomycin group as compared to the infected but untreated group with higher levels of Proteobacteria having translocated in Vancomycin-treated animals (two-way paired t-test, p = 0.0739).

**Conclusion:** While PCR has been relied upon in previous studies to show the presence of translocated bacteria, this study reveals that several translocated bacteria are replication competent and that dysbiosis could influence the types of bacteria which translocate. It remains to be seen whether reduced diversity in Vancomycin-treated animals is due to a further alteration in taxa crossing the epithelial barrier or a change in selection pressure once they’ve translocated.

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**SYNERGY BETWEEN TH1 AND TH22 IMPAIRS TH17 CELLS RECRUITMENT TO THE GUT ON ART**

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**Background:** During HIV-1 infection, a deep depletion of TH17 cells occurs early in the gut mucosa. Th22 cells are also initially depleted but appear to be able to efficiently recover on antiretroviral therapy (ART), while TH17 do not. A pro-inflammatory state also promotes TH17 cells recruitment to the gut on ART. Both TH1 and Th22 cells express CCR6 and could thus be recruited through the CCL20-CCR6 axis. However, we previously reported that CCL20 production by enterocytes is impaired in the duodenum on ART. But Th22 cells can alternatively use the CCL28-CCR10 axis to migrate to the gut. We hypothesized that Th1 and Th22 cells synergistically impair CCL20 production by the enterocytes thus preventing TH17 cells recruitment to the gut.

**Methods:** Duodenal biopsies were obtained from 10 HIV-1-infected subjects on ART and 10 healthy controls. Intestinal T cells were isolated and TH1 (CD3+CD4+CXCR3+CCR6–CCR5–), TH17 (CD3+CD4+CXCR3–CCR6–CCR5–CCR4+), and Th22 (CD3+CD4+CXCR3–CCR6–CCR5–CCR4+CCR10+) cell frequencies were analyzed by flow cytometry (BD Fortessa). A model of primary human intestine epithelial cell culture was used to decipher enterocyte response to cytokines and T cells in co-culture experiments. CCL20 and CCL28 expression was quantified by qRT-PCR (mRNA) and ELISA (protein).

**Results:** The frequency of TH17 cells in the duodenum of treated HIV-1-infected subjects remained lower than in healthy controls (4.3% vs 7.6%, P<0.05). By contrast, Th22 cells were restored to normal values (6.3% vs 5.4%, P=0.53), and TH1 cells were increased (9.0% vs 4.7%, P<0.01) in HIV-1-infected vs healthy subjects on ART. Both Th1 and Th22 cells express CCR6 and could thus be recruited through the CCL20-CCR6 axis. However, we previously reported that CCL20 production by enterocytes is impaired in the duodenum on ART. But Th22 cells can alternatively use the CCL28-CCR10 axis to migrate to the gut. We hypothesized that Th1 and Th22 cells synergistically impair CCL20 production by the enterocytes thus preventing TH17 cells recruitment to the gut.

**Conclusion:** Synonymous Th1 and Th22 impaired TH17 cells recruitment to the gut on ART.

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205 INFLAMMATION WITHIN THE SMALL INTESTINE IS ASSOCIATED WITH IMMUNE RECONSTITUTION

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**Background:** The relationship between immune reconstitution after starting cART in gut, peripheral blood and persistent systemic inflammation is poorly understood. We sought to investigate how gut immune reconstitution impacts residual systemic inflammation.

**Results:** Infection by RetroNectin-captured viruses resulted in threefold higher peak p24 output compared to infection with free viruses. RetroNectin-mediated infection was reduced by α4β7-blocking antibodies Act-1 and 2B4. Importantly, unlike infection by free viruses, infection by RetroNectin-captured viruses was resistant to neutralizing antibodies VR01, PG16, and 2G12. Cell-to-cell virus transmission was threefold higher in the presence of RetroNectin. CS1 fibronectin mRNA levels were twofold higher in fibroblasts co-cultured with HIV-infected vs. uninfected cells.

**Conclusion:** Results from these studies indicate that CS1 fibronectin may have previously unrecognized roles in HIV infection. These include facilitating infection by RetroNectin-captured viruses and α4β7-blocking antibodies on both modes of infection were compared. Cell-to-cell virus transmission between autologous T cells was measured by flow cytometry. The effect of infection on CS1 fibronectin expression was assessed by co-culturing fibroblasts with infected or uninfected lymphocytes, and measuring CS1 fibronectin mRNA by quantitative PCR.
Methods: Patients with chronic HIV (pts) naive to ART prior to start darunavir/ritonavir/tenofovir disoproxil fumarate/entecavir underwent duodenal biopsies (gut) and phlebotomy at baseline (BL) and at 12 mo of ART. 17 age, sex and risk group (MSM) matched HIV- controls (C) underwent identical procedures one time. T-cell subsets by FACS and lamina propria density by immunohistochemistry (IHC) in gut and PBC and a panel of inflammatory biomarkers were measured by ELISA at BL and 12-mo. Values are expressed as median [interquartile range] and non-parametric were used where appropriate.

Results: 18 HIV-positive men with a median baseline CD4+ count of 431 cells/dL (272-559) and HIV load of 40,500 copies/mL (19,750-84,250), were enrolled. HIV load became undetectable and CD4+ increased to 742 cells/µm3 [561,861.12-mo; p=0.001. 17 C were of similar demographics and age. Activated gut CD8+ and central memory (cm) T-cell subsets positively correlated with their peripheral counterparts (SpR=0.721 0.835 respectively; p=0.001). After 48-weeks of treatment only correlation in CD8+ central memory persisted (SpR 0.628 p=0.01). However, no correlations between the total CD4+ CD8+ T-cell between both sites were found suggesting that only activated phenotypes are in equilibrium between compartments. Gut T-cell density (IHC) were lower in pts at baseline 80 CD8+/µm2 (34-190) and 769 CD4+/µm2 (61-967) compared to 268 CD8+/µm2 (164-408; p=0.002 and 475 CD4+/µm2 (389-627); p=0.006 respectively. Although partially recovered, differences with controls persisted after 12-months 268 CD8+/µm2 (164-408; p=0.02 and 475 CD4+/µm2 (389-627); p=0.03. A significant correlation was found at baseline between gut + density and I-FABP (SpR 0.568 p=0.013) and Thromboplastin (SpR 0.668 p=0.002). Moreover, I-FABP levels at entry were negatively correlated with peripheral CD4+ T-cell recovery after ART (SpR -0.577 p=0.012).

Conclusion: Our data suggests the potential trafficking between activation phenotypes from GALT and peripheral T-cell subpopulations, and that these drive gut integrity biomarkers. Inflammation and immune changes within the small intestine compartment are associated with immune recovery at that level.

206 ALTERED GUT IMMUNITY IN IMMUNOLOGICAL NONRESPONDERS PARTLY RESTORED BY PROBiotics

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Background: Immunological non-responders (INR) have increased non-AIDS morbidity. A proposed mechanism for INR’s inferior prognosis is microbial translocation across gut mucosa, which promotes chronic immune activation. In-depth immune function in gut mucosa of INR has not been systematically assessed, nor have the effects of probiotics. Methods: In a cross-sectional study, we included three groups of Caucasian age-matched men: 20 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 20 HIV-negative controls. Mucosal biopsies from the terminal ileum and the sigmoid colon, fecal samples and blood were matched on nadir CD4 count; and 20 HIV-negative controls. Mucosal biopsies (gut) and phlebotomy at baseline (BL) and at 12 mo of ART. 17 age, sex and risk group (MSM) matched HIV- controls (C) underwent identical procedures one time. T-cell subsets by FACS and lamina propria density by immunohistochemistry (IHC) in gut and PBC and a panel of inflammatory biomarkers were measured by ELISA at BL and 12-mo. Values are expressed as median [interquartile range] and non-parametric were used where appropriate.

Results: INR had increased serum levels of iFABP and sCD14 compared with controls (p<0.05). The frequencies of gut mucosal Th17 and Th22 were not significantly different between the three groups. After stratifying INR and IR according to blood CD4/CD8 T cell ratio, INR with low (<0.5) CD4/CD8-ratio had significantly higher frequencies of gut mucosal Th17, Th22 and Th1 cells than IR with high (>1.0) CD4/CD8 T-cell ratio (p<0.01). In INR, probiotics for 8 weeks significantly reduced the frequency of Th22 cells in terminal ileum (p<0.05), with a corresponding increase in mucosa-adherent bacterial diversity (Shannon Diversity Index, p<0.01 and Phylogenetic Diversity, p<0.05), whereas no significant changes were observed for the soluble markers.

Conclusion: INR had increased markers of impaired mucosal barrier function. INR with low blood CD4/CD8 T cell ratio had elevated frequencies of mucosal CD4 subsets, indicating a more pro-inflammatory tissue environment. The alterations were partially reversed by probiotics, providing a rationale for further trials of gut targeted treatment in INR.

207 INCREASED ADENOSINE SIGNALING WITH DIPYRIDAMOLE DECREASES GUT MUCOSAL TREG FREQUENCY

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Background: Adenosine (ADO) production is increased during inflammatory states to limit tissue damage. In a study evaluating the anti-inflammatory effect of dipyridamole (DP) among virally suppressed people with HIV (PWH), we evaluated how DP-induced increase in ADO signaling can affect mucosal T cell populations.

Methods: Virally-suppressed adults on ART were enrolled, randomized 1:1, to receive DP (100mg 4x/day) or placebo, double blinded, for 12 weeks. In a subset of participants, we obtained rectosigmoid biopsies at baseline and 12 weeks, and processed these biopsies into mucosal mononuclear cells (MMC) for flow cytometry studies. We evaluated frequencies of T cells in gut MMC, including frequencies of the regulatory T cell (Treg) and Th17 cell subset to assess changes after 12 weeks of DP vs placebo. Plasma levels of DP, inosine (initial ADO metabolite and surrogate for ADO levels), and urine cAMP (produced when ADO binds to its receptor) were measured by mass spectrometry. Linear regression models on log-transformed outcomes were used for the primary 12-week analysis.

Results: Nine DP and 9 placebo participants with data from both baseline and 12 weeks were included in the analyses. Median peripheral blood baseline CD4+ T cell counts were 718 and 666 cells/mm3 for DP and placebo, respectively (p=0.70). At visits when participants had detectable plasma DP (9/9 in DP and 0/9 in placebo), median plasma inosine and urine cAMP levels were higher compared with each participant’s baseline (p=0.03 and p=0.05, respectively). Compared to placebo, DP participants had a significant decrease in absolute %Treg in gut mucosal CD4+ T cells from baseline to week 12 (5.99 to 2.09% for DP vs 2.91 to 4.76% for placebo; p=0.008). There was also a trend for increased gut mucosal %CD8+ T cells in the DP arm (36.0 to 40.9% in DP vs 40.7 to 35.3% in placebo; p=0.054). No differences were observed in the baseline to week 12 change in gut mucosal %CD4+ T cells, %Th17 and Th17/Treg ratios, or in baseline to week 12 change in peripheral blood CD4+ and CD8+ T cells and Treg.

Conclusion: Oral dipyridamole administered to PWH on ART was associated with a significant decrease in gut mucosal Treg frequencies and a trend for increased frequencies of gut CD8+ T cells. Our results suggest that modulating adenosine signaling among virally-suppressed PWH on ART could regulate gut mucosal immunity. How this regulation affects control of the gut HIV reservoir should be further studied.

208 PD-1HI CD4+ T CELLS ARE ASSOCIATED WITH REDUCED HIV-SPECIFIC RESPONSES

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Background: T cells with high expression of PD-1 (PD-1HI), a marker of T cell exhaustion, persist among people with HIV on antiretroviral therapy (ART). To assess whether PD-1HI expression may reflect exhaustion of T cells targeting HIV, we determined whether the frequency of PD-1HI T cells is associated with reduced HIV-specific T cell responses.

Methods: Peripheral blood mononuclear cells from participants in ACTG A5321 with documented viral suppression on ART for at least 4 years (N=93) were analyzed for percentage of CD4+ and CD8+ T cells with PD-1HI expression as determined by flow cytometry. HIV-specific T cell immunity was determined
by IFNγ ELISPOT in response to Gag, Pol, Env, Nef/Tat/Rev, Vpr/Vif/Vpu peptide pools as well as CMV-pp65 and EBV BZLF-1 peptide pools.

Results: Frequencies of both CD4+ and CD8+ PD-1HI T cell pre-ART significantly correlated with levels of pre-ART HIV-1 RNA (r=0.28, p=0.01 and r=0.24, p=0.03, respectively; Spearman correlation). At 4 years of viral suppression with a median CD4+ T cell count of 681 cells/mm3, participants had the same median (Q1-Q3) frequencies of PD-1HI CD4+ (0.3%; 0.1-0.5) and CD8+ (0.3%; 0.2-0.6) T cells. Both CD4+ and CD8+ PD-1HI T cell frequencies showed negative correlations with HIV-1 viral load and CD4+ T cell count (r=0.18, p=0.005 and r=0.18, p=0.01; Spearman). HIV-1 RNA levels correlated with %CD8+ and -CD4+ PD-1HI T cells (r=0.32, p=0.009 and r=0.27, p=0.03, respectively). At 4 years of viral suppression, the %CD8+ PD-1HI T cells showed a trend for higher viral loads compared to the same HIV peptide pools (Gag, r=-0.22, p=0.06; Env, r=-0.21, p=0.07). By contrast, no significant correlations were observed between PD-1HI T cell frequencies and responses to CMV or EBV peptides.

Conclusion: Peripheral blood frequencies of PD-1HI CD4+ T cells of people with HIV on ART were negatively associated with HIV-specific IFNγ responses, but not with CMV or EBV responses. These findings suggest that the PD-1HI CD4+ T cell subset contains HIV-specific cells that have decreased helper function and should be targeted to reverse immune dysfunction and improve immune control of HIV.

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PROPORTION OF SIV-INFECTED MEMORY T HELPER SUBSETS CORRELATED TO SIZE OF POPULATION

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Background: Naïve CD4 T cells can differentiate into multiple functionally-defined memory CD4 T cell subsets. The types of memory CD4 T cells which exist in tissues of HIV/SIV-infected individuals are perturbed compared to healthy individuals. The mechanisms underlying these functional perturbations remain unclear. Here we assess whether viral infection of functionally-defined memory CD4 T cells might contribute, and how these populations of memory CD4 T cells interact with CD4 T cells harbored more (or less) viral DNA than any other population of memory CD4 T cells, indicating that CD4 can be pharmacologically manipulated in natural hosts.

Methods: AGMs can become aviremic and apparently cured of SIV by down-regulating CD4 to maintain a large population of CD4-CD8aa+ virus-resistant T cells which retain CD4 helper functions. AGMs have been used to study the mechanisms of HIV/SIV coreceptor control in natural hosts. Single clones of CD4-CD8aa+ T cells revealed higher degrees of cytosine methylation at the CD4 gene promoter (p=0.04) and a region well-within the gene body (p=0.0001) when compared to these same genomic regions in CD4+ T cells.

Conclusion: These results suggest AGMs uniquely employ epigenetic mechanisms to durably silence the CD4 gene. Targeting proteins involved in DNA methylation, such as TET3, could provide avenues for modulating SIV/HIV-1 coreceptor expression in hosts that become progressively HIV/SIV infected.

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NATURAL HOSTS OF SIV EMPLOY UNIQUE DNA METHYLATION PROGRAMS TO SILENCE THE CD4 GENE

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Background: African green monkeys (AGMs) downregulate CD4 to maintain a large population of CD4-CD8aa+ virus-resistant T cells which retain CD4 helper functions. AGMs can become aviremic and apparently cured of SIV by down-regulating CD4 to completion. Thus, understanding mechanisms of HIV/SIV coreceptor control in natural hosts has important implications.

Methods: To understand the mechanisms of this process, purified CD4+ T cells from four AGMs, closely-related Patas monkeys, and rhesus macaques were stimulated with SEB for 5 days and RNAseq was performed on divided cells induced to downregulate CD4 (AGM, Patas) and those that divide and maintain CD4 expression (rhesus).

Results: 3,917 differentially-expressed genes (DEGs) were revealed to be common among divided, CD4-downregulated AGM and Patas T cells, yet unique from divided rhesus CD4+ T cells. Genes well-known to be regulated in natural hosts were selectively present in this dataset, including CD4, CD8A, and CIITA (p= 1.27e-27, 2.68e-5, 6.72e-15, respectively). Pathway analysis of DEGs revealed proteins involved in DNA methylation to be enriched in CD4-downregulated AGM and Patas T cells (p=0.013). Gene expression of the Ten-eleven translocation protein 3 (TET3), was downregulated in AGM and Patas T cells induced to downregulate CD4, but not in divided CD4+ rhesus T cells (p=1.35e-11). Unique downregulation of TET3 in CD4-downregulated AGM T cells was confirmed independently by qPCR (p= 0.0006). Methylation of cytosines is associated with gene silencing, and inhibition of the DNA methylation machinery with 5-aza-2 deoxycytidine inhibited CD4 downregulation in AGM CD4+ T cells induced to divide in vitro (p=0.005), indicating CD4 can be pharmacologically manipulated in natural hosts. Single clones of CD4-CD8aa+ T cells revealed higher degrees of cytosine methylation at the CD4 gene promoter (p=0.04) and a region well-within the gene body (p=0.0001) when compared to these same genomic regions in CD4+ T cells.

Conclusion: These results suggest AGMs uniquely employ epigenetic mechanisms to durably silence the CD4 gene. Targeting proteins involved in DNA methylation, such as TET3, could provide avenues for modulating HIV/SIV coreceptor expression in hosts that become progressively HIV/SIV infected.
Conclusion: Our data are the first from PLWH to support that USP18 upregulation facilitates HIV-1 evasion of endogenous antiviral control. USP18 has been reported to inhibit type 1 IFN responses in other viral infections, and could be exploited as a molecular target to control HIV-1.

212 SINGLE HOUSING OF MACAQUES INCREASES THE IMMUNE IMPACT OF SIV INFECTION
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Background: Simian immunodeficiency virus (SIV)-infected macaques are an essential animal model for the study of HIV infection, especially in the quest for an effective cure or vaccine. Macaques are a social species, yet are often singly housed for infectious disease research studies. Singly housed uninfected macaques show signs of stress, including decline in CD4+ T cell count and other changes in their immune response. SIV also causes perturbations to the immune system, as reflected most prominently by the decline in CD4+ T cell counts that is commonly used to monitor disease progression, yet the effect of single housing on the progression of SIV infection has yet to be explored. In the context of SIV and HIV, stress has previously been demonstrated to result in lower CD4+ T cell counts, more T cell activation, higher viral loads and increased mortality. We therefore hypothesized that singly housed SIV-infected macaques would demonstrate a greater impact on the immune system and less control of viral replication compared with singly housed SIV-infected macaques.

Methods: We compared retrospective data on lymphocyte subset counts, T cell activation and viral loads from 35 singly and 41 socially housed SIV-infected pigtailed macaques (Macaca nemestrina) for three pre-infection timepoints and two post-infection timepoints during acute infection using linear mixed effects regression modeling.

Results: Singly housed macaques demonstrated a more profound decline in the number of circulating CD4+ T cells (P = 0.0012), CD8+ T cells (P = 0.0003) and total lymphocytes (P = 0.0001) throughout acute infection compared to socially housed macaques. In the setting of CD4+ T cell decline in socially housed animals, we observed higher levels of plasma HIV-1 RNA (P < 0.0001), the consequent reduction in plasma HIV-1 RNA levels (r=0.69; P<0.05). Conclusion: Single housing of SIV-infected macaques may provide an exogenous cause of immune modulation and introduce increased variability in data, with the potential to confound results, reduce the translational value of the model and interfere with reproducibility.

213 ORAL CYTOKINE EXPRESSION IS LINKED TO ORAL HIV-1 LEVELS IN ACTG A5254
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Background: HIV infection is known to disrupt oral mucosal immunity, but the pathogenesis of this immune dysregulation remains unknown. We determined the levels of 11 soluble immune mediators in oral washings of people with HIV (PWU) with varying levels of plasma viremia and CD4+ T cell counts. We also evaluated whether these immune mediators are associated with levels of HIV in blood and oral washings with the aim of characterizing the mucosal immune response at variable stages of HIV infection.

Methods: Oral washings were obtained from participants of ACTG A5254, a cross-sectional study of PWU to evaluate oral complications of HIV. Participants were divided into 4 strata: A (n=148; 52% on ART), CD4≤200 cells/mm3, plasma HIV-1 RNA (VL)≤1000 copies/ml; B (n=82; 98% on ART), CD4>200, VL≤1,000, C (n=29; 21% on ART), CD4>200, VL>1000; D (n=29; 100% on ART), CD4>200, VL>1000. Levels of soluble markers were tested in oral washings using a multi-bead fluorescent platform, and were compared between strata. Associations between soluble marker levels and HIV in plasma or oral washings as well as CD4+ counts were determined.

Results: Stratum (St) A participants (CD4 ≤200, VL >1000) had higher levels of pro-inflammatory mediators IL-6, IL-17, TNFα, IL-1β, and IFNγ compared to St B and St D which had VL ≤1000 and where 98-100% of participants were on ART (p=0.02 to p<0.0001). Two pro-inflammatory markers, IL-12p70 and IL-6, and the anti-inflammatory marker IL-10 differentiated St A from the other 3 strata (p=0.046 to p<0.001). St B and D had no differences in the levels of soluble markers except for IFNγ (p=0.04). St A had higher levels of plasma HIV correlated with plasma HIV (r=0.76; p<0.0001), Spearman) and with IL-6, IL-1β, TNFα, IFNγ, and IL-10 (all r<0.4, p<0.001). Meanwhile, plasma VL only correlated with TNFα and IFNγ, and IL-10 (all r>0.4; p<0.001). Correlations were seen with IL-2, and only modest (r<0.35) correlations were seen with IL-17. No significant correlations were observed with CD4 count.

Conclusion: Our results suggest that high levels of oral HIV rather than low CD4 counts or plasma HIV are more linked to production of oral immune mediators. Despite severe immunosuppression, participants with AIDS demonstrated elevated levels of cytokines corresponding to both Th1 and Th2 T cell responses. The overlap of HIV and these immune mediators could be an important factor in the oral health of PWH.

214 HIV INFECTION AND SMOKING DIFERENTIALLY REGULATE ALVEOLAR MACROPHAGES
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Background: HIV infection impacts immune cells in the lung leading to pulmonary complications which persist with antiretroviral therapy (ART). Alveolar macrophages (AM) are principle immune cells type in bronchoalveolar compartment and as such play a pivotal role in host defense against pathogenic microorganisms and tissue remodeling. Examination of the effect of HIV on AM is complicated by the high prevalence of smoking in HIV infected subjects from the United States. Smoking increases auto-fluorescence of AMs, inhibiting the reliability and resolution of traditional flow cytometry. Cytometry by Time of Flight (CyTOF) utilizes pure metal conjugated antibodies and detection by mass cytometry which effectively bypasses auto-fluorescence. Here, we utilize CyTOF to comprehensively evaluate the effect of HIV infection and smoking on AM.

Methods: Bronchoalveolar lavage (BAL) cells from 10 untreated HIV-infected non-smokers, 9 untreated HIV-infected smokers, 10 HIV-seronegative non-smokers and 9 HIV-seronegative smokers was subjected to traditional flow cytometry and CyTOF. Our CyTOF panel consisted of 34 unique markers
and phenotypic analysis was performed using traditional methods and three unbiased clustering algorithms.

Results: Compared to those without HIV we found a decrease in CD206 (p = 0.0002), CD71 (p = 0.03) and CD164 (p = 0.002) positive cells, indicating a loss of alternatively activated M2s (M2) caused by HIV infection. The loss of M2 macrophages indicates an increased inflammatory environment. Smoking increased AM expression of CCR2 (p = 0.007) which is a marker of inflammatory macrophages. Together, compared to healthy non-smokers, smoking and HIV increased CXCR4 expression on AM (p = 0.006) demonstrating increased susceptibility to X4 tropic HIV infection.

Conclusion: While the aim of characterizing alveolar macrophages during HIV infection and smoking was our primary goal, this study also demonstrates the sensitivity of mass cytometry, and its ability to detect significant differences between patient groups which would have otherwise been masked by auto-fluorescence. Overall, these findings indicate that HIV and smoking drive alveolar macrophages toward an inflammatory state, leading to an overall more inflammatory environment in the lung.

215 HUMAN INFECTION WITH ZOONOtic SIAMIA FOAMY VIRUSES: ALTERED CD4 AND CD8 T LYMPHOCYTES

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Background: A spillover of simian foamy virus (SFV) to humans, following bites from infected nonhuman primates (NHPs), is ongoing in exposed populations. These retroviruses establish persistent infections of unknown physiological consequences to the human host. Replication-competent virus can be isolated from human blood cells, and SFV DNA has been detected in blood lymphocytes. Human infection with zoonotic SFV is thus a natural model to study the key steps of the emergence of retroviruses. Here, we aimed to assess whether SFV infection is associated with changes in the phenotype of peripheral blood mononuclear cells (PBMCs).

Methods: We performed a case-control study to compare 15 Camerounian hunters infected with gorilla SFV and 15 controls matched for age and ethnicity. All participants were men and had been injured by a NHP. Ages ranged from 22 to 75 years. SFV infection was defined by positive results for both western blots and polymerase chain reaction assays. The duration of SFV infection ranged from 1 to 45 years. CD4 and CD8 T lymphocytes, B and NK lymphocytes, and their major subsets were quantified by flow cytometry. Wilcoxon signed-rank tests were used to compare cases and controls.

Results: The cases had significantly higher percentages of CD8 T lymphocytes and lower CD4/CD8 ratios than controls (median: 17.6% vs. 13.7%, P = 0.03 and 3.1 vs. 3.5, P = 0.04, respectively). The percentage of CD4 T lymphocytes were similar for cases and controls (47.7% vs. 46.9%, P = 0.73). Programmed cell death 1 (PD-1) expression on memory CD4 T lymphocytes was higher for cases than controls (31.7% vs. 24.7%, P = 0.001). B and NK lymphocytes showed no differences between cases and controls (8.7% vs. 9.9%, P = 0.70 and 7.5% vs. 6.0%, P = 0.78, respectively).

Conclusion: This case-control study of apparently healthy SFV-infected Camerounian hunters showed phenotypic differences among blood T lymphocytes. Lymphocyte subsets affected in chronic untreated HIV infection were also affected in chronic SFV infection, albeit to a lower extent. The decreased CD4/CD8 ratio and increased expression of the exhaustion marker PD-1 are consistent with a T-cell response against viral infection. Although SFV has been reported to be nonpathogenic, our findings of T-lymphocyte activation and PD-1 are consistent with a T-cell response against viral infection. Although SFV is nonpathogenic, our findings of T-lymphocyte activation and PD-1 expression on CD4 T cells suggest that SFV infection may have implications for infected individuals.

216 CHARACTERIZATION OF PLASMA METABOLITE PROFILE IN HIV+ PERSONS WITH OR WITHOUT IRIS

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Background: Immune reconstitution inflammatory syndrome (IRIS) is an aberrant inflammatory response against an underlying infection after initiation of antiretroviral therapy (ART) in HIV+ persons and is associated with significant morbidity and mortality. Inflammation and T cell activation are dependent on cell metabolism and specific metabolic pathways could regulate T cell activation. We hypothesized that differences in metabolic profile could be used as biomarkers to further elucidate pathogenesis of IRIS.

Methods: Non-targeted global metabolomic profiling was performed on plasma samples derived from a prospective longitudinal study of 30 HIV patients (17 HIV non-IRIS and 13 HIV IRIS) pre-ART (CD4 ≤ 100 cells/mm3), 1-month post-ART, and 12-month post-ART timepoints by Metabolon, Inc. Metabolites were identified by liquid chromatography/mass spectrometry followed by comparison to a reference library. Plasma cytokines were measured using Meso Scale multiplex cytokine detection kit then correlated with metabolic pathways via Spearman correlation.

Results: A total of 832 metabolites were identified in plasma samples. Comparing HIV IRIS and HIV non-IRIS groups, more differentially expressed metabolites reaching statistically significance (p≤0.05) were identified at pre-ART and 1-month post-ART time points than the 12-month post-ART time point. Lipid and amino acid metabolites composed the majority of the compounds that achieved statistical significance. The IRIS group had significantly higher levels of select acylcarnitines, and lower levels of plasmalogen and phosphatidylcholine at pre-ART. Amino acids including tyrosine, glutamate, glycine, and tyrosine metabolism were found to be differentially expressed in IRIS and non-IRIS groups at pre-ART and 1-month post-ART. Spearman correlations revealed that glutamate metabolism was positively correlated with TNF, while tyrosine and glycine metabolism was negatively correlated with IL-10, and D-dimer respectively in the IRIS group at post-ART.

Conclusion: HIV+ persons who develop IRIS have a distinct metabolic profile with perturbed lipid and amino acid metabolism that is associated with known inflammatory mediators of IRIS. These data suggest that evaluation of immunometabolism and its role in inflammation associated with IRIS warrants further investigation.

217 EXTRACELLULAR VESICLE–ASSOCIATED CYTOKINES IN HIV-INFECTED HUMAN EX VIVO TONSILS

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Background: Cytokines play an important role in HIV infection. Some of these cytokines are associated with extracellular vesicles (EVs) either on their surface or being encapsulated. Here, we investigated the modulation of EV-associated cytokines during HIV infection and antiretroviral therapy (ART) in human ex vivo tonsils.

Methods: Ex vivo tonsils were infected with HIV-1 strains, X4-LAI04 or R5-SF162. HIV was either allowed to replicate for 15 days, or tissues were treated with ART (3TC and AZT) at day 2 post-infection. 33 cytokines in soluble or EV-associated forms were evaluated with multiplexed bead-based assays.

Results: Early in HIV infection there was a significant increase in soluble IFNα, MIP-1α, MIP-1β, RANTES, and TNFα. EV-associated cytokines that significantly increased were IL-13, IP-10, and MIP-1α for X4, and MIP-1α, MIP-1β, and RANTES for R5. In addition to increased concentrations, some cytokines also shifted their distribution: MIP-1α and MIP-1β to a higher percentage in EV-associated form, and RANTES to more soluble. In cumulative analyses, in X4-infected tissues there was an increase in the release of soluble IL-2, IL-21, IFNα, MIP-1α, MIP-1β, RANTES, and TNFα, and decrease of TGF-β. R5 infection increased total EV-associated IL-2, IL-7, IFNα, M-CSF, MIP-1α, MIP-1β, RANTES, R5 infection led to increased EV-associated IL-2 and RANTES. ART treatment halted HIV-1 replication, but most cytokine levels remained similar to those in HIV-infected controls, including MIP-1α, MIP-1β, and RANTES. In X4-infected tonsils treated with ART there was a significant decrease in only soluble IL-7, IP-10, and MIG, and an increase in IL-6; in R5-infected tissues treated with ART there was a decrease in soluble IL-1α, IL-1β, IL-6, IL-17, IL-18, MIG, and MIP-3α. ART treatment restored the levels of some soluble cytokines but did not restore EV-associated cytokines.

Conclusion: Cytokine levels increased during HIV infection in both soluble and EV associated forms. Cytokines most upregulated by HIV did not decrease even after 13 days of ART. The most affected EV-associated cytokines were chemokines, which were not restored by ART. ART-treated ex vivo infected human tissues provide a new model to study tissue activation after HIV.
replication is suppressed. These studies will assist in deciphering mechanisms of pathologies that develop in ART-treated patients.

218 MASSIVE RELEASE OF PLATELET-DERIVED EXTRACELLULAR VESICLES DURING HIV INFECTION

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Background: Extracellular Vesicles (EVs) derived from different cell types by exocytosis (microvesicles) or endocytosis (exosomes) may serve as intercellular messengers in pathogenic processes. Circulating mitochondrial DNAs (mtDNA) are potent danger-associated molecular patterns (DAMPs) found in inflammatory diseases including viral infections. We evaluate the EVs profile and plasma mtDNA levels in a well-characterized cohort of HIV-infected patients and controls.

Methods: Plasma samples from HIV-infected patients from the HIV Biobank-Spanish HIV/AIDS Network and 2 hospitals in Galicia were selected. Five groups were defined: 1) treatment-ART; 2) receiving ART with non-detectable viremia (ND) > 1 year; 3) elite controllers (EC) (<50 copies/mL without ART > 1 year); 4) viemic controllers-VC (HIV-RNA >50 and < 2000 copies/mL without ART for more than 1 year); and 5) a control group of HIV negatives. EVs (<1μm, CD9+) were quantified and characterized by flow cytometry using monoclonal antibodies targeting their source CD61/CD41 for platelets; CD16/CD11b for neutrophils. MitoTrackerDeepRed identified EVs containing mitochondria. mtDNA was quantified using a quantitative real-time PCR assay.

Results: 120 HIV-infected patients (30 naïve, 30 ND, 30 EC, and 30 VC) and 30 controls were included. The table shows the main characteristics of the study population and results. EVs numbers were expanded at least 10 fold in all HIV-infected groups compared to controls’ counts. Most EV had platelet markers (>79%) within the HIV groups, and few had neutrophil markers (<2%). A minority of platelet-derived EVs contained mitochondria, but most neutrophil-derived EVs did. Mitochondria+ EV were less frequent than those on ART in other HIV+ groups. A positive correlation was found between the number of platelet-derived mitochondria+ EVs and total plasma mtDNA levels (rho=0.727; p<0.001) but not for neutrophil-derived mitochondria+ EVs. Mitochondrial density (MFI) was greater in controls’ EVs than in HIV-infected groups, lowest levels for those on ART.

Conclusion: A massive release of platelet-derived EVs occurs during HIV infection regardless of HIV status. EVs count correlates with plasma mtDNA levels. HIV infection and ART both appear to diminish mitochondrial density in EVs yet as EVs numbers are expanded, total mitochondrial levels in plasma are preserved in HIV infection or increased. The mechanisms underlying these perturbations in EVs levels and the mitochondria within them in HIV infection are not known.

219 IN VIVO MODEL FOR HBV/HIV COINFECTION STUDIES

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Background: The interplay between innate immune responses of hepatocytes to HBV in the setting of ongoing HIV-1 replication require in vivo model system, and the underlying mechanisms by which HBV-induced liver pathogenesis, and mechanisms by which HIV co-infection accelerate that process remain unknown due in large part to the lack of small animal models. Such model is crucial for the development of novel therapies, treating HBV/HIV-coinfections and associated liver diseases. There are several unresolved problems in mice co-transplanted with human hepatocytes and immune cells: transplantation of mismatched by HLA genotypes hepatocytes and hematopoietic stem cells contain a risk for allograft rejection and the low functionality of adaptive immune responses. We hypothesize that human hepatocyte transplanted mice, infected with HBV and co-transplanted with human HIV-1 infected or uninfected macrophages will reproduce the features of viral interaction.

Methods: TK-NOG mice were transplanted with human hepatocytes, and after confirmation of the human albumin concentration in peripheral blood, animals were infected with HBV 107 GE/mouse (subtype D ayw). Following confirmation of HBV DNA presence in peripheral blood (~1.5x104 copies/ml), animals were infected with human monocyte-derived macrophages (MDM) or HIV-exposed MDM (5x106 cells/mouse i.p.) and controls kept without MDM. Animals were observed for 51 days and levels of HIV RNA, HBV DNA, HBsAg in plasma were monitored. At end-point liver tissues were analyzed for histopathology, presence of viruses and human MDM by RT-PCR, and staining for human cells and viral proteins.

Results: Multiphasic HBV viral kinetics — increase HBV DNA by day 13 and decline by day 51 in the presence of MDM, and exponential increase in HIV viral load were observed in the blood reaching steady levels at ~10 copies/ml by day 38. The plasma levels of HBsAg concentration also peaked at this point. Mice with HBV+HIV-MDM had higher content of HBV DNA, HIVgag RNA and human CD45 transcripts. Human hepatocytes in HIV infected mice showed strong expression of human HLA-DR, and proliferation. The plasma albumin concentration increased two folds in coinfected animals.

Conclusion: This study utilizes a novel humanized mouse model which will fill the critical knowledge gaps on the mechanism by which HIV/HBV co-infection accelerates liver diseases and is the first model to observe changes in both viral replication pattern and tissue histopathology.

220 AN EARLY DECLINE IN HIV ANTIBODY BREATHTH PREDICTS MORE RAPID DISEASE PROGRESSION

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Background: The HIV immune response evolves during infection and may be impacted by factors such as antiretroviral treatment (ART). We used a massively-multiplexed system to profile the antibody (Ab) response to HIV infection in individuals with early to late stage infection and to evaluate the relationship between Ab diversity and ART initiation.

Methods: Ab profiles were analyzed with the VirScan assay. This assay uses phage immunoprecipitation sequencing to quantify Ab binding to >3,300 HIV peptides spanning the HIV genome. The analysis included 403 samples from 57 African women with known duration of HIV infection (14 days to 8.7 years). ART was started at a CD4 count <250 cells/mm³; 32/57 women started ART during the study period (ART group). For each sample, network graphs were used to calculate the number of unique non-overlapping epitopes that had high levels of Ab binding (Ab breadth). We measured the change in Ab breadth 9–24 months after infection and compared time to ART initiation among those with declining vs. stable or increasing Ab breadth. We also analyzed the associations between the rate of change in Ab breadth over time, ART initiation, and other factors.

Results: In most persons, Ab breadth increased during the first 6 months of infection. In the non-ART group, Ab breadth reached a plateau (“Ab breadth set point”) 9–12 months after infection. In the ART group, analysis using a Cox proportional hazards model showed that those who had stable or increasing Ab breadth 9–24 months after infection started ART later than those with decreasing Ab breadth (log-rank test for earlier ART initiation: p=0.009, hazards ratio: 0.29, 95% CI: 0.11, 0.78, p=0.014). A faster decline in Ab breadth was correlated with lower baseline CD4 cell count (p=0.002) and higher pre-ART viral load set point (p=0.001). Ab breadth stabilized after ART initiation at levels similar to those seen in early HIV infection.

Conclusion: Deep profiling of the antibody response to HIV infection identified a novel feature of the anti-HIV immune response, Ab breadth, that was associated with clinically-significant outcomes.

221 HIV INFECTION ALTERS DYNAMIC MACROPHAGE-T CELL INTERACTIONS TO PROMOTE VIRAL SPREAD

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Background: Recent studies suggest that tissue macrophages and microglia represent an important, long-lived HIV reservoir in vivo. While T cells are the main target of HIV infection, antigen-presenting cells such as macrophages contribute to the activation/maintenance of these cells. HIV is known to be transmitted via cell-cell contact, but the cellular and molecular dynamics of HIV spread using 3D systems recapitulating the lymphoid structures remains unclear.

Methods: We developed a model to dynamically characterize macrophage-T cell contacts within 3D collagen matrices. HIV-infected monocyte-derived macrophages (MDM) were cocultured with autologous CD4+ T cells and changes in migration behaviors and cell-cell contact dynamics were visualized using live-cell microscopy. In parallel, viral spread kinetics was measured in collagen gels. The role of virus- and host-derived adhesive molecules in facilitating stable MDM-T cell contacts were assessed using blocking antibodies. The efficacy of various antiretroviral drugs was also explored during dynamic cell-cell transmission.

Results: We observed substantial changes in MDM morphology following HIV infection: the formation of long, irregular podosomal extensions were a direct result of Nef expression. While Nef-induced podosomes did not enhance T cell contacts, HIV infection of MDM led to a dramatic increase in stable conjugates. We show that such stable contacts are a pre-requisite for enhanced HIV dissemination. Antiretroviral drugs at concentrations that completely suppresses infection by cell-free HIV, only reduced infection to 43±19% (raltegravir), while tenofovir and emtricitabine reduced infection to 36±5% and 71±6%, respectively. We further show that gp120:CD4 interactions are key regulators of MDM-T cell contacts, which is further supported by LFA-1:ICAM-1 adhesive contacts. Blockade of LFA-1 led to destabilization of MDM:T cell contacts and translated into a substantial reduction (~70%) in infection. Interestingly, blocking LFA-1:ICAM-1 contacts caused long tethering events, which we interpret as a result of incomplete restraint of motile T cells.

Conclusion: This study highlights the importance of MDMs as a key contributor of persistent T cell infection through their ability to facilitate numerous cell-cell contacts in lymphoid tissues. Our 3D imaging approach allows for T cells to randomly migrate and engage HIV-infected macrophages, modeling their initial encounters and mimicking the main concepts of the same in-situ environment.

222 THE ROLE OF MIGRATORY DENDRITIC CELLS IN ESTABLISHING HIV DISSEMINATION

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Background: HIV-1 dissemination from the genital mucosal tract to the lymphoid organs is the first critical step towards systemic infection. HIV-1 can disseminate either as free-virus, or it can be transported to lymphoid tissues by migratory cells. Our previous studies strongly argued that the trafficking of cell-associated HIV-1 from the genital mucosa to lymphoid organs played a dominant role in viral spread early after sexual transmission in humanized mice. Here, we further extend these observations by addressing the role of migratory DCs in the capture, retention and transfer of HIV-1 to susceptible T cells through trans-infection, a route of viral transmission that occurs through cell-cell contact.

Methods: To characterize the molecular and cellular aspects of DC-T trans-infection, we modeled the dynamics of DC:HIV and DC:T cell interactions within a 3D collagen matrix that recapitulates the stromal networks of the lymph node. Two-photon microscopy was performed to visualize (1) the cellular dynamic of HIV capture and retention by DCs, and (2) the interaction between HIV-bearing DCs and T cells. We used blocking antibodies to dissect the molecular underpinnings of HIV capture by DCs, and the role of adhesion molecules ICAM-1 and LFA-1 in stabilizing DC:T cell contacts during trans-infection. To determine the role chemotactractant receptor-mediated DCs such as S1PR1 and CCR7 play in spreading HIV, we employed transwell chemotaxis assays and live-cell imaging studies of in situ DC migration within explanted mouse ears slices.

Results: Mature DCs captured HIV-1 on the cell surface, mediated by S1PR1, and that captured virus rapidly formed dense clusters near the uropodia of migrating DCs. The chemotactic responses of HIV-1 bearing DCs towards lymph node homing chemokines CCL19/21 and S1P were preserved. HIV-bearing DCs engaged in progressively stable contacts with T cells in 3D collagen, which was a pre-requisite for rapid HIV transmission at the contact site. Consistent with this, HIV-bearing DCs transmitted virus was five-fold more efficient at infected T cells compared to cell-free virus, and that LFA-1:ICAM-1 adhesive contacts played a critical role in this process.

Conclusion: DCs retain their ability to migrate into lymph node follicles following virus capture, and are able to engage T cells and form stable DC:T cell interactions. This suggests that blocking the movement of HIV+DCs out of the genital mucosa may be a novel approach to restrain virus dissemination and limit systemic viremia.

223 CHARACTERIZATION OF SHIV IMMUNOPATHOGENESIS IN RHESUS MACAQUES

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Background: Simian-human immunodeficiency viruses (SHIVs) have been utilized to test vaccine efficacy and characterize mechanisms of transmission and pathogenesis. However, the SHIV model has a significant limitation in that the majority of strains have been created using HIV-1 Env sequences from laboratory-adapted or multiply passaged viruses. Recently, a newly developed SHIV that incorporates the vpu-env(gp140) sequence from a transmitted-founder HIV-1 subtype C strain (CH505) was shown to retain attributes of primary HIV-1 strains. Here, we characterize the immunopathogenesis of this novel SHIV in peripheral and mucosal tissue of male rhesus macaques.

Methods: Male rhesus macaques (n=7) underwent multiple low-dose intrarectal challenges with SHIV C.H505.S75H.A.C.T. Viral challenge was halted when animals tested PCR positive for viral sequences in plasma. Blood, colon and rectum biopsies were collected pre- and post-infection and used to monitor plasma viral load and intestinal immune populations.

Results: All animals became productively infected within 6 challenges and exhibited similar acute viral replication kinetics, including a median peak viral...
load of $1 \times 10^8$ RNA copies/ml plasma (range=0.89x10$^{-10}$ – 5.5x10$^{-10}$) reached by two weeks post-infection. Set point viral loads ranged from 3.8x10$^{-10}$ – 0.99x10$^{-10}$ RNA copies/ml plasma. At week 2-post-infection, CCR5 + CD4 + T cells were significantly decreased in both the colon (p=0.01) and the rectum (p=0.01) compared to pre-SHIV infection. The frequency of CCR5 + CD4 + T cells remained consistently lower than pre-SHIV infection levels through week 8- and week 16-post-infection. In addition, by week 16-post-infection, there was a significant depletion of CCR6 + CD4 + T cells in both the colon (p=0.05) and rectum (p=0.01) compared to pre-SHIV infection.

Conclusion: In line with previous findings, we demonstrate that SHIV.C.C57BL/6.CD4+CD8- mice infected with SIV/HIV, including decreases in the intestinal frequency of a major cellular target population, CCR5+ CD4+ T cells. These findings affirm the value of this novel SHIV as a tool to evaluate SIV/HIV vaccine efficacy and viral pathogenesis.

224 PLASMA CXCL13 AS A MARKER OF HIV DISEASE PROGRESSION AND SYSTEMIC IMMUNE ACTIVATION
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Background: CXCL13 is preferentially secreted by Follicular Helper T cells (TFH) to attract B cells to germinal centers. Plasma levels of CXCL13 have been reported to be elevated during chronic HIV-infection, however there is limited data on CXCL13 levels during early phases of infection. Moreover, the contribution of CXCL13 to disease progression and systemic immune activation have been poorly defined. Herein, we assessed the relationship between plasma CXCL13 and validated markers of disease progression.

Methods: Study samples were collected in 146 people living with HIV (PLWH) who were in early (EHI) and chronic (CHI) HIV infection and 35 elite controllers (EC) compared to 28 uninfected controls (UC). A subset of 25 progressed were followed prospectively for 2 years, 11 of whom initiated ART. Plasma levels of CXCL13 were compared with CD4 T cell count, CD4/CD8 ratio, plasma viral load (VL), markers of microbial translocation (LPS, sCD14, and LBP), markers of B cell activation (total IgG, IgM, IgA, and IgG1-4), inflammatory cytokines (TNF-α, IL-6, and IL-1β), and immune activation markers (frequency of CD8+CD38+HLA-DR+ T cells, and PD-1 expression on CD4+ T cells).

Results: Plasma levels of CXCL13 were elevated in EHI (127.9±64.9 pg/mL) and CHI (229.4±28.5 pg/mL) compared to EC (71.3±20.1 pg/mL) and UC (33.4±9.4 pg/mL). Longitudinal analysis demonstrated that CXCL13 was significantly elevated after 24 months without ART (260.5±30.4 pg/mL, p<0.001) and was reduced without normalization 24 months after ART initiation (81.5±30.3 pg/mL, p=0.002). CXCL13 correlated positively with VL (r=0.390, p<0.001), negatively with CD4 T cell count (r=-0.298, p<0.001), CD4/CD8 ratio (r=-0.359, p<0.001), positively with markers of microbial translocation LPS (r=0.225, p=0.007) and sCD14 (r=0.260, p=0.03), markers of B cell activation total IgG (r=0.422, p=0.003), IgG1 (r=0.276, p=0.05), TNF-α (r=0.280, p<0.001), frequency of CD38+HLA-DR+ CD8 T cells (r=0.543, p=0.008) but not CD38+HLA-DR+ CD4 T cells (r=0.287, p=0.366), and PD-1 expression on CD4 T cells (r=-0.460, p=0.03).

Conclusion: Plasma CXCL13 levels increased during HIV disease progression. Early initiation of ART may reduce plasma CXCL13 and B cell activation without normalization. CXCL13 represents a novel marker of HIV disease progression and inflammation at the early and chronic phases of the infection, and may be a predictor of non-AIDS events.

225 MODULATION AND PATHOGENESIS OF HIV-1 X4 EVOLUTION IN DISEASE PROGRESSION
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Background: Emergence of CXCR4-using HIV-1 (X4) expands host cell range and is associated with advanced stage disease in the absence of therapy. Yet, the developmental program modulating X4 evolution remains elusive. This study tracked X4 evolution genetically during the natural history of pediatric HIV-1 infection to develop sequence profiles associated with functional characteristics of entry and tropism.

Methods: Archived longitudinal blood samples were collected over 2-10 years from 8 untreated perinatally HIV-infected children. Disease progression was monitored by CD4 T-cell inflection point and CD4 T-cell decline to <15%. A total of 831 HIV-1 Env single genome sequences were generated. Env evolution was inferred by time-calibrated phylogenetic trees. CCR5 and CXCR4 coreceptor use was predicted by position specific scoring matrix and verified functionally using coreceptor indicator cells. Single-cycle viruses pseudotyped with Env V1-V5 were constructed to test tropism and entry efficiency into blood lymphocytes and monocyte-derived macrophages (MDM).

Results: Infection was initiated by R5 variants in 7 cases or by X4 viruses in 1 case. R5 viruses persisted over years in 2 cases, while R5X4- and X4-predicted genotypes evolved from low frequency R5 viruses in 5 individuals prior to CD4 decline. Alignment of R5 and R5X4 Env sequences identified discontinuous nonsynonymous changes that altered neutralizing antibody epitopes initially in V1/V2 and subsequently in V3. Single-cycle viruses generated using R5 and R5X4 Env displayed entry into CD4 T-cells, but only R5X4 viruses infected MDM. In contrast to R5, R5X4 Env were more sensitive to sCD4 (CD4 antagonist) or 447-S2D (V3 antibody), indicating increased access to CD4 binding site and the V3 loop, but less sensitive to Maraviroc (anti-CCR5) or T20 (fusion inhibitor), consistent with increased CCR5-use and fusion efficiency.

Conclusion: X4 evolution follows a complex developmental pathway that includes R5 ancestral strains and R5X4 intermediates, expands HIV-1 cell tropism, enhances viral entry via increased access to the CD4 binding site and the V3 loop and increase in fusion efficiency. Evolution of coreceptor preference accompanied by changes in neutralizing epitopes may reflect escape from immune response.

226 HIV+ TO HIV− KIDNEY TRANSPLANT: TRACKING DONOR VIRUS IN RECIPIENT URINE AND BLOOD
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Background: HIV-positive individuals have increased risk of end-stage kidney disease due to the HIV-1 infection and associated treatments, yet now live longer. The HOPE Act allows individuals living with well-controlled HIV-1 to be eligible for organ transplant from HIV-1 positive donors that would have been otherwise discarded. One concern associated with HIV+ to HIV− transplantation is the risk of superinfection and/or viral recombination resulting from the transmission of a genetically distinct HIV-1 strain from the donor to the recipient. In this study we used analysis of viral sequences derived from donor and recipient specimens to determine the source of virus in urine and blood specimens in the transplant recipient.

Methods: Blood and urine specimens were obtained from both donor and recipient before transplantation and at different time points post-transplantation from the recipient. A renal biopsy from the donor kidney was obtained at time of procurement. We performed single genome amplification (SGA) of the full-length HIV-1 env gene with viral RNA extracted from urine, plasma and donor kidney biopsy as well as from viral DNA extracted from PBMC and urine derived renal cells. Neighbor-joining trees were constructed using the Kimura 2-parameter model.

Results: Multiple HIV-1 env sequences were obtained from the samples collected from both donor and recipient. We found that all the env sequences from the recipient’s urine collected at 12 hours post-transplant were genetically similar to those in the donor while subsequent urine-derived sequences were genetically similar to the recipient virus. Furthermore, the majority of the urine derived sequences formed a separate cluster from donor-derived blood sequences, suggesting that the majority of urine-derived viruses were produced by infected cells within the donor kidney. Although the donor viruses could be readily amplified from the recipient’s urine soon after transplantation, it became undetectable in the urine and plasma on the subsequent follow-up visits while the recipient was continuously maintained on ART.
Conclusion: Our study demonstrates that following HIV+ to HIV+ kidney transplantation viruses from the donor’s kidney are found in the urine of the recipient immediately following transplantation, suggesting that donor’s kidney as the source of these viruses. Our results warrant long term monitoring of viral populations in the recipient to fully assess any clinical and virologic implications of this finding.

227 GUT MICROBES DRIVE EXPANSION AND PREFERENTIAL HIV INFECTION OF GUT CD4 CTL EX VIVO
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Background: HIV infection is associated with disruption of gut homeostasis and changes in gut microbiome (dysbiosis). During early infection, HIV replicates to high levels in gut CD4 T cells concurrent with epithelial barrier breakdown and onset of microbial translocation. In transcriptome profiling studies using primary human lamina propria mononuclear cells (LPMC), we identified Granzyme G2 (GZB) and G2A induction in microbe and microbes/HIV stimulated gut CD4 T cells ex vivo (PMID 28241075). Here, we profiled microbe-induced human gut GZB-expressing CD4 T cells (termed CD4 CTLs) to determine the specificity of this response, potential mechanisms driving expansion and relative levels of HIV infection.

Methods: Jejunum LPMC (n=13 donors), peripheral blood mononuclear cells (n=5) or tonsil cells (n=5) were cultured with or without gut commensal Escherichia coli lystate as well as enteric pathogenic, probiotic or dysbiotic bacteria altered in people living with HIV (PLWH). LPMCs were pre-treated with HLA blocking/controls antibodies prior to addition of bacteria (n=7). LPMCs were infected with Transmitted/Founder HIV-1 strain CH40 (n=3). Cytolytic markers (GZB, perforin, CD107a), infection (intracellular p24) and proliferation (CFSE) were measured by flow cytometry. Paired t tests were used for analysis.

Results: Percentages of gut CD4 T cells expressing GZB were low at baseline (mean, SEM 1.4±0.5%), but exposure to multiple enteric bacteria increased % of GZB+ CD4 CTLs (Table 1), with greatest increases with E. coli (733-fold) and S. typhimurium (376-fold). E. coli induced a 4-fold increase in % of blood GZB+ CD4 CTLs (p=0.008), but did not induce GZB expression in tonsil CD4 T cells. HLA-DR blockade decreased the % of E. coli-driven GZB+ CD4 CTLs by 25±7.7% (p=0.008). GZB+ CD4 CTLs that expanded with HIV + E. coli exposure expressed GZB+ p24+. Of those, 25±7.7% had degranulated (CD107a+).

Conclusion: Diverse enteric bacteria induced GZB+ gut CD4 T cells that are preferentially infected by HIV-1 ex vivo. Microbe-driven GZB induction was prominent in the gut, but not blood and lymphoid tissue CD4 T cells and was partially MHC Class II dependent. Gut cytotoxic CD4 T cells may have evolved to preferentially infected by HIV-1 ex vivo. Microbe-driven GZB induction was prominent in the gut, but not blood and lymphoid tissue CD4 T cells and was partially MHC Class II dependent. Gut cytotoxic CD4 T cells may have evolved to preferentially infected by HIV-1 ex vivo. Microbe-driven GZB induction was prominent in the gut, but not blood and lymphoid tissue CD4 T cells and was partially MHC Class II dependent. Gut cytotoxic CD4 T cells may have evolved to preferentially infected by HIV-1 ex vivo. Microbe-driven GZB induction was prominent in the gut, but not blood and lymphoid tissue CD4 T cells and was partially MHC Class II dependent. Gut cytotoxic CD4 T cells may have evolved to preferentially infected by HIV-1 ex vivo. Microbe-driven GZB induction was prominent in the gut, but not blood and lymphoid tissue CD4 T cells and was partially MHC Class II dependent. Gut cytotoxic CD4 T cells may have evolved to preferentially infected by HIV-1 ex vivo. Microbe-driven GZB induction was prominent in the gut, but not blood and lymphoid tissue CD4 T cells and was partially MHC Class II dependent. Gut cytotoxic CD4 T cells may have evolved to preferentially infected by HIV-1 ex vivo. Microbe-driven GZB induction was prominent in the gut, but not blood and lymphoid tissue CD4 T cells and was partially MHC Class II dependent.

228 MODULATION OF GUT MICROBIOTA IMPROVES MUCOSAL PERMEABILITY IN HIV+ PATIENTS
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Background: Intestinal dysbiosis and the disruption of enterocytes tight junctions play a major role in the pathogenesis of HIV infection. Recent findings support the role of probiotics in restoring intestinal microbiota in HIV+ patients.

Methods: 15 Caucasian HIV+ positive patients on long-term suppressive combined antiretroviral therapy (cART) and 30 healthy control individuals matched by age and gender were recruited at the Department of Public Health and Infectious Diseases, “Sapienza” University of Rome (Italy). HIV+ participants received two sachets of Vivomix®, containing 450 × 10^9 billion bacteria each, twice a day for a period of six months. All patients underwent panocolonoscopy and fecal sample collection before (T0) and after 6 months of probiotic supplementation (T6). Mucosal biopsies taken from distal ileum and different colonic tracts of intestine were evaluated before and after the probiotics treatment. Occludin, Zonulin, E-cadherin and Claudin-2 expression was detected in biopsies at T0 and T6. Metabolomics investigation were performed by 1H-NMR (X).

Results: Occludin and Zonulin were significantly lower in the T0 samples compared to the T6 biopsies (T0 vs T6 p<0.0001). No significant differences were observed for E-cadherin and Claudin-2 expression before and after treatment, while, in the large intestine, Claudin-2 was significantly higher amongst the pre-treated HIV infected patients compared to the same patients after probiotic therapy (T0 vs T6 p=0.0001). Ultrastructural examination of biopsies revealed the morphological conformation of the tight junctions: open, for the structures near the basolateral pole of enterocytes, or for those detected at the intercellular contact sites, near the apical surface of the colonic cells, before the treatment (T0). By contrast, the junctional complex exhibited a closed conformation after 6 months of supplementation (T6). Although no difference was observed at baseline in fecal concentration of phenylalanine and tryptophan between HIV− subjects and controls, metabolomics investigation resulted in lower levels of tyrosine and a higher phe/tyr in HIV+ participants at baseline. At T6, HIV+ individuals showed a significant decrease of fecal tryptophan concentration and a lower phe/tyr.

Conclusion: Our data show evidence that supplementation with oral probiotics drives a beneficial functional modulation of intestinal microbiota with the recovery of mucosal integrity.

229 RECTAL MICROBIOME ALTERATIONS ASSOCIATED WITH TDF/FTC FOR PREEXPOSURE PROPHYLAXIS
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Background: Oral daily tenofovir (TFV) disoproxil fumarate/emtricitabine (TDF/FTC) for HIV pre-exposure prophylaxis (PrEP) is highly effective at preventing HIV infection, yet long-term adverse effects are not fully understood. We investigated the effects of PrEP on the rectal microbiome in a cohort of men who have sex with men (MSM).

Methods: Rectal swabs were obtained from an ongoing cohort (The mSTUDY) examining the effects of substance use on HIV-1 transmission and pathogenesis in young MSM. This cross-sectional analysis included HIV-negative participants currently on PrEP based on clinician review and confirmed by self-report (n=37). HIV-negative control participants not on PrEP (n=37) were selected using 1:1 matching on a propensity score which was calculated using multiple clinical and behavioral confounding factors (including sexual activity). Hair specimens were used to quantify TFV and FTC exposure over the past 6 weeks on a subset of participants. Microbiome composition was analyzed using targeted sequencing of the V4 region of the 16S rRNA gene followed by exact sequence inference using DADA2. Associations between PrEP use and microbiota abundance were performed by 1H-NMR (X).

Table 1. Induction of Granzyme-B-expressing gut CD4 T cells in response to exposure of lamina propria mononuclear cells to enteric bacteria or virus

<table>
<thead>
<tr>
<th>Bacterial strain</th>
<th>CD4+ control</th>
<th>Fold change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shigella flexneri</td>
<td>GN commensal</td>
<td>72.4±0.69</td>
</tr>
<tr>
<td>Salmonella typhimurium</td>
<td>GN pathogen</td>
<td>376±20</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>GP probiotic</td>
<td>45±8</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>GN commensal</td>
<td>45±8</td>
</tr>
<tr>
<td>Salmonella enterica</td>
<td>GP probiotic</td>
<td>45±8</td>
</tr>
<tr>
<td>Roseburia intestinalis</td>
<td>GP commensal</td>
<td>45±8</td>
</tr>
</tbody>
</table>

*CN: Gram-negative, GP: Gram-positive. *Values reflect the fold change in percentage of CD4+ CTLs in response to bacteria compared to unstimulated conditions; and are shown as means±SD (N=5). P values reflect paired t tests between percentages of Granzyme B-expressing CD4 T cells in bacteria-stimulated versus no-stimulation conditions. Microbe stimulation based on identification of mucosa-associated bacteria that were altered in PLVMH who were not using anti-retroviral drugs versus uninfected controls (PMID 20762145).

Results: Overall, TFV and FTC exposure was not significantly different between PrEP users and controls. We observed significant changes in the gut microbiome in the PrEP group compared to controls, particularly in gut commensals such as Bacteroides and Ruminococcus. These changes were associated with changes in gut permeability as measured by in vivo fluorescence imaging.
Results: The median duration of oral TDF/FTC use in the PrEP group was 7 months (IQR 2–13), and self-reported adherence was good to excellent among 86% of participants. Hair analyses on a subset (n=15) of PrEP participants showed median tenofovir concentrations of 0.027 ng/mg hair (IQR 0.022–0.031), consistent with adherence of 4 or more doses per week. No significant differences in rectal microbiome diversity were seen between PrEP and control participants, but changes in microbiome composition were seen. PrEP use was associated with significant increase in abundance of Streptococcus (adjusted p = 0.015) using ZINB models. Similar associations were selected using LASSO regression, confirming the increase in Streptococcus abundance and also showing increased Mitsuokella, Fusobacterium, and decreased Escherichia/Shigella.

Conclusion: Oral TDF/FTC for PrEP use is associated with changes in the rectal microbiome compared to well-matched controls not taking PrEP, specifically increased Streptococcus abundance. This study highlights the need for future investigation of the role of microbiome changes on HIV susceptibility and effectiveness of PrEP.

230 JOINT EFFECTS OF HIV AND OBESITY ON THE MICROBIOME OF YOUNG MEN WHO HAVE SEX WITH MEN

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Background: The prevalence of obesity among people living with HIV continues to rise rapidly. Both obesity and chronic HIV infection are pro-inflammatory conditions which can alter the composition and function of the gastrointestinal microbiome. However, the combined effects of HIV and obesity on the microbiome have not been examined.

Methods: Participants (N=381) with archived rectal swabs collected between 2014 and 2017 were selected from an ongoing cohort of diverse young men who have sex with men (The mSTUDY). Both HIV+ (n=182) and HIV- (n=199) participants were included. Obesity was defined as BMI > 30 or waist circumference > 40 inches. Microbiome composition was assessed by targeted sequencing of the V4 region of the 16S rRNA gene followed by exact sequence inference with DADA2. For analysis, specimens were compared between HIV+ and obese (H+O+) participants and HIV+/non-obese, HIV-/obese, and HIV-/non-obese controls. Analyses included permutation multivariate ANOVA (PERMANOVA) with Bray-Curtis distance to test for differences in overall composition and zero-inflated negative binomial (ZINB) models to test for differential abundance of specific genera. All analyses utilized inverse flow cytometry. The treatment effect was calculated for each biomarker with longitudinal mixed models. A rectal swab specimen was collected before and after study drug exposure among a subset of participants for microbiome study. The QIME 2.0 was used for a pairwise group comparison test.

Results: 54 participants were randomized and received study drug, with 50 completing the first period and 46 completing the second period. Median age was 51 years and CD4+ count was 651 cells/mm3; 89% were male, 72% white, and 39% with prior AIDS. Adherence and adverse events did not differ between rh-lactoferrin and placebo periods. Results for representative biomarkers and immunophenotypes are shown in Table 1, with no consistent evidence of a treatment effect demonstrated. The percent serum iron saturation significantly increased on rh-lactoferrin versus placebo by 2.6% (95%CI: 0.2, 5.0), but this effect did not reach significance for ferritin (5.8 ng/mL; 95%CI: -3.3, 15.0). Among a subset (n=12), intestinal microbiota analysis revealed stability in α diversity and in the abundance of Bacteroidetes and Firmicutes members over follow-up with no discernable treatment effect from rh-lactoferrin.

Conclusion: Oral rh-lactoferrin administration among HIV+ individuals receiving ART with viral suppression was safe and well tolerated, but had no effects on systemic inflammation or cellular immune activation, and exerted no changes in gut microbiome.
232 COTRIMOXAZOLE MODULATES IMMUNE CELL ACTIVATION & THE GUT MICROBIOTA IN HIV INFECTION

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Background: Long-term cotrimoxazole prophylaxis reduces mortality and morbidity in HIV infection but the mechanisms underlying these sustained clinical benefits are unclear. We have previously shown that long-term continuation of cotrimoxazole reduces systemic inflammation, a driver of HIV-1 ART-treated children. Here we explore the mechanisms that underlie the anti-inflammatory benefits of cotrimoxazole.

Methods: Circulating inflammatory mediators (CRP, IL-6, TNFa and soluble CD14) were quantified in plasma samples from HIV-positive Ugandan and Zimbabwean children receiving antiretroviral therapy in the ARROW trial randomised to continue (n=149) versus stop (n=155) cotrimoxazole. Using an in vitro model of systemic inflammation, we evaluated the direct effect of cotrimoxazole on immune cell activation in blood samples from HIV-positive (n=16) and HIV-negative (n=8) UK adults who were cotrimoxazole-naive. Since HIV enteropathy can drive systemic inflammation, we quantified biomarkers of intestinal inflammation (myeloperoxidase, neutrophin, alpha-1-antitrypsin and REG1b) and microbiome composition using randomised stool samples from ARROW. In a parallel in vitro model of gut inflammation (Caco-2 gut epithelial cell transwell cultures), we assayed the effect of cotrimoxazole on epithelial barrier function and chemokine production. Results: Inflammatory biomarkers (CRP and IL-6) were significantly lower among children continuing cotrimoxazole. This was not explained by global differences in symptomatic illness, viral suppression, CD4+ T-cell counts or activation status, or sub-clinical gut pathogen carriage. In vitro cotrimoxazole treatment reduced pro-inflammatory cytokine production in response to pathogen antigens by both HIV+ and HIV- adults. In stool samples from ARROW, myeloperoxidase levels were significantly lower in children continuing cotrimoxazole 84 weeks post-randomisation and this was associated with suppression of viridians group Streptococci and their mevalonate metabolism. Cotrimoxazole-treated Caco-2 produced less IL-8 in vitro.

Conclusion: Cotrimoxazole reduces systemic and intestinal inflammation both through its antibiotic properties and by direct immunomodulation of leukocytes and gut epithelial cells. Synergy between these pathways may contribute to the sustained clinical benefits of long-term cotrimoxazole prophylaxis despite high antimicrobial resistance, providing a further rationale for extending coverage among people living with HIV in sub-Saharan Africa.

233 DARUNAVIR/RITONAVIR THERAPY CONTRIBUTES TO INTESTINAL DYSFUNCTION IN HEALTHY MACAQUES

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Background: HIV infection results in damage to the gastrointestinal (GI) immune system that is incompletely restored with antiretroviral (ARV) therapy. Recent findings have implicated that GI immune system competency is dependent upon signaling originating from the commensal microbiota and that the composition of the microbiome is altered in some diseased states (dysbiosis). In Asian macaque models of HIV infection, we noted that the initiation of ARV therapy - though not SIV infection itself - was associated with dysbiosis. Similar to HIV-infected humans, this dysbiosis was characterized by an enrichment for Gammaproteobacteria at the expense of Clostridia sub-taxa. We thus postulated that ARVs might themselves contribute to dysbiosis and non-AIDS related comorbidities.

Methods: We treated 6 healthy rhesus macaques (RM; Macaca mulatta) with a Darunavir-Ritonavir (DRt) protease inhibitor regimen (400mg and 100mg b.i.d. respectively) for 90 days and evaluated immune function in intestinal lymphocytes by flow cytometry in these and 4 control animals. We further collected stool samples to evaluate changes in the intestinal microbiome by 16S Illumina sequencing.

Results: We observed that DRt-therapy was associated with increased systemic inflammation as compared to controls - most notably, increased IFNγ and TNFa expression from intestinal CD8+ memory T-cells. Among DRt-treated RM, deep sequencing of intestinal microbiota revealed a modest but prolonged expansion of Anaeroplasmataceae and Erysipelotrichiaceae which were associated with the increased inflammatory milieu we observed. Importantly, we did not observe an enrichment for Proteobacteria.

Conclusion: Our findings suggest that protease inhibitors contribute modestly to microbial dysbiosis and immune dysfunction in uninfected lentiviral infections. As such, the side effects of protease-inhibitors commonly observed in HIV-infected individuals are unlikely to be attributed solely to GI tract dysbiosis or inflammation. Further research is required to determine if other ARVs interfere with intestinal stasis and whether ARVs contribute to dysbiosis in the context of ongoing lentiviral infections.

234 THE MICROBIOME MAY MODIFY HIV INFECTION RISK ASSOCIATED WITH HORMONAL CONTRACEPTIVES

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Background: The injectable hormonal contraceptive depot medroxyprogesterone acetate (DMPA) has been associated with increased risk of HIV-1 acquisition in women, but these observations have been inconsistent. We examined whether the vaginal microbiome influences rates of HIV acquisition in women using different hormonal contraceptives in the CAPRISA 004 trial at study enrollment.

Methods: Mass spectrometry was used to characterize the bacterial metaproteome (microbiome) from cervicovaginal lavage samples collected from study participants.

Results: Among the 685 women included in this study, the majority were using hormonal contraceptives (92.7%) including DMPA (65.1%), norethisterone enanthate (NET-EN) (18.0%), and combined oral contraceptives (COC) (14.1%), and the majority did not switch contraceptives during the study (91.7%). Women belonged to two major vaginal microbiome profiles which were independent of contraceptive use. The majority did not switch contraceptives during the study (91.7%). Women belonged to two major vaginal microbiome profiles which were independent of contraceptive use. The majority did not switch contraceptives during the study (91.7%).
and COC users, respectively), and not significantly higher in those using DMPA compared to all other hormonal contraceptives (HR: 1.16, 95% CI: 0.56 to 2.40, P=0.70). However, in Lactobacillus-dominant women, DMPA use associated with an infection rate of 6.23 per 100 women-years compared to 1.74 and 2.15 per 100 women-years with NET-EN and COC, respectively – a > 3-fold increase for DMPA users relative to women using other hormonal contraceptives (HR: 3.39; CI: 1.61 to 7.15, P=0.0152). These observations were consistent in models adjusted for study arm, study site, age, sexual behavior and other clinical variables.

Conclusion: This suggests that the association between DMPA and HIV acquisition risk may depend on the composition of the microbiome, which may have important implications for safe contraceptive design and interpretation of future studies of contraceptives and HIV acquisition risk.

235 ROLE OF FREM1 IN PRO-INFLAMMATORY RESPONSES DURING VAGINAL HIV/SIV INFECTION
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Background: A single nucleotide polymorphism in FRAS1-related extracellular matrix 1 (FREM1) is associated with resistance to HIV. A splice variant of FREM1-Toll/Interleukin-1-like receptor regulator, (TILRR) is an IL-1RI co-receptor capable of potentiating inflammatory responses. This study investigated the role for FREM1 in modulation of immune responses during vaginal HIV transmission.

Methods: FREM1 protein expression was examined in human and Rhesus macaque (RM) female genital tissues, and changes in its expression measured following intravaginal SIV infection in RMs. FREM1 expression in both human and RM female genital tracts (FGTs) was similar, with high expression in the epithelium and submucosa.

Results: FREM1 levels increased following intravaginal SIVmac251 infection, accompanied by infiltration of SIV target cells into the genital mucosa. Different human immune cells in blood, expressed FREM1, including T cells, monocytes, and B cells to varying degrees. Notably, FREM1-expressing CD4+ and CD8+ T cells from women with the protective FREM1 allele had lower cellular activation. Only Escherichia coli LPS (TLR4 agonist), and not Imiquimod (TLR7 agonist) or ssRNA40 (TLR8 agonist) alters FREM1 expression on some T cells and monocyte subsets. Co-expression analysis of FREM1 and TLR4 in PBMCs and tissues also suggests close association between these proteins. Stimulation of human monocyte populations with a TL4 agonist or antagonist, alone and in combination with anti-FREM1 mAbs, indicates that FREM1 modulates pro-inflammatory cytokine production and co-stimulatory factor expression.

Conclusion: These results suggest FREM1 potentially regulates innate immune responses, based on its association with TLR4. These findings add to the understanding of early HIV transmission in the context of cellular structural proteins being influenced vaginal microbiota driven inflammation.

236 CERVICOVAGINAL MICROBIAL STRAINS ARE ASSOCIATED WITH DISTINCT IMMUNOPHENOTYPES
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1Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, 2Broad Institute of MIT and Harvard, Cambridge, MA, USA, 3National Microbiology Laboratory, Winnipeg, MB, Canada, 4Karolinska Institute, Stockholm, Sweden, 5Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, 6University of Nebraska—Lincoln, Lincoln, NE, USA

Background: Elevated inflammation in the female genital tract (FGT) is associated with an increased risk of HIV infection, and cervicovaginal bacteria have been shown to impact genital inflammation (Gosmann et al., 2017). These associations have been identified through bacterial 16S rRNA gene sequencing which has limited resolution and rarely achieves taxonomic assignment to the species-level. Within-species genetic differences can be vast, with some species-level pangenomes (all the unique genes observed for a species) exceeding the size of any single strain’s genome by orders of magnitude. Furthermore, 16S sequencing provides no functional information, limiting our mechanistic understanding of disease associations.

Methods: To better characterize strain-level variation in the FGT microbiota we generated species-specific pangenomes from single culture genome sequences (1000 primary bacterial isolates and 2000 publicly available genomes). We produced sample specific gene profiles by mapping metagenomic sequences from 300 North America and South Africa women to the species-specific gene catalogues. Profiles were partitioned using centroid based clustering to form groups containing similar gene complements (strains). Local inflammation was measured using Lumineux cytokine assays performed on cervicovaginal lavages from South African women with distinct strains.

Results: We show that most species possess a small core genome (~1000 genes) with an extensive pangenome (6000 to 30,000 genes). We find that Gardnerella vaginalis comprises 4 distinct strains and that some women possess enough genes to make 4 complete genomes, suggesting some women are colonised by multiple strains. Furthermore, we show that these strain complexes are associated with higher levels of cytokines in the FGT.

Conclusion: Our findings signify the importance of distinguishing microbial strains in the FGT when linking the endogenous microbiome to local inflammation influencing HIV acquisition risk.

237 GENITAL AND SYSTEMIC INFLAMMATION ASSOCIATED WITH FACTORS THAT MAY ALTER HIV RISK
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1University of Washington, Seattle, WA, USA, 2Public Health Agency of Canada, Winnipeg, MB, Canada, 3University of Manitoba, Winnipeg, MB, Canada, 4FHI 360, Durham, NC, USA, 5Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 6CDC, Atlanta, GA, USA

Background: Evidence suggests that epidemiologic factors modify susceptibility to HIV-1 acquisition by modulating innate inflammatory responses, and defining these changes may identify novel HIV-1 prevention interventions. However, few studies have assessed host responses to varied HIV risk altering exposures in the genital (vaginal and cervical) as well as systemic compartments. Here we compare vaginal, cervical and systemic inflammatory responses to potential HIV-1 risk modulating exposures (e.g., depot medroxyprogesterone acetate [MPA], bacterial vaginosis [BV], genital herpes [HSV-2], and oral HIV pre-exposure prophylaxis [PrEP]) to identify compartment-specific cytokine signatures.

Methods: We analyzed vaginal and cervical swabs and serum samples collected at 90 visits from 68 HIV-negative Kenyan and Ugandan women enrolled in the Partners PrEP Study. We measured compartment-specific concentrations of 28 cytokines using Milliplex beads, and tested for associations with PrEP use, serum MPA concentrations, BV and non-lactobacillus dominant (NLD) vaginal flora, and HSV-2 infection. We defined inflammation status as: 1) elevated IL1α or IL1β, or lowered IP10 (based on published literature), or 2) cytokine sets associated with each exposure from the 28 measured. We used logistic regression to assess associations of exposures with the IL1α/IL1β/IP10 signature and LASSO regularization to identify exposure-specific cytokine sets.

Results: In multivariable models, NLD flora (OR=13.4, 95% CI: 2.96-60.4) were associated with increased odds, and MPA (OR=0.15, 95% CI: 0.02-0.92) and PrEP exposure (OR=0.11, 95% CI: 0.02-0.59) were associated with reduced odds of the IL1α/IL1β/IP10 signature in the vagina (Table 1). No HIV risk modulators were associated with cervical or systemic inflammation. By LASSO regression, NLD...
flora were associated with IFNα2, IL-12 p40, IL-17A, IL1β, IL-1RA, IL-33, IL-8, IP-10, TNFα and SC104L concentrations in the vagina. BV was associated with IP-10 concentration in the cervix. PrEP cessation was associated with concentrations of IFNα2 and IL-21 in the vagina and IL-15, IL-1β, IL-1RA, IL-2, IL-21 and MMP-1β in the cervix. No systemic exposure-specific cytokine sets were identified.

**Conclusion:** We identified associations between inflammatory signatures in vaginal and cervical compartments and potential HIV risk exposures that warrant further investigation. To this end, we intend to assess for similar signatures in a larger, more diverse sample of HIV-1 seronegative African women.

**Table 1.** Association of epidemiological exposures with candidate inflammation signature (L: low, M: moderate, H: high). For each exposure, a Mann-Whitney U test was performed between vaginal, cervical, systemic, and systemic inflammation.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Vaginal Inflammation</th>
<th>Cervical Inflammation</th>
<th>Systemic Inflammation</th>
<th>Systemic Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L/H</td>
<td>L/H</td>
<td>L/H</td>
<td>L/H</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>Cytobrush</td>
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<td>0.0026</td>
<td>0.0008</td>
<td>0.0002</td>
</tr>
<tr>
<td>Male circumcision</td>
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<td>0.0032</td>
<td>0.0015</td>
<td>0.0011</td>
</tr>
<tr>
<td>Disability</td>
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<td>0.2562</td>
<td>0.5098</td>
<td>0.5098</td>
</tr>
<tr>
<td>Bloodborne HIV infection</td>
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<td>0.0012</td>
<td>0.0006</td>
<td>0.0004</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.0007</td>
<td>0.0003</td>
<td>0.0002</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stills</td>
<td>0.6000</td>
<td>0.5098</td>
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</tbody>
</table>

**238 CHLAMYDIA AND CERVICOVAGINAL MICROBIOTA MODULATE GENITAL-TRACT CD4+ T-CELL SUBSETS**

**Method:** We examined FGT CD4+ T-cell subsets in a cohort of 119 HIV-negative South African women (ages 18-24). We used flow cytometry of cervical cytobrush samples to enrich for Th17 cells and Tregs by gating on CD161+CCR6+ and CD25+CD127Lo- cells respectively. We identified bacterial STIs via commercial laboratory testing and characterized the microbiota using bacterial 16s rRNA sequencing. Data were analyzed with DADA2 and custom R scripts.

**Results:** Median cervical CD161+CCR6+ and CD25+CD127Lo- CD4+ T cell frequencies were 48.0% and 12.4% respectively. Subjects with chlamydia had higher numbers of activated CD4+ T cells, as well as higher frequency of CD25+CD127Lo- (Fig A), lower frequency of CD161+CCR6+ and lower ratio of CD161+CCR6+ / CD25+CD127Lo- CD4+ T cells (p < 0.002 for each, Mann-Whitney U test). Using 16s sequencing, we classified STI-negative women into CD161+CCR6+ / CD25+CD127Lo- CD4+ T cell subset compositions by both chlamydia and the non-STI genital tract microbiota.

**Conclusion:** We characterized FGT CD4+ T-cell subsets and showed they were associated with both chlamydia and the non-STI microbiota. Future work will investigate the mechanistic basis for these findings and implications for adaptive immunity and HIV.
FORESKIN HIV TARGET CELLS AND PENILE ANAEROBES ASSOCIATED WITH HIV SEROCONVERSION

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Background: Inflammation has been associated with risk for HIV seroconversion. Specific penile anaerobes may increase HIV risk in men by triggering a cascade of soluble pro-inflammatory factors, such as IL-8, resulting in the recruitment of CD4+ cells to the foreskin. To test this hypothesis, we evaluated the association between abundance of penile anaerobes with sub-preputial soluble immune factors and target cells.

Methods: We conducted a cross-sectional study of 88 HIV-negative heterosexual uncircumcised men from the Rakai Community Cohort Study in Uganda. Sub-preputial swabs and foreskin tissues were collected. Using DNA extracted from sub-preputial swab eluent, we estimated absolute abundance of all 21 seroconversion-associated penile bacterial species (log10 16S rRNA gene copies/swab by pan-bacterial real-time PCR and sequencing of the 16S rRNA V3-V6 region. Four negative control genera-Corynebacterium, Staphylococcus, Helcococcus, and Negativicoccus were also included in the analysis. We measured IL-8 concentration using multiplex mesoscale immunoassay and cell density (Table 1).

Results: Abundance of all 21 seroconversion-associated penile bacterial species correlated significantly with sub-preputial IL-8 (Spearman Rho range: 0.25-0.60; p < 0.05) while none of the negative control bacteria were significantly associated with IL-8. However, only seven species from three genera (Peptostreptococcus, Dialister, Prevotella) were correlated and associated significantly with increased CD4+ T-cell density (Table 1). The four negative control bacteria were not associated with sub-preputial IL-8 or foreskin immune cell density (Table 1).

Conclusion: The uncircumcised penis is enriched with sub-preputial anaerobes; the abundance of some of these anaerobes has been associated with HIV acquisition risk. HIV-associated anaerobes are associated with sub-preputial levels of the chemoattractant cytokine IL-8. Although collinearity of bacteria in the uncircumcised penile microbiome makes it difficult to assess independent IL-8 associations, only a subset of species were linked to the density of putative HIV target cells in the underlying foreskin tissue.
**BLOOD MICROBIOTA CORRELATES WITH INFLAMMATION AND ART-MEDIATED IMMUNE RESTORATION**

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**Background:** HIV infection impairs the mucosal immunity and leads to bacterial translocation, fueling chronic inflammation and disease progression. The compositional profile of the translocated bacteria remains undefined.

**Methods:** A total of 80 samples from 50 individuals were studied: 30 HIV-infected individuals with <350 CD4+ T-cells/μL or AIDS at diagnosis and after 48 weeks of first-line ART, and 20 controls matched by sex and age. HIV+ subjects were categorized by the median CD4/CD8 ratio fold increase during ART (cut-off: 2.5) to classify study participants as immunological responders (IR) or non-responders (INR). Total DNA was extracted from 50 μL of blood and was analyzed by highly sensitive 16S rDNA targeted metagenomic sequencing of V3-V4 regions using MiSeq Illumina and the FROGS metagenomic workflow. LEfSe analysis was used to identify bacterial biomarkers. Their correlations which markers of inflammation, bacterial translocation and peripheral T cell activation was calculated using Spearman’s regression.

**Results:** Alpha diversity was significantly higher in HIV+ vs. HIV- subjects, and these differences were attenuated after 48 weeks of ART. We did not detect differences in beta diversity. LEfSe analysis revealed that HIV+ subjects showed differences in beta diversity. LEfSe analysis was used to identify bacterial biomarkers. Their correlations which markers of inflammation, bacterial translocation and peripheral T cell activation was calculated using Spearman’s regression.

**Conclusion:** HIV infection impairs the mucosal immunity and leads to bacterial translocation, fueling chronic inflammation and disease progression. The immunological, biochemical and molecular mechanisms associated with poor immune recovery are far from known, and metabolomics profiling offers an additional value to traditional soluble markers. Here, we search for predictive markers of late immune response and disease progression in a cohort of HIV-subjects with increased CD4 T-cell turnover and inflammation preceding their poor immune recovery.

**Methods:** We executed a nuclear magnetic resonance (NMR) and mass spectrometry (MS)-based circulating metabolomics approach in 41 cART-naive HIV-infected patients who were initiating cART and subsequently followed up these patients for 96 weeks (n = 17). Random forest (RF) was performed to identify the variables that best partitioned the overall study population according to immune recovery predisposition. Network of metabolite-protein interaction and functional enrichment analyses were generated to identify the metabolomics pathways affected.

**Results:** Plasma L-tyrosine (P = 0.04), L-glutamate (P = 0.05), and phosphatidylcholine (PC) (P = 0.01) by univariate model, and hsCRP, IL-6 and palmitoylcarnitine (PalC) by Random Forest, were identified as predictive markers of late immune recovery. After 96 weeks of cART, CD4+ T-cell counts were positively correlated to glycyolic acid (r = 0.51, P = 0.04) and citrulline (r = 0.60, P = 0.03), and inversely correlated to lipopolysaccharide (LPS) (r = -0.61, P = 0.03) and DL-pipecolic acid (r = -0.94, P < 0.01). Compositional and structural changes on HDL and decreased glutamate concentrations were associated to immune recovery during cART.

**Conclusion:** Metabolomics improve the value of soluble parameters and shows novel and relevant data that may contribute to a better understanding of molecular mechanisms preceding discordant response and immunological progression under suppressive stable cART. The metabolomics signature of ART-naive HIV subjects with late immune recovery is the expression of pro-inflammatory molecules and glutaminolysis, which is probably related to their higher T-cell turnover.

**Table 1. Correlation between late immune response and biomarkers at baseline and week 96 of cART**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Baseline Correlation</th>
<th>Week 96 Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-tyrosine</td>
<td>-0.61 (P = 0.04)</td>
<td></td>
</tr>
<tr>
<td>L-glutamate</td>
<td>-0.60 (P = 0.03)</td>
<td></td>
</tr>
<tr>
<td>PC</td>
<td>0.51 (P = 0.04)</td>
<td>-0.94 (P &lt; 0.01)</td>
</tr>
<tr>
<td>hsCRP</td>
<td>-0.61 (P = 0.03)</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>0.60 (P = 0.03)</td>
<td></td>
</tr>
<tr>
<td>PalC</td>
<td>-0.51 (P = 0.04)</td>
<td></td>
</tr>
<tr>
<td>LPS</td>
<td>-0.61 (P = 0.03)</td>
<td></td>
</tr>
<tr>
<td>DL-pipecolic</td>
<td>-0.94 (P &lt; 0.01)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1. Toponomic biomarker discovery with LEfSe**
244 EXPANSION OF MYELOID-DERIVED SUPPRESSOR CELLS IN ART-SUPPRESSED HIV-INFECTED PATIENTS
Carla Serra Peinado*, Laura Luque-Ballesteros, Rein Willekens, Jordi Navarro, Adrià Curran, Joaquín Burgos, Esteban Ribera, Ariadna Torrella, Bibiana Planas, Rosa Badía, Josep Castelví, Vicenç Falco, Maria J. Buzó
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Background: The existence of HIV reservoirs represents the main obstacle to cure HIV. The role of the immune system at maintaining and regulating this viral persistence remains largely unknown. Here, we studied the role of the myeloid-derived suppressor cells (MDSC), a heterogeneous population of immature myeloid cells with high immunosuppressive effects on the HIV reservoir.

Methods: Samples from n=14 ART-suppressed and n=8 healthy controls were included in this study. Frequency of two subpopulation of MDSC (CD3-, CD3+), a heterogeneous population of immature myeloid cells with high immunosuppressive effects on the HIV reservoir, was assessed by multiparametric flow cytometry, as well as immune activation in CD4+ and CD8+ T cells (markers CD38 and HLA-DR). The functional status of MDSC was assessed by the expression of Indoleamine 2,3-dioxygenase (IDO) and Arginase-1 (ARG-1). Total HIV DNA and intracellular HIV-RNA were quantified by qPCR in purified CD4+ T cells. P24 expression and MDSC infiltration in B-cell follicles within lymph nodes of n=2 chronic infected patients was measured by immunohistochemistry.

Results: ART-suppressed patients presented significantly higher proportions of M-MDSC compared to healthy controls (0.24% vs. 0.6% in healthy and ART-suppressed donors, respectively). Importantly, this expanded M-MDSC population showed higher expression of IDO and ARG-1 (MF of 488 and 628 for IDO, 533 and 685 for ARG-1 in healthy controls and ART-suppressed, respectively), two enzymes highly related with the immunosuppressive capacity of the MDSC. Moreover, the percentage of M-MDSC in ART-suppressed patients positively correlated with the activation of CD4+ and CD8+ T cells (rho=0.830 p=0.0008 for CD4+ and rho=0.741 p=5495 for CD8+), which in turn correlated with intracellular HIV-DNA (rho=-0.742 p=0.0140 for CD4+ and, rho=0.6722 and p=0.0331 for CD8+) and HIV-RNA (rho=-0.837 p=0.0095 for CD4+ and, rho=0.877 and p=0.0042 for CD8+). Additionally, infiltration of MDSC in B-cell follicles was preferentially observed in association with the expression of p24 (rho=-0.372 p=0.039).

Conclusion: Overall, in ART-suppressed patients, MDSC might be an important player in the preservation of the HIV-reservoir. Finding new therapeutic strategies to modulate the immunosuppressive actions of the MDSC might significantly impact the HIV reservoir.

245 CIRCULATING B-D-GLUCAN AND INDUCTION OF IMMUNE ACTIVATION
Stéphane Isnard, Rayoun Ramenadra, Franck P. Dupuy, Vikram Mehraj, Rosalie Pont, Jun Chen, Cecilia Costinuk, Réjean Thomas, Jean-Guy Baril, Madeleine Durand, Cécile Tremblay, Petronella Ancuta, Nicole Bernard, Don C. Sheppard, Jean-Pierre Routy

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Background: (1→3)-β-D-Glucan (BDG) is one of the most abundant components of fungal cell walls. People living with HIV (PLWH) without invasive fungal infection have been reported to have elevated plasma levels of circulating BDG. Such elevation is correlated with markers of gut damage, immune activation, and the occurrence of non-AIDS events. However, the mechanisms by which BDG induces immune activation and contributes to disease progression remain undefined. We aim to 1) Correlate BDG levels with CD4 and CD8 T cell activation markers as well as integrated HIV DNA, 2) Correlate plasma levels of BDG with expression of its receptors, and 3) Demonstrate a direct effect of BDG on the induction of immune activation in vitro.

Methods: We analyzed plasma and peripheral blood mononuclear cells (PBMC) from participants receiving or not ART. We assessed the frequency CD4 and CD8 T cell activation (HLA+CD8+) in PLWH PBMC and CD4 T cell bearing integrated HIV DNA by nested qPCR. We used flow cytometry to measure the expression of the BDG receptors Dectin-1 and NKp30 on monocytes and NK cells respectively. We assessed the dynamics of BDG receptor expression up to two days after Saccharomyces-derived BDG stimulation compared to bacterial lipopolysaccharides (LPS) stimulation in vitro. We analyzed indoleamine 2,3-dioxygenase-1 (IDO-1) expression by flow cytometry and cytokine secretion in the supernatant by ELISA following stimulation with BDG and/or LPS.

Results: Higher plasma BDG levels correlated with higher frequencies of HLA+CD8+ cells (r=0.69, p<0.001) and CD8+ T cells (r=0.65, p<0.001, n=26), as well as HIV reservoir size in PLWH (r=0.41, p=0.04, n=24). Plasma BDG negatively correlated with the expression of its receptors Dectin-1 on monocytes (r=-0.58, p<0.01) and NKp30 on NK cells (r=-0.61, p<0.01) in 33 participants. In vitro, BDG stimulation prompted a reduction of Dectin-1 and NKp30 expression after 24 and 48 hours of stimulation. BDG stimulation predominantly induced IL-8, TNF-α and IDO-1 production over IL-1β and IL-6 in vitro.

Conclusion: BDG elevation correlated with the frequency of activated CD4 and CD8 T cells and HIV reservoir size. BDG induced immune activation independently of LPS by triggering Dectin-1 and NKp30 on monocytes and NK cells respectively, and inducing cytokine secretion mostly IL-6, IL-8 and IDO expression. Our results pave the way to new treatment strategies to reduce inflammation and prevent the development of non-AIDS events.

246 MINING FOR CD4 CELL RECOVERY PHENOTYPE REVEALS DISTINCT PATTERN FOR BLACK ETHNICITY
Teja Turk, Christian Thorhall, Jacques Fellay, Alexandra Trkola, Peter Ruster, Karin Metzner, Dominique L. Braun, Jürg Böni, Sabine Verly, Vincent Aubert, Thomas Klimkait, Huldrych F. Günthard, Roger Yousouf, for the Swiss HIV Cohort Study

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Background: With ever increasing majority of HIV-infected individuals receiving suppressive antiretroviral treatment (ART), one of the key questions is understanding the factors that govern the CD4 cell recovery in this population.

Methods: We explored a range of asymptotic growth curve models to describe CD4 cell recovery after ART initiation and to capture its saturation. A well-characterized ART-naive patient population of 2,583 individuals from the Swiss HIV Cohort Study (SHCS) receiving suppressive combination ART for at least 3 years (with >9 CD4 cell counts available) was used to establish the recovery phenotype and its population distribution, in particular the CD4 cell count plateau (ART-CD4-plateau) under suppressive ART (supp-ART). Individual ART-CD4-plateaus for a broader population of 4,089 ART-naïve SHCS patients under supp-ART (for at least 3 years with >5 CD4 observations) were inferred from the individual CD4 cell counts given the population distribution. The same approach was applied to CD4 cell percentage to obtain CD4 cell percentage plateaus (ART-CD4% plateau).

Results: Median ART-CD4 plateau in the supp-ART population based on a Janoschek growth model was 769 cells/μL (IQR [606-945]). Among patients of white ethnicity (76.1%) the median plateau was 785 cells/μL [620-968] compared to a lower median plateau of 720 cells/μL [560-872] observed in black population (14.9%). Lower nadir CD4 cell count, male sex, lower pre-ART HIV-1
RNA, older age at ART initiation and black ethnicity were identified as significant risk factors for lower ART-CD4-plateau in the multivariable model. Although the patients of black ethnicity were, when compared to patients of white ethnicity, younger at ART start (34 [28-39] vs. 40 [33-48]) and predominantly women (64.1% vs. 16.8%) the black population was found to have 61 cells/μL lower ART-CD4-plateau (95%-confidence interval [32-91]) even after adjusting for all cofactors (Fig. 1). Moreover, this finding was consistent among all the considered growth models. Lastly, the ART-CD4%-plateau was also found to be significantly lower for black ethnicity, indicating a different pattern of CD4 cell recovery.

Conclusion: Our approach established a CD4 cell recovery phenotype based on longitudinal data and revealed black ethnicity as an important subpopulation with a distinct CD4 recovery profile. Enabling in-depth analysis of determinants of immune system recovery in treated HIV infection highlights the utility of our method as component for precision medicine.

Results: Plasma samples were collected from 69 adults under clinical follow up in Madrid, Spain. Forty-nine were HIV-1-infected (20 drug naive and 29 under ART) and 20 HIV-1 free. Among ART treated, 13 were under virological failure and 16 had suppressed VL (<1.6log or <40 HIV-1 RNA copies/ml), with sexual transmitted coinfections (STI) in 5 of 16 cases. Plasma sPD-L1 levels were measured using ELISA Kit for Programmed Cell Death Protein 1 Ligand 1 and Cloud Clone Corp. A potential novel immune marker for HIV-1 infection and virologic failure

SPD-L1: A POTENTIAL NOVEL IMMUNE MARKER FOR HIV-1 INFECTION AND VIROLOGIC FAILURE

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Background: Despite viricidal control, basal chronic inflammation and its related comorbidities remains an unsolved problem among people living with HIV (PLWH). We explored the impact of HIV-1 infection, antiretroviral therapy (ART) exposure, viral load (VL) and sexual transmitted coinfections (STI) in soluble Programmed death-ligand 1 (sPD-L1) levels, a well-described inductor of T-cell exhaustion in other clinical contexts.

Methods: Plasma samples were collected from 69 adults under clinical follow up in Madrid, Spain. Forty-nine were HIV-1-infected (20 drug naive and 29 under ART) and 20 HIV-1 free. Among ART treated, 13 were under virological failure and 16 had suppressed VL (<1.6log or <40 HIV-1 RNA copies/ml), with sexual transmitted coinfections (STI) in 5 of 16 cases. Plasma sPD-L1 levels were measured using ELISA Kit for Programmed Cell Death Protein 1 Ligand 1 and Cloud Clone Corp.

Results: All 49 HIV-infected patients exhibited significant higher sPD-L1 levels than 20 uninfected adults (1.05ng/ml vs. 0.52ng/ml; p<0.001). Levels remained elevated in HIV-infection despite VL control, after comparing 16 infected with undetectable VL with 20 uninfected (0.75ng/ml vs. 0.52ng/ml; p=0.02). ART exposure seemed not to decrease sPD-L1 levels when comparing 16 treated infected with undetectable viremia vs. 20 naive (0.87ng/ml vs. 0.87ng/ml; p=0.199). We also found a significant impact of VL on sPD-L1 values. Thirteen ART treated subjects under virological failure exhibited the highest sPD-L1 levels, being significantly higher than in naive (1.66ng/ml vs 0.87ng/ml; p=0.002) or than in 16 ART treated subjects with suppressed viremia (1.68ng/ml vs. 0.79ng/ml; p=0.002). The last could be explained by differences in mean VL (5.10log vs. 3.70log vs. <1.6log, respectively). Along these line, there was a positive correlation between VL and sPD-L1 levels in plasma in the whole cohort (Spearman r=0.3; p=0.03). A non-significant decrease in sPD-L1 values was observed in HIV-1-infected subjects with controlled viremia with vs. without STI (0.57ng/ml vs. 0.88 ng/ml; p= 0.29).

Conclusion: sPD-L1 levels are significantly elevated during HIV-1 infection, despite control of viremia. This fact opens new avenues for this biomarker as a predictor factor of virological failure or VL during the clinical follow up of PLWH.

IMPACT OF HIV INFECTION AND ANTIRETROVIRAL THERAPY ON IMMUNE CELLULAR FUNCTIONS

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Background: Despite viral suppression by ART and restoration of CD4 T cells, immune activation and exhaustion persist in many of HIV infected individuals which might result in overall decreased cellular activity. In this study we analyze cellular metabolism, function and proliferation in context of HIV infection and immunological parameters.

Methods: Glycolysis and oxidative phosphorylation of lymphocytes from HIV infected treatment-naive (n=12), ART-treated (n=12) and HIV negative (n=12) individuals were analyzed using extracellular flux analyzer and expression of key metabolic genes was measured by qPCR. Changes in HIV-1 transcription factor were analyzed by western blot. We assessed the impact of ART regimens on proliferation capacity by CFSE staining ex vivo. We used ICS-staining to determine changes in cellular function and phenotype using multicolor flow cytometry. Comparison of mitochondrial mass was done by qPCR, mitochondrial membrane potential and production of mitochondrial ROS by flow cytometry.

Results: Respiration of CD4, CD8 T cells and NK cells from HIV infected treatment-naive individuals was significantly reduced compared to HIV negative subjects (p<0.001, p<0.0001, p<0.05). Both respiration and glycolysis of CD8 T cells were in strong correlation with expression of inhibitory receptor PD-1 (p<0.0001) and immune activation (HLA-DR+, CD38++; p<0.0001). While we expected ART to restore metabolic profiles, we observed that the respiration of CD4 T cells was significantly decreased (p<0.001). This was in particular the case for INSTI containing regimens. We observed that cells from these individuals showed significantly lower ex vivo proliferation compared to CD4 T cells from individuals receiving either PI (p<0.05) or NNRTI (p<0.001). We next assessed the impact of individual ART on CD4 T cells. Both INSTI, EVG and DLG, but not RAL, dramatically reduced respiration (EVG p<0.05; DLG p<0.0001) without having an impact on glycolysis, GLUT1 and PFK1 expression or HIF1α. We also observed decreased secretion of IL-2 (p<0.001), MIP-1β (p<0.001), CD107a (p<0.05) and INFγ (p<0.05) indicating impaired function of the cells. Both INSTI increased mitochondrial mass (EVG p<0.01; DLG p<0.05) and mitochondrial reactive oxidative species (EVG p<0.0001; DLG p<0.05), but had no impact on mitochondrial membrane potential.

Conclusion: We identified significant interference of INSTI with CD4 T cell respiration, proliferation and immune responses resulting in decreased immune cellular function.

HIV-1 DIVERSITY IN GUT IS ASSOCIATED WITH RESIDUAL MUCOSAL VIRUS PRODUCTION ON ART

Manon Nayrac1, Mary Requena2, Nicolas Jeanne1, Maud Mavigner4, Claire Loiseau1, Romain Carencac1, Michelle Cazabat4, Jacques Izopet2, Pierre Delobel3

1INSERM, Toulouse, France, 2CH de Toulouse, Toulouse, France, 3Emory Vaccine Center, Atlanta, GA, USA, 4Australian Institute of Tropical Health and Medicine, Cairns, Australia

Background: HIV-1 persists in cellular reservoirs and some anatomical compartments despite antiretroviral therapy (ART). We compared HIV-1 in gut and blood compartments on ART, regarding differences in target cells, residual HIV-1 DNA and RNA, coreceptor usage, and virus diversity.

Methods: Peripheral blood and duodenum samples were obtained from 17 HIV-1-infected subjects with sustained plasma VL <50 c/ml for 5 years. Blood and gut CD4+ T cells were phenotyped by flow cytometry (BD LSRHI). HIV-1 DNA was quantified in sorted blood and gut CD4+ T cells by qPCR. HIV-1 RNA was quantified in duodenum tissue by qRT-PCR. Virus quasispecies were characterized by next-generation sequencing of C2V3C3 env (454 GS Junior), with data cleaning and coreceptor usage prediction by Pyrovi software. Viral diversity in blood and gut compartments was assessed by haplotype numbers, adjusted-Shannon entropy, and Hill numbers. Phylogenetic analyses were performed using CLUSTAL W. A non-parametric test for panmixia was used to look for compartmentalization.
**Results:** CD4+ T cells in the gut were mainly CD45RO+CCR7- effector memory cells (88.2% vs 13.3% in blood, P<0.01). CD4+ T cells were more frequently activated (HLA-DR+, 15% vs 8.2%, P<0.05) and proliferating (Ki67+, 2.7% vs 2%, P<0.01), and expressed much more MHC I (53% vs 5.7%, P<0.01) in gut than in blood. HIV-1 DNA was 6.7-fold higher in gut than in blood CD4+ T cells (P<0.01). Low-level HIV-1 RNA was detected in duodenal tissue of 13/14 subjects (1-7 c/ml). HIV-1 quasispecies displayed compartmentalization between the gut and blood (test for panmixia, P<0.01). In the blood, 9 subjects harbored only RS viruses vs 8 R5/X4 dual-mixed (DM) viruses, while in the gut 13 harbored only RS viruses vs 4 DM viruses. Virus diversity in the V3 region was reduced in gut vs blood compartment: median haplotype numbers (7 vs 10, P<0.01), median adjusted-Shannon entropy (0.14 vs 0.18, P<0.05). Virus diversity in the gut, assessed by adjusted-Shannon entropy of C2V3C3 env, correlated with mucosal CCR5+CD4+ T cell frequency (p=0.71, P<0.05), and residual mucosal HIV-1 RNA level (p=0.57, P<0.05).

**Conclusion:** HIV-1 persists in the gut mucosa on ART with increased levels of infected cells compared to blood CD4+ T cells, and low-level mucosal HIV-1 RNA production. Virus diversity was reduced with enrichment in RS viruses and compartmentalization in gut compared to blood. Virus diversity in the gut was associated with reduced mucosal virus production.

**250 ASSOCIATION BETWEEN HIV ANTIBODIES AND D-DIMER: ROLE OF “DEFECTIVE” PROVIRUSES**

Hiromi Imamichi1, Tracey D. Zhai1, Nicole E. Winchester1, Francesca Scrimieri1, Mindy Smith1, Thomas Buerkert1, Ivery Davis2, Adam Rupert2, Robin L. Dewar2, Virginia Sheikh1, Peter Burbelo2, Irini Sereti1, Andrea Lisco1,

“DEFECTIVE” PROVIRUSES

"Defective" proviruses and stimulate the adaptive and innate immune response and immune activation/coagulation. "Defective" proviruses that are not able to produce HIV-1 RNA production and immune activation are of critical importance in advancing our understanding of HIV-1 persistence. Persistent immune activation and inflammation has recently received attention. The immune activation by looking at associations among proviral genome burden, proviral DNA and RNA production. Virus diversity was reduced with enrichment in RS viruses and compartmentalization in gut compared to blood. Virus diversity in the gut was associated with decreased mucosal virus production.

**Methods:** 15 HIV-infected pts on suppressive ART were included in this prospective study and followed longitudinally for 192 weeks after ART initiation. Demographic, virologic and clinical data were analyzed. Luciferase ImmunoPrecipitation Systems (LIPS) was used for detection of autoantibodies against CD4, CD8α, CD8β, CD3, CD3ε, IFNGR1, CD127, CD25, CTLA4, CCR5, Ro52. IgG deposition and natural killer (NK) antibody-dependent cell mediated cytotoxicity (ADCC) assays in PBMCs were developed to assess the binding of anti-lymphocyte autoantibodies and their possible biological effects.

**Results:** Out of the 204 patients tested with LIPS, 36 had (17.6%) CD4 autoantibodies (aCD4-Ab) and no other immuno-reactive protein was detected. Patients with aCD4-Ab had significantly lower CD4 reconstitution at week 48 compared to those without median CD4 of 162 CD4/μl vs 199 CD4/μl in patients with aCD4-Ab group vs 199 CD4/μl in the group without (p=0.037). After excluding patients who received immunomodulant treatment that could have affected CD4 T cell reconstitution, patients with aCD4-Ab had lower CD4 reconstitution at all timepoints (weeks 48, 96 and 192) in the aCD4-Ab group vs 199 CD4/μl in the group without (p=0.057). The aCD4-Ab binding site was mapped to the D3-D4 domain of CD4 by mutation analysis. No evidence of IgG deposition or ADCC was identified in any of the tested subjects with aCD4-Ab.

**Conclusion:** aCD4-Ab are associated with discordant immunological response to ART in patients with advanced HIV/AIDS. In this cohort, aCD4-Ab effects on CD4 T cell homeostasis was not explained by ADCC suggesting other potential mechanisms that may adversely affect T cell homeostasis.

**252 SEX DIFFERENCES IN CMV REPLICATION AND HIV PERSISTENCE DURING SUPPRESSIVE ART**

Sara Gianella1, Sarah McDonald Tran1, Milenka Vargas1, Gemma Caballero2, Michelle Faria de Oliveira2, Steven Lada2, Mitchell Zhao2, Jyoti S. Mathad3, Timothy Wilkin2

**Background:** A discordant immunological response to ART with poor CD4 T cells reconstitution is associated with increased inflammation, morbidity and mortality. We hypothesized that anti-CD4 autoantibodies could limit CD4 T cell recovery despite suppressed HIV-1 replication.

**Methods:** 204 HIV+ART naive patients with CD4<100 at baseline were included in this prospective study and followed longitudinally for 192 weeks after ART initiation. Demographic, virologic and clinical data were analyzed. Luciferase ImmunoPrecipitation Systems (LIPS) was used for detection of autoantibodies against CD4, CD8α, CD8β, CD3, CD3ε, IFNGR1, CD127, CD25, CTLA4, CCR5, Ro52. IgG deposition and natural killer (NK) antibody-dependent cell mediated cytotoxicity (ADCC) assays in PBMCs were developed to assess the binding of anti-lymphocyte autoantibodies and their possible biological effects.

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**Conclusion:** aCD4-Ab are associated with discordant immunological response to ART in patients with advanced HIV/AIDS. In this cohort, aCD4-Ab effects on CD4 T cell homeostasis was not explained by ADCC suggesting other potential mechanisms that may adversely affect T cell homeostasis.
EBV and CMV levels in blood are associated with non-AIDS events during ART

Sara Gianella, Carlee Moser, Andrej Vitomirov, Ashley McKhann, Laura Layman, Brianna Scott, Steven Lada, Nell Lurain, Alan Landay, Michael M. Lederman, Peter W. Hunt, Davey M. Smith

Background: Even with effective viral control, HIV-infected individuals are at a higher risk for morbidities associated with older age than the general population. In HIV-infected people, subclinical CMV replication in blood might be associated with increased morbidity/mortality, driven in part by increased inflammation. We sought to identify associations between cytomegalovirus (CMV) and Epstein–Barr Virus (EBV) DNA in peripheral blood mononuclear cells (PBMC) with occurrence of non-AIDS events and mortality during ART.

Methods: Participants (140 cases, 305 controls, 929 samples) were selected from the ACTG ALLRT trial; all were HIV suppressed on ART at year 1 and thereafter. Blood was collected: pre-ART (baseline), 1-year post-ART, and immediately pre-event (for cases). Cases included myocardial infarction/stroke, malignancy, serious bacterial infection or death. Controls had an event-free follow-up equal or greater than the relevant case. Participants were matched on age (within 10 years), sex, pre-ART CD4+ count (within 50 cells/mm3), ART regimen, and parent study. At each time-point, levels of CMV and EBV DNA were measured in PBMC by ddPCR. Levels of CMV and EBV IgG were measured at year 1 in plasma by ELISA. Other cellular and soluble biomarkers were obtained from previous projects (see table).

Conditional logistic regression analysis assessed associations of the biomarkers with events, adjusted for relevant covariates. Correlation between biomarker levels were assessed with Spearman’s correlations among controls.

Results: Cellular CMV DNA was detected in 25% of all time-points, while EBV was detected in >90%. Higher levels of EBV were associated with an increased risk of events at all time points (OR per one IQR = 1.4-1.8, p ranging 0.03-0.17). CMV and EBV levels were correlated only at the pre-event time point (r=0.18, p<0.0001). Levels of EBV DNA were associated with EBV IgG (r=0.37, p<0.0001), while CMV DNA was not associated with CMV IgG. Levels of CMV were correlated with all soluble markers at baseline, while EBV DNA was correlated with some biomarkers at each time point (see table).

Conclusion: Subclinical replication of EBV and (to lesser extent) CMV in blood were associated with increased inflammation and were predictive of non-AIDS events and mortality in ART suppressed HIV-infection.

Table 1: Sex differences in Demographics, CMV and HIV Reservoir Data

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Women (N=260)</th>
<th>Men (N=450)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity, n (%)</td>
<td>Asian</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Black</td>
<td>57 (47%)</td>
</tr>
<tr>
<td>Age, pre-menopause</td>
<td>Pre-menopause</td>
<td>26 (4%)</td>
</tr>
<tr>
<td>Age, post-menopause</td>
<td>Post-menopause</td>
<td>26 (5%)</td>
</tr>
<tr>
<td>HIV transmission, n (%)</td>
<td>VU2</td>
<td>10 (0%)</td>
</tr>
<tr>
<td>HIV RNA copies/mL</td>
<td>0</td>
<td>9 (0%)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>8 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Median CD4+</td>
<td>720 (200-1900)</td>
<td>621 (190-7797)</td>
</tr>
<tr>
<td>Median HIV Reservoir DNA</td>
<td>37 (13-45)</td>
<td>38 (20-42)</td>
</tr>
</tbody>
</table>

Table 1: Spearman’s correlations comparing CMV and EBV DNA with inflammatory biomarkers at each time-point among the controls.

Legend: Cells in grey show p-values based on Spearman’s correlation, CMV, Cytomegalovirus DNA; EBV, Epstein–Barr Virus DNA; ART, Antiretroviral Therapy; Baseline, pre-ART; Year 1, immediately post-ART; Pre-Event, immediately pre-event (for cases).

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GAMMA DELTA T-CELL IR SIGNATURES REVEAL DEVIANCE OF HEALTHY AND AVIREMIC HIV+ AGING

Anna C. Beklina1, Alina Starchenko, Katherine Drake1, Elizabeth Proctor, Riley Pihl1, Alex J. Olson, Douglas Lauffenburger, Nina Lin1, Jennifer Snyder-Cappione1

Background: Even with effective viral control, HIV-infected individuals are at a higher risk for morbidities associated with older age than the general population. In HIV-infected people, subclinical CMV replication in blood might be associated with increased morbidity/mortality, driven in part by increased inflammation. We sought to identify associations between cytomegalovirus (CMV) and Epstein–Barr Virus (EBV) DNA in peripheral blood mononuclear cells (PBMC) with occurrence of non-AIDS events and mortality during ART.

Methods: Participants (140 cases, 305 controls, 929 samples) were selected from the ACTG ALLRT trial; all were HIV suppressed on ART at year 1 and thereafter. Blood was collected: pre-ART (baseline), 1-year post-ART, and immediately pre-event (for cases). Cases included myocardial infarction/stroke, malignancy, serious bacterial infection or death. Controls had an event-free follow-up equal or greater than the relevant case. Participants were matched on age (within 10 years), sex, pre-ART CD4+ count (within 50 cells/mm3), ART regimen, and parent study. At each time-point, levels of CMV and EBV DNA were measured in PBMC by ddPCR. Levels of CMV and EBV IgG were measured at year 1 in plasma by ELISA. Other cellular and soluble biomarkers were obtained from previous projects (see table).

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Results: Cellular CMV DNA was detected in 25% of all time-points, while EBV was detected in >90%. Higher levels of EBV were associated with an increased risk of events at all time points (OR per one IQR = 1.4-1.8, p ranging 0.03-0.17). CMV and EBV levels were correlated only at the pre-event time point (r=0.18, p<0.0001). Levels of EBV DNA were associated with EBV IgG (r=0.37, p<0.0001), while CMV DNA was not associated with CMV IgG. Levels of CMV were correlated with all soluble markers at baseline, while EBV DNA was correlated with some biomarkers at each time point (see table).

Conclusion: Subclinical replication of EBV and (to lesser extent) CMV in blood were associated with increased inflammation and were predictive of non-AIDS events and mortality in ART suppressed HIV-infection.

Table 1: Spearman’s correlations comparing CMV and EBV DNA with inflammatory biomarkers at each time-point among the controls.

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population, and these serious non-AIDS events (SNAEs) track with plasma inflammatory and coagulation markers. The cell subsets driving inflammation in aviremic HIV infection are not yet elucidated. Also, whether ART-suppressed HIV infection causes premature induction of the inflammatory events found in uninfected elderly or if a novel inflammatory network ensues when HIV and older age co-exist is unclear.

Methods: In this study we measured combinational expression of five inhibitory receptors (IRs) on seven immune cell subsets and 16 plasma markers from peripheral blood mononuclear cells (PBMC) and plasma samples, respectively, from a HIV and Aging cohort comprised of ART-suppressed HIV-infected and uninfected controls stratified by age (≥35 or ≥50 years old). For data analysis, multiple multivariate computational algorithms (cluster identification, characterization, and regression (CITRUS), partial least squares (PLSR), and partial least squares-discriminant analysis (PLS-DA)) were used to determine if immune parameter disparities can distinguish the subject groups and to investigate if there is a cross-impact of aviremic HIV and age on immune signatures.

Results: IR expression on gamma delta (γδ) T cells exclusively separated HIV+ subjects from controls in CITRUS analyses and secretion of inflammatory cytokines and cytotoxic mediators from γδ T cells tracked with TIGIT expression among HIV+ subjects. Also, plasma markers predicted the percentages of TIGIT+ γδ T cells in subjects with and without HIV in PLSR models, and a PLS-DA model of γδ T cell IR signatures and plasma markers significantly stratified all four of the subject groups (uninfected younger, uninfected older, HIV+ younger, and HIV+ older).

Conclusion: These data implicate γδ T cells as an inflammatory driver in ART-suppressed HIV infection and provide evidence of distinct ‘inflamm-aging’ processes with and without ART-suppressed HIV.

255 SENESCENCE & EXHAUSTION OF T-CELL MEMORY SUBSETS INCREASED IN AGING PERSONS WITH HIV


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Background: Changes in adaptive immunity including activation, senescence, and exhaustion have been observed in aging and in HIV infection and have been associated with aging-related co-morbidities. We designed a prospective cohort study to examine the HIV- and aging-related changes of T lymphocytes among aging persons living with HIV (PLWH).

Methods: We recruited adults aged 30-39 years and ≥50 years with and without HIV infection in Nashville, TN. PLWH must have had HIV-1 RNA <40 copies/mL ≥1 year. We collected demographic, social, health, and aging-related data on all persons. PMBCs were analyzed with flow cytometry to evaluate the frequency and phenotypes of CD4 and CD8 T cell memory populations (naïve [Tn], central memory [Tcm], effector memory [Tem], and effector memory RA+ [TemRA] cells) and expression of markers of activation (HLA-DR+CD38+), senescence (CD57+KLRG1+), and exhaustion (PD-1+). We used linear regression and Fisher exact tests to assess age- and HIV-infection related differences in T cell phenotypes.

Results: Our baseline data of 80 persons includes 17 adults without HIV (10 aged 30-39 years, 7 aged ≥50 years) and 63 PLWH (19 aged 30-39 years, 44 aged ≥50 years). In all, 23% were women and 34% were African American; 59% of HIV-negative and 95% of PLWH were serorepositive for CMV, and the median CD4 cell count of PLWH was 779 [interquartile range: 507-938]. In general, increasing age was associated with decreased CD4 and CD8 naive T cell populations in both HIV-negative persons and PLWH (PLWH CD4 Tn β=-0.58% per year of age, p=0.002; HIV-negative CD4 Tn β=-0.85%, p=0.007) and increasing proportions of CD8 Tem and TemRA in PLWH (β=0.19% [p=0.050] and 0.29% [p=0.055], respectively). T cell activation was generally very low and did not significantly differ by HIV status or age. Increasing age was associated with increased senescence in CD4 and CD8 memory subsets (Figure 1a) and with increased exhaustion in CD4 subpopulations (Figure 1b). Overall, aging-related changes were similar between HIV-negative persons and PLWH. T cell phenotypes were not statistically associated with frailty in HIV-negative persons or PLWH.

Conclusion: Among PLWH with virologic suppression, increasing age was associated with loss of naive T cells and increasing proportions of highly differentiated, exhausted and senescent memory T cells. Further research into the mechanisms and effects of aging-associated adaptive senescence and exhaustion in PLWH is needed.

256 CLONAL HEMATOPOIESIS AMONG OLDER TREATED HIV+ PERSONS ENROLLED IN COCOMO

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Background: Clonal hematopoiesis (CH) is the expansion of blood cell subpopulations containing somatic mutations. CH increases with age and has been associated with death, cancer and cardiovascular disease in the general population. Here, we set out to investigate CH prevalence and its association with inflammation, T cell subpopulations and coronary calcium among older treated HIV+ persons enrolled in the COCOMO cohort.

Methods: Targeted error-corrected sequencing of 21 CH-associated genes was performed in stored buffy coats of COCOMO participants older than 55y, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-17A, IFNα and TNFα levels were measured in plasma using a multiplex assay. Flow cytometry identified T cell subpopulations. Agatston score was used to quantify coronary artery calcification among those participants undergoing a cardiac CT. Cytokine levels, T cell subpopulations and Agatston score were compared between participants with and without CH.

Multivariate logistic/regression identified independent associations.

Results: Out of 190 participants (median [IQR] age: 66y [61-70], 87% male, mean CD4+ cell count 678, 99.5% virologically suppressed), 49 (25.8%) had at least one mutation. In line with reports from general population, the most frequent mutations (n/%) were: DNMT3A (25/13.2), TET2 (12/6.3) and ASXL1 (9/4.7). Of the 123 (~64%) participants with at least one mutation. In line with reports from general population, the most frequent mutations (n/%) were: DNMT3A (25/13.2), TET2 (12/6.3) and ASXL1 (9/4.7). Of the 123 (~64%) participants with at least one mutation, 15% had two or more mutations.

In uninfected elderly or if a novel inflammatory network ensues when HIV and age on immune signatures.

CH remained associated with lower IL-10 (adjusted β [95%CI]: -0.10 [-0.20, -0.01], p=0.03). Participants with and without CH had similar proportions of T cell subpopulations (p=0.10 for all subpopulations investigated). Participants with and without CH had similar median Agatston scores (111 [5-357] vs. 76 [0-297], p=0.68). When compared to participants with no mutations, those with TET2 tended to have higher Agatston scores: 232 [46-874], p=0.07, but after adjustment for age and sex, TET2 was no longer associated with coronary calcium: β=-0.04 [-0.19, 0.10], p=0.57.

Conclusion: CH is common among older treated HIV+ persons. Albeit limited by sample size, our analyses suggest that CH may be associated with dysregulated inflammation.
Background: It remains unclear whether increased immunosenescence observed in people living with HIV (PLWH) is driven by high rates of cytomegalovirus (CMV) co-infection or underlying immune dysfunction. We investigate relationships between immune function, CMV IgG positive status (CMV+) and immunosenescence in PLWH and HIV- control subjects.

Methods: Using cryopreserved PBMC from subjects in HIV UPBEAT, a cohort of PLWH and HIV- controls from similar demographic backgrounds, we measured CD4 and CD8 T-cell immunosenescence by flow cytometry, defined as CD4/CD8+25, CD28−CD57+ T-cells. We used linear regression to explore associations between immunosenescence, HIV status, demographics, CMV+, CMV IgG titres and CD4:CD8 ratio. Data are median (interquartile range) or model estimate (ME) [95% confidence interval (CI)] unless stated.

Results: Of 219 subjects, 107 (48.8%) were PLWH (68% male, 34% African, age 47 [39–53] years, 30% smokers) and 112 were HIV- (48% male, 17% African, age 50 [44–56] years, 15% smokers). PLWH had lower CD4:CD8 ratios (0.89 [0.65–1.19] vs 2.3 [1.63–3.18], P<0.001), higher % of senescent CD4+ and CD8+ T-cells (4.2 [1.4–7.6] vs 0.5 [0.1–2.1] and 24 [21.0–45.4] vs 22.6 [14.4–35.0] respectively, both P<0.001) and were more likely to be CMV+ (89% vs 2.3 [1.63–3.18], P<0.001), higher % of senescent CD4+ and CD8+ (0.89 [0.65–1.19] vs 2.3 [1.63–3.18], P<0.001) and were more likely to be CMV+ (89% vs 2.3 [1.63–3.18], P<0.001). In univariate analyses, HIV status, lower CD4:CD8 ratio and CMV+ were associated with higher CD4+ and CD8+ senescence. In analyses adjusted for age, gender, ethnicity and smoking, HIV infection remained significantly associated with higher CD4+ (ME [95% CI] 1.668 [1.168–2.168], P<0.001) and CD8+ (0.306 [0.115−0.497], P=0.002) T-cell senescence. Additional adjustment for CD4:CD8 ratio or CMV+ attenuated this association (table 1), with both lower CD4:CD8 ratio and CMV+ associated with increased CD4+ and CD8+ senescence. When both were included in the model, CD4:CD8 ratio and CMV+ remained independently associated with increased T-cell senescence. CD4+ was similarly associated with CD4+ and CD8+ senescence in PLWH and HIV- subjects (interaction p=0.27 for each) but associations with CD4:CD8 ratio were slightly weaker among PLWH (interaction p=0.002 and p=0.001, respectively). Replacing CMV+ with CMV IgG titres did not alter these findings.

Conclusion: Increased CD4+ and CD8+ senescence in PLWH can be attributed to both immune dysfunction, reflected in lower CD4:CD8 ratios, and CMV status. Future research should focus on immunosenescence and its impact on clinical outcomes in PLWH.
the increased morbidity and mortality of LRTI in HEU. To start addressing this question, we compared functional T cell responses, proportions of regulatory T cells (Treg), T cell differentiation and antigen presenting cell (APC) phenotypes in HEU and HU and assessed correlations between function and phenotypes. 

**Methods:** Peripheral blood mononuclear cells (PBMC) collected at 1-2 days of age from 59 HEU and cord blood PBMC from 17 HU were stimulated with Staphylococcal Enterotoxin B (SEB) or mock for 72h, and tested by flow cytometry for proliferation and expression of IFN-γ, IL4, IL10, TGFB, CD39 and CD107a. Treg, T cell differentiation and APC phenotypes were measured in unstimulated PBMC. Data were analyzed by univariate and multivariate linear regression adjusting for HIV exposure status. P-values were adjusted using false discovery rate.

**Results:** HEU had significantly lower IFN-γ, IL4, IL10, TGFB and CD39 CD4+ + T cell functional responses (SEB/mock) and similar CD8+ + T cell responses. Phenotypic characterization of unstimulated PBMC revealed higher CD4+ + CD8+FOXP3+, CD4+CD8+FOXP3+CD25+ + CD8+ + IL10+ + Treg and CD27- and/or CD28- differentiated conventional T cells and Treg in HEU vs HU. CD4+ + TGFB+ + CD6+ + IL10+ + CD27+ + CD28+ naïve Treg were lower in HEU vs HU. HEU also had higher proportions of CD16− intermediate monocytes; more CD16+ and CD16− conventional dendritic cells type 1 (cDC1); and higher expression of the CD103 inhibitory ligand on CD16− cDC1. Regression analyses adjusted for HIV exposure showed that higher CD6+ + IL10+ + and CD6+ + FOXP3+ + Treg in unstimulated PBMC were significantly associated with lower CD8+ + IFN-γ+, CD6+ + CD107a+, CD8+ + CD19+ and/or CD8+ + IL4+ responses to SEB stimulation. There were no associations between T cell function and proportions of Treg in stimulated PBMC or between T cell function and T cell differentiation or APC phenotypes in PBMC.

**Conclusion:** T cell responses to SEB were lower in HEU vs HU. Although HEU and HU had multiple T cell and APC phenotypic differences in SEB-stimulated and unstimulated PBMC, only high proportions of Treg in unstimulated PBMC were associated with decreased T cell function.

**260** RNAPOL III CONNECTS RIG-I AND CGAS HIV-SENSING PATHWAYS IN DC FROM ELITE CONTROLLERS

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**Background:** HIV-1 elite controllers (EC) represent a small proportion of HIV-1-infected individuals capable of naturally controlling HIV-1 replication in the absence of therapy, likely as a result of complex interactions between innate and HIV-1 specific immune responses. Recent data suggest that enhanced detection of cytosolic HIV-1 nucleic acids in conventional dendritic cells (cDC) from EC may depend on the activation of specific intracellular nucleic acid sensors and may trigger potent antiviral effector cell responses in these patients. Here, we investigated molecular mechanisms of effective detection of intracellular HIV-1 DNA in cDC from EC.

**Methods:** Maturation of circulating cDC from n=22 EC and n=9 HIV negative individuals in response to nanoparticles loaded with HIV-1 Gag dsDNA probes was tested by flow cytometry. Subsequently, RNAseq characterization of transcriptional patterns in cDC from n=8 EC with different levels of response to in vitro stimulation was performed. Subsequent RNAseq analysis was also included using cDC from a larger cohort of HIV-1 controllers (n=23) and Progressors (n=14) was performed. siRNA-mediated gene silencing and Small inhibitors were used to validate the potential candidates predicted by our transcriptional study. Finally, analysis of single nucleotide polymorphisms (SNP) of selected candidate molecules was performed using public GWAS data.

**Results:** Frequencies of activated cDCs responding to intracellular HIV-1 dsDNA were significantly higher in EC patients compared to healthy individuals (p<0.01), thanks to a subgroup of EC with markedly superior responses (good responders).

**Conclusion:** The proteomic profile associated with the loss of virological control was characterized by higher levels of inflammation, transendothelial migration and coagulation. These proteins, especially Galectin-3-binding protein, could be considered as potential biomarker for the prediction of virological progression as well as members of this mechanistic pathways can be considered good candidates for potential drug targets for achieving persistent control. This finding enhances the recent idea that suggests that HIV controllers is a heterogeneous group of subjects being persistent controllers a good model of functional cure.
262 ANTI-GP120 ANTIBODY TITRES CORRELATE WITH AB-DEPENDENT FUNCTIONS IN HIV CONTROLLERS

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Background: Post-antigen (Ag) recognition, the Fc portion of antibodies (Abs) activates the complement cascade and also binds to Fc receptors (FcRs) on innate immune cells such as monocytes, triggering phagocytosis and natural killer (NK) cells inducing target cell lysis. Elite controllers (EC) and viremic controllers (VC) are treatment-naıve HIV+ individuals who maintain viral loads (VL) < 50 copies/ml plasma (c/mlp) and < 3000 c/mlp, respectively. AB-dependent (AD) functions have been implicated in playing a role in HIV control. Thus, EC & VC would differ from HIV+ untreated responders (UTP, VL > 20000 c/mlp), antiretroviral therapy (ART) treated individuals (TP, VL < 50 c/mlp) in terms of anti-HIV envelope (gp120)-specific IgG functionality. Here, we compared Abs from plasma in these groups that mediate AD complement deposition (ADCD), AD cellular phagocytosis (ADCP) and AD cellular cytotoxicity (ADCC).

Methods: Total IgG and anti-gp120 IgG concentrations in plasma from 18 UTP, 24 TP, 36 EC and 16 VC were quantified by ELISA. ADCD and ADCP assays assessed the frequency of HIV-infected CEM.NKCI.CCR5 (iCEM) target cells (T) positive for the cell surface C3b complement component and annexin V (AnV), respectively. The ADCP assay measured the phagocytosis of gp120-coated fluorescent beads by THP-1 (E) monocyte-like cells. Activity was expressed as the area under the curve (AUC) of the ADCD and ADCP score (% fluorescent T/E mean fluorescence intensity (MFI) of T/E), respectively for 2 plasma IgG concentrations. The ADCD readout was expressed as the AUC of the frequency AnV+/ T+ for 2 plasma IgG concentrations. Pooled plasma from HIV+ and HIV- individuals were used as positive and negative controls, respectively.

Results: UTP, EC and VC had significantly higher concentrations of anti-gp120 specific Abs than TP (p < 0.0001, Kruskal-Wallis tests with Dunn’s post tests). No statistically significant differences were found between UTP, EC and VC groups for the 3 AD assays, but each was significantly higher than results for plasma from TP (p < 0.001 for all, Dunn’s). When ADCD, ADCPC and ADCP results were normalized to the concentration of each sample’s anti-gp120 Ab, between group differences disappeared.

Conclusion: High concentrations of anti-gp120 Abs resulted in higher AD functions in UTP, EC and VC compared to TP. Therefore, between group differences in these AD functions are attributed to the between-group differences anti-gp120 Ab concentrations rather than AD function potency.

263 RAPID DECLINE OF IMMUNE ACTIVATION WITH ART IN HIV CONTROLLERS WITH LOW CD4 COUNTS

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Background: The benefits of antiretroviral therapy (ART) for HIV controllers (HCs) remain unclear, but studies have shown that HCs with low CD4+ T cell counts have very high levels of immune activation. Immune activation is classically measured by the dual expression of HLA-DR and CD38 on T cells, but a subset of activated cells, HLA-DR+CD38-CD8+ T cells, are thought to play a role in elite control. Here, we measured HLA-DR and CD38 expression pre and post ART initiation in 3 HCs with low CD4 cell counts to assess the contribution of low level viremia to immune activation.

Methods: HLA-DR and CD38 expression on CD4+ and CD8+ T cells and NK cells was determined by flow cytometry in 2 VCs (VC19 and VC20) and a post treatment controller (PTC) with low CD4+ T cell counts. Results at baseline and after 2 weeks of ART were compared to historical controls: elite controllers (EC) n=8, chronic progressors (CP) n=11 and HIV negative subjects (HN) n=16. Pre and post therapy viral loads (VL) were measured and compared to changes in immune activation.

Results: All data is presented in the order of VC19, VC20 and PTC2, respectively. Despite low baseline VL (509, 395 and 1073 copies/ml), CD4+ T cell counts in all 3 HCs were low (254, 154, and 77 cells/µl). Two weeks of ART dropped VL in all 3 HCs to < 50 copies/ml. The median percentage of HLA-DR/CD38 co-expression on CD4+ T cells, CD8+ T cells and NK cells was < 5 in ES, CP and HN controls. It was however elevated in all 3 HCs (5, 37 and 12% of CD4+ T cells, 26, 47 and 11% of CD8+ T cells, and 17, 31% and 7% of NK cells). There was a marked decline (> 67% reduction) in the frequency of these activation markers on all 3 lineages after ART that was associated with the degree of decline in viremia. There was no significant decline in the percentage of HLA-DR+CD38-CD8+ T cells in the first two weeks of ART.

Conclusion: While a prior study showed no effect of ART on the frequency of HLA-DR+CD38+ T cells in HCs after 4 weeks of treatment, we show here that there is a substantial decline in these cells in HCs with low CD4+ T cells as early as 2 weeks after the initiation of ART. This is not associated with a decline in the percentage of HLA-DR+CD38-CD8+ T cells that are thought to contribute to the control of viral replication. Given the association of T cell activation with HIV associated morbidity, this study offers an immunologic rationale for initiating ART in HCs with low CD4+ T cell counts.

264 ELITE CONTROL OF HIV-1 INFECTION IS ASSOCIATED WITH REDUCED TRAILSHORT EXPRESSION

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Background: Decline of CD4 T-cells in untreated HIV-1 infection is mainly due to apoptosis. TNF-related apoptosis inducing ligand (TRAIL) contributes to this CD4 T-cell decline but does not kill all infected cells. A novel protein, TRAILshort, which is expressed by HIV infected and uninfected cells, prevents the pro-apoptotic TRAIL from killing TRAIL receptor expressing cells and may promote HIV persistence. We hypothesized that HIV-1 elite controllers express less TRAILshort compared to viremic persons, leading to increased killing of HIV-infected cells, higher CD4 counts and lower HIV-1 reservoir size.

Methods: Two independent cohorts were studied. Elite controllers (ECs) had undetectable HIV-1 RNA viral load for > 1 year in the absence of ART (N=40 and 19 in discovery and validation cohorts), Viremic persons (VPs) had HIV-1 RNA viral loads > 10,000 copies/ml off therapy (N=42 and 17). Expression of TRAILshort and full length TRAIL in PBMCs was assessed by RNAseq and flow cytometry. Plasma concentration of TRAILshort was assessed by antibody bead array and full length TRAIL by ELISA. Reservoir size was estimated by ddPCR for total HIV-1 DNA in PBMCs.

Results: ECs were significantly older (51 yrs vs. 41 yrs, P<0.001) and had higher baseline CD4 T cell counts (991 cells/mm3 vs. 479 cells/mm3, P<0.001) compared to VPs. ECs had significantly lower total HIV-1 DNA content in PBMCs than VPs (82 copies/106 cells vs. 1572 copies/106 cells, P<0.001). In the discovery cohort, ECs had lower TRAILshort (P=0.002) and full length TRAIL (P=0.001) gene expression in PBMCs compared to VPs. TRAILshort surface expression on CD4 and CD8 T cells and monocytes was lower in ECs relative to VPs but not statistically significant. In the validation cohort, TRAILshort (P=0.06) and full length TRAIL (P=0.004) gene expression was lower in PBMCs of ECs vs. VPs. ECs had statistically significant lower plasma TRAILshort concentration (normalized to CD4 count) than patients with chronic HIV
infection (P<0.001), primary HIV infection (P=0.002) and patients on long term ART (P=0.002).

Conclusion: ECs have lower TRAIL short expression, higher CD4 T cell counts and lower HIV-1 reservoir size than VPs. Reduced TRAIL short expression may facilitate TRAIL-mediated killing of HIV-1 infected cells by the innate and adaptive immune system in ECs. TRAIL short may be an attractive novel target for immunomodulatory therapy to enhance immunologic control of HIV-1 infection.

265 HIV-DNA CONTENT IN PTFH CELLS IS ASSOCIATED WITH RESIDUAL VIREMIA IN ELITE CONTROLLERS

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Background: Low levels of HIV plasma viremia below the limits of detection of commercial assays (residual viremia) has been demonstrated in patients with cART-induced control as well as in those with spontaneous control of HIV replication. The source of residual viremia is highly debated and its potential relationship with levels of cell-associated HIV DNA has not been clarified to date. Herein, we have analyzed the HIV-DNA content in different CD4+ T cell subsets and its potential association with residual viremia in elite controllers and in patients with cART-mediated suppression of HIV replication.

Methods: Chronically HIV-infected patients maintaining undetectable pVL were included. T with spontaneous viral control (EC) and 9 with cART-mediated HIV replication control (cART-treated). Cell-associated HIV-DNA content was measured by ddPCR in purified resting T memory (rTm) and peripheral T follicular helper (pTfh) cell subsets as important compartments of HIV reservoir. Residual HIV viremia was quantified using a PCR single-copy assay (SCA) with a sensitivity of 0.3 copies/ml. Differences between groups were tested by non-parametric tests and associations by Spearman’s rho coefficient.

Results: Lower levels of cell-associated HIV-DNA (median[IQR] Log copies/million cells) was found in EC compared to cART patients in rTm (2.5[1.9–2.9] vs. 3.1[2.8–3.2]; p=0.059) and in pTfh (1.9[1.9–2.5] vs. 2.9[2.6–3.0]; p=0.025). In 3 of 7 EC (43%) and in 5 of 9 cART patients (56%) HIV could not be detected (<0.3 copies/ml). No significant differences (p=0.468) were found in median values of HIV-RNA between EC (9.5[1.5–16.8]) and cART patients (11.3[10.8]) in the subgroup of patients having detectable residual viremia (>0.3 copies/ml). Interestingly, we found a significant and positive correlation between the HIV-DNA levels in pTfh cells and the residual viremia (rho coefficient=0.928, p=0.008) in EC, and this was not observed in cART patients.

Conclusion: Our results suggest that pTfh cells could be an important source of residual plasma viremia in EC patients. This could be the consequence of higher transcriptional activity of HIV in pTfh cells of EC compared to that in cART patients, what could explain the similar levels of residual viremia in both groups in spite of the lower HIV-DNA content in pTfh cells of EC compared to cART patients. Further studies are warranted to check if administration of cART to EC patients could help to reduce HIV-DNA in pTfh cell compartment and/or residual plasma viremia.

266 CXCR3+ FOLLICULAR HELPER TC ARE ASSOCIATED WITH HIV CONTROL DURING CHRONIC INFECTION

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Background: Follicular Helper CD4+ (TFh) are antigen experienced T cells found in secondary lymphoid organs such as lymph nodes (LN). Recently, different TFh subsets has been described during chronic SIV infection based on chemokine receptors expression including CXCR3-TFh, CCR4-TFh and CCR6-TFh. We characterized TFh subsets proportions and activation patterns during chronic HIV infection and its association with disease progression and viral control.

Methods: Cervical LN mononuclear cells (LNMC) from 22 chronic-untreated (CHR) and 7 treated-untreatable (ART) patients were characterized by flow cytometry including CXCR3hiPD-1hi (TFh), chemokine receptors (R5, R4, R6, X3) and activation markers (CD38, HLA-DR, CD69). LNMC and PBMC HIV CA-DNA were measured by qPCR. T cell counts were assessed by BD True count kit. pVL was determined by m2000 system. Analysis were performed on Cytobank and Prism using non-parametric tests.

Results: CHR patients had an average CD4+Tc count of 454 cells/ul. CD4+Tc represented 21.43% of LNMC. TFh were 3.11% of total LN CD4+Tc. Significant negative correlation was detected between TFh and CD4+Tc count (Spearman r=-0.56, P<0.006). We found low beta chemokine receptors expression on TFh (Tfh2=2.6%, Tfh17=0.7%). CCR5 expression on TFh was 5.2% on CHR and 11.6% on ART, p=0.005. Of note, CXCR3+ Tfh are a prevalent population on both CHR (45.8%) and TAR (44.1%). Interestingly, Tfh1% from CHR negatively correlates with pVL (r=-0.55, P=0.007), PB CA-DNA (r=-0.58, P=0.004) and LN CA-DNA (r=-0.47, P=0.02). TFh clustered as separated population on viSNE analysis.

Furthermore, TFh1 expressed significantly higher levels of CCR5, HLA-DR, CD38, CD69 when compared to CXCR3 negative Tfh (p<0.0001 in all markers). Finally, CCR5 expressing Tfh1 were significantly higher on treated participants (9.5% CHR vs 26% ART; p<0.0001).

Conclusion: Our study defined preferential chemokine receptors expression patterns on TFh during HIV infection including higher proportions of CXCR3+ Tfh1 cells. TFh1 levels were associated with lower pVL and CA-DNA on LN and PB. Likewise, Tfh1 were found to be highly activated. These results suggest that TFh1 have a role controlling HIV during chronic infection. Furthermore, we showed that Tfh1 express higher CCR5 levels compared to other TFh populations. CCR5 expressing TFh1 are increased in treated individuals suggesting preferential infection on this subset. Our results encourage further Tfh1 studies to detail their role on HIV control and persistence.

267 METABOLOMERIC PROFILE ASSOCIATED WITH LOSS OF SPONTANEOUS HIV-1 ELITE CONTROL

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Background: Although Elite Controllers (EC) spontaneously control HIV-1 replication without antiretroviral therapy, approximately 25% of them lose virological control over time. Recently, it has been demonstrated that immunovirological factors characterized the loss of spontaneous control. To date, no longitudinal study elucidating the metabolomic profile associated with the loss of spontaneous HIV-1 elite control has been performed. In this sense, the aim of this work was to perform a metabolomic approach to identify the underlying mechanistic pathways and potential predictive biomarkers associated with the virological loss of control.
Results: Plasma samples from EC who spontaneously lost virological control (Transient Controllers, TC, n=8), at two and one year before the loss of control, were compared with a control group of EC who persistently maintained virological control during the same follow-up period (Persistent Controllers, PC, n=8), up to two determinations were performed at one-year interval. The determination of metabolites and plasma lipids was performed by GC-qTOF and LC-qTOF using targeted and untargeted approaches. Metabolite levels were associated with the polifunctionality of HIV-specific CD8+ T-cell response. A multivariate analysis was performed in order to select and evaluate the performance of the potential biomarkers.

Results: We were able to identify and quantify a total of 70 metabolites and 334 lipids in plasma samples. Before the loss of control, TC showed a metabolomic profile characterized by alterations in glycolysis, Krebs cycle, branched amino acid catabolism and lipid metabolism. Besides, CD8+ T-cell polyfunctionality from PC and TC before the loss of control was strongly associated with these metabolites and lipid levels (p<0.05 and r2>±0.6). Finally, the amino acid valine showed the highest discriminatory power between TC and PC (100% of sensitivity and specificity).

Conclusion: Our study determined a specific metabolomic profile associated with the spontaneous loss of virological control in EC. This profile was characterized by higher immunological activation, oxidative stress and mitochondrial dysfunction. Metabolites and lipid plasma levels were strongly correlated with immunological parameters. These key metabolites, mainly the amino acid valine, could not only be used as biomarkers for a rapid screening of future loss of virological control but also can be suggested as therapeutic targets in EC.
IAS–USA        Topics in Antiviral Medicine

270 PRIMARY ROLE OF KSHV IN PATHOGENESIS OF ENDEMIC AND EPIDEMIC KAPOSI SARCOMA

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Background: Kaposi sarcoma (KS) is associated herpesvirus (KSHV) is etiologically linked to all KS forms but mechanisms underlying KS development are unclear. The high incidence of KS in HIV-1+ individuals, epidemic KS (EpKS), implicates immune dysregulation in co-infection; however, the lack of in-depth comparison with KSHV immune responses in African endemic KS (EnKS) and the continued incidence of KS despite ART-mediated immune reconstitution make the pathogenetic role of HIV-1 in KS unclear.

Methods: We have utilized cohorts of Zambian and Tanzanian KS patients to compare immune responses and expression patterns between EpKS and EnKS patients or asymptomatic controls. Antibody and cytokine responses were investigated in histologically and PCR confirmed EpKS and EnKS patients, versus asymptomatic controls with and without KSHV infection. KSHV-vDNA, total anti-KSHV antibody, KSHV-neutralizing antibody and cytokines were quantified. RNASeq and bioinformatics analyses were used to compare transcriptomes from biopsied KS and normal skin in both KS groups versus asymptomatic controls.

Results: KSHV was consistently detected in tumors but variably detected in plasma and PBMCs from EpKS and EnKS patients. Consistent with elevated antibody-associated cytokines (IL-6, IL-5 and IL-10), total anti-KSHV and neutralizing antibody titers were higher in EpKS and EnKS patients than in controls (P<0.05). Also, titers of anti-KSHV antibody correlated with neutralizing antibody titers in KS patients (r=0.7384, P=0.0001). Despite HIV-1 co-infection in EpKS, total and neutralizing antibody titers were similar between EpKS and EnKS patients (P=0.3067). Likewise, analyses of transcriptomes from KS tissues with and without HIV-1 co-infection revealed remarkable similarities in gene expression patterns and dysregulated pathways.

Conclusion: The detection of similar antibody and cytokine responses as well as transcriptomes in EpKS and EnKS patients suggest that KS results not due to co-infections like HIV-1, but rather primarily due to KSHV-induced pathogenesis, wherein HIV-1 co-infection accelerates and exacerbates disease progression.

271 METABOLIC ABNORMALITIES IN CDB T CELLS FROM HIV+ INDIVIDUALS WITH KAPOSI SARCOMA

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Background: A subset of HIV-infected individuals suffer from Kaposi Sarcoma (KS) despite viral suppression and CD4 recovery under anti-retroviral therapy (ART). CD8 T cells are important for control of KS, the etiologic agent of KS. Upon activation, CD8 T cells upregulate glycolysis, enabling rapid generation of ATP and biosynthetic precursors. However, CD8 T cells infiltrating the tumor microenvironment must operate under conditions of glucose restriction. We hypothesized that CD8 T cells from individuals with persistent KS under ART exhibit functional and metabolic abnormalities.

Methods: Specimens were obtained from HIV-infected participants on ART with biopsy-confirmed KS (HIV KS; obtained from the AIDS and Cancer Specimen Resource; n = 8) and HIV-infected participants on ART with no known history of KS (HIV controls; n = 8). CD8 T cell differentiation (CD45RO, T-bet, Eomesodermin), metabolic phenotype (glucose transporter Glut1, mitochondrial master regulator PGC-1α), and senescence (CD57) were assessed by flow cytometry. Proliferation in response to PHA was measured by CFSE dilution, and mitochondrial activity using MitoTracker™ Deep Red.

Results: Relative to HIV controls, memory (CD45RO+) CD8 T cells from HIV KS participants were skewed toward a more terminally differentiated phenotype, with a lower frequency of T-bet+ Eomes+ CD57+ cells (p = 0.01). HIV KS participants displayed an expanded population of CD8+ T cells (median 9.3% of CD8+ T cells vs 3.1% in controls; p = 0.001). This population exhibited reduced expression of Glut1 (p = 0.008) and PGC-1α (p = 0.04) and increased CD57 expression (p = 0.02) compared with CD8+ T cells, suggesting impaired capacity to utilize glycolysis and proliferate. CD8 T cell proliferation and mitochondrial activity were compared in 10 mM and 5 mM glucose. Proliferation and mitochondrial activity were lower in 5 mM glucose in 2/4 HIV KS patients tested (replication index in 10 mM vs 5 mM glucose 11 vs 6.5 and 19 vs 16, respectively), indicating reduced metabolic flexibility when glucose is limiting. CD8 T cell proliferation and mitochondrial polarization were correlated (r = 0.73; p = 0.02).

Conclusion: Our data suggest that metabolic and functional abnormalities in CD8 T cells may contribute to KS persistence in HIV-infected individuals receiving ART. Therapeutic strategies to normalize CD8 T cell metabolism represent a novel approach to the treatment of persistent KS under ART.

272 SINGLE CELL EVALUATION OF KAPOSI SARCOMA TUMORS REVEALS COMPLEX IMMUNE INFILTRATE

Warren Phipps1, David Coffey1, Yuexiun Xu2, James Kafeero2, Peter Mooka2, Lazarus Okoch2,1, Diana Basemera3, Britta Flach4, Andrea Towlrider4, Edus H. Warren1

1Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 2Uganda Cancer Institute, Kampala, Uganda

Background: Kaposi sarcoma (KS) is highly associated with immunosuppression, and evidence suggests that KS oncogenesis is associated with loss of T-cell mediated control of human herpesvirus-8 (HHV-8). KS is a complex tumor, characterized histologically by spindle-like tumor cells infected with HHV-8 and marked inflammatory infiltrate. Identifying the elements that comprise the KS tumor, the phenotypic and translational state of these cell types, and how these cellular components interact in vivo will advance our understanding of KS tumorigenesis and guide the development of new targeted therapies.

Methods: We evaluated KS tumor and normal skin samples obtained from treatment-naive HIV-positive and HIV-negative adults with KS enrolled in an ongoing study at the Uganda Cancer Institute in Kampala, Uganda. RNA was extracted from tissue that had been snap frozen or preserved in RNAlater, and sequencing was performed on Illumina HiSeq 2500. Leukocyte composition

97s
within each biopsy was estimated using CIBERSORT, an analytic platform used to characterize cellular gene expression profiles. Single-cell suspensions of a subset of KS tumors were sorted and evaluated using targeted multiplex RT-PCR with primers specific for 24 genes relevant to immune cell lineage, function, proliferation, and exhaustion.

Results: CIBERSORT analysis of 39 KS tumors revealed that CD4 and CD8 T cells, monocytes, and macrophages represent the majority of intratumoral hematopoietic cells. To date, 2 cryopreserved single-cell suspensions have been analyzed. Candidate KS tumor cells with a CD34+/VEGFR3+/LYVE-1+ surface phenotype comprised 1.54% and 0.35% of cells from HIV+KS and HIV-KS subjects, respectively. Flow cytometric sorting showed populations of immune cells, including CD4/CD8, monocytes, and macrophages. Targeted transcriptional profiling of the single CD8+ T cells revealed significant heterogeneity in the expression of various genes, but uniformly low expression of genes associated with proliferation and functional activation, such as Ki-67, granzyme B, and TNFα (Figure). Analysis of additional KS tumor single cell suspensions is ongoing.

Conclusion: Our findings to date indicate that the immune infiltrate in KS tumors is dominated by T-cells and macrophages. Initial analyses suggest that the transcriptional profile of immune cells in KS tumors is consistent with an “exhausted” profile, which may have implications for the use of anti-PD1 or other immunotherapies targeting T-cell exhaustion in the treatment of KS.

Results: KSHV typing was contributive in 34/57 patients (19 KS, 11 MCD and 4 PEL) and 5/8 PrEP users. All pathologies combined, subtype C was the most prevalent (18/34) followed by subtype A (11/34). Most of subtype C fell in genotype variant C3 (15/18). Among KS patients, variant C3 was more associated with cutaneous and/or oral mucosa lesions than other subtypes (Odd ratio = 11.7, 95% CI 1.1-214.2, p = 0.023) regardless of the immunovirological status (CD4 count cells p = 0.97; HIV VL p = 0.89) and KSHV-DNA viral load (VL) in subtype A tend to be higher than those of subtype C (p = 0.055). Among PrEP users, 2 fell in variant C3 and 2 others in variant A4. Viruses of 5 patients (2 visceral KS, 1 MCD, 1 PEL and 1 PrEP user) were identified as “subtype F”. However, phylogenetic analysis showed that theirs sequences differed from 11% at amino-acid level of subtype F already described in Uganda (AY953882) as well as epidemiological context ( MSM Caucasian versus African subtype). Moreover, ORF-K1 sequence was closed (GD = 10–6) to that of KSHV described in a French MSM HIV+ patient with PEL in 2000 (AF178810).

Conclusion: Our study showed that subtype C, and specifically variant C3, was the most prevalent in MSM living in France and tend to be associated with less severe epidemic KS clinical form. We also reported 5 “subtype F” isolated in MSM and associated with severe diseases. We suggest that, in view of phylogenetic and epidemiological finding, subtype F could be subdivided in 2 genotypes variants.
KS significantly decreased from 78.1 to 0.3 per 1,000 person-years. Among those who developed KS before ART, the median time from clinic entry to KS was 29 days (interquartile range [IQR]: 1–162) and the median time from KS to ART was 20 days [10–36]. Among those who developed KS after ART, the median time to KS was 4.6 years [2.3–8.3] from ART. Risk of KS was significantly increased in persons with low CD4 cell counts and among men who reported sex with men (MSM) for both pre- and post-ART cohorts (p trend <0.05, each). Among PLWH with KS, those with KS before ART initiation had decreased risk of mortality (Figure, logrank test p = 0.08). In analyses accounting for country, HIV sexual risk factor, age, CD4 cell count, viral load, and calendar year, KS diagnosis before ART was associated with a 38% decreased risk of mortality (adjusted hazard ratio [aHR] = 0.62 [95% confidence interval: 0.38–1.02]). Low CD4 cell count (p trend = 0.01) and heterosexual HIV risk among women (aHR = 2.62 [1.27–5.39] vs. MSM) were also associated with mortality risk after KS.

Conclusion: With increasing ART access, KS incidence in Latin America has decreased in PLWH. However, mortality risk was increased among patients who developed KS after ART initiation. Further research into the determinants of HIV and KS outcomes in Latin America is needed.

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**KAPOSI SARCOMA INCIDENCE BETWEEN 2010 AND 2015 IN THE FRENCH DAT’AIDS COHORT**

Isabelle Poizot-Martin,1 Alain Makinson,1 Camelia Protoopoulos,1 Antoine Chéret,1 Marc-Antoine Valantin,4 and Véronique Obry-Roguet 1

Background: Kaposi sarcoma (KS) is a common complication of HIV infection, more frequent in men who have sex with men (MSM) than in other HIV-infected populations. The goal of this study was to determine KS incidence in a large French multicenter cohort and to report differences in KS incidence between population groups.

Methods: We performed a retrospective study using longitudinal data from the DAT’AIDS cohort from January 2010 to December 2015. KS cases were identified using ICD-10 codes. For incidence assessment, prevalent KS cases (occurring within 30 days after cohort enrollment) were excluded. Demographic, immunologic, and therapeutic characteristics were collected at the time of KS diagnosis.

Results: Among the 44,642 HIV-infected people followed-up in the DAT’AIDS cohort from January 2010 to December 2015, 209 patients developed KS, of which 130 were incident KS cases. The KS incidence [95% CI] among 41,744 patients without history of cancer accounting for 167,848 person-years (PY) was 77.5 [65.2–92.0]/105 PY, 106.1 [88.8–126.8]/105 PY in males and 16.7 [8.7–32.1]/105 PY in females. At the time of KS diagnosis, 48 (23%) patients were receiving ART for less than 6 months (median CD4: 227 [79–290]), 55 (26%) for at least 6 months (median CD4: 252 [53–469]) and 105 (50%) were not receiving ART (median CD4: 112 [36–219]) of which 41 patients had a concomitant HIV diagnosis (median CD4: 41 [25–160]). Patients’ characteristics are presented in table according to both ART exposure for at least 6 months and HIV viral load (VL).

Conclusion: In a resource-rich setting with high ART coverage, KS incidence remained high in recent years. Though such rates usually reflected a late HIV diagnosis and/or care access, KS also occurred despite prolonged ART exposure and/or controlled of HIV viremia in a quarter of cases. Multiplying the opportunity of HIV screening among the key populations to avoid useless delays to care should result in substantial reduction of KS incidence. We need to better define factors associated of KS in patients under ART and controlled viremia.
significantly improving the predictive performance of anal cytology alone to AUC 0.805.

Conclusion: We found anal-associated bacteria indicative of higher risk of precancerous anal lesions, which combination was highly specific. The microbiota could be exploited as a complementary diagnostic tool for anal cytology to overcome the low specificity and high rate of false positive results of the current screening strategy for anal cancer screening.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC ROC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
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<td>Anal cytology</td>
<td>72 (59-85)</td>
<td>57 (46-68)</td>
<td>-</td>
<td>0.062</td>
</tr>
<tr>
<td>Bacterial burden</td>
<td>37 (23-53)</td>
<td>90 (84-96)</td>
<td>0.737</td>
<td>0.002</td>
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<tr>
<td>Bacterial burden*</td>
<td>63 (51-79)</td>
<td>83 (74-90)</td>
<td>0.805</td>
<td>0.0006</td>
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</tbody>
</table>

277 TRANSCRIPTOME ANALYSIS IN HPV+-/HIV+- TISSUE REVEALS MARKERS OF HPV-DEPENDENT DYSPLASIA

Eva Riveira-Muñoz1, Ivan Galvan-Fernemia2, Rafael de Gó3, Antoni Tarrats1, Marta Piñol4, Francesc García-Cuyp5, Jose A. Este6, Roger Badia7, Guiliem Serela8, Ester Balan9

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Background: HPV is accepted today as the necessary but not sufficient etiological agent for anal and cervical neoplasia and HPV appears to be a cofactor in the association between HIV and cervical neoplasia. The objective of our study is the identification of a distinct transcriptomic signature that may serve as predictive markers of dysplasia and/or malignancy in HPV+-/HPV patients.

Methods: The study includes a unique cohort of 25 HIV-1 infected individuals co-infected with HPV with a clinical follow-up for more than 20 years. Tissue samples from individuals with signs of a high degree of anal dysplasia were chirurgical collected, together with samples from normal tissue from the same individual as control. After RNA extraction and quality control, RNA library was constructed (Illumina TruSeq RNA stranded) and sequencing was performed (Novaseq, 30M reads/sample). Data analysis was performed as implemented in the computational workflow for the detection of differentially expressed genes and pathways from RNA-sequencing data. Read alignment and count quantification was conducted using the Rsubread package and the statistical analysis was performed using the edgeR package. The differential expression analysis uses the quasi-likelihood functionality of edgeR.

Results: Whole transcriptome sequencing was performed to examine differential gene expression profiles, and to perform gene annotation based on gene ontology pathway information. Analyses were successfully performed on all 25 paired-ends samples with overall read mapping ratio above 95%. Thirty genes showed significant changes between biopsies showing a high degree of dysplasia and apparently healthy control biopsies. Hierarachic clustering of data demonstrated a clear discrimination between healthy and dysplastic tissues, indicating a common pattern of gene expression changes between individuals. The identified differentially expressed genes include chemokines, potential restriction factors, a miRNA and genes associated to cell proliferation and cell transformation. After filtering the results based on functionality, we selected for further validation a group of 15 genes that fulfill the criteria for becoming a biomarker.

Conclusion: Our analysis allowed the identification of at least 15 potential predictive markers of anal dysplasia in co-infected HIV/HPV individuals. Characterization of the selected genes may result in the development of new therapeutic approaches to treat HIV/HPV induced malignancies.

278 HPV CLEARANCE AND REINFECTION IN 2 YEARS AFTER RANDOMIZATION TO CRYOTHERAPY OR LEEP

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Background: Women with HIV are at increased risk of high-risk human papillomavirus (hrHPV) infection. We compared hrHPV clearance and reinfection in HIV-infected women randomized to cryotherapy or loop electrosurgical excisional procedure (LEEP) for treatment of cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3).

Methods: From June 2011 to July 2014, HIV-infected women enrolled at the Coptic Hope Center in Nairobi, Kenya with CIN2/3 were randomized to receive cryotherapy or LEEP and followed for 2 years with a Pap smear and HPV cervical swab every 6 months. hrHPV was defined as a positive result at least one of 13 types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) identified by the Roche Linear Array Genotyping Test. Clearance was defined as testing negative for the same hrHPV type/s detected at baseline on ≥2 consecutive visits ≥6 months apart. Time to clearance or duration of hrHPV infection was defined as the time elapsed from intervention to the date of the first negative hrHPV test. Reinfection was defined as new hrHPV infection after clearance. Outcomes were compared between arms using Chi-square tests and log-binomial regression.

Results: Of 400 women randomized to cryotherapy or LEEP, 95% (189 per arm) had baseline hrHPV results. Median age was 37 years [interquartile range (IQR): 31-43], median CD4 count was 180 cells/μl (IQR: 211-525), and median plasma HIV RNA viral load was 1.5 log10/mL (IQR: 1.5-2.8). The majority (88%) of women were on antiretroviral treatment (ART) at baseline, of whom 40% were on ART for ≥2 years. Baseline hrHPV prevalence was 93% in the cryotherapy arm and 92% in the LEEP arm (P=0.83). Clearance of hrHPV was significantly higher in LEEP than cryotherapy both at 6 months following intervention (36% vs 24%; P=0.015) and over two-year follow up (50% vs 39%; P=0.040). Median time to clearance was 6 months in each arm (P=0.16). Those who underwent LEEP were 50% (95% confidence interval (CI), 1.1-2.1; P=0.017) more likely to clear hrHPV than those receiving cryotherapy. The difference in reinfection with hrHPV following clearance of hrHPV in women with LEEP vs cryotherapy was not statistically significant (Relative risk: 0.67, 95% CI, 0.4-0.7; P=0.089).

Conclusion: Clearance of hrHPV in HIV-infected women after cervical treatment was limited; 40% experienced hrHPV reinfection within 2 years. However, women receiving LEEP were more likely to clear hrHPV than those receiving cryotherapy adding a reason to consider expanding LEEP in resource-limited settings.

279 HPV DNA TESTS FOR CERVICAL CANCER SCREENING OF HIV-INFECTED WOMEN

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Background: HPV DNA testing has excellent sensitivity but poor specificity for cervical cancer screening among HIV-infected women. We evaluated whether the point-of-care test, Xpert™ HPV, could be adapted to improve performance characteristics for screening HIV-infected women.

Methods: A clinical study of 586 HIV-uninfected and 535 HIV-infected women, aged 30-65 years, was conducted in Cape Town, South Africa. All women had a cervical sample collected that was tested on-site with Xpert HPV which is a cartridge-based PCR assay that detects HPV DNA in 5 channels: HPV 16, HPV 18, 45, HPV 31,33,52,58, HPV 51,59, and HPV 39,56,66,68. For each channel a cycle threshold (CT) value is generated and values below pre-determined cut-off levels are defined as positive. All women underwent colposcopy with histological sampling. Cervical intraepithelial neoplasia grade 2,3 or cancer (CIN2+) was diagnosed based on consensus pathology review. Sensitivity, specificity, positive and negative predictive values were calculated based on logistic regression and receiver operating characteristic curves.

Results: Of almost half (49.2%) of HIV-infected women tested positive for HPV DNA whereas 16.2% of uninfected women did (p<0.001). The prevalence of histology-confirmed CIN2+ was higher in HIV-infected women (17.0%) than in uninfected women (5.3%) (p<0.001). Sensitivity of detecting CIN2+ at the manufacturer-defined CT cut-off was 93.6% in HIV-infected women with a specificity of 59.9%. If screen-positive was limited to the 3 channels detecting HPV 16, HPV 18,45 and HPV 31,33,35,52,58, sensitivity remained high (90.7%) and specificity improved (67.5%). Shifting the CT values from these 3 channels...
such that sensitivity was set at 85%, resulted in improvements in specificity (77.0%). If sensitivity was set at 80%, specificity improved further (83.2%). At these CT cut-offs, positive predictive value was 49.4% and the proportion screen-positive was 27.4%.

**Conclusion:** Adapting Xpert HPV by restricting the definition of screen-positive to a limited number of high risk HPV types and making CT cut-offs more stringent (i.e. requiring higher levels of HPV DNA) can greatly improve performance characteristics of HPV DNA testing for cervical cancer screening in HIV-positive women. Making these adaptations limits the number of HIV-infected women who require further follow-up or treatment for cancer precursor lesions.

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**IMMUNE GENE EXPRESSION IN ANAL DYSPLASTIC LESIONS BY HIV STATUS AND ABLATION OUTCOMES**

Nikhil Shamapant, Xuyin Liu, Michael Gaia, Russell McBride, Keith M. Sigel

**Background:** The incidence of anal squamous cell carcinoma (SCCA) is 50-fold higher in HIV-infected persons and is a leading cause of morbidity among HIV patients. Anal high-grade squamous intraepithelial lesions (HSIL) are the precursors to SCCA. There has been limited study on the interactions between HIV infection, the immune microenvironment of HSIL and their natural history. In this study we compared immune gene expression profiles in HSIL lesions by HIV status and identified genes associated with post-ablation recurrence.

**Methods:** From the Mount Sinai anal cancer screening program we identified 44 persons (24 HIV+ and 20 uninfected persons) with HSIL and 4 with benign anal mucosal tissue as controls. All HSIL lesions were treated with electrocautery ablation and reassessed within 12 months for recurrence or regression. A targeted gene expression assay (Nanostring) was performed on the initial lesions consisting of 730 genes (including both an immuno-oncology panel and HIV and HPV related genes). After normalization we identified differentially expressed genes by HIV status and HSIL treatment outcome. All significance tests (q-values) were corrected for multiple testing.

**Results:** There was no difference in age by HIV status or lesion outcomes after treatment (median age 46 years); the cohort was largely men who have sex with men (93%), HIV+ subjects were virally suppressed in 71% of the cases, with a median CD4 count of 749 per mm3. We identified a single gene (CCL27) that was expressed significantly more in HIV-infected than in uninfected patients (Fold change=38.6; q=1.1E-4). CCL27 is a cutaneous cytokine associated with the attraction of T-cells to squamous epithelium during inflammatory responses. In this study we compared immune gene expression profiles in HSIL lesions by HIV status and identified genes associated with post-ablation recurrence.

**Conclusion:** We found a significant overlap in the genes involved in host immune response, with only one gene with differential expression in HSIL lesions by HIV status. In contrast, 27 genes were associated with recurrent lesions. These findings may be useful for risk stratification of lesions. Further studies will expand on these findings by localizing the tissue compartments and cells expressing these gene products.
282 HPV GENOTYPING IN 1,088 ANAL HSIL CASES: EXPECTED AND UNEXPECTED RESULTS

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Background: High-grade squamous intraepithelial lesions (HSIL), the anal cancer precursors, are caused by high-risk human papillomavirus (hrHPV). HrHPV-negative HSILs occur occasionally in clinical practice and constitute an unexpected departure from that rule leading to diagnostic and therapeutic challenges. Using 1,088 simultaneously collected anal swab and histologic HSIL specimens, we aimed to determine the distribution of hrHPV types associated with anal HSIL and to further evaluate hrHPV-negative cases using tissue HPV genotyping.

Methods: Anal swab and high-resolution anoscopy-guided biopsy were performed contemporaneously. Anal swabs were used for cytological diagnosis as well as Cobas® HPV DNA testing for HPV16, 18, and 12 other hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Cobas®-negative HSIL biopsy specimens were tested for HPV DNA using real-time PCR.

Results: 1,088 anal swabs were collected from 742 patients (median age 46 years, range 20-76) with biopsy-proven HSIL. Most subjects were HIV-infected (94%), 91% were men who have sex with men and 9% women. Cytological diagnoses were unsatisfactory (5%), benign (12%), ASCUS (36%), LSIL (34%), ASC-H (5%), and HSIL (8%). Cobas® HPV cotesting revealed that 4% of swabs were negative for hrHPV, 35% positive for HPV16/18, and 41% positive for other hrHPV types. HPV16/18-positivity correlated with a higher degree of cytological abnormalities (p<0.001). Significantly more HPV16/18-positive subjects had hrHPV types. HPV16/18-positivity was associated with a greater number of concurrent HSILs presumably explaining the improved performance of anal cytology in these patients. HPV-negative HSILs were primarily caused by rare hrHPV types not included in routine screens; these outliers must be interpreted with caution.

Conclusion: The assessment of HPV types in hrHPV-negative cases may help to refine diagnostic strategies.

Table 1: Differentially expressed genes between cured versus recurrent lesions

<table>
<thead>
<tr>
<th>Gene</th>
<th>Fold Change</th>
<th>q Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
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<tr>
<td>ARG1</td>
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<tr>
<td>CAMP</td>
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<td>CD1B</td>
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<td>CD207</td>
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<td>PAS3D1</td>
<td>0.59</td>
<td>0.045</td>
</tr>
<tr>
<td>PLAGL1</td>
<td>0.47</td>
<td>0.0002</td>
</tr>
<tr>
<td>PRAME</td>
<td>36.91</td>
<td>0.012</td>
</tr>
<tr>
<td>PRKCE</td>
<td>0.58</td>
<td>0.019</td>
</tr>
<tr>
<td>TRAF3</td>
<td>3.79</td>
<td>0.001</td>
</tr>
<tr>
<td>ZNF205</td>
<td>1.22</td>
<td>0.011</td>
</tr>
</tbody>
</table>

283 PRIMARY HPV SCREENING IN WOMEN LIVING WITH HIV

Howard D. Strickler1, Nancy A. Hessol1, Isam-Eldin Eltoum3, Mark Einstein4, Philip E. Castle1, L. Stewart Massad5, Lisa Flowers1, Lisa Rahangdale1, Adora Adimora1, Igho Ofotokun6, Meghan Huchko1, Gypsyamber D’Souza1, Joel Palefsky1, Robert Burk5, for the WHIS HPV Screening Study
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Background: Primary HPV Screening (PHS) utilizes an oncogenic human papillomavirus (oncHPV) assay as the initial cervical cancer screening test (instead of a Pap test). Recent US guidelines support PHS in women in the general population (30-65 years of age), but suggest oncHPV- women should be retested in 5 years. For oncHPV+ women, reflex HPV genotyping is recommended and possibly an additional test (e.g., Pap test) in order to determine appropriate follow-up or triage to colposcopy. However, the current study, to our knowledge, the first to assess PHS in WLWH. Cervical cancer screening strategies for WLWH need improvement as these women have elevated risk of cervical cancer relative to the general population, but current strategies result in a high rate of colposcopy that does not reflect clinically relevant cervical disease.

Methods: The study enrolled 865 WLWH comprised of 323 new enrollees in the Women’s Interagency HIV Study (WIHS) and 542 WLWH enrolled through colposcopy clinics affiliated with WHHS. Newly enrolled WHHS women represented WLWH undergoing routine screening. Colposcopy patients represented WLWH who had a recent abnormal screening test (e.g., ASC-US+). WIHS participants underwent routine screening using liquid-based Pap tests (ThinPrep) and were tested for oncHPV by the FDA-approved Cobas test. WIHS enrollees with a positive oncHPV or ASC-US+ received colposcopy, as did 15% of women with negative oncHPV and Pap results. Like WIHS enrollees, the WLWH enrolled at colposcopy had oncHPV and Pap tests. All Pap/histology was represented WLWH who had a recent abnormal screening test (e.g., ASC-US+). WIHS participants underwent routine screening using liquid-based Pap tests (ThinPrep) and were tested for oncHPV by the FDA-approved Cobas test. WIHS enrollees with a positive oncHPV or ASC-US+ received colposcopy, as did 15% of women with negative oncHPV and Pap results. Like WIHS enrollees, the WLWH enrolled at colposcopy had oncHPV and Pap tests. All Pap/histology was centrally reviewed by two expert pathologists.

Results: Mean age was 47 years for both WIHS enrollees and colposcopy patients; most were Hispanic or non-Hispanic African American. Median (IQR) CD4 count was 560 (342-843) and 631 (362-849), respectively, with 97% and 83% reporting cART use. There was a total of 70 CIN2+ of which 23 (33%) were CIN3+ (precancer). The Table shows sensitivity, specificity, and positive predictive value (PPV) to detect CIN3+, as well as the % of WLWH who would be triaged to colposcopy following several strategies. Results for PHS, as estimated by oncHPV with reflex Pap, had the highest PPV and lowest colposcopy rate; Co-Testing had moderately higher sensitivity and colposcopy triage rates.

Conclusion: The results show that PHS with reflex Pap testing is a potentially useful cervical cancer screening strategy in WLWH, but may sacrifice a moderate level of sensitivity for a moderate reduction in the rate of triage to colposcopy.

Table 1. HPV genotypes detected by Cobas® HPV test using anal swabs (n=1,088)

<table>
<thead>
<tr>
<th>HPV Genotype</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Negative</td>
<td>43 (4%)</td>
</tr>
<tr>
<td>Positive</td>
<td>1,045 (96%)</td>
</tr>
<tr>
<td>16</td>
<td>46 (4%)</td>
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<tr>
<td>18</td>
<td>6 (0.6%)</td>
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<tr>
<td>16, 18</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>16, others</td>
<td>521 (30%)</td>
</tr>
<tr>
<td>18, others</td>
<td>112 (11%)</td>
</tr>
<tr>
<td>16, 18, others</td>
<td>317 (10%)</td>
</tr>
<tr>
<td>Others</td>
<td>451 (41%)</td>
</tr>
</tbody>
</table>

Note: The remaining 1% were positive for other HPV types.
284LB REDUCED COVERAGE OF HPV VACCINE TYPES IN CERVICAL PRECANCER IN HIV INFECTION

Christina Carlander1, Camilla Lagnheiden2, Carina Eklund3, Sara Nordqvist Kleveland4, Philippe Wagner5, Aylin Yilmaz6, Kristina Elfgren4, Anders Sönnerborg1, Pär Sparén1, Joakim Dillner1

1Karolinska Institute, Stockholm, Sweden, 2Uppsala University, Uppsala, Sweden, 3Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden, 4Karolinska University Hospital, Stockholm, Sweden

Background: Our aim was to study to which extent cervical precancer in women living with HIV (WLWH) is associated with HPV types targeted by vaccination. The Swedish National HIV registry (InfCareHIV) includes all WLWH in Sweden and the women in this cohort were found to have an increased risk of cervical precancer (Carlander et al. UC 2016) and an increased risk of treatment failure of cervical precancer (Carlander et al. AIDS 2018). We requested all tissue blocks from cervical precancer in this cohort and subjected them to HPV genotyping.

Methods: By linking InfCareHIV, the Swedish Population Registry and the Swedish National Cervical Screening Registry we identified all WLWH, mainly migrants (70%), living in Stockholm or Gothenburg sometime between 1983 and 2014, with high-grade cervical precancer (CIN2+). For each WLWH we randomly selected two HIV-negative control women (HNW), living in the same counties and also diagnosed with CIN2+, matched for country of birth. We retrieved and HPV genotyped the archived cervical tissue blocks. Type-specific HPV prevalence was compared using prevalence ratios (PR), calculated with Poisson regression analysis. All models were adjusted for age, grade of cervical lesion and region of birth.

Results: 108 WLWH and 183 HNW had valid HPV genotype results (100 [93%] WLWH and 164 [90%] HNW were HPVP-positive). WLWH were less likely to be infected with HPV16 (PR: 0.6, 95% CI: 0.4-0.9) than HNW. HPV35 (not included in the 9-valent HPV vaccine) was the second most common HPV type in WLWH and three times more common than in HNW (PR: 3.1, 95% CI: 1.3-7.4). WLWH were more likely to be infected with multiple HPVs (30 vs. 20%; PR: 1.5, 95% CI: 1.0-2.4). HPVs targeted by the 9-valent HPV vaccine were significantly less common in WLWH (57%) compared to HNW (80%) (PR = 0.7, 95% CI: 0.6-0.9).

Conclusion: This national population-based cohort study, controlled for country of birth of migrants, found that cervical precancer in WLWH contained HPVs targeted by vaccination to a lower extent than in HNW, implying that cervical screening remains highly important in WLWH, even if HPV vaccinated.

285 CD4/CD8 RATIO AS A PREDICTOR OF HIV-ASSOCIATED CANCERS IN CNICS

Chad J. Achenbach1, Brian Joyce2, Lifang Hou3, Elizabeth Hibler3, Jeffrey N. Martin4, W. C. Mathews5, Richard D. Moore6, Thibaut Davy-Mendez7, Benigno Rodriguez8, Kenneth H. Mayer9, Michael Saag10, Mari Kitahata11, for the CFAR Network of Integrated Clinical Systems (CNICS)

1Northwestern University, Chicago, IL USA, 2University of California San Francisco, San Francisco, CA USA, 3University of California San Diego, San Diego, CA USA, 4Johns Hopkins University, Baltimore, MD USA, 5University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 6Case Western Reserve University, Cleveland, OH, USA, 7Fenway Health, Boston, MA, USA, 8University of Alabama at Birmingham, Birmingham, AL, USA, 9University of Washington, Seattle, WA, USA

Background: CD4/CD8 ratio is available in routine HIV practice and has been associated with immunocompromise, aging and cancer. We aimed to evaluate associations between low CD4/CD8 ratio, prior to and on ART, and individual cancer types.

Methods: We studied persons with HIV (PWTH) in care 1996-2014 at 8 CNICS sites across the US, who initiated ART and had a pre-ART CD4/CD8 ratio value and at least 6 months of follow up. We assessed quartiles of the lowest CD4/CD8 ratio prior to and the highest CD4/CD8 ratio on ART as predictors of cancer overall and individual types from ART initiation to cancer event or last clinic visit using Cox regression models adjusted for age, sex, race, time on ART, HIV co-infection, tobacco and alcohol use.

Results: Among 10,817 PWTH with 63,514 person-years on ART, 80% were male, 51% non-white race, 61% MSM, 17% IDU and 21% had HIV co-infection. Prior to ART, median nadir CD4 count was 229 cells/µl (IQR 89, 361), max CD4 count was 980 cells/µl (IQR 680, 1380), lowest CD4/CD8 ratio < 0.29 (IQR 0.14, 0.47) and HIV RNA 4.9 log10 copies/mL (IQR 4.3, 5.4). On ART, 91% achieved HIV RNA suppression <200 copies/mL and median highest CD4/CD8 ratio achieved was 0.76 (IQR 0.47, 1.11). 529 PWTH developed invasive cancer: 93 NHL, 86 KS, 53 lung, 43 anal, 38 prostate, 33 Hodgkin lymphoma, 20 liver, 19 breast, 18 colorectal, 16 oropharynx, 11 melanoma and 99 others. After adjustment, pre-ART CD4/CD8 ratio <0.14 (lowest quartile) was significantly associated with greater risk of cancer overall (HR 1.8, 95%CI 1.4-2.3), anal cancer (HR 4.7, 95%CI 1.5-13.0) and NHL (HR 3.9, 95%CI 1.7-8.8) compared to ratio ≥0.47 (highest quartile). On ART, CD4/CD8 ratio <0.47 (lowest quartile) was also associated with KS, lung cancer and Hodgkin lymphoma compared to ratio ≥1.11 (highest quartile)(Table). We did not find statistically significant associations between CD4/CD8 ratio prior to or on ART and melanoma, colorectal, breast, kidney, prostate or liver cancer.

Conclusion: As has been observed with other age-related diseases, CD4/CD8 ratio is a potential biomarker routinely obtained in HIV care that could be used for prediction of certain cancers and risk stratification for HIV-associated cancer screening strategies.

286 CAUSES OF DEATH AFTER CANCER DIAGNOSIS AMONG PLHIV ON ART: COHORT COLLABORATION

Adam Trickey1, Michael John Gill2, Dominique Costagliola3, Sophie Grabar4, Amy C. Justice5, Suzanne Ingle6, Julia Del Amo7, Antonella D’Aminio Monforte8, Fabrice Bonnet9, Joerg Janne Vehreschildi10, Ferdinando Witi11, Katharina Grabmeier-Pfisterhammer12, Leah Shepherd13, Ramon Teira14, Jonathan Sterne15

1University of Bristol, Bristol, UK, 2University of Calgary, Calgary, AB, Canada, 3INSERM, Paris, France, 4Hôpital Universitaire, New Haven, CT, USA, 5Institute of Health Carlos III, Madrid, Spain, 6University of Milan, Milan, Italy, 7University of Bordeaux, Bordeaux, France, 8Cologne University Hospital, Cologne, Germany, 9Stichting HIV Monitoring, Amsterdam, Netherlands, 10Insbruck Medical University, Innsbruck, Austria, 11University College London, London, UK, 12Hospital Sierrallana, Torrelavega, Spain

Background: People living with HIV (PLHIV) are more likely to develop AIDS-defining malignancies (ADMs) and several non-ADMs (NADMs) than the general population. However, there is a lack of information on cause-specific mortality after diagnosis of cancer among PLHIV.

Methods: We investigated causes of death within 5 years of first cancer diagnosis in PLHIV enrolled in 10 European and North American HIV cohorts that are part of the Antiretroviral Cohort Collaboration (ART-CC). Eligible adults were aged ≥16 years, started ART between 1996-2015 and were subsequently

Table 1. Comparison of HPV genotypes detected in HIV-positive women diagnosed with CIN2+/CIN3+ confirmed by a high-risk HPV test

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>WLWH</th>
<th>HNW</th>
<th>Starnes ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>97</td>
<td>10</td>
<td>15</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td>31</td>
<td>109</td>
<td>109</td>
<td>0.9 (0.8-1.1)</td>
</tr>
<tr>
<td>33</td>
<td>94</td>
<td>94</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>45</td>
<td>10</td>
<td>10</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td>52</td>
<td>10</td>
<td>10</td>
<td>1.0 (0.9-1.2)</td>
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<tr>
<td>58</td>
<td>10</td>
<td>10</td>
<td>1.0 (0.9-1.2)</td>
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<tr>
<td>59</td>
<td>10</td>
<td>10</td>
<td>1.0 (0.9-1.2)</td>
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<tr>
<td>66</td>
<td>10</td>
<td>10</td>
<td>1.0 (0.9-1.2)</td>
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<tr>
<td>68</td>
<td>10</td>
<td>10</td>
<td>1.0 (0.9-1.2)</td>
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<tr>
<td>70</td>
<td>10</td>
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<td>73</td>
<td>10</td>
<td>10</td>
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<tr>
<td>74</td>
<td>10</td>
<td>10</td>
<td>1.0 (0.9-1.2)</td>
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<tr>
<td>81</td>
<td>10</td>
<td>10</td>
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</tr>
<tr>
<td>103</td>
<td>10</td>
<td>10</td>
<td>1.0 (0.9-1.2)</td>
</tr>
</tbody>
</table>

*All p-values < 0.05.**
diagnosed with cancer. We used CoDe classifications of cause of death https://chip.dk/Tools-Standards/CoDe/About. We calculated cause-specific mortality rates (MR) per 1000 years following diagnosis of specific cancers and compared all-cause MR between 2007-15 and 2016-2019, for ADMs and NADMs.

Results: After 4209 cancer diagnoses (ADM=2162, NADM=2047) among 8416 PLHIV, there were 4514 deaths within 5 years. Of 604 PLHIV who died after diagnosis of ADM, 292(48%) deaths were due to an ADM while 467/847 (55%) deaths after diagnosis of NADM were due to an NADM. MR were higher for diagnoses between 1996-2005 compared with 2006-15: ADMs 102 (95% CI 92-113) vs 88 (78-100) and NADMs 213 (191-239) vs 184 (169-200). The table shows mortality rates for the 7 most commonly diagnosed cancers: these were higher after diagnoses of NADMs than ADMs and were very high for lung, liver, non-Hodgkin’s lymphoma, and head and neck cancers. Patterns of cause-specific mortality suggest that cause of death was likely to have been from the diagnosed cancer for head and neck and lung cancer. A substantial proportion of deaths from liver cancer had been classified as due to viral hepatitis by our process for assigning CoDe cause of death classifications.

Conclusion: Among ART-treated PLHIV diagnosed with cancer, mortality rates and causes of death varied according to the type of cancer, with highest mortality for the NADMs liver cancer and lung cancer. Among those who died within 5 years of a diagnosis of lung cancer there was a high chance that death was from cancer and not from AIDS.

Table 1. Rates per 1000 years (95% CI) of all-cause and cause-specific mortality during the 5 years after specific cancer diagnoses

<table>
<thead>
<tr>
<th>Diagnosis (number of deaths)</th>
<th>All cancers</th>
<th>Lung cancer</th>
<th>Liver cancer</th>
<th>Head and neck cancers</th>
<th>Non-Hodgkin’s lymphoma</th>
<th>Breast cancer</th>
<th>Prostate cancer</th>
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</thead>
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<tr>
<td>Cause of death</td>
<td>(204)</td>
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</tbody>
</table>

287 AIDS PROGRESSION AND NON-AIDS DEATH IN PEOPLE WITH HIV FOLLOWING CANCER TREATMENT

Keri Calkins1, Geetanjali Chander1, Corinne Joshi2, Kala Visvanathan3, Anthony T. Fojo1, Catherine R. Lesko1, Richard D. Moore2, Bryan Lau3
1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 2Johns Hopkins University School of Medicine, Baltimore, MD, USA, 3Washington DC VA Medical Center, Washington, DC, USA, 4VA Greater Los Angeles Health Care System, Los Angeles, CA, USA, 5VA North Texas Health Care Center, Dallas, TX, USA, 6VA Connecticut Healthcare System, West Haven, CT, USA, 7Baylor College of Medicine, Houston, TX, USA, 8Massachusetts General Hospital, Boston, MA, USA, 9James J. Peters VA Medical Center, Bronx, NY, USA, 10University of Washington, Seattle, WA, USA

Background: Cancer is a leading cause of morbidity and mortality for people living with HIV (PWH). Mortality risk indices, like Veterans Aging Cohort Study (VACS) Index 2.0, that incorporate routine laboratory and diagnostic data may be useful for supporting clinical decision-making and assessment of prognosis. We evaluated VACS Index 2.0, a well-validated index among PWH, as a predictor of long-term survival for cancer patients, both with and without HIV infection. Methods: We linked VACS data to Veterans Affairs Cancer Registry data, identifying 7,087 patients (1,855 PWH and 5,232 uninfected) with primary prostate, lung, colorectal, liver cancer or lymphoma. For all subjects we collected demographic data, tumor staging and VACS index 2.0 values and calculated Charlson comorbidity index (CCI) scores at time of cancer diagnosis. We fit multivariable survival models for the cohort of all, and for individual, cancers with VACS Index 2.0 alone (adjusting for tumor stage and demographics) and then fit alternate models including tumor stage and CCI to determine the relative predictive value of these indices.

Results: Patients did not differ by HIV status at age (median 52 years), sex (>99% male). PWH had higher median VACS index score at cancer diagnosis (61 vs. 37; p<0.001). For the cohort combining all cancer types in PWH and uninfected, the VACS index predicted overall survival in adjusted models with significant hazard ratios (HRs) for mortality for each quartile (Figure 1; all p<0.001) of the index, whereas the CCI had more limited predictive value. Adjusted models including the VACS index also had the best discrimination (c=0.82 versus c=0.73 for CCI model) and in models including both risk scores the VACS index was a strong independent predictor (p<0.001) CCI was of borderline significance (p=0.05). In models stratified by tumor stage, VACS index discriminated risk of mortality more effectively for early stage (I-II) than advanced cancers; in stage IV cases it was not associated with survival (all p>0.2). For individual cancers, the VACS index also predicted survival for both PWH and uninfected persons.

Conclusion: The VACS index 2.0, a prognostic index accurately predicted cancer survival after accounting for cancer stage, outperforming a traditional comorbidity index for both PWH and uninfected Veterans with cancer.

Camelia Protopopescu1, Antoine Chéret2, Alain Makinson2, David Rey3, Claudine Duvivier1, Clotilde Allavena3, Pascal Fuglie4, Tristan Ferry5, Thomas Huleux6, Pierre Debélot7, André Cabié8, Isabelle Lamaury9, Patricia Carrieri1, Isabelle Poizot-Martin10, for the Dat’AIDS study group

WISERH, Marseille, France, Hôpital Bichat, Le Kremlin-Bicêtre, France, CHU de Montpellier, Montpellier, France, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, Hôpital Paris, Paris, France, CHU Hôtel-Dieu, Nantes, France, Nice University Hospital, Nice, France, Hospices Civils de Lyon, Lyon, France, Centre Hospitalier de Tourcoing, Tourcoing, France, CHU de la Guadeloupe, Pointe à Pitre, France, Assistance Publique–Hôpitaux Marseille, Marseille, France

Background: Although antiretroviral therapy has reduced the risk of developing AIDS-defining cancers, people living with HIV (PLWH) still have a high risk for some cancers, in particular virus-related. Given the increased life expectancy of PLWH, incidence of age and behavioral related cancers are expected to increase. However, data concerning recent incidence trends are scarce. We analyzed the data of a large French multicenter cohort to estimate incidences of AIDS defining cancers (ADC) and non-ADC (N-ADC) between 2010 and 2015.

Methods: We performed a retrospective study using longitudinal data from the DAT’AIDS cohort from 01/2010 to 12/2015. Cases were identified using ICD-10 codes. For incidence assessment, prevalent cases, occurring within 30 days after enrollment in the cohort, were excluded. If more than one cancer occurred in the same patient during the study period, only the first case was considered in the analysis. We performed a focus on some N-ADC (breast, colorectal, prostate, anal, liver, lung, Hodgkin lymphoma (HL), bladder, head and neck).

Results: Among the 44,642 HIV-infected people followed-up in the DAT’AIDS cohort during the study period (median age 43 (36–50) years, 69.7% male), 1440 cancer cases were diagnosed, including 538 ADC of which 345 were first cases (non-Hodgkin lymphoma: n=194, Kaposi sarcoma: n=135, and cervical cancer: n=16). Among the 1082 N-ADC, 989 were first cases (76 patients were diagnosed with two different N-ADC during the study period, 7 with 3 and one with 4). Prostate cancer (n=111) was the most frequent N-ADC followed by liver (n=96), lung (n=90) and HL (n=82). Of note, head and neck cancer (n=66) was more frequent than anal cancer (n=53). Breast, colorectal and bladder cancer accounted for 54, 38 and 23 cases, respectively. The cancer incidence [95% CI] among the 44,642 patients accounting for 180,216.4 person-years (PY) between 2010 and 2015 was 191.4 (172.3–212.7) per 105 PY for ADC and 548.8 [515.6–584.1] per 105 PY for N-ADC. Incidence rates by calendar year and sex are reported in the table.

Conclusion: The incidence of N-ADC remained relatively stable over the 2010–2015 period overall and for both sexes, whereas ADC incidence decreased. This study highlights the growing importance of prostate, and head and neck cancers.

290 CANCER INCIDENCE AMONG A COHORT OF PERSONS RECEIVING HIV CARE IN WASHINGTON, DC

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1Georgetown University, Washington, DC, USA, 2George Washington University, Washington, DC, USA, 3Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA

Background: The incidence of AIDS-related cancers (ADCs) has declined in this era of effective combination antiretroviral therapy with increases in certain non-AIDS-related cancers (NADCs). We examined the incidence of ADCs and specific NADCs as well as eligibility for age-related cancer screening among persons living with HIV (PLWH) in the District of Columbia (DC).

Methods: Participants actively enrolled in the DC Cohort, a longitudinal study of PLWH which enrolled patients starting in 2011, through 12/2017 were included. Cancer diagnoses were determined through ICD-9/10 coding, and incidence was calculated among patients at risk using total person-time at risk through the observation period. Eligibility for cancer screening was determined based on age, sex, smoking history, and co-morbidity data available through the cohort and IDSA, USPSTF, or AASLD guidelines.

Results: Among 7912 participants, 72.4% were male, 77.8% black, and median age was 50 (IQR 45–55) years. Sixty-five percent of participants had smoking history and 12.7% chronic Hepatitis C Virus (HCV). Median CD4+ count was 572 cells/μL (IQR 420–795) and 84.4% had HIV RNA <200 copies/mL at most recent testing. In this cohort, cancer screening eligibility based on recommended guidelines was as follows: colorectal 4010 (51%), anal 3301 (42%), breast 2144 (49.2%), and lung cancer 1250 (15.9%) with 264 (3.3%) eligible for hepatocellular carcinoma (HCC) screening. The incidence rate of ADCs was 12.1 (95% CI 10.7,13.8) and NADCs 1.6 (95% CI 0.6,4.6) per 1000 person-years. The most common incident ADCs were prostate 2.3 (95% CI 2.1,2.5), breast 2.6 (95% CI 1.7,3.5), lung 1.5 (95% CI 0.8,3.1), and colorectal 0.9 (95% CI 0.4,1.4) incident diagnoses/cases per 1000 person-years. The incidence of NADCs were: non-Hodgkin’s lymphoma (NHL) 0.9 (95% CI 0.3,2.5), cervical cancer 0.7 (95% CI 0.1,4.4), and Kaposi sarcoma (KS) 0.3 (95% CI 0.0,0.7) diagnoses/cases per 1000 person-years.

Conclusion: In this aging cohort of PLWH, there were more incident NADCs versus ADCs in contrast to older cohort studies where ADC predominated and reflective of newer data showing higher incident rates of NADCs. A large proportion of this cohort is eligible for age-related cancer screening for NADCs.

291 HIGH CD20 LEVELS IN LUNG CANCER TISSUE FROM PLWH ASSOCIATED WITH IMPROVED SURVIVAL

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**Background:** Non-small cell lung cancer (NSCLC) is the most common non-AIDS defining cancer among people living with HIV (PLWH) and is associated with increased mortality. This study used quantitative immunofluorescence (QIF) to evaluate differences in the NSCLC tumor microenvironment between HIV+ and HIV- patients.

**Methods:** Paraffin-embedded tumor tissue from patients with NSCLC at Yale New Haven Hospital between 2001-2016 were reviewed. 18 HIV+ cases and 19 HIV- controls (matched for age, sex, histologic subtype, cancer stage, and year of cancer diagnosis). Clinical grade chromogenic assay was used to calculate whether the tumor expressed PDL1 (> 5% cut-off for positivity). In addition, QIF was used to measure expression of PD1, CD4, CD8, and CD20 both within the tumor and surrounding stroma. Early stage cancer was defined as Stages I-II while late stage was defined as Stages III-IV. t-tests and chi-square tests were used to compare continuous and categorical variables, respectively.

**Results:** Median age was 53 and 59 among HIV+ and HIV- patients. Median CD4 count and viral load among HIV+ were 440 cells/μL and 2,051 copies/ml, respectively, with 77% of patients on ART at time of NSCLC diagnosis. No difference in mortality was observed in early stage NSCLC between HIV+ and HIV- groups (HR 1.59 [95% CI 0.58-4.16]). However, among late stage NSCLC, HIV+ patients had higher mortality rate (HR 5.92 [95% CI 1.87-16.46]). Tumor cells from 44% of HIV+ compared to 21% of HIV- patients were positive for PD-L1 by chromogenic assay (p = 0.14). QIF analysis revealed no statistical differences in CD4 or CD8 infiltrate between HIV+ and HIV- tissues. Cox regression analysis found higher intra-tumor CD20 expression was associated with improved survival [HR 0.775 (95% CI 0.614-0.978)]. This effect was greater in HIV- (HR 0.603) compared with HIV+ cases (HR 0.894), though this difference did not reach statistical significance (p = 0.18).

**Conclusion:** After controlling for age, date of diagnosis, and stage in a well-matched cohort of NSCLC, we found that PLWH have a worse prognosis with late stage NSCLC. Tumors from HIV+ patients are more likely to express PD-L1 compared to HIV- cases (HR 0.894). High CD20 signal was associated with improved survival in NSCLC and HIV status may be a moderator of this interaction. Further characterization of specific T cell inhibitory and regulatory pathways within the tumor immune microenvironment is critical to understand how immune dysfunction in HIV impacts outcomes of disease.

**293 LONG BOOST INTERVALS OF ALVAC-HIV/AIDSVAX B/E INCREASED GENITAL HIV ENV IGG RESPONSES**

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**Background:** Anogenital mucosae are the primary sites of HIV acquisition. Boost with AIDSVAX B/E, with or without ALVAC-HIV, after receiving the RV144 vaccine regimen in the RV305 and RV306 trials induced HIV Env-specific IgG in cervico-vaginal mucus (CVM) and seminal plasma (SP). Here, we evaluated the effect of boosting intervals to magnitude and persistence of antibody responses in CVM and SP.

**Methods:** IgG and IgA to gp120 and gp70V1V2 scaffold proteins two weeks post vaccination in CVM and SP were quantified by ELISA. The effect of boosting interval was assessed by comparing peak responses after receiving the RV144 vaccine series with peak responses following a late vaccine boost of AIDSVAX B/E, with or without ALVAC-HIV, at varying boosting intervals.

**Results:** IgG to gp124 and gp70V1V2 scaffold proteins in CVM significantly increased with late ALVAC-HIV/AIDSVAX B/E boost at 15 months and 18 months compared to peak responses post received RV144 series (A2244G0 / gp70V1V2 titer range = 800-1600/38-300), p<0.03. IgG to gp70V1V2 CaseA2 in CVM increased after the additional boost of AIDSVAX B/E in participants who received boost of ALVAC-HIV/AIDSVAX B/E or AIDSVAX B/E alone 3-4 years earlier (titer=50), p<0.05. In SP, boosting with ALVAC-HIV/AIDSVAX B/E at 18 months led to significantly higher IgG to gp120 A244G0 (titer=100) and gp70V1V2 92TH023 (titer=25) compared to peak responses post RV144 series, p<0.05. Boosting with AIDSVAX B/E at 9-12 years significantly increased IgG to gp120 MN0G0 in SP (titer=150) compared to peak responses post received RV144 series (titer=50), p=0.02. Fold decrease of IgG to all proteins tested over 24 weeks post final vaccination in CVM was not significantly different among boosting groups. In SP, fold decrease of IgG to 92TH023 over 24 weeks post late AIDSVAX B/E boost in participants who received boost of ALVAC-HIV/AIDSVAX B/E or AIDSVAX B/E alone 3-4 years earlier was significantly lower than those who received late boost of ALVAC-HIV/AIDSVAX B/E at 18 months (p<0.03). HIV Env-specific IgA was not detected in any samples tested by ELISA.

**Conclusion:** Late boosts with AIDSVAX B/E, with or without ALVAC-HIV, produced higher peak HIV Env-specific IgG in CVM and SP at longer boosting intervals. Additional boosting with AIDSVAX B/E improved persistence of IgG to gp70V1V2 92TH023 in SP (measured by fold decrease over 24 weeks).
Optimization of functional antibody responses hypothesized to correlate with protection in mucosal compartments may increase vaccine efficacy.

### 294 A VACCINE TARGETING HIV MATURATION PROTECTS AGAINST VAGINAL SIVMAC251 ACQUISITION

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**Background:** After over three decades of research, an effective vaccine against HIV–1 remains elusive. Great genetic diversity, rapid mutation and targeting CD4+ T cells are major challenges for developing an effective HIV vaccine. Studies have shown that immunization activates CD4+ T cells and enhances susceptibility to HIV–1. Current candidate HIV vaccines focus on generating strong, broad and durable immune responses to deal with genetic diversity and rapid mutation of HIV-1. None of them have addressed the challenges to develop a vaccine for a virus targeting the immune system itself. Learning from natural immunity observed from a group of HIV resistant Kenyan sex workers we developed a novel HIV vaccine approach, targeting the sequences surrounding the 12 protease cleavage sites (PCS vaccine). In this study we evaluated the efficacy of protection of this novel vaccine using a Macaque/SIV model.

**Methods:** Thirty-two Freeman Mauritian Cynomolgus macaques were immunized with VSV vector, PCS vaccine (VSVp2cs and NANOpc5), Gag/Env vaccine (VSVGag/env and NAMPgag/env), or NANOpc5 vaccine (3 PCS peptides). Mucosal and systemic antibodies, as well as C1L inflammatory cytokines were analyzed with an in-house developed multiplexed Bead array assay using Bioplex200, and Western blot, T cell responses were analyzed using INF-gamma ELISPOT assay and FACs analysis. After immunization and boosts the vaccinated macaques and controls were challenged intravaginally with SIVmac251. 250 TCD50 every two weeks until majority of controls were infected. Kaplan-Meier survival analysis Cox regression model were used to compare vaccine efficacy.

**Results:** Both PCS vaccine and Gag/Env vaccine significantly protected macaques from pathogenic SIVmac251 infection (p=0.04) after 6 intravaginal challenges. Per-exposure risk reduction was >80%. The magnitude of mucosal neutralizing antibody level and the magnitude of antigen specific INF-gamma ELISPOT response after the last boost do not correlate with protection. The higher magnitude of mucosal MIP-1B/CCL4 (after the last boost) is correlated with an increased risk of SIVmac251 infection.

**Conclusion:** Our study showed for the first time that a candidate HIV vaccine targeting sequences surrounding the 12 protease cleavage sites, other than full Gag and Env can provide significant protection against pathogenic SIVmac251 intravaginal challenges. Generating immune response while modulating mucosal inflammatory environment may be the key for an effective prophylactic HIV vaccine.

### Hazard Ratio of SIV Mac251 Infection

<table>
<thead>
<tr>
<th>Groups</th>
<th>Hazard Ratio (95% CI)</th>
<th>Per-exposure risk reduction</th>
<th>P-Value 1</th>
<th>P-Value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS Vaccine</td>
<td>0.105 (0.032–0.382)</td>
<td>0.095%</td>
<td>0.030*</td>
<td>0.022*</td>
</tr>
<tr>
<td>Gag/Env Vaccine</td>
<td>0.100 (0.080–0.971)</td>
<td>0.90%</td>
<td>0.046*</td>
<td>0.024*</td>
</tr>
<tr>
<td>Control</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

1 Wald test of Cox model regression coefficients. 2 Log-rank test.

### 295 SIV- AND HIV-SPECIFIC IMMUNE RESPONSES ELICITED BY PIVS PRIME/VLP BOOST VACCINATION

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**Background:** An ideal preventive HIV vaccine may be expected to generate immune protection at mucosal ports of entry and systemically. Parainfluenza virus type 5 (PIVS) is a paramyxovirus that is non-pathogenic in humans and readily generates mucosal and systemic immune responses in animal models. We developed a series of PIVS vectors expressing SIVgag and HIV gp140 and administered them intranasally to rhesus macaques, in order to evaluate the potential of this mucosal vaccine vector as an HIV vaccine.

**Methods:** HIV–1 JR-FL Env and SIVmac239 Gag were inserted individually into the PIVS genome, and replication and expression of gene products validated in cell lines. Virus-like particles (VLPs) consisting of SIVmac239 Gag core and HIV–1 JR-FL Env were produced in stable, inducible manner from mammalian cells and purified. Macaques received four doses of PIVS-SIVgag + PIVS–HIV–1 gp140 by intranasal administration, followed by boosting with SHIV virus-like particles (VLPs). Humoral and cellular immune responses to SIV and HIV antigens and to the PIVS vector were measured over time.

**Results:** Monkeys immunized with PIVS constructs developed HIVEnv and SIV Gag-specific binding Ab titers in a dose-dependent manner. VLP boosting further enhanced SIV/HIV-specific responses, including when the VLP boost followed priming with the lowest intranasal dose of PIVS. Gp120 binding titers correlated to the magnitude of antigen specific plasmablasts measured in blood on days 5 post boost, except for a peak plasmablast response after the initial VLP boost. Presensitization with a heterologous PIVS vector decreased the frequencies of gp120-specific plasmablasts detected following PIVS-delivered immunizations. CD4+ and CD6+ T cell responses were elicited by PIVS vectors and boosted following VLP administration. HIV and SIV–specific IgG and weak IgA responses were detected at mucosal sites. Neutralizing antibodies and ADCC responses remain under evaluation at the time of submission of this abstract.

**Conclusion:** We demonstrate here for the first time that intranasal administration of PIVS-SIV/HIV vectors are well-tolerated and immunogenic. VLP boosting enhanced HIV–1 and SIV–specific humoral and cellular immune responses. This prime-boost approach may provide a novel approach to the development of systemic and mucosal protective responses against HIV.

### 296 NOVEL ANTIGEN ELICITS BROADLY NEUTRALIZING ANTI-HIV MONOCLONAL ANTIBODIES IN MICE

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**Background:** Although broadly neutralizing HIV antibodies are detected in infected (and sometimes uninfected) humans, immunization with HIV–1 antigens generally do not elicit broadly neutralizing antibodies. Clinical studies found that GBV-C E2 antibody is associated with improved survival in HIV and GBV–C co-infected individuals, and E2 antibody neutralizes HIV–1 infectivity by reducing virus entry in vitro. To determine if GBV-C E2 elicits broadly neutralizing HIV monoclonal antibodies (MAbs), we immunized mice with either E2 (lacking C-terminal transmembrane domain) or a synthetic peptide we previously demonstrated is involved in HIV entry and generated anti-E2 MAbs against both antigens. Here, we examined the interactions of both MAbs for their ability to inhibit HIV–1 infectivity, precipitate HIV–1 particles, and bind HIV–1-specific structural protein antigens.

**Methods:** GBV-C E2 protein was expressed in CHO cells, and a synthetic peptide generated of the 17 amino acid E2 region involved in HIV entry. Mice were immunized with 25 ug E2 protein or peptide in IFA four times prior to sacrifice, and hybridomas generated. One anti-E2 and one anti-peptide hybridoma cell line (8H2 and tC4 respectively) were identified from more than 2,000 independent cultures using a capture E2 ELISA. HIV–1 envelope proteins (gp120, gp140 and gp41), gp41 peptides (Miper and T-20), and X4- and R5-tropic HIV–1 isolates representing clades A, B, and D were studied.

**Results:** Both GBV-C E2 antibodies precipitated HIV–1 particles and neutralized X4 and R5-tropic HIV isolates from diverse geographic regions representing three clades (IC50 ranging from 2.5 to 7.5 ug/mL). These antibodies did not neutralize mumps or yellow fever viruses, demonstrating specificity. 8H2 reacted with HIV–1 gp140 and gp41 proteins, but not gp120 using two types of ELISA methods. Both 8H2 and tC4 recognized the HIV–1 gp41 fusion (Miper) peptide in immunoblot assays.

**Conclusion:** Although HIV–1 antigens do not elicit broadly neutralizing HIV–1 antibodies, GBV-C E2 and an E2 peptide elicited HIV–1 neutralizing MAbs in mice. Since GBV-C E2 antibodies are associated with prolonged survival in three clinical studies, these data illustrate the potential for a novel antigen to incorporate into HIV–1 vaccine strategies.
297LB TRANSCRIPTOMIC HOST RESPONSES TO RHCMV/SIV VACCINATION IN RHESUS MACAQUES
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Background: The rhesus cytomegalovirus (RHCMV) strain 68-1 vaccine against simian immunodeficiency virus (SIV) induces a T cell response that protects over 50% of vaccinated rhesus macaques (RM) to clear infection against multiple SIV challenges including distinct challenge routes. To define the molecular features of the host response to vaccination and the underlying gene signature of vaccine protection we assessed the transcriptional responses of protected and non-protected RMs following vaccination prior to challenge.

Methods: Two groups of 15 RMs were administered 68-1 RHCMV/SIV vaccine via oral or subcutaneous delivery. Following vaccination, RMs were subjected to repeated limiting dose intrarectal SIVmac239 challenge until infected as detected as plasma virus or the de novo development of SIV VIF-specific T cell response. During the vaccination phase, blood samples were collected at time points near prime, boost, and before challenge. mRNA-seq was performed followed by bioinformatics analysis including differential gene expression, co-expression clustering, and functional enrichment analyses.

Results: In the subcutaneous and orally-vaccinated groups, 53% and 60% of RMs cleared SIV infection after virus challenge, respectively. Protected RMs showed both an acute and sustained increase in gene expression indicative of myeloid cell responses, including genes and gene networks involved in Toll-like receptor signaling, inflammasome induction, and monocyte activation. We identified a noncanonical T cell signaling signature in protected animals that was characterized by a decrease in of Zap70 and Tbx21 with concomitant increase in Idol expression. Importantly, we identified an interleukin (IL)-15/STAT5 signaling module that links with immune cell trafficking and protection from SIV infection. A rule-based machine learning analysis confirmed that gene expression signatures controlling TLR activation of macrophages and myeloid cell activation, could predict vaccine protection. Assessment of an independent cohort of naive RM treated with IL-15 revealed gene networks of the IL-15 response. Integration analyses were conducted to identify a subset of IL-15 response genes in vaccinated animals whose induced expression tracks with vaccine protection. This gene expression signature was maintained post-virus challenge.

Conclusion: Our results define noncanonical T cell activation, inflammatory signaling, myeloid cell activation, and IL-15 response as features of RHCMV-SIV vaccine protection.

299 IMPROVED CD4 T CELLS RESPONSES WITH EARLY TREATMENT DURING PRIMARY HIV INFECTION
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Background: Treatment as soon as possible, limiting viral replication, has been shown to reduce the expansion of the HIV reservoir (Laanani et al., CID, 2015). We investigated the impact of early control of HIV replication on CD4 and CD8 T cell functions. We studied the kinetics of CD4 and CD8 T cell responses during PHI and investigated the relationship between the control of viral load (VL) after 3 months of treatment (M03) and the quality of CD4 and CD8 T cell responses at month 24 of treatment (M24).

Methods: In 50 subjects included in the ARNS-147 OPTIPRIM study, cytokine production (IL-2, MIP-1β and IFN-γ) was measured on peripheral blood mononuclear cells by flow cytometry after a 1-hour stimulation with relevant optimal peptide pools according to the subjects’ HLA-A and B alleles or p24 for CD8 and CD4 T cells, respectively at inclusion and at M24. In parallel, the capacity of CD8 T cells to suppress p24 production by autologous CD4 T cells in coculture was measured and expressed as Log10 of p24 decrease. Cytokine production at inclusion was explored according to the time after the estimated date of contamination by the Loess curve.

Results: Analysis of cytokine production kinetics during PHI highlights the existence of a peak of CD4 T cells responses around 30 days after the estimated date of contamination. CD8+ T cell-mediated HIV suppression which was weak during PHI (median 0.092 Log10 of p24 decrease, IQR [0.019-0.305]) did not improve after 24 months of treatment (0.144 Log10 of p24 decrease, IQR [0.019-0.305]) (p=0.62). At M24, the proportion of CD4 T cells producing at least one cytokine in response to p24 stimulation tended to be higher in subjects with undetectable viral load at M03 compared with subjects that still had a detectable plasma viral load at M03 (threshold = 50 HIV-RNA copies/mL) (0.068% [0.035-0.340] vs 0.028% [0.008-0.044%] of CD4 T cells, respectively; p=0.06). IFN-γ production contributed greatly to the difference, with 0.016% [0.008-0.096] of IFN-γ producing CD4 T cells in subjects with undetectable VL at M03 vs 0.003% [0.002-0.007] in subjects with detectable VL at M03, p<0.0001.

Conclusion: Achieving a control of viral replication during the first 3 months of treatment initiated at PHI is crucial to protect the CD4 T cell function at long term. This is an additional argument for not delaying treatment initiation in PHI.

300 EFFECT OF TELMISARTAN GIVEN AT ART INITIATION IN PHI ON IMMUNE CELLS IN LYMPH NODES
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1University of Washington, Seattle, WA, USA, 2Uppsala University, Uppsala, Sweden, 3Oregon Health and Sciences University, Portland, OR, USA

Background: HIV-related hyperactivation of mucosal B cells was observed despite early ART initiation. However, early ART appears to limit the loss of Bmem compared to CHI as well as prevent increased IgA production by PB. These results provide further insights on mucosal B cell dynamics in HIV infection and another potential mechanism how early ART may limit immune system damage at the mucosal barrier.

Results: Median gut HIV RNA was 3.8 log10 [copies/mg tissue] at AHI diagnosis and undetectable after 24 months of ART in 17/18 participants (p≤0.001). There was no difference observed in the frequency of PB and Bmem between the time of AHI diagnosis and HIV-individuals (PB: 6.3% vs 8.2%, Bmem: 58.0% vs 53.7%, respectively). However, 24 months post ART initiation a significant increase in the frequency of PB to 17.1% was observed compared to time of AHI diagnosis (6.3%, p≤0.01) and compared to HIV (8.2%, p≤0.0001), which was similar to the frequency of PB in CHI (74.8%, p=0.24). The frequency of Bmem decreased from 53.0% during AHI diagnosis to 50.1% at 24 months post ART initiation (p≤0.01). Following 24 months of ART the frequency of Bmem (50.1%) was lower compared to HIV (53.7%, p=0.03), but remained significantly higher compared to CHI (35.0%, p≤0.05). Interestingly, the expression of IgA, the most abundant isotype produced by mucosal PB, was higher in CHI compared to AHI following 24 months of ART (10.8% vs 4.7%, p=0.03), with no increase observed between AHI diagnosis and 24 months post ART initiation (6.1% vs 4.7%, p=0.43).

Conclusion: HIV-related hyperactivation of mucosal B cells was observed despite early ART initiation. However, early ART appears to limit the loss of Bmem compared to CHI as well as prevent increased IgA production by PB. These results provide further insights on mucosal B cell dynamics in HIV infection and another potential mechanism how early ART may limit immune system damage at the mucosal barrier.
ART and subsequently reduce immune activation/inflammation. Here, we report results from a clinical trial conceived to evaluate the effect of 12 weeks of metformin (mTOR inhibitor) therapy on the size of HIV reservoirs (primary objective) and immune activation (secondary objective) in ART-treated HIV-infected adults (HIV+ART).

**Methods:** Metformin (850 mg bid) was administered orally for 12 weeks in n=22 HIV+ART. Participants were non-diabetic, on ART for >3 years, with c<40 HIV-RNA copies/ml plasma for >3 months, and CD4/CD8 ratios ≥0.7. Blood was collected at baseline (Visit 1), after 12 weeks of metformin (Visit 2), and 12 weeks after metformin discontinuation (Visit 3). Sigmoid colon biopsies (n=32 biopsies/participant) were collected at Visits 1-2 from n=13 participants. HIV-DNA was quantified by real-time nested PCR. Replication-competent HIV was quantified by viral outgrowth assay (VOA). Matched blood/colon memory CD4+ T-cells were analyzed for surface/intracellular molecule expression and simultaneously sorted by flow cytometry (BD AriaIII). Plasma soluble factors were quantified using R&D Systems Multiplex Assay and ELISA.

**Results:** Metformin was well tolerated. Total HIV-DNA levels in blood/colon CD4+ T-cells and the frequency of blood CD4+ T-cells carrying replication-competent HIV was stable between Visits 1-3. However, investigations on matched blood/colon samples revealed a positive effect of metformin as reflected by a decreased infiltration of CD4+ T-cells in the colon (median: 7.3% vs. 4.7%, Visit 1 vs. 2, p=0.019), indicative of reduced colon infection; ii) decreased mTOR phosphorylation in colon CD20+ B-cells (median: 13.0% vs. 7.9%, Visit 1 vs. 2, p=0.0087); iii) a tendency for decreased expression of the HIV co-receptors CCR5 and integrin β7, and increased expression of the HIV restriction factor SAMHD1 in colon CD4+ CD8+ T-cells; and iv) decreased cCD4 plasma levels (mean: 1.893 vs. 1.519 ng/ml, Visit 1 vs. 3, p=0.02).

**Conclusion:** This pilot study reveals metformin-mediated benefits in controlling inflammation, in part via mTOR regulation, and prompts us to further investigate the immunological/virological benefits of long-term metformin supplementation in HIV+ART individuals.

### 302 METFORMIN THERAPY WITH IMMUNE CHECKPOINT INHIBITORS IMPACTS ANTI-HIV T-CELL RESPONSES

**Glen M. Chew**1, Dominic Chow2, Scott A. Souza3, Danielle M. Clements4, Michael J. Corley5, Alina P. Pang1, Alan J. Korman2, Mariana Gerschenson1, Cecilia M. Shikuma1, Lishomwa C. Ndhlovu1

1University of Hawaii at Manoa, Honolulu, HI, USA, 2Bristol-Myers Squibb, Redwood City, CA, USA

**Background:** Despite suppressive antiretroviral therapy (ART), chronic HIV is associated with T cell exhaustion, defined by the overexpression of negative immune checkpoint receptors. The efficacy of immune checkpoint blockade (ICB) in reversing T cell dysfunction and improving cancer survival is variable. Metformin (MET) is an oral hypoglycemic therapy for type II diabetes and has previously unrecognized therapeutic effects against age-related conditions. Recently, ICB in combination with MET has yielded favorable clinical outcomes in oncology (M.Z. Afzal et al. 2018). We assessed the ex vivo anti-HIV T-cell responses to ICB during adjunctive MET therapy in banked blood from a clinical trial of MET conducted in HIV+ adults.

**Methods:** We conducted an open label, 8-week (wk) pilot study in seven euglycemic adults on ART, stable for >1 year with plasma HIV RNA <50 copies/ml, median age of 60.5 years and all male. MET dosing was 500mg at entry increasing to 1000mg at wk4. In cryopreserved PBMCs, we measured ex vivo HIV-specific T cell responses (CD107a, IFN-γ, IL-2) to an HIV Gag peptide pool in the presence of blocking anti-TIGIT and/or anti-PD-L1 monoclonal antibodies and an isotype control (IgG1). Since monocyte frequencies (%) at entry have been shown to be associated with melanoma survival in response to anti-PD-1 blockade (C. Krieg et al. 2018), we also quantified monocyte subsets by flow cytometry. Statistical analysis included non-parametric Wilcoxon rank-sum test and Spearman’s rho for correlations.

**Results:** MET did not improve HIV-specific CD8 T cell responses in the absence of blockade. In the presence of anti-PD-L1, MET improved HIV-specific CD8 T cell responses (CD107a+IFN-γ+IL-2+) (Fold Change between IgG1 and anti-PD-L1; entry: 0.19 ±(−0.28, 0.41), wk 8, 1.21 (−0.06, 2.39) =p 0.04). Monocyte frequencies (%) remained unchanged. Baseline % of inflammatory (CD14+CD16+) and patrolling (CD14lowCD16+) monocytes positively correlated with wk8 HIV-specific T cell responses (CD107a+IFN-γ+IL-2+) to anti-PD-L1 blockade (r=0.89,
ZINC SUPPLEMENTATION AND INFLAMMATION IN TREATED HIV

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Background: In HIV, the prevalence of zinc deficiency appears to be high and low plasma zinc levels have been linked with disease progression and an increased risk of death. In this study, we explored the effect of zinc supplementation on the heightened state of inflammation and monocyte activation observed in ART-treated HIV infection.

Methods: This is a pilot open labeled randomized double arm study, studying the efficacy and safety of zinc therapy on inflammation in ≥ 18 years old HIV-infected patients, on stable ART (for at least 12 weeks) and with zinc levels ≤ 75 µg/dL in the last 60 days. Patients were randomized 1:1 to zinc gluconate daily for 16 weeks. We assessed the following markers at baseline and 16 weeks: cytokines, using Luminex. ADCC activity was measured using the Chromium-51 (51Cr) release assay. Last, levels of integrated HIV DNA in CD4+ T cells were examined using qPCR. Wilcoxon signed-rank test and Spearman’s correlations were used for statistical analysis. The Bonferroni method was used to correct for multiple comparisons.

Results: Overall, a total of 52 participants were enrolled (25 participants in the low-dose arm and 27 participants in the high-dose arm). Mean age was 49 years, 77% were males and 73% were African Americans. At baseline, mean zinc levels were 75 µg/dL. After 16 weeks, loss to follow up was minimal with 92% retention of the participants in the low-dose arm and 96% in the high-dose arm. In addition, 88% of participants in the low-dose arm and 96% in the high-dose arm reached zinc levels > 75 µg/dL. Overall, biomarkers decreased with a margin of reduction ranging between 8 and 33% (figure 1). There was a larger margin of change in sCD14 and IFABP in the participants in the low-dose arm, however the reductions were greater for hsCRP and LBP in the high-dose arm. This change was meaningful with large effect size (Cohen’s ranging from 5-19).

Conclusion: In this pilot study we found that zinc supplementation is safe and effective at increasing circulating zinc levels. In addition our findings provide novel data that zinc can impact a biological signature in patients with HIV and modulate biomarkers that have been associated with clinical comorbidities.

GLYCOMIC DETERMINANTS OF INTERFERON-α MEDIATED REDUCTION OF HIV PERSISTENCE IN VIVO

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Background: Interferon-α (IFNα) therapy was associated with significant suppression of HIV viremia and reduction in levels of HIV DNA during suppressive antiretroviral treatment (ART). Cytokines modulate host glycosylation, and glycosylation plays a critical role in mediating several antibody (mainly immunoglobulin G; IgG) immunological functions, including antibody-dependent cell-mediated cytotoxicity (ADCC), and anti-inflammatory activities. Nevertheless, the impact of IFNα on host glycosylation machinery remains unknown.

Methods: We assessed the impact of pegylated IFNα2a (Peg-IFNα2a) immunotherapy on isolated IgG glycomes of 18 HIV-mono-infected individuals on suppressive ART, using capillary electrophoresis. We also examined the plasma levels of 1) the immunomodulatory lectins, galectin-1, -3, -9, E-selectin, P-selectin, and L-selectin; and 2) 16 pro- and anti-inflammatory markers and cytokines, using Luminox. ADCC activity was measured using the Chromium-51 (51Cr) release assay. Last, levels of integrated HIV DNA in CD4+ T cells were examined using qPCR. Wilcoxon signed-rank test and Spearman’s correlations were used for statistical analysis. The Bonferroni method was used to correct for multiple comparisons.

Results: Peg-IFNα2a treatment was associated with a significant increase in the proportion of the pro-inflammatory, bisected GlcNAc glycan structures (such as G0FB; Bonferroni-corrected p<0.05). Fold induction of G0FB glycan trait correlated positively with the IFNα-mediated induction of the pro-inflammatory soluble markers (sCD14 and sCD163; rho>0.56, p<0.016). Peg-IFNα2a also induced the plasma levels of the inflammatory mediators galectin-9 (p=0.0001), L-Selectin (p=0.027), and E-Selectin (p=0.008). Peg-IFNα2a-mediated reduction of the anti-ADCC total fucosylated glycans (p<0.05) correlated with increased levels of the immunomodulatory lectins, galectin-1, -3, -9, E-selectin, P-selectin, and L-selectin.
negatively with fold change in ADCC activity (h = -0.52, P = 0.026). Last, IFNα-mediated reduction of A2G2S1 glycan trait (p = 0.04) correlated positively with change in ADCC activity (h = 0.62, P = 0.007), and with IFNα-mediated reduction of integrated HIV DNA levels (h = 0.57, P = 0.037).

**Conclusion:** IFNα immunotherapy in HIV-infected individuals on suppressive ART is associated with glycomic alterations, that are known to mediate higher inflammatory responses and higher innate effector functions. Our data suggest that host glycans-lectin interactions may mediate signals that inform and/or determine host immune responses to HIV persistence during IFNα treatment.

**Methods:** HIV envelopes derived from pre-ART plasma and PBMCs from 1 and 3 years of ART from each of 65 chronically HIV-infected participants of the ART naïve trial A5257 were tested for neutralization susceptibility to seven bnAbs (VRC01, VRC07.523S, 3BNC117, N6, 10-1074, CAP256-262.15, 10E8) using the PhenoSense nAb assay, which generates pseudovirions from plasma vRNA or PBMC proviral DNA-derived HIV envelopes. PBMCs from 9 participants at entry to AS340, which evaluated VRC01 during ART interruption, were also tested. Rank-based Spearman Correlation and Fisher’s exact tests were used for statistical analyses.

**Results:** Participants’ median CD4 count was 340 cells/mm^3 and 40% had a baseline VL > 100,000 copies/mL. IC50s varied more than 3 logs for each bnAb, but pre-ART plasma, year 1 and 3 PBMC values were highly correlated (Spearman r = 0.9, P = 0.004). In 9 participants with entry PBMCs, VRC01 IC50s did not significantly correlate with time to rebound (Spearman r = -0.35, P = 0.37), but IC50 < 0.5 µg/mL was associated with delayed time to rebound (>8 weeks) (P = 0.0278).

**Conclusion:** We found a wide range in baseline neutralization susceptibilities to clinically relevant bnAbs with highly correlated values across plasma and PBMC derived samples over 3 years of ART. In AS340, PhenoSense nAb susceptibilities on entry PBMCs were similar to published pre-ART values and IC50 < 0.5 µg/mL was associated with delayed rebound after ART. Results support the utility of screening for neutralization susceptibility prior to therapeutic bnAb use and suggest PhenoSense nAb PBMC testing may be a valid approach in suppressed individuals.

**Background:** High throughput infection based antibody dependent cellular cytotoxicity (ADCC) assays are needed to gain insights into the role of ADCC in preventing transmission. Current infection based assays often use a natural killer (NK) cell resistant CD4 T cell that expresses the CCR5 receptor (CSEM-NK-CCR5) as target cells, but transmitted viruses, such as those circulating in infected individuals, often cannot replicate in these cells. Furthermore, primary cells demonstrate highly variable susceptibility to primary HIV-1 strains.

**Methods:** Two different CD4 T cell lines, PM1 and MT4, were transduced with a CCR5 and a tat-inducible luciferase expression plasmid. Target cells were exposed to primary and lab-adapted HIV-1 strains and cultured with the NK cell line, KHYG-1, in the presence and absence of antibody. Percent ADCC was calculated as the loss of luciferase expression in the presence compared to the absence of antibodies.

**Results:** Incubation with NK cells, without HIV-1 antibodies, decreased luciferase in infected PM1-CCR5-Luc (4.0%, r = 0.79) and MT4-CCR5-Luc (1.09%, r = -0.41), suggesting PM1 but not MT4 cells were highly susceptible to background NK cell killing. Thus, PM1-CCR5-Luc cells were not examined further and MT4-CCR5-Luc cells were deemed NK cell resistant. NL4-3 infected CEM-NK-CCR5-Luc (62.8%, r = 0.79) and MT4-CCR5-Luc cells, fold luciferase expression over background was only elevated in the MT4-CCR5-Luc cells after infection with primary CCR5-using variants, such as CH058 (42.5 fold), CH077 (2 fold), ZM247Fv2 (29.53 fold), and variants, such as PM1 but not MT4 cells were highly susceptible to background NK cell killing. Thus, PM1-CCR5-Luc cells were not examined further and MT4-CCR5-Luc cells were deemed NK cell resistant. NL4-3 infected CEM-NK-CCR5-Luc (62.8%, r = 0.79) and MT4-CCR5-Luc (70.6%, r = 0.79) yielded similar ADCC estimates in the presence of 500ug/ml HIV-1 IgG (p = 0.79). While NL4-3 replicated in both CEM-NK-CCR5-Luc and MT4-CCR5-Luc cells, fold luciferase expression over background was only elevated in the MT4-CCR5-Luc cells after infection with primary CCR5-using variants, such as CH058 (4.54 fold), CH077 (2 fold), ZM247Fv2 (29.53 fold), and BJ0200 (42.5 fold). In MT4-CCR5-Luc cells, similar ADCC estimates were obtained in the presence of heat inactivated plasma compared to isolated IgG (p = 0.31). Breast milk isolated IgG, heat inactivated infant and maternal IgG (p = 0.22) and maternal IgG (p = 0.02) were used with mother-infant pairs where transmission did and did not occur in order to determine if ADCC is a correlate of protection in MTCT.
IMPACT OF ATI ON B-CELL REGULATION BY IGG3 IN CHRONICALLY HIV-INFECTED INDIVIDUALS

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Background: Numerous immunologic abnormalities have been described in HIV infection, especially in the absence of antiretroviral therapy (ART). B-cell abnormalities include loss of classical memory B cells and gain of activated, exhausted and differentiated B cells. We recently reported a role for IgG3 in regulating B-cell activation in certain individuals with chronic HIV viremia. Here, we investigated the dynamics of IgG3 regulation in a longitudinal cohort of HIV-infected individuals undergoing analytical treatment interruption ( ATI).

Methods: Longitudinal immunologic and virologic analyses were conducted on specimens obtained from seven individuals prior to receiving ART, after several years of ART, during ATI, and following re-initiation of ART. The dynamics of HIV plasma viremia, changes in B-cell populations and IgG3 binding in the peripheral blood were evaluated longitudinally. The immunologic assays were performed by multiparameter flow cytometry.

Results: In the absence of ART (pre-ART), four of seven individuals had IgG3 bound to their IgM+ B cells. After a median of ten years on ART (pre-ATI), none of the individuals had IgG3 + IgM+ B-cells. Following ATI, varying degrees of IgG3 binding to B cells was observed at peak viremia in the same four individuals who had the profile pre-ART. The IgG3 + IgM+ B-cell profile was again extinguished following re-initiation of ART. During ATI, for all seven HIV-infected individuals studied, total B-cell percentages decreased significantly and contained a higher percentage of plasmablasts compared to ART-naive, pre- and post-ATI time points. During ATI, the percentage of activated memory B cells also increased significantly compared to the pre-ATI period, while the percentage of tissue-like memory B cells did not change, remaining significantly lower compared to the pre-ART period. The percentage of classical memory B cells decreased significantly during ATI compared to pre- and post-ATI periods, but remained higher compared to the pre-ART period.

Conclusion: We provide evidence that ATI elicits significant changes in B cells of HIV-infected individuals as a result of rebounding plasma viremia. The presence of circulating IgG3 + IgM+ B cells is a property consistently observed in certain HIV-infected individuals during chronic plasma viremia and closely associated with active viral replication. The profile is present pre-ART, extinguishing itself during effective ART and gradually returns when individuals undergo ATI and plasma viremia rebounds.

PTEN OVEREXPRESSION IN ANTIGEN-SPECIFIC B CELLS FROM HIV-INFECTED INDIVIDUALS ON ART

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Background: Memory B cells (MBC) respond to secondary antigen challenge to protect against infection and to boost immunity following vaccinations. Despite effective treatment, chronic HIV infection disturbs MBCs by reducing numbers and altering functionality due to hyper-activation and increased apoptosis leading to suboptimal antibody responses against common infectious agents such as Influenza. We and others have shown that influenza-specific responses in B cells are impaired in HIV-infected individuals in both young and old (>60 years) individuals. However, these studies have largely been performed using bulk cell analysis from in vitro antigen-stimulated culture experiments and technological advances in single cell analysis now allow for deeper interrogation of cellular states in cell populations with diverse functions, such as MBC.

Methods: We used single cell gene expression analysis to evaluate post-vaccination antigen-specific memory B cells isolated from peripheral blood of virally-suppressed HIV-infected individuals and healthy controls stratified by serum H1N1 antibody response 3 weeks post-administration of the seasonal trivalent inactivated influenza vaccine. We used a fluorescent probe to isolate influenza H1N1-specific B cells and a multiplexed and targeted RT-PCR approach (Fluidigm BioMark) to measure expression levels of 96 genes involved in B cell activation and function. H1N1-specific B cells were also analyzed for memory phenotype and Ig isotype by flow cytometry to integrate with gene profiles.

Results: Single cell gene profiling revealed a 4-gene predictive signature containing IL10RA, APOBEC3G, TLR7 and the phosphoinositol-3 kinase (PI3K) inhibitor, PTEN, for identifying antigen-specific MBC from HIV-infected individuals compared to healthy controls. Gene co-expression analysis showed that in addition to overexpression of PTEN, there was increased co-expression of type I interferon-associated genes with PTEN on single cell level in HIV compared to controls.

Conclusion: Overall, this signature reinforces the concept of an imbalance in the interferon pathway leading toward an impairment of the ability of B cells to mature where PTEN seems to play a central role. Further, this study provides a framework for analysis of antigen-specific cells using single cell gene expression analysis and provides insight into persistent defects in B cell-mediated immunity in the context of treated HIV infection and introduce potential targets of intervention to improve vaccine responses.

AUTOLOGOUS NEUTRALIZING ANTIBODIES DRIVE VIRUS EVOLUTION DURING REBOUND AFTER ATI

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Background: Characterization of the viral dynamics and host immune pressures present during HIV-1 rebound after analytical treatment interruption (ATI) provides insight into the environment in which therapeutic and curative strategies must act.

Methods: We studied plasma samples from a previously conducted clinical trial (NCT00051818) in which chronically-ART initiated participants underwent a single or multiple sequential ATIs. Single genome sequencing of env genes was performed on plasma vRNA from first detectable rebound through up to 1 year of ATI. Select envs were cloned and tested as pseudoviruses for sensitivity to autologous plasma neutralizing antibody (nAb) responses in the TZM.bl assay.

Results: Phylogenetic analysis of env sequences from first detectable plasma rebound in 11 participants undergoing a single ATI revealed multiple genetically distinct lineages replicating in each participant (median=5, range 2 to >10). Over time, total env diversity and the number of genetically distinct lineages expanded, with evidence of virus evolution, recombination, and reactivation of new populations. In 6 of 7 participants with adequate sampling, however, all or many of the initial rebounding lineages were not sampled in subsequent timepoints. Virus lineages that were cleared were significantly more sensitive to autologous plasma nAbs than those that persisted (median reciprocal IC50 titers of 906 vs. 153, p=0.0028, by Wilcoxon). IgG from plasma at the time of ART interruption had modest activity against cleared viruses; IgG from week 4 and 8 of ATI increased its potency against rebound viruses by 100 to 10,000-fold (p=0.0079, by Wilcoxon). In 2 participants from the multiple ATI arm of the study, initial rebound was comprised of multiple distinct lineages (6-7 lineages). Over 3 subsequent ATIs, a substantial number of initial lineages were no longer sampled, with autologous nAbs showing a non-significant trend towards greater potency against cleared viruses.

Conclusion: In ART suppressed individuals undergoing ATI, we found that multiple virus populations arise from latency and diversify rapidly over ATI, with selective sweeps of initial rebound virus populations observed in most participants. Autologous nAbs are modest initially, but quickly expand to drive virus selection over subsequent weeks. Results suggest that autologous nAbs are an important component of the immune dynamics of rebound and should be considered in immunotherapeutic approaches to virus suppression and cure.
A NOVEL PHAGE-DISPLAY APPROACH MAPS LINEAR EPITOPEs OF GP41-SPECIFIC mABs

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Background: Antibodies targeting the HIV Envelope (Env) protein can limit viral infection and provide immunity. However, the field has yet to generate a vaccine capable of producing protective antibodies in humans. With epitope-based vaccine design we can engineer immunogens to elicit antibodies against specific regions of Env, but we are limited in part by the low throughput nature of current epitope mapping methods. Here we developed and tested a high-throughput, comprehensive approach to map the epitopes of recently identified HIV-specific monoclonal antibodies (mAb)s that mediate ADCC.

Methods: We applied a phage display method that used deep sequencing, Phage Immunoprecipitation-Sequencing (PhIP-seq), to identify the linear epitopes of four newly identified gp41-specific monoclonal antibodies (mAbs): QA255.006, QA255.016, QA255.067, and QA255.072 as well as 240-D, a gp41-specific antibody previously mapped using peptide arrays. We first generated a synthesized oligonucleotide library encoding for 39 amino acid long peptides that tile along the entire length of several Env and full-length HIV sequences from different clades. This library was cloned into a T7 bacteriophage display vector. To perform a PhIP-seq experiment, mAbs were coated on beads and incubated with the phage library. Samples were sequenced in parallel, and then peptides specifically enriched by the mAb were computationally identified. Competition ELISAs were performed to compare epitope mapping results using a more traditional approach.

Results: We mapped the linear epitope of QA255.067 and QA255.072 to Env amino acids 592-606 and 596-609 (HXB2 numbering), a region corresponding to the immunodominant C-C loop region of gp41. Competition ELISAs confirmed these results. We also more finely mapped the epitope of 240-D to amino acids 596-605, which is consistent with findings from structural studies. We were unable to see specific enrichment of any peptides in PhIP-seq with QA255.006 and QA255.016, but competition ELISA results indicated these mAbs target a discontinuous epitope on gp41.

Conclusion: PhIP-seq mapped overlapping but distinct epitopes of two newly identified gp41 mAbs and 240-D. This method may be useful for mapping HIV antibodies that target linear epitopes, and particularly, antibodies that recognize the gp41 protein, which is an attractive vaccine target because it is relatively conserved.

RAPID DEVELOPMENT OF AN INFANT-DERIVED HIV-1 BROADLY NEUTRALIZING ANTIBODY

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Background: Antibodies from HIV-infected infants develop broadly neutralizing plasma responses with more rapid kinetics and lower somatic hypermutation than adults, suggesting the ontogeny of infant responses could inform a better path to achievable vaccine targets. We previously isolated BF520.1, the first and only infant-derived broadly HIV-neutralizing antibody (bnAb). A thorough investigation of how BF520.1 developed will highlight possible pathways of rapid bnAb development that may be useful in vaccine design. Furthermore, resolving the structural basis of BF520.1’s interaction with HIV envelope will inform the design of effective vaccine immunogens.

Methods: We sequenced antibody genes from a blood sample collected midway between HIV infection and the isolation of BF520.1. We developed robust computational methods to reconstruct the developmental lineage of BF520.1 that include using personalized germline gene sets to infer the antibody sequences of BF520.1’s naive ancestor, identifying midpoint sequences that were clonally-related to BF520.1, and phylogenetically determining likely mutational pathways that generated the mature bnAb. We compared our Bayesian lineage reconstruction approach to lineage inference by maximum likelihood, a common approach in the field. Lastly, we used single particle cryo-electron microscopy to explore the structural interaction of BF520.1 with the HIV envelope trimer BG05.S05P.S64.

Results: We computationally validated that our method of lineage reconstruction was more accurate than maximum likelihood at identifying ancestral sequences for simulated antibody lineages similar to BF520.1. Our inferred naive precursor bound HIV Env with a KD of 46M. A bnAb evolved within six months of infection and required only 3% somatic hypermutation. Kappa chain substitutions were critical for bnAb functionality, validated by the observation of extensive contacts between the CDRL1 loop and the N332 glycan in our 4.8Å cryo-EM map. For the heavy chain, CORH1 and CORH2 mutations were important for developing breadth and potency.

Conclusion: Overall, the developmental pathway of this infant antibody includes features distinct from adult antibodies, including several that may be amenable to better vaccine responses. Our analysis highlights the importance of considering both the heavy and light chain in the development of HIV-specific bnAbs and the fact that light chain specificity can potentially be harnessed to develop vaccine approaches that elicit such bnAbs with relatively little mutation.

PROFILING ANTIBODY CROSS-REACTIVITY AMONG SIV ISOLATES USING A PEPTIDE MICROARRAY

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Background: In the past decade, a number of broadly neutralizing human immunodeficiency virus (HIV) antibodies have been identified; however, tools for assessing antibody cross-reactivity are still relatively low throughput. Ultradense linear peptide arrays enable the determination of antibody reactivity to as many as six million peptides in a single assay. Identification of antibodies capable of binding a wide variety of HIV strains has potential to help guide the development of vaccines and therapeutics. Here we prototyped the use of an ultradense peptide microarray to assess antibody cross-reactivity from cynomolgus macaques infected with SIVmac239 against a panel of simian immunodeficiency virus (SIV) species used to infect macaques.

Methods: Proteins represented on the array included the complete Env proteins of 21 strains of SIV and the complete proteome of SIVmac239, tiled in peptides 16 amino acids in length which overlapped by 12 amino acids. We assessed serum and plasma samples taken prior to infection and 125 days to 1 year after infection with SIVmac239 and compared pre-infection and post-infection antibody binding to proteins represented on the array. Fluorescence intensity from the application of a secondary antibody indicated regions in which primary antibodies had bound peptides representing the SIV proteins.

Results: No or minimal binding against SIV viral peptides was observed prior to infection. Following infection, evidence of antibody binding was consistently observed in peptides representing the Gag, Pol, and Env proteins of SIVmac239, with the highest levels of binding in Env. Antibody binding against other SIVmac239 proteins was also observed, though these results were less consistent between animals. We observed variable levels of antibody binding to peptides from other SIV strains, though all animals assessed showed some degree of cross-reactive binding to some number of SIV strains other than the infecting strain.

Conclusion: Serum profiling of antibody binding throughout the proteome of SIVmac239 and throughout the the Env proteins of multiple strains of SIV reveals cross-reactive antibody binding and highlights the potential of ultradense peptide arrays for high-throughput assessment of antibody binding specificity to diverse viruses.

REGULATION OF HIV-SPECIFIC CD8+ T-CELL FUNCTIONAL CAPACITY

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Background: HIV-1 infection and provide immunity. However, the field has yet to generate a vaccine capable of producing protective antibodies in humans. With epitope-based vaccine design we can engineer immunogens to elicit antibodies against specific regions of Env, but we are limited in part by the low throughput nature of current epitope mapping methods. Here we developed and tested a high-throughput, comprehensive approach to map the epitopes of recently identified HIV-specific monoclonal antibodies (mAb)s that mediate ADCC.
Background: Many HIV cure strategies propose to elicit HIV-specific CD8+ T cell responses to control and/or eradicate the virus. We previously reported that the T cell memory- and stem cell-associated Wnt signaling transcription factor, TCF-1, is expressed at significantly higher levels in HIV-specific CD8+ T cells from individuals who naturally control HIV infection. Moreover, its expression correlates with the proliferative capacity of these cells. Here, we explored the relationship between HIV-specific CD8+ T cell functional capacity and other molecular pathways associated with CD8+ T cell memory.

Methods: HIV-specific CD8+ T cells were identified in the peripheral blood from Viremic (VL>8,000 copies/mL; n=14), ART-suppressed (VL<40 copies/mL not on ART; n=112) HIV-infected individuals by staining with MHC Class I multimers. The expression of transcription factors, effector molecules, and surface proteins was measured in multimer+ CD8+ T cells and proliferation was evaluated after 6-day in vitro peptide stimulation. Whole-genome RNA sequencing and DNA methylation analysis were performed on sorted multimer+ cells from a subset of participants.

Results: In addition to mounting greater proliferative responses and expressing higher levels of TCF-1 in all memory T cell subsets, multimer+ HIV-specific CD8+ T cells from Controllers (compared to Viremic or ART-suppressed individuals) were more likely to express CD127 and less likely to express PD-1, Granzyme B, and Tbet. Unstimulated multimer+ cells from Controllers (compared to ART-suppressed) were enriched for the expression of genes in the Fatty Acid metabolism pathway, which is associated with a quiescent metabolic profile (p<0.05). They also had a higher level of expression of “stem-ness” associated genes, including HOXB7, lower expression of the gene encoding the exhaustion-associated transcription factor Fox, and a distinct DNA methylation pattern in the WNT3 gene body (59% vs 29% methylation, p<0.01).

Conclusion: HIV-specific CD8+ T cells from Controllers share several molecular features with long-lived memory CD8+ T cells. The mechanisms by which these pathways may support the persistence of functional HIV-specific T cells remains to be investigated. However, our data provide a rationale for future studies to evaluate Wnt signaling and other programs that control long-lived memory T cells as a target to enhance the efficacy of CD8+ T cell-based HIV cure strategies.

315 IMPACT OF INTEGRASE INHIBITORS ON CD8 T-CELL FUNCTION AND ACTIVITY
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Background: HIV-specific CD8 T cells play a crucial role in controlling HIV replication. Although they have efficient effector function, CD8 T cells fail to clear HIV infection even in the presence of ART. Here we describe how ART can impact CD8 T cell effector function and therefore interfere among other factors with clearance of HIV infected cells.

Methods: PBMCs from HIV+ (n=44) and healthy (n=32) individuals were analyzed via flow cytometry to determine phenotype and functional properties of HIV-specific CD8 T cells in the presence of ART drugs and performed ex vivo proliferation assays of PBMCs from treated HIV+ individuals. We used a viral inhibition assay to determine CD8 T cells clear HIV infected cells and analyzed metabolic profiles using extracellular flux analyzer.

Results: We assessed CD8 T cell functions in HIV+ ART-treated individuals ex vivo and observed a reduction in cellular function compared to CD8 T cells of HIV+ treatment naive individuals (p<0.01). We next assessed the proliferation index ex vivo and found a reduction in CD8 T cells of individuals treated with INSTI-based ART regimen (2.43±0.36) compared to both PI (2.79±0.35; p<0.05) and NNRTI (2.92±0.28; p<0.01) based regimens. As we saw a significant impact of INSTI-based regimens on CD8 T cell function, we cultured CD8 T cells with individual ART drugs and determined the impact on CD8 T cell function of each drug individually. CD8 T cells had reduced functional properties with significantly lower expression of IFNγ (p<0.01), IL-2 (p<0.01) as well as TNFα (p<0.01) after treatment with INSTI, but not with other ART drugs. Due to the observed decrease in cytokine expression we decided to examine the killing ability of HIV-specific CD8 T cells in presence of individual ART regimens. Previously INSTI-treated CD8 T cells demonstrated reduced viral inhibitory activity against HIV-infected CD4 T cells compared to PI or NNRTI treated cells. We used a live cell imaging assay to determine the migratory capacity of CD8 T cells treated with different ART regimens. CD8 T cells had significantly reduced migratory capacity with significantly less cell migration per well compared to PI and NNRTI treated cells. We used a live cell imaging assay to determine the migratory capacity of CD8 T cells treated with different ART regimens. CD8 T cells had significantly reduced migratory capacity with significantly less cell migration per well compared to PI and NNRTI treated cells.

Conclusion: Our data shows that the choice of ART can have a significant impact on CD8 T cell effector function. This may have important implications for HIV eradication strategies.
C08 T-CELL INHIBITORY RECEPTOR EXPRESSION IS ASSOCIATED WITH CANCER AMONG PLWH ON ART

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Background: After controlling for traditional risk factors and viral suppression, people living with HIV (PLWH) have increased incidence of some cancers. Perturbations of the immune system persist despite virologic control on ART. This study explores the role of T-cell subsets on incidence of HIV-associated cancer among ART-treated virally suppressed patients.

Methods: The United States Military HIV Natural History Study (NIH) is a well-characterized longitudinal cohort of Department of Defense beneficiaries. The NIH repository was used to identify cell samples from 25 cases and 87 controls. Cases had lung cancer, lymphoma, and HPV-associated cancers diagnosed after durable HIV-suppression. Cases and controls were matched for CD4+ T cell count, duration of HIV infection and viral suppression, and sample availability. Cryopreserved PBMCs from cases were obtained at least 6 months prior to cancer diagnosis. Using flow cytometry, PBMCs were measured for expression of markers of maturation (CD27, CD28, CCR7, CD45RA), inhibitory receptors (PD-1, LAG-3, TIM-3, CD160), immune activation (CD38, HLA DR) and transcription factors (T-bet and Eomesodermin). Mann-Whitney U test was performed for comparison between groups.

Results: Cases and controls were well-matched (Table 1). All patients were virally suppressed. Expression of individual immune inhibitory receptors on total CD8+ T cells were not significantly different between the groups, though there was a trend towards higher PD-1 expression in cases compared to controls (25.8% vs 21.8%, p=0.067). The frequency of CD8+ T cells co-expressing three inhibitory receptors (PD-1+CD160+CD24+) was significantly higher among compared to control patients (11.3% vs 7.8%, p=0.03). In addition, among cases, expression of the transcription factor T-bet was higher on effector memory CD8+ T cells in cases compared to controls (24.1% vs 15.6%, p=0.0001). There was no difference in the frequency of naive/memory subsets (using CD38, CD27, CD45RA, CCR7) or activation (CD38+HLADR+) among CD8+ T cells between the two groups.

Conclusion: Co-expression of inhibitory markers has been associated with significant impairment of antigen-specific responses in both HIV infection and the tumor microenvironment. Our study shows that in a well-controlled sample set, the co-expression of multiple T cell inhibitory markers (PD-1, CD160+ CD24+) is associated with a subsequent diagnosis of cancer, supporting the importance of studying the role persistent immune dysfunction on cancer incidence among PLWH.

Table 1: Baseline table by characteristics of patients in the study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Case</th>
<th>P value</th>
</tr>
</thead>
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<tr>
<td>Age at HIV diagnosis</td>
<td>33.0 (28.30,36.0)</td>
<td>32.0 (26.0,40.0)</td>
<td>0.8175</td>
</tr>
<tr>
<td>Age at cancer dx or sample collection</td>
<td>48.0 (40.54,50.0)</td>
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<tr>
<td>Duration of HIV infection at cancer dx</td>
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<td>14.0 (8.20,18.0)</td>
<td>0.5561</td>
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<tr>
<td>CD4 at cancer dx or sample collection in years</td>
<td>209.0 (126.0,250.0)</td>
<td>259.0 (270.0,675.0)</td>
<td>0.1775</td>
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<tr>
<td>Race</td>
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<td></td>
<td>0.0980</td>
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<tr>
<td>Caucasian</td>
<td>35 (40.4%)</td>
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<td></td>
</tr>
<tr>
<td>African American</td>
<td>36 (41.4%)</td>
<td>13 (26.0%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16 (18.4%)</td>
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<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>81 (92.3%)</td>
<td>25 (92.0%)</td>
</tr>
<tr>
<td>PB based ART</td>
<td>Yes</td>
<td>46 (52.3%)</td>
<td>14 (56.0%)</td>
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</table>

IMPACT OF ART ON T-CELL REPERTOIRES OF HIV-INFECTED ADULTS WITH AND WITHOUT CANCER

Abrahams Omoking1, Andrea Towlerton1, David Coffey2, Warren Phipps3, Edus H. Warren4

1Uganda Cancer Institute, Kampala, Uganda, 2Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Response to treatment of HIV-associated malignancies is likely influenced by the restoration of the T-cell repertoire and immune function after initiation of antiretroviral therapy (ART). To understand the impact of immune reconstitution on HIV-associated lymphoma outcomes, we compared the T-cell repertoire in 2 cohorts of HIV-infected adults initiating ART - one without cancer and one with pathologically confirmed diffuse large B cell lymphoma (DLBCL). We hypothesize that one-year survival after a diagnosis of DLBCL in ART-naive HIV+ adults will be associated with superior immune reconstitution of the T-cell repertoire.

Methods: For cohort 1, serial peripheral blood mononuclear cell (PBMC) samples and clinical data were collected from 30 HIV+ adult subjects enrolled on prospective studies conducted by the Center for AIDS Research (CFAR) at the University of Washington, Seattle, WA. 14 PBMC samples were collected pre-ART and 2-6 PBMC samples post-ART from each subject. PBMC samples were also collected from 16 HIV+ adult control subjects. For cohort 2, serial PBMC samples and clinical data are being collected from HIV+ adult subjects presenting to the Uganda Cancer Institute – Fred Hutchinson Cancer Centre in Kampala, Uganda for treatment of pathologically confirmed DLBCL. To date, PBMC samples have been collected from 50 subjects. High-throughput T-cell receptor β chain (TRB) sequencing has been performed on all 168 samples from the HIV+ cohort; analysis of the HIV+ lymphoma cohort is ongoing.

Results: The TRB repertoire in the HIV+ cohort prior to ART initiation was significantly more “clonal” (less diverse) than that observed in the HIV- controls. Following initiation of ART, an increase in repertoire diversity was observed, accompanied by a substantial improvement in CD4+ T-cell count. Increased repertoire diversity was associated with an increase in the number and frequency of “public” TRB sequences, many of which are associated with CD8+ T-cell responses to HIV epitopes.

Conclusion: Initiation of ART in HIV+ adults was associated with changes in the global and pathogen-specific T-cell repertoires. ART initiation was also associated with increases in the frequency of “public” TRB sequences associated with immunodominant CD8+ T-cell responses to HIV and other viral pathogens, suggesting that recovery of CD8+ T-cells may enable expansion of pathogen-specific and tumor-specific CD8+ T-cells.

FINDING THE CELLS AMIDST THE DATA

Boris P. Heijblum1, Daniel Commenges2, Charif Alkhassim1, Raphael Gottardo2, François Caron1, Rodolphé Thiebaut1

1INSERM, Bordeaux, France, 2Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 3University of Oxford, Oxford, UK

Background: Flow and mass (CyTOF) cytometry are high-throughput technologies quantifying multiple surface and intracellular markers at the level of a single cell. Improvements of these technologies allow to describe millions of individual cells from a single blood sample according to several dozens of markers (up to 2-30 cell populations with 30 markers). This generate high-dimensional datasets, whose manual analysis, called manual gating, is highly time-consuming and poorly reproducible. We have developed 2 machine learning approaches to perform automatic gating without human intervention.

Methods: The first method is a new Bayesian nonparametric approach (NPflow) with Dirichlet process mixture (DPM) of multivariate skew t-distributions to perform model-based clustering of flow-cytometry data. DPM models directly estimate the number of cell populations from the data, avoiding model selection issues, and skew t-distributions provides robustness to outliers and non-elliptical shape of cell populations. To accommodate repeated flow-cytometry measurements, such as in a clinical trial, a sequential strategy relying on a parametric approximation of the posterior is also proposed (NPFow seq). The second one (cytometree) is based on the construction of a binary tree, whose nodes represents cellular sub-populations. At each node, a binary split between different cellular populations is done according to the normalized difference of Akaike Information Criteria (AIC) between the two normal mixture models considering either one or two possible sub-populations. Post-processing of the tree structure and derived populations allows us to automatically provide a complete annotation of the derived populations.

Results: The good performance of the methods are shown on simulated data and on an experimental benchmark datasets (FLOWCAP1) as shown in Table 1, as well as in a real dataset from an HIV vaccine trial. Compared to other available approaches the new methods, especially cytometree, performed at the top
position with the shortest runtime. Also, the F-measures >0.90 demonstrate the validity of the new methods in comparison with the gold standard (consensus of 8 experimentalists).

**Conclusion:** The constant increase of the number of markers available to characterize cell populations leads to an untractable situation with manual gating. However, improvements of machine learning approaches allow for the automatic analysis of cytometry samples, yielding the relative count for all possible cell populations.

### Table 1: Average F-measures (between 6 and 7), the closer to 1 the better agreement) comparing automated gating results with consensus manual gating over several benchmark datasets.

<table>
<thead>
<tr>
<th>Method</th>
<th>GvHD</th>
<th>HSST</th>
<th>Dataset</th>
<th>DBLP</th>
<th>WHD</th>
<th>ND</th>
<th>Mean</th>
<th>Runtime per sample</th>
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<tr>
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</tr>
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</tbody>
</table>

**319 MACHINE LEARNING REVEALS T-CELL ACTIVATION PATHWAYS INDUCED BY INFLUENZA VACCINE**

Megan Cole1, Zainab Saeed1, A. Torn Shaw1, Yanping Gu1, Katja Hoschler1, Alan Winston1, Graham S. Cooke1, Sarah Fidler1, Graham P. Taylor1, Katrina Pollock1

1 Imperial College London, London, UK, 2 Public Health England, London, UK

**Background:** Seasonal influenza vaccine responsiveness is dependent on a specialised subset of CD4+ T-cells that are susceptible to infection with HIV. The role of CXCR5+ circulating T-follicular helper cells (cTFH) in this response is unclear in individuals with treated suppressed HIV infection. Investigations of potential biomarkers for HIV integration have identified rare CD4+ T-cells highly expressing the FC gamma receptor CD32, but with unknown function. We hypothesised that CD32 is upregulated on cTFH in response to seasonal influenza vaccine and used unsupervised computer algorithms to explore the cellular relationships arising.

**Methods:** 16 men with treated, suppressed HIV infection and 14 healthy control subjects receiving quadrivalent influenza vaccine (QIV) during the 2017-18 Northern Hemisphere influenza season were studied. Peripheral blood mononuclear cells (PBMCs) were collected prior to and after vaccination. Thawed PBMCs were stained with a pre-optimised cocktail of fluorochrome-conjugated antibodies, before acquisition on a BD Fortessa flow cytometer. The data were analysed using T-stochastic neighbour embedding analysis (t-SNE) and Spanning-tree progression analysis of density-normalized events in FlowJo v10.4.2 and FCS express v6plus.

**Results:** cTFH more frequently expressed CD32 at Day 7 post QIV (p=0.0009) and returned to baseline at Day 28 (p<0.0001) with no difference in those with and without HIV infection. t-SNE identified three populations (P1, P2 and P3) of CD4+ T-cells that were defined by their expression of CXCR5 and CD32. P1 (CXCR5hiCD32hi) and P3 (CXCR5midCD32lo/mid) frequency was constant but P2 (CXCR5lo/midCD32lo/mid) was more frequent at Day 7 (p=0.0261) and expressed the cTFH activation markers programmed cell death 1 (PD-1) and inducible T-cell co-stimulator (ICOS). SPADE indicated a branched hierarchy of clustered nodes corresponding to P1, 2 and 3. Consistently, a central memory CXCR5mid node gave rise to a CXCR5hiCD32hi node that was unaffected by QIV and two vaccine-inducible activated ICOS+PD-1+CD38+CXCR5+CD32midhi/hi nodes.

**Conclusion:** Circulating CXCR5+CD4+ T-cells fall into three major related populations. A parent population of tTFH-like cells gives rise to a vaccine-responsive tTFH population that upregulates CD32 and a vaccine-unresponsive population persistently expressing CD32 and CXCR5. These relationships were present irrespective of HIV infection in individuals receiving QIV and could be used to inform vaccine design.

### 320 COMPARATIVE ANALYSIS OF THE MAGNITUDE AND QUALITY OF VACCINE-ELICITED T-CELL RESPONSE

Bianca Schulte1, Franco Pissani2, Michael A. Eller1, Bruce T. Schultz1, Mary Marovich1, Prasert Thongcharoen1, Somchai Sriprianchan1, Supachai Reksw-Ngarm1, Punnee Pitsutthithum1, Stefan Esser1, Galit Alter1, Merlin L. Robb1, Jerome H. Kim1, Nelson L. Michael1, Hendrik Streeck1

1 University of Duisburg-Essen, Essen, Germany, 2 US Military HIV Research Program, Silver Spring, MD, USA, 3 Mahidol University, Bangkok, Thailand, 4 Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, 5 Ministry of Public Health, Nonthaburi, Thailand, 6 University Hospital Essen, Essen, Germany, 7 Massachusetts General Hospital, Boston, MA, USA

**Background:** CD4 T cell responses that provide efficient help for B cells to generate a long-lived, high-affinity antibody response are considered to be an important component of an HIV vaccine. However, it is unknown how to elicit effective HIV-specific CD4 T cell responses and which vaccine strategy induces optimal T follicular helper (TFH) cell responses. Here we evaluated and compared the TFH responses from chronic HIV infection to several phase one and phase II clinical trials, which differed in the immunogen, adjuvant and route of delivery.

**Methods:** We characterized the functional profiles of CD4 T cells using multicolor flow cytometry on cryo-preserved PBMCs isolated from chronically infected patients or vaccination study participants. The phase one and phase II clinical vaccination trials included in this analysis were RV139, RV172, RV114, RV132, RV135, RV158, and RV144.

**Results:** The HIV-specific CD4 T cell response in chronic natural HIV infection and the response to different vaccine modalities differed markedly. While chronic HIV infection provoked a higher frequency of HIV-specific CD4 T cells than vaccination (p<0.001, n=6 for chronic HIV infection, n=97 for vaccination), the functional profiles between the responses induced in natural HIV infection versus after vaccination were also significantly different. Chronic natural HIV infection showed an HIV-specific CD4 response dominated by Tfh polarization than intramuscular injection. Additionally, the choice of prime and boost influenced the degree of multifunctionality induced in T cells. The prime/boost combination ALVAC-HIV/gp160 (RV132) led to the highest frequency of HIV-specific CD4 memory T cells with a polyfunctional profile (p=0.028 for the frequency of IFNy and p=0.035 for TNFα expressing cells compared to the other vaccine modalities).

**Conclusion:** Overall, we describe the varying functional T cell response to different vaccination strategies and the differences in responses to chronic HIV-1 infection vs. vaccination. Future approaches to vaccine design will be informed by this and further studies with the goal to induce polyfunctional T cell responses, which support the production of protective antibodies.

### 321 REGULATORY T CELLS IN HIV-INFECTED PREGNANT WOMEN

Katelyn J. Rittenhouse1, Humphrey Mwape1, John Mwale1, Gabriel Chipili2, Joan T. Price2, Bellington Vwalika2, Kristina De Paris1, Elizabeth M. Stringer1, Jeffrey S. Stringer1

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

**Background:** Maternal HIV infection and its treatment are associated with increased risk of preterm birth (PTB). Conventional wisdom holds that an expansion of regulatory T cells (Tregs) during the 2nd trimester plays an integral role in maternal tolerance of the fetal allograft. However, recent studies (in HIV-negative subjects) have shown that regulatory T cells during the 2nd trimester do not play a role in maternal tolerance of the fetal allograft. However, recent studies (in HIV-negative subjects) have shown that regulatory T cells during the 2nd trimester do not play a role in maternal tolerance of the fetal allograft. Hence, the study aimed to explore the role of Tregs during the 2nd trimester in HIV-infected pregnant women.

**Methods:** Between May 2017 and January 2018, we immunophenotyped 64 1st trimester (HIV-: 53, HIV+: 11) and 270 2nd trimester (HIV-: 222, HIV+: 48) peripheral blood specimens collected from women enrolled in the Zambian Preterm Birth Prevention Study (ZAPPS), a prospective cohort ongoing in Lusaka. We quantified Treg frequencies by flow cytometry (CD4+CD25+CD127low FOXP3+). The frequency of IFNy and TNFα expressing cells was measured using a Treg cell functional assay.

**Conclusion:** The HIV-infected (HIV+) pregnant women had decreased peripheral Treg frequencies compared to their HIV uninfected (HIV-) counterparts. The frequency of IFNy and TNFα expressing cells was significantly lower in HIV-infected pregnant women compared to HIV-uninfected pregnant women (p<0.05). The frequency of TNFα expressing cells was significantly lower in HIV-infected pregnant women compared to HIV-uninfected pregnant women (p<0.05). The frequency of IFNy expressing cells was significantly lower in HIV-infected pregnant women compared to HIV-uninfected pregnant women (p<0.05). The frequency of IFNy expressing cells was significantly lower in HIV-infected pregnant women compared to HIV-uninfected pregnant women (p<0.05).

**Results:** The HIV-specific CD4 T cell response in chronic natural HIV infection and the response to different vaccine modalities differed markedly. While chronic HIV infection provoked a higher frequency of HIV-specific CD4 T cells than vaccination (p<0.001, n=6 for chronic HIV infection, n=97 for vaccination), the functional profiles between the responses induced in natural HIV infection versus after vaccination were also significantly different. Chronic natural HIV infection showed an HIV-specific CD4 response dominated by Tfh polarization than intramuscular injection. Additionally, the choice of prime and boost influenced the degree of multifunctionality induced in T cells. The prime/boost combination ALVAC-HIV/gp160 (RV132) led to the highest frequency of HIV-specific CD4 memory T cells with a polyfunctional profile (p=0.028 for the frequency of IFNy and p=0.035 for TNFα expressing cells compared to the other vaccine modalities).

**Conclusion:** Overall, we describe the varying functional T cell response to different vaccination strategies and the differences in responses to chronic HIV-1 infection vs. vaccination. Future approaches to vaccine design will be informed by this and further studies with the goal to induce polyfunctional T cell responses, which support the production of protective antibodies.
serostatus groups in either 1st or 2nd trimesters (figure). Additionally, individuals on preconceptional ART and with suppressed viral load were not found to differ significantly from their non-preconceptional ART and unsuppressed viral load counterparts, respectively. In individuals with repeat specimens, there were no statistically significant differences between groups for both CD4+CD25+CD127low (p = 0.67) and CD4+CD25+CD127lowFoxP3+ (p = 0.42) phenotypes.

**Conclusion:** Exploratory data from this African cohort established specifically to study PTB do not demonstrate significant aberrations in peripheral Treg frequencies in HIV infected pregnant women. Although Tregs may play a role in HIV-associated PTB at the maternal-fetal interface, this finding indicates that their role is unlikely to be systemic.

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**THE IMPACT OF HIV EXPOSURE ON PLACENTAL PATHOLOGY AND TREG CELLS**


**University of Cape Town, Cape Town, South Africa**

**Background:** One of the main roles of the placenta is to maintain fetal-maternal (FM) tolerance. HIV and/or antiretroviral (ARV) exposure may interfere with this tolerance but data are sparse. We characterized placental decidua T regulatory cells (Treg) from HIV-infected women who initiated ART late in pregnancy compared to uninfected controls.

**Methods:** Placentas of HIV-infected women were drawn from an ongoing study in which women commence antiretroviral therapy (ART) at or after 28 weeks’ gestation (n=14) and HIV-uninfected controls (n=6). The maternal decidua and villous tissue were dissected and enzymatically digested to obtain lymphocytes which were characterised using 15 colour multiparametric flow cytometry. Placenta tissue sections were formalin-fixed and wax embedded for Treg cell characterisation using immunofluorescence and pathology scoring based on the Amsterdam placental workshop group consensus statement.

**Results:** A higher incidence of preterm deliveries was reported in the HIV infected mothers, 75% were very preterm (28+0-31+6 weeks), 18% moderate or late preterm (32+0-36+6 weeks) and 12% term (>37 weeks). The frequency of decidual CD4+ T cells was lower in placenta from HIV infected women when compared with HIV uninfected controls (p=0.005) and similarly, total CD8+ T cells were significantly higher in the HIV infected group (p=0.006). The variable expression of TIGIT (T cell Ig and ITIM domain) and CD45RA, expression on CD4+ T cells within decidual membranes was higher in HIV infected women vs uninfected. We identified a series of Treg subsets within the decidua that were all CD3+CD4+CD127+CD25highFoxP3++ with variable expression of CD39, CTLA4 and TIGIT. Highly suppressive Treg cells, co-expressing all three markers were all CD3+CD4+CD127-CD25hiFoxP3++ with variable expression of CD39, TIGIT and CD45RA, expression of which women commence ART late in pregnancy compared to uninfected controls.

**Conclusion:** The T cell phenotype in the maternal decidua appears to have a predominately adult systemic footprint while the villous tissue mirrors foetal cells; an increased influx of naïve cells. There are unique and multiple Treg signatures in the placenta which appear to be associated with pre-term birth and may be influenced by HIV exposure and ARV that warrant further investigation.

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**HIV RESERVOIR SIZE IS CORRELATED TO NK-MEDIATED KILLING OF EFFECTOR MEMORY CD4 CELLS**

Antonio Astorga Gamaza1, Judith Grau-Expósito1, Laura Luque-Ballesteros1, Ariadna Torrella1, Bibiana Planas1, Rosa Badia1, Esteban Ribera2, Joaquin Burgos1, Jordi Navarro1, Adrià Curran2, Vicenç Falci1, Maria J. Buzón1

1Vall d’Hebron Research Institute, Barcelona, Spain, 2Hospital Universitario de la Vall d’Hebron, Barcelona, Spain

**Background:** The identification of immune control mechanisms of the viral reservoir might help to develop new strategies to cure HIV. Antibody-dependent cell-mediated cytotoxicity (ADCC), largely mediated by natural killer (NK) cells, has been reported highly relevant to control HIV. However, the role of ADCC-NK at controlling the cells that compose the viral reservoir is currently unknown.

**Methods:** The intrinsic susceptibility of Naïve (NA), Stem Cell Memory (SCM), Central Memory (CM), Effector Memory (EM) and CD20dim CD4 T cells, to ADCC NK-mediated killing was measured by a novel flow cytometry-based assay. n=10 ART-suppressed and 5 elite controllers (EC) patients were included. Isolated CD4 T cells were stained with the markers eF670 and PKH67 and coated with the gp120Bal protein. Cells were incubated with plasma from an HIV positive patient and autologous NK cells at ratio 1:1 for 3 hours. Then, cells were stained with CD3, CCR7, CD45RO, CD95, CD20 and HLA DR antibodies. NK-mediated killing was calculated as the disappearance of cells measured with the addition of flow cytometry particles. Total HIV-DNA and HIV-RNA was quantified by qPCR.

**Results:** Results from all analyzed patients showed that each subset had a different susceptibility to killing, being CD20dim<CM<EM<NA<SCM more prone to be killed (ANOVA Friedman test p<0.0001). Moreover, whereas no differences in the killing of the whole CD3 population were observed between cohorts (Mann-Whitney test, p=0.5122), EC showed higher potency to kill CD20dim and EM (median 61.6, 52.0, 48.0, 33.6 and 33.4% for CD20dim, EM, CM, NA, SCM, respectively) (ANOVA Friedman test p=0.0081), while ART-suppressed patients were more efficient at killing CM and CD20dim cells (median 49.5, 38.7, 37.6, 35.7 and 29.9% for CM, CD20dim, NA, EM, SCM, respectively) (ANOVA Friedman test p=0.0005). A more efficient killing of CD20dim cells was detected in EC compared ART-suppressed patients (Mann-Whitney test, p=0.0383).

Importantly, an inverse correlation between the capacity of NK cells to kill the EM subset and the viral reservoir was observed (rho=-0.6000 p=0.0261 for viral DNA and rho=-0.8857 p=0.0333 for viral RNA).

**Conclusion:** The susceptibility of different CD4 T subsets to ADCC-NK killing differs. The ADCC activity against EM cells, one of the most HIV-transcriptionally active cell subsets, was highly correlated to the size of the persistent HIV-reservoir. Inducing the specific killing of EM cells might significantly help to diminish the persistent reservoir.
325 IMPACT OF A NOVEL NATURAL KILLER CELL SUBSET ON IMMUNE RECONSTITUTION

University of California Davis, Davis, CA, USA

Background: We have identified a novel subset of NK cells, called ‘g-NK cells’, which display adaptive immune features, including clonal-like expansion and long-term persistence. The presence of g-NK cells is associated with previous infection by cytomegalovirus and has enhanced response to broad range of viral-infected cells in the presence of virus-specific antibodies. We hypothesize that g-NK cells contribute to low CD4 counts in HIV patients and CD4 recovery during ART.

Methods: In a cohort of 18 MSM chronically infected HIV patients naïve to treatment before and 12 months after starting a PI-based cART, the presence of g-NK cells, as well as their frequencies and phenotypic characteristics, were measured by flow cytometry after intracellular staining of FcR-gamma signaling protein following cell surface marker staining. 17 HIV-negative control underwent identical procedures. Plasma biomarkers of inflammation were measured by ELISA and cytokine production by g-NK cells and conventional NK cells after stimulation with HIV-infected cells in the presence or absence of HIV-seropositive plasma.

Results: We observed that (1) HIV patients possessed higher frequencies of g-NK cells compared to HIV-negative control groups (39.9% and 10.33%, p=0.0320), (2) HIV patients with readily detectable g-NK cells show a trend toward lower CD4+ T cell count before (p<0.08) and 1 yr after cART (p<0.01), (3) g-NK cells did not change levels before and after the treatment, and (3) compared to conventional NK cells, g-NK cells produced greater amount of IFN-γ and TNF-α in response to HIV-infected cells in the presence of HIV-seropositive plasma.

Conclusion: g-NK cells are more frequent in HIV-infected patients compared to controls and may contribute to low CD4 counts in HIV patients and poor recovery during ART. g-NK cells may be a useful biomarker for predicting how the CD4+ T cell population may recover during HIV treatment.

326 LIPIDOMIC FINGERPRINTING TO IDENTIFY HIV RESERVOIRS IN VITRO AND IN VIVO

Christina Gavegnano1, Yong Jiang1, Sijia Tao1, Ruby Kleinbard1, Anush Arakelyan2, Andrea Lisco1, Irini Sereti3, Leonid Margolis4, Raymond F. Schinazi1
1Emory University, Atlanta, GA, USA, 2National Institute of Child Health and Human Development, Bethesda, MD, USA, 3National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

Background: One of the most important questions in designing cure-based strategies in HIV research is the origin(s) of the reservoir. It is well established that HIV rebounds upon withdrawal of Highly Active Antiretroviral Therapy (HAART) leading to viral breakthrough and HIV envelopes contain lipids originating from the membrane of the virus producing cells. Thus, an innovative highly sensitive, clinical sample-validated Virus Lipidomic Mapping (VLM) assay was developed to accurately quantify lipid compositions of HIV-1 virions (< 5 copies/mL) and host cells, allowing virus to be mapped to host cell origin.

Methods: Primary human CD4+ T cells or monocytes were isolated (healthy buffy coats; magnetic sorting; n = 12). HIV-1Bal was used to infect CD4+ T cells or differentiated macrophages (MΦ). HIV from CD4+ T cell or MΦ origin (n = 4) was captured from viremic plasma of HIV+ individuals with magnetic beads (LSM) and further processed to enrich for T cells or MΦ-specific proteins incorporated into virions followed by virus purification and exosome removal. Lipids were extracted from cells; profiles, abundance and ratios (cells and virus) were determined by LC-MS/MS (Q-Exactive Plus).

Results: For all donors, the cellular lipid profiles for CD4+ T cells were distinct from MΦ lipid profiles. Virions grown in each cell type contained unique lipids that match unique lipids on host cell origin. Distinctive profiles for MΦ cellular and virion lipids included mono- and dietherphosphatidylcholine (MePC, PC) and ceramides (Cer), glucosylceramide (GlcCer), dicylglycerol (DG), phosphatidylcholine (PC), phosphatidyethanolamine (PE), sphingomyelins (SM), and triglyceride (TG); unique profiles for T-cell virion and cellular lipids include subtypes SM(d35) and CerG1(d18). For all donor samples, virions that carried specific T-cell proteins showed unique lipid profiles compared to virions that carried MΦ-specific proteins; Cer (d17, d18), DG(d35), PC(d34), PE(d42), PI(d18), SM(d35), and ChE(d18).

Conclusion: Conclusions: For the first time, the VLM method 1) identified host cell origin of persistent HIV-1 in vivo, even with low-prevalence populations of mixed virions, and 2) determined unique lipid profiles for virions from T-cells versus MΦ, which match cellular lipid profiles on host cell origin. This information provides a foundation for cure-based strategies to identify and eliminate key cells harboring persistent HIV not eliminated by HAART.

327 CHARACTERIZING THE HIV DNA RESERVOIRS IN WHOLE-BODY TISSUES IN THE “LAST GIFT” COHORT

Michelli Faria de Oliveira1, Benjamin Murrell1, Thomas Vollbrecht1, Susanna Concha-García1, Venkatesh Kumar1, Magali Perruchas2, Brianna Scott1, Laura Layman1, Caroline Ignacio1, Sara Gianella1, Davey M. Smith1
1Emory University, Atlanta, GA, USA, 2National Institute of Child Health and Human Development, Bethesda, MD, USA

Background: One of the most important questions in designing cure-based strategies in HIV research is the origin(s) of the reservoir. It is well established that HIV rebounds upon withdrawal of Highly Active Antiretroviral Therapy (HAART) leading to viral breakthrough and HIV envelopes contain lipids originating from the membrane of the virus producing cells. Thus, an innovative highly sensitive, clinical sample-validated Virus Lipidomic Mapping (VLM) assay was developed to accurately quantify lipid compositions of HIV-1 virions (< 5 copies/mL) and host cells, allowing virus to be mapped to host cell origin.

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**Background:** HIV persistence in cellular reservoirs is the main barrier to a cure. The size and composition of HIV DNA populations in solid tissues during suppressive antiretroviral therapy (ART) is not well characterized.

**Methods:** We examined the distribution and genotypic composition of the HIV DNA populations across paired post-mortem tissues from one virally suppressed person living with HIV (PLWH) from the Last Gift (LG) Cohort. The LG cohort enrolls altruistic, terminally-ill PLWH, who are closely followed until the time of death and donate their “whole-body” for HIV research. Blood and tissues are collected by rapid-autopsy and cryopreserved within 6h from death. From each sample, we extracted total DNA and quantified HIV DNA (pg) levels by droplet-digital PCR. The genotypic composition of the HIV DNA in tissues was evaluated using a high-throughput single genome amplification and the PacBio platform to deeply sequence full-length HIV envelope (FL HIV-env).

**Results:** The participant was a 72-year-old man with chronic HIV infection and metastatic pancreatic cancer. He enrolled in the LG study 5 months prior death. He was on ART and had undetectable HIV RNA in blood plasma, up to 7 hours before death (<20 copies/ml). From 26 paired post-mortem tissues, HIV DNA was detected in 24 samples, including brain (3-11 cpi HIV/106 cells), gastrointestinal (45-211), urogenital tract (46-377), lymphoid (22-243) and adipose (13-874) tissues. HIV DNA was undetectable in parietal and motor cortex. We obtained 107 individual FL HIV-env sequences across 10 tissues (median 10.7 sequences/tissue), of which 60 were unique. The maximum likelihood phylogeny (figure) showed a deep divergence, segregating the tree into two lineages, which differed by co-receptor tropism, based on in silico tropism prediction (geno2pheno). Interestingly, 100 FL HIV-env sequences were genetically intact, while 7 sequences were non-functional, with major deletions, frameshifts, and stop codon mutations. HIV-env migration appeared to be extensive, with many identical sequences sampled in multiple body tissues.

**Conclusion:** HIV DNA was detected in most body tissues despite long-term ART and confirmed undetectable HIV RNA at the time of death. Based on the FL HIV-env sequencing, most HIV reservoirs appeared to be intact provirus and may present different viral tropisms. The LG cohort poses a unique opportunity to characterize the HIV reservoirs in anatomic compartments, which is crucial to provide insights for future HIV cure strategies.

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HIV-INFECTED CD4 T-CELL ISOLATION USING A MICROFLUIDIC MAGNETIC LEVITATION SYSTEM

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1Stanford University, Stanford, CA, USA, 2University of California San Francisco, San Francisco, CA, USA
Background: Strategies to identify and isolate HIV infected cells at various states of latency or transcriptional activation are urgently needed. We developed and implemented a novel microfluidic system that is able to sort untouched CD4+ T cells from HIV-infected individuals based on levitation heights within a magnetic field (i.e. magnetic density). We compared HIV DNA and unspliced RNA burden and immune phenotypes in cells from high and low density populations.

Methods: Untouched CD4+ T cells from 15 ART-suppressed individuals were sorted based on magnetic density using our novel microfluidic magnetic cell levitation and sorting system (Figure). A microfluidic chip-based platform incorporates collection channels for high-throughput isolation of cells levitating at different heights in a biocompatible paramagnetic medium for downstream characterization of HIV burden and immune phenotype.

Results: Overall, CD4+ T cells from infected participants on ART levitated higher than cells from uninfected controls (229.6 vs 169 μM), but cell radii were similar. Two subpopulations of CD4+ T cells from ART-suppressed individuals were then isolated based on levitation height (the higher density populations contained 2.3-fold more cells). Markers of CD4+ T activation, immune checkpoint, and naive/memory phenotype (CD69, HLA-DR, CD38, PD1, CCR5, CD45RA, CCR7, CD4, CD3), as well as cell viability, were similar in both high and low density layers by flow cytometric analysis. Interestingly, HIV RNA levels from ART-suppressed individuals were significantly lower in the lower density subpopulation (0.81 log10 fewer copies/10^6 CD4+ T cells, P=0.007). Although there were no overall significant differences in HIV DNA levels between high and low density subpopulations, HIV DNA from three participant samples was highly enriched in lower density CD4+ T cells (>3 log10 copies/10^6 cells higher than in the higher density layer).

Conclusion: We demonstrate that HIV infected CD4+ T cells of various transcriptionally active states have unique magnetic levitation/density characteristics that may be unrelated to expression of commonly tested surface protein markers, cellular activation state, and cell size. In addition, HIV DNA was observed almost exclusively in lower density CD4+ T cells in three samples, suggesting that isolating cells based on magnetic levitation has the potential to be refined and applied to various HIV reactivation, latency or eradication studies.

A NEW PUBLIC DATABASE FOR NEAR FULL-LENGTH HIV SINGLE-GENOME SEQUENCES

Wei Shao1, Jingyi Shan1, Wei-Shau Hu2, Elias K. Halvas3, Brian Luke1, John W. Mellors1, John M. Coffin1, Mary F. Kearney1

1Leidos Biomedical Research, Inc, Frederick, MD, USA, 2National Cancer Institute, Frederick, MD, USA, 3University of Pittsburgh, Pittsburgh, PA, USA, 4Tufts University, Boston, MA, USA
Background: Despite the success of ART, HIV persists in reservoirs and viremia reactivation and eradication are urgently needed. We developed and implemented a novel microfluidic system that is able to sort untouched CD4+ T cells from HIV-infected individuals based on levitation heights within a magnetic field (i.e. magnetic density). We compared HIV DNA and unspliced RNA burden and immune phenotypes in cells from high and low density populations.

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correlated with 469 genes and pathways included: mTOR, p53, IL2-induced STAT5 and MYC signaling. **Conclusion:** Our study revealed biologically intuitive associations between host genetic pathways and HIV persistence. The strong positive correlation between HIV DNA and expression of the PDCD1 gene encoding PD-1 confirms T cell exhaustion as a mechanism underlying HIV persistence. The ST3GAL5 gene product catalyzes the production of GM3 which is a key regulator of cellular proliferation, trafficking, and survival; this finding is consistent with clonal proliferation as a key factor determining reservoir size. These data also demonstrate the profound and sustained effect of early versus late ART on CD4+ T cell function, and identifies several potential targets for immunotherapy.

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**333 EX VIVO CD4+ T-CELL DIFFERENTIATION IMPROVES HIV RESERVOIR QUANTIFICATION**

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1Southern Research Institute, Frederick, MD, USA, 2National Cancer Institute, Frederick, MD, USA, 3Blood Systems Research Institute, San Francisco, CA, USA, 4University of California San Francisco, San Francisco, CA, USA, 5Emory University, Atlanta, GA, USA

**Background:** Quantifying the number of cells harboring latent, replication-competent HIV provirus is critical in evaluating the efficacy of interventions aimed at reducing the viral reservoir. However, the low frequency of these cells makes this measurement extremely challenging. The quantitative viral outgrowth assay (QVQA) is based on ex vivo activation of resting CD4+ T cells to measure HIV persistence during anti-retroviral therapy (ART). Recent studies have shown that QVQA does not detect all latently infected cells assayed, potentially due to sub-optimal virus reactivation under standard culture and activation conditions. Here, we applied our observation that differentiation into effector CD4+ T cells more effectively promotes HIV latency reversal to improve proviral reactivation in the QVQA, termed differentiation QVQA (dQVQA).

**Methods:** Peripheral blood samples from virally suppressed donors (n=12) were enriched for resting CD4+ T cells and plated in replicate limiting dilution. Cells were then either activated according to the standard QVQA procedure, or induced to differentiate into effector lineages prior to activation. CD4+ T cell phenotypes were assessed by flow cytometry and culture supernatants were induced to differentiate into effector lineages prior to activation. CD4+ T cell function, and identifies several potential targets for immunotherapy.

**Results:** Coupling CD4+ T cell differentiation with activation in dQVQA induced a 14-fold average increase (95% CI 4- to 24-fold) in the estimated frequency of cells with replication competent HIV compared to standard QVQA, indicating that promoting effector lineage differentiation significantly increases expression of latent HIV. Viral kinetics and SGS analyses demonstrated the replication competence of reactivated virus. dQVQA reservoir measurements demonstrated a correlation with clinical markers in addition to a large reduction in the coefficient of variation, suggesting that understanding the key mechanisms of latency reversal will reduce the reliance upon stochastic HIV reactivation, which improves assay reproducibility.

**Conclusion:** Differientiation into effector phenotype supports more effective latency reversal of replication competent HIV in resting CD4+ T cells and offers key insights into mechanisms of HIV latency reversal that may offer potential targets for therapeutic interventions.

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**334 CYTOF CHARACTERIZATION OF THE IN VIVO LATENT HIV RESERVOIR IN BLOOD AND TISSUES**

Jason Neidleman1, Xiaoyu Lui1, Grace Xie1, Rebecca Hoh1, Peter W. Hunt1, Steven G. Deeks1, Warner C. Greene1, Marielle Cavrois2, Nadia R. Roan1

1University of California San Francisco, San Francisco, CA, USA, 2Gladstone Institute of Virology and Immunology, San Francisco, CA, USA

**Background:** One of the major hurdles for directly phenotyping the in vivo latent HIV reservoir is the need to stimulate these cells ex vivo. As the cells are stimulated, they change expression of many cell surface markers making precise phenotyping of the latent cells difficult. We recently established an approach called PP-SLIDE (Predicted Precursor as determined by SLIDE) that can effectively backtrack in time to establish the cell surface phenotype of a cell before infection (Cavrois et al 2017) using high-dimensional datasets generated by CyTOF phenotyping. This approach was implemented to chart the in vivo latent HIV reservoir and identify biomarkers of these cells.

**Methods:** The ability of PP-SLIDE to trace the phenotype of a reactivated cell to its precursor (non-stimulated) state was first confirmed in an in vitro model of HIV latency. Then, freshly isolated blood and lymph node cells from ART-suppressed, HIV-infected individuals from the SCOPE cohort were stimulated with PMA/ionomycin, and reactivated cells (expressing Gag) were deep-phenotyped using a 39-parameter latency-focused CyTOF panel. PP-SLIDE was used to map the reactivated cells onto a T cell atlas of unstimulated cells created for each patient sample analyzed.

**Results:** Comparison of latent to non-latent cells revealed unique signatures associated with latency. Receptors preferentially expressed on latently-infected T cells from blood include previously described markers such as PD1, TIGIT, and OX40, as well as novel ones including homing integrin a4b1. Latent cells from lymph nodes also preferentially expressed PD1, TIGIT, and OX40, and differed from latent cells in blood in that they exhibited features of resident memory cells and preferentially expressed the T follicular helper marker CXCR5 and the costimulatory molecules CD28 and ICOS.

**Conclusion:** By simultaneously detecting the expression of 39 proteins in individual reactivated cells and mapping this information onto an atlas of unstimulated cells, we have begun to establish a high-resolution view of the types of latent cells that persist in HIV-infected individuals. Applying this method to chart the reservoir in blood and tissues of additional donors will provide a more complete picture of the nature of the persistent reservoir. Our findings thus far reveal that latent cells exhibit unique features, some of which differ between blood and tissues consistent with the notion that unique mechanisms of persistence are present in tissues.

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**335 TREASURE HUNT: HIV DNA IN DISTINCT SUBSETS IN THE BLOOD, TERMINAL ILEUM, AND RECTUM**

Max Augustin1, Sarah Horn1, Meryem S. Ercangul1, Vincent Bondet2, Isabelle Suarez2, Seung-Hun Chon3, Dirk Niehoff1, Elena Knops4, Eva Heger1, Mark Oette3, Clara Lehmann1

1Cologne University Hospital, Cologne, Germany, 2Institut Pasteur, Paris, France, 3Academic Hospital Augustinerinnen, Cologne, Germany

**Background:** The associated lymphatic tissue (GALT) shows major differences in immune cell composition along the intestine. The largest part of the GALT is located in the terminal ileum (TI), and the HIV reservoir has been associated with CXCR3 and PD1 expression on CD4+ T cells, and the chemokine IP-10. However, in contrast to the rectum (R), studies of the TI are scarce due to the difficulty in obtaining biopsies. The aim of this study was to compare the interplay of IP-10, CXCR3, PD-1 and the size of the viral reservoir between peripheral blood (PB), R and TI in HIV+ patients on ART.

**Methods:** Paired PB, TI and R samples from 20 HIV+ patients (HIV-RNA < 20 cop/ml) and 11 healthy controls were studied (median CD4+ T cells of HIV+...121
transplantation. Purified CD4+ T cell populations were analyzed using the intact HIV-infected, virally suppressed participants immediately prior to solid organ lymph node samples. We characterized total intact, defective, and inducible virus in paired blood and subset of intact proviruses are readily activated in vitro. To resolve these issues by many assays but is not of concern in cure strategies. Additionally, only a Measuring the LR is complicated by an excess of defective virus that is detected in defective virus per million between these sites (median=789, IQR=357-104 (IQR 48-591) in lymph nodes and 61 (IQR=43-440) in blood; this difference was median=9.9%. Only a small proportion of the intact provirus population was inducible (median=5.7%, IQR=3.3-10.8%) with an even smaller subset of inducible defective provirus (median=1.3%, IQR=0.9-2.3%). Intact and inducible provirus correlated (r=0.779, P=0.0006).

**Conclusion:** Using two novel assays to analyze different properties of the HIV-1 LR we found no quantitative differences between the peripheral blood and lymph nodes. Taken together with previously reported data showing no difference in the distribution of HIV-1 proviral sequence variants between these sites, we conclude that levels of intact and inducible HIV-1 in blood provide a reasonable approximation of frequencies in the lymph nodes.

**Distribution of HIV-DNA in different CD4+ memory subsets in peripheral blood, terminal ileum and rectum.**

**HIV-DNA/WWC (copies)**

<table>
<thead>
<tr>
<th>Subset</th>
<th>Blood</th>
<th>T-cell memory</th>
<th>T-central memory</th>
<th>T-effector memory</th>
<th>T-transitional memory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV DNA</td>
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**336 PROPORTION OF INDUCIBLE AND INHIBIT-1 T-1 IN BLOOD IS REFLECTIVE OF LYMPH NODES**

**Alyssa R. Martin**, Alexandra M. Bender, Kyunguyo J. Kwom, Diane M. Browne, Niraj Desai, Dorry Segev, Thomas C. Quinn, Aaron Tobian, Christine Durand, Andrew D. Redd, Robert Siliciano

**Background:** The latent reservoir (LR) for HIV-1 persists in CD4+ T cells and is a barrier to cure. The LR has been well characterized in peripheral blood, but lymph nodes have been proposed as a unique sanctuary with concerns that they harbor a greater proportion of latently infected cells, and that measurements in the LR in peripheral blood would not be representative of other tissue sites. Measuring the LR is complicated by an excess of defective virus that is detected by many assays but is not of concern in cure strategies. Additionally, only a subset of intact proviruses are readily activated in vitro. To resolve these issues we characterized total intact, defective, and inducible virus in paired blood and lymph node samples.

**Methods:** Peripheral blood and lymph node samples were collected from 8 HIV-infected, virally suppressed participants immediately prior to solid organ transplantation. Purified CD4+ T cell populations were analyzed using the intact proviral DNA assay (IPDA) to determine the number of intact and defective proviral genomes by ddPCR, and by a novel quantitative viral induction assay (QVIA) to determine the number of inducible proviruses in each sample by quantification of cell-associated RNA at limiting dilution.

**Results:** No difference in inducible virus was detected between lymph node and blood samples (median=4.3, 79 inducible proviruses per million, respectively). The median number of intact provirus per million CD4+ T cells was 104 (IQR 48-591) in lymph nodes and 61 (IQR=43-440) in blood; this difference did not reach statistical significance (P=0.109). There was also no difference in defective virus per million between these sites (median=789, IQR=357-3642; median=584, IQR=299-1530; P=0.95). The ratio of intact to total virus was median=9.9%. Only a small proportion of the intact provirus population was inducible (median=5.7%, IQR=3.3-10.8%) with an even smaller subset of inducible defective provirus (median=1.3%, IQR=0.9-2.3%). Intact and inducible provirus correlated (r=0.779, P=0.0006).

**Conclusion:** Using two novel assays to analyze different properties of the HIV-1 LR we found no quantitative differences between the peripheral blood and lymph nodes. Taken together with previously reported data showing no difference in the distribution of HIV-1 proviral sequence variants between these sites, we conclude that levels of intact and inducible HIV-1 in blood provide a reasonable approximation of frequencies in the lymph nodes.
A METHOD TO DETERMINE BOTH THE INTEGRATION SITES AND SEQUENCES OF HIV-1 PROVIRUSES

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Background: Most of the HIV-1 reservoir on ART is likely contained within clonally-expanded cells carrying intact proviruses. Current methods used to characterize the reservoir include near full-length single-genome sequencing (NFL-SGS) and integration site analysis. However, new technologies are needed to link proviruses to their integration sites. We describe a method, called full-length integrated proviral single-genome sequencing (FLIP-SGS), to solve this problem.

Methods: Genomic DNA from PBMC or lymph node mononuclear cell samples (LNMC) from 4 donors was diluted to much less than one provirus per well. An in-house optimized multiple-displacement amplification (MDA) method was performed on each of the wells, generating multiple copies of genomic DNA in each well. Aliquots of the MDA products were then used to obtain the integration sites and to PCR amplify and sequence the corresponding proviruses. The near full-length (NFL) sequences were compared to the sequences of viruses obtained in quantitative viral outgrowth assays (qVOA) to identify clones with replication-competent proviruses.

Results: FLIP-SGS was applied to evaluate identical P6-PR-RT sequences identified by standard SGS in PBMC or LNMC. We obtained the integration sites and NFL sequences from several clones that contained defective proviruses and one clone with an intact provirus that matched the NFL sequence of an infectious virus identified by qVOA. In 3 donors, identical sequences identified by P6-PR-RT SGS were confirmed to be of clonal origin by FLIP-SGS (identical integration sites) but we also found proviruses with identical P6-PR-RT sequences that had different integration sites, i.e. “false clones.” Such false clones were more common in donors with low proviral diversity or with drug resistant variants.

Conclusion: We describe a new method that can link the sequence of a provirus with its integration site. This method can differentiate 1) identical proviral sequences that are within a cell clone from those that are not; and 2) intact from defective proviruses in cell clones. We identified a second in vivo clone that contains a replication-competent provirus, providing additional evidence that the HIV-1 reservoir is comprised, at least in part, of infectious proviruses in clonally expanded cells. In donors with low proviral diversity or other genetic bottlenecks (e.g. selection of drug resistant variants), identical proviral sequences may or may not be in clones of cells.

DISTINCT CHROMOSOMAL POSITIONS OF INTACT HIV-1 PROVIRUSES

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Background: CD4+ T cells harboring integrated HIV-1 DNA represent a long-lasting viral reservoir that can persist for decades in infected individuals despite effective antiretroviral therapy (ART). A small minority of these proviral sequences are genetically intact yet transcriptionally silent during ART, though the mechanisms that maintain this viral latency remain unclear. Chromosomal positions of intact proviruses may critically influence viral transcriptional activity, but have been insufficiently characterized in the past, primarily due to the lack of experimental techniques enabling simultaneous analysis of proviral sequences and corresponding integration sites.

Methods: Proviral HIV-1 sequences from CD4+ T cells of 3 long-term ART-treated individuals were diluted to single genomes and subjected to whole-genome amplification using phi29 polymerase. Products containing 1,000-10,000 copies of an identical proviral sequence were split and separately used for near full-length viral sequencing and for integration site analysis using integration-site loop amplification or ligation-mediated PCR. Chromatin accessibility and gene expression in autologous CD4+ T cells were analyzed by ATAC-Seq and RNA-Seq.

Results: We identified paired proviral sequences and integration sites for 100 intact and 84 defective proviruses. Among these, we detected several clusters of clonally-expanded proviruses exhibiting identical viral sequences and integration sites (8 intact clusters, 6 defective clusters). Relative to defective proviruses, intact proviruses were enriched for non-genic or pseudogenic sites (16% vs 8%, p=0.03) and more frequently displayed an opposite orientation relative to host genes (74% vs 57%, p=0.02). Additionally, intact proviruses were preferentially integrated either in relative proximity (2 participants) or with increased distance (1 participant) to active transcriptional start sites and to accessible chromatin regions, suggesting an enrichment of sites that are either more susceptible to transcriptional interference or located in genomic regions with more limited access to host transcriptional machinery, respectively.

Conclusion: Our results suggest that prolonged ART is associated with a selection of intact proviruses with multiple discrete features of deeper latency, likely due to immune-mediated selection pressure. The intact reservoir may thus be vulnerable to interventions aimed at accelerating the selection of proviruses with deeper latency and reduced ability to fuel rebound viremia.

RELATIONSHIP BETWEEN INTACT HIV-1 PROVIRUSES AND PLASMA REBOUND VIRUSES

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Background: Combination antiretroviral therapy controls but does not cure HIV-1 infection due to a small fraction of cells harboring latent viruses that can produce rebound viremia upon therapy interruption. The circulating intact latent reservoir has been documented by either viral outgrowth assays (VOAs), or by amplifying near full length (NFL) proviral sequences from DNA. Analysis of samples obtained in clinical studies whereby individuals underwent analytical treatment interruption (ATI), showed little overlap between latent viruses from VOAs pre-ATI, and viruses isolated from plasma during viral rebound. To determine whether intact proviruses from DNA are more closely related to rebound viruses than those obtained from VOAs, we assayed 32 individuals who underwent ATI after infusion of two broadly neutralizing anti-HIV-1 antibodies (bNAbs).

Methods: NFL proviral genomes were amplified from DNA extracted from CD4+ T cells obtained from 2 leukapheresis samples (pre- and post-bNAb infusions) from 9 individuals that maintained viral suppression for >12 weeks after ATI. A single pre-infusion sample was also available for 3 additional individuals that experienced viral rebound within 12 weeks of ATI due to pre-existing bNAbs-resistant proviruses in the latent reservoir. VOA was performed on all of these samples to determine the number the inducible replication-competent proviruses.

Results: The env sequences from 435 intact proviruses obtained by NFL sequencing were compared with 650 latent viruses from VOAs and 246 plasma rebound viruses. Although, intact NFL and outgrowth culture sequences showed similar levels of stability and diversity with 39% overlap, the size of the reservoir estimated from NFL sequencing did not correlate with that obtained by VOA. Although all of the rebound viruses in plasma were >96% identical to at least one sequence from the reservoir, we did not find a single instance of 100% env identity among intact NFL sequences and rebound viruses. Moreover, only 12 out of 246 rebound sequences could be accounted for by mutation of reservoir sequences during the ATI window. However, 48% of the rebound viruses could be derived from recombination between intact NFL and/or VOA proviruses.

Conclusion: We find that intact proviruses obtained from DNA overlap in part with those obtained by VOA, but do not overlap with rebound viruses. However, nearly half of all rebound sequences appear to be recombinants derived from circulating latent viruses characterized by VOA or NFL sequencing.

LANDSCAPE OF HIV-1 INTEGRATION SITES IN LYMPHOID TISSUE FROM ART-TREATED INDIVIDUALS

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Background: The integration of HIV DNA into the host genome occurs from the activity of both viral proteins and host cellular factors. Prior analyses in cell
lines and peripheral blood mononuclear cells (PBMC) samples have assessed the HIV-1 integration site distribution and characterized regions such as active transcription units that favor integration. The host encoded LEDGI/p53 protein tethers HIV-1 integrase at active transcription units, accounting for this bias. To date, no studies have compared integration site distributions within tissue resident cells – namely in lymphoid tissues where HIV-1 is known to replicate and persist even after antiretroviral treatment (ART). 

Methods: Tonsil samples were collected from three ART-treated and HIV-infected patients to sort into non-naive CD4+ cell subsets: circulating (HLA-DR - CD69 - ), tissue-resident (HLA-DR - CD69 + ), and germinal-center Tfh (HLA-DR - CXCR5 + PD-1 hi ) cells. Genomic DNA was extracted from the different cell types, sonicated, and then uniquely labeled by cell subset and patient. Libraries were created via ligation-mediated PCR and sequenced using the MiSeq platform (Illumina). Downstream analyses were done using the INSPIRED software pipeline and R.

Results: Of the integration sites sequenced, the majority across patients were found to be enriched within transcription units. Viral-host junctions were detected in 21 of the human autosomal chromosomes as well as the X chromosome in the combined dataset. We detected an average ratio (integration sites per one thousand cells) of 0.046 ± 0.025 for circulating cells, 0.137 ± 0.106 for tissue resident cells, and 0.067 ± 0.065 for Tfh cells. Curiously, we observe little to no overlap in integration site coverage between the circulating, tissue resident, and germinal-center Tfh cells by patient.

Conclusion: Our findings agree with previous studies regarding HIV-1 integration within transcription units. However, the lack of gene overlap across cell subsets may suggest unique integration signatures in lymphoid tissue. The novelty of these results demonstrates the need for further analysis on integration sites in lymphoid resident cells as well as PBMC cells at different stages of HIV-1 progression. Analyzing the integration site signature in the lymphoid resident cells will help contribute more insight to the goal of understanding and eliminating the latent reservoir.

342 GENETIC AND AGE DISTRIBUTION OF LATENT HIV SEQUENCES IN CD4+ T-CELL SUBSETS

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Background: HIV latency is the main barrier to cure, but our understanding of within-host latent proviral landscapes, particularly in distinct CD4+ T-cell subsets, is incomplete. We characterized sequence diversity and estimated age distribution of latent HIV sequences in naïve, central memory (CM), transitional memory (TM) and effector memory (EM) CD4+ T-cells from HIV-infected individuals with long-term viremia suppression on cART.

Methods: CD4+ T-cell subsets were sorted from PBMC from 5 participants with a median 9 (IQR 9-13) years pVL suppression on cART. Proviral DNA was sequenced from these subsets using single-genome approaches (nef region); sequence compartmentalization was assessed using the Slatkin-Maddison (SM) test following maximum likelihood phylogenetic inference. For 4 participants, single-genome HIV RNA sequences were also obtained from a median 11 (IQR 6-15) pre-cART plasma samples spanning a median 8 (IQR 3-11) years; these data were analyzed in a novel within-host phylogenetic approach to infer proviral sequence ages.

Results: 539 nef proviral sequences were isolated; 424 (78%) were genetically intact, of which 347 (82%) were unique. Intact sequence percentage varied between hosts (68-93%) and between T-cell subsets (naïve 71%; CM 79%; EM 86%; TM 88%). EM harbored the lowest % uniqueness (56%) and CM the highest (96%). Within-host latent HIV phylogenetic diversity varied between hosts (average tip-to-tip phylogenetic distances 2.1e-2-9.6e-2 nucleotide substitutions/site), though there was no clear relationship between within-host latent HIV diversity and length of uncontrolled viremia, or length of cART suppression. In 3 participants, proviral genetic diversity differed between subsets (Kruskal-Wallis p<0.05). Two of these participants, plus one other showed evidence of genetic compartmentalization (SM p<0.01). Proviral sequence ages varied markedly between hosts (median 10.4 max 23 years) and in two cases also differed between subsets: for example, in one participant, latent HIV sequences in naïve T-cells were younger than the other subsets (p=0.01).

Conclusion: The latent HIV proviral landscape differs markedly between individuals, and sometimes between different CD4+ T-cell subsets within the same individual: eradication strategies may need to take this into consideration. Inference of proviral sequence ages in different HIV T-cell subsets can yield insight into latent HIV dynamics and persistence.

343 B CELL-T CELL DOUBLES IN GALT ARE ENRICHED FOR TFH CELLS BUT NOT FOR HIV DNA

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Background: Gut-associated lymphoid tissue (GALT) is a key HIV reservoir site and may play a role in HIV persistence on ART. T follicular helper (Tfh) cells and CD32+CD4+ T cells have been proposed to be enriched for HIV DNA. Here, we show that CD32+CD4+ T cells in GALT are B-cell-T-cell (BT) doublets and that sCD40 (a soluble marker shed after B:T cell interaction through CD40/CD154 signaling) but not CD32 is associated with HIV DNA in GALT.

Methods: GALT from the terminal ileum (TI), rectum (R) & tonsil tissue (n=11) was obtained from consenting individuals treated during primary HIV infection (PHI). HIV DNA was quantified in GALT biopsies by qPCR. Concurrent plasma samples were used to measure IL-4, IL-5, IL-6, IL-10, IL-15, MCP-1, MIP-1a, MIP-1b, IP-10, sCD163, CD40 & CD40L by Lumixen (n=23). CD32 expression on GALT CD4 T cells was measured by flow cytometry (n=19) and imaging cytometry assessed CD19, CD3, CD4, ICOS, HLA-DR & CD32 expression in healthy control GALT and HIV+ tonsil. Associations between HIV DNA & CD32 were tested by Spearman’s correlation. LASSO regression analyses were used to test for associations between GALT HIV DNA & plasma variables.

Results: 23 PHI individuals were studied; median (IQR) HIV DNA was significantly higher in TI compared to R (2.82 (2.58-3.05) vs 2.73 (2.42-2.96) log10 CPM gut T cells, p=0.03). CD32 expression on GALT CD4 T cells was not associated with HIV DNA. Imaging cytometry analysis showed that CD32 expression on CD4 T cells was measured by flow cytometry (n=19) and imaging cytometry assessed CD19, CD3, CD4, ICOS, HLA-DR & CD32 expression in healthy control GALT and HIV+ tonsil. Associations between HIV DNA & CD32 were tested by Spearman’s correlation and LASSO regression analyses were used to test for associations between GALT HIV DNA & plasma variables.

Conclusion: These data show that CD32 expression on CD4 T cells in GALT and tonsil when gated as singlets using standard methodology is due to B-cell-Tfh cell doublets, with CD32 expression primarily on B cells. The enrichment for TFH cells within these doublets raises the issue of whether they are artefactual or physiological. Plasma sCD40, a marker of the B:T cell interaction, & sCD14, a marker of bacterial translocation, were the factors most associated with HIV DNA, while CD32 expression was not. This suggests that the B:T cell interaction & microbial translocation in GALT may be supporting HIV persistence while CD32 is a surrogate marker of this interaction.
**CD38+CXCR3+ TFH CELLS SERVE AS ACTIVE HIV RESERVOIR IN THE TOTAL TFH CELL POPULATION**

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**Background:** TFH follicular helper cells (TFHs) are a phenotypically heterogeneous cell population generally defined by the expression of CXCR5 and PD-1. TFHs serve as a major reservoir for HIV transcription and production in both viremic and long-term ART treated subjects. In the presents study, we have dissected the phenotypic and functional heterogeneity of TFHs and the role of the different TFH populations in serving as HIV reservoir and their relationship with HIV-specific B cell responses.

**Methods:** Lymph nodes (LN) biopsies were obtained from 17 HIV uninfected, 27 viremic untreated and 23 aviremic ART treated subjects. Definition of B and T cell populations and cytokines was performed by mass cytometry using a panel of 40 metal-conjugated antibodies. To dissect the heterogeneity of TFH cells, we performed self-organizing map (FlowSOM) and consensus clustering. Cell-associated HIV-RNA was assessed in TFH cells sorted on the basis of CD38 and CXCR5 expression (CD38+CXCR5+, CD38+CXCR5-, CD38-CXCR5+ and CD38-CXCR5-).

**Results:** Unsupervised clustering identified 20 different populations of Tfh cells within CXCR5+PD-1+ cells. CD38+CXCR5+ TFHs significantly increased in viremic (41.18%) as compared to ART treated (17.8%) and HIV uninfected (6.9%) subjects (p<0.0001). Frequencies of CD38+CXCR5+ TFH cells positively correlated with the percentage of total germinal center B cells (r=0.58, p<0.0001) and GC IgG+ B cells (r=0.65, p<0.0001). CD38+CXCR5+ TFHs expressed higher levels of expression of BCL-6, ICOS, CD57, CD40L, CCR5, HLA-DR, T-bet as compared to the CD38+CXCR5-, CD38-CXCR5+ and the CD38-CXCR5- and of production of the TFH signature cytokine IL-21 (averages of 33%) as compared to the other three TFH cell populations (p<0.0002). Of note, only the percentage of CD38+CXCR5+ TFHs positively correlated with viremia (r=0.5, p=0.01) in untreated subjects. More importantly, CD38+CXCR5+ TFHs were greatly enriched in cell-associated HIV-RNA as compared to CD38+CXCR5- (average 3.3 fold), CD38-CXCR5+ (average 6.24 fold) and CD38-CXCR5- (average 8.24 fold) TFH cell populations (p<0.05).

**Conclusion:** CD38+CXCR5+ TFHs correspond to a population of phenotypically and functionally active TFH cells. The higher levels of expression of CXCR5 may render these cells more susceptible to HIV infection and it explains why CD38+CXCR5+ TFH cells serve as the major active HIV reservoir within the total TFH cell population.

**RESIDENT MEMORY T CELLS ARE A CELLULAR RESERVOIR FOR HIV IN THE CERVICAL MUCOSA**

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**Background:** Viral reservoirs, which represent the main obstacle to cure HIV, are easily established in different tissues. Target cells in peripheral tissues where HIV is acquired, such as the female genital mucosa, may express CD69 as a hallmark of their resident memory T cell (TRM) phenotype. Some of the features of TRM reported for other tissues, including long-lived and self-renewal capacities, shape them as an ideal cellular reservoir for HIV. However, the contribution of this relatively novel subset of cells to the pathogenesis and persistence of HIV remains unknown.

**Methods:** TRM were phenotyped in fresh cervical tissues obtained from HIV-infected women undergoing hysterectomy for non-neoplastic reasons (n=6-9). Activation of CD103+/-CD4+TRM subsets were compared between healthy and antiretroviral therapy (ART)-suppressed HIV+ women (n=6). The cervical explant model of HIV infection was established to determine proviral DNA (vDNA) content by qPCR and productive infection by p24 antigen expression in TRM subsets (n=7). In addition, we determined vDNA in purified cell subsets derived from blood and cervix obtained from ART-suppressed HIV+ woman (n=6). Finally, we also assessed viral HIV-RNA in cervical tissues from suppressed HIV+ women by fluorescence in situ hybridization in combination with immunohistochemistry (n=4).

**Results:** Cervical CD4+ TRM cells expressed a unique repertoire of clusters of differentiation on their surface compared to non-CD4+TRM that shaped them highly susceptible to HIV infection (w476, CXCR4, CXCR6 and CCR6) while revealed self-renewing potential (CD122, CD132, CD127) (p<0.032 for all markers). CD4+TRM preferentially sustain HIV infection ex vivo and harbored more HIV protein (p=0.003) and DNA (p=0.002) than non-TRM from the same tissues. Conclusively, cervical tissue from ART-suppressed HIV+ women contained up to two logs more molecules of viral DNA per cell (median 12,929) compared to blood (median 1,092), and the CD4+TRM fraction was the principal contributor to this reservoir (median of 98.25%). Further, persistent viral RNA was detected within CD69 positive cells in cervical samples from ART-suppressed HIV+ women.

**Conclusion:** Here we identified first the cervical mucosa as an overlooked HIV sanctuary and second CD4+TRM as a critical cellular reservoir. Thus, the contribution of CD4+TRM to viral persistence in tissues requires major attention in order to reach a functional cure in HIV infected patients.

**CD32+CD4+ T CELLS ARE ENRICHED IN HIV DNA**

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**Background:** CD32 was reported to mark the HIV reservoir, but several recent reports challenged this finding. We aimed to confirm or deny the role of CD32 as a marker of the viral reservoir and to further characterize the phenotype of these CD32+CD4+ T cells.

**Methods:** CD32 expression and co-expression of HLA-DR, PD-1, TIGIT, LAG-3 was measured by flow cytometry on PBMCs from ART-suppressed HIV-infected individuals with undetectable plasma viremia. HIV DNA was quantified in bulk PBMC samples and in CD32+ and CD32- fractions of CD4+ T cells obtained by magnetic sorting (negative selection to isolate CD4+ T cells followed by positive selection to isolate CD32+CD4+ cells).

**Results:** The median frequency of CD32+CD4+ T cells in HIV-infected individuals (n=19) was 0.07%. We found a positive correlation between the percentage of CD32+CD4+ T cells and total HIV DNA load in PBMCs (r=0.58; p=0.012). CD32+CD4+ T cells demonstrated increased expression of LAG-3 (p=0.016), TIGIT (p=0.016) and HLA-DR (p<0.0001) compared with CD32-CD4+ T cells. CD32+CD4+ T cells were not enriched for HIV DNA (normalized to the total cell numbers) compared with CD32-CD4+ cells. However, the CD32+ fraction was found to contain many B cells, due to the abundance of CD32+ B cells in the input sample, of which some remained after one round of CD4+ T-cell purification. Remarkably, when HIV DNA was normalized to CD3G T-cell specific mRNA, a significant positive enrichment in the CD32+ fraction was observed (p=0.0001). Therefore, we optimized the protocol to isolate a more pure fraction of CD32+CD4+ T cells from an additional set of HIV-infected individuals (n=19). An extra round of CD4+ purification resulted both in a more pure fraction of CD32+CD4+ T cells and in a 19-fold decrease in B-cell contribution to the CD4+CD32+ fraction (p<0.0001) and in an 11-fold enrichment in HIV DNA in this fraction (p=0.0007).}

The median frequency of CD32+CD4+ T cells was 0.08%.
In lymphoid tissues, the frequency of intact proviruses is highest in less differentiated cells such as NV cells, while in blood the frequency is highest in more differentiated EM cells. Tissue-based HIV+ T cells may act as progenitors of the total reservoir during ART, whereas in the periphery this reservoir is maintained within the EM T cell population, perhaps by clonal proliferation.

348 PERSISTENT HIV LOW-LEVEL VIREMIA CAN ARISE FROM AN ACTIVE PROVIRAL CLONE

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Background: Persistent low-level viremia (LLV) is not uncommon among patients with HIV despite receiving continuous antiretroviral therapy (ART), but the mechanism behind this finding remains unclear. We describe one individual with persistent low-level viremia (200-700 copies/ml) across 16 viral load measurements over >3 years despite ART intensification to a DTG, DRV/r, TAF/FTC ART regimen. We hypothesized that the persistent LLV arose either from an expanded clone of transcriptionally-active reservoir cells or from ongoing viral replication.

Methods: Commercial ARV drug levels and resistance genotyping were performed at multiple time points. We performed plasma single-genome sequencing for the Pro-RT region at 3 different timepoints, each 1 year apart. Confirmatory near-full length plasma sequences were obtained at the first time point. We also performed a novel next-generation single-genome proviral sequencing (NG-SGS) assay from PBMCs that combines near-full length proviral amplification and integration site analysis.

Results: The LLV persisted despite detectable plasma ARV levels and the presence of at least 2 fully active ARVs by resistance genotyping. Across all 3 time points, 86% of all single-genome plasma sequences were comprised of one viral clone (range 67% - 100% at each time point). Intact near-full length proviruses exactly matching the majority plasma clone were identified, which constituted only 6% of all intact proviruses. Near-full length plasma HIV sequences confirmed the clonality of this population and the lack of known drug resistance mutations. Integration site analysis showed that this provirus is integrated into CD200R1, a gene encoding a transmembrane receptor expressed on CD4+ T cells.

Conclusion: Persistent LLV can arise from the integration of HIV into a transcriptionally-active region of a clonally-expanded CD4+ population without evidence of ongoing viral replication. In this setting, further intensification of the ART regimen is unlikely to be effective and suppression of the LLV will require targeting of this transcriptionally-active reservoir.
simulations, to obtain an estimate for the rate of latent cell reactivation on ART and for rebound off ART.

Results: A rate of latent cell reactivation of ~1 x 10^-6/day resulted in simulated virus production that ranged between 0.5 and 4 HIV RNA copies/ml, consistent with in vivo ultraviolet-induced virus load quantitation on ART. Simulating a single HIV-infected individual for 100 days off ART, 234 viral reactivations occurred, with 26 that transitioned to exponential viral growth, appearing in the first 20 days. This result was typical of 9 other simulated HIV-infected individuals. The mean time to greater than 100 HIV RNA copies/ml was 19 days (SD 3 days). The time interval between 100 HIV RNA copies/ml to 1 x 105 copies/ml was ~1 week. After a 1200-fold initial reservoir reduction, 5 of 10 individuals had rebound during 41 years.

Conclusion: The frequency of rebound reactivations predicted here within single simulated individuals is consistent with that estimated previously in vivo. Synergy between two reactivations was very rare, however, reactivations may not be independent, particularly for in vivo expanded clonal populations. The rate of simulated viral rebound, once virus was clinically detected, was faster than that documented in vivo, perhaps because parameters were estimated from ex vivo cultures that used maximally stimulated target cells. In addition, immune responses, not considered here, could decrease the rate of viral reactivation or rebound.

350LB VR0C1 EPITOPE MOTIFS PREDICTED REBOUND KINETICS AFTER VR0C1/ TREATMENT INTERRUPTION
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Background: Ongoing antibody-mediated prevention clinical trials are testing infusions of the broadly neutralizing antibody VR0C1 as a strategy for HIV prevention, yet the impact of VR0C1 on founder viruses is unknown. We evaluated the impact of VR0C1 on homogeneous HIV populations characterizing of acute infection through an Analytic Treatment Interruption (ATI) study (RV397) that enrolled 18 acutely-treated participants who had been on ART for rebound off ART.

Methods: HIV sequencing was performed via endpoint-dilution on plasma samples in Fiebig I-III acute infection (10 genomes) and post-rebound (~15 pol and env). Env were tested for VR0C1 neutralization sensitivity using the TZM-bi neutralization assay.

Results: After ATI and concurrent VR0C1 infusion, viral rebound was modestly delayed in the VR0C1 group (median: 29 vs 14 days, p=0.051). Post-rebound, pol and env sequences differed by 1-2 nucleotides from the founder sequence derived pre-ART and all sequences were intermingled in phylogenetic trees demonstrating no evidence of VR0C1-mediated escape during the ATI. For each participant, VR0C1 neutralization sensitivity did not differ between acute infection and post-rebound (p=0.875). However, viral strains differed in their sensitivity to VR0C1 neutralization, with two infections with VR0C1-resistant viruses. The most sensitive strains trended to rebound slower than less sensitive strains (Rho=-0.62, p=0.033). We developed an epitope similarity score that weighted sites based on their importance in the VR0C1/Env interaction and compared our sequences to known VR0C1-susceptible strains. Our predictor was associated with the time to rebound (Rho=-0.70, p=0.007) and with neutralization results (Rho=-0.59, p=0.049). Sequences from participants who rebounded early were enriched for D at site 279, compared to N in late rebounders, placebo and known VR0C1-sensitive strains.

Conclusion: Clearing the latent reservoir to induce drug-free viral control remains a challenge, even if our findings showed that the presence of VR0C1 for a few weeks, in the absence of standing HIV variation, did not select for escape. Our ability to predict how the responsiveness to VR0C1 infusion varies across viral sequences could be useful to interpret results of future trials.

351 TRIFUNCTIONAL T-CELL ENGAGERS TARGETING PD-1 AND TIGIT IN CHRONIC HIV/SHIV INFECTIONS
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Background: Immune checkpoint inhibitors, such as PD-1 and TIGIT, are crucial dysregulators of CD8 T cell function during chronic HIV-1/SIV infections. Importantly, these checkpoint inhibitors are highly expressed on the surface of CD4 T cells that harbor latent HIV. We have previously demonstrated that an anti-HIV/anti-CD3 bispecific T-cell engager (BITE) can be used to redirect functionally compromised follicular CD8 (CD8+) T cells to kill HIV infected cells in vitro. Here, we hypothesize that adding an extra specificity to target PD-1 and TIGIT to the BITE will further enhance the functional activities of CD8 T cells and simultaneously lower the threshold for reactivation of latent infected cells in HIV infection.

Methods: We generated trifunctional anti-HIV/anti-CD3/anti-PD-1 and anti-TIGIT cell-engagers by linking the scFvs from either anti-TIGIT and anti-PD-1 antibodies to the BITE molecule. HIV-infected cell lines and primary cells isolated from lymph nodes (LN) of chronically SHIV-infected rhesus macaques were used as target cells in the in vitro and ex vivo killing assays to test whether trifunctional T-cell engagers could enhance the cytolytic activities of functionally compromised CD8 T cells. We also examined whether trifunctional T-cell engagers could stimulate CD8 T-cell lysis of HIV-infected CD4 T cells using a primary HIV latency model. Furthermore, multiparameter flow cytometry was used to investigate the effects of trifunctional T-cell engagers on CD8 and CD4 T cell polyfunctionality.

Results: We found that trifunctional anti-HIV/anti-CD3/anti-TIGIT and anti-PD1 increased the killing capability of CD8 T cells compared to the bifunctional anti-HIV/anti-CD3 BITE in the in vitro and ex vivo killing assays. We also demonstrated that trifunctional anti-HIV/anti-CD3/anti-TIGIT and anti-PD1 enhanced the CD8 T cell lysis of latent infected cells. Furthermore, trifunctional HIV-1/anti-CD3/anti-TIGIT and anti-PD1 were shown to increase antigen-specific CD107a degranulation, levels of granzyme B, cytokine and chemokine release by CD8 T cells, which could potentially underlie the observed increase in the killing capability of CD8 T cell populations.

Conclusion: Our results indicate that the use of trifunctional T cell engagers targeting immune checkpoints, PD-1 and TIGIT, may serve as novel immunotherapeutic strategies to eliminate infected cells in HIV infected individuals.

352 IMPACT OF RAPAMYCIN ON SIV PERSISTENCE IN RHESUS MACAQUES ON ANTIRETROVIRAL THERAPY
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Background: The mammalian target of rapamycin (mTOR) is a key regulatory kinase that controls glucose metabolism and cell growth. Inhibition of mTOR has been linked with several immune regulatory functions that may limit HIV persistence, including: 1) reducing CCR5 expression, 2) limiting CD4+ T cell homeostatic proliferation, 3) reducing PD-1 expression and 4) increasing anti-viral CD8+ effector T cell responses. Here we evaluated the impact of long-term mTOR inhibition on SIV DNA and RNA in blood and tissues of SIV-infected rhesus macaques (RM) on combination antiretroviral therapy (cART). We also evaluated whether potent T cell activation can induce latent SIV reactivation in the presence of rapamycin.

Methods: A total of 14 adult male RM were intravenously infected with SIVmac239 followed by cART (tenofovir, emtricitabine and dolutegravir) 12 days later. After 219 days of cART, RM were randomized into 2 groups that received twice daily IM injections of rapamycin at 0.02mg/kg (n=7) or vehicle control for 312 days. After 464 days of cART, RM on rapamycin received 2 doses of a non-depleting anti-CD3LALALA monoclonal antibody at 0.5mg/kg IV at
21-day intervals. Plasma viral loads and cell-associated SIV RNA and DNA were quantified by qRT-PCR and qPCR, respectively. Lymphocyte populations were evaluated by flow cytometry.

Results: After 24 weeks, there were significant decreases in the frequencies of Ki67+ (p = 0.0006), HLA-DR+ (p = 0.0026) and PD-1+ (p = 0.04) CD4+ memory T cells in blood of ramapycin-treated RM versus controls. In addition, surface expression of CR5 (p = 0.007) and the glucose transporter Glut1 (p = 0.007) were also significantly reduced in ramapycin-treated RM. Despite these perturbations in CD4+ T cell homeostasis, cell-associated SIV DNA and RNA in blood and peripheral lymph nodes remained stable over time with no significant difference observed between treatment groups. However, 4 of 7 ramapycin-treated RM had blips in plasma viral loads >2 logs above threshold (1 RNA copy/ml) in response to anti-CD3LALA, suggesting T cell activation in the presence of ramapycin can induce SIV reactivation in vivo.

Conclusion: Despite profound changes in markers of immune activation, proliferation and T cell exhaustion, ramapycin had minimal effect the stability of the SIV reservoir. However, these data indicate that ramapycin used in synergy with potent T cell activation may be an effective strategy to induce viral reactivation while inhibiting global immune activation and T cell proliferation.

**353 COMBINATION OF CRISPR AND LASER ART PREVENTS HIV REBOUND IN HUMANIZED MICE**

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Background: Advances in CRISPR-Cas9 gene editing technology and its in vivo delivery by AAV9 vectors together with cell based nanotechnology for long-acting slow effective release antiretroviral therapy (LASER ART), were used in NSG-CD4+1 humanized mice to facilitate eradication of HIV-1 in vivo.

Methods: CRISPR-Cas9 proviral DNA excision followed two months of treatment with long-acting slow effective release antiretroviral therapy (LASER ART), rilpivirine, myristolyated dolutegravir, lamivudine, and abacavir in infected animals treated with LASER ART and CRISPR in 39% of animals. Ultra deep, whole genome sequencing was employed to assess in vivo delivery by AAV9 vectors together with cell based nanotechnology for long-acting slow effective release antiretroviral therapy (LASER ART), rilpivirine, myristolyated dolutegravir, lamivudine, and abacavir in infected animals treated with LASER ART and CRISPR-Cas9 alone.

Results: Results from three independent sets of studies showed restorations of CD4+ T cells due to ART treatment and complete eradication of replication competent virus by CRISPR in 39% of animals. Ultrasensitive nested and digital droplet PCR and RNA scope assays failed to detect HIV-1 in blood, spleen, lung, kidney, liver, gut-associated lymphoid tissue and brain. Excision of proviral DNA fragments spanning theLTRs and the Gag gene from the integrated proviral DNA was identified, while no off target effects were observed. The absence of viral rebound following cessation of ART with no progeny virus infection after in vivo adoptive transfer of human immunocytes from dual-treated virus-free animals to uninfected humanized mice verified HIV-1 eradication by the combined treatment strategy. In contrast, HIV-1 was readily detected in all infected animals treated with LASER ART or CRISPR-Cas9 alone.

Conclusion: CONCLUSIONS: The sequential application of LASER ART and CRISPR-Cas9 therapies administered to HIV-1 infected humanized mice provides the first proof-of-concept that viral sterilization is possible.

**354 A HUMANIZED MOUSE MODEL FOR EVALUATION OF AUTOLOGOUS HIV-SPECIFIC T-CELL THERAPIES**

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Background: Ex vivo expanded HIV-Specific CD8+ T-cell (HST) immunotherapy offers great promise toward achieving an HIV cure. While plans to test HST therapies in humans are currently underway, a small animal model would enable the rapid and cost-effective pre-clinical evaluation of multiple approaches. We have developed a humanized mouse model reconstituted with only the memory subset of human CD4+ T-cells, which has greatly mitigated the effects of GVHD and allows for the in vivo analysis of autologous HST therapies.

Methods: NSG mice were engrafted with 5 x 10^6 memory CD4+ T-cells isolated from HIV- or HIV+ donor leukapheresis samples. Autologous HSTs were generated by stimulating T-cells with pools of overlapping Cleave B consensus peptides or peptides representing only conserved viral epitopes. Four to six weeks post humanization, mice were simultaneously infected with JR-CSF and treated with autologous HSTs. Weekly blood samples were analyzed by flow cytometry to measure changes in the human CD4+/CD8+ cell levels as well as qRT-PCR to measure viral load. Plasma RNA was subsequently sequenced for the presence of viral escape mutations.

Results: Mice engrafted with only the memory CD4+ T-cell subset survived significantly longer than mice engrafted with total CD4+ T-cells and were able to support robust HIV infection sustained out to 20 weeks post engraftment. Daily ARV injections resulted in viral suppression and CD4+ T-cell reconstitution, followed by viral rebound and CD4+ T-cell loss upon ARV cessation. Mice that received autologous HSTs saw significant, transient decreases in plasma viral load compared to the No Treatment group (p < 0.0001). Sequencing analysis of plasma virus revealed a dominant escape mutation in one mouse in the HST group suggesting immunological pressure. Early results from an additional in vivo experiment demonstrated similar, significant decreases in viral loads with 66% of mice receiving HST therapy reaching an undetectable viral load 4 weeks post therapy initiation.

Conclusion: We have demonstrated that our novel memory CD4+ T-cell humanized mouse model accurately recapitulates many aspects of natural HIV infection while significantly reducing the effects of GVHD. Using this model, we have observed significant decreases in viral load in mice receiving clinically relevant HST products. This platform provides opportunities to assess a variety of immunotherapeutic strategies as well as immunomodulatory approaches in an in vivo, autologous target/effecter setting.

**355 DIFFERENTIAL EFFECTS OF IL-15 TREATMENT DELIVERED BY DIFFERENT ROUTES IN MACAQUES**

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Background: Heterodimeric interleukin-15 (hIL-15) is a native stable form of the cytokine that activates and expands cytotoxic T and NK cells. We have reported that hIL-15 treatment delivered subcutaneously in SHIV infected macaques results in significant decrease in viral RNA within peripheral lymph nodes (LN) and plasma viral loads. In this study, we have expanded the analysis of the hIL-15 effects on virus-specific CD8+ T cells, as well as the general lymphocyte population, in immunized Mamu-A01+ rhesus macaques treated with hIL-15 subcutaneously (sc), intraperitoneally (ip), intravenously (iv) and intramuscularly (im).

Methods: Eight DNA-immunized rhesus macaques received injections of hIL-15 over 2 weeks using increasing doses of cytokine (step-dosing) by four different routes (sc, ip, iv and im). At the end of the treatment, hIL-15 effects on different lymphocyte populations were monitored by multi-parametric flow cytometry.

Results: All four protocols resulted in systemic expansion of CD8+ T lymphocytes and NK cells with higher granzyme B content. These cells were found in both effector sites, such as liver, vagina and rectum, and secondary lymphoid tissues. A significant increase in cytotokic effector memory CD8+ T cells was found in lymph nodes from all hIL-15-treated macaques. CM9 tetramer staining demonstrated that the increase of CD8+ effector T cells in lymphoid organs included actively proliferating HIV-specific T cells with higher granzyme content. Some effects of hIL-15 treatment were restricted to the specific delivery route. Macaques treated ip showed the highest levels of proliferation in CD8+ lymphocytes obtained from the gastrointestinal tract (duodenum, jejunum, ileum and colon), although the proliferating T cells from the gut did not show any increase in granzyme content.

Conclusion: Step-dose administration of hIL-15 by four different routes is well-tolerated and results in systemic activation and expansion of virus-specific cytotoxic leukocytes that infiltrate LN and peripheral effector sites. The differences observed between LN and the gastrointestinal tract suggest that tissue-specific homeostatic mechanisms may modulate the response of the tissue-resident lymphocytes to hIL-15. These results suggest that hIL-15 could be useful in promoting the entry of cytotoxic T cells into areas of chronic HIV replication and contributing to a functional cure of the infection.
GS-9722: FIRST-IN-CLASS EFFECTOR-ENHANCED BROADLY NEUTRALIZING ANTIBODY FOR HIV CURE

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Background: Select broadly neutralizing anti-HIV antibodies (bNAbs) are capable of simultaneously engaging gp120/gp41 on the surface of infected CD4+ T-cells, and Fc-gamma receptors (FcγRs) on the surface of innate immune effector cells. Such bNAbs can kill HIV infected cells and may thus be capable of reducing or eliminating the HIV reservoir. PGT121 is a particularly promising bNAb in this class, having demonstrated potent in-vitro cell killing as well as in-vivo efficacy in SHIV infected monkeys (Borducchi et al., Nature, in press). Here we describe GS-9722, an engineered variant of PGT121 with enhanced effector function and improved drug-like-properties.

Methods: A panel of PGT121 crystallizable fragment (Fc) mutations was tested in Fc-receptor (FcR) binding assays, primary cell killing assays and preclinical PK studies in order to optimize effector function and PK properties. In parallel with these efforts, in-silico and in-vitro approaches were used to guide the selection of PGT121 antibody binding fragment (Fab) mutations that reduced immunogenic risk and improved drug-like-properties.

Results: The Fc engineering campaign identified mutations that enhanced binding to activating FcγRs as well as the neonatal Fc-receptor (FcRn). The resulting antibody demonstrated significantly enhanced killing of HIV infected CD4+ T-cells by primary natural killer (NK) cells isolated from multiple human donors (mean values: Emax=77%, EC50=0.23 µg/mL) compared to PGT121 (mean values: Emax=11%, EC50=3.4 µg/mL). The Fab engineering campaign identified mutations that removed immunogenic Fc-cell epitopes, removed glycosylation motifs and improved thermodynamic stability. The Fab mutations had minimal impact on neutralization breadth or potency when tested on a panel of clade B patient isolates (60% at IC95=15 µg/mL, median IC95=0.18 µg/mL) compared to PGT121 (58% at IC95=1 µg/mL, median IC95=0.33 µg/mL). GS-9722 incorporates all mutations identified in the Fc and Fab engineering campaigns and exhibits a pharmacokinetic profile similar to PGT121 in non-human primate studies.

Conclusion: GS-9722 is a first in class effector-enhanced bNAb for the targeted elimination of HIV infected cells and is currently in Phib clinical testing. Future studies will explore GS-9722 in combination with additional effector enhanced bNAbs, immune-modulatory agents (e.g. GS-9620), latency reversal agents and therapeutic vaccines in a multi-pronged approach to reduce or eliminate the HIV reservoir.

PASSIVE INFUSION OF FC-MODIFIED NAB DOES NOT AFFECT DYNAMICS OF PLASMA VIRUS DECAY

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Background: Passive bNAb infusion leads to a reduction of HIV plasma viremia in infected people as well as in SHIV-infected rhesus macaques. Potential mechanisms of viral reduction include neutralization of free virus as well as Fc-dependent effector functions that can clear infected cells. Prior mathematical modeling of plasma virus decline during ART treatment can be applied to passive bNAb therapy to delineate the potential mechanism(s) of action.

Methods: We generated several Fc-variants of the human IgG1 NAb VRC07-523 and characterized them for neutralization, complement binding, ADC, phagocytosis, and binding to rhesus FcgRIII. All variants contained a two amino acid mutation termed LS, that increased affinity for FcRn. Based on these assays, we down selected two variants - LS-LALA and LS-DEL, that showed knock-out or increase in ADC and phagocytosis respectively, with complement binding knocked out in both. These mAbs were administered at a single dose of 20 mg/kg i.v. to rhesus macaques chronically infected with SHIV-SF162P3 for 6 weeks (n=10 per group). Animals were followed for rate of plasma virus decay, antibody PK (serum and cell-bound) and viral rebound.

Results: LS-LALA and LS-DEL groups were similar in the following characteristics - 1) plasma virus decay was delayed for 24h after mAb infusion in both groups 2) between day 2 and day 5, the rate of virus decay remained the same 3) plasma virus decay was independent of FcgRIII genotype. Pharmacokinetic analysis confirmed that during this period, both groups maintained serum antibody titers at ten-fold excess of the in vitro IC80 for SHIV SF162P3 neutralization, with higher serum concentrations for the LS-LALA antibody. Further, unlike the LA-LALA antibody, the LS-DEL antibody was able to engage natural killer cells as well as monocytes in vivo through interactions with FcgRIII.

Conclusion: Increased or decreased Fc-effector function did not affect the timing or rate of plasma virus decay in vivo, highlighting that initial impact on plasma viremia by passive mAb therapy with VRC07-523-LS is predominantly mediated by virus neutralization rather than ADC or phagocytosis. Measurements of decay of infected cell load and functionality of mAb-bound cells are ongoing.

RELATIONSHIPS BETWEEN neutralization, binding and ADC of bNAbs against reservoir HIV

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Background: HIV-specific broadly neutralizing antibodies (bNAbs), may contribute to the elimination of HIV reservoirs by binding to reactivated cells, targeting them for antibody dependent cell-mediated cytotoxicity or phagocytosis (ADCC/ADCP). Harnessing virus neutralization, along with these functions, will provide additional benefit. Few studies have assessed the activities of bNAbs against viruses reactivated from patient-derived reservoirs. The relationships between neutralizing activity, ADCC function and binding to reservoir virus infected primary CD4+ T cells has not been comprehensively studied.

Methods: Quantitative viral outgrowth assays (QVOAs) were performed with CD4+ T cells from participants on long-term ART from a clade B-infected cohort. A panel of 15 bNAbs were tested for binding and ADC to cells infected with 36 reservoir isolates by flow cytometry, and for neutralizing activity against the same viruses using a TZM-bl assay. ADCC assays were performed with the same viruses, same bNAbs and a hαN cell line (a NantKwest product) as effectors.

Results: Considering all bNAbs together, we observed overall correlations between: ADCC and infected cell binding (r=0.49, p<0.0001), neutralization IC80 and binding (r=0.56, p<0.0001), and neutralization IC80 and ADCC (r=0.46, p<0.0001). At the level of individual antibodies: 7/15 bNAbs showed significant correlations between neutralization and binding, and 10/14 bNAbs showed significant correlations between neutralization and binding. Despite the overall-correlation, we did not observe statistically significant correlations between ADCC and infected cell binding, nor between ADCC and neutralization for any individual bNAb. PGT121 and 10-1074 showed broad and potent activity for all functions with 66-67% neutralization of reservoir isolates, 42-47% binding, and >15/36 ADCC. P9G and PGDM1400 showed 22-36% neutralization with intermediate potency, and 72-75% binding; while CD4 binding site bNAbs displayed broader activity but generally lower potencies. Combinations of CD4bs bNAbs with V3-Glycan/
V1/V2 bNAb, resulted in coverage of up to 100% reservoir isolates for infected cell binding.

**Conclusion:** We observed substantial heterogeneity in binding, ADCP, and neutralization profiles of each bNAb to reactivated reservoir viruses. While we observed overall significant correlations between each of the functions tested, these were not always detected in terms of individual antibodies. Further study of this complexity may help guide the development of polyfunctional bNAb therapeutics.

### 359 MULTISPECIFIC ANTI-HIV DUOCAR-T CELLS POTENTLY ELIMINATE BNAB-RESISTANT HIV IN VIVO

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**Background:** Adoptive immunotherapy using chimeric antigen receptor gene-modified T cells (CAR-T) has made significant contributions to the treatment of certain B-cell malignancies. Such treatment modalities also show promise for the development of a single treatment for HIV/AIDS and obviating the need for long-term anti-retroviral drug therapy. We hypothesized that HIV-1 based lentiviral vectors encoding chimeric antigen receptor (CAR) targeting multiple highly conserved sites on the HIV-1 envelope glycoprotein (Env) using a two-molecule CAR architecture, termed duoCAR, would facilitate effectual binding of multiple targeting domains while improving CAR potency, breadth, and resistance to HIV-1 infection.

**Methods:** To assess CAR functionality, we adapted a previously described neutralization assay that utilizes replication-competent infectious molecular clones of HIV (IMC) encoding different env genes and a Renilla luciferase reporter (Env-IMC-Luc) to allow for sensitive detection of HIV infection in primary cells to monitor the inhibitory activity of different CARs.

**Results:** We show that transduction with lentiviral vectors encoding multi-specific anti-HIV duoCARs confer primary T cells with the capacity to potently suppress HIV infection in contrast to conventional CAR-T cells, while simultaneously protecting them from genetically diverse Env-IMC-LucR viruses in vitro. Furthermore, the genetically modified CAR-T cells also potently suppressed broadly neutralizing antibody (bNAb)-resistant Env-IMC-LucR strains, including a VRC01/3BNC117-resistant virus. Lastly, multi-specific duoCAR-T cells effectively suppressed HIV infection in a humanized intrasplenic NOD/SCID/IL-2Rγ-/- model (hu-spl-PBMC NSG) infected with VRC01/3BNC117-resistant virus in contrast to control-treated, HIV-infected mice.

**Conclusion:** We conclude that multi-specific duoCAR-T cells are superior to conventional CAR-T cells and are highly efficacious against broad and bNAb-resistant Env-IMC-LucR viruses in vivo and in vitro, respectively. Collectively, our work represents a powerful and universal multi-targeting HIV-1 immunotherapy that has strong implications for a functional cure.

### 360 LIMITATIONS OF HIV SPECIFIC CAR-T CELLS TO LYSE CELLS BEARING HIV IMMUNE COMPLEXES

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**Background:** We have recently reported that latently infected CD4+ T cells may resist CD8+ T cell killing through a presently unknown mechanism. Studies by Cummins et al have reported that CD4+ T-cell from HIV-infected individuals may resist apoptosis due to increased expression levels of Bcl-2. In cancer settings, Bcl-2 antagonists can sensitize tumors overexpressing Bcl-2 to cancer settings. Bcl-2 antagonists can sensitize tumors overexpressing Bcl-2 to cancer settings.

**Methods:** To assess the ability of the Bcl-2 inhibitor ‘ABT-199’ to reduce the resistance of latently infected cells to CD8+ T cell killing, we investigated the ability of the Bcl-2 inhibitor ‘ABT-199’ to reduce the resistance of latently infected cells to CD8+ T cell killing.

**Results:** In ‘spiked’ HIV assays, lower proportions of QVDA wells contained NL4-3 vs patient-virus in conditions treated with HIV-specific CD8+ T cell effectors, suggesting preferential killing of latently model cells. In HIV assays from 6 participants, combinations of LRAs and CD8+ T cell effectors led to significant decreases in HIV DNA, but not in IUPM (n=7, p=0.02, p=0.3, respectively). The addition of ABT-199 led to consistent, significant decreases in both HIV DNA (n=6, p=0.03) and IUPM (n=10, p=0.002), with no viral

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**Figure 1.** Multi-specific duoCAR-T cells broadly and potently eliminate Env-IMC-LucR infected PBMC.

Summary of the in vitro HIV-1 killing assays expressed as log inhibition of HIV-1 infection. Log inhibition is calculated relative to HIV-infected untransduced T cells after background subtraction using uninfected PBMCs. The data represents an average of at least three independent donors.

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**Table 1.** Limitations of HIV Specific CAR-T Cells to Lysing Cells Bearing HIV Immune Complexes.
outgrowth observed in QVOAs following three of these HIV-1 assays. Lastly, combinations of LRs and ABT-199 did not significantly decrease levels of viral DNA or IUPM (n=10, p=0.17, p=0.18, respectively).

**Conclusion:** This study provides further evidence that ex vivo, latently infected CD4+ T cells exhibit a resistance to CD8+ T cell killing that is not seen in primary cell models of latency. ABT-199 is a clinical stage Bcl-2 inhibitor that, in combination with CD8+ T cells and LRAs, enabled substantial reductions in HIV reservoirs. However, appreciable levels of ABT-199 induced bystander toxicity emphasize the need for further studies into the mechanisms underlying these observations to develop more targeted approaches.

### 362 BCL-2/XL ANTAGONISTS REDUCE HIV RESERVOIRS FROM IN VITRO MODELS NOT EX VIVO CD4 CELLS

**Methods:** Primary CD4+ cell latency models were generated with cells from HIV+ donors (‘cultured TCM model’, Bosque lab). Ex vivo patient CD4+ T cells were isolated from leukapheresis samples. HIV Eradication assays (HIWE) were conducted by treating cells with senolytics (ABT-199, A-1155463 or A-1331852) alone, or combined with Bystroxin. Cell viability and phenotypes were assessed by flow cytometry. HIV DNA was measured by digital droplet PCR (ddPCR). Inducible replication competent HIV reservoirs were measured by QVOA and expressed as infectious units per million cells (IUPM).

**Results:** Treatment of cells with the Bcl-2 inhibitor ABT-199 resulted in high levels of non-specific cell death at 1µM, and moderate levels at 100nM. The selective Bcl-X inhibitors A-1155463 and A-1331852, showed modest effects on cell viability. Combinations with Bystroxin substantially reduced toxicity. Care was taken to standardize IUPM calculations for input of viable cells in each condition. The latency model showed substantial decreases in both HIV DNA and IUPM for both concentrations of ABT-199, and for A-1331852 as single agents (HIV DNA p<0.0001; IUPM p<0.03), and in combinations with bystroxin (HIV DNA p<0.0001; IUPM p<0.01). In analogous experiments using ex vivo CD4+ T-cells from 6 ARV-treated participants, we did not observe significant decreases in IUPM in any individual, nor across the sample set (p>0.15), with similar results for HIV DNA (p>0.3).

**Conclusion:** Our results are consistent with previous reports in demonstrating the elimination of infected cells from latency models with ABT-199, and extend this to Bcl-X inhibitors. Unexpectedly, combination with an LRA was dispensable for these effects. These latency-mode results were not recapitulated in ex vivo patient CD4+ T-cells, where elimination of reservoir-harboring cells was not detected. It is of interest to determine if the addition of CTL to these combinations may result in reservoir reductions.

### 363 IN VIVO ANTIVIRAL EFFECT OF DASATINIB IN HUMANIZED MICE INFECTED WITH HIV-1

**Methods:** Human CD4+ hematopoietic stem cell-engrafted NSG mice (hu-CD34) were treated for 5 days with dasatinib 20mg/kg/day (n=5) or with placebo (citrate buffer solution) (n=5). Then, all mice were intraperitoneally injected with purified HIV-1NL4-3 (17,500 TCID50) and treated for 21 days with dasatinib or placebo, in the absence of antiretroviral treatment (ART).

**Results:** 1) Viral load in hu-CD34 mice treated with dasatinib was 4.7-, 3.8- and 3.5-fold lower than the placebo group after 7, 15 and 21 days of infection, respectively. Two mice from dasatinib group persistently showed undetectable viral load. 2) Proviral load in blood of mice treated with dasatinib remained 1.6-, 4.6- and 2.2-fold lower than the placebo group after 7, 15 and 21 days post-infection, respectively. 3) Proviral load in GALT was 3.0-fold smaller at 21 days post-infection in the dasatinib-treated group. 4) Treatment with dasatinib affected the distribution of CD4 and CD8 subpopulations: CD4 and CD8 TCM cells were respectively 2.0- and 2.7-fold lower than the placebo group; CD4 and CD8 TEM cells were 4.0- and 6.3-fold lower; CD4 and CD8 TEMRA cells were 1.5- and 3.5-fold lower; whereas CD4 and CD8 naive T cells were 1.5- and 1.4-fold higher.

**Conclusion:** Daily oral treatment with dasatinib in the absence of ART interfered with HIV-1 acute infection in hu-CD34 mice. Dasatinib reduced viral load and proviral reservoir size in blood and GALT, and modified the distribution of CD4 and CD8 subpopulations. This study is the first proof of concept that dasatinib decreases HIV-1 reservoirs in vivo, supporting the use of dasatinib in combination with ART to reduce the reservoir size, particularly in patients with acute infection.

### 364 A BACTERIOPHAGE T4 NANOPARTICLE PLATFORM FOR TARGETED CURATIVE THERAPY AGAINST HIV-1

**Methods:** ABT-199 targets HIV-1 infected cells and disrupts the proviral genome.

**Conclusion:** The phage T4 nanoparticles could carry therapeutic cargo and deliver it specifically to HIV-1 infected CD4+ T cells to disrupt the viral genome, potentially leading to the eradication of HIV-1 reservoirs.
Background: Potent antiretroviral therapy leads to suppression of HIV-1 replication but is associated with establishment of a stable reservoir of latently infected cells that can fuel rebound viremia upon treatment discontinuation. Intraclonal cellular immune responses mediated by NK cells have been inversely associated with reductions in viral reservoir size during antiretroviral therapy, suggesting that latently infected CD4 T cells may be susceptible to NK cell-mediated immune effects.

Methods: Primary CD4 T cells were activated and in vitro infected with a dual-reporter virus allowing us to distinguish cells with productive or latent HIV-1 infection, followed by flow cytometry-based analysis of NK cell receptor ligands; moreover, the same analysis was performed in primary CD4 T cells from ART-treated patients. Single-cell RNA-Seq analysis of in vitro, latently infected cells was performed and compared to the transcriptome of productively infected and uninfected cells. The susceptibility of latently infected CD4 T cells to NK cell-mediated killing was analyzed using functional cytotoxicity assays.

Results: In vitro, latently infected CD4 T cells expressed significantly higher levels of the activating NK cell ligand ULBP1, and were significantly enriched for a population of cells simultaneously expressing a combination of the three NKGD2 ligands ULBP1, MICA and MICB. Upregulation of these molecules was associated with transcriptional activation of the ATM DNA damage response pathway. Functional assays demonstrated an increased susceptibility of latently-infected CD4 T cells to NK cell-mediated killing; this vulnerability to cytotoxic immune effects of NK cells was most obvious in latently-infected CD4 T cells expressing ULBP1, MICA and MICB, and was abrogated by antibodies directed against NKGD2. An upregulation of NKGD2 ligands was also observed in patient-derived CD4 T cells from ART-treated patients, and denoted a subset of CD4 T cells characterized by increased expression of immune checkpoint and activation markers.

Conclusion: Latently-infected CD4 T cells seem to express a distinct signature of activating NK cell receptors, likely in response to activation of DNA damage response signals that may result from viral latency. Expression of activating NK cell receptors on latently-infected CD4 T cells can increase the susceptibility to NK cell killing, and may represent a distinct vulnerability of the viral reservoir that provides novel targets for therapeutic viral eradication studies.

**369** PKC AGONIST EXPOSURE SUFFICIENT TO ACTIVATE T CELLS IN VIVO ALSO CAUSES COAGULOPATHY

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Background: Activation of latent HIV reservoir is part of a strategy for HIV cure as it should enable the elimination of infected cells by immune-mediated clearance mechanisms and facilitate long-term remission or cure. Protein kinase C (PKC) agonists are highly effective at activating latent HIV. However, effective use of PKC agonists is limited by their severe toxicity, with a mechanism not clearly elucidated.

Methods: A novel small-molecule PKC agonist, C232A, was identified and characterized in vitro and in vivo. PKC activation was assessed by fluorescent microscopy of GFP-labeled PKC in ASC49 cells. Resting CD4 T cells from ART-suppressed HIV-infected donors were treated with C232A and HIV RNA in culture supernatants was assessed by qPCR. Flow cytometry was used to quantify CD62P on platelets and CD69 on T cells in whole blood. Dose escalation studies were performed in both rats and rhesus macaques. Activation markers and cytokines were measured by flow cytometry, quantitative PCR and multiplex immunassay. Investigational toxicology endpoints were assessed, including hematology, coagulation and anatomic pathology.

Results: C232A induced PKC translocation from the cytoplasm to cellular membranes, consistent with PKC agonist activity. HIV transcription was activated ex vivo to the same magnitude as seen with prostratin, but with 5-fold higher potency. IV infusion of C232A in rhesus macaques induced dose dependent expression of CD69 on T cells. However, similar to other PKC agonists, dose levels sufficient to activate >50% of T cells in vivo also caused a rapid onset of moribundity in treated animals. Toxicity was mediated by platelet activation and ultimately manifested in disseminated intravascular coagulation, a lethal coagulopathy marked by consumption of clotting factors, thrombus formation and hemorrhage. Using a whole blood in vitro assay, dose-dependent platelet activation has been observed across multiple chemical series of PKC agonists at doses similar to those that activate T cells. Consistent with this data, expression of several PKC isoforms has been confirmed in platelets.

Conclusion: Platelet activation is a critical safety liability associated with PKC agonists and should be carefully monitored in any preclinical or clinical studies. In addition, the developed in vitro screening tools should facilitate structure-based design of novel PKC agonists with improved activity in T cells and minimal platelet activation.

**370** ACTIVATION OF HIV-SPECIFIC CD8+ T CELLS FROM HIV+ DONORS BY VESATOLIMOD

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Background: Vesatolimod (GS-9620) is a Toll Like Receptor 7 (TLR7) agonist that directly activates human pDCs, B lymphocytes, and induces the production of cytokines such as type I interferon. GS-9620 is currently being evaluated in HIV-1 infected participants as part of an HIV remission strategy. Here we investigated the potential of GS-9620 to trigger indirect induction of HIV-specific CD8 T cells, using immune cell cultures derived from HIV+ donors.

Methods: Peripheral blood mononuclear cell (PBMC) cultures derived from HIV+ donors virologically suppressed on stable antiretroviral therapy (n=39) were profiled. PBMCs were collected by leukapheresis, separated by Ficoll
centrifugation, and treated with GS-9620 (20 and 1000 nM) or vehicle alone for 24 hours. HIV pentamers (Proimmune) composed of five MHC Class I peptide-complexes were used to detect CD8+ T cell HIV specificity. Pentamers were selected according to donors’ HLA type(s). Cells were incubated with HIV specific pentamers, surface stained with anti-CD3, CD4, CD8, CD69 fluorescent conjugated antibodies, stained intracellularly with anti-CD107a, TNF-α, and IFN-γ fluorescent conjugated antibodies, and analyzed by flow cytometry (FACS). Donors with GS-9620 activated HIV-specific CD8+ T cells scored as positive using a cut-off of 0.5% Pentamer binding.

Results: In vitro treatment of PBMCs with GS-9620 resulted in all 39 donor cultures demonstrating an increase in CD8+ T cell activation of up to 80% as measured by CD69 expression compared to no treatment. Of these, 17/39 donors showed HIV-specific CD8+ T cell activation with 5/17 donors positive at 20 nM, and 17/17 donors positive at 1000 nM GS-9620. Intracellular staining was done in a subset of donors (n=13), resulting in 4 donors showing HIV-specificity, 2 of which were positive for degranulation (CD107a), 3 positive for TNF-α, and none positive for IFN-γ.

Conclusion: Vesatolimod treatment of HIV+ donor derived PBMCs resulted in robust activation of CD8+ T cells as demonstrated by expression of the activation marker CD69. Furthermore, HIV-specific CD8+ T cell activation was observed in approximately half of the donors tested, with 3 of the donors’ CD8 T cells also up-regulating expression of CD107a and/or TNF-α. These data support the in vivo potential of Vesatolimod to induce HIV-specific CD8 mediated killing of latently infected cells as part of an HIV remission strategy.

371 DEBIO 1143 IS AN ATTRACTIVE HIV-1 LATENCY REVERSAL CANDIDATE

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Background: Antiretroviral therapy (ART) suppresses HIV replication, but does not cure the infection because replication-competent virus persists within latently infected CD4+ T cells throughout years of therapy. These reservoirs contain integrated HIV-1 genomes and can replenish active virus. Thus, the development of strategies to eliminate the reservoir of latently infected cells is a research priority of global significance.

Methods: We tested the ability of a new inhibitor of apoptosis protein antagonist (IAPa) called Debio 1143 (D1143) at reversing HIV latency and investigated its mechanisms of action.

Results: D1143 activates HIV transcription via NF-kB signaling by degrading the ubiquitin ligase baculoviral IAP repeat-containing 2 (BIRC2), a repressor of the non-canonical NF-kB pathway. D1143-induced BIRC2 degradation results in the accumulation of NF-kB inducing kinase (NIK) and proteolytic cleavage of p100 into p52, leading to nuclear translocation of p52 and RELB. D1143 greatly enhances the binding of RELB to the HIV-1 LTR. These data indicate that D1143 activates the noncanonical NF-kB signaling pathway by promoting the binding of RELB:p52 complexes to the HIV-1 LTR, resulting in the activation of the LTR-dependent HIV-1 transcription. Importantly, D1143 reverses viral latency in HIV-1 latent T cell lines. Using knockdown (siRNA BIRC2), knockouts (CRISPR NIK) and proteosome machinery neutralization (MG132) approaches, we found that D1143-mediated HIV latency reversal is BIRC2 degradation- and NIK stabilization-dependent. D1143 also reverses HIV-1 latency in resting CD4+ T cells derived from ART-treated patients or HIV-1-infected humanized mice under ART. D1143 has been tested as cancer therapy in various human clinical trials. Interestingly, daily oral administration of D1143 in cancer patients at well-tolerated doses elicited pharmacodynamic effects on BIRC2 in clinical trials. Interestingly, BIRC2 binds to cIAP1 and cIAP2, which are involved in the regulation of NF-kB, thus providing a potential target for HIV latency reversal.

Conclusion: Vesatolimod treatment of HIV+ donor derived PBMCs resulted in robust activation of CD8+ T cells as demonstrated by expression of the activation marker CD69. Furthermore, HIV-specific CD8+ T cell activation was observed in approximately half of the donors tested, with 3 of the donors’ CD8 T cells also up-regulating expression of CD107a and/or TNF-α. These data support the in vivo potential of Vesatolimod to induce HIV-specific CD8 mediated killing of latently infected cells as part of an HIV remission strategy.

372 HIV-1 PROVIRAL CLONE-SPECIFIC DIFFERENCES IN RESPONSE TO LATENCY REVERSING AGENTS

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Background: Latent HIV-1 infections are a major obstacle to an HIV-1 cure, and efforts are ongoing to understand and develop strategies to eliminate this reservoir. One of these strategies is the “shock and kill” approach, where virus expression is induced by latency reversing agents (LRAs), allowing infected cells to either expose themselves for clearance. Some studies have shown inconsistencies in the potency of LRAs using different models of HIV-1 latency. Since HIV-1 integrates quasi-randomly into active genes, it seems likely that proviruses might be subject to locus-specific gene regulation. Hence, different classes of LRAs may have differential effects on proviral-clones’ response.

Methods: Here, we infected Jurkat cells with an Env-Vpr-PuroR virus harboring gfp in the nef ORF to generate a polycional proviral pool, with proviruses marked with “zipcodes”-sequence tags within viral sequences that identify clonal progeny of individual integration events. The GFP-negative subpopulation was FACS-sorted and treated with different classes of LRAs. Latency reactivation was quantified by the frequency of GFP positive cells, and the total amount of virus released. We also determined the extent of reactivation per proviral clone by quantifying the zipcodes in released virion RNA by high-throughput sequencing for each LRA treatment.

Results: Our results suggest that only a fraction of the proviral clones were reactivated by any tested LRA, and clones responded to LRAs to differing extents. Some clones were unique to specific LRAs, with similar classes of LRAs reactivating similar proviral clones. Clonal analysis of the class I-specific histone deacetylase inhibitor (HDACi), entinostat and pan HDACi, SAHA treatments revealed proviral clones that were only reactivatable by SAHA but not entinostat, suggesting HDACIs other than class I may play a role in HIV latency. Characterizing individual cell clones revealed differences from the total population’s behavior. For example, while one LRA combination showed additive reactivation when monitored total viral release in this pool, clonal analysis revealed that a few proviral clones were reactivated to greater extents than they were by one LRA, while other clones’ expression appeared to be reduced by dual LRA treatment.

Conclusion: The total levels of reactivation can misrepresent the clonal behavior of a latency pool in response to different LRA classes, and mechanisms that act to reactivate one clone may act to silence another.

373 HIV-2 DYNAMICS DURING LATENCY REVERSAL

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Background: HIV-2 infection is associated with lower plasma virus loads and slower disease progression when compared to HIV-1 infection. Prior work has suggested that, in viremic participants, levels of total viral DNA are similar between HIV-1 and HIV-2 infection but HIV-2 cell-associated RNA (caRNA) levels may be lower. We hypothesized that this difference may extend to virus latency during treated infection and investigated the effects of latency reversal agents (LRAs) on HIV-2 reactivation.

Methods: We recruited participants with HIV-1 or HIV-2 infection and isolated PBMCs from whole blood. Blood draw volumes precluded the isolation of pure resting CD4+ T cell populations. Reversal of HIV latency was measured ex vivo following 24- or 48-hour exposures to a panel of LRAs with different mechanisms of action: bryostatin 10nM, romidepsin 20nM (RMD), the TLR7 agonist GS-9620 1000 nM, PMA/ionomycin, and anti-CD3/anti-CD28 beads (1:1 ratio). Total HIV DNA, cell-associated RNA (caRNA), and supernatant viremia levels were determined by validated real-time quantitative PCR (qPCR) assays. Results were normalized for input HIV DNA copy number.

Results: While HIV caRNA/DNA ratios were consistently lower for HIV-2 reactivation (3.2 – 11.6, HIV-2; 5.3 – 54.1, HIV-1) for the LRA conditions we tested in 24 and 48 hours of drug exposure, no statistically significant differences were observed in HIV caRNA levels between HIV-1 and HIV-2. Interestingly, levels of supernatant viremia were significantly lower during HIV-2 reactivation, when compared to HIV-1. HIV-2 supernatant viremia levels at 24 hours, corrected for HIV DNA input, were 39-, 77-, 10-, 152-, and 117-fold lower after bryostatin, RMD, GS-9620, PMA/ionomycin, and anti-CD3/anti-CD28 beads treatment, respectively. These differences persisted at 48 hours.

Conclusion: Latency reversal agents reactivate virus transcription in HIV-2 infection. Whereas levels of HIV-1 and -2 caRNA were similar during latency reversal, when normalized to HIV DNA copy number, statistically significantly less supernatant virus RNA was produced during HIV-2 latency reversal. This
suggested that a post-transcriptional block may affect the ability of HIV-2 to produce virions during reactivation from latency.

374 VPU CONTROLS HIV-1 LATENCY THROUGH MODULATION OF THE NF-κB PATHWAY
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Background: The long-lived and persistent latent viral reservoir in memory T cells represents one of the main obstacles for an HIV-1 cure. Novel therapies that aim at purging the HIV-1 reservoir using latency reversal agents (LRAs), targeting cellular host proteins, have limited effects in vivo and can induce severe side effects, emphasizing the need for alternative approaches to reverse HIV-1 latency. Accessory HIV-1 proteins play an important role in optimizing viral replication, enabling HIV-1 to evade host restriction and immunity, but their role in regulating HIV-1 latency remains largely unknown.

Methods: CRISPR/Cas9 knockout was used to access the accessory HIV-1 genes vpu, nef and vif in the latently HIV-1-infected J89 T cell line. The proportion of HIV-1-1GFP+ (i.e. HIV-1 reactivated) cells was traced using flow cytometry and immunofluorescence microscopy. We re-introduced 89.6 Vpu protein and vpu/vpr45SK DNA in J89Δvpu cells using Cell Squeeze® and Amaza® Cell Line Nucleofector® Kit V technologies, respectively. NK-x8 pathway activity was quantified using a dual luciferase reporter assay and ImageStreamX Mark II Imaging Flow Cytometer technique.

Results: Our data showed that J89Δvpu cells completely lost control over viral latency, while knockout of nef and vif had no impact. Re-introduction of Vpu protein alone restored HIV-1 latency in a median of 55% of J89Δvpu cells. The proportion of latently HIV-1-infected (HIV-1(GFP)-) cells significantly inversely correlated with the proportion of Vpu-FLAG+ J89Δvpu cells. Furthermore, Vpu-FLAG+ J89Δvpu cells showed reduced tetherin surface levels, demonstrating functionality of the Vpu-FLAG protein. As Vpu has been reported to suppress the NF-κB pathway, we measured NF-κB p65 nuclear translocation and observed that J89Δvpu cells showed higher NF-κB activation levels than parental J89 cells. Introduction of vpuR45K, encoding a Vpu mutant that selectively fails to inhibit the NF-κB pathway, did not affect HIV-1 gene expression in J89Δvpu cells, while re-introduction of wild-type Vpu restored HIV-1 latency, indicating a critical role of the NF-κB pathway.

Conclusion: These data identified Vpu as a viral protein involved in the maintenance of HIV-1 latency through a modulation of the NF-κB pathway, and provides strong rationale to screen for novel Vpu inhibitors as potential HIV-1 LRAs.

375 FORMATION OF THE REPLICATION-COMPETENT HIV-1 RESERVOIR COINCIDES WITH ART INITIATION
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Background: Although antiretroviral therapy (ART) is highly effective at suppressing HIV-1 replication, the virus persists in a latent reservoir during therapy. The HIV-1 reservoir is present in all HIV-infected people, even when ART is initiated soon after infection, suggesting that it forms early and persists despite long-term viral suppression.

Methods: We investigated the temporal origins of the long-lived reservoir in 10 women from the CAPRISA 002 acute infection cohort who initiated treatment in chronic infection. After a median of 4.5 yrs of untreated infection, nine of these women initiated ART and were well suppressed for a median of 4.9 yrs. Plasma-derived virus was sequenced on average every six months from acute/early infection to ART. These evolving sequences were compared to sequences of replication-competent reservoir viruses grown out of the latent reservoir. We used this same approach to analyse the viral reservoir in one woman for whom treatment initially failed. Illumina MiSeq with Primer ID was used to sequence partial env, gag and nef genes from pre-ART time points and PacBio sequencing was used to generate nearly full-length genome sequences of outgrowth viruses. The relatedness of reservoir and pre-ART viruses was evaluated using approximate maximum-likelihood analyses with phylogenetic placement.

Results: Reservoir viruses (mean = 16; range 6-48) were sequenced from the 10 women. In the nine individuals on long-term suppressive ART, a median of 78% of reservoir viruses were most similar genetically to viruses circulating in the year before ART. We expand on this initial result by examining reservoir formation in an individual who experienced treatment failure but was virologically suppressed after ART optimization. In this individual, the reservoir contained a high percentage of variants from the time when she initiated her first and second ART regimen.

Conclusion: In a cohort of nine well-suppressed women we observed that the vast majority of the persistent, replication-competent reservoir was established near the time of ART initiation. Analysis of an individual who experienced treatment failure suggests that variants may be seeded into the reservoir each time that an individual initiates therapy with a subsequent reduction in viral load. These observations suggest new strategies for reducing the size of the latent reservoir through viral clearance of variants circulating late in untreated infection.

376 TCR-ACTIVATED CD8+ T CELLS PROMOTE THE ESTABLISHMENT OF HIV LATENCY IN CD4+ T CELLS
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Background: Virus persistence in latently-infected CD4+ T cells despite ART is the major barrier to cure HIV infection. While HIV-specific cytotoxic T lymphocytes are known to control virus replication, recent studies showed that CD8+ T cells may also suppress HIV-1 in ART-treated macaques. Identifying the mechanisms responsible for CD8+ T cell-mediated HIV silencing might reveal molecular targets to disrupt the establishment and maintenance of the HIV reservoir.

Methods: CD4+ and CD8+ T cells were isolated from healthy donors, separately labeled with CellTrace Violet and CellTrace Red, and activated by TCR stimulation. CD4+ T cells were infected with an HIV reporter virus expressing eGFP under HIV-LTR control and CD8+ T cells were added for co-culture. Expression of activation markers (HLA-DR, HLA-ABC, and HLA-E), cell survival and cell proliferation were measured by flow cytometry. The non-productively-infected (eGFP-)-CD4+ T cell-population from mono- or co-culture were sorted and the inducible HIV reservoir was quantified by measuring eGFP expression 24h post reactivation.

Results: CD8+ T cells significantly suppressed eGFP expression in infected CD4+ T cells during co-culture as compared to CD4+ T cells cultured alone, under multiple-round and single-cycle infection conditions (mean 57%, p = 0.0078, n = 8, and mean 14%, p = 0.0011, n = 14, respectively). This observation suggests that CD8+ T cells not only inhibit virus spread but also suppress LTR-dependent viral transcription. Concomitantly, the suppressor activity of CD8+ T cells resulted in a 25% reduction of cell proliferation in the eGFP-CD4+ T cell population (mean fold change in CellTrace Violet MFI compared to CD4+ T cells alone, p = 0.0009, n = 14). Moreover, CD8+ T cells mitigated virus-induced cell death thus increasing CD4+ T cell survival (mean 10% increase in live CD4+ T cells, p = 0.0078, n = 8) and down-modulated the expression of activation markers on both productively infected (eGFP+) and eGFP- CD4+ T cells. Finally, CD8+ T cells increased the inducible HIV reservoir in CD4+ T cells by 62%, as shown by reactivation of sorted eGFP- CD4+ T cells from co-culture with CD8+ T cells as compared to CD4+ T cells from mono-culture (p = 0.0078, n = 8).

Conclusion: TCR-activated CD8+ T cells from HIV uninfected donors reduce virus production by autologous in vitro HIV-infected CD4+ T cells by mitigating their level of cell activation and proliferation, and ultimately facilitate the transition of these CD4+ T cells into latent HIV infection.

377 METHYLATION PROFILES OF HIV-1 PROViral DNA IN ART-SUPPRESSED INDIVIDUALS
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Background: The latent HIV-1 reservoir is populated with clones of cells infected with stably integrated, intact, but transcriptionally-silent proviruses. Previously, we described the integration site of one such clone harboring a replication-competent provirus called AMBI-1. We hypothesized that the silencing of HIV-1 gene expression from this and other clones was due to DNA methylation of the 5’LTR promoter. To address this question, we investigated methylation at the single–proval level in known CpG islands in the HIV-1 proviral genome, including one in the 5’LTR promoter region.

Methods: Using a bisulfite-based, methylation-specific single-genome-sequencing (SSS) assay, we measured the levels of methylation in CpG islands from ART-suppressed, chronically-infected individuals with samples from PBMC and lymph node mononuclear cells (LNMC) (including the donor with the AMBI-1 clone).

Results: From 4 individuals an average of 30 (range: 13 to 91) bisulfite-treated SSS were obtained from each PBMC and LNMC sample. We found no significant difference in any provirus between the level of methylation of the CpG island in the 5’LTR promoter and the assay background of cytosines not in CpG sites (averaging 3.8% and 3.3% respectively p=0.9). Furthermore, the presumed AMBI-1 provirus (matching LTR sequence) was not found to be methylated above assay background. Interestingly, we did find a significantly higher level of methylation in the CpG island in the env-tat-rev overlapping reading frame in multiple proviruses in each of the samples (averaging 21% of all CpG sites methylated vs. an average of 6% assay background (p=0.03)). In each PBMC and LNMC sample, 78% of genomes were methylated at >1 CpG site in the env-tat-rev island and 46% were methylated at ≥3 CpG sites.

Conclusion: Surprisingly, we did not find evidence that methylation of the 5’LTR promoter maintains HIV-1 latency in vivo, including LTRs of proviruses that are known to be intact and latent. Significant levels of methylation were found in a CpG island in env but its role, if any, in transcriptional silencing is unknown. Since it is well known that methylation of transcriptional enhancers located many kilobases from mRNA start sites can result in gene silencing, it is important to determine if the methylated CpG island in the env gene has any function in HIV-1 latency in vivo.

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

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Background: We have reported that an antisense transcript (Ast) expressed from a promoter located in the HIV-1 3’LTR induces the establishment and maintenance of HIV-1 latency. We have shown that Ast recruits the Polycomb Repressor Complex 2 (PRC2) to the HIV-1 5’LTR. PRC2 catalyzes trimethylation of lysine 27 on histone H3 (H3K27me3), an epigenetic mark that leads to 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). To identify Ast modifications, Ast was affinity-purified via complementary biotinylated oligos and streptavidin, enzymatically digested and analyzed by MS.

Results: To identify the functional domains of Ast, we divided the transcript into 5 segments and produced substitution and deletion mutants. A 376-nt segment at the 5’ end of Ast (SAST, mapping in the U3 region of the 3’LTR) mediates binding of Ast to the U3 region in the proviral 5’LTR via sequence homology. We divided the Ast sequence downstream of SAST into four segments (A through D), and generated a substitution mutant for each of them. Mutation of segment A or B impaired significantly Ast function. Indeed, mutation of 70nt within segment B containing a possible PRC2-binding motif greatly reduced Ast activity. Mutation of either segment C or D did not have a major effect, whereas concurrent mutation or deletion of both segments did. This suggests that segments C and D cooperatively recruit additional factors. Indeed, MS studies found that Ast interacts with additional transcription and epigenetic repressors such as NuRD, CTCF, YY1, TDP-43. Cell lysate fractionation through a sizing column showed that Ast purifies in high molecular weight fractions of ~2MDa that also contain Ast binding partners. We also found that Ast interacts with members of the C/EBP box and H/ACA box complexes, which catalyze RNA ribose methylation and pseudouridylation. Indeed, MS analysis of affinity-purified Ast showed that it contains these post-transcriptional modifications in vivo.

Conclusion: We identified the PRC2-binding motif of Ast, and showed that Ast binds other transcription repressors. We also found that Ast carries modifications affecting its stability and interaction with protein partners. Our studies suggest that Ast induces HIV-1 latency via multiple pathways.
identify infectious variants with sequences matching the RV. We hypothesized that during long-term ART, prevalent RV will be maintained over time and contribute to infectious viremia, and thus to persistence of the reservoir.

**Methods:** Extracted RNA from at least 4 pre-ART, 4 on-ART (viral RNA <500copies/ml), and 2 post-ART interruption time points was subjected to endpoint-PCR of C2V5env, sequenced, and assembled into a maximum-likelihood tree. QVOA was performed on all 3 subjects from a time point with undetectable viral load (<500copies/ml). Predicted cell tropism was performed using PSSM.

**Results:** RV variants were often clonal in participants 1 and 2 (n=21/113), n=28/38, respectively), with clonal variants observed for at least 3yrs on ART, but included multiple variants in participant 3. RV across participants 1, 2, and 3 were predominantly CCR5(R5)-tropic (57%, 99%, and 84%, respectively), with the remaining being CXCR4-tropic. In participant 1, a RV clone (n=4) had an identical C2V5 to a QVOA variant. This RV clone (R5-tropic) was observed for at least 7yrs since pre-ART. A match between a QVOA variant and a monotypic plasma pair (n=2) in participant 3 was also observed and maintained for 3yrs on ART. R5-tropic RV monotypic variants detected during ART in participants 1 and 2 were also detected post-ART interruption and re-suppression and these variants were maintained for 7 and 2yrs, respectively.

**Conclusion:** These findings suggest that RV represent a non-latent part of the infectious reservoir that upon ART interruption could fuel new cycles of infection. Furthermore, persistence of certain monotypic clones over time suggests that cells harboring these virions may be resistant to immune clearance or regularly renewed.

381 **PD-1/PD-L1 INTERACTION REGULATES HIV TRANSCRIPTION IN LYMPH NODES OF TREATED SUBJECTS**

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**Background:** Follicular helper (Tfh) cells expressing high levels of PD-1 were recently shown to serve as a major site of active and persistent HIV transcription despite prolonged ART. The present study aimed to determine the potential role of immune checkpoint (IC)/IC-Ligand (IC-L) interactions on HIV transcription in lymph node (LN) microenvironment.

**Methods:** To address this issue, we assessed the expression of ICs and IC-Ls on LN cell populations and the impact of IC/IC-L interactions on T-cell proliferation, reactivation of HIV production and HIV transcription in LN memory CD4 T cell populations from viremic and aviremic ART-treated HIV-infected subjects (N=47).

**Results:** We showed that PD-1 and TIGIT are the two major ICs expressed on Tfh cells of healthy, viremic and ART-treated HIV-infected subjects ex vivo. We subsequently showed that PD-1 and a lower extent CD155 (TIGIT ligand) recombinant proteins significantly reduced TCR-mediated T-cell proliferation and reactivation of HIV production in vitro (P<0.05), demonstrating that PD-1 and TIGIT signaling pathways were functionally active on PD-1+/Tfh cells and regulate TCR-mediated HIV transcription and production. We therefore explored the phenotype, the frequency and the tissue distribution of IC-L expressing cells and showed that PD-1 and CD155 were predominantly co-expressed on LN HLA-DRhighCD1chigh dendritic cells (DCs). The frequencies of PD-1+/DCs in viremic infected subjects directly correlated with HIV viral load (r=0.93, P=0.0002) and significantly dropped after prolonged ART (P<0.05). Interestingly, PD-1 expressing cells were detected in both extrafollicular and germinal center (GC) areas of viremic HIV-infected subjects, but were barely detectable in GCs of ART treated subjects, suggesting that ART initiation had a profound impact on IC-L tissue distribution and that PD-1/PD-L1 interactions might be selectively reduced in GCs of ART-treated subjects. Finally, the frequencies of LN PD-L1+DCs inversely correlated with HIV transcription (r=-0.89; P<0.05) in LN memory CD4 T cells, indicating that PD-L1+DCs contribute to control HIV transcription in vivo.

**Conclusion:** HIV exploits the IC regulatory mechanism of T cell activation and function to favor persistence of HIV transcription/production in treated aviremic HIV-infected subjects. It also indicates that an imbalance in IC/IC-L interactions is a novel mechanism contributing to HIV persistence in germinal centers.

382 **CELLULAR PROLIFERATION MAINTAINS GENETICALLY INTACT AND DEFECTIVE HIV-1 OVER TIME**

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**Background:** A thorough understanding of the cellular mechanisms maintaining replication-competent virus will be needed to design future HIV eradication therapies. We examined the relative proportions of genetically identical and defective proviruses within memory CD4+ T cell subsets from individuals on prolonged ART.

**Methods:** Naïve, central (CM), transitional (TM) and effector (EM) memory CD4+ T cells, as well as CD45RA-HLA-DR+ and CD45RA-HLA-DR- CD4+ T cells, were sorted from the peripheral blood of eight participants on long-term ART. Additional sequences from four participants were obtained four years later. We used the full-length individual proviral sequencing assay, which amplifies single HIV proviruses followed by next-generation sequencing, to characterise proviruses as intact or defective (containing insertion, deletion, stop codons or hypermutation). Duplicated sequences were classified as ≥2 identical HIV DNA sequences.

**Results:** At the early time-point, 1041 sequences were obtained, and only 4% were considered intact. The proportion of intact proviruses was different across cell subsets (p=0.001), with the highest proportion observed in EM and HLA-DR+ cells. Equivalent amounts of duplicated sequences were identified in defective and intact proviruses. However, when stratified by treatment duration, the proportion of duplicated sequences was higher in those on therapy for >14 years. Of note, no intact duplicated sequences were observed in participants on therapy for <5 years. Duplicated intact sequences were predominantly found in EM and HLA-DR+ cells; representing 24% and 17% of all intact sequences in these subsets respectively. These intact duplicated sequences were observed in two participants four years later. In one participant where no intact provirus was observed, a large expansion of defective sequences predominated (28/68 sequences; 41%). These defective sequences expanded four years later, representing 78% of all sequences isolated (167/215 sequences).

**Conclusion:** Cellular proliferation contributes to the expansion of both genetically intact and defective proviruses. Expansions of defective proviruses may dilute the number of intact proviruses and therefore lead to difficulty in their identification in some participants. Notably, genetically identical intact proviruses are enriched in HLA-DR+ and EM cells and these proviruses are stable over time, indicating the latent HIV reservoir is maintained in these T cell subsets in the peripheral blood by proliferation.

383 **INCREASED NUMBERS OF INTACT HIV SEQUENCES IN A487 T CELLS DURING ACUTE SEROCONVERSION**

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**Background:** Memory CD4 T cells expressing the integrin α4β7 seem highly susceptible to HIV-1 infection, and may represent a preferential site for viral infection and reservoir establishment. Recent studies suggested that when used in combination with regular antiretroviral therapy during acute SIV infection, monoclonal antibodies blocking α4β7 may enable rhesus macaques to control viremia after ART discontinuation. In contrast, a clinical trial with α4β7 blocking antibodies in humans with chronic HIV-1 infection has recently been completed, without markedly increased frequencies of individuals achieving post-treatment control.

**Methods:** PBMCs were isolated from HIV-1 positive patients (n=4) during acute seroconversion before ART initiation (Fiebig stage III-V). CD4 T cells were enriched by negative MACS selection, and the α4β7-positive and β7-negative memory CD4 T cell populations were sorted by FACS. Near-full-length, single-genome HIV-1 DNA sequencing of total CD4 T cells, β7-positive and β7-negative memory CD4 T cell subsets was performed, as described previously. Phylogenetic
Sex and Obesity are Associated with Residual Viremia in ART-Suppressed Individuals

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Background: The sex of an individual influences HIV levels prior to antiretroviral therapy (ART) and adipose tissue has been proposed to harbor a primary target site for viral replication during the earliest stages of HIV-1 infection, and raise the possibility that administration of α4β7 antibodies during acute HIV-1 infection may reduce viral reservoir establishment.

Methods: Participants who initiated ART during chronic infection with sustained virologic suppression had measurements of plasma HIV RNA by single copy assay (SCA), cell-associated HIV DNA and RNA (CA-DNA, CA-RNA). We assessed the effect of age, sex (reported at birth), BMI, waist circumference (WC), years on ART, pre-ART HIV RNA, pre-ART CD4 count, initial ART regimen (PI, NNRTI or INSTI) on HIV persistence. Assessments were done at study entry or, for WC, at pre-study visit.

Results: 295 participants (53 females) were evaluated; median (IQR) age 48yr (41, 54); yrs on ART 7 (6, 10); BMI 24 (21, 28); WC 94cm (87, 102). CA-DNA, CA-RNA and plasma SCA were positively correlated with pre-ART HIV RNA (r=0.35, 0.29, 0.20, respectively, p-values<0.001), and negatively with pre-ART CD4 count (-0.35, -0.21, -0.12, respectively, all p<0.05). Males were more likely to have plasma SCA values ≥0.4 copies/mL (52% vs 29%; p=0.003) (Figure), even after adjusting for age, pre-ART HIV RNA and CD4 count, years on ART and BMI (p<0.004). Higher BMI and higher WC were each associated with higher SCA levels (r=0.12 and 0.13, p<0.04) after adjustment for age, sex, pre-ART HIV RNA and CD4 count, and years on ART. The proportion of participants with detectable residual viremia increased in a step-wise fashion by BMI category: normal/underweight 38%; overweight 50%; obese 55% (Figure). Sex, BMI and WC were not associated with CA-DNA or CA-RNA.

Conclusion: Higher BMI and obesity are associated with higher levels of residual viremia in persons on long-term ART. Adipose tissue may be an important site of HIV production due to its proinflammatory milieu or altered ARV penetration. The finding that females have lower residual viremia than males may reflect effects of estrogen on HIV expression or other biologic and immunologic differences. Studies of the mechanism by which obesity and sex affect HIV persistence are needed to inform cure strategies.
prolonged mediation viral reactivation (15.8% to 2.9% or 9.2%, respectively; P=0.0001).

Conclusion: Cell-surface fucosylation and enhanced carbohydrate metabolic activity are associated with higher T cell activation and persistent HIV transcriptional activity during suppressive ART. T cell surface fucosylation is known to be critical for memory T cell activation and trafficking. Together, the role of T cell-surface fucosylation and altered carbohydrate metabolic activity in HIV persistence warrants further investigation, in order to identify glycan-based interactions that can be targeted for novel HIV immunotherapies.

**Results:**

Phosphorylation was examined by Phospho-Kinase antibody arrays. Individual plasma levels of the immunomodulatory galectin-9 (Gal-9) are elevated during HIV infection and remain elevated after antiretroviral therapy (ART) suppression. We recently reported that Gal-9 regulates HIV transcription and potently reactivates latent HIV ([PMID 27253379](https://pubmed.ncbi.nlm.nih.gov/27253379/)). Given that galectins are known to modulate TCR-signaling, we hypothesized that TCR signaling transduction contributes to the Gal-9-mediated modulation of HIV transcriptional activity. We tested this using an anti-phosphorylated-CD3-ζ antibody and a pharmacological inhibitor of Lck activity, we evaluated the role of TCR signaling in Gal-9-mediated 1) latent HIV reactivation, 2) T cell activation, and 3) cytokine secretion using the J-Lat 5A8 HIV latency model and CD4+ T cells from 5 HIV+ individuals on suppressive ART. Effects of Gal-9 on TCR-downstream kinase signaling, we hypothesized that TCR signaling transduction contributes to the Gal-9-mediated modulation of HIV transcriptional activity.

**Methods:** Using an anti-phosphorylated-CD3-ζ antibody and a pharmacological inhibitor of Lck activity, we evaluated the role of TCR signaling in Gal-9-mediated 1) latent HIV reactivation, 2) T cell activation, and 3) cytokine secretion using the J-Lat 5A8 HIV latency model and CD4+ T cells from 5 HIV+ individuals on suppressive ART. Effects of Gal-9 on TCR-downstream kinase phosphorylation was examined by Phospho-Kinase antibody arrays.

**Results:** Gal-9 induced CD3-ζ phosphorylation (11.2% to 32.1%; P=0.008). Inhibition of Lck activity reduced Gal-9-mediated viral reactivation in the J-Lat SAB cells (15.8% to 1.5%; P<0.0001). In addition, Lck inhibitor reduced both Gal-9-mediated T cell activation (10.4% to 1.6% CD69/CD25 co-expression; P<0.0001), and IL/2/TNF secretion (P<0.001), in primary CD4+ T cells. Gal-9 increased the phosphorylation of the TCR downstream signaling molecules ERK1/2 (26.7 fold) and CREB (6.6 fold). ERK and CREB inhibitors reduced Gal-9-mediated viral reactivation (15.8% to 2.9% or 9.2%, respectively; P=0.0001).

Given that the immunosuppressive rapamycin uncouples HIV latency reversal from cytokine-associated toxicity ([PMID 28094770](https://pubmed.ncbi.nlm.nih.gov/28094770/)), we investigated whether rapamycin could uncouple Gal-9-mediated latency reactivation from its concurrent pro-inflammatory cytokine production. Rapamycin reduced Gal-9-mediated secretion of IL-2 (4.4-fold, P=0.001) and TNF (4-fold, P=0.02) without impacting viral reactivation (16.8% compared to 16.4%; P=0.2).

**Conclusion:** Gal-9 modulates HIV transcriptional activity through TCR/Lck-dependent ERK1/2-CREB phosphorylation pathway. Our findings could have implications for understanding the role of endogenous galectin interactions in modulating TCR signaling and maintaining chronic immune activation during HIV infection. In addition, uncoupling Gal-9-mediated viral reactivation from undesirable pro-inflammatory effects, using rapamycin, may increase the potential utility of recombinant Gal-9 within the reversal of HIV latency eradication framework.

**Conclusion:**

Gal-9 mediates HIV transcription by inducing TCR-dependent ERK signaling.

**Results:**

In Gal-9-mediated infected CD4+ T cells, Gal-9 increased the phosphorylation of the TCR downstream signaling molecules ERK1/2 (26.7 fold) and CREB (6.6 fold). ERK and CREB inhibitors reduced Gal-9-mediated viral reactivation (15.8% to 2.9% or 9.2%, respectively; P=0.0001). Given that the immunosuppressive rapamycin uncouples HIV latency reversal from cytokine-associated toxicity ([PMID 28094770](https://pubmed.ncbi.nlm.nih.gov/28094770/)), we investigated whether rapamycin could uncouple Gal-9-mediated latency reactivation from its concurrent pro-inflammatory cytokine production. Rapamycin reduced Gal-9-mediated secretion of IL-2 (4.4-fold, P=0.001) and TNF (4-fold, P=0.02) without impacting viral reactivation (16.8% compared to 16.4%; P=0.2).

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**Conclusion:** Multiple TNFSR members are upregulated at the transcriptional and protein level in cells with in vitro-induced productive and latent infection. Increased expression of these markers is associated with transcriptional induction of cell survival signatures. Our data lay the foundation for future investigation on roles of TNFSRs in naturally-infected CD4+ T cells to fully appreciate their impact on viral reservoir persistence.

**388 HIV PROVIRAL DNA METHYLATION IN SEROCONVERTERS, CONTROLLERS, AND ART-TREATED PATIENTS**

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**Background:** DNA methylation is a well-known epigenetic modification that drives gene transcription, but its role in the HIV-1 proviral genome is largely unknown. In latency models, hypermethylation has been linked to silencing, while loss of methylation stimulates reactivation. However, due to low HIV-1 proviral DNA levels and high genomic heterogeneity, obtaining reliable and reproducible patient-derived data has been difficult. This has resulted in the past in conflicting publications. We therefore have performed an in-depth evaluation of the HIV-1 proviral methylation state in a well-characterized HIV-1 patient cohort.

**Methods:** To reliably measure DNA methylation in HIV-1 proviruses from clinical samples, we used a bisulfite-based deep sequencing assay to measure the methylation state of 4/5 CpG islands (CpGIs) found in the HIV-1 genome (2 in LTR, 2 in env). This assay was used to compare methylation in PBMCs from 72 individuals, divided in four groups: early ART-treated HIV-1 seroconverters (ET, N=15), late ART-treated patients (LT, N=23), ART-naive seroconverters (SRCV, N=6) and long-term non-progressors (LTNP, N=7). Data was mapped to a reference HIV-1 genome using Bismark (v0.10.1) and analyzed with the methylKit package (version 1.6.2).

**Results:** We show (i) that CpGIs inside the LTR region have low overall methylation level (median <5%) as compared to CpGIs in the env region (median up to 40%), and (ii) that LTR CpGIs are equally methylated in all 4 groups (differential methylation (DM) <5%). (iii) CpGIs in the env region show no DM between patients controlling HIV-1 replication (ET, LT, LTNP), but a decrease of 29.92% in SCR as compared to these groups. Within the cohorts on long-term ART (median of 10 years), we found no correlation between the time of initiation of therapy and the methylation percentage (Spearman's rank correlation: p = 0.2131).

**Conclusion:** Our results using this sensitive assay show a paucity of DNA methylation in the HIV-1 promoter region in all patient groups with the absence of ART or different timing of ART initiation suggesting that LTR methylation is not involved in regulating latency, which contradicts the latency model results. Methylation in env on the other hand is higher, and found in all patients who are chronically viral suppressed suggesting that env DNA methylation has latency regulating effect.

**389 ANALYTICAL TREATMENT INTERRUPTION (ATI) IN PATIENTS WITH VERY SMALL HIV RESERVOIR**

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**Background:** No single parameter reliably predicts post-treatment control (PTC) among HIV infected patients. However, both total HIV-1 DNA (tDNA) and cell-associated RNA (caRNA) have been individually associated to delayed viral rebound after ATI. We evaluated the predictive value of the combination of low DNA and caRNA in the identification of PTC.

**Methods:** The study is a two-step single arm multi-centric non-randomized prospective trial (NCT02590354). Major inclusion criteria in step 1 were: nadir CD4+ T-cell count >350 cells/μl and plasma viral load (pVL) <50 cps/ml since ≥2 years. The size of the HIV reservoir was determined by droplet digital PCR measurement of tDNA and caRNA in peripheral blood mononuclear cells (PBMCs). In step 2, consenting patients with tDNA <66 cps/10^6 PBMCs and caRNA <10 cps/10^6 PBMCs underwent a leucapheresis prior to ATI. cART was re-initiated whenever pVL measured every other week, was >1,000 cps/ml at two consecutive measurements or at pVL > 10,000 cps/ml. tDNA and caRNA were measured at every visit during ATI as well as 4 and 12 weeks after cART re-initiation. Quantitative viral outgrowth assays (qVOA), viral release assays (VRA) and ultra-sensitive pVL were performed on pre-ATI samples. Associations between clinical, virological or immunological parameters and viral rebound dynamics were assessed with Kaplan-Meier estimates and Cox proportional hazard models.

**Results:** Of the 114 participants, 37 (32.5%) met the viral reservoir criteria for ATI. Of them, 16 (14.0%) consented and underwent ATI. All 16 participants experienced rapid viral rebound two to eight weeks after ATI (figure), with 13/16 (81.3%) reporting an adverse event (AE) but none with serious AE. All participants suppressed viremia to levels below the limit of detection within 14 weeks of cART re-initiation. tDNA and caRNA returned to baseline levels within the 12 weeks after cART re-initiation. No correlations were observed between viral rebound dynamics and current or nadir CD4+ T-cell count, ultra-sensitive pVL, tDNA or caRNA, qVOA, VRA or any other clinical parameters.

**Conclusion:** We report on the first prospective study evaluating ATI in participants selected on the basis of a very small and transcriptionally silent HIV reservoir. No PTC was identified. ATI was shown to be safe, despite rapid viral rebound. The impact of ATI on the reservoir size after cART re-initiation was limited. None of the measured baseline parameters were predictive for viral rebound dynamics.

**390 N-803 INDUCES ROBUST SIV REACTIVATION IN ART-TREATED CDB8-DEPLETED MACAQUES**

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Background: The current paradigm in HIV cure research is that virus production must be reactivated in latently infected cells prior to clearance (shock and kill). Since depletion of CD8+ lymphocytes in SIV-infected ART-treated rhesus macaques (RM) results in increased plasma viremia, we propose that CD8 depletion may act synergistically with latency reversing agents (LRA) in reactivating virus production. To test this hypothesis we used the IL-15 superagonist N-803, an agent that shows LRA activity in vitro and may also boost antiviral cellular immune responses.

Methods: 35 SIV-infected RM started ART 8 weeks post-infection. After 1 year, 7 RM received four weekly doses of N-803 (100 µg/kg), 14 received 50 mg/kg of the CD8a-depleting Ab MT-807R1, and 14 RM received both treatments. All animals underwent ART interruption 3 weeks after the last N-803 dose and/or CD8 reconstitution. SIV reactivation was monitored by plasma viremia and total cell-associated SIV DNA. Immunological changes were studied by flow cytometry and RNA sequencing. Diversity of the virus emerging after N-803 and/or CD8 depletion was assessed via single genome amplification.

Results: In ART-treated RM, N-803 alone did not reactivate virus production; however, its administration in CD8-depleted RM resulted in loss of virus suppression (>60 copies/ml) in 14/14 animals (100%) in 41/56 samples (73.2%) collected 1 week after each dose. In addition, viremia >1,000 copies/ml was observed in 6/14 animals (42.9%) and 13/56 (23.2%) time points, with a maximum of 21,000 SIV copies/ml. Preliminary virus sequence analysis indicated a diverse range of circulating virus after CD8 depletion and N-803 treatment. Despite this very robust level of virus reactivation, all groups of RM showed stable levels of cell-associated SIV DNA in CD4+ T cells following treatment and a rapid rebound of viremia after ART interruption.

Conclusion: N-803 administration in CD8-depleted, ART-treated SIV-infected RM induces the most robust and persistent reversal of latency observed to date in humans or nonhuman primates. In absence of a clearance intervention, we did not observe a significant reduction of the reservoir size. Combining N-803 and CD8 depletion with an immune-clearing component (i.e. neutralizing antibodies, CD4 mimetics or immunotoxins) may be a powerful shock and kill strategy that profoundly affects reservoir size and stability in ART-treated HIV/SIV infections.
HIV RNA rebound in semen occurred significantly later (median of 66 vs 42 days post ART interruption) and reached lower levels (164 vs 16,224 copies/mL). Paired sequence data were available for 5 participants. All presented compartmentalized viral rebound between blood and semen (FST, p<0.05 for all genes). Phylogenetic analysis confirmed the presence of compartment-specific monophyletic HIV RNA populations in at least one HIV region in 3 out of the 5 participants in longitudinal time-points, suggesting that rebound originated within genital compartment rather than migrating from blood (Figure 1 panel A). Interestingly, despite early ART start, genetic diversity after adjusting for variant frequency was higher in semen compared to blood in all three coding regions (Significant for gag and pol (<0.01) but not in env (p=0.06)), Figure 1 panel B.

**Conclusion:** HIV reservoirs in the genital compartment might contribute to viral rebound in PLWH interrupting ART. Higher diversity in the genital compartment illustrates viral compartmentalization and distinct evolutionary dynamics. Reservoirs in all anatomic compartments need to be actively targeted to achieve a complete functional cure.

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**393 SEEKING SUPPRESSION IN HAVARTI: VIREMIA & T CELLS AFTER VEDOLIZUMAB & ATI IN HIV/ART**

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**Background:** HAVARTI is a dose-ranging trial of vedolizumab and analytical treatment interruption (ATI) in HIV/ART.

**Methods:** Eight healthy HIV+ adults on ART for 2-10 years had vedolizumab given 3 times in 6 weeks before, and 4 times in 14 weeks after ATI at, 300mg doses in 4 (Group 1) and 150mg in 4 (Group 2). Monthly follow-up for adverse events (AE), plasma viremia (pVL) and T cell count outcomes informed clinical judgement for ART retreatment.

**Results:** Groups had similar mean age, nadir CD4, pre-ART pVL, ART duration & baseline CD4 count. No serious clinical or severe laboratory AE occurred. One case had non-sustained pVL suppression <40 copies/mL in 2 sequential measures. CD4 T-cell count response varied, but none had sustained CD4 <350 cells/µL. Percent 4+7+ CD4 T cells in rectal mucosa decreased in Groups 1 and 2 respectively from 46.90 ±23.30 and 30.63 ±9.86 before, to 2.77 ±1.73 and 3.05 ±2.47 after vedolizumab. Group 1 pVL rebounded in 3 of 4 at 2 weeks, and all 4 at 6 weeks into ATI. pVL doubling time (T2) from ATI week 2 to 6 was 7.67 ±4.41 days, to a peak pVL level below pre-ART in each by mean 1.21 ±0.56 log10 copies/mL, sustained on average to 22 weeks, before a consistently rising pVL trajectory after 26 weeks, 12 weeks after last vedolizumab dosage. Group 2 pVL rebounded in 1 of 4 at 2 weeks, and all 4 at 6 weeks into ATI. T2 was 2.58 ±0.79 days, to week 6 peak pVL above pre-ART in 3 of 4 by mean 0.26 ±1.37, falling below mean pre-ART pVL to 14 weeks, with consistent rising trajectory onset after 18 weeks, 4 weeks after last vedolizumab dosage.

**Conclusion:** Viremia rebound appears attenuated in group 1 compared with group 2, supported by individual consistency of much slower T2 (p=0.057), and much lower pVL peak compared to pre-ART (by 1.47 log10), sustained 2 months longer after last vedolizumab dosage. This difference is corroborated by historical controls with calculated T2 of 3.4 days (and from literature about 2-3 days) and pVL rebound to +0.72 log10 > pre-ART at 6 weeks, as in Group 2. Limitations include small numbers, and high variation. Strengths include coherence of a biologically large effect size on pVL rebound dynamics, on kinetics and on time to loss of activity by dosage group, suggesting dose- and exposure-related vedolizumab effects. Deeper biological study in these cases, and further data from greater numbers, doses and duration is needed to validate and confirm activity of vedolizumab in pursuit of pVL suppression after ART.

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**394B ANALYTIC TREATMENT INTERRUPTION (ATI) AFTER ALLOGENEIC CCR5-D22 HSCT FOR AML IN 2013**

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**Background:** A 49y-old HIV-infected male patient received unmodified HSCT from a 10/10 CCR5-d22 donor in Feb 2013 because of acute myeloid leukaemia (AML) while in 2nd complete remission (CR). At time of HSCT proviral HIV DNA load was 1.45 log10copies/Mio PBMCs. All anticipated antibodies were detected by western blot. HIV coreceptor-usage was predicted R5 (Sanger: FPR 44.5%; NGS: 0.14% X4 at 3.5% FPR, geno2pheno), confirmed by phenotyping test (TropChase). He had a 2nd relapse of AML in Jun/13 but after 8 courses of 5-azaC and 4 donor lymphocyte infusions CR was achieved. Immunosuppression was stopped in Oct/17. During HSCT the patient remained on ART until Nov/18 with undetectable plasma viral load.

**Methods:** PBMC and tissues were analysed by ddPCR, qPCR and in situ hybridization in several laboratories as well as humoral and T-cell responses. Infectious virus was analysed on CD4+ T-cells (qVOA, MVOA). Patient was registered to lOStem as #19.

**Results:** Almost all PBMC samples were negative for proviral HIV-DNA by qPCR/ddPCR at multiple time points. CSF (Jul/14), rectum (Apr/15, Mar/16), ileum (Mar/16) and bone marrow (Aug/15) were negative. Further testing with 0.1 Mio cells from ileum showed in 1/4 replicates one positive droplet with LTR, but none with gag-primers. There was also a signal in TCM 0.2 Mio cells (ddPCR 1 positive droplet, qPCR neg) and in TEM 0.36 Mio cells (PCR Scp/Mio cells, ddPCR neg) while all other T-cell subsets were negative in ddPCR & qPCR. No HIV-DNA could be detected by PCR in lymph nodes of May/17, but in situ hybridization assays (RNAscope, DNA-scope) detected few positive signals. Viral outgrowth assays (qVOA) in Feb/16, Mar/16 and May/16 were negative (23 Mio CD4+ T-cells, IPMN<0.031/Mio CD4+ T-cells). Mouse VOA (Apr/16: Rag2-/-;scid/-, Apr/17: NOD-SCID IL2gR-/-) were also negative. Gp160 was the only remaining band on the blot. Peptide stimulation assays revealed the presence of CCR5-negative HIV-1 specific CTL recognizing HLA-A2-restricted RT-epitope Y99 and HLA-B7-restricted Gag-6 epitope Y19.

**Conclusion:** Despite low signals in ultrasensitive assays no virus could be detected in qVOA/mVOA in the Duesseldorf patient. Taking into account the homogous CCR5-d22 status we consider a viral rebound to be unlikely. An ATI is the only way to find out whether HIV has been eradicated by allogeneic CCR5-d22 HSCT. Therefore ART was stopped in Nov/18 after thorough discussion with the patient. Despite all plasma samples being negative after ATI longer surveillance is essential.

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**395 TELMSARTAN DECREASES HIV-1 RNA IN LYMPH NODES IN TREATED HIV INFECTION**

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**Background:** Chronic inflammation in HIV infection can lead to lymph node (LN) fibrosis and limit CD4+ T-cell recovery. Telmsartan, an angiotensin receptor blocker and PPAR-γ agonist, is anti-inflammatory and anti-fibrotic.
DEPLETION OF BLOOD PD-1+ CD4 T CELLS BY A-PD-1 ADC SUPPRESSES HIV INFECTION IN VITRO

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Background: Despite the efficacy of antiretroviral therapy (ART) at suppressing HIV-1 viral replication, treatment interruption results in viral rebound in the majority of individuals. HIV resurgence is due to the persistence of a long-lived virus reservoir that is not susceptible to ART. Recent studies have shown that PD-1+ CD4 T cells serve as a major cellular reservoir for HIV-1 replication and may be differentially affected by the intervention. This study investigated the effect of romidepsin on the HIV transcription profile in participants from the REDUC part B clinical trial.

Methods: Seventeen participants on suppressive antiretroviral therapy were vaccinated with six doses of the therapeutic vaccine Vacci-4x followed by treatment with three doses of romidepsin. Samples from nine study participants were available for HIV transcription profile analysis. Read-through, total (TAR), elongated (longLTR), polyadenylated (polyA) and multiply-spliced (TatRev) HIV transcripts and total HIV DNA were quantified at baseline (visit1) and 4 hours after the second (visit 10b) and third (visit 11b) romidepsin infusions, using qRT-PCR, qPCR and droplet digital PCR.

Results: We observed a significant increase in read-through (1.7-fold, p<0.02), total (1.9-fold, p<0.01), elongated (2.4-fold, p<0.01) and polyadenylated (1.9-fold, p=0.03) HIV RNA/10^6 PBMCs after the second romidepsin infusion (visit 10b), and a 1.9-fold increase in elongated transcripts after the third romidepsin infusion (visit 11b) (p<0.01). No significant changes were observed in multiply-spliced HIV RNA or HIV DNA. No change was observed in the ratio of read-through/total HIV transcripts. The ratio of elongated/total HIV RNA increased after both the second and third romidepsin infusions (p=0.02), while the ratio of polyadenylated/elongated HIV decreased after the third infusion (p=0.02).

A strong negative correlation was observed between HIV DNA and the time to rebound (VL>50 copies/ml) at visit 1, 10b, and 11b (Rho=-0.81, -0.88, and -0.91; p=0.02, p<0.01, and p<0.01, respectively). Levels of all HIV RNAs tended to correlate negatively with the time to rebound. This association was strongest for the comparison between elongated transcripts and time to VL>1,000 copies/ml after romidepsin administration (Rho=-0.78, p=0.03 at visit 10b; Rho=-0.77, p=0.03 at visit 11b).

Conclusion: In these patients, romidepsin increased early events in HIV transcription (initiation and especially elongation), but had less effect on later stages (completion, multiple splicing) that may be required for comprehensive latency reversal and cell killing. Without cell death, increased HIV transcription before or after latency reversal may hasten viral rebound after therapy interruption.

398 THE IMPACT OF VORINOSTAT AND THERAPEUTIC VACCINE ON GUT HIV DNA: THE RIVER GUT STUDY

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Background: Reversing HIV-1 latency has been suggested as a strategy to eradicate HIV-1. We investigated the effect of romidepsin on the HIV transcription profile in participants from the REDUC part B clinical trial.

Methods: Seventeen participants on suppressive antiretroviral therapy were vaccinated with six doses of the therapeutic vaccine Vacci-4x followed by treatment with three doses of romidepsin. Samples from nine study participants were available for HIV transcription profile analysis. Read-through, total (TAR), elongated (longLTR), polyadenylated (polyA) and multiply-spliced (TatRev) HIV transcripts and total HIV DNA were quantified at baseline (visit1) and 4 hours after the second (visit 10b) and third (visit 11b) romidepsin infusions, using droplet digital PCR.

Results: We observed a significant increase in read-through (1.7-fold, p<0.02), total (1.9-fold, p<0.01), elongated (2.4-fold, p<0.01) and polyadenylated (1.9-fold, p=0.03) HIV RNA/10^6 PBMCs after the second romidepsin infusion (visit 10b), and a 1.9-fold increase in elongated transcripts after the third romidepsin infusion (visit 11b) (p<0.01). No significant changes were observed in multiply-spliced HIV RNA or HIV DNA. No change was observed in the ratio of read-through/total HIV transcripts. The ratio of elongated/total HIV RNA increased after both the second and third romidepsin infusions (p=0.02), while the ratio of polyadenylated/elongated HIV decreased after the third infusion (p=0.02).

A strong negative correlation was observed between HIV DNA and the time to rebound (VL>50 copies/ml) at visit 1, 10b, and 11b (Rho=-0.81, -0.88, and -0.91; p=0.02, p<0.01, and p<0.01, respectively). Levels of all HIV RNAs tended to correlate negatively with the time to rebound. This association was strongest for the comparison between elongated transcripts and time to VL>1,000 copies/ml after romidepsin administration (Rho=-0.78, p=0.03 at visit 10b; Rho=-0.77, p=0.03 at visit 11b).

Conclusion: In these patients, romidepsin increased early events in HIV transcription (initiation and especially elongation), but had less effect on later stages (completion, multiple splicing) that may be required for comprehensive latency reversal and cell killing. Without cell death, increased HIV transcription before or after latency reversal may hasten viral rebound after therapy interruption.
RIVER sub study compares HIV DNA, markers of immune activation & exhaustion in GALT, and microbial translocation by study arm.

**Methods**: ART was commenced within 4 weeks of confirmed PHI diagnosis at enrolment. At week 24, when plasma HIV RNA was suppressed, participants were randomized (1:1) to receive either ART or ART plus a prime-boost T-cell vaccination (ChAdV63.HIVconsv and MVA.HIVconsv) or 10 doses of 400mg of vorinostat (ART+V+V). Following completion of the RIVER study protocol individuals (from each arm) consented to the gut sub study; individuals underwent colonoscopy, with terminal ileum and rectal biopsies taken for HIV DNA quantification (qPCR) and assessment of immune activation and exhaustion (PD-1 and HLA-DR/CD38 expression on CD4+ cells) by flow cytometry. Plasma microbial translocation markers (sCD163 & sCD14) were measured in plasma using Luminex. P24 antigen was measured in stimulated tissue explant supernatants by ELISA.

**Results**: Eleven men were enrolled in the RIVER gut study, five in the ART-only arm and six in the ART+V+V arm, all were male. The median total HIV DNA in the terminal ileum was 2.8 (ART+V+V) and 3.1 (ART) log10 copies per 106 gut cells (P=0.25), and in the rectum 2.8 (ART+V+V) and 3.0 (ART) log10 per 106 gut cells. (P=0.14). No significant differences in expression of PD-1 and HLA-DR/CD38 co-expression on CD4+ T-cells from GALT were observed between study arm, median p24 levels measured from explant supernatants (n=7) were similar in each arm. Significantly higher sCD163 (P=0.03) but not sCD14 (P=0.55) levels were observed in plasma from participants in the ART+V+V arm compared with ART only.

**Conclusion**: These data suggest that vorinostat in combination with a T-cell prime-boost vaccine did not impact the GALT HIV reservoir, nor measures of immune exhaustion & activation on GALT CD4+ T-cells in ART+V+V treated individuals compared with ART alone during PHI. Measures of bacterial translocation appear to be increased in ART+V+V over ART-only warranting further investigation.

**Figure 1.**

- HIV DNA measured from (a) terminal ileum and (b) rectum GALT from the RIVER study arms is shown. ART plus intervention arm (blue) and ART only arm (green). (c) HDAC inhibition may have beneficial effects on HIV persistence, immune function, and gene expression.

**Table**: Levels of viral DNA quantitation at PMBCs among patients of G6 at baseline (week 0), week 24, week 48 and 96 weeks after 3 doses of autologous DCs. In one patient of G6, viral DNA in PMBCs was below the limit of detection after treatment with intensified ART + NA + DORI, and, in another, viral DNA became undetectable after the DCs. One patient from G6, interrupted ART after week 48 and before DCs by his own decision, and presented a residual in virions, which reflected an increase in viral DNA in PMBCs (double undetected in the table). Another patient from G2 was also interrupted ART after week 48 followed by a rebound in virions.

**400 IMPACT OF EVEROLIMUS THERAPY ON HIV PERSISTENCE, IMMUNE FUNCTION, AND GENE EXPRESSION**

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**Background**: mTOR inhibition may have beneficial effects on HIV persistence, including reducing T Cell CRS and PD-1 expression and promoting HIV transcriptional silencing. We previously observed lower cell-associated HIV DNA levels in renal transplant recipients that received sirolimus, an mTOR complex 1 (mTORC1) inhibitor, but prospective data are lacking. Therefore, we conducted a single-arm study of the impact of everolimus, an mTORC1/2 inhibitor on
401 NEUROTOXICITY WITH HIGH-DOSE DISULFIRAM AND VORINOSTAT USED FOR LATENCY REVERSAL

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Background: The histone deacetylase inhibitor, vorinostat (VOR), and disulfiram (DSF), a drug used to treat alcohol dependence, reverse HIV latency in vivo by different pathways and have been safely administered to people with HIV. Three days of 2000 mg DSF has been safely given as a latency reversal agent.

Methods: HIV-infected adults on suppressive antiretroviral therapy (ART) were enrolled in a prospective single arm study of DSF 2000 mg daily for 28 days and VOR in addition for 1 day. Participants had increased CD4+ T cells and were stable on ART for at least 6 months. The primary endpoint was plasma HIV RNA and CD4+ T-cell count (as opposed to plasma HIV RNA) at day 22 and 24. VOR was given on day 23 with DSF on days 18-24. HIV RNA was quantified by Roche COBAS TaqMan HIV-1 with lower limit of detection of 50 copies/mL. A total of 14 participants

Results: The first two participants (P1 and P2) experienced grade 3 neurotoxicity (altered mental status possibly and probably related to DSF and VOR on day 24). P1 presented with confusion, lethargy, and ataxia. P2 had increased CA-US RNA following study drugs, which persisted for weeks after drug cessation. Both participants had increased CA-US RNA following study drugs, which persisted for weeks after drug cessation (Figure). P2 also had increased plasma viremia from day 8-37 (peak 81 copies/mL on day 21) with therapeutic ART drug levels. Low but detectable levels of VOR and histone acetylation were seen in both participants.

Conclusion: The study drug combination was not safe with significant but reversible neurotoxicity, which we suspect was related to prolonged high dose DSF. There was evidence of latency reversal in both participants. Prolonged high dose DSF, with or without VOR, should not be further pursued.

402 ANOGENITAL HIV Detected During Analytic Treatment Interruption in Remission Trials

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Background: Analytic treatment interruption (ATI) is a temporary and carefully monitored withdrawal of antiretroviral therapy (ART) often used to assess new interventions in early phase HIV remission trials. Rebound viremia during ATI presents a risk for HIV transmission to sexual partners.

Methods: The SEARCH010/RV254 cohort in Thailand enrolls participants who start ART during acute HIV infection (AHI). Participants are randomized into 3 substudies that included ATI opted to provide semen and anal (swab or sponge) samples up to 4 times: AH1 prior to ART, pre-ATI, viral rebound during ATI, and after ART re-initiation. HIV RNA was extracted using modified High Pure System method and quantified by Roche COBAS TaqMan HIV-1 with lower limit of detection of 1.5 (all HIV RNA values reported as log10 copies/mL).

Results: 47 male participants who underwent ATI provided anogenital samples at one or more time points. At AHI all had plasma viremia with median (range) HIV RNA 5.7 (3.7-7.2). HIV RNA was detected pre-ART in 63% of semen (median 3.3, range 1.9-5.0) and 67% of anal samples (median 2.6, range 1.7-4.1). Prior to ATI after median (range) ART duration of 136 (73-243) weeks, all participants were aviremic and all semen (n=34) and anal (n=39) samples were HIV RNA undetectable. During ATI, all but one participant experienced viral plasma rebound (median HIV RNA 3.7, range 1.7-5.4). No viremia was detected in 11% (2/19) of semen and 33% (5/15) anal samples at viral rebound; and at low level ranging from 2.1 to 2.4. HIV RNA in semen and/or anus was predominantly detected when plasma HIV RNA was >4.0 (6/12 samples) and uncommon below this level (1/22 samples) (p=0.008 by Fisher exact). After ART re-initiation and subsequent viral suppression, at a median of 48 (range 9-52) weeks, all semen (n=14) and anal (n=16) samples were undetectable for HIV RNA.

Conclusion: Viral rebound after ATI can be associated with detectable HIV RNA in the semen and anal secretions, but at low levels and predominantly when the plasma HIV viral load is above 4.0 log10 copies/mL. This is relevant to future HIV remission trials that require longer periods and higher levels of viremia to assess intervention efficacy. ART re-initiation and suppression of plasma viremia clears HIV RNA from the semen and anus. Study participants and their sexual partners should be counseled on potential risk for HIV transmission during ATI
and should employ standard HIV prevention methods such as condom use and/or preexposure prophylaxis.

403 IMPACT OF ATI ON HIV RESERVOIRS AND IMMUNE PARAMETERS IN EARLY TREATED INDIVIDUALS

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Background: Eradication of HIV from an infected individual is not feasible with current antiretroviral therapy (ART) and the vast majority of individuals experience viral rebound upon cessation of therapy. Given the current requirement for life-long therapy in individuals whose virus has been successfully suppressed with ART, novel therapeutic strategies aimed at achieving drug-free HIV remission are being explored in infected individuals who began ART during the acute/early phase of infection. Such strategies would require analytical treatment interruption (ATI) for proof of concept. Thus, it is of considerable interest to investigate the impact of ATI on the HIV reservoir and immune parameters in such infected individuals.

Methods: Longitudinal immunologic and virologic analyses were conducted on specimens obtained from 22 individuals treated early in the course of infection who previously participated in a therapeutic vaccine trial. The dynamics of HIV reservoirs and immunologic parameters were examined in the study subjects prior to ATI, during ATI, and following reinstitution of ART.

Results: The median duration of the ATI phase was 124 days (range 56-242). At baseline, the frequency of CD4+ T cells carrying replication-competent HIV positively correlated with that of cells carrying HIV DNA and inducible cell-free virions. Following discontinuation of ART, all study subjects experienced plasma viral rebound and significant increases in the frequency of CD4+ T cells carrying HIV proviral DNA and cell-associated RNA, as well as the level of immune activation in the CD8+ T cell compartment (CD38+DR+). In addition, the levels of CD4+ T, B, and natural killer cells decreased following plasma viral rebound during the ATI phase. However, the size of the HIV reservoirs, including replication-competent virus and inducible cell-free virions, and all immune parameters returned to baseline (pre-ATI) levels after ART was resumed and maintained for a median of 58 months (range 30-89).

Conclusion: Our findings demonstrate that short-term ATI does not cause permanent expansion of HIV reservoirs nor irreparable damages to the immune system in individuals who initiated ART during the acute/early phase of infection. Therefore, our data support the use of ATI as a crucial component of clinical trials designed to examine the efficacy of therapeutic interventions as a substitute for ART in infected individuals who initiated ART during the early phase of infection.

404 DETECTION OF CELL-ASSOCIATED HIV-1 NUCLEIC ACID IN BLOOD AFTER EARLY ART

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Background: Initiation of HIV-1 antiretroviral drug therapy (ART) during acute infection can delay HIV vireonversion and reduce the HIV viral reservoir. The Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test v2.0 (CAP/CTM), capable of detecting both HIV RNA and DNA, was used to measure the levels of Cell Associated HIV-1 (CAH) nucleic acid in Peripheral Blood Mononuclear Cells (PBMCs) prior to and post initiation of ART during acute HIV infection.

Methods: PBMCs from 37 participants enrolled in the HIV early treatment study (RV254/SEARCH010, Bangkok, Thailand) were selected based upon Fiebig Stage (FI-VI) at time of ART initiation: FI (N=9), FII (N=6), FIII (N=7), FIV (N=7), FV (N=5), and FVI (N=3). Cell lysates of 1 million PBMCs collected at week 0 and weeks 1/2, 8 and 60 post ART initiation were tested in triplicate by CAP/CTM.

Results: Plasma HIV-1 RNA levels prior to ART initiation ranged from 2.43-5.16 and 4.17-6.9 log c/ml for individuals in F1 and FII-FVI, respectively. Initiation of ART resulted in a rapid loss of plasma HIV-1 RNA and suppression of HIV virus in all individuals by week 8. CAH levels averaged 1.44 log c/ml PBMCs in F1 untreated individuals, with 5/9 (55.6%) at or below Limit of Quantitation (LOQ: 1.42 log c/ml PBMCs) for the assay. The average CAH log c/ml PBMCs for untreated FII was 4.08 and 3.61 for untreated FIII-FVI. CAH at week 8 for F1 treated individuals was near or at the LOQ (3.9), and 6/9 (67%) were not detected. At week 60, 8/9 (88.9%) FI treated individuals were undetectable. At week 8, 4/13 (30.8%) FII/FIII treated individuals were near or below LOQ; and 6/13 (46.2%) by week 60. Only 2/13 (15.4%) were undetectable. For individuals treated at FIV-FVI, 4/15 (26.7%) were near or at the LOQ by week 60 with CAH levels in 10/15 individuals ranging from 1.44-3.01 log c/ml PBMCs.

Conclusion: HIV nucleic acid persists in PBMCs of infected individuals under therapy and can be readily monitored by the CAP/CTM assay in the absence of detectable plasma HIV-1 RNA. Only F1 treated individuals had consistently undetectable CAH by week 8. ART resulted in a logarithmic decline in CAH with an initial rapid loss followed by a more gradual decrease. The residual HIV reservoir at 60 weeks increased when treatment was initiated at later Fiebig stages. Testing of PBMCs by the Roche CAP/CTM assay provides a convenient measure of residual HIV reservoir in blood and may be useful for monitoring patients under therapy and in HIV remission studies.

405 ALTRUISM IN END OF LIFE HIV RESEARCH: INSIGHTS FROM LAST GIFT STUDY

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Background: End-of-life (EOL) HIV cure–related research provides a novel approach to study HIV reservoirs and promising HIV cure research interventions. The Last Gift is a clinical research study at the University of California San Diego enrolling terminally ill persons living with HIV (PLWH) to contribute towards HIV cure science without personal benefits. As part of a socio–behavioral sub-study we elucidate motivations for participation and experiences while in the study.

Methods: The Last Gift study enrolled 7 participants since summer 2017 (n=7 males; aged 45–72 years). All were first-time HIV care research participants but were not new to clinical research. Along with HIV, they had a terminal illness with a prognosis of <6 months. Ante-mortem procedures involved blood draws, baseline and follow-up interviews. Post-mortem procedures involved a rapid autopsy (<6 hours of death) to characterize the size, distribution and molecular characteristics of HIV reservoirs in various tissues. Results from the socio–behavioral interviews to Last Gift participants and their Next of Kin (NOK) were transcribed verbatim and coded using thematic analysis. Questions included (1) motivation for participation, (2) perceived benefits, (3) understanding of the study goals, (4) meaning of the Last Gift study, (5) post-mortem insights or concerns (NOK only).

Results: Deep altruism (but not monetary compensation) was the main motivator to participation. All Last Gift participants and NOK expressed concerns (NOK only).
were distinct (Fig 1A). Early inflammatory profiles predicted subsequent NC performance in both women. Immune components 1-4 were common across groups (e.g., immune function predicted domain-specific performance. Among HIV-, immune component 1 was associated with cognitive performance across multiple domains (e.g., learning, memory, attention) following the 12 year follow-up at ≥ 1 time points. We searched for latent immune profiles (underlying patterns of marker changes) that might benefit from interventions tailored to their particular pattern of change and risk factors. Here, we applied a novel statistical method to identify clusters of individuals with distinct patterns of age-related change in declarative memory in HIV+ and HIV-uninfected (HIV-) women.

Methods: We included 1530 women from the Women's Intergenerational HIV Study who completed the Hopkins Verbal Learning Test at two or more visits. To derive subgroups with similar patterns of decline by HIV-serostatus, we applied a novel modeling strategy that simultaneously considers multiple longitudinal declarative memory outcomes. This model adopts a linear mixed-effects framework to model the trajectory of each cognitive outcome over time, while also jointly clustering individuals via a factor analysis model. We tested for differences in demographic and clinical characteristics between the clusters using a multivariable-adjusted multinomial model.

Results: Of the 1530 included participants, 1167 were HIV+ (69% African-American [AA]; 31% white other [W/O]) and 363 were HIV- (68% AA; 32% W/O). Stratification by race was necessary to optimize clustering. In the HIV+ AA's, we identified three subgroups: one with minimal decline, two with accelerated decline, and a subgroup with stable impairment in learning and memory (Fig 1A). In the HIV+ AA's, we identified three subgroups: one with lesser decline and two with accelerated decline (Fig 1B). In multivariable adjusted models, individuals with accelerated decline were more likely to be less educated (P<0.001) and have a history of depression (P<0.001) versus those in the minimal decline subgroups (Fig 1C). Similarly classified subgroups were identified in W/O HIV+ and W/O HIV- participants.
CAPTURING DNA METHYLATION CHANGES IN MONOCYTES WHEN INITIATING ART IN ACUTE HIV

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Background: Monocytes are involved in HIV pathogenesis, persistence, and are associated with adverse clinical outcomes. We previously revealed in monocytes the identification of an epigenetic footprint of HIV-related cognitive impairment in chronic infection (PMCID: PMC3029304). Yet, knowledge about epigenetic changes during acute HIV infection (AHI) in monocytes, the effects of early initiation of combination anti-retroviral therapy (cART), and the implications on CNS outcomes remains unknown.

Methods: We investigated early HIV-related DNA methylation changes in highly purified monocytes from AHI adults initiating early ART in a prospective study (RV254/SEARCH010) and uninfected controls (RV304/SEARCH013). DNA methylation was measured genome-wide using the Illumina HumanMethylationEPIC array. We also examined DNA methylation changes longitudinally during AHI at entry and post-cART.

Results: We examined 15 AHI adults (n=6 Fiebig stage (F) I/II and n=9 (FIII) with median days of infection of 17.5 days (baseline). Twelve adults were examined after initiating cART up to 48 weeks (post-cART). Matched HIV-uninfected adults (n=8) served as controls. In cell sorted purified monocytes obtained from peripheral blood, we observed 2,847 CpG sites showing absolute mean differences in methylation greater than 5% between during AHI and uninfected participants (Δβ-value > 0.05) and significant at FDR adjusted P < 0.05. The majority (94.55%) of sites were hypomethylated in AHI compared with median days of infection of 17.5 days (baseline). Twelve adults were examined after initiating cART up to 48 weeks (post-cART). Matched HIV-uninfected adults (n=8) served as controls.

Conclusion: Our data-driven modeling approach successfully identified clinically meaningful subgroups of individuals with distinct phenotypes of declarative memory decline. Depression was a key, potentially modifiable determinant of membership in a subgroup characterized by more rapid decline.

PLASMA (1→3)-β-D-GLUCAN LEVELS CORRELATE WITH NEUROCOGNITIVE PERFORMANCE IN HIV

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Background: Although antiretroviral therapy (ART) has improved survival and morbidity, people living with HIV (PLWH) have higher rates of non-AIDS disorders, such as neurocognitive (NC) impairment (NCI), than the general population. (1→3)-β-D-glucan (BDG) is a fungal cell wall component which — in the absence of fungal infections — serves as biomarker for gut barrier integrity failure and microbial translocation. The objective of this study was to determine whether higher plasma and cerebrospinal fluid (CSF) levels of BDG are associated with NCI in PLWH.

Methods: Paired blood and CSF samples were collected from 61 PLWH who underwent a NC assessment as part of the prospective CHARTER study between 2005-2015. Raw NC test scores were converted to a demographically-adjusted T-score and used to derive a Global T-score (higher scores=better performance). Individual T-scores were also converted to deficit scores and averaged to derive a global deficit score (GDS) which was used to classify NCI (i.e., GDS<0.5). Specimens were stored at -80°C within 90 minutes of collection. BDG was measured using the Fungitell assay (Associates of Cape Cod, Inc.) and soluble urokinase plasminogen activator receptor (suPAR; marker of monocyte activation and chronic inflammation) using the suPARnostic assay (ViroGates, Copenhagen, Denmark). Blood plasma samples were also tested for sCD14 (marker of monocyte activation), intestinal fatty acid binding protein (IFABP, marker of gut epithelial dysfunction), and blood CD4/CD8 ratio. Spearman's rho correlation analysis assessed associations between BDG, other biomarkers and NC performance variables.

Results: Overall, 58/61 participants had undetectable HIV RNA in blood plasma at the time of sampling. Median BDG level was 18 pg/mL in plasma (range: 2-60 pg/mL) and 20 pg/mL in CSF (range: 0-830 pg/mL). Higher levels of plasma BDG were associated with lower Global T-Scores (Spearman rho=-0.32; p=0.013) and NCI (p=0.027, see Figure). A plasma BDG cut-off of >30pg/mL showed 30% sensitivity for NCI and 100% specificity. There was also a trend towards higher CSF BDG levels among those impaired versus unimpaired (p=0.083). No other significant associations were observed between the remaining biomarkers and the NC variables. Plasma levels of BDG correlated significantly with plasma suPAR levels (rho=0.31, p=0.016), but not with other biomarkers.

Conclusion: Elevated plasma levels of BDG may be a biomarker for detection of NCI in PLWH on suppressive ART.
411LB NEURON-DERIVED EXOSOMES IDENTIFY COGNITIVE IMPAIRMENT AND GENDER DIFFERENCES IN HIV

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Background: Cognitive impairment in chronic well-controlled HIV infection continues to affect up to 60% of individuals. Mechanisms are still unknown but probably associated with continued neuroinflammation. Plasma neuron-derived exosomes (NDE) are a peripheral biomarker for investigating the health of neurons in real time. NDE carry proteins that can serve as new and more accurate biomarkers of cognitive impairment.

Methods: We obtained 80 plasma specimens from NIH-sponsored tissue banks, that included 8 groups of 10 persons with various neurocognitive diagnoses, HIV positive and negative, 51 women and 29 men, with 4 groups ≤ 45yo and 4 groups ≥50yo. All had extensive epidemiology, clinical and neurocognitive data. We isolated NDE from plasma using a 2-step procedure and LC/ICAM, a neuron specific antibody. We performed mass spectrometry (MS) on 10 NDE samples. ELISA was used to quantify several proteins of interest. Proximity extension analysis (PEA) for 184 neural-associated proteins was performed on 48 samples.

Results: Neuronal enrichment of NDE was confirmed with elevated synaptophysin as well as over 100 neuronal proteins identified by MS. HMGB1 and neurofilament light (NF-L) proteins were significantly increased in NDE from cognitively impaired men but not for women. NDE from HIV+ men had decreased p-tau181-tau, a positive marker for Alzheimer’s disease, compared to no difference in women. Using PEA, 25 proteins were significantly differentially expressed in HIV infected patient. Eleven proteins significantly identified cognitive impairment, both asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), in HIV+ women; 2 were also markers for MND in men. NDE from men and women had statistically significant divergent results with ezrin, an axonal protein and SCARAS5, a scavenger protein in neurons. NDE from women had significantly increased cathepsin S, tau, neuronal cell adhesion molecule and granzyme A, in ANI.

Conclusion: These findings show that NDE are from a neuronal source and that HIV infection alone causes neuronal dysfunction. There are several significantly differentially expressed NDE proteins that can separate ANI from MND in women and some can identify cognitive impairment in men compared to women. These results suggest possible mechanistic gender differences to therapy associated with cognitive impairment.

412 REDUCED SCYLLO-INOSITOL CORRELATES WITH NEUROCOGNITIVE IMPAIRMENT IN HIV+ INDIVIDUALS

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Background: Biochemical mechanisms underlying HIV-associated neurocognitive disorder (HAND) and the depressive symptoms seen in many HIV+ individuals are unclear. In Alzheimer’s disease, scyoilo-inositol (sI) treatment has ameliorated cognitive deficits in transgenic mice and in clinical trials has decreased cerebrospinal fluid amyloidβ42 and increased brain sI. However, it has been little studied in HIV. We examined sI and other metabolites as potential biomarkers of neuropsychiatric measures in an HIV+ population.

Methods: HIV+ individuals on stable antiretroviral therapy > 1 year and diagnosed with mild- to moderate-neuropsychological (NP) impairment at screening underwent cross-sectional magnetic resonance spectroscopy (MRS) and NP testing. The Beck Depression Inventory (BDI)-II was administered. We computed global and 8 domain-specific NP z-scores (working memory [NPZw], language [NPZlang], motor [NPZmotor], etc.). Single-voxel 1H-MRS at 3T (PRESS sequence with TE/TR=35/2000 ms) quantified metabolites including sI (concentrations; ratios to total creatine [tCr]) using ‘LCModel’ analysis in left frontal white matter (FWM) and basal ganglia (BG). Multi-voxel magnetic resonance spectroscopic imaging yielded ratios of N-acetylaspartate (NAA) to choline (Cho) in bilateral regions. Pearson (r) or Spearman (ρ) correlation and bootstrapped 95% confidence intervals assessed metabolite relationships to NP and BDI-II scores.

Results: We evaluated 30 HIV patients (26 males; age 57±7 years; 90% with plasma HIV RNA < 20 copies/mL; median current and nadir CD4 count 594 and 165 cells/µL). Decreased FWM sI and sI/tCr correlated to NP deficits (Table; e.g., sI/tCr correlated with NPZlang (r=0.39, p=0.003). Total NAA (NAA) in FWM and BG also showed significant positive associations with NP z-scores. Lower gamma-aminobutyric acid (GABA) in BG related to slower psychomotor speed (r=0.41, p=0.033). Frontal, temporal and BG tNAA/Cho correlated positively with NP performance. Reduced GABA and glycerophosphocholine (GPC) in BG were linked to higher BDI-II (r= −0.4, p=0.03). Among NP z-scores, only NPZmotor correlated to BDI-II (r= −0.4, p=0.028). Nadir CD4 correlated with FWM sI (r=0.58, p=0.006) and sI/tCr (r=0.48, p=0.029) but not NP z-scores. Conclusion: Scyllo-inositol in FWM of HIV+ individuals may provide a biomarker of NP functioning not mediated by mood. Reduced sI may reflect NP effects of past HIV disease. The role of sI in HAND warrants further study, as do GABA and GPC in relation to HIV-associated depression.

Table. Significant correlations (r=0.05) between NP z-scores and metabolite levels measured by single-voxel 1H-MRS in left frontal white matter of 30 HIV+ participants. Backward-eliminated 95% confidence intervals (CI) are given. We required Cramer’s Rho Lower Bounds (CRLB)=0.05 for scyllo-inositol (sI) concentrations and CRLB=0.20 for total N-acetyl compounds (NAA), resulting in N=23 for sI and N=10 for NAA correlations.

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>NP domain</th>
<th>Correlation</th>
<th>P-value</th>
<th>95% CI</th>
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<tr>
<td>sI</td>
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<tr>
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<td>Language</td>
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<tr>
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<td>0.040</td>
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<td>0.013</td>
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<td>Language</td>
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<td>NAA</td>
<td>Global</td>
<td>0.43</td>
<td>0.018</td>
<td>0.08, 0.66</td>
</tr>
</tbody>
</table>

MRS=magnetic resonance spectroscopy, NP=neuropsychological, sI=scyoilo-inositol, NAA=n-acetylaspartate, tCr=total creatine, CRLB=95% confidence interval
1 Bivariate correlation coefficients were computed by Spearman correlation for sI and by Pearson correlation for NAA.
2 Based on 20 tests.

413 LEGACY EFFECTS ON COGNITIVE FUNCTIONS AMONG HIV-INFECTED MEN

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Background: Prior to the use of combination antiretroviral therapy (cART), HIV-infected subjects were at high risk for developing significant neurological and neuropsychological dysfunction. However, such risk has declined after using cART, while the rate of milder forms of impairment has remained relatively unaffected. It is unclear from existing data how cognitive functions in HIV-infected subjects changed after beginning cART and the extent to which cognitive impairment prior to cART is associated with subsequent cognitive functions (i.e., legacy effect). This report aims to describe trajectories of cognitive functions in HIV-infected subjects over 15 years following the use of cART.
**Methods:** We matched HIV-infected subjects from the Multicenter AIDS Cohort Study who had used cART with uninfected men using propensity scores computed with demographics and baseline cognitive functions (measured in 1996). These matched pairs were aligned such that time T0 corresponded to the first cART use visit by the HIV-infected men. We applied the Multivariate Normative Comparison method to all six NP domain scores to detect any abnormality in cognitive functions. We coded subjects as having prior impairment if there were any cognitive abnormalities at any visit prior to T0. We plotted the LOWESS trajectories of cognitive functions from T-5 to T+15 separated as a function of HIV and cognitive status prior to cART.

**Results:** 537 matched pairs were utilized in the study. 121 of the infected men and 100 of the uninfected controls were found to have prior impairment. We did not observe significant differences between HIV-infected and uninfected men in trajectories of cognitive functions regarding executive processing, speed of information processing, learning and memory, working memory, and attention. However, faster decline in motor speed and coordination was observed among HIV-infected subjects without prior impairment approximately 10 years after the start of cART. Overall, subjects without prior impairment had higher scores in all six NP domains compared with subjects with prior impairments. Cognitive functions of HIV-infected men with prior impairment did not improve after beginning cART.

**Conclusion:** By matching HIV-infected subjects with uninfected controls we were able to evaluate the relative cognitive decline among the infected men after they began using cART. The trajectories suggest that cognitive functions remain largely stable and that any prior impairments in cognition have a lasting effect over follow-up.

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**414 CLUSTER ANALYSIS OF COGNITIVE FUNCTIONING IN HIV+ AND HIV-SUBJECTS**

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**Background:** Although several definitions have been proposed to define HIV-associated neurocognitive disorders, no universally accepted definition has emerged. Previous investigations have employed cluster analyses (CA) to identify neurocognitive performance subgroups among HIV patients. However, no previous studies have included both HIV+ and HIV- subjects in such CAs. We plotted the LOWESS trajectories of cognitive functions from T-5 to T+15 separated as a function of HIV and cognitive status prior to cART.

**Methods:** Baseline visits of 324 HIV+ and HIV- subjects (M age =50.4; 245 males; 47.8% Black, 44.8% White, 23% Other) who underwent comprehensive neuropsychological assessment were included. HIV+ and HIV- subjects did not differ in age, gender, or race (p >.13), but controls were more educated (p <.01). In the first of a two-stage CA, 15 measures of attention, executive functioning, information processing, verbal fluency, learning, psychomotor, and memory that are commonly used to assess HAND were entered into a hierarchical CA, in which two clusters were identified. Group membership was finalized through a k-means CA which produced two groups defined as low or high performing. Out of 96 controls, 40 (41.7%) were classified as low performing and 56 (58.3%) were high performing. Out of 228 HIV+ subjects, 120 (52.6%) were classified as low performing and 108 (47.4%) were high performing.

**Results:** The two clusters were compared to cognitive impairment (CI) based on Global Deficit Score (GDS; ≥0.5). In comparison to CI, the CA had high sensitivity (100%) but low specificity (62.1%). Chi-square analyses found that the low performers were characterized by lower employment (p <.01), more PTSD (p <.03), higher rate of current smokers (p <.01), and more individuals taking psychiatric medication (p <.01). Mann-Whitney tests also found that the low performers endorsed more symptoms of depression (Beck Depression Inventory; p <.01), lower premorbid IQ (Wechsler Test of Adult Reading; p <.01), and lower everyday functioning (Texas Functional Living Scale; p <.01). As expected, the low performers had significantly lower GDS (p <.01) and overall T-scores on cognitive measures (p <.01). Low and high performers did not differ in HIV status (p =.07), education (p =.38) or age (p =.64).

**Conclusion:** Using CA on neuropsychological performance of HIV+ and HIV-subjects, we identified low and high cognitive performers. We concluded that cognitive impairment is not HIV-status specific. Other psychiatric, health, and functional characteristics had stronger associations with cognitive performance than HIV status did.

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**415 ALZHEIMER’S DEMENTIA CEREBROSPINAL FLUID BIOMARKERS IN HIV-POSITIVE PATIENTS ON cART**

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**Background:** Evidence regarding cerebrospinal fluid (CSF) Alzheimer’s dementia (AD) biomarkers in HIV-positive patients is conflicting. The study aimed to describe total tau (tTau), phosphorylated tau (p-tau) and β Amyloid 1-42 (βA42) CSF concentrations and clinical correlates among on cART HIV-positive patients.

**Methods:** On cART HIV-positive adults undergoing lumbar puncture for clinical reasons were enrolled and divided into 4 groups by CSF age-adjusted tTau and βA42 cut-offs: A (both normal), B (normal tTau, low βA42), C (high tTau, normal βA42), D (both altered). CSF biomarkers were measured by immune-enzymatic (tTau, p-tau, βA42), ELSA (neopterin) and immunoturbidimetric (CSF-serum albumin ratio (CSAR), CSF IgG synthesis) methods. Data were analysed through non-parametric tests.

**Results:** 181 patients were included: 150 (82.9%), 15 (8.3%) and 15 (8.3%) resulted in group A (CSF tTau 116 [51-199], βA42 899 [788-1079] pg/mL), B (CSF tTau 37 [17-128], βA42 374 [302-443] pg/mL) and C (CSF tTau 544 [466-750], βA42 965 [754-1267] pg/mL). Only 1 patient was in group D (tTau 580 and βA42 404 pg/mL) and was diagnosed with AD. Demographic, clinical,
416 CSF HIV-SPECIFIC T CELLS PERSIST DURING ART AND ASSOCIATE WITH LOWER CNS INFLAMMATION

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Background: During acute HIV infection (AHI), CD8 T cells compose the majority of cells infiltrating the cerebrospinal fluid (CSF). They are highly activated and contain HIV-specific cells. It is unknown whether these HIV-specific CD8 T cells persist in the CSF during antiretroviral therapy (ART) and how their presence associates with markers of HIV neuropathogenesis. Their presence could serve as a surrogate marker of HIV persistence in the CNS.

Methods: Twelve RV254 Thai participants treated in AHI underwent lumbar puncture at 24 and 96 weeks post-ART. CD4 and CD8 T cells from the CSF samples were separated, and HIV-specific CD8 T cells were cocultured with autologous EBV cells loaded with CRF01_AE HIV peptide pools and HIV-specific CD8 T cell responses were assessed by flow cytometry using intracellular staining for IFN-γ. HIV DNA was measured in CD4 T cells by ultrasensitive qPCR.

Results: In AHI, HIV-specific CD8 T cells were detected in the CSF at low frequencies in Feibig I-II (0.5%, n=3), and at higher frequencies in Feibig III-V (8%, n=6, Fig 1A). As previously shown, HIV-specific CD8 T cells were positively associated with CSF viral load and inflammation in AHI. After 24 weeks of ART, plasma and CSF HIV RNA were undetectable. However, HIV RNA was detected in CSF CD4 T cells from 1 participant at week 24, and from 2 participants at week 96. HIV-specific CD8 T cells were still detected in 9 donors at week 24 and in 8 donors at week 96 (Fig 1A). They targeted all HIV proteins (Fig 1B). After ART, the frequency of CSF HIV-specific CD8 T cells negatively associated with CSF inflammatory markers sCD14, IL-6ra, sgp130 and TNFR1 (all r<0.50, and p<0.04) and with the CSF neuronal injury marker S100b (r=-0.65, p=0.001; Fig 1C). It was also positively associated with MRS neuronal integrity marker, N-acetylaspartate, in basal ganglia (r=0.4, p=0.04) and frontal gray matter (r=0.5, p=0.01) and negatively associated with MRS inflammatory markers including choline (r=-0.63, p=0.02) and glutamate/glutamine (r=-0.49, p=0.02) in frontal white matter.

Conclusion: These data highlight the persistence of HIV-specific CD8 T cells over 2 years of suppressive ART started in AHI. The persistence of these cells after treatment suggests the presence of HIV antigen in the CNS during effective ART. Nonetheless, associations with CSF biomarkers indicate that they may play an effective role in resolving neuroinflammation after treatment.
418 NEUROCOGNITION, FRAILTY, AND MORTALITY AMONG PERSONS AGING WITH HIV AND SUBSTANCE USE

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Background: With effective antiretroviral therapy (ART), HIV-infected persons are living longer. Yet, survival disparities remain, particularly for persons with a history of injecting drugs (PWID). Such disparities have been attributed to an increased burden of aging-related phenotypes including frailty, which we have shown to be heightened in HIV and predictive of mortality. Cognitive impairment is a key aging-related phenotype prevalent in HIV. However, limited data exist on the relationship of cognitive impairment to frailty and its impact on mortality in the ART era.

Methods: Standard neurocognitive assessments were performed cross-sectionally among HIV-infected and uninfected PWID in the ALIVE cohort from 2010 through 2012 in 5 domains: executive function, attention, learning/memory, information processing and motor processing. Global cognitive performance was determined as the average of z scores from each domain. Frailty was assessed based on the 5 physical frailty phenotype domains—weight loss, low physical activity, exhaustion, decreased grip strength, and slow gait speed. Mortality was ascertained through 2016 through linkage to the National Death Index. Cox proportional hazards models were used to estimate the risk (hazard ratios [HR] with 95% confidence intervals [CI]) for all-cause mortality.

Results: Among 519 ALIVE participants with a median age of 52 years, 41% were HIV positive. In multivariate analyses, older age and hazardous alcohol use were significantly associated with impairments in executive function, information processing, motor processing and global cognitive impairment. Being both frail and HIV-infected was associated with heightened information and motor processing impairments. Adjusting for sociodemographics, premorbid IQ, comorbidity, substance use and HIV disease stage, impaired information processing (aHR 1.45; 95% CI, 1.06, 1.98), motor processing (aHR 1.61; 95% CI, 1.30, 1.98) and global cognitive impairment (aHR 1.67; 95% CI, 1.10, 2.56) were significantly associated with increased mortality; global cognitive impairment and frailty (aHR 2.32; 95% CI, 1.30, 2.50) were independently associated with mortality.

Conclusion: Cognitive impairment is a significant predictor of death among persons with HIV, independent of HIV disease stage, chronic disease comorbidity, and frailty. Further elucidation of the epidemiologic and biological underpinnings of cognitive impairment in HIV and PWID could facilitate interventions to improve survival for these populations.

419 ASSOCIATIONS BETWEEN PLASMA NRTI CONCENTRATIONS AND COGNITIVE FUNCTION

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University College London, London, UK, Imperial College London, London, UK

Background: Limited data exist on the effects, either beneficial or detrimental, of nucleoside-reverse transcriptase inhibitor (NRTI) exposure on cognitive function in people living with HIV (PLWH). We investigated the associations of plasma tenofovir (TDF), emtricitabine (FTC), lamivudine (3TC) and abacavir (ABC) pharmacokinetics (PK) with cognitive function among PLWH recruited in the POPPY study.

Methods: PK sampling and cognitive function (6 domains) were obtained from 638 PLWH on TDF, FTC, 3TC or ABC. For each drug, four different PK parameters were considered: area under the curve over 24 hours (AUC), maximum concentration (Cmax), trough concentration (CT) and clearance (CL/F). Cognitive scores were standardized into Z-scores (mean=0, sd=1) and averaged to obtain domain and global Z-scores. Associations between PK parameters and Z-scores were assessed using rank regression adjusting for age, gender, race, education, BMI, weight, recreational drug use, alcohol consumption, use of boosted protease inhibitors or efavirenz, as appropriate.

Results: The 638 PLWH were predominantly male (87%), with a median (IQR) age of 52 (47, 59) years and 93% had a HIV RNA <50 copies/mL. 520 were on TDF, 483 on FTC, 123 on 3TC and 93 on ABC. The median (IQR) global Z-score was 0.06 (0.31, 0.40); 0.00 (-0.25, 0.40); 0.09 (0.32, 0.32) and 0.11 (-0.36, 0.33) in recipients of TDF, FTC, 3TC and ABC, respectively. After adjusting for potential confounders, including efavirenz use, none of the four TDF and FTC PK parameters were associated with global cognitive scores, with only weak associations with 3TC PK parameters (Table). Higher ABC AUC and CT were associated with better cognitive scores (both p's=0.02), while increased CL/F was associated with poorer scores (p=0.04). In particular, ABC AUC (adjusted rho: 0.26 (0.05, 0.47), p=0.02) and CT (adjusted rho: 0.24 (0.03, 0.45), p=0.03) were associated with better visual attention, while associations with other domains were non-significant [adjusted rho's ranging from 0.12 and 0.08 (executive function) to 0.18 (psychomotor) for AUC and CT, respectively; all p's>0.05].

Conclusion: Whilst we found no evidence of detrimental effects of NRTI exposure on cognitive function, greater ABC (but not TDF, FTC and 3TC) plasma exposure was associated with better cognitive scores. Although confounding due to adherence and other unmeasured factors may exist, these results could have implications for the design of future research programmes for PLWH with cognitive disorders.

Table: Abridged association structure between drug exposure and cognitive function

<table>
<thead>
<tr>
<th>TDF</th>
<th>FTC</th>
<th>3TC</th>
<th>ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>-0.03 (-0.13, 0.05)</td>
<td>0.68 (-0.55, 0.15)</td>
<td>0.31 (-0.01, 0.62)</td>
</tr>
<tr>
<td>CT</td>
<td>-0.02 (-0.13, 0.09)</td>
<td>0.66 (-0.55, 0.14)</td>
<td>0.22 (-0.02, 0.46)</td>
</tr>
<tr>
<td>CL/F</td>
<td>0.08 (0.02, 0.15)</td>
<td>0.12</td>
<td>0.00 (0.01, 0.03)</td>
</tr>
</tbody>
</table>

Notes: All associations adjusted for age, gender, ethnicity, education, use of boosted protease inhibitors, use of efavirenz plus NNRTIs and recreational drug use. CI: confidence interval. DD: drug dose. PK: pharmacokinetic.
(40%) controls were classified with no CI at both baseline and follow-up; 1 (8%) PWH and 2 (40%) controls moved from not having CI to have CI.

**Conclusion:** We observed different dynamics of change in cognitive function within this cohort. A substantial proportion of PWH who were classified as having CI initially, did not meet criteria for CI after 2 years; only less than half of both PWH and controls who significantly declined, stably met the definition of CI. Linkage of these detailed cognitive phenotypes with biomarker and neuroimaging findings may assist in understanding the underlying pathogenic mechanisms and developing future targeted management approaches.

### 421 ASSOCIATION BETWEEN NEUROFILAMENT LIGHT PROTEIN AND IMPAIRED COGNITION IN TREATED HIV

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1National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, 2National Heart, Lung, and Blood Institute, Bethesda, MD, USA, 3National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, 4NIH, Bethesda, MD, USA

**Background:** Neurofilament light protein (NFL) concentrations in CSF can be used as sensitive biomarkers to evaluate CNS injury and dysfunction. Elevated NFL has been associated with CNS dysfunction in untreated HIV infection. This study investigates NFL concentrations in virologically controlled HIV patients in correlation with clinical variables and neuropsychological testing in men and women compared to matched controls.

**Methods:** 67 patients with chronic HIV-infection on ART for >12months (HIV+) and 21 demographically matched control subjects (HIV-) were included in this study. All participants completed a research lumbar puncture for CSF and a standardized battery of neuropsychological tests. CSF was analyzed for HIV RNA and NFL was measured using the Quanterix SIMOA Digital Immunoassay. NFL levels were correlated with clinical outcomes including Global Deficit Score (GDS) and average T-scores. An abnormal GDS score (≥1.5) was classified as Neurocognitive Impairment (NCI).

**Results:** There were no significant differences in age, race, or sex between the HIV+ and HIV- groups. In the HIV+ group, plasma viral load was <40 c/mL in 67 (100%), CSF NFL was higher in those with NCI compared to those with a normal GDS (1086 pg/mL, 73 pg/mL respectively, p<0.01). In the HIV+ control group, there were no differences in NFL by cognitive impairment (456 pg/mL, 612 pg/mL, p=0.22). Similarly, when looking at average demographically corrected T-scores across the battery of NP tests, higher NFL was associated with lower T-scores only in the HIV group (p=0.03), not in the control group (p=0.88). The Brief Visual Memory Test and Wisconsin Card Sort Test were significantly correlated with higher NFL in the HIV+ group (p<0.001, p<0.01, respectively). In the HIV+ group, this increase in NFL in those with NCI was significant for men only (r=0.44, p<0.01, Cohen’s d=6.12 for men; r=0.23, p=0.97, Cohen’s d=0.07 for women). There were no significant associations between NFL and HIV CSF escape (n=7) with CSF HIV >40 c/mL, nadir CD4 (median 206.3 c/mL) time since HIV diagnosis (mean 17.3 years) or time on ART (mean 8.5 years).

**Conclusion:** When HIV-infected individuals have been on ART for >12months, there is still a significant association between higher levels of NFL and NCI. This is particularly significant in men, but a larger sample of women is needed to establish a significant effect size to determine whether this association between elevated NFL and NCI can be applied to HIV+ women.

### 422 SCD14, SICAM-1, AND SVCAM-1 CORRELATE WITH NEUROCognitive FUNCTION IN YOUTH WITH HIV

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1Duke University School of Medicine, Durham, NC, USA, 2University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 3University of California San Diego, La Jolla, CA, USA, 4Children’s Diagnostic & Treatment Center, Fort Lauderdale, FL, USA, 5Hunter College, CUNY, New York, NY, USA, 6University of Houston, Houston, TX, USA, 7WH, Bethesda, MD, USA

**Background:** HIV infection affects cognitive performance through immune activation and related mechanisms. We hypothesized that in youth with HIV (YW), biomarkers of macrophage activation and vascular injury are associated with impairment in distinct neurocognitive domains.

**Methods:** YWH, ages 20 to 28, enrolled in ATN 071/101 were assessed for biomarkers of macrophage activation and vascular injury using ELISA/multiplex assays. Participants completed standardized neuropsychological tests. Demographically corrected z-scores were combined to form indices of attention, motor functioning, executive functioning, and both verbal and nonverbal memory. We performed a cross-sectional analysis of the relationship between blood levels of four key biomarkers (sCD14, sICAM-1, and VCAM-1) and performance in each of these neurocognitive domains. Linear regression models were fit for the log-transformed biomarker value for each combination of biomarker and cognitive domain score. These models were adjusted for demographics, socioeconomic status, substance use, and depression.

**Results:** Study included 128 YWH [mean age 23.8 (SD 1.7) years, 86% male, 68% African American]. We found moderate evidence for the following associations: sCD14 was negatively associated with executive function (adjusted estimate -0.69 (95% CI [-1.43, 0.05]), and non-verbal memory [-0.99 (-1.89, -0.10]). Soluble ICAM-1 was negatively associated with verbal memory [-0.31 (-0.64, 0.03)], while sVCAM-1 was positively associated with attention [0.32 (-0.04, 0.69;], executive function [0.68 (0.29, 1.08;) and non-verbal memory [0.56 (0.04, 1.07;]. Soluble CD163 was not significantly associated with any domain. None of the key biomarkers were significantly associated with the motor domain.

**Conclusion:** Biomarkers of macrophage activation and vascular injury were differentially associated with distinct cognitive domains, especially executive function and memory, among YWH. Intriguing positive associations of soluble VCAM-1 with executive function and nonverbal memory may indicate a link between vascular flow and cognitive performance among YWH who are at early stage of disease.

### 423 METABOLIC PROFILE OF HIV PATIENTS WITH AND WITHOUT HIV-ASSOCIATED DEMENTIA

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**Background:** HIV-associated dementia (HAD) is the most important clinical expression of HIV-mediated neurotoxicity, and even though CART has lowered its incidence, HIV-related neurocognitive disorders remain a major issue. The exact mechanism explaining the neurological decline observed in HIV-infected patients is still only partly understood. Thus, we have exploited metabolomics as a new approach to detect novel biomarkers of HAD among the small molecules of both cerebrospinal fluid (CSF) and plasma.

**Methods:** Metabolomics was performed in paired CSF and plasma samples of 20 untreated patients with HAD, 20 HIV-infected, neurologically asymptomatic
patients (ASYM) and 20 HIV negative controls (NEG) by Metabolon (Durham, NC) using both liquid and gas chromatography/mass spectrometry. Molecules were identified by comparison to library entries or purified standards and analysed by Welch’s two samples t-test. Differences with a p value <0.05 and a q value <0.1 were considered significant.

**Results:** HAD and ASYM had, respectively, a median CD4+ cell count of 22 (IQR, 3-148) and 151 (IQR, 91-261) cells/mm3, a median plasma HIV RNA of 202,000 (IQR, 53,000-679,500) and 22,424 (IQR, 717-70,550) copies/ml and a median CSF HIV RNA of 106,250 (IQR, 13,570-218,250) and 2,232 (IQR, 49-70,550) copies/ml. A total of 146 and 312 metabolites have been identified respectively in CSF and plasma, grouped in 19 and 23 different metabolic pathways. Significant differences were identified in molecules involved in glutamate, biliary acids and fatty acid metabolism. Table displays metabolic pathways found to have >1 molecule showing a fold change of HAD vs. ASYM >1.5 or < 0.5, either in CSF or plasma.

**Conclusion:** HAD untreated patients show a perturbation in glutamate, bile acids and fatty acids homeostasis, which may result from impaired cell metabolism induced by HIV both systemically and in the central nervous system. The increased production of compounds possibly exerting neurotoxic effects, such as glutamate, 5-oxoproline and primary bile acids, might contribute to the neuronal damage and foster neurological impairment in HAD. On the other hand, changes in lipid metabolism may reflect both an enhanced adipose reserves’ breakdown and mitochondrial dysfunction with impairment in β-oxidation. These markers, tested in untreated patients, may have a potential for identifying and studying the pathogenesis of HIV-mediated neuronal damage also in ART treated patients.

### Table: Relationship Between Cognitive Impairment and Odds of Fall in Women

<table>
<thead>
<tr>
<th>Model/Unadjusted</th>
<th>Model/Unadjusted</th>
<th>Model/Unadjusted</th>
<th>Model/Unadjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.24</td>
<td>0.01</td>
<td>0.19</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.01</td>
<td>0.42</td>
<td>0.05</td>
</tr>
<tr>
<td>Education</td>
<td>0.28</td>
<td>0.22</td>
<td>0.13</td>
</tr>
<tr>
<td>HIV status</td>
<td>0.01</td>
<td>0.00</td>
<td>0.02</td>
</tr>
<tr>
<td>HAND stage</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>HIV RNA</td>
<td>0.00</td>
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</table>

**425 HIV-ASSOCIATED NEUROCOGNITIVE DISORDER LEADS TO DEATH**

Deanna Saylor1, Gertrude Nakigozi2, Noeline Nakasujja1, Alice Kisakye1, Aggrey Anok3, Richard Mayanja2, James Batte2, Kevin Robertson4, Ronald H. Gray5, Maria Wawer6, Ned Sacktor1

1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Rakai Health Sciences Program, Kalisizo, Uganda, 3Makerere University College of Health Sciences, Kampala, Uganda, 4University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 5Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** Neurocognitive impairment has been associated with increased mortality in both antiretroviral therapy (ART)-treated and ART-naïve populations. However, mortality risk associated with specific HAND stages (i.e. normal, asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND), and HIV-associated dementia (HAD)) has not been assessed. Moreover, there is current debate regarding the clinical significance of ANI.

**Methods:** 399 HIV+ ART-naïve participants in rural Rakai, Uganda were assessed with a neurological examination, neuropsychological test battery, depression screening, and functional status assessments, and a HAND stage was assigned based on Frascati criteria. All participants were immediately offered ART. After two years and again after 5 years, participants were traced with phone calls and, if unreachable, through a proxy phone contact and/or study personnel home visits to confirm vital status. Those unable to be traced were classified as lost to follow-up (LTFU). Logistic regression analyses were used to assess the relationship between baseline HAND stage and two-year and five-year all-cause mortality.

**Results:** At baseline, participants’ mean age was 35 (SD 8) years, 53% were male, and mean years of education was 5 (SD 3). After two years, 337 participants (84%) were alive, 17 (4%) were confirmed dead, and 45 (11%) were LTFU. After five years, 152 participants (39%) were alive, 20 (5%) were dead, and 222 (56%) were LTFU. Omitting those LTFU, every one-stage increase in HAND stage was associated with a fold change of HAD vs. ASYM >1.5 or < 0.5, either in CSF or plasma.

**Conclusion:** NC impairment in executive function, psychomotor speed, and motor skills domains is associated in fully adjusted models. Among HIV+ women, associations of executive function, psychomotor speed, and motor skills were attenuated and no longer significant after adjustment for demographic and comorbid conditions (Table). Among HIV- women, impaired executive function and motor skills were associated in unadjusted models and the associations were strengthened in fully adjusted models.
participants with normal cognition at both two and five years. In multivariate analyses controlling for baseline CD4 count and demographic factors, each one-stage increase in HAND severity was associated with a 58% increased odds of death at two years, which was borderline significant (OR 1.58, 95%CI (0.97, 2.57), p=0.06), and 83% increased odds of death at 5 years (OR 1.83, 95%CI (1.13, 2.96), p=0.01) (Table).

Conclusion: We found a dose-dependent relationship between death during follow up and HAND at baseline. This is the first study of mortality and HAND in a resource-limited setting in the ART era. Our results suggest that early initiation of ART, prior to progression in HAND stage with advanced immunosuppression, may reduce mortality.

<table>
<thead>
<tr>
<th>TWO-YEAR MORTALITY</th>
<th>P5-YEAR MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds of Death</td>
<td>Odds of Death</td>
</tr>
<tr>
<td>for Each One Stage Increase in HAND Stage</td>
<td>for Each One Stage Increase in HAND Stage</td>
</tr>
<tr>
<td>Odds of Death</td>
<td>Odds of Death</td>
</tr>
<tr>
<td>for Each HAND Stage Compared to Normal/Cognition</td>
<td>for Each HAND Stage Compared to Normal/Cognition</td>
</tr>
</tbody>
</table>

426 ANEMIA AND NEUROCOGNITIVE IMPAIRMENT: A LONGITUDINAL MULTICOHORT STUDY

Oluwakemi Okwuegbuna1, Asha R. Kallianpur2, Jennifer Ludicello2, Ajay Bhati1, Ronald J. Ellis1, Allen McCutchan1, Scott L. Letendre1 1University of California San Diego, San Diego, CA, USA, 2Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA, University of California San Diego, La Jolla, CA, USA

Background: Anemia in persons living with HIV (PLWH) may occur from multiple causes and has been identified as a predictor of morbidity and mortality. Prior studies identified associations between anemia and worse neurocognitive (NC) performance in PLWH, but most studies have been cross-sectional and were not limited to those taking antiretroviral therapy (ART). This study compared erythrocyte and anemia biomarkers to NC performance over time in a large cohort of PLWH taking ART.

Methods: We evaluated 1,338 participants from multiple neuroHIV cohorts in San Diego, all on ART and followed for a mean of 29.5 months. Demographic and medical characteristics, including hemoglobin and erythrocyte indices, were collected. Anemia was defined as hemoglobin concentration of <14.0 g/dl in men and <12.0 g/dl in women, macrocytosis as mean corpuscular volume >99fl. NC performance was assessed using demographically adjusted domain and global T scores. Statistical methods included linear regression and mixed effects modeling.

Results: At baseline, participants were mostly middle aged (mean 43 years), men (77.8%), of European (54.9%), Hispanic (23.9%) or African (16.7%) ancestry. Most (69.8%) had undetectable viral load; the median nadir CD4+ cell count was 206 cells/μl; and 18.8% were currently on zidovudine. 297 (22.3%) were anemic. Anemia (p<0.0001) and macrocytosis (p=0.07) were associated with worse NC performance at baseline (model p<0.0001). Anemia remained significant (p=0.02) on multivariate analysis. Anemia was specifically associated with worse NC performance in speed of information processing (p<0.01), recall (p=0.04), working memory (p<0.01) and motor speed (p<0.01) with trends in executive function (p=0.06) and learning (p=0.08). Over time, lower hemoglobin concentration (p<0.0001) was associated with worse global T scores (model p<0.0001). Adjusting models for covariates, including age, sex, CD4+ count and HIV RNA did not weaken this association.

Conclusion: Anemia and macrocytosis are associated with worse NC performance over time in PLWH on ART. Macrocytosis is an indicator of mitochondrial dysfunction which is implicated in pathogenesis of neurological decline. Diagnosis of anemia is relatively easy: prompt and adequate treatment may prevent or improve the severity of NC deficit.

427 SHIV GENE EXPRESSION IN CSF CD4 T CELLS DURING ACUTE INFECTION OF RHEUS MACAQUES

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Background: The origin and extent of viral replication within the CNS during early HIV-1 infection remains unclear. We aimed to assess cerebral spinal fluid (CSF) for host cells actively transcribing virus in acutely SHIV infected macaques and compare infected cell frequency and cellular activation status to that observed in peripheral blood and lymph nodes.

Methods: Rhesus macaques (n=18) were infected intrarectally with a subtype C, HIV-1 env SHIV (1157ipd3N4), CSF, peripheral blood, and lymph node mononuclear cells (PBMC and LNMC) were analyzed at weeks 2-12 post-infection (PI). CD4 and CD8 T cells and macrophages were sorted, using flow cytometry, from each specimen directly ex vivo. SHIV RNA+ cells were identified by RT-qPCR assays specific for unspliced (gag) and spliced (env) viral RNA. Infected cell frequency was estimated by Poisson distribution statistics for PBMC and LNMC or assigning one infected cell to positive CSF replicates. Markers of cellular activation were measured by flow cytometry (surface staining) and gene expression (RT-qPCR).

Results: CSF specimens yielded an average 620 (120-2,840) CD4 T cells and 130 (2-400) macrophages after sorting. Infected, transcriptionally active (env+ gag+) CD4 T cells were detected within the CSF in 25% of animals 4 weeks PI and 12% 12 weeks PI. In animals with SHIV RNA+ CSF CD4 T cells, infected (gag or env RNA+), respectively) CD4 T cell frequency was similar across CSF (0.05-2%, 0.3-1%), PBMC (0.02-7%, 0.02-2%), and LNMC (0.03-2%, 0.06-0.09%), indicating comparable T cell infection rates in these compartments in early HIV-1 infection (Figure 1). CSF blood contamination was minimal by ELISA and distinct cell composition. While macrophage infection was less frequently observed in CSF, the limited number of these cells constrained sampling depth. Surface expression of CD38 was elevated on CD4 and CD8 T cells in both PBMC and CSF during acute SHIV compared to uninfected controls (p<0.05). In contrast, the monocyte activation marker CD169, as well as CD38, was elevated on monocytes in PBMC (p<0.05) but not CSF, indicating T cell but not monocyte activation in CSF during acute infection. CSF CD4 T cells and macrophages both upregulated CXCL10 compared to uninfected controls and therefore might contribute to early CNS inflammation.

Conclusion: Our data supports a model of productive CD4 T cell infection within the CNS during acute HIV/SHIV infection, distinct from the role of macrophages in end-stage neuroencephalitis.

428 IN VIVO REPPLICATION AND NEUROPATHOGENESIS OF T/F CLADE C SHIVs

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1University of Nebraska Medical Center, Omaha, NE, USA, 2Duke University, Durham, NC, USA

Background: Several substantial vaccine efforts against HIV-1 have so far failed primarily because to date we have failed to identify the correlates of protective immunity and the optimal vaccine formulation that can induce such protective immune responses in vivo. The knowledge that only select single or limited virus species are transmitted via the mucosal route has advanced the concept of transmitter/founder (T/F) viruses that are preferentially transmitted...
should be the target of HIV vaccine. Therefore, we developed T/F SHIVs using env of HIV molecular clones from Zambian transmission pairs.

**Methods:** Env gene of HIV3618MTF was cloned in to SHIV8Δ8-EO using In-Fusion cloning, named SHIV-4MTF-15. To enhance macaque CD4 binding, we introduced N375 mutation. New SHIVs were transfected to 293T cells and supernatant was used to infect macaque PBMCs to generate virus stock. Viruses were inoculated via intravenously (IVAG) route under the temporarily ablation of NK cells using JAK3 inhibitor. Sample collection was carried out (blood, CSF, RB, CVL, LN and feces) on various time points. Immune dynamics and degree of pathogenesis was measured using multiparametric flow cytometry. Next some macaques were treated with ART starting from week 10 for 3 months to monitor post-treatment interruption and to evaluate viral variants. Tissues and organs including brain were evaluated using immunohistochemistry.

**Results:** The newly generated SHIVs are replication competent and shown to be tier 2 neutralization sensitive phenotype. Animals inoculated under the depletion of JAK3 inhibitor showed persistently high viral loads in both plasma and CSF for more than 6 months. After necropsy tissues were investigated for viral loads in different tissues and organs. Next CNS tissues showed mild pathology and very few virus positive cells suggesting that mild infection to CNS. The reisolated virus was again inoculated IVAG to non-JAK treated animals and showed peak viral loads (108) and persistent viral loads up to 6 months. Next, Animals with ART treated showed virus rebounded after post treatment interruption and currently monitoring for viral set points and measuring viral variants.

**Conclusion:** The newly generated SHIVs are replication competent in macaques, maintained viral set points for longer periods and neurotropic. These novel SHIVs will be useful tools for HIV cure studies as well as evaluating anti-HIV drugs, microbiocides, and vaccine strategies.

### 429 EVOLVING SIV REGIONAL BRAIN INJURY AND RECOVERY ARE LINKED TO ANTI-OXIDANT EXPRESSION

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**Background:** Brain dysfunction in HIV infection can evolve despite ART suppression. Brainstem regions, including those with dopaminergic functions, may be more vulnerable to injury for unclear reasons. In the SIVmac251 model, we previously demonstrated regional brain differences in protective host anti-oxidant responses (heme oxygenase-1/HO-1) and we hypothesized that such differences would predict regional brain injury. To define evolving brain injury, we have now assessed neuronal markers of pre- and post-synaptic integrity and neurotransmitter phenotype in these animals, and correlated expression with oxidative response markers.

**Methods:** Eighteen rhesus macaques (2-3 y) infected with SIVmac251 were sacrificed 5, 10, 13, 20, 41, and 90 days post infection (dpi). Nine brain regions (midbrain, parietal, basal ganglia, medulla, pons, frontal, pre-frontal, deep frontal, and cerebellum) were analyzed by western blot for neuronal markers PSD95, SYN1, synaptophysin, and tyrosine hydroxylase (TH), and the anti-oxidant response markers, HO-1, GPX1. Statistical analyses were by two-way ANOVA, post-hoc tukey’s test, post-test for linear trend, and multivariate linear regression.

**Results:** Acute SIV infection (13-20dpi) correlated with neuronal injury markers (decreased PSD95, synaptophysin, p<0.01) and neuronal functional responses (increased SYN1, p<0.05) in most brain regions (brainstem and cortical), and specific dopaminergic neuronal responses (decreased TH, p<0.05) in basal ganglia. Chronic infection (40-90dpi), showed sustained, but not progressive, neuronal injury from day 20 to day 90 (no significant changes in PSD95, synaptophysin), and no changes in dopaminergic responses (TH). However, cortical regions, but not brainstem regions, did show significant increases in PSD95 from day 13 to day 90pi, which suggests possible spontaneous regional brain recovery from acute injury. In acute and chronic phases antioxidant HO-1 expression correlated with PSD95 and synaptophysin (p<0.001).

**Conclusion:** Neuronal injury in both brainstem and cortical regions occurs early in SIV infection and is sustained through chronic infection, with evidence for spontaneous recovery in cortical, but not brainstem regions. Because brainstem regions express lower antioxidant response enzymes (HO-1, GPX1) and because neuronal injury correlates negatively with HO-1 expression, our results support the hypotheses that lower brainstem antioxidant capacity accounts for brainstem vulnerability to, and less recovery from, SIV/HIV injury.

### 430 DOLUTEGRAVIR ACCUMULATES IN THE FETAL BRAIN FOLLOWING IN UTERO EXPOSURE

**Aditya N. Bade**, Benson Edagwa, Jelily McMillan, Gary E. Sizudak, Howard E. Gendelman

1University of Nebraska Medical Center, Omaha, NE, USA, 2The Scripps Research Institute, La Jolla, CA, USA

**Background:** Dolutegravir (DTG)–based antiretroviral drug regimens will roll out worldwide with up to 15 million people receiving the drug within the next five years in resource-limited countries (RLCs), where most people infected with the human immunodeficiency virus (HIV) are women of child-bearing age. To this end, DTG has been shown to be highly effective due to its potent antiretroviral activities and high-barrier to viral resistance. Cautionary notes remain in surface, in recent months, regarding its safe use during pregnancy. Increased number of birth defects have emerged which warrants further investigation. Indeed, an observational study conducted in Botswana identified a potential risk of DTG in the development of neural tube defects. We recently reported that DTG crosses the blood brain barrier and can induce brain oxidative stress in adult mice. Herein, initial experiments were designed to determine whether administration of DTG to mothers could result in high levels of the drug in the fetal brains.

**Methods:** DTG was administered intramuscularly to C57BL6 female mice every 72 hours at 45 mg/kg dose. Treatment was initiated 3 days prior to mating and during pregnancy. Treatment was stopped at the day of birth of pups. Plasma was collected from dams for DTG quantification before and during pregnancy. At post-natal day 0.5, neonatal whole brains were processed to quantify DTG following in utero exposure by UPLC-MS/MS.

**Results:** Plasma DTG concentrations were consistent among female mice with 13.5 µg/mL (Cmax) during pregnancy (Panel a). DTG concentrations in brains of all neonates from the same litter were similar (Panel b), averaging 114±2 ng/g. 114±2 ng/g.

**Conclusion:** We conclude that placental transfer of DTG during pregnancy can result in high drug levels in fetal developing brain. With previous data in hand, we posit that such an exposure could lead to oxidative stress subsequently affecting fetal brain development. Future experiments are designed to determine such linkages.

### 431 HIV BASAL-GANGLIA INJURY CORRELATES WITH ANTI-OXIDANT & ENDOTHELIAL ADHESION MARKERS

**Analise Gruenewald**, Rolando Garza, Yoelvis Garcia-Mesa, Patricia J. Vance, Benjamin B. Gelman, Dennis L. Kolson

1University of Pennsylvania, Philadelphia, PA, USA, 2University of Texas at Galveston, Galveston, TX, USA

**Background:** Regional brain vulnerability to HIV is well-known but its determinants are not. Blood-brain barrier damage in the highly vulnerable basal ganglia correlates with cognitive impairment, suggesting vulnerability linked to endothelial dysfunction. We previously identified reduced pre-frontal cortex expression of the antioxidant heme oxygenase-1 (HO-1), as a risk for HIV encephalitis and cognitive dysfunction; in recent macaque studies we identified regional brain HO-1 variation that correlated with neuronal injury. We hypothesize that human brain HO-1 expression also varies regionally and correlates with endothelial cell adhesion molecule expression and neuronal injury in HIV.

**Methods:** Thirteen brain regions grouped as: i) cortical: frontal, temporal, occipital, anterior and posterior cingulate, motor, and sensory cortices; ii) basal ganglia: caudate, globus pallidus; and iii) others: frontal white matter; amygdala, cerebellum; pons) were dissected from 10 autopsies (7 HIV+, 3
**432 PLATELET-ENDOTHELIAL INTERACTIONS MAY PROTECT AGAINST VIRAL ENTRY IN THE BRAIN**

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**Background:** The brain is an important sanctuary site for HIV and these viral reservoirs are an important barrier to cure. In the SIV-infected macaque model, perivascular infiltrates of infected cells are characteristic of central nervous system (CNS) disease. Platelet decline occurs due to multiple mechanisms in SIV, and is associated with increased risk for the development of CNS disease. We sought to determine if activated platelet-endothelial interactions contribute to platelet decline and are associated with these infected perivascular infiltrates in the SIV-infected pigtailed macaque, and to define how these interactions affect the blood-brain barrier.

**Methods:** Platelet activation was monitored throughout infection for SIV-infected macaques and uninfected controls. Brains were evaluated to determine CNS disease status and for immunohistochemistry for platelet-endothelial binding and perivascular macrophage cuffs. Confluent monolayers of brain microvascular endothelial cells (BMECs) were exposed to washed platelets or media in transwells and permeability quantified.

**Results:** Platelets harvested from infected macaques that went on to develop CNS disease during terminal infection demonstrated less activation than macaques without CNS disease during acute (P = 0.04) and asymptomatic (P < 0.0001) infection. Brains from SIV-infected macaques were more likely than brains from uninfected controls to have platelets bound to vascular endothelium during acute (RR 4.0, P < 0.03) and terminal (RR 3.6, P < 0.04) infection. 6 of the 10 SIV+ macaques had CNS disease during terminal infection, and resident Mac387+ (RR 3.4, P = 0.0001) or CD163+ macrophages (RR 1.44, P = 0.0005) but not non-resident CD68+ macrophages (RR 1.2, P = 0.2) were observed with increased likelihood around platelet-lined vessels in these animals. SIV-infected macrophages were similarly observed with increased likelihood around platelet-lined vessels (RR 1.5, P < 0.007). Permeability of BMECs decreased two-fold following incubation with platelets from SIV infected macaques compared with uninfected macaques (P = 0.01).

**Conclusion:** Activated platelet-endothelial interactions may represent a protective mechanism against development of infected macrophage infiltrates in CNS disease that is removed in the context of HIV-associated thrombocytopenia.

**433 HIV-1 INDUCED NEUROPATHOLOGY OF A HUMANIZED MICROGLIAL MOUSE**

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**Background:** Studies on HIV central nervous system infection and brain viral reservoirs have been hampered with the dearth of small animal models. Immune deficient mice reconstituted with human immune system are susceptible to HIV infection and have proven to be potent tools to study HIV pathogenesis, prevention and therapeutic development. However, any reflection of CNS has been hampered by a lack of human glial cells in any currently available rodent models. Human macrovascular macrophages, microglia and astrocyte need be present to mimic brain viral reservoirs and virus-induced neuropathogenesis. To this end, we developed a new immunodeficient strain supplemented with human interleukin-34 (IL-34) transgene to support microglial development in humanized mice. These human microglial mice were used to study HIV-1 induced neuropathogenesis.

**Methods:** Human CD34+ hematopoietic stem cells transplanted NOD.Cg-PrkdcscidIl2rγtm1SugJftg(CMV-IL34)1/Jc (CD34-NOG-hIL-34) mice developed human “microglia like” in the presence of tissue specific ligand-IL-34. To identify relationships between HIV-1 infection of microglia and neuropathology, mice at 6 months of age were infected with HIV-1AAD and brain tissues were subjected for histopathological (glial and neuronal) and transcriptomic (mouse and human) profiling by next generation sequencing.

**Results:** CD34-NOG-hIL-34 mice showed sustained plasma viremia with CD4+ T cell loss and productive human microglial infection. Reductions in neuronal and synaptaptic architectures was observed in brain subregions by reduced expression of synaptophysin, MAP2 and neurofilament-H. Reductions in synaptic signaling were observed due to increased expression of toll-like receptor and pattern-recognition receptor indicating activation of innate immune response and increased inflammation. Whilst analysis of mouse genes indicated that ERK, integrin, MAPK, apoptosis signaling etc. were differentially regulated in association with neurodegeneration.

**Conclusion:** Human microglial mouse closely reflects the pathobiology of HIV-1 infection with astroglisosis, microglisis, productive viral infection of microglia, synaptic alterations and inflammatory responses. This model will prove useful for studies of neural-glial cross talk and studies designed to locate and eliminate the virus reservoir.
with executive function DRS and TS (p<0.05 for both), and recall TS (p=0.03). Other domains did not differ by haplogroup B status.

Conclusion: Previously identified NC differences in Hispanic CHARTER participants with mtDNA haplogroup B were greatest for the delayed recall and executive function domains. If validated in independent cohorts, this finding could inform neuroimaging and other assessments to define mechanisms by which mtDNA variation may influence NC performance in PLWH.

435 MECHANISMS OF WHITE-MATTER LOSS DUE TO HIV INFECTION AND ANTIRETROVIRAL THERAPY
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Background: White matter pathologies including corpus callosum thinning and disruption of white matter microstructures persist in HIV-positive patients on combination antiretroviral (ARV) therapy (cART). Thinning of the corpus callosum increases with time on cART. Thus, we hypothesized that HIV-infected macrophages and/or antiretroviral compounds alter oligodendrocyte differentiation, function, and/or survival and sought to identify the mechanism underlying this effect.

Methods: To model the effect of HIV infection in the CNS on oligodendrocytes, we stimulated primary rat oligodendrocyte precursor cells (OPCs) to differentiate into mature oligodendrocytes in vitro, with concomitant treatment with HIV-infected monocyte-derived macrophage supernatant (HIVMDMS) or ARV compounds from the integrase strand transfer inhibitor class, elvitegravir, raltegravir or cobicitab, the bioavailabilityibility test. To examine the effect of ARV drugs on remyelination, we treated mice with cuprizone, a demyelinating compound, for five weeks and allowed them to recover for three weeks (a time frame that permits remyelination) or treated them with daily intrajugular injection of elvitegravir and cobicitab during the three-week recovery phase. Brains were harvested, and the corpus callosum was sectioned and stained for myelin by luxol fast blue, mature oligodendrocytes by ASPA and neuroinflammation by GFAP and Iba1.

Results: In our in vitro model, OPC differentiation was inhibited by HIVMDMS and elvitegravir, whereas raltegravir and cobicitab did not affect oligodendrocyte differentiation. The inhibition of OPC differentiation by HIVMDMS and elvitegravir was reversed by inhibiting the integrase stress response using the small molecule trans-ISRIB. Finally, administration of elvitegravir during the recovery phase following cuprizone-induced demyelination resulted in failure of remyelination, indicated by reduced ASPA and luxol fast blue staining. Persistent neuroinflammation was evident in the corpus callosum in elvitegravir-treated mice compared with the untreated controls.

Conclusion: These studies suggest that both HIV infection and elvitegravir inhibit OPC differentiation in vitro and in vivo. Further studies of the effects of HIV and/or first-line ARV compounds are warranted to provide insights into the observed persistent white matter changes seen in patients with HIV-associated neurocognitive disorders and their potential contribution to cognitive impairment.

437 POLYPHARMACY IS ASSOCIATED WITH WORSE NEUROCOGNITIVE PERFORMANCE IN AGING ADULTS
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Background: Persons living with HIV (PLWH) have more aging-related diseases, use more prescribed drugs, and are more likely to have neurocognitive (NC) impairment than the general population. Medical and psychiatric comorbidities increase risk of NC impairment in PLWH but the neurotoxicity of drugs used to treat these diseases remains understudied.

Methods: 956 PLWH taking antiretroviral therapy (ART) and enrolled in neuroHIV cohorts underwent NC assessment. Demographically-adjusted T-scores were computed for seven cognitive domains and global performance. The most common classes of concomitant drugs were antidepressants (31.1%), antimicrobials (26.2%), non-steroidal anti-inflammatory drugs (21.0%), opioids (16.0%), gastric acid drugs (15.8%), antipsychotics (12.6%), antihypertensives (11.2%), and anxiolytics (10.9%). Polypharmacy was defined as taking ≥5 concomitant drugs. Psychiatric and substance use diagnoses were available for 719 participants. Stepwise multivariable linear regressions using the Akaike Information Criterion modeled NC performance as a function of concomitant medications, adjusting for age, sex, and HIV disease and treatment characteristics.

Results: Participants were generally middle-aged (mean 44.1) white (53.1%) men (86.2%) who had AIDS (56%), viral suppression (71.7%), and immune recovery (median CD4+ count 488/µL). The mean number of concomitant drugs was 3.3 (range 0-24). Overall, PLWH who took more concomitant drugs had worse global performance (r=0.15, p<0.001), as did those who took ≥5 concomitant drugs (d=0.28, p<0.001). Worse global performance was associated with use of anxiolytics (p<0.001), protease inhibitors (p=0.006), opioids (p=0.008), antimicrobials (p=0.009), and antipsychotics (p=0.03) (Model p<0.001). Concomitant drug classes were most frequently associated with worse executive functioning and learning (see figure). Accounting for psychiatric, medical, and substance use diagnoses and did not significantly weaken the associations between concomitant drugs and global performance.

436 SWITCHING TO FTC/TAF FROM ABC/3TC OR FTC/TDF DOES NOT AFFECT CNS HIV-1 INFECTION
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Background: Despite suppressive antiretroviral therapy (ART), many HIV-infected individuals have low-level persistent immune activation in the central nervous system (CNS). Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) and abacavir/lamivudine (ABC/3TC) have been the most widely used nucleoside analogues for several years. In 2015, when this study was initiated, a new prodrug for tenofovir, tenofovir alafenamide fumarate (TAF), was introduced. One potential concern regarding TAF and its effect in CNS is that TAF is a stronger substrate for P-glycoprotein (P-gp) than TDF, which could theoretically decrease its CNS exposure since substrates for P-gp are subject to active blood-brain barrier efflux. Our aim was to investigate if switching from FTC/TDF or ABC/3TC to FTC/TAF would lead to changes in residual intrathecal immune activation, viral load, or neurocognitive function.

Methods: In this prospective study, we included 20 HIV-infected neuroasymptomatic adults (11 on ABC/3TC and 9 on FTC/TDF) selected from the prospective Gothenburg HIV CSF study cohort who for backward comparison recently had undergone a previous research lumbar puncture when on treatment with the same regimen as on baseline. We performed lumbar punctures, veni punctures, and neurocognitive testing at baseline and after three and 12 months. At the baseline visit all participants changed their nucleoside analogues to FTC/TAF without any other changes to the ongoing ART regimen. We analysed CSF and plasma HIV RNA, CSF neopterin, CSF β2-microglobulin, IgG index, albumin ratio, and CSF NFL at the pre-study visit, baseline and follow-up. Cognitive function in five domains was assessed by CogState.

Results: After three and 12 months of follow-up, there were no significant changes in CSF and plasma HIV RNA, CSF neopterin, CSF β2-microglobulin, IgG index, albumin ratio, CSF NFL, or neurocognitive function in any of the groups (see figure). CSF and plasma HIV RNA and Cogstate results not shown.

Conclusion: Switching to FTC/TAF from ABC/3TC or FTC/TDF was neutral on HIV CNS infection and inflammation.
Conclusion: Concomitant drug use is associated with worse NC performance. Distinguishing the effects of concomitant drugs from those of underlying diseases is complex but our analyses support that certain drug classes may cause reversible or irreversible neurotoxicity. Different drug classes were associated with different cognitive patterns, suggesting that they differently affect the neurobiological pathways underlying these abilities.

438 CENTRAL NERVOUS SYSTEM SAFETY OF A KICK-AND-KILL STRATEGY WITH ROMIDEPSIN

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Background: Romidepsin (RMD) is a histone deacetylase inhibitor (HDACi) able to induce HIV transcription in vitro and in vivo. Its effects on the brain during antiretroviral strategies are unknown. We investigated cognitive, neuroimaging, and functional outcomes in the BCN02-Romi Study, a trial that assessed the effects of an HIVconv vaccine in combination with RMD in early-treated HIV-infected persons (clinicaltrials.gov: NCT02616874).

Methods: The BCN02-Romi Study tested a kick&kill strategy that combined 2 administrations of an HIVconv vaccine (pre and post RMD, weeks 0 and 9), with 3 weekly infusions of RMD (Smg/m2; weeks 3, 4, and 5), a monitored antiretroviral pause (MAP, starting at week 17), and a 24-week period after the reinstitution of cART. Inclusion in the BCN02-Neuro Substudy was offered to the 15 individuals recruited in the BCN02-Romi Study and 11 accepted to participate (Intervention Group, IG, n=11). Early-treated but not vaccinated individuals were recruited as controls (Control Group, CG, n=10). CNS assessments were performed before RMD administration (Pre), after final RMD administration (Post), and after MAP + 24-week cART reinstitution (Final). Study variables comprised cognitive functioning (NPZ6, 3T magnetic resonance imaging (voxel-wise whole-brain structural changes), and functional outcomes (daily functioning, adverse events, and emotional symptoms). Study endpoints were based on between-arm differences in change from Pre to Post and Final assessments.

Results: Global cognitive functioning was comparable between groups at the 3 study timepoints (mean NPZ6 [SD]): Pre: IG: 0.28 (0.64), CG: 0.28 (0.63), p=0.98; Post: IG: 0.42 (0.54), CG: 0.31 (0.61), p=0.66; Final: IG: 0.41 (0.59), CG: 0.55 (0.76), p=0.69. Analysis of change confirmed these results (mean NPZ6 change [SD]): Post: IG: 0.13 (0.31), CG: 0.03 (0.32), p=0.45; Final: IG: 0.15 (0.43), CG: 0.27 (0.35), p=0.56. Neuroimaging analyses did not find differences between groups at any timepoint (all p values >0.10). No differences were also observed in daily functioning outcomes, CNS adverse events, or emotional symptoms.

Conclusion: No detrimental effects of a kick&kill strategy with RMD were observed on cognitive functioning, neuroimaging, or functional outcomes in this small study. The HIV cure approach investigated, including the use of an HIVconv vaccine, administration of RMD, and cART interruption with posterior 24-week therapy reinitiation, appears to be safe for the brain.

439 CENTRAL NERVOUS SYSTEM EFFECTS OF THERAPY INITIATION WITH INTEGRASE INHIBITORS

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Background: Data about the possible CNS toxicity of integrase strand transfer inhibitors (INSTI) in people living with HIV (PLWH) are growing. We investigated this in the ARBRE Study, an observational trial that assessed the impact of antiretroviral therapy with INSTI on brain outcomes according to the time of therapy initiation.

Methods: The ARBRE Study included 3 study arms: early-treated PLWH (G1: <3 months since estimated date of infection, n=12), chronically treated (G2: >6 months, n=15), and matched seronegative controls (G3, n=15). Both HIV+ groups were treated with an INSTI-containing regimen (dolutegravir, elvitegravir, raltegravir). Assessments were performed at baseline (prior to therapy initiation), week 4, and week 48, and evaluated cognitive functioning (6 domains, NPZ212), 3T magnetic resonance imaging (voxel-wise whole-brain structural changes), and functional outcomes (daily functioning, adverse events, and emotional symptoms). Study endpoints were based on difference in change at week 48 among arms.

Results: Baseline cognitive functioning and neuroimaging parameters were comparable among groups. Regarding functional outcomes, daily functioning and CNS adverse events were also comparable, although participants in G1 had more depressive symptoms (p=0.03), anxiety (p=0.04), and perceived stress (p=0.03) than the other groups. At week 4, no significant changes were observed in cognitive functioning or functional outcomes. Neuroimaging analyses detected a significantly more reduced gray matter volume in the medial orbitofrontal cortex in G2 (p=0.005). At week 48, cognitive performance did not significantly improve or differ between groups (p=0.14). The decreased medial orbitofrontal volume found in G2 persisted, although to a lesser extent (p=0.04). Emotional symptoms improved significantly in G1, reaching comparable levels among groups (p=0.10).

Conclusion: Cognitive outcomes were similar between PLWH initiating therapy with INSTI during early infection or later than 6 months after HIV transmission. However, participants who initiated therapy later had more reduced gray matter volume that persisted for 48 weeks, which is consistent with prior reported data showing cortical thickness abnormalities in virally suppressed HIV+ patients. An extended follow-up is required to ascertain the future progression of CNS outcomes in PLWH on therapy with INSTI.

440 NEUROPSYCHIATRIC OUTCOMES BEFORE AND AFTER SWITCHING TO DOLUTEGRAVIR-BASED THERAPY

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Background: Dolutegravir (DTG) is a 2nd generation HIV integrase inhibitor currently recommended as 1st-line antiretroviral therapy (ART). Neuropsychiatric (NP) adverse events have been reported with DTG but NP symptoms have not been systematically quantified using structured scales. This study examined mood and cognitive parameters before and after a planned transition from a non-DTG to a DTG-based regimen within a longitudinal study.

Methods: Participants on ≥ 24 weeks of ART started in acute HIV infection (AHI) underwent NP assessments before and after transition to DTG. They underwent: 1) Patient Health Questionnaire-9 (PHQ-9), a 9-item survey (score range 0–27) that evaluates both somatic and affective/cognitive symptoms of depression; 2) a 2-Questions screening that has been validated locally for major depression; 3) Distress Thermometer for anxiety/stress (scores 0–10); and 4) a 4-test battery that included Color Trails 1 and 2, Trails Making A and non-dominant hand grooved pegboard test. Outcomes before and after DTG
were compared by McNealon and Wilcox signed-rank tests; multivariate linear regression examined factors that were correlated with the change of PHQ-9 scores.

**Results:** 256 individuals (95% male, median age 30 [IQR 25-36]) switched to DTG-based ART after a median 144 [IQR 24-192] weeks of ART (82% efavirenz-based) initiated in AHI. Serial assessments were done at median 19 [IQR 8-35] weeks before and median 37 [IQR 24-48] weeks after the switch. PHQ-9 scores were higher in 48% of participants, lower in 31%, and unchanged in 21% after switching. The proportion of participants with at least moderate depression symptoms (PHQ-9≥10) rose from 9% to 16% (p=0.007), while the percentage of those with moderately severe symptoms (PHQ-9≥15) did not change (3% vs. 3%). The PHQ-9 sub-scores of somatic symptoms (sleep/appetite/energy level) had a more significant increase than that of cognitive/affective symptoms (p=0.005 vs. p=0.052). Multivariate analysis showed that viral suppression (Mean difference -2.9, 95%CI [-0.9 to -5.0], p=0.005) and higher PHQ-9 scores (Mean difference -2.7, 95%CI [-1.2 to -4.2], p<0.001) prior to DTG were linked to decreased PHQ-9 score after DTG. NPZ-4, CD4+ T-cell counts and CD4/CD8 ratio improved after DTG (Table).

**Conclusion:** DTG-associated NP adverse effects in this cohort were primarily related to somatic symptoms including insomnia, whereas there was no change in the prevalence of severe depressive symptoms or major depression.

### Table: Neuropsychological and CES-D mean scores before and after EFV switch (with 95% confidence intervals).

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean before switch</th>
<th>Mean after switch</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>40.2</td>
<td>38.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Speed</td>
<td>46.09</td>
<td>44.86</td>
<td>0.07</td>
</tr>
<tr>
<td>Memory</td>
<td>49.45</td>
<td>48.76</td>
<td>0.06</td>
</tr>
<tr>
<td>Working memory</td>
<td>49.10</td>
<td>48.92</td>
<td>0.11</td>
</tr>
<tr>
<td>Executive function</td>
<td>49.07</td>
<td>48.94</td>
<td>0.16</td>
</tr>
<tr>
<td>Learning</td>
<td>49.00</td>
<td>48.90</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Each score was modelled separately. High neuropsychological T scores indicate good performance. Higher CES-D scores indicate worse depression.

**EFV, efavirenz; CES-D, Center for Epidemiologic Studies Depression Scale.**

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**442 MEMORY AND LEARNING DYSFUNCTION WITH INTEGRASE STRAND TRANSFER INHIBITORS USE**

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**Background:** Integrase strand transfer inhibitors (INSTIs) have been associated with neuropsychiatric symptoms in post marketing analysis. However, limited data exists on the effect of these drugs on neurocognitive function. We assessed neurocognitive function and neuroimaging in people living with HIV (PLWH) on INSTI-based regimens.

**Methods:** We performed a cross-sectional analysis of PLWH on ART aged >18 years. PLWH with cART for 3 months were included. We recruited 402 PLWH. Neurocognitive assessment was performed using standardized neuropsychological tests. The neurocognitive assessment included as standard measures the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and the Wechsler Memory Scale-Revised (WMS-R).

**Results:** Of 402 PLWH, median (IQR) age 55 (48, 60) years, 152 (75%) male, 136 (67%) black, median recent CD4+ T cell count 573 (401, 810) cells/μL, 96% HIV RNA <200 copies/ml, 99 (49%) were on INSTI-based ART (40.4% raltegravir, 67% black, median recent CD4+ T cell count 573 (401, 810) cells/μL, 96% HIV RNA <200 copies/ml, 99 (49%) were on INSTI-based ART (40.4% raltegravir, 30.3% dolutegravir), while 103 (51%) were on non-INSTITI based ART. Of those with moderately severe symptoms (PHQ-9≥15) did not change (3% vs. 3%). The PHQ-9 sub-scores of somatic symptoms (sleep/appetite/energy level) had a more significant increase than that of cognitive/affective symptoms (p=0.005 vs. p=0.052). Multivariate analysis showed that viral suppression (Mean difference -2.9, 95%CI [-0.9 to -5.0], p=0.005) and higher PHQ-9 scores (Mean difference -2.7, 95%CI [-1.2 to -4.2], p<0.001) prior to DTG were linked to decreased PHQ-9 score after DTG. NPZ-4, CD4+ T-cell counts and CD4/CD8 ratio improved after DTG (Table).
CEREBRAL FUNCTION PARAMETERS IN PEOPLE LIVING WITH HIV SWITCHING INTEGRASE INHIBITOR

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Background: Different antiretroviral therapy (ART) agents and combinations may have differing effects on cerebral function. We assessed detailed changes in cerebral function parameters in people-living-with-HIV (PLWH) on ART switching integrase inhibitor.

Methods: Neurologically asymptomatic PLWH on tenofovir-DF/emtricitabine plus raltegravir 400mg twice daily with plasma HIV RNA <20 copies/mL for at least 3 months were randomly allocated on a 1:2 basis to remain on raltegravir (Arm1) or to switch to dolutegravir 50 mg once daily (Arm2) for 120 days. Changes in several cerebral function parameters were assessed which included cognitive function (reported as a z-score composite of 7 domains), patient-reported outcome measures (PROMs; PHQ-9 and Beck’s depression questionnaires), cerebrospinal fluid (CSF) parameters (CSF HIV RNA, tryptophan and phenylalanine metabolites, neopterin, ART exposure and an in-vitro CSF antiretroviral infectivity assay using astrocyte derived cell cultures) and cerebral magnetic resonance (MR) imaging (proton spectroscopy (H1-MRS) in three anatomical locations). CSF infectivity models are expressed as half-maximal inhibitory concentration scores (-log2IMIC50) and ART concentrations were measured by HPLC–tandem mass spectrometry with geometric means (GMs) and 95% CIs calculated.

Results: Of 20 subjects completing study procedures, 19 were male, 14 were of white ethnicity, median age (IQR) was 43 (11.5) years and mean (SD) baseline CD4+count was 717 (298) cells/µL. No treatment related adverse events were observed and plasma HIV RNA remained <20 copies/mL in all. Over 120 days, no statistically significant differences in changes in overall cognitive performance, PROMs, CSF tryptophan metabolite ratios, CSF antiretroviral activity scores or cerebral metabolite ratios were observed (Table 1). A small difference was observed in CSF neopterin concentration between treatment arms (Table 1). CSF HIV RNA was <5 copies/mL at day 120 in all subjects. GM CSF dolutegravir concentration assessed pre-dose was 7.6 ng/mL (95% CI: 5.2-11.1).

Conclusion: In this comprehensive assessment of cerebral function parameters in virologically suppressed PLWH switching integrase inhibitor, we observed no significant changes in clinical, CSF biomarker or cerebral imaging parameters.

444 EARLY ART IN ACUTE HIV LIMITS DETERMINAL CX3CR1 MONOCYTES LINKED TO CNS DYSFUNCTION

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Background: CX3CR1 on immune cells drives tissue homing. In chronic HIV (CHI), inflammatory and patrolling monocytes express reduced CX3CR1 density compared to uninfected (HIV-) controls. In addition, CX3CR1 on microglia has been reported to have neuromodulatory effects in the brain. We investigated the dynamics of CX3CR1 density on monocyte subpopulations in individuals who initiate combination antiretroviral therapy (cART) during acute HIV infection (AHI) and assessed the relationship with central nervous system (CNS) outcomes.

Methods: We examined 18 AHI adults (n=10 Fiebig stage (F)II/III and n=8 FIII) who initiated cART. As controls CHI adults (n=27 pre-cART; n=30 and n=19 at 24 and 48 weeks post-cART, respectively) and demographically matched HIV-adults (n=13) were included. CX3CR1 density (geometric mean fluorescence intensity [GMFI]) was measured on monocytes (classical and CD16+) from peripheral blood mononuclear cells by multiparametric flow cytometry using a protocol capturing maximal chemokine receptor recycling and expression. Neuropsychological (NP) tests performed included Trail Making A, Color Trails 1 and 2, and Grooved Pegboard to compute a summary NPZ-4. Nonparametric statistics were used.

Results: The median age was 30, 33, and 31 years for AHI, CHI and HIV-, respectively, 61% of HIV+ and 67% of HIV- were male. In CHI at baseline, CX3CR1 density on inflammatory monocytes was lower compared to uninfected (HIV-) and residual CX3CR1 monocyte density correlated with worse NP testing scores (global NPZ; rho=-0.308, p=0.038 and rho=-0.486, p=0.035 for 24 and 48 weeks post-cART, respectively). At baseline, CX3CR1 density on inflammatory monocytes in AHI was lower than in HIV- (p's<0.01). However post-cART, CX3CR1 levels normalized and unlike in CHI, were not associated with NP test scores. While differential CX3CR1 densities on classical and patrolling monocytes were noted between AHI, CHI and HIV- at baseline and post-cART, these subsets were not associated with either global or subdomain NP test scores.

Conclusion: Unlike in treated CHI, early cART instituted in AHI restores perturbed CX3CR1 density on inflammatory monocytes. This may halt a detrimental cascade initiated by monocyte trafficking to the CNS that is linked
ART in early infection improves neurocognition regardless of infection duration

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Background: The CNS is a sanctuary and reservoir for HIV, which is known to enter the CNS within days of primary infection. We sought to assess whether early ART would improve neurocognitive performance (NP) in the SABES study, a cohort of men who have sex with men (MSM) and transgender women (TW) in Lima, Peru randomized to start ART at diagnosis (within 30-90 days of estimated date of detectable infection (EDDI)) vs. after a short delay. We hypothesized that, by limiting CNS infection, ART initiation within 30 days of HIV acquisition would improve NP compared to ART initiation later in early infection.

Methods: A subset of SABES participants had neurocognitive assessments and blood collection, and in some cases, lumbar puncture. NP was measured with a 15-test battery covering Gross motor, Attention, Executive, Learning, Memory, Speed of Processing, and Fine Motor domains at weeks 12, 24, 48, 72, and 96 after randomization. Estimated date of infection (EDDI) was derived from an algorithm compiling test parameters of last negative and first positive HIV tests.

Results: The 112 participants were all Hispanic MSM or TW, had a mean age of 26.4 years (SD=7.4), mean education grade level of 12.5 (SD=2.3) and mean baseline CD4+ cell count of 443.4 (SD=219.4). Seventy-seven observations came from participants with an EDDI to ART initiation interval of <30 days, 190 from participants who started ART after 31-90 days, and 262 from those who started ART 91 to 249 days after EDDI (>90 days). NP did not differ significantly between the EDDI to ART categories over time (mean total z for <30 = .42, 31-90 = .39, >90 = .32, p=ns). However, NP significantly improved with ART out to 120 weeks of follow up (F=(5, 394)=35.9, p<.0001), across categories (mean total z score at week 0 = 0.09, week 12 = 0.28, week 24 = 0.41, week 48 = 0.47, week 72 = 0.50, week 96 = 0.52). As a check for practice effects, gait (resistant to practice) was significantly improved over time (F=(5, 391)=2.94, p<.05), indicating that ART had a substantial impact on NP.

Conclusion: In this unique early infection cohort, time between primary infection and ART initiation was not associated with neurocognition. Initiation of ART improved neurocognitive functioning regardless of treatment category: this cohort of persons who started ART during or just following acute infection had improved cognitive performance as time on ART increased. These findings underscore the importance of initiating ART early to protect the CNS.

Neurocognitive Performance in Early HIV Days from Infection to ART Initiation

445 ART IN EARLY INFECTION IMPROVES NEUROCOGNITION REGARDLESS OF INFECTION DURATION

446 NEUROSYMPOMATIC HIV CSF ESCAPE CAN BE PRODUCED BY REPLICATION IN T CELLS IN THE CNS

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Background: Some HIV-infected individuals presenting with neurologic symptoms have increased levels of cerebrospinal fluid (CSF) HIV-1 RNA despite being on antiretroviral therapy (ART) and having undetectable, or low, plasma viral load (VL). i.e. neurosymptomatic (NS) CSF escape. Genetic diversity and phenotypic characteristics of NS CSF escape viruses have not been previously examined, and the cells producing these populations are unknown.

Methods: We examined archived blood plasma and CSF samples from 11 individuals with NS CSF escape. All individuals were ART-treated and had a CSF VL >40 copies/ml and greater than the VL in plasma. Single genome amplification (SGA) and/or Illumina MiSeq deep sequencing with Primer ID were used to assess diversity in env and drug resistance in pro-pol. Full-length env genes were cloned from the CSF of three individuals and assessed for macrophage tropism based on their ability to efficiently enter cells with a low density of CD4 on their surface.

Results: For these 11 participants, median values were: CSF VL = 1,493 copies/ml, plasma VL = 163 copies/ml, blood CD4 count = 552 cells/μl and CSF WBC = 44 cells/μl. 73% (8/11) of participants had a genetically diverse CSF escape HIV-1 population. 67% of individuals examined for drug resistance (4/6) had mutations in their CSF virus conferring at least partial resistance to their current ART regimen. 3 of 6 participants experienced an improvement in neurologic symptoms upon ART optimization. Four individuals were examined longitudinally and three had persistent CSF escape. The three participants examined for viral tropism had CSF HIV-1 variants that were adapted to entering CD4+ T cells rather than macrophages (i.e. RS T cell-tropic).

Conclusion: Most individuals with symptomatic CSF escape have characteristics that are consistent with ongoing viral replication such as genetically diverse CSF viral populations, CSF drug resistance and resolution of neurologic symptoms after ART optimization. The results here suggest that NS CSF escape virus can be adapted to entering T cells and is likely produced by CD4+ T cells in the CNS (Example shown in Fig. 1). It remains unknown whether these infected cells represent long-lived viral reservoirs in the CNS or transient populations producing virus during treatment failure due to drug resistance or nonadherence.
447 RELAPSE OF SYMPTOMATIC CSF HIV ESCAPE UPON PREVIOUSLY OPTIMIZED cART REGIMEN CHANGES

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Background: Neuro-symptomatic cerebrospinal fluid (CSF) viral escape is a condition of persons receiving combination antiretroviral treatment (cART), who show a discordant HIV replication between CSF and plasma, associated with neurological symptoms and magnetic resonance imaging (MRI) white matter changes, and it is usually reverted upon cART optimization. Our aim was to identify and characterize possible cases of relapse in the long-term follow-up.

Methods: A cohort of 21 cases of symptomatic CSF escape was followed between 2003 and 2017. Cases were defined as onset of new neurological symptoms and/or signs in cART-treated patients with HIV-RNA detectable in CSF, but not in plasma, or CSF HIV-RNA higher than plasma level. Relapse was defined as the re-occurrence of symptomatic CSF escape following clinical and, if follow-up CSF sample of first episode was available, virological regression of first episode.

Results: In the 21 CSF escape cases, median CSF HIV-RNA was 1056 c/mL (IQR 63-75,000); plasma HIV-RNA was detectable in 10 of 21 patients, median 1055 c/mL (IQR 92-8194); cognitive impairment was observed in 12 patients and cerebellar symptoms in 11. MRI demonstrated diffuse bilateral white matter hyperintensities on T2-weighted sequences in 15 of 20 patients. During a median follow-up of 66 months (range 12-121) after cART optimization, CSF escape relapsed in 5 of 21 cases (24%) as a consequence of cART simplification, which included zidovudine (AZT) withdrawal, in 3, or poor adherence in 2 (Table). CSF resistance mutations were identified in 2 cases. There were no significant differences between first escape and relapse as for current CD4+ cells (median 300 vs. 722/µL), CSF HIV-RNA (median 1000 vs. 853 c/mL), HIV-RNA detectability in plasma (40% vs. 60%), clinical and MRI findings.

cART re-optimization according to resistance profile and/or predicted neuropenetration, including AZT in 3 patients, lead to clinical resolution in all patients and HIV-RNA clearance in all of the tested cases. At last follow-up, 3 patients had underwent cART simplification, either maintaining AZT (n=1), or switching to a new dolutegravir-containing regimen without AZT (n=2), with no new escape episodes.

Conclusion: CSF escape may relapse months to years after recovery, if cART efficacy in the CNS is weakened by simplification or loss of adherence. These observations also support, at least in some patients, the presence of a viral reservoir within the CNS.

448 CNS ESCAPE OF DRUG-RESISTANT HIV IN PML-IRIS AND CONSEQUENT PERIPHERAL DISSEMINATION

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Background: Inflammation and tissue influx of activated T cells affects the compartmentalization and dynamics of HIV viral replication, but the role of compartmentalized virus populations in the emergence of drug resistant mutations (DRMs) and virological failure is uncertain. Herein, we describe viral escape with high viral RNA levels and DRMs in CSF during an episode of unmasking PML-IRIS.

Methods: PBMCs and CSF mononuclear cells were used for immunophenotyping along with a flow cytometric T cells responses assay to JC virus (JCV), BKV and CMV. Plasma and CSF ARV concentrations were measured by tandem mass spectrometry. Phylogenetic analysis of CSF, plasma, rectal mucosa and cervical lymph node HIV variants was performed.

Results: A man with HIV/AIDS [CD4: 6 cells/µL, HIV plasma viral load (VL): 716531 c/ml, CSF VL: 1200 c/ml, no DRM(s) presenting with PEP, achieved prompt clinical improvement after TMP-SMX, Prednisone and ETVG/TAF/FTC initiation. 12 weeks after starting ARV, with suppressed HIV VL <40c/ml (bLOD) in plasma and CSF, he developed new ataxia and dysmetria with multiple parenchymal enhancing lesions on MRI. JCV DNA was detectable in CSF, HIV VL remained bLOD and unmasking PML-IRIS was diagnosed, which resolved with addition of Prednisone, Maraviroc and Mirtazapine. After Prednisone was tapered, PML-IRIS flared with new hand tremor: CSF analysis revealed pleocytosis with CSF HIV VL of 1544 c/ml and plasma VL to 185 c/ml. HIV genotype in CSF revealed a new E92Q DRM in Integrase (INT) and M184V/I in RT. Prednisone was restarted with clinical improvement and suppression of both plasma and CSF HIV VL bLOD. Follow-up monitoring of plasma VL showed a progressive increase up to 509 c/ml with the new appearance of E92Q INT and M184V/I RT in plasma and CSF, he developed new ataxia and dysmetria with multiple parenchymal enhancing lesions on MRI. JCV DNA was detectable in CSF, HIV VL remained bLOD and unmasking PML-IRIS was diagnosed, which resolved with addition of Prednisone, Maraviroc and Mirtazapine. After Prednisone was tapered, PML-IRIS flared with new hand tremor: CSF analysis revealed pleocytosis with CSF HIV VL of 1544 c/ml and plasma VL to 185 c/ml. HIV genotype in CSF revealed a new E92Q DRM in Integrase (INT) and M184V/I in RT. Prednisone was restarted with clinical improvement and suppression of both plasma and CSF HIV VL bLOD. Follow-up monitoring of plasma VL showed a progressive increase up to 509 c/ml with the new appearance of E92Q INT and M184V/I RT in plasma and CSF. Retrospective drug level analysis documented subtherapeutic EVG concentration in CSF (5.5 ng/ml), which was >300 fold lower than concurrent plasma EVG (1730 ng/ml). Robust specific CD4 T cells responses to JCV, but not to BKV or CMV were documented in CNS and peripheral lymph node HIV variants was performed.
Background: Sustained viral replication and evolution in a tissue can produce compartmentalized viral lineages that are genetically distinct from populations in the blood. Compartmentalized viral populations have previously been observed in the cerebrospinal fluid (CSF) of individuals infected with subtype B HIV-1, particularly those with HIV-associated dementia (HAD). Less is known about rates of CSF compartmentalization in individuals infected with other viral subtypes and/or lacking severe neurocognitive disorders. HIV-1 replication in the CNS is thought to contribute to neurocognitive impairment in HIV-infected people, but this hypothesis has not been previously examined.

Methods: 50 antiretroviral-naïve HIV+ individuals were enrolled in Rakai, Uganda and assessed with a neuromedical examination, neuropsychological test battery, and functional status assessments to define HAND staging based on Frascati criteria. Viral RNA was isolated from plasma and CSF samples, and Illumina MiSeq deep sequencing with Primer ID was used to sequence env V1-V3. A neighbor joining phylogenetic tree was constructed for each person to compare HIV-1 populations in the CSF and blood. Phylogenetic trees were visually examined and CSF compartmentalization identified when approximately half or more of the CSF sequences formed lineages that were genetically distinct from blood sequences.

Results: Individuals in this cohort had moderate CD4+ T cell counts (median=356 cells/µl) and CSF viral loads (median=38,905 RNA cp/ml). HIV-1 subtype frequency was A (33%), D (19%), A-D recombinants (33%), A-C recombinants (5%), and other recombinants (10%). HAND stage frequency was: 36% normal cognition, 8% with asymptomatic neuropsychological impairment, 34% with mild neurocognitive disorder, and 22% with HAD. 64% of individuals had CSF compartmentalization. There was a trend for compartmentalization to be associated with impaired cognition (p=0.37, figure 1) and compartmentalization was a significant predictor of impaired verbal fluency (p=0.006).

Conclusion: A cohort of HIV+ individuals with subtypes A, D, and recombinants was observed to have a very high rate of CSF compartmentalization. This rate exceeds our previous estimate for a similar cohort of individuals infected with subtype B HIV-1, suggesting that subtypes A and/or D may colonize and establish replicating populations in the CNS more readily than subtype B variants. High rates of compartmentalization may impact long-term neurocognitive performance in this cohort.

DEEP SEQUENCING REVEALS EXTENSIVE CSF COMPARTMENTALIZATION IN HIV+ PEOPLE IN UGANDA

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Background: Despite suppression of HIV viral replication in the periphery by antiretroviral therapy (ART), up to 10% of treated individuals have quantifiable HIV in the CSF, termed CSF escape. CSF escape may be asymptomatic but has also been linked to progressive neurological disease. CSF escape has not yet been assessed after initiation of ART during acute HIV infection (AHI).

Methods: Thai AHI participants underwent blood sampling and optional cerebrospinal fluid (CSF) sampling at baseline followed by immediate ART, and then longitudinally at weeks 24 and 96. HIV RNA was quantified using Roche Amplicor and COBAS TaqMan assays with a lower limit of quantitation of 20-50 copies/ml in plasma and 80 copies/ml in CSF. Participants with quantifiable CSF HIV RNA and plasma HIV RNA less than 50 copies/ml or CSF HIV RNA greater than 1-log higher than plasma HIV RNA during ART were identified as cases of CSF escape.

Results: 187 participants had paired blood and CSF sampling in at least one visit at baseline, week 24, or week 96. The participants were 97% male (182/187) with a median age 26 years and baseline Fiebig stage 3 (83/186, 45%), CD4 count 388 cells/mm3, and plasma HIV RNA 5.84 log10 copies/ml. ART was started at a median of 19 days post estimated infection. At baseline, 126/149 participants (85%) had quantifiable CSF HIV RNA (median 3.15 log10 copies/ml). At week 24 (n=89), four participants (4%) had quantifiable CSF HIV RNA, with one case of CSF escape identified with plasma HIV RNA < 50 copies/ml and CSF HIV RNA 2.50 log10 copies/ml. At week 96 (n=46), one participant (2%) had quantifiable CSF HIV RNA, which did not meet criteria for CSF escape. All other cases of quantifiable CSF HIV RNA were due to ART failure. The participant with CSF escape was treated with efavirenz/tenofovir/lamivudine and had a CD4 count of 840 cells/mm³ and CSF WBC and CSF protein of 10 cells/mm³ and 30 mg/dL. His MRI at week 24 showed a small nonspecific T2/FLAIR hyperintense focus in the right high frontal white matter. He did not have a lumbar puncture performed at baseline nor at subsequent visits.

MINIMAL INCIDENCE OF CSF ESCAPE AFTER INITIATION OF ART IN ACUTE HIV INFECTION

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Background: Suppression of CSF HIV viral replication in the periphery by antiretroviral therapy (ART), up to 10% of treated individuals have quantifiable HIV in the CSF, termed CSF escape. CSF escape may be asymptomatic but has also been linked to progressive neurological disease. CSF escape has not yet been assessed after initiation of ART during acute HIV infection (AHI).

Methods: Thai AHI participants underwent blood sampling and optional cerebrospinal fluid (CSF) sampling at baseline followed by immediate ART, and then longitudinally at weeks 24 and 96. HIV RNA was quantified using Roche Amplicor and COBAS TaqMan assays with a lower limit of quantitation of 20-50 copies/ml in plasma and 80 copies/ml in CSF. Participants with quantifiable CSF HIV RNA and plasma HIV RNA less than 50 copies/ml or CSF HIV RNA greater than 1-log higher than plasma HIV RNA during ART were identified as cases of CSF escape.

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**451** **TREATMENT REGIMENS FOR MANAGING SYMPTOMATIC CSF HIV ESCAPE IN PUNE, INDIA**

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**Background:** Symptomatic CSF HIV escape (sCVE) in limited resource countries (LRCs) has been reported in patients on 2nd line protease inhibitor (PI)-based ART. Management includes performing CSF and plasma genotypic resistance testing (GRT) and changing ART accordingly; however GRT is not routinely available in LRCs. Hence ART modification is done by including drugs with excellent CNS penetration like Zidovudine (AZT intensification) or shifting to a new PI and Integrase inhibitor (PI/INSTI intensification).

**Methods:** In this retrospective cohort study conducted between 1st March 2009 and 1st March 2018, we included patients developing s CVE on 2nd line PI-based ART. sCVE was defined as either undetectable CSF viral load (VL >20 copies/mL) with undetectable plasma VL or b)CSF VL ≥0.5 log10 higher than plasma VL. Individuals in whom GRT could not be performed or drug resistance mutations (DRM) could not be identified were prescribed AZT intensification or shifting to PI/INSTI intensification.

**Results:** Among 204 patients, 41 patients were identified: 20 in Group 1 and 21 in Group 2. Baseline characteristics in both groups are shown in Table 1. After AZT intensification there was complete resolution of symptoms in 17 (85%) patients. Follow up plasma and CSF VL were available for 18 patients: 16 (88.9%) had undetectable plasma VL. Of these, 13 (81.2%) had undetectable CSF VL while 3 (18.8%) had detectable CSF VL ≥0.5 log10 higher than plasma VL. In individuals GRT could not be performed or drug resistance mutations (DRM) could not be identified were prescribed AZT intensification to current ART (Group 1). Those patients demonstrating DRMs on GRT or already taking AZT as part of PI based ART or having history of AZT toxicity were shifted to a new PI, INSTI and NNRTI (Group 2). Plasma and CSF VL was repeated after 6 months of ART modification.

**Conclusion:** Despite potential selection bias (lack of GRT in Group 1) this is a unique cohort of patients with sCVE with homogeneous treatment interventions. AZT intensification was effective in improving symptoms and reducing plasma and CSF VL in majority of subjects. Additional studies including GRT, pharmacokinetics and adherence measurements are needed to select the most appropriate treatment for sCVE in LRCs.

***Table 1: Pretreatment characteristics of patients with sCVE***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n=20)</th>
<th>Group 2 (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>0.0223</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>10 (50)</td>
<td>11 (52.3)</td>
<td>0.703</td>
</tr>
<tr>
<td>Duration of ART (months)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>0.326</td>
</tr>
<tr>
<td>CSF − Plasma VL ≥0.5 log10</td>
<td>12 (60)</td>
<td>6 (28.6)</td>
<td>0.230</td>
</tr>
<tr>
<td>PI/INSTI intensification</td>
<td>16 (80%)</td>
<td>12 (57.1)</td>
<td>0.150</td>
</tr>
</tbody>
</table>

**452** **PRESENCE OF INTACT HIV DNA VARIANTS IN THE BRAIN AND LYMPHOID TISSUES DURING ART**

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**Background:** Although antiretroviral therapy (ART) reduces HIV RNA below the detection limit in blood plasma, HIV reservoirs persist in cellular compartments. Here, we characterize the size and composition of the HIV DNA reservoirs in brain and lymphoid tissues.

**Methods:** We evaluated post-mortem brain and peripheral lymphoid tissues from 12 persons living with HIV (PLWH) obtained from the National NeuroAIDS Tissue Consortium. All donors died between 2001-2014, with virologic suppression on ART (<50 copies/mL) assay-dependent, and without evidence of central nervous system opportunistic disease. Presence of ART in post-mortem brain was confirmed by mass spectrometry. Total DNA was extracted from each tissue sample and levels of HIV DNA (gag) were quantified by droplet-digital PCR. The genotypic composition of the HIV DNA populations was evaluated by high-throughput single genome amplification using the PacBio platform to sequence Full-length HIV envelope (FL HIV-env).

**Results:** We evaluated post-mortem tissues from 9 men and 3 women with a median age of 52 years (range: 40-66). Donors were on ART at the last visit, which occurred a median of 3 months prior to death (range: 1-4). Presence of Tenofovir or Lamivudine was confirmed in 6 out of 8 donors’ brain tissues by mass spectrometry. All donors had detectable HIV DNA in brain (frontal [FC] or occipital [OC] cortex) and lymphoid tissues (lymph node [LN] or spleen [SP]). A total of 180 individual FL HIV-env sequences were obtained across brains and lymphoid tissues. Maximum likelihood phylogeny (figure) suggests that HIV compartmentalization patterns differ between donors, with four donors showing evidence of HIV DNA compartmentalization (p<0.05). Overall, 143 FL HIV-env sequences were genetically intact, while 37 sequences were non-functional, with major deletions, frameshift and stop codon mutations (figure). For one donor, we found 23 clonal sequences with a frameshift mutation that was present in both brain and spleen, suggesting migration of cells with clonal provirus between tissue compartments.

**Conclusion:** Presence of intact HIV DNA in brain and lymphoid tissues during ART is consistent with the presence of clonal HIV DNA populations. These populations may represent a reservoir of HIV DNA that is resistant to ART and could contribute to future HIV cure strategies.
ASSOCIATION OF CEREBRAL SMALL VESSEL DISEASE WITH THE BRAIN IN HIV INDIVIDUALS

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**Background:** Emerging evidence has suggested that people living with HIV (PLWH) have increased risk of developing cerebral small vessel disease (CSVD). This may account for some of the cognitive impairment that continues to be common even in those with good viral suppression. In this study, we investigated whether PLWH had worse CSVD compared to demographically similar controls (CTL), and provide evidence of the impact CSVD has on brain volumetrics and cognition.

**Methods:** Virologically suppressed PLWH on combination antiretroviral therapy (cART) and CTL participants underwent MRI and comprehensive neuropsychological testing. The total volume of white matter hyperintensities (WMH) on MRI was used as a surrogate marker for CSVD severity. Tensor-based morphometry and cortical modeling estimated regional brain volumes and cortical thickness, respectively. Rasch measurement theory was applied to the cognitive test scores, yielding an estimate of overall cognitive ability. Linear models were used to compare the WMH load, brain volumes and cognition between the two groups. These models controlled for age and sex. In addition, separate linear models assessed the association of brain volumes, cognition and factors commonly linked with vascular disease, including hypertension (defined as systolic blood pressure ≥140mmHg or diastolic ≥90mmHg), smoking, body mass index and waist circumference, with the WMH load. These models included all participants and controlled for HIV serostatus, age and sex.

**Results:** 119 PLWH and 55 CTL were included in the study (PLWH age [mean±SD]: 56±8; education:13±3; sex:81% male; CTL age: 56±12; education:14±2; sex:51% male). PLWH had smaller brain volumes and poorer cognitive performance compared to the CTL group. Total WMH load and factors commonly linked with vascular disease were similar between the two groups. Older age and hypertension were significantly associated with greater WMH load for all participants (Fig. 1A). Higher WMH load was significantly associated with reduced brain volumes and cortical thickness and worse cognitive function in all participants, independent of HIV status (Fig. 1B-D).

**Conclusion:** We observed that the PLWH in this study did not have greater WMH load. However, WMH load was associated with reduced brain volumes and poorer cognition in the entire sample. These findings suggest that CSVD could explain some of the brain atrophy and cognitive impairment found in people living with HIV.

1H MRS IDENTIFIES SUBCLINICAL NEURONAL INJURY DESPITE CHRONIC VIRAL SUPPRESSION

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**Background:** The significance of proton Magnetic Resonance Spectroscopy (1H MRS) abnormalities in chronic suppressed HIV infection is unclear. Previous studies have included unsuppressed patients and did not relate findings to markers of current neuronal injury such as neurofilament light-chain (NFL), nor to non-AIDS comorbidities. We hypothesized that 1H MRS would identify active brain injury.

**Methods:** 22 HIV+ men (aged 48.7±12.3) with plasma and CSF viral suppression (<20cp/mL) underwent 1H MRS scanning to assess in vivo brain injury in the frontal white matter (FWM), posterior cingulate cortex (PCC), and basal ganglia (BG). Brain metabolite concentrations for N-Acetyl-Aspartate (NAA), Choline (Cho), Creatine (Cr), Glutamate (Glu) and myo-Inositol (MI) were quantified in jMRUI and referenced to H2O. As MRS data are amenable to data reduction techniques to yield a single robust component, we extracted a composite neurochemical in vivo marker - “CNM” (more negative values indicate greater brain injury; Fig. 1). Participants also completed neuropsychological testing and lumbar puncture to assess CNM’s potential as a marker of active brain injury. Besides NFL, CSF biomarkers included neopterin, CCL2, and CSF tat. Neurocognitive impairment (NCI) was classified using standard criteria (37.5%, none demented). Univariate correlations with CNM were tested for CSF biomarkers, HIV disease markers, demographics, neocognition, psychiatric and alcohol/drug use comorbidities, current psychological distress, and non-AIDS comorbidities (cardiovascular/renal diseases, sleep disorders, malignancies, neuropathy/pain, and loss of consciousness>30min from non-traumatic causes). Predictors at p<0.10 were retained in a logistic regression model (stepwise forward selection, best model fit by Akaike information criterion (AIC)).

**Results:** CSF NFL (r=-.53, p<.02), non-AIDS comorbidities (r=.48, p<.03), nadir CD4 (r=.41, p=.05), age (r=-.42, p<.05) and NCI (r =-.39, p=.07) were associated with greater brain injury (lower CNM). Non-AIDS comorbidities remained a significant predictor (p<.03) yielding the best model fit (AIC=111.17).

**Conclusion:** Composite 1H MRS signal identifies currently active brain injury, well below the threshold for NCI, in regions known to be associated with HIV related brain injury and pathological aging. This injury is dominantly driven by non-AIDS co-morbidities and expressed through an HIV-related pathway, implying that HIV is the driver of the co-morbidities.
INFLAMMATORY PLASMA BIOMARKERS CORRELATE WITH DIFFUSION TENSOR IMAGING IN CHRONIC HIV

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Background: Despite adherence to combination antiretroviral therapy (cART) and suppression of plasma viral RNA, a large proportion of people living with HIV experience cognitive symptoms. This study investigated correlations between plasma inflammatory biomarkers and diffusion tensor imaging (DTI) measures of brain white matter injury.

Methods: Participants underwent neuropsychological testing, blood draw, and DTI scans on one of two separate 3 Tesla MRI scanners. Plasma biomarkers, sCD163, sCD14, neopterin, IP-10, and MCP-1, were quantified by Luminox/ELISA. DTI metrics fractional anisotropy (FA) and mean diffusivity (MD) were averaged across a priori defined regions known to be affected by HIV – the corpus callosum (CC), corona radiata (CR), and superior longitudinal fasciculus (SLF). These were regressed against biomarker levels and the results of global, executive domain, and attention domain neuropsychological testing, reported as z-scores relative to standard norms (NPZ), controlling for age, duration of infection, and scanner model. Voxelwise analysis by Tract-Based Spatial Statistics (TBSS) compared FA and MD to biomarker levels, controlling for age and duration of infection.

Results: 43 HIV+ participants (median age 64 [IQR 62-66] years, 91% male) enrolled, all of whom were on cART with suppressed plasma HIV RNA and self-reported cognitive symptoms. 38 met criteria for HIV-associated neurocognitive disorder (37 with Mild Neurocognitive Disorder, 1 with dementia), and 5 were considered cognitively normal. ROI analysis revealed positive correlations between MCP-1 and MD in the CC, bilateral anterior and superior CR, and left SLF, and between neopterin and MD in the genu of CC (p<0.05). Negative correlations existed between MCP-1 and FA in the CC, and between sCD14 and FA in the bilateral superior CR (p<0.05). Voxelwise analysis detected areas of direct correlation between MCP-1 and MD (p<0.05). Lower FA in parts of the CC, CR, and SLF directly correlated with worse neuropsychological performance globally and in the executive domain, and increased MD in the CC and left superior CR directly correlated with lower global neuropsychological scores (p<0.05).

Conclusion: In virally suppressed HIV+ elders, inflammatory markers correlate with worse metrics of brain white matter injury. These metrics predict poorer cognitive performance, supporting the hypothesis that inflammation persisting despite viral suppression impacts brain integrity and may contribute to cognitive impairment in the cART era.

456 WHITE MATTER HYPERINTENSITIES INCREASE AS A FUNCTION OF CVD RISK AND HIV DISEASE

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Background: White Matter Hyperintensities (WMH) are a marker of cerebral small vessel disease. We have previously shown that HIV infection and diabetes mellitus interact to increase the volume of WMHs. The purpose of the present study was to evaluate the rate of change of WMH volume over a four year follow-up.

Methods: 119 men from the MACS MRI subsidy contributed data: 43 uninfected and 76 with HIV Disease. There were no differences between the infected and uninfected men in the rates of diabetes, hypertension, Caucasian race, or syndrome depression. A greater proportion of the infected men were enrolled after 2000. 16% of the infected men had had an AIDS-defining illness. Cerebral WM and cerebellum WM masks were created using both T1w MPRAge and T2w FLAIR images using unified multispectral segmentation/normalization procedure in SPM12. Given the observation that there were very few lesions in the cerebellum in our patients, the mean and standard deviation of the cerebellar WM was used to Z-transform the T2w FLAIR image (Z-T2w FLAIR). On the Z-T2w FLAIR images, voxels greater or equal than 2 and within the cerebral WM mask were identified white matter lesions in the brain. WMH volume was expressed as the ratio between WMH and total WM. The dependent variable was the rate of change (i.e., Z/T2-T1)/year.

Results: First, we replicated and extended our cross-sectional data (Wu et al., 2018) by finding that the annualized rate of change in WMH volume was elevated only among the HIV-infected men with diabetes (See Figure). The rate of change was virtually identical among the uninfected men and those with HIV Disease but not diabetes. Second, although we did not find a relationship between hypertension and WMHs in the cross-sectional analysis, this was not true as we tracked change over time. The normotensive, uninfected men had no change in their WMH volume over time. By contrast, the men with hypertension had a nearly 30% annual increase in WMH volume. The normotensive, infected men had a rate of change that was almost as high (20%) as that of the hypertensive men, and greater than that of the normotensive, uninfected men.

Conclusion: These data emphasize the importance of cerebrovascular risk in the brain health of men with HIV Disease. The presence of infection acts to increase the rate of change of WMHs as a function of hypertension and diabetes – even though these conditions were treated. Abnormal levels of WMHs reduce brain reserve capacity and increase risk of expressing cognitive impairment.
IN ACUTE HIV

RESTING-STATE CONNECTIVITY ASSOCIATES WITH DEPRESSION SYMPTOMS

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Background: The prevalence of depression symptoms in HIV can be relatively high and has been associated with increased morbidity and mortality. Previous research has revealed that HIV-related biological factors (e.g., CD4 count) are related to depressive symptoms in acute HIV (AHI). However, it is unclear whether neurobiological measures are also correlated with depression symptoms in AHI. The purpose of this study was to determine whether resting-state functional connectivity (rsFC, i.e., correlations in spontaneous low frequency fluctuations in brain activity) of anterior cingulate cortex (ACC) regions implicated in depression was associated with depression symptoms or anxiety in AHI.

Methods: Thai participants with AHI (n=74) and uninfected controls (n=30) underwent resting-state functional magnetic resonance imaging. Seed-based voxelwise rsFC was computed for 3 ACC seed regions of interest (ROIs) implicated in depression. T-tests were performed to compare rsFC of ACC seed ROIs for AHI versus CO groups. Within the AHI group, we conducted voxelwise regression analyses to examine the relationship between depression symptoms, anxiety, and distress and rsFC for the ACC seed ROIs. All significant rsFC findings were family-wise error (FWE) corrected at the whole brain level, pFWE<0.017.

Results: The AHI group had a mean (SD) CD4 count of 395 (±209) cells/μL, 6.03 (±1.1) log10 copies HIV RNA and estimated duration of infection of 19.0 (±6.6) days. There were no differences in rsFC of ACC for AHI versus CO groups. Within the AHI group, greater depression symptoms were associated with increased rsFC of ACC seeds with lateral and medial prefrontal regions as well as cerebellum (pFWE<0.017; Fig. 1). Greater depression symptoms were also related to decreased rsFC of ACC regions with precuneus/posterior cingulate cortex, ventral temporal and lateral parietal regions (pFWE<0.017; Fig. 1). Anxiety symptoms and distress were unrelated to rsFC of ACC. Only HIV RNA was negatively correlated with rsFC between posterior subgenual ACC and left uncus (p<0.05).

Conclusion: We found that depression symptoms were associated with altered rsFC of ACC regions in AHI, consistent with previous neuroimaging literature in depression. Longitudinal research in this cohort will be necessary to determine whether these early alterations in rsFC of ACC are associated with long-term depression symptoms and HIV-related biological factors after antiretroviral therapy.

LOWERFRONTAL GREY-MATTER BRAIN VOLUMES AND BASAL-GANGLIA
ENLARGEMENT IN PERINATAL HIV

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Background: Brain volume loss has been observed in HIV patients despite initiation on combined antiretroviral treatment (cART), but studies on perinatally HIV-infected patients (PHIV) are scarce. We aim to evaluate the neurologic state and neuroimaging phenotype of stable PHIV youths.

Methods: Cross sectional study. 33 PHIV patients and 33 HIV negative peers (HIV-) matched by age, sex and socioeconomic status (SES) participated. Magnetic Resonance Imaging (MRI) and neuropsychological (NP) testing was conducted. The Computational Anatomy Toolbox (CAT12) standard processing pipeline was used for quantification of the MRI T1-W images. Native segmented images were parceled in regions of interest (ROI) and tissue volumes (mm3) were estimated for each ROI and normalized to total intracranial volume for each subject. These normalized data were used to explore differences between groups (ANCOVA tests). NP assessment tested fluid intelligence and Processing Speed (PS) by 7 NP tests (PSZ7). Psychopathological symptoms were also obtained. Differences between groups and effects of HIV-related variables on brain volumes were studied using appropriate statistical tests.

Results: 63 participants were included (58.7% females, median age 20 years [IQR 19-23], 65.1% caucasians). No differences regarding level of education, fluid intelligence, PSZ7 or psychopathological symptoms were found between groups. Regarding PHIV: 40% AIDS (13% encephalopathy), median CD4% nadir (IQR 5-17). At assessment, 80% had viral load <50 cp/ml (uVL), median CD4 706 cel/mm3 (IQR 488-916), median time on cART 16.6 years (IQR 13.3-18.5) and median time with uVL 9.8 years (IQR 6.4-12.4). No differences were observed between groups for total grey matter (GM), total white matter, total intracranial volume or cerebrospinal fluid. In relation to GM regional volumes, a decrease in PHIV was observed. Differences between groups and effects of HIV-related variables on brain volumes were studied using appropriate statistical tests.

Conclusion: Despite good control of HIV infection and no differences in PSZ7 values, PHIV show lower volumes in frontal areas. Moreover, a negative correlation between B6 volumes and CD4 Nadir and AIDS suggests that HIV may cause structural compromise to these regions.
**PBR-PET IMAGING OF NEUROINFLAMMATION NOT ELEVATED IN HIV+ PARTICIPANTS**

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**Background:** Despite combined antiretroviral therapy (cART), HIV associated neurocognitive disorder (HAND) still develops in people living with HIV (PLWH). Persistent neuroinflammation caused by viral reservoirs in the brain is a potential contributor. This study used the positron emission tomography (PET) tracer [11C]-PBR28 (PBR28) to evaluate neuroinflammation in virologically suppressed (<200 copies/mL) PLWH.

**Methods:** 13 HIV- controls and 24 PLWH underwent neuroimaging (magnetic resonance imaging (MRI) and PET) and cognitive testing. Standard uptake value ratios (SUVRs) were calculated for 20 predefined regions of interest (ROIs) affected by HIV. The whole cerebellum was used as a pseudo-reference region. SUVRs were compared between the two groups using a Wilcoxon Rank-Sum test after correcting for genotype which can affect the tracer’s affinity for TSPO. Within PLWH, additional analyses compared SUVR with clinical markers (current CD4 cell count, nadir CD4, and duration of infection) and cognition (global deficit score (GDS)).

**Results:** SUVRs in the 20 ROIs were not significantly different (p > 0.05) between PLWH and HIV- controls (Table 1). Within PLWH, GDS correlated with SUVR in the superior parietal and supramarginal white matter (p ≤ 0.05); duration of infection correlated with SUVR in the lateral occipital cortex (p ≤ 0.05). After correcting for multiple comparisons, these three correlations were not significant. No association was seen between other clinical measures (current and nadir CD4 cell count) and SUVR for the 20 ROIs.

**Conclusion:** This study reveals no significant increase of neuroinflammation as measured by PBR28 in PLWH compared to HIV- controls. Within PLWH, neither cognitive status nor clinical disease markers correlated with SUVR. Limitations exist for PBR28 and additional studies using magnetic resonance imaging (diffusion basis spectral imaging) and cerebrospinal fluid markers of neuroinflammation need to be performed in virologically suppressed PLWH.

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**Figure:** Basal ganglia volumes are correlated with HIV-related variables.
PI DRUG LEVEL TESTING AS A SCREENING TOOL FOR DRUG RESISTANCE IN 2ND-LINE ART FAILURE

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Background: An increasing number of patients are on 2nd line PI-based ART in low- and middle-income countries (LMIC). In event of virological failure a switch to individualized 3rd line ART is recommended if PI resistance is present. We hypothesize that qualitative PI drug level testing could identify patients most at risk for harboring PI resistance.

Methods: We performed a single-centre pilot study followed by a large regional feasibility study in patients with virological failure of LPV/r-based 2nd line ART. In the pilot, LPV level testing on dried blood spots (DBS) was performed by liquid chromatography mass spectrometry (LCMS). In the feasibility study LCMS was performed as a reference and compared to a low-cost qualitative immunoassay (IA; ARK diagn). LPV levels were defined positive or negative based on prespecified limits of detection (LCMS-DBS: 0.25, LCMS-plasma: 0.04 mg/L). Population sequencing of pol was performed.

Results: 548 patients with confirmed LPV/r-based ART failure were included (50 pilot, 498 feasibility). Overall, median age was 41.1 years (IQR: 33.5–48.6), 58.8% was female. Median HIV RNA was 4.9 (4.3–5.4) c/mL. PI resistance was detected in 12% of patients in the pilot and 27.2% in the feasibility study. Most common mutation profiles were M46I+I54V+L76V+V82A (26.1%) and M46I+I54V+V82A (25.4%). In the pilot, only 40% of patients had a positive LPV level. Sensitivity and negative predictive value (NPV) of a positive LPV level for presence of PI resistance was 100%, with a specificity of 68%. In the feasibility study, 52.9% of patients had positive LCMS-LPV level and 54.4% had a positive IA-LPV level. Positive LCMS-LPV level had a sensitivity of 89% [95%CI: 83–94], NPV of 94% [90–97], and specificity of 61% [55–66] for PI resistance. A positive IA-LPV level had a sensitivity of 89% [95%CI: 82–93], NPV of 93% [89–96], and specificity of 58% [53–63] for presence of PI resistance.

Conclusion: In this largest-to-date analysis of PI-based 2nd line failure, non-adherence was objectively demonstrated in half of cases. PI resistance was infrequent, but extensive when present. Negative LPV levels established either by LCMS or a low-cost qualitative assay excluded the presence of PI mutations in pol with a high degree of certainty. Drug level testing at PI failure is a highly accurate screening strategy to identify patients who would benefit from costly drug resistance testing.
TENOFOVIR DIPHOSPHATE IN DRIED BLOOD SPOTS FOLLOWING ESCALATING TAF/FTC DOSING

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Background: The DISCOVER study will compare daily tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) versus tenofovir alafenamide (TAF)/FTC (25mg/200mg) as HIV pre-exposure prophylaxis (PrEP). DISCOVER uses tenofovir-diphosphate (TFV-DP) in red blood cells measured with dried blood spots (DBS) as an objective adherence measure as it exhibits a 17 day half-life and has a large dynamic range of accumulation that is proportional to adherence. Adherence benchmarks were previously established following TDF/FTC dosing, but not TAF/FTC dosing. This independent study assessed expected TFV-DP concentrations in DBS from weeks 10, 11, & 12 (first TAF/FTC regimen) were analyzed.

Methods: HIV-uninfected adults at low risk for HIV infection were randomized to one of 6 sequences consisting of two directly observed TAF/FTC dosing regimens (33%, 67% or 100% of daily dosing). Each regimen was given for 12 weeks, separated by a 12-week washout. Doses were observed in person or by video streaming. Blood was collected pre-dose and 4 hours post-dose on day 1, then weekly throughout the study including washout. DBS (5x25 µL) were collected on protein saver cards. TFV-DP was quantified from various punch sizes to target adherence benchmarks close to those previously observed for TDF/FTC dosing. Available samples from weeks 10, 11, & 12 (first TAF/FTC regimen) were analyzed.

Results: Twenty-six participants began study treatment; one was excluded for protocol violations. Nine of 25 were randomized to receive TAF/FTC dosing, but not TAF/FTC dosing. This independent study assessed expected benchmarks for TFV-DP in DBS with TAF/FTC dosing.

Conclusion: Following TAF/FTC dosing, two 7mm punches resulted in TFV-DP benchmarks and CVs comparable to those previously established for TDF/FTC. TFV-DP concentrations appeared to increase in direct proportion to dose, supporting the use of TFV-DP in DBS as an objective adherence measure for TAF/FTC regimens.
465 URINE FTC AND TFV CONCENTRATIONS AS POTENTIAL BIOMARKERS FOR ARV ADHERENCE

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Background: Antiretroviral drug (ARV) efficacy in both treatment of chronic HIV infection and prevention of HIV infection in pre-exposure prophylaxis (PrEP) regimens is contingent on high levels of adherence to daily dosing regimens. Urine provides a potential noninvasive specimen that could be amenable to the development of rapid point of care (POC) tests to detect ARV adherence to track and improve individual adherence. This study sought to determine if urine could provide an accurate biomarker of plasma drug exposure for currently approved PrEP and HIV treatment regimens.

Methods: Urine and peripheral blood were collected from 34 HIV-negative men who have sex with men aged 18-49 years enrolled in a clinical trial comparing pharmacokinetics of 2 ARV regimens. Specimens were collected 4 and 24 hours after a single oral dose of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) (n=10) or tenofovir alafenamide (TAF)/FTC/cobicistat (COBI)/elvitegravir (EVG) (n=9), or after 4 and 10 days of daily oral TDF/FTC (n=8) or TAF/FTC/COBI/EVG (n=7). Tenofovir (TFV), FTC, and EVG were measured by high performance liquid chromatography-mass spectrometry with a lower limit of quantification of 10 ng/mL and specific gravity was evaluated by urine dipstick analysis.

Results: Median urine FTC concentrations at 4 and 24 hours were similar between men receiving TDF/FTC (4 hours 147 µg/mL; 24 hours 10 µg/mL) and men receiving TAF/FTC/COBI/EVG (4 hours 333 µg/mL, p=0.173; 24 hours 13 µg/mL, p=0.681). However, median urine TFV concentrations were significantly reduced among men receiving TDF/FTC/COBI/EVG (4 hours 1.2 µg/mL; 24 hours 0.8 µg/mL) compared to men receiving TDF/FTC (4 hours 17 µg/mL, p<0.001; 24 hours 7 µg/mL, p=0.001). Urine FTC, but not TFV or EVG, concentrations suggested recent dosing among all men receiving daily dosing as values were greater than minimum concentrations observed 24 hours following a single dose. Urine FTC concentrations, but not TFV or EVG, were correlated with plasma concentrations for all study participants at all visits (r=0.766, p<0.001). Urine FTC (p=0.022) and TFV (p=0.039) concentrations were associated with specific gravity measures.

Conclusion: Urine FTC levels, but not TFV or EVG, may provide a good surrogate for plasma FTC concentrations and could be useful in developing POC tests to assess adherence. These results suggest urine may provide an appropriate noninvasive specimen type for measuring adherence to FTC-containing regimens used in HIV treatment and prevention.

466 POLYPHARMACY, INAPPROPRIATE DRUGS, AND DRUG-DRUG INTERACTIONS IN HIV-INFECTED ELDERLY

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Background: Antiretroviral therapy has transformed HIV infection from a deadly disease into a chronic condition. HIV-infected individuals live longer, experience age-related physiological changes and comorbidities and are thus predisposed to the risk of polypharmacy, drug–drug interactions (DDIs) and inappropriate medication use which may harm this vulnerable population. This study compared the prevalence of these issues in young and elderly person living with HIV (PLWH).

Methods: Individuals enrolled in 2 centres from the Swiss HIV Cohort Study were contacted before their bi-annual follow-up visit to fill in a form with all their current medications. Drugs were grouped according to the ATC classification. The medications use, polypharmacy (defined as being on > 5 non-HIV drugs) and potential DDIs (PDDIs) were compared in patients < 65 and ≥ 65 years old (elderly). Inappropriate medications included anticholinergic drugs (anticholinergic risk scale > 3) and benzodiazepines, as these drugs have been associated to an increased risk of falls, impaired cognition, loss of independence and hospitalization in the elderly. PDDIs for the most prescribed therapeutic classes (i.e. cardiovascular and central nervous system (CNS) drugs) were screened using the Liverpool drug interaction database.

Results: A total of 906 PLWH were included: 794 were < 65 (median 49, IQR 40-55) and 112 ≥ 65 (71, 67-73) years old. 47% of PLWH received an integrase inhibitor based regimen and this proportion did not differ between the 2 groups. Elderly had a higher number of comedinations (median 4, IQR 2–6) than younger PLWH (1, 0–3). Polypharmacy was more frequent in elderly compared to the younger group: 44% vs 12%. Type of medications and PDDIs differed according to the age group: cardiovascular drugs use and PDDIs (amber, red) with this drug class were more common in elderly (21% of overall prescribed drugs; 14% of cardiovascular drugs involved in PDDIs) whilst CNS drugs were more prescribed and mainly involved in PDDIs in younger PLWH (12%, 12%) (figure 1). Inappropriate medications were found in 13% of elderly, mostly benzodiazepines.

Conclusion: PDDIs remain common in the era of integrase inhibitors and inappropriate prescribing practices constitute an additional burden in elderly. Research efforts must be pursued to improve the care of PLWH, particularly elderly. Clinicians should maintain a proactive approach for the recognition and management of DDIs or prescribing issues traditionally encountered in geriatric medicine.

467 DRUG INTERACTION MAGNITUDES IN YOUNG VS ELDERLY: EXAMPLE OF RIVAROXABAN–DARUNAVIR/R

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Background: Aging of the HIV population complicates patient care due to a higher prevalence of comorbidities and related use of comediations leading to
an elevated risk for drug-drug interactions (DDIs). However, our understanding of how age impacts the magnitude and subsequently the management of DDIs in elderly is limited. This study aimed to simulate the DDI magnitude between boosted darunavir (DRV/ri) and ruxolitinib in young and elderly subjects using a physiologically based pharmacokinetic (PBPK) model. Ruxolitinib is a narrow therapeutic index drug characterized by a complex metabolism; thus, its DDI with boosted HIV regimens has not yet been fully elucidated.

**Methods:** A whole-body PBPK model was built in Matlab™ including age-dependent physiological changes for the simulation of elderly subjects. The DRV/ri drug model was successfully verified against observed clinical data in young volunteers. The predictive performance of our ruxolitinib model was checked against observed clinical data in a) young, b) elderly, and c) young individuals treated with ritonavir (600 mg BID at steady state) and ruxolitinib. The verified drug models were used to assess the effect of age on the DDI magnitude between DRV/ri (800/100 mg QD at steady state) and ruxolitinib (10 mg single dose) in 100 virtual subjects considering 5 age groups: a) 20-49, b) 50-64, c) 65-74, d) 75-84, and e) 85-94 years.

**Results:** The developed PBPK model predicted the pharmacokinetics of ruxolitinib in young and elderly currently. Predicted versus observed mean ruxolitinib AUC were 1148 and 1000 ng*h/mL for young and 1491 and 1839 ng*h/mL for elderly volunteers. The simulated versus observed ruxolitinib AUC in the presence of ritonavir was 2655 ng*h/mL and 2529 ng*h/mL with a resulting AUC ratio (ruxolitinib with/without ritonavir) of 2.31 and 2.53, respectively. Age did not impact the DDI magnitude between ruxolitinib and DRV/ri (Table 1), because all drugs are similarly affected by age-dependent physiological changes. Of interest, virtual individuals aged 50-64 years commonly defined as "elderly" in HIV medicine, showed only a 12% increase in the AUC compared to younger subjects suggesting that this age cut-off is too low for pharmacological studies.

**Conclusion:** PBPK modeling is a useful tool to overcome limited clinical data. Our predictions showed an age-dependent increase in the AUC of ruxolitinib in the absence and presence of DRV/ri, but no changes in the DDI magnitude with age suggesting a similar management of this DDI in the elderly.

**Table 1:** Predictions of DDI magnitudes between DRV/ri and ruxolitinib. a = age group and r = reference group (20-29 years)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>AUC [ng*h/mL] (ruxolitinib alone)</th>
<th>AUC [ng*h/mL] (ruxolitinib + DRV/ri)</th>
<th>AUC ratio (geometric / ratio ari</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 49</td>
<td>1555</td>
<td>2341</td>
<td>2.22</td>
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<tr>
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<td>85 – 94</td>
<td>1481</td>
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**469 INTRACELLULAR SOFOSBUVIR (SOF) CONCENTRATIONS IN PERSONS WITH HCV AND COCAINE USE**

Kristina M. Brooks, Jose R. Castillo-Mancilla, Mary Morrow, Samantha Malwhinney, Ryan T. Huntley, Joshua Blum, David L. Wyles, Lane R. Bushman, Peter L. Anderson, Jennifer J. Kiser

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**Background:** There are limited data on the effects of drug use on direct acting antiviral (DAA) pharmacokinetics (PK). Certain drugs, such as cocaine, may affect DAA PK through enzyme or transporter modulation or immune activation. We examined the influence of cocaine on GS-331007 triphosphate (007-TP; also known as GS-461203) concentrations, the active anabolite of SOF, in PBMCs and dried blood spots (DBS) in persons who use drugs receiving ledipasvir (LDV)/SOF for HIV treatment.

**Methods:** Persons with HIV/HCV or HCV mono-infection and self-reported drug use within 30 days of screening were eligible for the study. Adherence to LDV/SOF was monitored through directly (video-based) or wirelessly (Wisepill™) observed therapy. A self-reported (SR) drug use questionnaire documenting yes/no use of cocaine, a urine toxicology screen (UTox), and convenience PK samples were collected bi-weekly over 12 weeks of LDV/SOF. 007-TP concentrations in PBMCs and DBS were quantified using LC-MS/MS. A mixed-effects model was used to analyze the influence of average adherence over the previous 2 weeks (adherence was a significant predictor of 007-TP concentrations in PBMCs and DBS, quantified using log-transformed 007-TP concentrations in PBMCs and DBS). Cocaine use was examined by SR, UTox, and both combined.

**Results:** Samples and questionnaires were available from 46 participants (43 HIV/HCV, 3 HCV only; 235 person-visits). Fifteen participants (33%) used cocaine by SR or UTox at 39 person-visits. Median (IQR) adh2wk in cocaine users was 86% (64%, 100%) vs. 100% (91%, 100%) in non-users. Adh2wk was a significant predictor of 007-TP concentrations in PBMCs and DBS (p<0.0001 for both). After controlling for adherence, overall cocaine use was associated with 43% lower 007-TP concentrations in PBMCs (95% CI -60%, -19%); p=0.0017. SR showed a trend towards 25% lower 007-TP in PBMCs (95% CI -47%, 7%); p=0.11 and UTox-positive revealed 46% lower 007-TP BMC concentrations (95% CI -63%, -23%); p=0.0009. 007-TP in DBS did not significantly differ by cocaine use (p>0.3).
Conclusion: Intracellular 007-TP concentrations in PBMCs, but not DBS, were lower in cocaine users. This difference was stronger by Utox, suggesting a temporal or frequency effect of cocaine use on 007-TP in PBMCs. Differences in findings between cell types may be due to differences in cell-specific expression of DAA-converting enzymes or transporters, or immune activation of PBMCs by cocaine. Further research is needed to elucidate a possible mechanism consistent with this interaction and whether these differences impact SVR.

Conclusion: A PBPK model of CAB was developed and validated that accurately predicted human pharmacokinetics observed in healthy volunteers. OAT1/OAT3 substrate drugs such as tenofovir, cidofovir, methotrexate were predicted to have a minimal risk of DDIs when administered with CAB. Similar CAB concentrations following oral and LA administration suggest that these results would apply to CAB LA. The predicted lack of interactions supports co-administration with OAT1/OAT3 substrates without dose adjustments.

471 INFLUENCE OF UGT1A*28 ON RALTEGRAVIR PK/PD IN THE NEAT001/ANRS143 STUDY

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Background: Raltegravir (RAL) is metabolised by UGT1A1 and polymorphisms in the UGT1A1 gene have been associated with plasma concentrations in some but not all previous studies. This analysis represents the largest study to date for the effect of UGT1A1 polymorphisms on RAL PK/PD.

Methods: NEAT001/ANRS143, a randomised study (n=805 participants), demonstrated non-inferiority of first-line darunavir/ritonavir (DRV/r; 800/100 mg o.d) plus RAL (400 mg b.d) compared with DRV/r plus tenofovir/emtricitabine (245/200 mg o.d). Random, single samples were collected at weeks 4 and 24 post-therapy initiation for drug measurement. DNA was extracted and UGT1A1 polymorphisms genotyped using the Sequenom MassARRAY iPLEX. Nonlinear mixed effects modelling (NONMEM v. 7.3) was used to estimate PK parameters. Weight, age, sex, ethnicity and genotypes were investigated in the model for association with RAL apparent oral clearance (CL/F). Kaplan–Meier estimates and Cox regression were used to assess the relationship between virological failure by week 96 and UGT1A1 genotypes.

Results: A total of 602 samples (n=313 week 4, n=289 week 24) from 349 patients were used in the model (n=264 with genotypes). UGT1A1 activity was defined as normal (*1/*1, *1/*36), reduced (*1/*6, *1/*28, *1/*37, *28/*36, *36/*37) or low (*28/*28, *28/*37, *37/*37). Although none of the covariates were statistically significant, RAL CL/F was reduced by 21% in patients with *28/*28 UGT1A1. A post-hoc analysis assessed the impact of UGT1A1*28 on predicted RAL AUC0-12 and C12 low activity (n=40) vs normal/reduced activity (n=224). Geometric mean ratios (95% CI) were 1.35 (0.99-1.84; p=0.062) and 1.32 (0.99-1.77; p=0.062), respectively, suggesting minimal impact of UGT1A1*28 on RAL PK. By week 96, virological failure was seen in 16%, 22% and 2.5% of patients with normal, reduced and low UGT1A1 activity, respectively. Failure rates were lower in patients with low activity UGT1A1 (p=0.012; Figure). The relationship remained significant when adjusted for baseline CD4 count (p=0.048) but not when adjusted for baseline VL (p=0.082) or both CD4 and VL (HR [95% CI]: 0.18 (0.02-1.30); p=0.08).
Conclusion: The NEAT001/ANRS143 study analysed UGT1A1 genotypes with the largest sample size to date and suggested little impact on RAL PK. However, UGT1A1 genotype may be a better correlate of RAL pharmacodynamics because of the high intra-subject variability in RAL PK.

**472 PHARMACOGENETICS OF WEIGHT GAIN AFTER SWITCH FROM EFAVIRENZ TO INTEGRASE INHIBITORS**


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**Background:** Weight gain has been reported in virologically suppressed HIV-positive patients who switch to integrase inhibitor (INI)-based antiretroviral therapy (ART). We studied pharmacogenetics of weight gain following switch from efavirenz (EFV)- to INI-based ART.

**Methods:** Patients at an HIV clinic in the southeastern USA were on EFV-based ART for at least 2 years and with no viral load >1000 copies/mL within 6 months prior to switch. Weight gain from date of switch to weeks 24 and/or 48 (± 4 weeks) was assessed. We genotyped CYP2B6 and UGT1A1 polymorphisms that predict increased plasma EFV and INI exposure, respectively. Associations were tested with linear regression models.

**Results:** The 101 evaluable participants (n=83 for week 24, n=66 for week 48) included 65 (64%) white, 27 (27%) black, 84 (83%) male, and 17 (17%) female participants. INIs were 58 (57%) dolutegravir, 34 (34%) elvitegravir, and 9 (9%) raltegravir. Median baseline weight was 81.7 kg (interquartile range: 69.7, 94.7). There were 30 (30%), 54 (55%), and 15 (15%) CYP2B6 normal, intermediate, and slow metabolizers, respectively, and 38 (40%), 41 (43%), and 16 (17%) UGT1A1 normal, intermediate, and slow metabolizers, respectively. CYP2B6 slow metabolizer genotype was associated with weight gain at week 48 (B=7.2, p=0.009). In CYP2B6 normal, intermediate, and slow metabolizers, at week 48, average weight gain was 0.2 kg, 2.8 kg, and 2.0 kg, respectively. After controlling for sex, age, and weight at switch, associations persisted at week 48 (B=6.97, p=0.012). CYP2B6 genotype was associated with weight gain in whites at week 48 (B=11.25, p=0.003), but not in blacks (B=0.58, p=0.090) (Figure). The above significant associations also tended to be present at week 24 (p=0.05 to p=0.09). UGT1A1 genotype was not associated with weight change at week 24 (B=-0.33, p=0.83) or week 48 (B=0.70, p=0.77).

**Conclusion:** Among virologically suppressed patients who switch from EFV-based ART to INI-based ART, CYP2B6 genotype that is known to predict higher EFV plasma exposure pre-switch may be associated with greater weight gain after switch. These findings warrant replication in other cohorts. We hypothesize that patients with greater plasma EFV concentrations before switch may have sub-clinical intolerance. These patients may therefore gain more weight after switch from EFV-based ART to INI-based ART.

**473 HORMONAL CONTRACEPTIVES DO NOT ALTER CABOTEGRAVIR PK IN HIV-UNINFECTED WOMEN HPTN 077**

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**Background:** Long-acting Injectable Cabotegravir (CAB LA) is a novel strand-transfer integrase inhibitor, currently in development for HIV prevention and treatment. Unexpected drug-drug interactions (DDI) between ARVs and hormones for contraception or cross-sex therapy have been noted for other ARVs, ranging from 13% to 38% reduction in tenofovir exposure (AUC) in the setting of estrogen with or without anti-androgen use. Understanding such DDIs is critical to acceptability and scale up of novel treatment and prevention paradigms.

**Methods:** We performed a secondary analysis of cisgender women who were enrolled in HPTN 077, a Phase 2a multicenter study that enrolled HIV-uninfected, low risk individuals in Malawi, Brazil, South Africa, and the US. Participants received 4 week oral CAB lead-in, followed by CAB LA 800mg Q12w IM (Cohort 1) or 600mg Q8w IM (after a 4 week initial interval between injections; Cohort 2) over 41 weeks. Participants were followed 52-76 weeks subsequent to their final injection. Linear regression was used to evaluate differences in pharmacokinetic (PK) parameters (peak concentration [Cmax], trough [Ct], exposure after the last injection [AUC-t], and apparent terminal half-life after the last injection [T1/2app]) between hormonal contraception (use vs not) and contraception type (oral, injectable, vaginal ring, implants, other) controlling for body mass index (BMI) and CAB dose cohort.

**Results:** 85 cisgender females enrolled in HPTN 077 and received at least 1 dose of active CAB LA. In this study population, BMI associated with 1% reduction (per unit increase in BMI) in Cmax, Ct, and AUC-τ and 2% increase in T1/2app. Median BMI was 22.7 in Cohort 1 and 25.7 in Cohort 2. Use of any type of hormonal contraception, individually or in aggregate, did not result in statistically significant changes in Cmax, Ct, and AUC-τ. The difference in T1/2app (Table, all p >0.05, CAB-AUC-τ not shown). No pregnancies occurred among those receiving active CAB LA during the study period. We did not assess the impact of CAB on estrogen concentrations.

**Conclusion:** Among HIV-uninfected females in HPTN 077, use of hormonal contraception did not alter the CAB concentration profile during injections or during the pharmacokinetic tail. While there is no anticipation of an effect of CAB on estrogen concentration, the effects of CAB LA on hormonal treatment for both contraception and gender-affirming treatment warrant evaluation.
474 BICTEGRAVIR CONCENTRATIONS AND VIRAL SUPPRESSION IN CSF HIV-INFECTED PATIENTS

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Background: Bictegravir (BIC) is a novel, potent, once-daily, unboosted inhibitor of HIV-1 integrase specifically targets IN strand transfer activity. BIC differs from previously known structures in that it contains a unique bridged bicyclic ring and a distinct benzyl tail consisting of a tri substituted 2,4,6-trifluorobenzyl moiety. These changes resulted in increased plasma protein binding to improve its solubility. These two physicochemical characteristics are crucial determinants of drug penetration. The aim of our study was to determine BIC levels in cerebrospinal fluid (CSF) as well as HIV viral load in this compartment.

Methods: This is a single-arm, open-label, single-center study. After an initial assessment, 15 patients switched from stable ART to FTC/TAF/BIC (Biktarvy®). At week 4, plasma and CSF concentrations of BIC were measured 24 hs post-dose, using a validated LC-MS methodology (assay calibration range is 10-10,000 ng/mL for plasma and 1-100 ng/mL for CSF). HIV RNA was measured in plasma and CSF by RT-PCR (LLQ: 40 copies/mL).

Results: A total of 15 plasma an 15 CSF samples were collected. At baseline, median CD4 count was 776 cells/μL (613 – 905). Most patients switched from Genvoya® and Triumeq® (57,2%). One patient presented with unexpected low BIC concentrations in plasma and CSF while concomitantly taking self-prescribed magnesium supplements*. For HIV-1 RNA viral load, the 95% HDI of 0.95 (0.71,1.17) and 0.78 (0.50, 1.06) respectively. Across all tissues/species, only EFV and TFV concentrations were proportional to plasma. Largest slopes (log-log scale) were seen for EFV (HDI) includes 0). Across all tissues/species, only EFV and TFV concentrations were proportional to plasma. Largest slopes (log-log scale) were seen for EFV and TFV in NHP spleen with median values and lower and upper bounds of the 95% HDI of 0.95 (0.71,1.17) and 0.78 (0.50, 1.06) respectively.

Conclusion: NHP dosing strategies result in similar tissue concentrations to humans. For RAL and FTC, it is unlikely that increasing doses will increase tissue penetration substantially. For TFV and EFV, it may be possible to increase tissue penetration by adjusting doses. Changing tissue concentrations for other ARVs is dependent on drug/tissue type. These results add to current data on tissue concentration relationships.

475 WHICH PRECLINICAL SPECIES MIMICS TISSUE PENETRATION OF ARV DRUGS IN HUMANS?

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Background: For HIV cure strategies like “kick and kill” to succeed, antiretroviral (ARV) drugs must reach protective concentrations in putative viral reservoirs, including lymphoid tissue and sequestered sites like the brain and genital tract. Extrapolating outcomes of animal studies to humans requires understanding the specifics of ARV tissue distribution. Here, we characterize penetration of 6 ARVs in 2 humanized mouse models, nonhuman primates (NHPs), and HIV+ humans.

Methods: ARVs/doses were selected based on published strategies for animals and humans (Thompson, AIDS, 2017). 12 BLT humanized mice and 36 RAG-hu mice (female) were used. 17 macaques (5 female, 12 male) and 19 human subjects (3 women/16 men) were used. Animals were dosed for 10 days before necropsy. Human samples were obtained from the National NeuroAIDS Tissue Consortium harvested 8-47h post dose. These drugs were investigated: tenofovir (TFV), emtricitabine (FTC), raltegravir (RAL), maraviroc (MVC), efavirenz (EFV) and atazanavir (ATZ). 8 tissue types were snap frozen and stored at -80°C. ARV concentrations were assayed by LC-MS/MS (LLOQ: 0.002-0.01 ng/ml). A Bayesian measurement-error model was used to characterize plasma and tissue concentration relationships.

Results: Across species, variability in ARV concentrations was similar among plasma (CV 0.4-3.2) and tissues (CV 0.3 - 3.3). For a given plasma concentration, tissue concentrations were most similar among NHPs and humans. With few exceptions, tissue exposure from highest to lowest were: human > NHP > BLT > RAG-hu (Figure). For RAL and FTC, under most conditions, the relationship between plasma and tissue concentration was flat (95% highest density interval (HDI) includes 0). Across all tissues/species, only EFV and TFV concentrations were proportional to plasma. Largest slopes (log-log scale) were seen for EFV and TFV in NHP spleen with median values and upper and lower bounds of the 95% HDI of 0.95 (0.71,1.17) and 0.78 (0.50, 1.06) respectively.

Conclusion: NHP dosing strategies result in similar tissue concentrations to humans. For RAL and FTC, it is unlikely that increasing doses will increase tissue penetration substantially. For TFV and EFV, it may be possible to increase tissue penetration by adjusting doses. Changing tissue concentrations for other ARVs is dependent on drug/tissue type. These results add to current data on tissue penetration of ARVs and have implications on interpreting HIV treatment, prevention, or cure interventions between models.
preliminary data suggest that HIV may persist in the OM despite antiretroviral treatment. **Methods:** Patients with neurocognitive disorders were included in a diagnostic study and OM samples were obtained through nasal brushing. The analysis of ARVs concentrations in swabs was performed as follows on frozen swabs. They were weighed upon extraction and then inserted in PTFE tubes along with 40µl of internal standard (marked with stable isotopes) working solution plus 500 µl of water:methanol solution (30:70 v/v). These tubes were then vortex-mixed 10 sec, sonicated for 10 minutes at 4°C. The dry extracts were dissolved in 110 µl of water; acetoxetilnic acid (94.9:5.1 v:v) solution and 10 µl of acid phosphate (0.5 X) and incubated for 1 hour at 37°C, in order to convert phosphate metabolites of NRTIs to the free form. The resulting extracts were analyzed by using HPLC/MS-MS, obtaining absolute amounts (ng): these results were then normalized for the estimated weight of the extracted material (the difference between the initial weight and after the extraction process). The lower limit of quantification was 0.3 pg/mg sample, corresponding to a mean concentration of 3 pg/mg of OM swab. **Results:** 31 patients were included. They were mostly male (80.6%) and of European ancestry (96.8%); median age and BMI were 51 years (46-58) and 23.5 Kg/m2 (19.7-27.7). Median current and nadir CD4+ T-cells was 469 (205,720) and 260 (110,310) respectively. Serum samples were available from 24 participants (48 observations). Geometric mean (%CV) for TFV-mE and TFV AUC were 93.9 (46.8%) and 1986.0 (73.2) h*ng/mL. Visit 1 TFV-DP was 45.3 (48.2%) fmol/punch in DBS and 10.8 (42.4%) fmol/10^6 cells in PBMCs. Visit was a significant predictor of TFV-DP in DBS, but not PBMC, with 55.1% higher concentrations at visit 2 (95% CI 59.2%, 139.0%) p<0.0001 (Table), consistent with the ~17 day half-life for TFV-DP in DBS. TFV-mE AUC was a significant predictor of TFV-DP in both PBMC and DBS. For every 10 h*ng/mL increase in TFV-mE AUC, TFV-DP concentrations increased by 3.8% (95% CI 0.8%, 6.8%) p=0.015 in PBMCs and 4.3% (95% CI 1.5%, 7.2%) p=0.005 in DBS, the latter of which was controlled for study visit. Conversely, TFV AUC was not significantly associated with TFV-DP concentrations in PBMCs (p=0.11) or DBS (p>0.99). Randomization sequence, formulation, other clinical variables did not significantly influence TFV-DP in either cell type.

**Conclusion:** Plasma TFV-mE AUC was a significant predictor of intracellular TFV-DP concentrations in PBMC and DBS, whereas plasma TFV AUC was not. TFV-mE contributes to cell loading in vivo, influencing TFV-DP concentrations in PBMC and DBS.

**478 DEPO-MEDROXYPROGESTERONE EFFECTS ON TENOFOVIR-DP AND LAMIVUDINE-TP IN CERVICAL TISSUE**

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**Background:** Effective concentrations of antiretrovirals in the female genital tract (FGT) are critical for suppression of viral shedding, or, in the case of pre-exposure prophylaxis, HIV prevention. The disposition of tenofovir diphasphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) in the FGT have been previously described. However, despite widespread lamivudine use, lamivudine triphosphate (3TC-TP) exposure in FGT is unknown. Furthermore, to facilitate development of multipurpose prevention for contraception and HIV, a better understanding of exogenous hormone effect on FGT antiretroviral exposure is needed.

**Methods:** HIV-positive, virologically suppressed, non-pregnant women, receiving combination TDF/3TC as part of antiretroviral therapy, were recruited in Kampala, Uganda. Women receiving depot-medroxyprogesterone (DMPA) group or using non-hormonal contraception (non-HC) group participated in a single visit study. Cervical biopsies were obtained for quantification of TFV-DP, FTC-TP, and endogenous dATP and dCTP using liquid chromatography with tandem mass spectrometry. Blood plasma was collected to assess medication adherence. Differences between groups were tested using multiple linear regression on log-transformed data and adjusted for age, weight, and plasma drug concentrations (for tissue) or time since last dose (for plasma).

**Results:** Fifty women aged 21-34 years were enrolled between Nov 2017 and March 2018. One subject in the DMPA group and two in the non-HC group were excluded from antiretroviral quantification as plasma concentrations were a 14-day washout. Blood for PK assessments were collected serially through 72 hours post-dose, and PBMC and DBC were isolated at 24 hours post-dose at both visits. TFV-mE and TFV were quantified via LC/MS-MS. Area under the concentration-time curve extrapolated to infinity (AUC) of plasma TFV-mE and TFV were calculated via noncompartmental methods (Phoenix WinNonlin v8.0). A mixed-effects model was used to examine TFV-mE AUC, TFV AUC, visit, randomization sequence, formulation, sex, BMI, and eGFR as fixed effects and subjects as random effects, with TFV-DP in DBS or PBMC as primary outcomes (SAS Enterprise v9.4).

**Results:** Samples were available from 24 participants (48 observations). Geometric mean (%CV) for TFV-mE and TFV AUC were 93.9 (46.8%) and 1986.0 (26.9%) h*ng/mL. Visit 1 TFV-DP was 45.3 (48.2%) fmol/punch in DBS and 10.8 (42.4%) fmol/10^6 cells in PBMCs. Visit was a significant predictor of TFV-DP in DBS, but not PBMC, with 55.1% higher concentrations at visit 2 (95% CI 59.2%, 139.0%) p<0.0001 (Table), consistent with the ~17 day half-life for TFV-DP in DBS. TFV-mE AUC was a significant predictor of TFV-DP in both PBMC and DBS. For every 10 h*ng/mL increase in TFV-mE AUC, TFV-DP concentrations increased by 3.8% (95% CI 0.8%, 6.8%) p=0.015 in PBMCs and 4.3% (95% CI 1.5%, 7.2%) p=0.005 in DBS, the latter of which was controlled for study visit. Conversely, TFV AUC was not significantly associated with TFV-DP concentrations in PBMCs (p=0.11) or DBS (p>0.99). Randomization sequence, formulation, other clinical variables did not significantly influence TFV-DP in either cell type.

**Conclusion:** Plasma TFV-mE AUC was a significant predictor of intracellular TFV-DP concentrations in PBMC and DBS, whereas plasma TFV AUC was not. TFV-mE contributes to cell loading in vivo, influencing TFV-DP concentrations in PBMC and DBS.
indicative of non-adherence. One additional biopsy in DMPA group was excluded due to sample processing error. Unadjusted medians (25th, 75th percentile) are reported in attached table. Concentrations of 3TC-TP were significantly higher than TFV-DP in cervical tissues with a geometric mean ratio of 17.3. Cervical TFV-DP was 64% higher in DMPA users compared to non-HC users (p=0.02). No differences were found between groups for TFV or 3TC in plasma, or in 3TC-TP, dATP, dCTP in cervical tissues.

Conclusion: These data provide the first information on drug exposure of 3TC-TP in the FGT following oral dosing. Similar to reports of FTC-TP, 3TC-TP was significantly higher than TFV-DP in cervical tissue, suggesting it may be an option for prophylaxis. TFV-DP was significantly higher in DMPA users compared to women using non-hormonal contraception, suggesting prevention efficacy is unlikely to be compromised by injectable progestin contraceptive use.

A QUANTITATIVE APPROACH TO EVALUATE ARV PROXIMITY TO VIRUS AND CELLS IN LYMPH NODES

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Background: We have previously shown that ARV distribution within lymphoid tissue can be highly heterogeneous. Understanding potential consequences of diverse ARV accumulation requires quantitative methods to characterize ARV proximity to virus and target cells. Here, we developed a novel analytical approach based on a combination of mass spectrometry imaging (MSI), in situ hybridization (ISH) and immunohistochemistry (IHC) to understand the consequences of ARV distribution in lymph nodes (LN).

Methods: Axillary LN were collected and snap frozen at necropsy from RT-SHIV infected rhesus macaques dosed 10 days with emtricitabine (FTC) + tenofovir (TFV) (N=6) in combination with either efavirenz (EFV) + raltegravir (RAL) (N=3), cohort FTER, or maraviroc (MVC) + atazanavir (ATZ) (N=3), cohort FTMA. Tissue accumulation of ARVs and metabolites was measured by infrared matrix-assisted laser desorption electrospray ionization (MALDI) MSI from 10 mm thick cryosections at 0.1 mm spatial resolution. Serial sections of tissue were analyzed for viral RNA (vRNA) by RNAscope ISH and for CD4+ cells by IHC. Spatial relationships were evaluated by nearest neighbor search (NNS) on co-registered images using MATLAB.

Results: MSI simultaneously measured all detectable ARVs (FTC, RAL < limits of detection: 0.05-0.37 ng/mg tissue) and the blood biomarker, HEME. Based on NNS analysis between ARVs and HEME (reflecting ARV in the vasculature), 57% of all ARVs in LN were <0.1 mm from HEME. The greatest tissue penetration was found for TFV and EFV (up to 1.7 mm from HEME). The degree of colocalization between ARVs and vRNA varied (Fig B. TFV: 1-9%; ATZ: 4-16%; MVC: 54-68%; EFV: 89-99%). Yet NNS analysis indicated that >95% of all vRNA was <0.1 mm of a detectable ARV response in each cohort (Fig C). However, proximity of vRNA to ARV concentrations in vitro IC50 values was farther (vRNA<0.3 mm: FTER=0-60%; FTMA=88-97%). Similar results were observed for NNS analysis of CD4+ T cells (Fig D. CD4<0.3 mm: FTER=0-94%; FTMA=96-99%).

Conclusion: A quantitative approach has been developed for analysis of spatial relationships between drug and targets such as virus, blood, and T cells. ARV coverage extends to >73% of the LN, better for CD4 (>64%) than vRNA (>58%), but may not be adequate everywhere relative to known inhibitory concentrations. The flexibility of this framework allows ARVs to be evaluated individually or in aggregate, and offers a tool help optimize pharmacokinetics and pharmacodynamics to ARV treatment.

![Image](https://via.placeholder.com/150)

479 GS-6207 is a potent and selective first-in-class long-acting HIV-1 capsid inhibitor

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Background: We describe the in vitro pharmacological profile of GS-6207, a first-in-class HIV capsid (CA) inhibitor optimized for long-acting antiretroviral (ARV) treatment administered monthly or less frequently.

Methods: GS-6207 binding to HIV-1 CA hexamer was evaluated by surface plasmon resonance and x-ray crystallography. Antiviral potency and cytotoxicity were assessed in human T-cell lines and primary cells. HIV-1 and -2 laboratory strains and clinical isolates as well as HIV-1 recombinant mutants resistant to other ARV drug classes were used for antiviral profiling. Effect of the multiplicity of infection (MOI) on antiviral potency was tested using a reporter HIV-1. Cytotoxicity was profiled in 4 non-target human cell lines and primary hepatocytes. GS-6207 activity was evaluated in combination with marketed classes of ARVs.

Results: GS-6207 binds with high affinity to CA hexamer (Kd = 0.2 nM) at the interface between two adjacent CA monomers. GS-6207 displays potent and selective antiviral activity in MT-4 cells (EC50 = 0.1 nM, CC50 = 27 µM) and exhibits a mean EC50 of 0.05 nM (0.02 - 0.16 nM) in human PBMCs against 23 HIV-1 clinical isolates spanning all major subtypes. The human serum protein-adjusted EC50 for GS-6207 (4 nM) is >10-fold lower than that of efavirenz (EFV), rilpivirine, dolutegravir (DTG) and atazanavir (ATZ). In primary human CD4+ T-cells and macrophages, GS-6207 is >10-fold more potent and >22-fold more selective than EFV, DTG and ATZ. GS-6207 also suppresses HIV-2 replication. As with other ARVs, GS-6207 antiviral activity decreases with increasing MOI but remains >5- to >100-fold more potent than 4 commonly used ARVs. GS-6207 exhibits low cytotoxicity in 4 human cell lines and primary hepatocytes (CC50 > 44 µM) and shows synergistic antiviral activity when combined pairwise with agents from each of 4 marketed ARV classes. Finally, GS-6207 retains full potency against a broad range of HIV-1 mutants resistant to other ARV classes, including those with naturally occurring Gag polymorphisms conferring resistance to maturation inhibitors.

Conclusion: GS-6207 is a novel HIV capsid inhibitor with picomolar potency and a unique resistance and pharmacokinetic (PK) profile that make it a suitable...
candidate for a low-dose long-acting subcutaneous administration to treat HIV-1 infection, including variants resistant to current ARV therapies. The safety and PK of GS-6207 is now being evaluated in healthy human subjects.

481 MK-8591 POTENCY AND PK PROVIDE HIGH INHIBITORY QUOTIENTS AT LOW DOSES QD AND QW
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1 Merck & Co, Inc, West Point, PA, USA, 2 Merck & Co, Inc, Upper Gwynedd, PA, USA

Methods: MK-8591-TP, TFV-DP, 3TC-TP, and FTC-TP IC50 levels were determined in activated, uninfected human peripheral blood mononuclear cells (PBMCs) after 24 hr incubation with varying concentrations of MK-8591, TDF, 3TC, or FTC followed by lysis and analysis by LC-MS/MS. MK-8591 IC50 for wild-type (wt) HIV-1 were calculated as the ratio of steady state Ctrough,IC50 as observed with qd followed by lysis and analysis by LC-MS/MS. MK-8591 IC50s for wt and NRTI-resistant HIV-1 were calculated to assess the likelihood of virologic response and barrier to resistance at clinically relevant doses.

Conclusion: The MK-8591-TP IC50 for wt HIV-1 is >4-fold lower than any marketed NRTI. MK-8591 IC50s at steady state with 0.25 mg qd and 10 mg qw dosing are 85.3 and 101, respectively, and proportionately greater for higher dose levels. Common NRTI mutations, including M184V/I, thymidine analog mutations, K65R, and K70E, confer low fold-shifts in antiviral potency, and MK-8591 retains greater IC50s against these NRTI-resistant viruses than those of TDF, TFV, and FTC with wt virus.

483 LONG TERM SAFETY & EFFICACY OF FOSTEMSAVIR IN TREATMENT-EXPERIENCED HIV PARTICIPANTS
Melanie Thompson1, Fernando Mendo Urbina2, Gulam Latiff3, Sandra Trevino Perez2, Edwin DeJesus, Natalia Zakharova, Marcelo Martins, Johannes Bogner, Li Y1, Amy Pierce2, Shiven Chabria1, Peter Ackerman1, Cyril Llamoso1, Max Latailade1, for the 205889 Investigative Study Team
1 AIDS Research Consortium of Atlanta, Atlanta, GA, USA, 2 Hospital Nacional Elogando Rebagliati Martins, Lima, Peru, 3 King-Zulu-Natal Research Institute for TB and HIV, Durban, South Africa, 4 Mexico Centre for Clinical Research, Mexico City, Mexico, 5 Orlando Clinical Research Center, Orlando, FL, USA, 6 Center of AIDS and Infectious Diseases Prevention and Treatment, St Petersburg, Russian Federation, 7 Instituto Oulton, Cordoba, Argentina, 8 University of Munich, Munich, Germany, 9 Gloansmichelline, Gallegiene, PA, USA, 10 HIV Healthcare, Research Triangle Park, NC, USA, 11 WV HealthCare, Bradenton, FL, USA

Conclusion: Our study confirms that FTR 800 mg BID is well tolerated, shows long-term virologic and immunologic efficacy, and is acceptable and well tolerated in treatment-experienced HIV patients.

482 FAVOURABLE OUTCOME OF IN VITRO SELECTIONS WITH NOVEL NRTI PRODRUG GS-9131
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1 Lady Davis Institute for Medical Research, Montreal, QC, Canada, 2 McGill University, Montreal, QC, Canada

Results: After 40 weeks of sustained drug treatment, none of the CBMC viral virucidal tests yielded major resistance mutations. Despite the lack of changes in the RT region, most of the isolates were able to endure moderate to very high concentrations of the drugs, 300-20,000-fold increase for GS-9131 and 100-20,000-fold for TDF. Using 3TC as a control, the M184V or Y mutations rapidly arose in most viruses. Previous studies with GS-9148, for which GS-9131 is a prodrug, were done in MT-2 cells, and some resistance patterns were identified. In our experience using MT-2 cells, no major resistance pathways emerged.

Conclusion: These data suggest that the L187M mutation, which was also identified in the previous study.
(5%), and for REF were nausea, dizziness (8% each), and AEs related to bilirubin elevation (e.g., jaundice, scleral icterus; 8-18%).

**Conclusion:** Among HIV-1-infected TE participants, FTR with RAL+TDF demonstrated favorable safety compared to ATV/r with RAL+TDF with lower cumulative rates of Grade 2-4 related AEs, Grade 3-4 AEs, and AEs leading to discontinuation despite longer median exposure (4.5 vs. 2.9 years). FTR had comparable rates of virologic suppression to ATV/r throughout 192 weeks. These results support the ongoing Phase 3 evaluation of FTR in heavily TE adults with limited therapeutic options (<2 classes of ARVs remaining) due to resistance, tolerability issues or contraindications (NCT02362503).

**4.85** IBALIZUMAB: 96-WEEK DATA AND EFFICACY IN PATIENTS RESISTANT TO COMMON ANTIRETROVIRALS

**Brinda Emu**1, Jay Lalezari2, Princy Kumar3, Steven Weinheimer4, Stanley Lewis5, Brandon Cash6, Zvi Cohen7

1Yale University, New Haven, CT, USA, 2Quest Clinical Research, San Francisco, CA, USA, 3Georgetown University, Washington, DC, USA, 4Immunetics Biologics USA, Irvine, CA, USA, 5Synexus Health, Somerset, NJ, USA, 6Theratechnologies, Inc, Montrose, QC, Canada

**Background:** Ibalizumab (IBA) is a CD4-directed post-attachment HIV-1 inhibitor that binds to the CD4 domain 2 and blocks viral entry into host cells without immunosuppression. Here, we report the efficacy outcomes of IBA with OBR in patients resistant and susceptible to two widely used antiretrovirals (ARV), dolutegravir (DTG) and darunavir (DRV) as well as the the long-term safety and efficacy through 96 weeks of treatment.

**Methods:** In TMB-301, heavily treatment-experienced patients with MDR HIV-1 received an intravenous loading dose of 2000 mg followed by 800 mg doses every 2 weeks up to Week 25. An OBR with at least 1 additional sensitive agent was added 7 days after the loading dose. Following completion of the TMB-301 study, eligible patients continued to receive IBA at 800 mg every 2 weeks under TMB-311 for up to 96 weeks.

**Results:** Among the 40 enrolled patients in TMB-301, 18 (45%) had DTG resistance, of which 11 had major DTG resistance mutations (Q148 plus additional mutations). Of 18 DTG resistant patients, 10 received DTG in their OBR while 16 of 22 DTG susceptible patients received DTG as OBR. Twenty-seven patients (68%) had DRV resistance. DRV was included as OBR in 26 patients: 18 with DRV resistant HIV and 8 with DRV susceptible HIV. Long-term results were obtained for 27 patients who continued to receive treatment in study TMB-311, of which 22 (82%) completed treatment up to 96 weeks. The reasons for discontinuations were death (2 patients), consent withdrawal (2 patients) and physician decision – all 5 were non IBA-related. IBA plus OBR was well tolerated with no new safety concerns emerging between Week 25 and 96. For these 27 patients, median viral load (VL) reduction from Baseline (of TMB-301) was 2.5 log10 at Week 25 and 2.8 log10 at Week 96 in the Intent-to-Treat-Missing-Equals-Failure analysis. Of 16 patients with HIV RNA <50 copies/mL at Week 25, 14 maintained viral suppression through Week 96, with one additional patient achieving viral suppression by Week 96. Median CD4+ T cell increase was 42 cells/µl from Baseline to Week 25 (n=27), and 45 cells/µl at Week 96 among those who remained on study (n=22).

**Conclusion:** Safety and efficacy of IBA observed at Week 25 in the Phase 3 trial were maintained through 96 weeks for patients continuing on treatment. IBA is an effective, safe and durable treatment for MDR HIV-1 infected patients.
SC in a 1:1 ratio as randomized controlled, two-arm study. In an ongoing part 3, 47 participants are to be randomized to receive 525 or 700 mg PRO 140 SC in a 1:1 ratio.

**Results:** Of the 327 patients enrolled, median age was 51 yrs (21-77) with the majority reported as male (79%) and 37% were non-white. On average, participants were diagnosed with HIV-1 infection for 16.8 yrs and were on cART regimen for 14.8 yrs. This abstract focuses on preliminary results from patients randomized 1:1 to 350 mg (N=73) or 525 mg (N=74) PRO 140 SC on SAMT. While the study is ongoing, a key interim finding from 147 patients (4-48 weeks on SAMT) indicate that an odds ratio of 4.43 for the virologic response rates with 525 mg compared with 350 mg PRO 140 SC. Virologic failure is defined as two consecutive plasma HIV-1 RNA levels of ≥ 200 c/ml. The frequency and severity of injection site reactions were comparable between the three dose groups and the incidence or severity of injection site reactions was not increased in patients receiving higher doses. Overall, PRO 140 SC was generally well tolerated at all dose levels in this study.

**Conclusion:** Higher doses of PRO 140 SC are required to maintain virologic suppression on SAMT in the majority of patients infected exclusively with CCR5-tropic HIV-1. After testing both 350 mg and 525 mg, 700 mg of weekly PRO 140 SC is currently underway and will be presented. PRO 140 SC has the potential as a SAMT for long-term suppression of HIV-1 replication.

487 IN SILICO SIMULATION OF LONG-ACTING TENOFOVIR ALAFENAMIDE SUBCUTANEOUS IMPLANT
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1University of Liverpool, Liverpool, UK, 2RTI International, San Francisco, CA, USA, 3Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** Subcutaneous implants support the long-acting delivery of drugs, circumventing non-adherence issues with daily oral regimens. The aim of this study was to simulate pharmacokinetic (PK) profiles of tenofovir alafenamide (TAF) subcutaneous implants for HIV pre-exposure prophylaxis using physiologically-based pharmacokinetic (PBPK) modelling.

**Methods:** A subcutaneous mechanistic modelling approach was integrated into a previously published whole-body PBPK model using Simbiology 2018a. The model was qualified against available PK data of oral TAF at steady state (GS-US-320-1382). The PBPK model was assumed to be qualified if the mean simulated values were within ± 50% from the mean observed values as per convention. TAF subcutaneous implants were simulated in five hundred virtual healthy women (average BMI – 29.2 kg/m2) for 28 consecutive days and the area under the plasma concentration curve (AUC) and average plasma concentration (Cavg) were described. PK of plasma TAF and tenofovir, tenofovir diphosphate (TFV-DP) in peripheral blood mononuclear cells (PBMCs), and TFV-DP in cervical and rectal tissues were simulated considering data from clinical studies. TAF PK from the subcutaneous implant was simulated with zero-order release rates between 0.5–0.8 mg/day. TFV-DP concentrations of 48 fmol/10⁸ PBMCs was considered as the target trough concentration.

**Results:** AUC and Cavg of plasma TAF/TFV and PBMC TFV-DP concentrations resulting from administration through subcutaneous implants at different zero-order release rates are shown in the table. Our simulations indicate that TAF subcutaneous implant with a minimum release of 0.6 mg/day will support sustained TFV-DP concentrations well above the target concentration of 48 fmol/10⁸ cells. The TFV-DP cervical and rectal concentrations ranged between 1.47 – 2.44 fmol/10⁸ cells and 0.95 – 1.57 fmol/10⁸ cells, respectively between the release rates of 0.5 – 0.8 mg/day.

**Conclusion:** These data inform the possible dosing and release rate needed for TAF such that the simulated PBMC TFV-DP concentrations remained over the target concentrations. A 2.5 mm x 40 mm implant rod, like that of contraceptive implants, containing 120 mg of TAF and delivering at 0.6 mg/day could provide protective levels for over 6-months. TAF subcutaneous implants may represent a valuable strategy to address issues arising from sub-optimal adherence to oral regimens, and may find application in HIV prevention.

**Table:**

<table>
<thead>
<tr>
<th>Release rate</th>
<th>Compound</th>
<th>AUC (ng h/ml)</th>
<th>Cavg (ng/ml)</th>
<th>Simulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8 mg/day</td>
<td>TFV, plasma</td>
<td>430 ± 42.9</td>
<td>0.641 ± 0.062</td>
<td>Yes (94.1%)</td>
</tr>
<tr>
<td></td>
<td>TFV-DP, PBMC</td>
<td>598 ± 56.2</td>
<td>0.092 ± 0.087</td>
<td>Yes (94.1%)</td>
</tr>
<tr>
<td></td>
<td>TFV-DP, PBMC</td>
<td>75.3 ± 46.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.7 mg/day</td>
<td>TFV, plasma</td>
<td>374 ± 37.5</td>
<td>0.771 ± 0.078</td>
<td>Yes (94.1%)</td>
</tr>
<tr>
<td></td>
<td>TFV-DP, PBMC</td>
<td>520 ± 52.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TFV-DP, PBMC</td>
<td>70.5 ± 41.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.6 mg/day</td>
<td>TFV, plasma</td>
<td>321 ± 32.1</td>
<td>0.679 ± 0.048</td>
<td>Yes (94.1%)</td>
</tr>
<tr>
<td></td>
<td>TFV-DP, PBMC</td>
<td>446 ± 44.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TFV-DP, PBMC</td>
<td>0.666 ± 0.067</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.5 mg/day</td>
<td>TFV, plasma</td>
<td>374 ± 37.8</td>
<td>0.481 ± 0.040</td>
<td>Yes (94.1%)</td>
</tr>
<tr>
<td></td>
<td>TFV-DP, PBMC</td>
<td>0.098 ± 0.057</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TFV-DP, PBMC</td>
<td>47.8 ± 37.2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are represented as mean ± standard deviation. AUC is measured for 28 days (FTI hours) subsequent to implant administration.

488 LONG-ACTING EMTRICITABINE PRODRUGS PROVIDE PROTECTION FROM HIV INFECTION IN VIVO
Paul Curley, 1James J. Hobson, Neill Liptrott, Amer Al-Khouja, David Meyers, Caren Freil Meyers, Charles W. Flexner, Marco Siccardi, Steve Rannard, Larisa Y. Poluektova, Andrew Owen
1University of Liverpool, Liverpool, UK, 2Johns Hopkins University, Baltimore, MD, USA, 3University of Nebraska Medical Center, Omaha, NE, USA

**Background:** Antiretroviral drugs are predominantly administered orally for both therapy and pre-exposure prophylaxis (PrEP). Despite ease of administration, oral delivery is prone to patient non-adherence exacerbated for some drugs by pill fatigue and gastrointestinal intolerance. By decreasing frequency of administration, long-acting injectable (LAI) medications are effective strategies to circumvent these issues. We report here a preclinical assessment of LAI semi-solid prodrug nanoparticle (SSPN) formulations of novel emtricitabine (FTC) prodrugs to prevent HIV infection.

**Methods:** SSPN of FTC carbonate/Carbonate prodrugs were generated using a proprietary emulsion-templated freeze-drying technology. 2 lead formulations were tested for their ability to prevent HIV infection in NSG-cmah-/- mice humanised by CD34+ cell transplantation. Animals received 140 mg/kg FTC equivalent (SSPN 9 or 10) via 2 intramuscular injections vs an untreated control (n=7-6 per group). At days 7 and 14 mice were challenged intraperitoneally with a 103 TCID50 dose of HIVADA. Animals were sacrificed at 28 days post infection. Plasma samples were taken for determination of viral load (VL). Tissue samples were collected for viral RNA and proteins detection via RT-PCR and immunohistochemistry.

**Results:** Mice treated with SSPN 9 and 10 demonstrated undetectable VL (700 copies/mL detection limit), and HIV RNA remained undetectable 28 days post infection in plasma, spleen, lung and liver in all animals for the 7 challenge. Following 14-day challenge, mice treated with SSPN 9 demonstrated undetectable HIV in plasma and all tissues. Mice treated with SSPN 10 demonstrated 2 mice had detectable plasma VL (4.77 ± 10⁴ copies/mL) and 3 mice showed presence of HIV RNA in plasma and proteins in spleen, lung and liver in day 28. HIV was detectable in all untreated animals.

**Conclusion:** The data presented here demonstrate both formulations were 100% effective at preventing HIV infection 7 days post LAI administration. Following 14 days SSPN9 prevented HIV infection in 100% of mice while SSPN 10 prevented infection in 50% of mice. These data indicate great potential for delivering FTC via LAI and the approach may support LAI development for PrEP. Further studies will aim to optimise formulations to produce exposure beyond 14 days and to assess applications in therapy as part of a combination.

489 PRODRUGS EXTEND THE HALF LIFE AND POTENCY OF CABOTEGRAVIR
Tannay A. Kulkarni, Aditya N. Bade, Brady J. Sillman, Bhagya Dayvar Shetty, Melinda Wojtkeiwicz, JoElyn McMillan, Benson Edagwa, Howard E. Gendelman
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**Background:** Prevention of new infections, reduction in transmission rates and management of chronic infection characterize once a month dosing of the current long acting cabotegravir (CAB). Previously we demonstrated that potency, bioavailability and tissue distribution of CAB can be improved up to 3-fold by myristoylation, increasing drug lipophilicity. This extended PA-IC₉₀ up to 3 months in Rhesus macaques after a single 45 mg/kg CAB equivalent intramuscular (IM) injection. We now report stearylization of CAB (termed M2CAB) designed to reduce dosing frequency while improving viral reservoir targeting and drug activity.
**Methods:** We reacted CAB with stearoyl chloride in anhydrous dimethylformamide using N,N-diisopropylethylamine base under argon. The created M2CAB ester was purified by silica column chromatography and characterized by 1H-NMR and FTIR spectroscopy. Nanoparticles were produced by high pressure homogenization (NM2CAB). Human monocyte derived macrophages (MDM) were used as a biological platform to measure drug uptake and retention. Drug levels were quantitated in cell lysates by UPLC-TUV. After MDM treatment with 100 µM NM2CAB cells were challenged with HIV-1 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-1p24 antigens recorded by immunohistochemistry. Female NSG mice were injected with 45 mg/kg CAB equivalents of NCAB, NMCAB and NM2CAB (unmodified CAB, first and second generation prodrug nanof ormulations). Plasma was collected weekly after injection and CAB and prodrug levels were analyzed.

**Results:** NM2CAB, NMCAB and CAB LAP (referred to as NCAB) uptake in MDM was 57, 44 and 2 nmol/10^6 cells over 24 hours. Only NM2CAB was retained in MDM activi ty in MDM as seen over 30 days compared to 15 and 1 day for NMCAB and NCAB respectively. After a single 45 mg/kg CAB IM injection of NM2CAB in mice, plasma CAB levels were consistently 4 times PA-IC50 for 4 months compared to 2.5 and 1 month for NMCAB and NCAB.

**Conclusion:** The hydrophobicity and sustained slow hydrolysis of prodrug M2CAB facilitate NM2CAB to harness the injection site as a primary drug depot as well as macropages and other tissues as secondary drug depots for months. This can potentially reduce frequent dosing and injection volume improving patient adherence to antiretroviral therapy.

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**491 HIV REPLICATION AT <40C/mL FOR DTG+3TC VS DTG+TDF/FTC IN THE GEMINI 1 & 2 STUDIES**

**Mark Underwood**, Rimpala Urbaiti, Choy Man, Jörg Sievers, Ruolan Wang, Brian Wynne, Allan-Raymond Tenorio, Alexander Currie, Keith Pappa, Justin Koteff, Martin Gartland, Michael Aboud

**Background:** The GEMINI-1&2 studies in treatment-naïve adults with screening HIV-1 RNA ≤500,000c/mL showed dolutegravir+lamivudine (DTG+3TC, 2DR) was non-inferior to dolutegravir+tenofovir disoproxil/emtricitabine (DTG+TDF/FTC, 3DR) at Week 48 by FDA snapshot algorithm; 91% (655/716) in the 2DR group versus 93% (669/717) in the 3DR group achieved HIV-1 RNA <50c/mL. Abbott RealTime HIV-1 assay used in the studies measures viral load (VL) from 40c/mL to 10,000,000c/mL, and provides qualitative target detected (TD) or target not detected (TND) for VL <40c/mL. Clinical and subject management implications of more stringent low level VL data needs clarification. We assessed the proportion of participants with TND over time and by baseline (BL) VL for 2DR versus 3DR.

**Methods:** Subjects were randomised 1:1 to treatment with 2DR or 3DR. The proportion of subjects with HIV-1 RNA <40c/mL and TND status at Week 48 was analysed using a Cochran-Mantel-Haenszel test stratified by plasma HIV-1 RNA ≤100,000 vs >100,000 copies/mL and CD4+ cell count ≤200 vs >200 cells/mm^3 at BL. Proportion of subjects with TND Status were summarised by Visit and at Week 48 by BL HIV-1 RNA Subgroup. Time to Plasma HIV-1 RNA <40c/mL and TND Status Overall and by BL HIV-1 RNA Subgroup were estimated using non-parametric Kaplan-Meier method.

**Results:** At Week 48 similar proportion of subjects had snapshot TND in the 2DR and 3DR arms (77% [553/716] vs 73% [525/717], adjusted difference 3.8%, 95% CI 0.6%, 8.2%) and proportions were also similar at earlier visits: Weeks 4 (3% vs 2%), 8 (52% vs 49%), 12 (60% vs 57%), 16 (59% vs 56%), 24 (65% vs 63%), and 36 (65% vs 68%). While similar response rates were seen in subjects with BL VL >100,000c/mL, response rates were higher in 2DR vs 3DR with subjects BL VL >100,000c/mL. Median time for 2DR vs 3DR to TND was 57 days for both overall, 57 days for both in ≤100,000c/mL at BL strata, and 113 days vs 169 days for BL >100,000c/mL subgroup.

**Conclusion:** DTG+3TC and DTG+TDF/FTC had similar proportions of TND by snapshot at all Weeks. Snapshot response rates based on TND status at Week 48 were similar between arms at ≥100,000c/mL BL group and higher for DTG+3TC in >100,000c/mL BL category. Median time to TND was similar overall and in BL VL ≤100,000c/mL subgroup, and less for DTG+3TC vs DTG+TDF/FTC if >100,000c/mL at BL. These data, utilizing a more stringent snapshot criteria, continue to demonstrate the effectiveness and potency of DTG+3TC in treatment-naive subjects.

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**Table:** Proportion of Subjects with Plasma HIV-1 RNA <40c/mL and TND at Week 48

<table>
<thead>
<tr>
<th>Baseline VL strata (c/mL)</th>
<th>n(N%)</th>
<th>n(TND)</th>
<th>Treatment differencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100,000</td>
<td>463/576 (80)</td>
<td>446/564 (79)</td>
<td>1.3 (-3.4 to 6.0)</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>90/140 (64)</td>
<td>79/153 (52)</td>
<td>12.7 (1.4 to 23.9)</td>
</tr>
<tr>
<td>&gt;250,000</td>
<td>25/41 (49)</td>
<td>20/46 (43)</td>
<td>5.5 (-14.3 to 25.4)</td>
</tr>
<tr>
<td>&gt;400,000</td>
<td>5/19 (28)</td>
<td>6/24 (25)</td>
<td>2.8 (-2.4 to 29.8)</td>
</tr>
</tbody>
</table>

a Number Responded/Number Assessed (%); b Unadjusted proportion of DTG+3TC - proportion of DTG+TDF/FTC (%).
492 IMPACT OF DUAL THERAPY ON THE CD4/CD8 RATIO IS SIMILAR TO TRIPLE THERAPY AT 48 WEEKS

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1Fundación Huipil, Buenos Aires, Argentina, 2Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, 3Hospital Civil Fray Antonio Alcalde, Guadalajara, Mexico, 4La Paz University Hospital, Madrid, Spain, 5Asociacion Civil Impacta Salud y Educacion, Lima, Peru, 6Hospital Agorien, Buenos Aires, Argentina, 7Centro de Estudios Infectológicos, Buenos Aires, Argentina

Background: The requirement for lifelong ART for HIV infection has highlighted interest in dual therapy (DT) to minimize cumulative drug exposure. One of the enduring concerns regarding DT is its impact on markers of immune dysfunction and its potential clinical implications. A recent retrospective study suggests that when compared with triple therapy (TT), DT regimens might decrease the CD4/CD8 ratio. A low CD4/CD8 ratio has been associated with an increase in non-AIDS associated events, and thus warrants further investigation in patients treated with DT.

Methods: Sub-analysis of the GARDEL and ANDES randomized controlled trials, both based on ritonavir-boosted protease inhibitors (bPI) plus 3TC. Patients’ CD4/CD8 ratios were compared between DT and TT arms at baseline and at 12, 24, 36 and 48 weeks. Follow-up was censored at any of the following: virological failure, opportunistic infection, severe disease (defined as requiring hospitalization) or pregnancy. Main outcomes were median CD4/CD8 ratio and proportion of patients achieving a CD4/CD8 ratio >1, both measured at 48 weeks of follow-up. Subgroup analysis of patients >50 years of age, baseline CD4 count <200 cells/ml, HIV viral load >100,000 copies/ml and bPI treatment were performed. Comparisons were made utilizing regression to the median adjusted on socio-demographic, immuno-virologic and ARV history-related variables was used for analyses.

Results: Overall, 3848 patients receiving 2DR were included: DTG/RPV (n=974, 28%), RAL/ETR (n=869, 25%), DTG/3TC (n=677, 19%), DRV/RAL (n=604, 16%) and DRV/3TC (n=360, 10%). Characteristics of patients on 2DR are presented in the table. Treatment interruptions occurred in 1178 cases due to AE (n=417, 38%), RAL/ETR (n=325, 28%), RAL/ETR (n=325, 28%), RAL/ETR (n=325, 28%), DRV/RAL (n=285, 25%), DTG/3TC, darunavir/ritonavir/RAL (DRV/3TC) and DRV/3TC. Primary objective was to investigate the associated factors with virologic failure (VF) defined as 2 consecutive pVL >50 c/mL and occurrence of adverse events (AE). Cox proportional hazards model adjusted on socio-demographic, immunologic and ARV history-related variables was used for analyses.

Conclusion: With the recently reported virologic success of DT regimens, addressing its long-term impact on immune markers remains an important subject. These results show that the impact of DT regimens on the CD4/CD8 ratio is similar to that of TT during the first year of treatment. Longer follow-up of larger populations of patients on DT should address the rates of non-AIDS associated events related to these regimens. Also, these results should be confirmed in INSTI-based DT.
494  EFFECTS OF ART SIMPLIFICATION IN THE SPANISH AIDS RESEARCH NETWORK, CORIS

Sergio Serrano-Villar1, Ima Jarrin2, Pompeyo Viciana3, Federico Pidulio3, Francesc Vidal4, Enrique Bernali1, Carlos Galera1, Santiago Moreno1, for the CoRIS
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Background: The number of drugs needed to maintain lifelong HIV RNA suppression is currently debated. We aimed to compare the effects of ART simplification strategies on the risk of virological failure in CoRIS.

Methods: We selected ART-naive patients initiating triple ART from 2004 to 2017 in CoRIS who achieved undetectable viral load in the first 48 weeks of ART and either remained in triple therapy during their entire follow-up or were subsequently simplified to dual or monotherapy. The outcome was virological failure, defined as at least two consecutive viral loads >50 copies/ml. The type of regimen (triple, dual or mono) and time on regimen were analyzed as time-varying covariates. We calculated cause-specific cumulative incidence curves and used multivariate Cox proportional hazards models adjusted for potential confounders to estimate hazard ratios (HR). The proportional hazards assumption was checked graphically and by tests based on Schoenfeld residuals. HR were calculated for <24 and ≥24 months of ART to meet the proportional hazards assumptions.

Results: From 14458 patients, 8416 met the inclusion criteria; 7665 remained in triple therapy, 424 switched to dual therapy and 327 to monotherapy. At baseline, subjects who remained in triple therapy were more likely to be men, younger, HCV negative, HBs antigen positive, showed higher pre-ART CD4 counts and initiated ART more recently than those who switched to dual or monotherapy (all P<0.05). The median time from enrolment to censoring date was 4.9, 6.9 and 8.4 years in the triple, dual and monotherapy groups, respectively (P<0.001). In the dual and monotherapy groups, the median time of regimen maintenance was 1 and 1.3 years, and 15% and 34% switched to triple therapy during follow-up, respectively. After adjustment for potential confounders, ART simplification was associated with greater risk of virological failure after 24 months from simplification (P=0.003), which was driven by higher risk in the monotherapy group.

Conclusion: Conclusions: In this large cohort representative of a real-life setting, we found that the durability of the simplified ART regimens was limited and, compared to triple therapy, monotherapy was associated with greater risk of virological failure in the monotherapy group, with no significant differences between dual and tripe therapy. While additional information on long-term outcomes is needed, our results are consistent with the data reported in clinical trials.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group</th>
<th>Time to Event</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological failure</td>
<td>First 24 months of ART</td>
<td>Triple</td>
<td>533/7823</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dual</td>
<td>7439</td>
<td>0.9 (0.76-1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mono</td>
<td>56/41</td>
<td>1.2 (0.35-4.1)</td>
</tr>
<tr>
<td>Virological failure</td>
<td>After 24 months of ART</td>
<td>Triple</td>
<td>390/7746</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dual</td>
<td>2/127</td>
<td>1.0 (0.37-4.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mono</td>
<td>20/131</td>
<td>1.5 (0.54-3.3)</td>
</tr>
</tbody>
</table>

Co proportionality hazards models adjusted for age, sex, transmission subgroup, additional viral load, CD4+ count, CD4/CD8 ratio, HIV RNA viral load, NNRTIs, PI, PIs resistance, adherence, year of ART initiation.

495  DISCONTINUATIONS & VIROLOGIC RESPONSE IN LATE PRESENTERS WITH INSTI- OR PI-BASED ART

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Background: Active opportunistic infections and/or low CD4+ T-cell (CD4+<200) counts are exclusion criteria in most clinical trials. Late presenters (LP) are therefore inadequately represented in studies comparing efficacy of antiretroviral regimens, leading to a lack of data on optimal treatment options. Our study aimed to investigate the efficacy and safety of first line ART with integrase-inhibitor (INSTI) or protease-inhibitor (PI) based regimens in patients with low CD4+ counts and/or an AIDS-defining disease.

Methods: We conducted a retrospective, multicenter analysis to investigate discontinuation rates and clinical outcome in patients with a CD4 cell count <200/mL and/or an AIDS defining disease after starting first line ART. Data were collected in three European HIV clinics: University Hospital Frankfurt, Kings College London and Hospital Fundación Jimenez Diaz Madrid. All patients with CD4<200/mL and/or an AIDS defining disease who started INSTI or PI-based first line ART between January 2014 and December 2016 were included in this study. Percentages of those discontinuing ART and with adverse events were compared using univariate analysis. Virologic response was analyzed by using FDA snapshot analysis (HIV-1 RNA <50 copies/ml at week 48).

Results: A total of 218 LP were included in the study, 13.8% women, 23.8% non-European ethnicity with a mean (SD) baseline CD4 91.9 (112) and CD4/CD8 ratio of 0.11 (0.19). 131 LP were started on INSTI-based regimen and 87 on PI’s. Between-group differences are presented in table 1. Those commenced on PI were more likely to be older; 91.8% of the INSTI and 92.4% of PI treated patients had a viral load <50 copies/ml at week 48, discontinuation rates due to adverse events were 3.4% in the INSTI and 8.1% in the PI group respectively. No significant differences in discontinuation rates were observed at week 12 or 48 between INSTI and PI-based regimens (p=0.78 and 0.47 respectively). Virologic response was equally good in those receiving integrase or protease inhibitors (91.8% vs. 92.4%; p=0.88; odds ratio (95% CI) 1.05 (0.38–2.82).

Conclusion: In a European cohort of LP starting first line INSTI or PI based ART regimens, there were no significant differences in discontinuation rates or virologic response at week 48. Our results indicate that the choice between INSTI and PI can be made on an individual basis of the patient presenting late for first line ART. Future research will focus on the identifying factors associated with regimen selection in this cohort.

### Table 1: Discontinuation & Virologic Response in Late Presenters

<table>
<thead>
<tr>
<th>Variable</th>
<th>INSTI (n=131)</th>
<th>PI (n=87)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>53.3 ± 10.7</td>
<td>54.5 ± 10.9</td>
<td>0.64</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>97/34</td>
<td>76/11</td>
<td>0.24</td>
</tr>
<tr>
<td>AIDS status at enrollment</td>
<td>57/74</td>
<td>59/28</td>
<td>0.35</td>
</tr>
<tr>
<td>Baseline CD4 (cells/µL)</td>
<td>92 (50-200)</td>
<td>99 (50-200)</td>
<td>0.31</td>
</tr>
<tr>
<td>Baseline CD4/CD8 ratio</td>
<td>0.8 (0.3-1.6)</td>
<td>0.7 (0.3-1.6)</td>
<td>0.54</td>
</tr>
<tr>
<td>Baseline VL (log copies/mL)</td>
<td>4.2 (3.5-4.9)</td>
<td>4.3 (3.5-5.2)</td>
<td>0.76</td>
</tr>
<tr>
<td>VL at week 12</td>
<td>25 (10-35)</td>
<td>25 (10-35)</td>
<td>0.85</td>
</tr>
<tr>
<td>VL at week 48</td>
<td>11 (5-20)</td>
<td>11 (5-20)</td>
<td>0.78</td>
</tr>
<tr>
<td>Adverse events</td>
<td>3.4%</td>
<td>8.1%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

### Table 2: Quality of Life and Adherence as Predictors of Second-Line ART Virological Failure

Thiago S. Torres1, Linda J. Harrison2, Alberto M. La Rosa1, Lu Zheng3, Ann Collier4, Michael D. Hughes5, for the AIDS Clinical Trials Group (ACTG) A5273 Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>INM (n=111)</th>
<th>PI (n=109)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>50.6 ± 10.5</td>
<td>50.6 ± 10.8</td>
<td>0.93</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>82/29</td>
<td>83/26</td>
<td>0.72</td>
</tr>
<tr>
<td>AIDS status at enrollment</td>
<td>52/59</td>
<td>52/57</td>
<td>0.84</td>
</tr>
<tr>
<td>Baseline CD4 (cells/µL)</td>
<td>92 (50-200)</td>
<td>90 (50-200)</td>
<td>0.53</td>
</tr>
<tr>
<td>Baseline VL (log copies/mL)</td>
<td>4.2 (3.5-4.9)</td>
<td>4.2 (3.5-4.9)</td>
<td>0.51</td>
</tr>
<tr>
<td>VL at week 12</td>
<td>11 (5-20)</td>
<td>11 (5-20)</td>
<td>0.78</td>
</tr>
<tr>
<td>VL at week 48</td>
<td>11 (5-20)</td>
<td>11 (5-20)</td>
<td>0.78</td>
</tr>
<tr>
<td>Adverse events</td>
<td>3.4%</td>
<td>8.1%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Quality of Life and Adherence as Predictors of Second-Line ART Virological Failure
Background: Poor adherence to antiretroviral therapy (ART) predicts virologic failure (VF). Self-reported adherence and health-related quality of life (QoL) have been associated with 1st-line ART failure in resource-limited settings (RLS). Our objective was to assess whether QoL metrics add to self-reported adherence data at 4 weeks after starting 2nd-line ART in predicting early VF.

Methods: ACTG A5273 was a randomized clinical trial conducted between 2012 and 2014, which showed non inferior virologic efficacy of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/elvitegravir/cobicistat (E/TCV) vs. ritonavir-boosted lopinavir (LPV/r) + TDF/FTC in RLS, with a 8 QoL domains each scored between 0 (worse) and 100 (best). Adherence was dichotomized as incomplete (self-report of any dose missed in the first 4 weeks of 2nd-line ART) and complete (no missed dose). Logistic regression was used to assess whether QoL metrics could add to self-reported adherence at week 4, categorized in each domain as high (score ≥75), medium (50-<75), and low (<50), enhanced prediction of early 2nd-line VF in addition to adherence.

Results: 512 eligible adults (49% male, median age 39 years) were included, including 500 with assessments for QoL and adherence at week 4 and for early VF; 7.4% (n=37/500) had early VF and 20.6% (103/500) reported incomplete adherence at week 4. Mean QoL improved (p<0.04) from baseline to week 4 in all domains: from 67 to 72 (general health perceptions), 91 to 93 (physical functioning), 80 to 83 (role functioning), 91 to 93 (social functioning), 91 to 94 (cognitive functioning, CF), 83 to 84 (pain, 85 to 89 (mental health), and 80 to 83 (energy/fatigue, E/F). Early VF was more common among participants who self-reported incomplete adherence (14/103, 13.6%) versus complete adherence (2/37, 0.5%) (p=0.000). In analyses (both unadjusted and adjusted for adherence), lower QoL in CF and E/F categories at week 4 were associated with significantly higher odds of early 2nd-line VF (overall p<0.04 (Table)).

Conclusion: Lower QoL, particularly in CF and E/F, adds to self-reported incomplete adherence after 4 weeks of 2nd-line ART in predicting VF at week 24. Evaluation is needed to assess whether patients with poorer QoL might be targeted for greater support to reduce risk of VF.

<table>
<thead>
<tr>
<th>QoL Domain</th>
<th>QoL Score Category</th>
<th>Time</th>
<th>VF</th>
<th>OR (95%CI)</th>
<th>p-values</th>
<th>OR [adj for adherence]</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive functioning</td>
<td>High (≥75)</td>
<td>350</td>
<td>41</td>
<td>1.88</td>
<td>0.85-3.98</td>
<td>0.23</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td>Medium (50-&lt;75)</td>
<td>133</td>
<td>12</td>
<td>1.18</td>
<td>0.53-2.46</td>
<td>0.17</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>Low (&lt;50)</td>
<td>13</td>
<td>2</td>
<td>1.00</td>
<td>0.43-2.27</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Energy/fatigue</td>
<td>High (≥75)</td>
<td>181</td>
<td>20</td>
<td>1.40</td>
<td>0.66-2.98</td>
<td>0.30</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>Medium (50-&lt;75)</td>
<td>202</td>
<td>17</td>
<td>1.80</td>
<td>0.80-3.99</td>
<td>0.19</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td>Low (&lt;50)</td>
<td>57</td>
<td>5</td>
<td>1.00</td>
<td>0.43-2.27</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table: Associations of QoL domains at week 4 with early 2nd-line VF (unadjusted and adjusted for adherence)
and adjusted analysis (table), older age, lower baseline HIV-1 RNA, higher CD4 count, and lack of resistance to any NRTI (multivariable only) were significantly associated with higher virologic suppression rate at week 48. Associations with sex and CPI+SOC were not statistically significant. 145 (51%) experienced confirmed virologic failure ≥ 1000 c/mL and 141 had GT available at failure; 48 (34%) had development of new resistance mutations, predominantly NRTI-related.

Conclusion: In this 3rd-line ART trial in RLS, fewer than 50% of participants with no lopinavir resistance at entry who continued their 2nd-line ART had VL suppression at 48 weeks. Participants with more advanced disease or any resistance mutations had worse rates of suppression. This group likely represents individuals with continued poor ARV adherence.

500 WEEK 96 SUBGROUP ANALYSES OF D/C/F/TAF IN HIV-1 TREATMENT-NAIVE & SUPPRESSED ADULTS

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Background: Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10mg, currently approved in the EU, US and other countries, is being investigated in two Phase 3 randomized non-inferiority trials, EMERALD (virologically suppressed adults; NCT0269917) and AMBER (ART-naive adults; NCT02431247). We present a wk 96 preplanned subgroup analysis of the D/C/F/TAF arms by baseline viral load (VL) and CD4+ count (screening stratification factors), WHO clinical stage in AMBER, and prior virologic failure (VF), ART experience, screening bPI (stratification factor) and boosting agent in EMERALD.

Methods: Patients in the D/C/F/TAF and control arms of both trials (study designs described previously) continued on or switched to D/C/F/TAF in a single-arm, open-label extension phase until wk 96 provided they consented to continue to derive benefit. Wk 96 efficacy endpoints were % patients with cumulative confirmed VL<50c/mL (virologic rebound) (EMERALD) and VL<50 c/mL (virologic response) and VF<50c/mL (FDA snapshot) (both trials). No wk 96 comparisons were made between arms during the open-label phase. This analysis focuses on long-term efficacy and safety of D/C/F/TAF over 96 wks in the D/C/F/TAF arms.

Results: In AMBER, high response and low VF rates were seen at wk 96 across the baseline VL, CD4+ count and WHO clinical stage subgroups (Table). In EMERALD, 58% had received ≥5 ARVs (including screening ARVs and boosters) and 15% had prior non-DR VF. High response rates, low VF and low virologic rebound rates were maintained through wk 96 across ART experience and prior VF, and screening bPI and boosting agent subgroups (Table). In both trials, low denominators in some subgroups resulted in wider 95% CIs and data should be interpreted with caution. No DRV, primary PI or TFV RAMs were seen through wk 96.

549 PREDICTORS OF VIROLOGIC OUTCOME WHILE CONTINUING A PI-BASED ART REGIMEN IN ACTG A5288

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Background: Antiretroviral (ARV) choices are challenging in resource-limited settings (RLS) after failure of 2nd-line therapy. Many failing 2nd-line therapy without resistance remain on their 2nd-line therapy. Our objective was to evaluate demographic and predictors of successful virologic suppression in this prospective study.

Methods: A5288 was an open-label strategy study in RLS in HIV-1 infected persons with confirmed plasma HIV RNA (VL) ≥1000 c/mL after 24 weeks of PI-based 2nd-line ART. The study sought to use newer ARVs (darunavir/r, etravirine and raltegravir) along with genotyping (GT), a cellphone adherence intervention (CPi) or standard of care (SOC), and real-time HIV VL monitoring to achieve VL suppression at week 48. Participants were assigned to 1 of 4 intervention (CPI) or standard of care (SOC), and real-time HIV VL monitoring to achieve VL suppression at week 48. Participants were assigned to 1 of 4
502 96 WEEK EFFICACY AND SAFETY OF B/F/TAF IN TREATMENT-NAÏVE ADULTS AND ADULTS ≥50 YRS

Samar K. Gupta1, Anthony Mills2, Cynthia Brinson1, Kimberley Workowski3, Amanda Clarke1, Andrea Antinori4, Jeffrey L. Stephens5, Ellen Koenig6,Jose R. Arribas7, David M. Asmuth8, Douglas Ward9, Jurgen K. Rockstroh10, Mingjin Yan11, Diana Brainard12

1Indiana University, Indianapolis, IN, USA, 2Men’s Health Foundation, Los Angeles, CA, USA, 3Central Texas Clinical Research, Austin, TX, USA, 4Emory University, Atlanta, GA, USA, 5Brighton & Sussex University Hospitals NHS Trust, Brighton, UK, 6Lazzaro Spallanzani Institute, Milan, Italy, 7Men’s University, Miami, FL, USA, 8Instituto Dominicano de Estudios Virológicos, Santo Domingo, Dominican Republic, 9La Paz University Hospital, Madrid, Spain, 10University of California Davis, Davis, CA, USA, 11Dupont Circle Physicians Group, Washington, DC, USA, 12Bonn University Hospital, Bonn, Germany, 13Gilead Sciences, Inc, Foster City, CA, USA

Background: As the population living with HIV ages, identifying effective and safe regimens for older patients is of heightened importance. The single-tablet dualintegrase, emtricitabine, tenofovir alafenamide (B/F/TAF) is a guidelines-recommended regimen that may benefit older patients 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-naïve adults, Study 1489: B/F/TAF vs dolaprevir, abacavir, and lamivudine (DTG/ABC/3TC) and Study 1490: B/F/TAF vs DTG + F/TAF. A pre-specified pooled analysis assessed efficacy as the proportion with HIV-1 RNA <50 c/mL (FDA Snapshot) and safety at Week (W) 96. Proteinuria and bone mineral density (BMD) were measured in Study 1489 only. We performed a post-hoc analysis in adults ≥50 yrs.

Results: 1274 were randomized and treated (634 B/F/TAF, 315 DTG/ABC/3TC, 325 DTG + F/TAF); 196 were age ≥50 yrs (96 B/F/TAF, 41 DTG/ABC/3TC, 59 DTG + F/TAF). Efficacy was high for all treatments and for age ≥50 subgroup (Table). Overall, the most common AEs were nausea (10% B/F/TAF, 24% DTG/ABC/3TC, 11% DTG + F/TAF), diarrhea (17% B/F/TAF, 16% DTG/ABC/3TC, 16% DTG + F/TAF), and headache (15% B/F/TAF, 16% DTG/ABC/3TC, 15% DTG + F/TAF). Treatment-related AEs occurred in 24% B/F/TAF, 40% DTG/ABC/3TC (p<0.001 B/F/TAF vs DTG/ABC/3TC), and 28% DTG + F/TAF. The most common treatment-related AE was nausea: 4% B/F/TAF, 17% DTG/ABC/3TC, 5% DTG + F/TAF. Treatment related AEs in those age ≥50 yrs were similar to the full population: 23% B/F/TAF, 37% DTG/ABC/3TC, 29% DTG + F/TAF. Overall, AEs leading to drug discontinuation were reported for 1% on B/F/TAF, 2% on DTG/ABC/3TC and 2% on DTG + F/TAF, and in age ≥50 yrs: 2% B/F/TAF, 5% DTG/ABC/3TC and 7% DTG + F/TAF. In Study 1489 mean % changes in hip and spine BMD, proteinuria, and renal biomarkers were similar. There were small changes from baseline in fasting lipids at W96 overall and no significant differences between treatments in participants ≥50 yrs.

Conclusion: Through two years of treatment B/F/TAF resulted in high rates of virologic suppression, was safe and well tolerated with fewer treatment-related AEs compared to other guidelines-recommended regimen; similar results were found in adults ≥50 yrs. There were no clinically significant impacts on bone and renal safety or on fasting lipids.

501 INTEGRATED EFFICACY ANALYSIS OF DORAVIRINE IN HIV-1-INFECTED TREATMENT-NAÏVE ADULTS

Chloe Orkin1, Jean-Michel Molina1, Johan Lombard1, Wing-Wai Wong1, Edwin DeJesus1, Anthony Rodgers6, Xia Xu6, Sushma Kumar6, Elizabeth Martin6, George G. Hanna6, Carey Hwang6

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Background: DOR is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with once-daily dosing and potent in vitro activity against wild-type virus and the most common NNRTI-resistant variants (K103N, Y181C, G190A). DOR has demonstrated non-inferior efficacy to darunavir plus ritonavir (DRV+r) and efavirenz (EFV) in two ongoing, double-blinded, phase 3 trials: DRIVE-FORWARD (NCT02275780) and DRIVE-AHEAD (NCT02403674).

Methods: This prespecified analysis pooled Week 48 data from DRIVE-FORWARD and DRIVE-AHEAD. Data from the DOR groups were pooled, in which 747 participants received DRV/TDF or DOR (100 mg QD) with FTC/TDF or ABC/3TC. The control groups were analyzed separately, in which 383 received DRV+r (800/100 mg QD) with FTC/TDF or ABC/3TC, and 364 received EFV/FTC/TDF (600/200/300 mg QD). Efficacy was assessed by proportion of participants with HIV-1 RNA <50 copies/mL (primary) and change in CD4+ T-cells (secondary) after 48 weeks of treatment.

Results: At Week 48, HIV-1 RNA <50 copies/mL was achieved by 84.1% of DOR-treated participants versus 79.9% of the DRV+r, and 80.8% of the EFV/FTC/TDF groups (Table). No clinically meaningful differences in proportions of patients with HIV-1 RNA <50 copies/mL was seen across demographic/prognostic subpopulations, including baseline plasma HIV-1 RNA (≥ vs <100,000 copies/mL), gender (male/female), race (white vs black/African American), ethnicity (yes vs no Hispanic/Latino), and subtype (B vs non-B). Mean increases from baseline in CD4+ T-cell count at week 48 were 195.5 cells/mm3 for DOR, 185.6 cells/mm3 for DRV+r, and 184.4 cells/mm3 for EFV/FTC/TDF.

Conclusion: DOR, as a single entity (administered in combination therapy with other antiretroviral agents) and as a fixed-dose combination consisting of DOR/3TC/TDF, was efficacious compared with DRV+r and EFV as assessed by the proportion of HIV-1-infected, treatment-naïve adults with HIV-1 RNA <50 copies/mL. Consistent efficacy was seen regardless of demographic/prognostic baseline characteristics.

501 INTEGRATED EFFICACY ANALYSIS OF DORAVIRINE IN HIV-1-INFECTED TREATMENT-NAÏVE ADULTS

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Background: DOR is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with once-daily dosing and potent in vitro activity against wild-type virus and the most common NNRTI-resistant variants (K103N, Y181C, G190A). DOR has demonstrated non-inferior efficacy to darunavir plus ritonavir (DRV+r) and efavirenz (EFV) in two ongoing, double-blinded, phase 3 trials: DRIVE-FORWARD (NCT02275780) and DRIVE-AHEAD (NCT02403674).

Methods: This prespecified analysis pooled Week 48 data from DRIVE-FORWARD and DRIVE-AHEAD. Data from the DOR groups were pooled, in which 747 participants received DRV/TDF or DOR (100 mg QD) with FTC/TDF or ABC/3TC. The control groups were analyzed separately, in which 383 received DRV+r (800/100 mg QD) with FTC/TDF or ABC/3TC, and 364 received EFV/FTC/TDF (600/200/300 mg QD). Efficacy was assessed by proportion of participants with HIV-1 RNA <50 copies/mL (primary) and change in CD4+ T-cells (secondary) after 48 weeks of treatment.

Results: At Week 48, HIV-1 RNA <50 copies/mL was achieved by 84.1% of DOR-treated participants versus 79.9% of the DRV+r, and 80.8% of the EFV/FTC/TDF groups (Table). No clinically meaningful differences in proportions of patients with HIV-1 RNA <50 copies/mL was seen across demographic/prognostic subpopulations, including baseline plasma HIV-1 RNA (≥ vs <100,000 copies/mL), gender (male/female), race (white vs black/African American), ethnicity (yes vs no Hispanic/Latino), and subtype (B vs non-B). Mean increases from baseline in CD4+ T-cell count at week 48 were 195.5 cells/mm3 for DOR, 185.6 cells/mm3 for DRV+r, and 184.4 cells/mm3 for EFV/FTC/TDF.

Conclusion: DOR, as a single entity (administered in combination therapy with other antiretroviral agents) and as a fixed-dose combination consisting of DOR/3TC/TDF, was efficacious compared with DRV+r and EFV as assessed by the proportion of HIV-1-infected, treatment-naïve adults with HIV-1 RNA <50 copies/mL. Consistent efficacy was seen regardless of demographic/prognostic baseline characteristics.
503 CD4+ RECOVERY AFTER ART INITIATION: A COMPARISON BETWEEN DOLUTEGRAVIR AND EFAVIRENZ

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Background: CD4 cell count recovery is an important predictor of AIDS-related morbidity and mortality, especially among those who start antiretroviral therapy (ART) with lower counts. In this study, we aimed to compare CD4 count recovery in patients starting ART in Brazil with TLE (tenofovir+lamivudine+efavirenz) vs TLD (tenofovir-lamivudine-dolutegravir). These were the regimens recommended as preferred 1st-line in the most recent treatment guidelines in the country, released in Dec 2013 (TLE) and in Jan 2017 (TLD).

Methods: Data was extracted from two information systems from the Brazilian Ministry of Health, which record every viral load (VL) and CD4 counts performed within the country’s public health system, and every ART prescription. We included patients aged 15 and over, starting ART from Jan 2014 to Jul 2017. These were the regimens recommended as preferred 1st-line in the most recent treatment guidelines in the country, released in Dec 2013 (TLE) and in Jan 2017 (TLD).

Results: Of the 12568 persons included, 6156 were on an INSTI (2117 (34%) ART-naïve) and 6412 on non-INSTI regimen (2616 (41%) ART-naïve). In an on-treatment analysis, 4982/5106 (98%) on INSTIs and 4979/5211 (96%) on non-INSTIs had a VL<400 cp/mL at 12 months (p<0.0001). A total of 7560 (60%) experienced cVO success (3850 (63%) on INSTIs and 3710 (58%) on non-INSTIs, P<0.0001). The most common reasons for cVO failure were any regimen change (1375 (2%) vs 1201 (2%), p<0.0001) and AIDS event (79 (1%) vs 122 (2%), p=0.008) or death (62 (1%) vs 44 (1%), p=0.6). After adjustment, the odds of cVO success at 12 months was significantly higher for persons on INSTIs compared to non-INSTIs (adjusted odds ratio 1.16 [95% CI, 1.07-1.26]), consistent for ART-naïve and ART-experienced with or without viral suppression at baseline (figure, p=0.4, interaction test). The odds of immunologic success at 12 months were also higher on INSTIs than non-INSTIs (1.18 [1.06-1.33]), consistent according to ART status (figure, p=0.1, interaction test).

Conclusions: In this large cohort collaboration, persons on INSTIs were more likely to achieve CD4+ and immunologic success and immunologic success at 12 months, compared to non-INSTIs, although confounding by indication cannot be excluded.

504 VIROLOGIC AND IMMUNOLOGIC OUTCOMES OF INTEGRASE INHIBITORS (INSTIs) IN RESPOND

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Background: Although outcomes of INSTI use have been evaluated in several randomized controlled trials, experiences from large, demographically heterogeneous real-life settings are limited.

Methods: Logistic regression was used to analyse virologic and immunologic outcomes from 1/1/12 to 1/10/17 among participants in the RESPOND cohort collaboration, starting an INSTI- compared to other contemporary non-INSTI containing regimens (efavirenz, rilpivirine, boosted darunavir- or atazanavir) with 12 months follow-up (FU) ± 3 months. Virologic outcomes were assessed by a composite endpoint (cVO) with success defined as viral load (VL) <400 cp/mL at FU and failure as 21 of either: VL ≥400 cp/mL, unknown VL, any antiretroviral treatment (ART)-regimen change, AIDS event or death. Immunologic success was defined as a 25% increase in CD4 count from baseline at 12 ± 3 months. Analyses were repeated at 6 ± 3 months. Sensitivity analyses using VL< 50 cp/mL for cVO success, excluding those with unknown VL or any ART change were also performed.

Results: Of the 12568 persons included, 6156 were on an INSTI (2117 (34%) ART-naïve) and 6412 on non-INSTI regimen (2616 (41%) ART-naïve). In an on-treatment analysis, 4982/5106 (98%) on INSTIs and 4979/5211 (96%) on non-INSTIs had a VL<400 cp/mL at 12 months (p<0.0001). A total of 7560 (60%) experienced cVO success (3850 (63%) on INSTIs and 3710 (58%) on non-INSTIs, P<0.0001). The most common reasons for cVO failure were any regimen change (1375 (2%) vs 1201 (2%), p<0.0001) and AIDS event (79 (1%) vs 122 (2%), p=0.008) or deaths (62 (1%) vs 44 (1%), p=0.6). After adjustment, the odds of cVO success at 12 months was significantly higher for persons on INSTIs compared to non-INSTIs (adjusted odds ratio 1.16 [95% CI, 1.07-1.26]), consistent for ART-naïve and ART-experienced with or without viral suppression at baseline (figure, p=0.4, interaction test). The odds of immunologic success at 12 months were also higher on INSTIs than non-INSTIs (1.18 [1.06-1.33]), consistent according to ART and VL status at baseline (figure, p=0.1, interaction test). Similar results were seen at 6±3 months and across all sensitivity analyses.

Conclusion: In this large cohort collaboration, persons on INSTIs were more likely to achieve CD4+ and immunologic success and immunologic success at 12 months, compared to non-INSTIs, although confounding by indication cannot be excluded.
505LB 12 MONTH OUTCOMES ON DOLUTEGRAVIR-BASED REGIMENS IN BOTSWANA: THE BEAT COHORT STUDY

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Background: Botswana became the first country in Africa to implement a “Treat All” strategy using Dolutegravir based regimens (DBR) in June 2016. The Botswana Epidemiological ART Treatment Cohort Study (The BEAT), is an observational research cohort tracking virologic and clinical outcomes of people living with HIV (PLHIV) starting DBR. We present 12-month outcomes for treatment naïve, switched and highly treatment experienced patients (HTE) on DBR in routine care settings.

Methods: Data were extracted from the Botswana Ministry of Health and Wellness electronic records and National HIV and laboratory databases from 11 urban and semi-rural facilities. Additional information was extracted from clinic registers and patient files. Rates of adverse events (AEs) using toxicity grading scale of the Division of AIDS (DAIDS) 2017 v.2.1. Lost to follow-up (LTFU), death and viral load (VL) suppression (HIV RNA load <400 copies/mL) were assessed by site and treatment category.

Results: A total of 2,257 PLHIV were included in this analysis: 1523 previously treatment naïve, 638 treatment switches and 140 HTEs. Median age was 39 years (range 32-48), 63% were women. Overall VL suppression was high among individuals initiating DBR within the past year (Table 1). AEs requiring intervention and treatment switch from DBR occurred in <0.1% (n=2) of treatment naïve patients (severe itching and rash that resolved upon discontinuation of DBR) and 1 HTE patient (subsequently not considered related to DBR). All patients had advanced AIDS - cryptococcal meningitis, cervical cancer, and pulmonary TB with anemia of unknown origin. Deaths occurred in 1.3% (n=30) of patients. Men comprised 67% of all deaths. Average time to death was 43.7 days. No neural tube defects were recorded in 77 deliveries (11 receiving DTG before conception).

Conclusion: The introduction of DBR in Botswana is associated with favorable clinical outcomes with high rates of viral load suppression at 12 months and few toxicities or evidence of treatment failure. These findings are reassuring and suggest that the decision to implement “Treat All” and introduce DBRs was an important step to controlling the HIV epidemic in Botswana. Efforts to improve electronic VL laboratory results.
Conclusion: Two years after its introduction in Switzerland, more than 50% of patients within the SHCS were switched to TAF, with the highest proportions among men, patients >50 years, as well as in those with renal impairment or on PI-based ART. However, we noted large differences in switching rates across centers, potentially driven by clinical and programmatic factors.

507 SEVEN-YEAR TREATMENT RESPONSES IN SUBTYPE A1 VS D HIV-1 INFECTIONS IN MBARARA, UGANDA
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Background: Subtype D HIV-1 has been associated with more rapid progression to AIDS in untreated infections. In a previous study, we found that subtype A1 and D infections did not differ in initial response to short term therapy: 86% of individuals achieved undetectable viremia within 6 months. Here, we compared long-term treatment responses and odds of detecting drug resistance between subtype A1 versus D HIV-1 infections.

Methods: 500 chronically-infected individuals enrolled just prior to initiation of NNRTI-based therapy between 2005-2010 were followed >7 years in the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort. Pre-therapy plasma HIV-1 genotype was obtained by Sanger sequencing of HIV-1 RT and reverse transcriptase (RT)-polymerase chain reaction (PCR) amplicons. Results: A total of n=198 subtype A1 and n=156 subtype D infections were processed with QIIME, R, and Phyloseq.

Results: A total of n=198 subtype A1 and n=156 subtype D infections were detected. Pre-treatment, subtype D was associated with a marginally lower proportion of drug resistance compared to A1. Upon therapy initiation, 84% A1 and 88% D individuals achieved virologic suppression within 6 months. Over the >7 years follow-up, neither viral load, CD4 trajectories nor adherence differed (percent change in CD4+ T cell count and CD4+ T cell prevalence between baseline and year 7: -0.13%, p=0.001). Four HCs from A5308 and 6 HCs from the UCSF SCOPE study lost to follow-up (all Mann-Whitney p<0.03).

Conclusion: We found no difference in treatment outcomes between people in Uganda infected with subtype A1 or D HIV-1 and initiated on NNRTI-based therapy over 7-years of observation.

508 HIV CONTROLLERS MAINTAIN VIRAL SUPPRESSION DESPITE WANING T-CELL RESPONSES ON ART
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Background: Robust HIV-specific T cell responses are a hallmark of HIV controllers (HCs). We assessed the impact of antiretroviral therapy (ART) on HIV-specific T cell responses and the ability of HCs to maintain HIV suppression after discontinuation of ART.

Methods: A5308 is a prospective, open-label study of rilpivirine, emtricitabine and tenofovir disoproxil fumarate (RPV/FTC/TDF) in ART-naive HCs with viral loads (VLs) <5000 copies/mL for ≥32 months. HIV-specific T cell responses were measured by intracellular cytokine staining assays in response to HIV gag pool stimulation. Outcomes were evaluated by repeated measures GEEM models. In addition, viral load outcomes from HCs in the UCSF SCOPE cohort were included if they had been treated with ART with subsequent VL measurements after ART discontinuation.

Results: Thirty-five HCs completed ≥24 weeks of ART in A5308 and were analyzed. Before ART, higher levels of HIV-specific CD4+ and CD8+ T cell responses were associated with undetectable viremia either by the integrase single copy assay or the Abbott viral load assay. After 24–48 weeks of ART, significant decreases were observed in a broad range of HIV-specific CD4+ and CD8+ T cell responses. These included CD4+ T cells expressing IFN-γ (-0.32 ± 0.02 percentage points [%], 95% confidence interval [-0.50%, -0.14%], p<0.001), IL2 (-0.19% [-0.37%, -0.02%], p=0.03), TNFa (-0.53% [-1.1%, 0.02%], p=0.06), and CD8+ cells expressing IFN-γ (-0.23% [-0.47%, 0.05], p=0.05), TNFa (-0.32% [-0.58%, -0.07%], p=0.01), and CD107 (-0.38% [-0.82%, 0.06%, p=0.09). Furthermore, significant reductions were found in the percentages of polyfunctional HIV-specific CD4+ and CD8+ cells expressing multiple cytokines (CD4+ IFN-γ+ TNFa+ CD107+: -0.32% [-0.58%, -0.07%], p=0.01), and CD107 (-0.38% [-0.82%, 0.06%, p=0.09). Four HCs from A5308 and 6 HCs from the UCSF SCOPE study discontinued ART after a median (Q1, Q3) of 33 (25, 65) weeks of treatment. Two of the HCs had detectable VLs immediately preceding ART initiation. In the first 24 weeks after ART discontinuation, only 1 of the 10 HCs had a detectable VL (107 HIV-1 RNA copies/mL). This participant also had the highest pre-ART VL (5300 (400-6790) copies/mL).

Conclusion: ART significantly reduces both HIV-specific CD4+ and CD8+ T cell responses in HIV controllers. ART did not adversely affect controller status as HIV controllers maintained a low viral load after ART discontinuation.

509 RESTRICTED MEAN SURVIVAL TIME AS A TREATMENT MEASURE IN HIV/AIDS CLINICAL TRIALS
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Background: Under- or over-estimation of the hypothesized failure rates in the definition of non-inferiority bounds for a hazard ratio (HR) estimand can significantly impact on the probability of a trial demonstrating non-inferiority.
for a hazard ratio and complicate the interpretation of the study findings. The restricted mean survival time (RMST) measure have not been used as primary measure of efficacy in HIV/AIDS clinical trials and may offer a powerful alternative to the hazard ratio. We compared analysis based on the difference in RMST (Δ-RMST) measure with 2-treatment-effect measures in a recent HIV equivalence trial, and investigated the performance and characteristics of Δ-RMST-based analysis.

Methods: Primary and secondary virologic failure (VF) outcome measures from ACTG A5257 were reanalyzed using hazard ratio (HR) and Δ-RMST estimands and compared to the results of the original study results based on risk difference estimated by Kaplan-Meier (RDKM). A5257 equivalence bounds were transformed for each estimand assuming exponential VF distributions and A5257 design characteristics. The performance and operating characteristics of Δ-RMST-based analysis in the setting of non-proportional hazards ratio were investigated in a simulation study.

Results: Table summarizes results of the analyses in the ACTG 5257 study and alternative analyses. Analyses based on Δ-RMST globally led to similar conclusions as the published findings based on RDKM. In contrast, analyses based on HR provided some discordant equivalence conclusions compared both with the initial analyses based on RDKM and the Δ-RMST despite that appeared driven by very low failure rates in one group. Results of our simulation study indicated that the violation of the proportional hazards assumption may negatively impact the probability of declaring equivalence for a Δ-RMST based analysis.

Conclusion: The RMST based analysis could be a promising alternative measure of efficacy in HIV/AIDS clinical trials although further discussion to define non-inferiority bounds is needed.

511 EFFECTIVENESS OF SINGLE- VS MULTIPLE-TABLET REGIMENS AS 1ST-LINE ART IN ICONA COHORT

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Background: Complexity of antiretroviral therapy (ART) has been associated with adherence and virological control. Single-tablet regimens (STRs) are currently recommended for ART initiation. However, the availability of both new and generic treatment options prompts the need of an updated comparison of STRs vs multiple tablet regimens (MTRs)’ effectiveness as first-line therapy.

Methods: All naïve patients (pts) enrolled in Icona cohort, starting ART from 2011 to 2017 with currently recommended STRs or MTRs, were included. MTRs were divided in: MTR1 (2 pills QD) and MTR2 (3 pills QD or BID). Probability of virological failure (VF) [confirmed viral load (VL)<200 copies/mL after 6 months of ART] was estimated by Kaplan-Meier curves according to treatment group. The risk of VF in STRs vs MTRs group was compared by Cox regression analysis. In the subset of patients starting an integrase-inhibitors (INSTI)-based regimen a sensitivity analysis on the main end point of risk of VF and a separate analysis on the chance of achieving virological suppression (VS) [confirmed VL<50cp/mL] were performed. An ITT approach, ignoring treatment changes, was applied.

Results: 5,349 pts were included. STRs were started in 2,240 pts and MTRs in 3,109 pts (1,128 pts MTR1; 1,981 pts MTR2). ART was started in: 2011-2013 in 3,098 pts, 2014-2015 in 1,904 pts, 2016-2017 in 1,347 pts (STRs were 22%, 52% and 59% of the regimens, respectively). Regimens were based on: INSTI and generic treatment options prompts the need of an updated comparison of STRs vs multiple tablet regimens (MTRs’) effectiveness as first-line therapy.

Conclusion: Home refill is associated with improved clinical, immunological, and virologic outcomes compared to self-refill for HIV-infected adults in this private AIDS programme in South Africa. Home refill offers a promising additional option to the growing ART service delivery models and should facilitate the UNAIDS 90–90–90 targets in LMICs.
Conclusion: Among currently recommended ART regimens, STRs and 2-pills QD MTRs showed a similar impact on virological control, a proxy of patient's adherence. Among INSTI-based regimens, the number of pills/daily administrations does not seem to influence virological outcome.

Conclusion: Despite initial concerns of reduced ART adherence amongst clinically well HIV-positive people initiating ART with high CD4 counts, participants in this study initiating ART with CD4 count ≥500 cells/µL had much better virological outcomes than those with baseline CD4 count <500 cells/µL.

Figure 1: Kaplan-Meier failure estimates of confirmed virological failure (two consecutive viral loads >1000 copies/ml) according to baseline CD4 count strata after starting antiretroviral treatment.
engage hard-to-retain patients, and to increase VS among those retained under care.

### 514 PROJECT RHAE: A PILOT STUDY OF RAPID ART START AND RESTART IN BALTIMORE CITY


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**Background:** Rapid HIV Treatment Initiation (RHTI) has shown good clinical outcomes in a variety of settings. Data are limited on the feasibility of RHTI in areas predominately affecting African Americans with high rates of poverty and in previously diagnosed patients. We conducted a pilot study of RHTI and treatment reinitiation (RHTRI) in an academic medical center and public health STD clinic in Baltimore.

**Methods:** We recruited patients newly diagnosed (ND) or previously diagnosed (PD) with HIV not on ART from the Johns Hopkins (JH) John G. Bartlett Specialty Practice, the JH inpatient HIV service, the JH Emergency Department and the Baltimore City Health Department STD clinics. A baseline and 4-week survey of demographics; mental health and substance use; barriers and facilitators to care; and acceptability of RHTI/RHTRI was performed. A survey-only phase began 2/13/17 and 8/30/17 a RHTI and RHTRI phase was added in which clinic and inpatient providers prescribed ART at first clinic visit or during hospitalization. We evaluated survey, ART initiation (rapid vs. delayed) and VL data for patients recruited through 9/1/18 with >12 week follow up. VL ≥ 200 copies/mL or no post-ART VL was considered detectable.

**Results:** From 2/13/17 to 9/1/18, 70 patients enrolled (38 ND, 32 PD). Most were African American (84%), male (70%) with HIV risk factor MSM (34%) or heterosexual sex (30%). Mean age was 35±12 years and 41% had an annual household income of <$5,000/yr. 25% reported recent panic symptoms (PHQ-A), 22% major or severe depressive symptoms (PHQ-8) and 41% at-risk substance use and housing instability, immediate ART initiation after HIV diagnosis (RAPID ART).

**Conclusion:** Of 225 patients referred to the Ward 86 RAPID ART program from 2013–17, 4 declined ART, 3 were not offered ART and 2 were lost to follow-up before the RAPID visit. Of the 216 patients (96%) started on immediate ART, median age was 31 years; 7.9% women; 11.6% African American, 26.9% Hispanic, 36.6% white; 51.4% with substance use disorder; 48.1% with major mental health diagnosis; 30.6% unstably housed; median baseline CD4 441; median VL 37,011 copies/mL. Median time from HIV diagnosis to ART start: 7 days; from RAPID intake to ART start: 0 days; from HIV diagnosis to <200: 60 days. The median follow-up time for the sample was 1.09 years (0-3.92). By 1 year after follow-up, 95.8% had achieved VL suppression to <200 at least once. Among patients who initially suppressed, 15% experienced one or more episodes of viral rebound, but most (75%) resuppressed to <200 copies/mL. The median number of VL measures for the cohort over the period of follow-up was 4 (1-22). At the last recorded VL result, 92.1% of all patients were suppressed.

**Conclusion:** In an urban HIV clinic with high rates of mental illness, substance use and housing instability, immediate ART initiation after HIV diagnosis resulted in virologic suppression in >90% at last VL measurement at a median of 1.09 years after ART start. Rapid ART implementation within safety-net populations is acceptable, feasible, and successful with a multidisciplinary care team and municipal support.

### 515 HIGH RATES OF VIROLOGIC SUPPRESSION AFTER RAPID ART START IN A SAFETY-NET CLINIC

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**Background:** Little is known about long-term viral suppression outcomes for patients initiating antiretroviral therapy (ART) the same day as or shortly after HIV diagnosis (RAPID ART).

**Methods:** The Ward 86 HIV Clinic in San Francisco is a public health funded clinic that adopted immediate ART for persons newly diagnosed with HIV in 2013. Patients were referred from San Francisco testing sites or the hospital to Ward 86, offered same or next-day intake appointments, and received multidisciplinary evaluation, with education, support, and insurance enrollment/optimization. Patients were offered same-day ART and provided 3–5-day starter packs and prescriptions of ART, check-in calls, and follow-up appointments within 1-2 weeks. Demographic characteristics, baseline CD4 counts, and viral loads (VL) were extracted from the medical record. Subsequent VLs were obtained from public health surveillance data, regardless of testing site. Kaplan–Meier curves summarized distribution of times to 1st virologic suppression and suppression at the last VL measurement.

**Results:** Of 225 patients referred to the Ward 86 RAPID ART program from 2013-17, 4 declined ART, 3 were not offered ART and 2 were lost to follow-up before the RAPID visit. Of the 216 patients (96%) started on immediate ART, median age was 31 years; 7.9% women; 11.6% African American, 26.9% Hispanic, 36.6% white; 51.4% with substance use disorder; 48.1% with major mental health diagnosis; 30.6% unstably housed; median baseline CD4 441; median VL 37,011 copies/mL. Median time from HIV diagnosis to ART start: 7 days; from RAPID intake to ART start: 0 days; from HIV diagnosis to <200: 60 days. The median follow-up time for the sample was 1.09 years (0-3.92). By 1 year after follow-up, 95.8% had achieved VL suppression to <200 at least once. Among patients who initially suppressed, 15% experienced one or more episodes of viral rebound, but most (75%) resuppressed to <200 copies/mL. The median number of VL measures for the cohort over the period of follow-up was 4 (1-22). At the last recorded VL result, 92.1% of all patients were suppressed.

**Conclusion:** In an urban HIV clinic with high rates of mental illness, substance use and housing instability, immediate ART initiation after HIV diagnosis resulted in virologic suppression in >90% at last VL measurement at a median of 1.09 years after ART start. Rapid ART implementation within safety-net populations is acceptable, feasible, and successful with a multidisciplinary care team and municipal support.
Background: HIV-infected (HIV+) women appear more vulnerable to neurocognitive impairment (NCI) than HIV+ men, perhaps due to mental health factors. We assessed the combined effects of depression, HIV-serostatus, and biological sex on NCI.

Methods: 858 HIV+ (429 women; 429 men) and 562 HIV- (281 women; 281 men) from the Women's Interagency HIV Study (WIHS) and Multicenter AIDS Cohort Study (MACS) completed the Center for Epidemiologic Studies Depression (CES-D; 16 cutoff) scale and measures of psychomotor speed/attention (Trail Making Test [TMT] Part A, Stroop word reading and color naming trials, Symbol Digit Modalities Test [SDMT]), executive (TMT Part B, Stroop color-word [interference] trial), and motor function (Grooved Pegboard) over multiple visits. WIHS and MACS participants were matched according to NCI-serostatus, age, and race, and education. Generalized linear mixed models were used to examine the combined and separate associations of depression (time-varying), sex, and HIV-serostatus on NCI (T-scores<40) after covariate adjustment. Covariates included education, age, income, alcohol, recreational, and cigarette use, and prior test exposure. In HIV+, analyses, we also controlled for antiretroviral use, CD4 count (current and nadir), viral load, and prior AIDS diagnosis.

Results: The association between depression and Stroop interference trial performance differed by HIV-serostatus and sex. HIV+ depressed women had a greater odds of impairment versus HIV+ depressed men (OR=3.29, 95%CI 1.25-8.69, P=0.02) whereas HIV- depressed women and men showed a similar probability of impairment. Not only did depression exacerbate the interactive association between HIV and sex, but it also exacerbated the HIV+ female vulnerability as HIV+ depressed women also had a greater odds of impairment versus HIV- depressed women (OR=5.03, 95%CI 1.36-18.61, P=0.01) and HIV- depressed men (OR=3.14, 95%CI 1.09-9.06, P=0.03). Among HIV+ depressed individuals, women remained at a higher odds of impairment after accounting for HIV-related factors (OR=3.93, 95%CI 1.24-12.46, P=0.02). Regardless of HIV-serostatus and sex, depression was associated with greater impairment on SDMT, Stroop word reading, TMT Part B, and GP non-dominant hand (P's<0.05).

Conclusion: Depression contributes to NCI across a broad range of cognitive domains in HIV+ and HIV- individuals, but HIV+ depressed women show greater vulnerabilities in executive function. Treating depression may help to improve cognition in patients with HIV infection.

517 GENDER AND COINFECTIONS CONTRIBUTE TO IMMUNE ACTIVATION IN TREATED HIV INFECTION

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Background: Immune activation, a central component of HIV pathogenesis, has been associated with morbidity and mortality even in successfully ART-treated individuals. However, the underlying mechanism of persistent immune activation is not well understood. Here we analyze how gender and co-infections such as hepatitis B (HBV), hepatitis C (HCV) or tuberculosis contribute to persistent, low-level immune activation.

Methods: From the observational African Cohort Study (AFRICOS), 2745 specimens were collected from January 2013 to December 2016 along with medical history, sociodemographic, non-infectious comorbidities and co-infection (tuberculosis, hepatitis B/C, syphilis) data at 11 HIV clinic care and treatment sites across 5 programs in the 4 countries (Nigeria, Uganda, Tanzania, and Kenya). In total, 13 soluble immune parameters were measured by Luminox and ELISA and the data were evaluated using univariate and multivariate methods such as random forest, principal component analyses (PCA) and Bayesian multilevel logistic regression models. *P - Probability of negative effect from Bayesian multilevel logistic regression model

Results: 2745 specimens from 2268 HIV-positive and 477 HIV-negative individuals were included in this analysis. Within the 1147 cART treated and virologically suppressed HIV-positive individuals (<50 copies/ml), our study revealed significant gender specific immune activation expression patterns not present in HIV-negative individuals. Levels (pg/ml) of IP-10 (Male: 58.19, Female: 70.45, p < 0.0001), sCD163 (M=232233, F=252025, p=0.0001), and sCD25 (M=337.9, F=383.3, p=0.0012) were significantly higher in females compared to males. We next applied Bayesian multilevel logistic regression models to find associations between immune parameters and the presence of co-infections. We observed that the parameters IL-6, IP-10, and CXCL9 were significantly upregulated in patients with tuberculosis (Probability of no association p< 0.01). HCV Bayesian logistic regression model analyses revealed that patients with high levels of IFN-alpha are less frequently infected with HCV (P= 0.008).

Conclusion: Taken all together, we demonstrate the contribution of gender to immune activation in virologically suppressed individuals infected with HIV on cART (<50 copies/ml). Furthermore, elevated immune activation markers in co-infected individuals reveal that co-infections contribute to immune activation.

518 IMPORTANT SEX DIFFERENCES IN OUTCOMES FOR INDIVIDUALS PRESENTING FOR THIRD-LINE ART

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Background: Sex differences in antiretroviral therapy (ART) outcomes and in drug exposure have been reported supporting the conclusion that some ART combinations may not be as well tolerated in women compared to men. We evaluated disparities in outcomes between men and women participating in ACTG A5288, an interventional strategy trial for individuals failing 2nd-line ART in low and middle-income countries (LMIC).

Methods: Participants were assigned to cohorts based on resistance profiles and ART history: Cohort A had no LPV/r resistance, susceptibility to at least one NRTI, and stayed on their LPV/r- or ATV/r-based 2nd-line regimen; others with increasing resistance were assigned to Cohorts B, C or D and changed to a regimen that generally included DRV/r, RAL with ETR or best available NRTIs (except for those with DRV/r resistance or prior RAL exposure). The primary endpoint was virologic suppression at week 48 (VL ≤200 c/ml). In this secondary analysis, we evaluated sex differences in the primary endpoint; in confirmed virologic failure (VF: VL ≥1000 c/ml); clinical outcomes and adverse events (intent-to-treat).

Results: Women comprised 258/545 (47%) of the study population. More women than men were assigned to Cohort A. Median follow-up was 72 weeks.
Women switching from TDF to TAF experienced decreases in tubulin proteinuria (p<0.001; Table) and increases in BMD (p<0.001; Table) at W96.

Conclusion: Similar to the overall results in pivotal naive and switch trials of FTC/TAF-based regimens, cis-women who initiated or switched to TAF had significantly improved bone and renal safety parameters compared to TDF, with similar rates of virologic suppression through W96. These pooled data from 7 studies demonstrate a safety advantage for initiating therapy with or switching to TAF compared to TDF in women.

Table: Renal Urine Biomarkers and Bone Mass Density at Week 96: Female Participants

<table>
<thead>
<tr>
<th>Treatment/Regimen</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF (n=264)</td>
<td></td>
</tr>
<tr>
<td>B2m/Cr</td>
<td>0.121</td>
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<tr>
<td>BUN/Cr</td>
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<tr>
<td>ALP/Cl</td>
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<tr>
<td>Creatinine/Cr (mg/dL)</td>
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<tr>
<td>Retinol binding protein/Cr (mg/dL)</td>
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<tr>
<td>TAF (n=263)</td>
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<td>B2m/Cr</td>
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<tr>
<td>Retinol binding protein/Cr (mg/dL)</td>
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</tr>
</tbody>
</table>

520 EFFECT OF ANTIRETROVIRAL THERAPY AND IMMUNE RECONSTITUTION ON VAGINAL MICROBIOME

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Background: Host factors, including menarche, menstruation, and pregnancy are known to impact vaginal microbiome composition. Both HIV infection and the immune reconstitution associated with antiretroviral therapy (ART) can cause broad immunological changes in the vaginal microbiome. We assessed vaginal microbiome after starting ART and its association with immune reconstitution (>50 increase of CD4+ T-cells post ART initiation).

Methods: We characterized the vaginal microbiota of HIV-1 and HSV-2 coinfected women (n=94) who initiated ART in a trial of HSV-2 suppression with acyclovir in Rakai, Uganda. Vaginal swabs were collected 1-month pre-ART and at 4- and 6-months after ART initiation. Proportional and absolute abundance of vaginal bacteria was estimated by sequencing of the 16S rRNA V3V6 region.

Vaginal community state types (CSTs) were identified using proportional abundance data with Bray-Curtis distance and hierarchal clustering by Ward’s method. Microbiome composition was compared using permutational MANOVA. Changes in absolute and proportional abundance of indicator bacteria were assessed using Wilcoxon signed-rank test. Characterizing anaerobes selected by indicator analysis.

Results: We identified five vaginal CSTs among HIV+ women prior to ART initiation: one characterized by Gram-positive anaerobes (CST1), one characterized by Gram-negative anaerobes (CST2), one characterized by Gardnerella (CST3), and one characterized by Lactobacillus iners (CST4). Prior to ART, the likelihood of having a particular vaginal CST did not vary by HIV viral load or CD4+ T-cell count. ART did not have a significant impact on overall vaginal microbiome composition (p=0.74). However, among two CSTs: CST1 and CST3-abundance of Gram-positive (Anaerococcus, Finegolia) and Gram-variable (Gardnerella) indicator bacteria decreased significantly six-months post-ART (Table 1). In contrast, indicator bacteria abundance did not change significantly for women with CST2 and CST4 post-ART. Immune reconstitution was not associated with significant vaginal microbiome changes and pre-ART vaginal CST was not associated with immune reconstitution.

Conclusion: ART initiation was associated with decreases in abundance in indicator bacteria from two vaginal CSTs, which are associated with bacterial

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* Cochrane-Mantel-Haenszel Test stratified by cohort group (A vs. B/C/D)

519 TENOFORV ALAFENAMIDE VS TENOFORV DF IN WOMEN: POOLED ANALYSIS OF 7 CLINICAL TRIALS

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Background: Globally, the majority of people living with HIV are cis-women, who are underrepresented in clinical trials. Tenoforv alafenamide (TAF) has demonstrated an improved renal and bone safety profile relative to tenoforv disoproxil fumarate (TDF) in multiple randomized trials with similar efficacy. We pooled 7 studies to evaluate the efficacy and safety of TAF vs. TDF for ART initiation or switch in women.

Methods: Data from 779 cis-women in 7 randomized, double-blind clinical trials (2 in treatment-naive adults, 5 in virologically suppressed adults) through W96 were analyzed. All participants who initiated or switched to TAF-based regimens (elvitegravir/cobicistat/emtricitabine [FTC]/TAF, rilpivirine/FTC/TAF, or bictegravir/FTC/TAF) were compared with those who initiated or switched to TDF-based regimens (p<0.001; Table) at W96.

Results: Similar to the overall results in pivotal naïve and switch trials of FTC/TAF-based regimens, cis-women who initiated or switched to TAF had significantly improved bone and renal safety parameters compared to TDF, with similar rates of virologic suppression through W96. These pooled data from 7 studies demonstrate a safety advantage for initiating therapy with or switching to TAF compared to TDF in women.
521 IMMEDIATE ART INITIATION IN ACUTE INFECTION IMPROVES CLINICAL OUTCOMES, SABES STUDY

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WA, USA, 3PATH, Seattle, WA, USA, 4University of California San Francisco, San Francisco, CA, USA, 5Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Current standard of care recommends immediate ART initiation after HIV diagnosis, but recommendations are grounded in data on established infections. Aside from the high public health benefit of reduced transmission, individual benefits of starting ART in early (acute and recent) HIV infection have not been well characterized.

Methods: Two-hundred sixteen participants diagnosed with early HIV infection via monthly screening in the Sabes study (a treatment-as-prevention intervention among MSM and transwomen in Lima, Peru) were randomized to start ART immediately or after a short delay, and were categorized as having started ART within 30, 90, or >90 days after estimated date of HIV infection (EDDI). Survival analyses with log-rank tests evaluated rates of virologic suppression and adverse events in the first year after HIV diagnosis. We tested differences in CD4+ counts with Kruskal-Wallis tests. Analyses were adjusted when appropriate, for time under observation or time on ART.

Results: All 105 participants who were offered delayed ART started ART; five of 111 offered same day ART did not start during the study period (p=0.03). Total adverse events and non-ART-related adverse events were less frequent in persons starting ART within 30 days of EDDI, with a trend toward fewer ART-related events than in those who started ART after 30 or 90 days (Table). While a higher proportion of the >90-day group reached virologic suppression by 24 weeks remained significantly higher than in those who started ART after 30 or 90 days (p=0.005). Increase in CD4+ on study was not different when adjusted by time on ART, but the greatest improvements in CD4+/CD8+ ratio were in the 31-90 day group, which began with the lowest ratios (+0.55, p=0.005).

Conclusion: In early HIV infection, those who began ART within 30 days of estimated date of HIV infection had better clinical outcomes, including fewer adverse events during the first year. While several observational studies have suggested similar findings, the Sabes study is likely the only demonstration of this effect in a randomized study, where risk of confounding is minimized.

522 VIRAL BLIPS AFTER TREATMENT INITIATION DURING ACUTE HIV INFECTION

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Background: Transient episodes of low-level HIV viremia, or blips, are observed in up to 50% of individuals on suppressive antiretroviral therapy (ART) initiated during chronic HIV infection and may be associated with clinical failure, virologic evolution, and blunted reservoir decay. We described the incidence and predictors of blips after ART initiation during acute HIV infection (AHI).

Methods: Participants were offered ART during AHI from May 2009 to August 2018 in Bangkok, Thailand. Those who continued ART for ≥1 year after viral suppression (confirmed HIV RNA <50 copies/mL) were included in these analyses. A blip was defined as any HIV RNA 50-999 copies/mL immediately preceded and followed by HIV RNA <50 copies/mL without a change in ART. Negative binomial regression was used to calculate rate ratios (RRs) and 95% confidence intervals (CIs) for associations of participant characteristics at ART initiation with blips. Fiebig stage and factors that were significant (p<0.05) in unadjusted models were included in the final multivariable model.

Results: Of 299,004 samples screened, 564 participants were enrolled during AHI and 416 satisfying inclusion criteria were monitored for blips for a median of 2.7 (interquartile range [IQR] 1.9-3.9) years after achieving viral suppression. Participants had median age 26 (IQR 23-31) and were predominantly heterosexual with sex with men (92.6%) with HIV subtype CRF01_AE (77.2%). Thirty (7.2%) participants demonstrated blips with incidence 2.7 (95% CI 1.8-3.7) per 100 person-years. Among 35 blips observed, 18 (51.4%) were 50-75 copies/mL, 14 (40.0%) were 76-199 copies/mL, and 3 (8.6%) were 200-999 copies/mL. Characteristics at ART initiation that were independently associated with blips included HIV RNA >6 log10 copies/mL (RR 2.51 [95% CI 1.04-6.04], compared to ≤6 log10 copies/mL and CD4 ≤350 cells/mm3 (RR 2.46 [95% CI 1.00-6.03], compared to >350 cells/mm3). There was a non-significant trend towards increased blips after ART initiation in later Fiebig stages (Fiebig III/IV RR 1.45 [95% CI 0.63-3.13], Fiebig V RR 2.74 [95% CI 0.73-10.35], compared to Fiebig I/II), controlling for HIV RNA and CD4.

Conclusion: Viral blips were uncommon and of generally low magnitude after ART initiation during AHI, suggesting a potential benefit of early ART initiation. As with ART initiation during chronic infection, higher HIV RNA and lower CD4 were predictive of blips. Further follow-up is needed to evaluate associations with viral reservoirs and clinical outcomes.

523 BENEFITS OF INSTI-BASED REGIMEN AT THE TIME OF PRIMARY HIV INFECTION

Raphael Veil1, Isabelle Poizot-Martin2, Jacques Reyes3, Cécile Goujard4, Remonie Seng1, Pierre Delobel1, Laurent Cottele1, Claudine Duvivier5, David Rey5, Laurent...
what time the protective effect of ART is achieved in reservoirs, e.g. the rectum or semen, which is particularly important in men who have sex with men (MSM). We carried out this study to quantify HIV-1 RNA decay in rectal mucosa and semen over 64 weeks (64w) in ART-naive HIV-infected MSM starting dolutegravir + abacavir + lamivudine (DTG/ABC/3TC).

Methods: Longitudinal cohort study of ART-naive HIV-infected MSM. Rectal mucosal sampling was performed by high-resolution anoscopy (HRA) when possible, or by insertion of swab directly into rectum. Seminal plasma was obtained by centrifugation of semen collected at home within 2 hours before HIV-1 RNA quantification (COBAS® Ampliprep/Taqman) of rectal mucosa and seminal plasma samples was performed at day 1 of initiating-ART (baseline) and every 4 weeks until w20 (all) and w64 (6 of 12).

Results: 118 plasma, 117 seminal (66-HRA and 31-direct) and 89 seminal samples from 12 MSM, with median (IQR) age 36 (32-42) years and median baseline-CD4+ 459 (401-520) cell/µL, were included. At baseline, HIV-1 RNA was detectable in all plasma, seminal and 10 of 12 rectal samples with median viral load (VL) of 4.58 (4.32-4.84) log_{10} copies/mL, 4.10 (3.59-4.44) log_{10} cp/mL and 4.54 (3.82-5.11) log_{10} cp/swab, respectively. All participants achieved plasma virologic suppression by w20 (7 of them by w4) (Figure). At w20, HIV-1 RNA was detectable in 5 of 12 seminal and 6 of 12 rectal samples with median VL of 2.50 (2.08-2.73) log_{10} cp/mL and 2.24 (2.14-2.46) log_{10} cp/swab, respectively. Of them, 3 seminal and 3 rectal samples were from aviremic individuals at w4. Median w20-CO = was 678 (532-797) cell/µL. At w64, HIV-1 RNA was only detectable in 1 of 6 seminal (VL=2,26 log_{10} cp/mL) and 1 of 6 rectal (VL=1,81 log_{10} cp/swab) samples.

Conclusion: Viral decay after initiating DTG/ABC/3TC is slower in rectal mucosa and semen than in plasma. Half of the patients achieve undetectable HIV-1 RNA level in secretions at six months, although in some patients viral shedding persists up to one year.

525 MODELING ANTIRETROVIRAL DRUG RESISTANCE IN SOUTH AFRICA, THE MARISA PROJECT

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Background: The scale-up of antiretroviral therapy (ART) from 2004 in South Africa substantially reduced AIDS-related deaths and new HIV infections. However, its success is threatened by the emergence of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI). In this context, the MARISA project (Modelling Antiretroviral drug Resistance In South Africa) aims at investigating the time trends and driving factors of NNRTI resistance by integrating local specificities of HIV epidemiology and the evolution of drug resistance.

Methods: MARISA is a compartmental model built to capture the emergence and spread of NNRTI resistance in South Africa in 2005-2016. A first dimension accounts for the continuum of care: infection, diagnosis, first-line treatment with suppression or failure, and second-line treatment. Other dimensions include: disease progression (CD4 counts), NNRTI resistance, and gender. Model parameters are informed using data from the IeDEA-SA cohorts and literature.
estimates, or fitted using outputs from the Thembisa/UNAIDS models. Countertropical scenarios are examined to assess the impact of increased treatment rates, earlier implementation of the treat-all policy, early switch to second-line treatment in case of failure, and drug-resistance testing of ART initiators.

**Results:** MARIISA can reproduce the time trends of HIV in South Africa in 2005-2016, with a decrease of new infections, undiagnosed individuals, and AIDS-related deaths (Fig 1). It also captures the dynamics of NNRTI resistance spread: a steady increase of acquired drug resistance (ADR, affecting 83% of individuals falling first-line treatment in 2016), and of transmitted drug resistance (TDR, reaching 7% of ART initiators in 2016). During that period, increasing treatment coverage would have resulted in fewer new infections and deaths, at the cost of higher TDR (>34% in 2016 for doubling the treatment rate). Earlier implementation of the treat-all policy by 5 years would have had a similar effect. Conversely, improving switching to second-line treatment would have led to lower TDR (18% in 2016 for doubling the switching rate) and fewer new infections and deaths. Implementing baseline drug resistance testing would have had little impact.

**Conclusion:** A rapid ART scale-up and delayed switching to second-line treatment were the key drivers of the observed spread of NNRTI-resistance in South Africa. Timely switch to second-line ART would have reduced but not prevented the spread of NNRTI resistance.

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Robert P. McClung, Cheryl B. Ocephia, Neeraja Saduvala, Alexandra M. Oster, Walid Heneine, Jeffrey A. Johnson, Angela L. Hernandez

**Background:** Drug resistance testing based on protease (PR) and reverse transcriptase (RT) gene mutations is recommended for all patients at entry to HIV care and should include testing for integrase (IN) mutations when transmitted resistance to integrase strand transfer inhibitors (INSTIs) is a concern. HIV sequence data from drug resistance tests are reported to the U.S. National HIV Surveillance System (NHSS) as a part of routine surveillance activities. We analyzed data from 2013−2016 to understand trends in HIV sequence reporting and the prevalence of transmitted drug resistance-associated mutations (TDRMs).

**Methods:** For persons with HIV infection diagnosed during 2013–2016 and no evidence of prior antiretroviral therapy use, we analyzed sequences collected within 3 months of diagnosis and reported to NHSS by 12/2017. We included states in which >20% of HIV diagnoses during the 4-year period had a analyzable sequence and defined TDRMs using the CDC HIV-1 surveillance mutation list. We examined reporting by sequence type, prevalence of TDRMs and temporal trends for sequence types reported and TDRMs detected from 2013–2016.

**Results:** The 23 states reported sequences for 36,288 (32%) of 113,121 HIV diagnoses from 2013–2016. Among persons with eligible sequences, prevalence of IN sequences obtained increased from 3.7% in 2013 to 23.0% in 2016 while prevalence of PR/RT sequences decreased from 99.2% to 93.0%. TDRMs were detected for 6,680 (10.9%) sequences, including TDRMs to non-nucleoside reverse transcriptase inhibitors (NNRTIs) (11.9%), nucleoside reverse transcriptase inhibitors (nRTIs) (6.8%), protease inhibitors (PI) (4.3%), and INSTIs (0.8%). INSTI TDR prevalence did not differ by sex, age group, or race/ethnicity. Prevalence was low for TDRMs to 2 drug classes (2.4%) or ≥3 drug classes (0.3%). TDRM prevalence increased from 2013 to 2016 for NNRTIs (11.3% to 12.4%, p<0.012) and INSTIs (0.8% to 1.1%, p<0.041) but not for other drug classes.

**Conclusion:** NNRTI TDR prevalence continues to increase, outpacing all other HIV drug classes. During this period of increasing INSTI use (and IN sequence reporting) INSTI TDRM prevalence also increased. Though drug resistance testing based on PR/RT gene sequencing is recommended for all new HIV diagnoses, an increasing proportion have only an IN sequence reported, precluding detection of TDRMs for nRTIs, which remain a critical backbone of multidrug therapy.

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**IMPACT OF PRETREATMENT DRUG RESISTANCE ON TREATMENT OUTCOME IN THE ITREMA TRIAL**

Lucas E. Hermans, Laura Marije Hofstra, Rob Schuurman, Rob ter Heine, Hugo Tempelman, Willem D. Venter, Monique Nijhuis, Annemarie Wensing

**Background:** Prevalence of pre-treatment drug resistance (PDR) in sub-Saharan Africa has risen during scale-up of antiretroviral treatment (ART) and may result from either exposure to previous ART or infection with resistant viral strains. We assess prevalence of PDR and its impact on treatment outcomes in the first year of ART.

**Methods:** The ITREMA open-label randomized clinical trial (ClinicalTrials registration NCT03357588) compares treatment monitoring approaches in response to viral rebound in rural South Africa. Of 501 participants, 294 were on stable first-line ART, and 207 initiated first-line ART. For these 207, plasma collected prior to initiation was analysed batchwise. Population-based RT sequencing was performed. PDR was defined as detection of at least one 2017 IAS-USA listed major mutation. Viral load testing was performed at week 24 and week 48 of ART, and annually thereafter. Logistic regression adjusted for gender, age and baseline CD4-count was used to estimate adjusted odds ratios (aOR) for viral rebound (viral load ≥1000 copies/mL) within the first year of ART.

**Results:** All 207 newly initiated patients received efavirenz-based ART. 60.4% (125/207) were female. Median age was 38.8 years (IQR: 31.4–46.7). Median CD4-count at ART initiation was 191 cells/mm3 (IQR: 70–355). 194 patients had a baseline sample with viral load ≥250 copies/mL available for sequencing. PDR was detected in 12.9% (25/194): 20.6% of patients (34/165) with available follow-up had viral rebound during the first year of ART. Patients with PDR more frequently experienced rebound (53.3% versus 17.4%, p<0.003). 13 patients reported prior use of ART, which was associated with PDR (aOR 1.37 [95%CI: 1.13–1.67], p=0.0017). When correcting for sex, age, baseline CD4 and disclosed previous ART exposure, PDR remained associated with viral rebound (aOR 1.42 [1.22–1.64], p<0.0001). Upon differentiation between NNRTI-PDR and dual-class PDR, dual-class PDR was strongly associated with viral rebound (aOR 2.56 [1.22–1.64], p<0.0001). When correcting for sex, age, baseline CD4 and disclosed previous ART, which was associated with PDR (aOR 1.37 [95%CI: 1.13–1.67], p=0.0017). When correcting for sex, age, baseline CD4 and disclosed previous ART exposure, PDR remained associated with viral rebound (aOR 1.42 [1.22–1.64], p<0.0001). Upon differentiation between NNRTI-PDR and dual-class PDR, dual-class PDR was strongly associated with viral rebound (aOR 2.56 [2.00–3.27], p<0.0001) but NNRTI-PDR was not (aOR 1.12 [0.96–1.31], p<0.06). 13 patients reported prior use of ART, which was associated with PDR (aOR 1.37 [95%CI: 1.13–1.67], p=0.0017). When correcting for sex, age, baseline CD4 and disclosed previous ART, which was associated with PDR (aOR 1.37 [95%CI: 1.13–1.67], p=0.0017). When correcting for sex, age, baseline CD4 and disclosed previous ART, which was associated with PDR (aOR 1.37 [95%CI: 1.13–1.67], p=0.0017). When correcting for sex, age, baseline CD4 and disclosed previous ART, which was associated with PDR (aOR 1.37 [95%CI: 1.13–1.67], p=0.0017). When correcting for sex, age, baseline CD4 and disclosed previous ART, which was associated with PDR (aOR 1.37 [95%CI: 1.13–1.67], p=0.0017).

**Conclusion:** PDR was detected in 13% of patients initiating first-line ART in this study. Dual-class PDR increased the risk of viral rebound, but solitary NNRTI-PDR did not. Reported prior ART use increased the risk of PDR. Efforts to uncover previous ART use should be made before initiating first-line treatment.

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**INTEGRATE GENOTYPIC TESTING AND DRUG RESISTANCE AMONG NEW HIV DIAGNOSES IN NEW YORK**

Zhengyan Wang, Randall V. Collura, Mark Rosenthal, Jayleen K. Gunn, Joanne Gerber, Brenda Moncur, Bridget J. Anderson

**Background:** HIV treatment guidelines state that genotypic resistance testing should be obtained at diagnosis. Integrase strand transfer inhibitors (INSTIs)
have emerged as initial regimens for persons newly diagnosed with HIV because of their clinical effectiveness and tolerability. However, with widespread use of INSTIs, the concerns of transmitted integrase (IN) drug resistance and risk of virologic failure are rising among clinicians. The aims of this analysis were to explore 1) the frequency of IN testing and risk factors associated with IN testing, 2) the rate of transmitted IN drug resistance, and 3) common clinically significant INSTI-resistance mutations among persons with newly diagnosed HIV in New York State (NYS).

Methods: Persons aged 13 and older diagnosed between 2013–2017 and reported to the NYS HIV registry were included in the study. The first IN nucleotide sequence for an individual was identified and flagged as an “initial” test if ordered within 3 months of the HIV diagnosis date. Persons with 1) incomplete diagnosis or test dates or 2) invalid sequences were excluded. Multivariable analysis was used to test the association between IN initial testing and sociodemographic factors. Sequences were analyzed using the NYS in-house Resistance Analysis System and compared with major INSTI resistance mutations published on Stanford HIV Drug Program website.

Results: Overall, 15,345 persons were included; 59.2% had any resistance testing within 3 months of diagnosis. 20.9% (3,209) had initial IN testing; 2.5% had only IN testing. Initial IN testing increased significantly from 5.6% in 2013 to 32.4% in 2017. The likelihood of having initial IN test was lower in minorities than whites (RR: 0.87, 95% CI: 0.79-0.96), and higher among males with a history of male-to-male sexual contact than heterosexuals (RR: 1.31, 95% CI: 1.09-1.58). Resistance to zidovudine (ZDV) was seen in 0.7% (24) of 3,209 persons with initial IN tests. The most commonly clinically significant INSTI-resistance mutations were: E138A/K, N155H/S, Q148R/H/K/R, E92Q/G, T69A/Y, G140C/S, Y143C/R.

Conclusion: Clinician ordering of initial resistance testing lags current guidelines. These data indicate that initial IN testing has increased among persons newly diagnosed with HIV. While IN drug resistance remains low, clinically significant major mutations observed suggests that transmitted IN resistance is emerging; it is important for clinicians to order IN test at time of HIV diagnosis for treatment decision.

529 HIV-TRANSMITTED DRUG RESISTANCE IN CISGENDER MSM AND TRANSGENDER WOMEN IN LIMA, PERU

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Background: Transmitted drug resistance (TDR) mutations threaten the efficacy of first-line antiretroviral therapy (ART) in individuals initiating treatment. In Peru, genotypic resistance profiling is not routinely performed at ART initiation, and administration of a partially effective regimen can select for further resistance and lead to virologic failure. In Peru, previously reported TDR prevalence ranged from 1.0 – 4.7% as last reported before 2012.

Methods: We obtained HIV sequence data from 3 parent studies conducted in 2013 – 2017 of ART-naive cisgender men who have sex with men (cis-MSM; n=332) and transgender women (TW; n=144) in Lima, Peru. Consensus gene sequences of the 2,510 – 3,209 region of HIV pol (not codifying the entire protease and integrase genes) were interrogated for TDR using the Stanford HIVdb interpretation algorithm and scored for resistance to common nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). We calculated binomial proportions with a 95% confidence interval. y

Results: Eighty (16.8%) of 476 individuals had TDR (95% CI: 13.6, 20.5). Twenty-two unique base changes totaling 94 TDR mutations were present. Mutations conferring resistance to NNRTIs represented 88% of total TDR, and prevalence of a singular mutation (15.1%) was more common than 2 (1.3%), or 3+ (0.4%) mutations. TDR conferring high-level resistance to any ART was found in 44 (9.2%) individuals (95% CI: 6.8, 12.2). Cis-MSM were not more likely than TW to have acquired TDR (16.9% vs 16.7%, p=1.00). Year of diagnosis, age, diagnosis as incident or prevalent infection, or residence district were likewise not associated with risk of TDR.

Conclusion: TDR prevalence within these cohorts was nearly 4-fold higher than the highest previously reported prevalence in any population in Peru. Over half of observed TDR conferred high level resistance to drugs used in first-line ART, and resistance was largely to NNRTIs. Our findings support the WHO recommendation to consider integrase strand transfer inhibitors in first-line regimens, since empiric use of NNRTIs may often fail in this population. Our study also represents the first differentiated evaluation of TDR in cis-MSM vs TW in Peru and demonstrates that although TW are at higher risk of HIV acquisition than cis-MSM, they are at similar risk of acquiring virus with TDR.

PREDICTION OF ART-NAIVE DRUG RESISTANCE IN BOTSUWANA

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Background: Population-level monitoring of pre-treatment drug resistance (PDR) to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and integrase strand transfer inhibitors (INSTIs) in the era of antiretroviral therapy (ART) scale-up and the treat-all strategy, can inform public health strategies and interventions.

Methods: We investigated the rate of PDR in a large community cluster-randomized study termed Botswana Combination Prevention Project (BCPP) conducted across 30 Botswana communities in 2013-2018. BCPP enrolled all consenting adult citizens residing age 16–64 who lived in a random sample of approximately 20% of households. Blood specimens from HIV-positive ART-naive participants including seroconverters were collected from 2013 to 2018. HIV sequences were obtained by long-range HIV genotyping. PDR was identified by the presence of surveillance drug resistance mutations (SDRMs) associated with NRTI, NNRTI and major INSTI according to the Stanford HIV DRM database. Viral sequences were screened for G- to A hypermutations (HM).

Results: Among 4473 participants with available viral sequences, 807 (18%) were ART-naive at the time of sampling. Prevalence of pre-treatment SDRM associated with NRTI-, NNRTI- and INSTI among ART-naive participants was 1.6%, 4.9% and 1.5%, respectively. The proportion of communities with pre-treatment SDRM and ranges of SDRM across communities are shown in Table 1. Overall, prevalence of SDRMs was low across participating communities. Among NRTI SDRM, M184V was the most common and was identified in 20% of the communities. NRTI SDRM were detected in all the communities, with the most common T180M found in 30% of communities. The most common INSTI SDRM was K263X which was identified in 17% of communities. In a subset of 83 ART-naive seroconverters, the prevalence of TDR mutations associated with NRTI, NNRTI- and INSTI-resistance was 1.2%, 3.6% and 5.2%, respectively. The most common TDR mutations were: NRTI (K219E/S, 1.2%), NNRTI (A98G, 1.2%), 1.2%, R263K, 1.2%; INSTI (E92Q 1.2%; Q95K 1.2%; G163K/R, 1.2%).

Conclusion: We found a low prevalence of pre-treatment NRTI-, NNRTI- and INSTI-associated SDRM and TDR among ART-naive persons in this large population-based sample of HIV-positive adults from across Botswana. Seroconverters identified in large cohorts and trials provide valuable assessment of TDR mutations on a population level.
Background: Increasing numbers of HIV-positive adolescents and adults in South Africa are developing virological failure on second-line, protease inhibitor-based antiretroviral therapy (ART) regimens. HIV drug resistance testing is performed routinely in the public sector to determine the need for third-line ART and to inform regimen selection. We conducted an analysis of the routine data to assess the frequency and patterns of HIV drug resistance and to estimate the predicted need for third-line ART.

Methods: Cross-sectional analysis of all HIV genotypic resistance tests conducted by the National Health Laboratory Service in KwaZulu-Natal, South Africa (Jan 2015 – Dec 2016), for adults and adolescents (age ≥10 years) on second-line, protease inhibitor-based ART regimens. HIV drug resistance mutations were defined as major, accessory, or other according to the HIVdb algorithm. PR mutations were defined as major, accessory, or other according to the HIVdb algorithm.

Table 2. Distribution of pre-treatment drug-resistant mutations among ART-experienced participants across KwaZulu-Natal communities (MTR=2015/2016) and Marico (2017).

Results: Three hundred and fifty-two people were included (59% female, median age 34 years). The median duration of second-line ART was 30 months (IQR 18–48), and 95% were on a lopinavir/ritonavir-based regimen. Median viral load at time of genotyping was 4.98 log10 copies/mL. Overall, 284/352 (81%) had at least one RT mutation and 117 (33%) had at least one major PR mutation. Among those with major PR mutations, the median number of major PR mutations was 3 (IQR 3–4) and the median number of total PR mutations was 5 (IQR 4–6). Presence of at least one major PR mutation was associated with longer duration on second-line ART (>24 months vs. ≤24 months, aOR 2.28, 95% CI 1.39–3.73) and older age (for each additional year, aOR 1.01–1.05). Of those requiring third-line ART, 21 (18%) had intermediate or high-level resistance to darunavir/ritonavir, 34 (29%) had intermediate or high-level resistance to efavirenz, and 44 (38%) had intermediate or high-level resistance to tenofovir and zidovudine (Figure).

Conclusion: Most people did not have major PR mutations and thus would not need third-line ART. Of those requiring third-line ART, most would need an integrase inhibitor ± etravirine in addition to DRV/r and recycled nucleoside reverse transcriptase inhibitors to form a suitable third-line regimen.
IN-DEPTH CHARACTERIZATION OF HIV RESISTANCE TO INTEGRASE INHIBITORS IN BRAZIL

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Background: Due to increasing HIV drug resistance, Brazil was one of the first countries to adopt Dolutegravir (DTG) in first-line antiretroviral therapy (ART). The Ministry of Health of Brazil offers genotyping tests to all individuals under an integrase inhibitor (INI) based regimen experiencing virological failure. Using real life data, we aimed to characterize HIV genotypic resistance toRaltegravir (RAL) and DTG in Brazil in order to better understand factors related to the development of INI resistance-associated mutations (RAM), and to depict INI RAM transmission chains.

Methods: HIV integrase sequences from 2012-2018 were selected from the National System for Genotyping Control. The presence of INI RAM (Stanford HIVdb Program) and HIV subtype (Rega HIV Subtyping tool) were characterized. Socio-demographic, clinical (CD4 count and viral load;VL), and ART history data were assessed. A Pearson Chi-square test was carried out. INI RAM transmission clades were characterized by Bayesian phylogenetics.

Results: We analyzed 1,467 HIV integrase sequences from RAL- and/or DTG-experienced individuals. HIV resistant strains were identified in 21.7% for RAL and 0.7% for DTG. In 2017, following the use of DTG in first-line ART, individuals on RAL-based regimen switched to DTG. As a reflection of DTG's higher genetic barrier, resistance to INI has been slightly decreasing to 13.7% and 0.3% in 2018 for RAL and DTG, respectively. Indeed, we did not identify any DTG resistant lineages in samples from individuals under DTG first-line ART. The prevalence of RAL and DTG resistant strains was similar, regardless of demographic and clinical data, including regional sustained VL levels. INI RAMs at positions G140 (7.0%) and E138 (1.0%) were most prevalent. Overall, subtype B (69.9%) was the most prevalent, followed by C (13.7%), F (8.9%) and recombinant forms (6.7%). Sequences presenting INI RAM were dispersed in phylogenetic trees for subtypes B and C, showing no specific INI RAM transmission clade, considering both the national level and the five Brazilian geographic regions, separately.

Conclusion: INI RAM monitoring revealed a short-term decrease in resistance to INI, even after DTG large-scale use. In addition, phylogenetics revealed that INI RAM does not occur in a particular population group or geographic region. Hence, the successful pioneering implementation of DTG goes beyond costs savings but healthcare efficacy, corroborating to sustainability of DTG as first-line ART in a public health program.

IN-G-RESISTANCE DYNAMICS FROM 2007 TO 2017 IN ITALIAN CLINICAL ISOLATES

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Background: We evaluated the prevalence of resistance to integrase inhibitors (INIs) over-time in clinical isolates from HIV-1 infected patients (pts) according to the type of treatment received.

Methods: We included 3004 integrase plasma genotype resistance tests (GRTs) from 2598 HIV-1 infected pts (INI-naïve (drug-naïve and -experienced) and INI-treated). INI-resistance (INI-R) prevalence and genotypic susceptibility (GS) were evaluated from 2007 to 2017. To estimate the extent of pts with limited drug-options, cumulative class resistance (≥1 major resistance mutation [MRM] to PI, NRTI, NNRTI and/or INI among all GRTs available) was evaluated.

Results: Overall, INI-R decreased from 13.7% in 2007 to 4.7% in 2017 (p=0.001), in conjunction with an increased full GS to all INIs (p<0.05; Figure 1A). Among 2493 isolates from INI-naïve pts (N=2224), INI-R was stably low over time (≤1.3%) in association with a high GS to all INIs (≥95.6%; Figure 1B). INI MRRMs were found in 10 drug-naïve pts: T66I (N=1); E138K (N=1); Y143C/H/R (N=1); Q148H=V150M=140N (N=1); N155H (N=1); R263K (N=5). Among 511 isolates from 374 INI-treated pts, INI-R decreased from 42.9% in 2007 to 28.7% in 2017 (p=0.039). Concerning the type of treatment, in isolates under INI±2 drug classes INI-R decreased from 45.7% to 20.6% (p=0.006), in conjunction with an increased full GS to INIs (Figure 1C). Similar trends were found in isolates under
**536 ANTIRETROVIRAL DRUG RESISTANCE IN PATIENTS RECEIVING CARE AT ETHIOPIAN HEALTH CENTERS**

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Lund University, Lund, Sweden

**Background:** We have previously reported high rates of virological suppression in patients starting antiretroviral treatment (ART) at Ethiopian health centers, with no impact related to concomitant tuberculosis (TB) therapy. We further investigated patterns of antiretroviral drug resistance during ART among these persons, with particular regard to the effect of TB on selection of drug resistance.

**Methods:** Participants were identified from a cohort of 812 ART-naive adults at Ethiopian health centers (recruited 2011-2013). At inclusion into the cohort, all subjects were investigated for active TB. Sequencing was performed on plasma samples from subjects with viral load (VL) ≥500 copies/ml (cpm) at 6 and/or 12 months after ART initiation. Pre-ART plasma samples were genotyped at the BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, University of British Columbia, Vancouver, BC, Canada.

**Background:** The Kingdom of Eswatini (formerly known as Swaziland) has the highest global adult prevalence of HIV at 27.2%. The country has expanded access to HIV testing services and increased antiretroviral treatment (ART) coverage in recent years from 49% (2013) to 85% (2017). The MaxART Early Access to ART for All Implementation Trial launched in 2014 to assess the scalability and clinical outcomes of offering ART to all people living with HIV (PLHIV) in Eswatini, regardless of CD4 cell count and WHO clinical stage. As a secondary endpoint, we sought to determine the extent of HIV drug resistance (HIVDR) in all treatment-naive individuals initiating ART in the Hhohho region of Eswatini.

**Methods:** The trial was a 3-year randomized stepped-wedge design open to enrolment for PLHIV attending 14 rural health facilities in the Hhohho region. Exclusion criteria included age (<18yo), pregnancy, breastfeeding, and previous antiretroviral (ARV) drug exposure except for prevention-of-mother-to-child-transmission interventions. Pre-ART plasma samples were genotyped at the BC Centre for Excellence in HIV/AIDS, Canada. Sanger sequences were generated targeting the protease and reverse transcriptase genes. HIVDR was predicted using the Stanford HIVdb algorithm (v.8.6.1).

**Results:** 3485 PLHIV were enrolled, with pre-ART samples and HIV sequences available for 2626 (75.4%) and 2585 (74.2%) participants, respectively. HIVDR was detected in 658 (25.3%) sequences, with 289 sequences (11.2%) containing mutations conferring HIVDR to first-line drugs efavirenz/nevirapine (EFV/NVP; Table 1). E138A was detected in 12/64 (18.8%) patients with DRM who had TB. Conclusion: The first cases of transmitted INI-R, the stable INI-R prevalence under dual regimens and the consistent proportion of INI-exposed pts showing exhausted treatment options remain important concerns. These findings confirm that INI-R monitoring remains crucial for all categories of pts to avoid loss of treatment options.

**Table 1. Factors associated with acquiring antiretroviral drug resistance in patients receiving ART at Eswatini health centers.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>N</th>
<th>Value</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>577</td>
<td>32 (28-40)</td>
<td>1.01 (1.00-1.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Male gender</td>
<td>577</td>
<td>274 (47.1%)</td>
<td>1.72 (1.0-2.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>CD4 count (cells/mm³)</td>
<td>576</td>
<td>195 (71-274)</td>
<td>1.01 (1.00-1.01)</td>
<td>0.09</td>
</tr>
<tr>
<td>Viral load (log10)</td>
<td>562</td>
<td>5.1 (4.9-5.5)</td>
<td>2.41 (1.2-3.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>577</td>
<td>55 (15.5%)</td>
<td>1.15 (0.5-2.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>MUAC (cm)</td>
<td>577</td>
<td>23 (21-25)</td>
<td>0.00 (0.0-0.8)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

**Figure 1. Prevalence of resistance to integrase inhibitors (INI) and proportion of nucleoside with full genotypic susceptibility in this Eswatini cohort from 2011 to 2015 in any ART group, according to treatment types.**

**Conclusion:** INI-R is decreasing in Italy, confirming a good clinical practice. However, the first cases of transmitted INI-R, the stable INI-R prevalence under dual regimens and the consistent proportion of INI-exposed pts showing exhausted treatment options remain important concerns. These findings confirm that INI-R monitoring remains crucial for all categories of pts to avoid loss of treatment options.
surveys should be routinely implemented to assess predicted efficacy of current and possible future ARV regimes as the programme expands.

<table>
<thead>
<tr>
<th>Resistance Level</th>
<th>EFV Class</th>
<th>NNRTI Class</th>
<th>NNRTI Class (3-4)</th>
<th>NNRTI Class (5-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-level</td>
<td>7.3% (7.2-7.4%)</td>
<td>6.0% (4.0-7.0%)</td>
<td>7.2% (6.2-8.2%)</td>
<td>7.5% (6.5-8.5%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8.9% (8.2-9.3%)</td>
<td>6.2% (4.0-8.0%)</td>
<td>9.1% (7.2-11.2%)</td>
<td>8.6% (6.7-10.7%)</td>
</tr>
<tr>
<td>High-level</td>
<td>9.2% (8.4-10%)</td>
<td>9.3% (7.3-11.3%)</td>
<td>23.3% (21.1-25.6%)</td>
<td>22.2% (19.6-24.8%)</td>
</tr>
</tbody>
</table>

**Conclusion:** Our model shows the potential benefit of the introduction of DTG for attenuating the rise of NNRTI PDR. As safety issues related to neural tube defects in newborns may limit the use of DTG in women with child-bearing potential, the model shows that the effect of introducing DTG would be largely reduced if its use is limited to men only. However, this can be almost completely overcome if DTG is used in women with low risk of pregnancy.

539 A COMPARATIVE EVALUATION OF HIV-1 CAPSID INHIBITOR SUSCEPTIBILITY

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**Background:** Inhibitors that target HIV capsid assembly and virion maturation represent a promising new class of antiretroviral compounds. In this study, we used an enhanced cell-based infectivity assay, based on the assembly of resistance test vectors (RTV), to evaluate the susceptibility of patient isolates and gag gene site-directed mutants to several maturation and assembly inhibitors.

**Methods:** Gag–protease coding regions from 111 HIV patient isolates, previously submitted for routine drug resistance testing, were amplified from plasma specimens and used to generate gag–pro RTVs that express firefly luciferase. In addition, gag–pro substitutions associated with reduced susceptibility to assembly or maturation inhibitors were introduced into an RTV containing a “wild-type” gag–pro sequence; site-directed mutants (SDM). Susceptibility to two maturation (CA-SP1 cleavage site) inhibitors and one capsid assembly/disassembly inhibitor (CAI) were determined.

**Results:** Susceptibility to both CA-SP1 cleavage site inhibitors varied more than 100-fold across the 111 patient isolates, while susceptibility to the CAI varied less than 4-fold. Consistent with previous studies, viruses containing naturally occurring polymorphisms (68/111, 61%), or site directed mutations, within the “QVT” motif (aa positions 369-371) exhibited large reductions in CA-SP1 cleavage site inhibitor activity. In addition, six of 43 isolates lacking QVT polymorphisms also exhibited notable reductions in CA-SP1 inhibitor susceptibility. In contrast, only one patient isolate contained a polymorphism (N74D) that has been associated with reduced susceptibility to CAI (L56I, M66I, Q67H, N74D, A105E). SDMs containing single L56I, M66I and A105E substitutions exhibited large reductions in CAI susceptibility (FC>200), whereas the impact of Q67H and N74D was small (FC=1.8 and 2.6, respectively). Notably, L56I, M66I and Q67H substitutions also conferred modest cross-resistance (3 to 10-fold) to the CA-SP1 cleavage site inhibitors.

**Conclusion:** Susceptibility to HIV-1 capsid inhibitors that vary in their mechanism of action were assessed using a cell-based pseudovirus reporter assay. Variation in susceptibility across more than 100 patient isolates was much more pronounced for CA-SP1 cleavage site inhibitors compared to a CAI. A small number of mutations conferred large reductions in CAI susceptibility and cross-resistance to CA-SP1 cleavage site inhibitors.
IDENTIFICATION OF ARV-RESISTANCE MUTATIONS OUTSIDE OF THE DRUG-TARGET GENE

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Background: Resistance to antiretrovirals (ARVs) continues to impair the overall quality of life for some HIV-infected individuals, despite the effectiveness of combination antiretroviral therapy (cART). The goal of this study was to explore the ability of HIV-1 to escape inhibition by ARVs in vitro by acquiring resistance mutations outside of the drug-target gene.

Methods: We propagated HIV-1 in T-cell lines and measured virus replication kinetics in the presence or absence of low (sub-IC50) concentrations of ARVs, testing at least one representative of each class of inhibitor. We selected for viral escape mutants exhibiting at least partial resistance to ARVs as indicated by efficient replication in the presence of the inhibitors. A number of analyses were then performed to validate the ability of the selected mutations to confer ARV resistance.

Results: Long-term passage of wild-type (WT) virus in the presence of ARVs led to the selection of ARV-escape mutants lacking changes in the target gene, but instead containing substitutions in the envelope (Env) glycoprotein and occasionally in Vpu. We have now identified a panel of partially ARV-resistant NL4-3 Env mutants that arose in the presence of protease, reverse transcriptase (RT), and integrase inhibitors. Mutations were selected in the context of two different T-cell lines, Jurkat and CEM12D7, that favor cell-cell and cell-free transmission, respectively. Remarkably, the same ARV-resistant Env mutant was selected in both cell lines. We extended our analyses to a transmitted-founder, subtype C virus, CH185_TF, which acquired a mutation in Env when propagated in the presence of Dolutegravir (DTG). These data demonstrate that ARV-resistant Env mutants arise in the context of three different T-cell lines and two viral subtypes with different coreceptor tropism. Finally, we found that several of the Env mutation positions are highly conserved within and across HIV-1 clades but that these mutations do appear in patient isolates.

Conclusion: These results demonstrate that mutations in Env can contribute to HIV drug resistance in vitro. A combination of in vitro selections and in vivo analyses is ongoing and may establish a role for Env mutations in ARV resistance in patients and help guide the development of more effective therapies.

EMERGENCE OF GAG MUTATION, A364V, IDENTIFIED AS THE KEY IN VITRO RESISTANCE MUTATION

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Background: The in vitro virology profile has been previously presented (Jeffrey et al, CR01 2015). These data demonstrated that GSK2838232, a second-generation HIV maturator inhibitor, has a broad spectrum antiviral profile against viruses from various clades and viruses resistant to marketed antiretrovirals. The current study was aimed to identify drug resistance mutations via in vitro resistance passage.

Methods: Recombinant viruses containing the gag/protease fragments of two representative protease-treated HIV-infected individuals susceptible to GSK2838232 (N0877: IC50 1.8nM and RTI04: 0.9nM) and laboratory strain NL4-3 (IC50 1.5nM) were serially passaged in SupT1 cells. Experiments were started by efficient replication in the presence of the inhibitors. A number of analyses were then performed to validate the ability of the selected mutations to confer ARV resistance.

Results: After 5 passages, at GSK2838232 concentrations 10-20 fold over the initial IC50 (~24nM) for inhibiting the parent virus, gag and protease was fully sequenced. Remarkably, in all experiments the gag A364V amino acid change at the p1 site in the CA/P2 cleavage site was observed. A site-direct mutant containing the A364V was generated in the NL4-3 parental virus and demonstrated a high level of resistance to GSK2838232 (>400nM). Lastly, the frequency of A364V among HIV gag sequences in the Los Alamos National Labs HIV database was investigated and found to be less than 0.1% of these sequences.

Conclusion: The resistance profile of GSK2838232 is consistent with previous mutation inhibitors. Based on the infrequent presence of the A364V mutation, pre-existing resistance in an HIV-positive human patient population is expected to be low. As GSK2838232 progresses through clinical development, these in vitro resistance data will help decipher the genotypic and phenotypic observations from those clinical studies.

COMPARISON OF NEXT-GENERATION SEQUENCING ANALYSIS PIPELINES FOR HIV-1 DRUG RESISTANCE

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Background: NGS is a potentially useful tool for HIV-1 drug resistance (HIVDR) testing because of its sensitivity for detecting low abundance drug resistant variants. Many NGS HIVDR data analysis pipelines have been independently developed, with variable outcomes and potential discrepancies. Standardization of analytic methods and comparison of pipelines is lacking, yet may impact interpretation and be significant in downstream applications.

Methods: We compared the performance of five NGS pipelines using samples from the Sanger-based genotyping proficiency testing administered by the NIAID Virology Quality Assurance (VQA) program. Ten VQA panel specimens were genotyped (protease and reverse transcriptase) by each of six laboratories using their in-house NGS assays. Raw NGS data were processed in each laboratory using one of five different pipelines: HyDRA, MiCall, PASeq, Hivmer and DEEPGEN (Table 1). All laboratories uploaded their raw NGS and analytic comparisons were performed centrally, including: linear range for AAV frequency (linear regression analysis), analytic sensitivity and specificity, and variation of detected AAV frequencies. Amino acid variants (AAV) detected by at least four of the five pipelines at median frequency ≥1% were considered for subsequent performance assessment.

Results: A total of 657 AAVs were detected; median 67 per sample. All pipelines demonstrated good linearity in AAV frequency measurements between 1% and 100%. The pipelines showed an average sensitivity of 99.3% (range: 98.8-99.8%) and specificity of 94.1% (85.7-99.7%). The majority (473 of 657, 72%) of AAVs were present at frequencies ≥20% and these frequency measurements contained fewer discrepancies as compared to AAVs with median frequencies ≤ 20% (Table 1).

Conclusion: Comparison of five different NGS-based HIVDR genotyping analysis pipelines in detection of AAVs present at frequencies ≥20% using VQA panel specimens demonstrated good correlation across pipelines. Specificity was decreased at AAV frequencies ≥20% and more outliers were observed, which may be due to differences in quality control criteria among the pipelines. Findings from this study highlight the need for well-defined quality assurance strategies for NGS HIVDR data processing, especially for low abundance variant reporting.

| Table 1. Comparison of Pipelines for automated NGS-based HIVDR data analysis |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Pipeline        | HyDRA           | MiCall          | PASeq           | Hivmer          | DEEPGEN         |
| Positive ARV    | No              | No              | No              | Yes             | N/A             |
| Negative ARV    | Yes             | Yes             | Yes             | Yes             | Yes             |
| Cloud Based     | No              | No              | No              | No              | No              |
| Web Interface   | Yes             | Yes             | Yes             | Yes             | Yes             |
| Designed for HIVDR | Yes     | Yes             | Yes             | Yes             | Yes             |
| Ref Database    | HIVdb           | HIVdb           | HIVdb           | HIVdb           | HIVdb           |
| Output format   | cont            | cont            | cont            | cont            | cont            |
| N outliers% 20% | 2               | 6               | 12              | 3               | 10              |
| N outliers < 20% | 10              | 9               | 15              | 9               | 9               |

Outliers were determined using a 10% (4/5, 5%, 10% and 20% for variant frequencies at ≥10%, 70%-80%, 40%–70%, and ≥10%, respectively).
544 DETECTION OF ARCHIVED MUTATIONS IN PATIENTS INFECTED WITH MULTICLASS RESISTANT HIV-1

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Background: Deep sequencing (DS) assays may represent a reproduce approach to analyse HIV-1 mutation patterns in proviral DNA, even at frequencies below those that are detectable by standard population sequencing. DS data on pts with multiple drug resistance-associated mutations (DRMs) and with V5 (less than 50 HIV RNA copies) is scarce.

Methods: LOWER is a nation-wide study of 243 pts with presence of major DRMs available from all historical resistance reports. Among NRTI DRMs, re-detection rates were highest for T69D/N (77.1%) and lowest for K65R/E/N (21.1%) and L74V (26.2%). For NNRTIs, rates were newly detected with DS, and a lower cut-off of 2% yielded a total of >6,000 patient samples submitted for routine testing in the US were included in the analysis. The data were evaluated to assess frequency of RAMs, temporal trends from 2015 to 2018 and associations with gender, age and geography.

Results: At least one RAM was identified in 58.6% of specimens with 1, 2, 3 and 4-class RAMs observed in 28.2%, 19.1%, 10.2% and 1.1%, respectively. The most frequent DRMs observed in each class were PI: RTLQ (7.5%), NRTI: M184V (27.2%), NNRTI: K103N (19.8%), and INI: N155H (1.5%). Common RAMs (M41L, D67N, K70R, T215F/Y) were present in 9–13% of specimens. Overall, the prevalence of individual RAMs, as well as samples with any RAMs, was observed to decrease between 2015 and 2018. The prevalence of RAMs was higher in patients under 20 and over 50. Differences across gender and geographic regions were subtle but statistically significant.

Conclusion: Analysis of a large set of HIV DNA sequencing test results submitted for routine testing demonstrated that DRMs are commonly identified. Minor differences in the prevalence of RAMs were associated with gender and geographic location. More striking changes were associated with age. Increased prevalence of RAMs was observed in patients over 50 and may reflect increased rates of exposure to multiple regimens. We also noted an increased prevalence of RAMs in patients under 20 that warrants further study.

545LB LTR TRANSLATION MUTATIONS UNDER HIGH-LEVEL CABOTEGRAVIR MAINTAIN HIV REPLICATION

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Background: Recent reports have described HIV replication under high levels of the integrase (IN) inhibitor, dolutegravir (DTG), was associated with mutations in the 3‘PPT with no resistance mutations observed in the integrase gene (int). Cabotegravir (CAB), a longer-acting analogue of DTG, has a high genetic barrier to resistance emergence. We examined for int drug resistance mutations in vitro both with increasing concentrations of CAB and under continuous high concentration. We also looked for changes in IN-binding regions in the long terminal repeats (LTR).

Methods: For dose escalation, CEMx174 cells were infected with wild-type HIV-1IB (5.0X10^8 cp/1M cells) beginning with 0.1nM CAB. After visualization of cytopathology (CPE), CAB concentration was doubled for 12 culture passages up to 205mM. In a second experiment, 300mM CAB (~350-times EC50) was added to cultures 24h after infection with wild-type HIV-1IB. Int sequences in viral RNA (vRNA) and DNA were analyzed weekly by both Sanger and deep sequencing. vRNA LTR 5‘R-3’ and 3‘U3-R, proviral U3-LTR and 2-LTR DNA junction regions were also sequenced.

Results: Increasing CAB concentrations over a year generated no int mutations despite continued, albeit prolonged, appearance of CPE. Initiating cultures with 300nM CAB quickly yielded vRNA LTR mutations by day 7 at a 1% frequency (f) (VL=3x10^8 cp/mL) and 48% at day 105 (VL=3x10^9). Provirial LTR mutations were first detected (f=14%) at day 14, with 98% of amplified proviral LTRs mutated at day 105. These mutations were in the LTR 3‘R and are similar to previously described DTG-associated 3‘PPT mutations. We have identified the mutations as translocated copies of the LTR US IN cleavage site, which introduced adjacent to the U3 cut site another IN binding/cleavage site but in complementary orientation. Deletions in U3 were also observed. 2-LTR circles accumulated rapidly and had majority wild-type junction sequences; also present were circles with tandem repeats in U3 3‘-flanking the junction.

Conclusion: We propose that replacing sequences adjacent to the US IN cleavage site with a US cleavage motif is a functional mutation that permits HIV integration in the presence of high-level IN inhibitor, possibly by an altered IN complex conformation. These variant proviral sequences may form by erroneous IN processing of preintegration LTRs. The nearly ubiquitous presence of the US site in U3 proviral LTRs after 100 days in culture supports this as a mechanism for HIV persistence in vitro under CAB.

546 ANTIVIRAL ACTIVITY OF TENOFOVIR ALAFENAMIDE AGAINST HIV-1 HARBORING K65R

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Background: Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are prodrugs of the HIV-1 nucleotide reverse transcriptase (RT) inhibitor tenofovir (TFV). In vivo, TAF achieves ~4-fold higher intracellular levels of TFV diphosphate (TFV-DP) in PBMCs, compared to TDF. Although rare, K65R is a resistance-associated mutation (RAM) for several NRTIs, including TAF and TDF, lowest for V108I (33.3%) and IS4-L/M (29.0%). Re-detection rates showed no association with length of ART or of V5, current antiretroviral regimens or other factors such as current or nadir CD4 cells.

Conclusion: In this large cohort study of pts with multidrug resistant HIV infection, DS of proviral DNA regained more than half of the DRMs that had emerged during previous virologic failures. Almost 10% were newly detected and a lower cut-off of 2% yielded almost 15% additional DRMs. However, detection consistency between DS and historical testing was low for specific mutations. Re-detection rates were not associated with any factor analyzed, including length of viral suppression or current ART regimen.
and is the main RAM to emerge during in vitro selection studies with tenofovir. Here, we evaluated the in vitro activity of TAF at pharmacological concentration in a large set of K65R-containing HIV-1, with or without M184V/I.

**Methods:** HIV primary isolates (n=42) with K65R ± M184V/I spanning 5 different subtypes were selected. Samples with mutation mixtures at RT residues K65 and/or M184 were not included. The PR-RT region was amplified and cloned into the pXPLAT proviral DNA vector and transfected into virus producing cell lines; viral isolates were harvested after 48 h. Antiviral drug susceptibilities (EC50 fold change FC) relative to wild-type were determined in MT-2 cells using a 5-day Multi-Cycle HIV assay. Comparison of TAF and TDF resistance barriers were further assessed in viral breakthrough assay performed at clinically relevant drug concentrations.

**Results:** TAF mean FC for all tested viruses was 4.0 (n=42; range 1.0-27.4). The TAF FC of the viruses harboring K65R with M184V/I (average FC of 3.3; n = 28) was numerically lower than the TAF FC of the viruses without M184V (average FC of 5.4; n = 14). All 42 mutant isolates were subsequently assayed at TAF or TDF physiological concentration in viral breakthrough assay (28 days), resulting in 4/42 mutants breaking through under TAF treatment (average FC of 12.2 for viruses breaking through; range 6.1-27.4), and 18/42 mutants breaking through under TDF treatment (average FC of 6.1 for viruses breaking through; range 3.2-27.4).

**Conclusion:** In a viral breakthrough assay mimicking the 4-fold higher intracellular levels of TFV-DP delivered by TAF compared to TDF in vivo, TAF inhibited breakthrough of the majority of K65R-containing HIV-1 evaluated compared to TDF, emphasizing the higher resistance barrier provided by TAF vs TDF. These differences were observed for HIV isolates regardless of their subtypes or genetic diversity around the K65 position.

**GSS of NRTI-backbone predicts time to virological failure of INI-based regimens**

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**Background:** INI-based regimens are the mainstay of antiretroviral therapy (ART). We evaluated the impact of NRTIs backbone-associated drug resistance mutations (DRM) at the start of a INI-based regimen on the onset of virological failure (ART). **Methods:** The sum of genotypic susceptibility scores (GSS) obtained by Stanford HIVdb algorithm version 6.6.1 (classified as: 0 for high-level resistance, 0.5 for low or intermediate-level resistance, 1 for potential low-level resistance or susceptible) for each NRTI was calculated for patients starting 2 NRTIs and is the main RAM to emerge during in vitro selection studies with tenofovir. Here, we evaluated the in vitro activity of TAF at pharmacological concentration in a large set of K65R-containing HIV-1, with or without M184V/I.

**Results:** Among 24 patients included in the PRESTIGIO cohort used for the sequencing of gp120 region, while viral tropism and susceptibility to TMR were assessed through a home-made phenotypic assay involving pseudotyped viruses expressing patient derived Env protein. Patient demographics and laboratory data are described as median (Q1-Q3), mean (±SD) or frequency (%).

**Conclusion:** In this study, TMR RAMs were detected in 3/21 samples and the polymorphic RAM M426L was associated with variable reduction of TMR susceptibility. Except for viruses harboring M426L, the susceptibility to TMR was comparable to wild-type strains in all the samples, irrespective of coreceptor usage or exposure to other entry inhibitors.

**In vitro activity of DTG/BIC/CAB on first-generation INSTI-resistant HIV-1**

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**Background:** Fostemsavir (FTR) is a prodrg of the investigational HIV-1 attachment inhibitor temsavir (TMR) currently under evaluation for the treatment of highly experienced patients with limited treatment options. This study aims to characterize the genotypic profile and the phenotypic susceptibility to TMR in a panel of samples collected from patients harboring multi resistant HIV-1 enrolled in the Italian PRESTIGIO cohort and potentially candidate for FTR treatment.

**Methods:** Plasma samples from 24 patients included in the PRESTIGIO cohort were used for the sequencing of gp120 region, while viral tropism and susceptibility to TMR were assessed through a home-made phenotypic assay involving pseudotyped viruses expressing patient derived Env protein. Patient demographics and laboratory data are described as median (Q1-Q3), mean (±SD) or frequency (%).

**Results:** Among 24 patients, 18 (75%) were male, median age 54 years (52-59), time since HIV-1 diagnosis 26 years (24-29), time on ART 25 years (22-26), 11 (46%) with a previous AIDS diagnosis, a median viral load at first sample collection of 3.87 log10 copies/mL (3.1-5.0) and a median CD4+ cell count of 242 cells/µl (137-387). At the time of sample collection, 12 (50%) were receiving entry inhibitors (MVC and/or T-20). Among 21/24 (88%) gp120 sequences obtained, all belonged to subtype B and TMR RAMs (Y167F, A204D, 353M/N/H/N, M426L, M434I, M475I) were detected in only 3 cases (13%), two 426L and one 375N. Viral tropism was X4, RS, and dual-mixed (DM) in 9, 7 and 4 out of 24 cases, respectively. Pseudotyped viruses were obtained from 23/24 samples and median IC50 to TMR was 0.5 nM (0.3-1.2). The reference wild-type viruses NL4-3 (X4), AD8 (RS) had mean IC50 of 1.1±0.6 nM and 1.3±0.7 nM, respectively, while the two samples harboring RAM 426L (both X4-tropic) had mean IC50 of 6.9±2.9 nM and 1110.6±798.2 nM, resulting in FC values of 6.2 and 1009, respectively. According to viral tropism, median IC50 values were 1.2 nM (0.4-4.2), 0.4 nM (0.3-1.2) and 0.6 nM (0.3-0.8) for X4, RS and DM viruses, respectively. Concomitant use of MVC or T-20 also did not impact TMR IC50 values.

**Conclusion:** In this study, TMR RAMs were detected in 3/21 samples and the polymorphic RAM M426L was associated with variable reduction of TMR susceptibility. Except for viruses harboring M426L, the susceptibility to TMR was comparable to wild-type strains in all the samples, irrespective of coreceptor usage or exposure to other entry inhibitors.
550 SUSCEPTIBILITY TO BICTEGRAVIR IN HIGHLY ARV-EXPERIENCED PATIENTS AFTER INSTI FAILURE

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Background: Integrase strand transfer inhibitors (INSTIs) are a potent drug class. Bictegravir (B) has a favorable in vitro resistance profile with improved activity compared to all other INSTIs. Non-inferior efficacy with no resistance development was shown for BIC/tenofovir alafenamide (B/F/TAF) in two studies in treatment naïve patients through Week 96 and in two switch studies in virologically suppressed patients through Week 48. The goal of this study was to characterize the genotypic and phenotypic resistance profile to BIC and other INSTIs in patients who have failed twice daily raltegravir (RAL)- or DTG-based regimens.

Methods: This analysis used samples collected after failure on an INSTI-based regimen in highly treatment-experienced HIV-1 infected patients with multidrug resistant virus and recorded in the Italian PRESTIGIO registry. Genotypic resistance mutations and phenotypic susceptibility to INSTIs were detected by GeneSeqIN and PhenoSenseIN assays with individual INSTI resistance cutoffs defined separately by the assay. Patients’ demographics are described as median (Q1-Q3) or frequency (%). No resistance development was noted.

Results: Twenty-two samples from 17 patients were evaluated: 12 (71%) were male, median age 49 years (45, 53), time since HIV-1 diagnosis 20 years (Q1-Q3; 16, 25), time on ART 20 years (Q1-Q3; 16, 18), 10 (59%) with a previous AIDS diagnosis, median viral load at first sample collection of 4.5 log10 copies/mL (4.1, 5.3) and median CD4+ cell count of 168 cells/µl (68, 439). The primary INSTI-resistance substitutions E138A/K, Y143C/H/R, Q148H, and N155H were found in 14/22 samples and were associated with resistance to one or more INSTIs, with G140S+Q148H present in 11/22 samples. Of these 14 samples, all showed resistance to EVG and RAL and two were resistant to BIC and DTG. The two isolates with resistance to BIC and DTG contained L47M, E138K, G140S, and Q148H or L74M, T97A, S147G, E138K, G140S, Y143R and Q148H. Intermediate resistance was reported for 8/14 isolates for BIC and 9/14 isolates for DTG. Overall, for the 14 INSTI-resistant isolates, the median fold-change (range) values were: BIC 3.1 (0.6, 66), DTG 6.1 (0.8, >186), EVG >164 (2.6, >164), and RAL >188 (2.7, >157).

Conclusions: In vitro, BIC retained activity against most isolates derived from patients failing INSTI regimens. These data support the study of BIC once-daily in patients with INSTI-resistance.

551 HIGH LEVEL OF PREEXISTING NRTI RESISTANCE PRIOR TO SWITCHING TO B/F/TAF: STUDY 4030

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Background: Bictegravir (B) is coformulated with the nucleoside/tide reverse transcriptase inhibitors (NRTIs) emtricitabine (F) and tenofovir alafenamide fumarate (TAF) (B/F/TAF). Study 4030 is an ongoing, fully enrolled, phase 3, randomized, double-blinded study (n=565) of HIV-1 RNA suppressed participants on QD dolutegravir (DTG) + F/TAF or F/Tenofovir disoproxil fumarate (TDF) switching 1:1 to DTG + F/TAF or B/F/TAF for 48 weeks. Documented INSTI resistance was not enrolled if known at randomization, but all NRTI, NNRTI, and PI resistance was allowed.

Methods: Proviral DNA genotypes (GenoSure Archive) from baseline samples and historical plasma HIV-1 RNA genotypes were analyzed. Documented or suspected NRTI resistance was assigned to group 1) K65R/E/N or ≥2 TAMs containing M41L or L210W (TAMs: D67N, K70R, L210W, T215F/Y, and K219O/ E/N/R), group 2) M184V/I, any other set of TAMs, M70E/G/M/S/T/L, L74V, L75V/S/M/T, Y115F, T69D, or Q151M, or group 3) no major NRTI resistance. Virologic outcomes used last available on-treatment HIV-1 RNA with the blinded Week 12 IDMC data cut.

Results: Historical genotypes were available from 285/565 participants (50%). Retrospective analysis of archived mutations by HIV DNA genotype were determined for 377/565 participants; 20% also had historical genotypes. In total, 82% (462/565) of participants had pre-switch genotypic data available resulting in 24% with major NRTI resistance: 5% (29/565) in group 1 (K65R or ≥3TAMs) and 18% (104/565) in group 2 (other NRTI mutations). M184I/V was present in 17% (77/462) of participants with data. HIV DNA genotyping identified previously unknown major NRTI resistance in 15% of participants (58/377).

Pre-existing INSTI mutations were found in 5% of participants (19/399): 19TA (n=12), 155S (n=1), Y143H (n=2), R263K (n=2), Q148H+G140S (n=1), and S147G (n=1). Primary non-nucleoside RT inhibitor and protease inhibitor resistance mutations were present in 24% (113/462) and 8% (36/462) of participants. At this interim analysis, HIV-1 RNA <50 copies/mL was maintained in 99% of participants, 97% (28/29) in group 1, 99% (103/104) in group 2, 97% (75/77) with M184V/I, and 100% (19/19) with INSTI-R.

Conclusion: This study found frequent NRTI resistance in suppressed participants switching from a DTG + F/TDF or B/F/TDF regimen, much of which was previously undocumented. Early data show high suppression using potent triple therapy of B/F/TAF or DTG + F/TDF.

552 LONG-TERM B/F/TAF SWITCH EFFICACY IN PATIENTS WITH ARCHIVED PREEXISTING RESISTANCE

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Background: Studies 1844 and 1878 demonstrated non-inferior efficacy of switching suppressed HIV-1-infected adults to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) versus continuing dolutegravir (DTG) or boosted protease inhibitor (PI)-based regimens. At week 48, 93% in the B/F/TAF groups versus 95% in the DTG group and 89% in the PI group had HIV-1 RNA <50 copies/mL by snapshot algorithm, after which B/F/TAF treatment continued open-label. Here, we present resistance analyses and virologic outcomes after 2 years of B/F/TAF treatment.

Methods: Archived preexisting HIV-1 drug resistance was assessed by historical genotypes (documented resistance to study drugs was exclusionary) and retrospective baseline proviral DNA genotyping (Archive assay, Monogram Biosciences). Participants with resistance to study drugs detected post-randomization were allowed to continue on study. Virologic outcomes were based on last available on-treatment HIV-1 RNA.

Results: Altogether, 572 participants switched to B/F/TAF and were treated for a median of 108 weeks (IQR 106-118 weeks). Pre-switch reverse transcription (RT) genotypic data were available for 78% (447/572) of B/F/TAF-treated participants; integrase data were available for 55% (314/572). Preexisting primary NRTI resistance (-R), NNRTI-R, and INSTI-R substitutions were observed in 16% (71/447), 21% (93/447), and 1.9% (6/314), respectively. High frequencies of INSTI-R substitutions M184V or M184I (9.8%, 44/447) and thymidine analog mutations (TAMs; 8.5%, 38/447) were detected by DNA genotyping.
Substitutions associated with resistance to the NNRTI rilpivirine (RPV) were observed in 9.6% (43/447). At the time of analysis, 99% (564/572) of B/F/TAF-treated participants were suppressed (HIV-1 RNA <50 copies/mL), including 95% (42/44) with archived M184V/I, 95% (36/38) with TAMs, 98% (42/43) with RPV-R, and 100% (6/6) with INSTI-R. There was no resistance development in B/F/TAF-treated participants through week 48, and no participants met criteria for resistance testing after week 48.

Conclusion: Preexisting RT resistance was common among suppressed participants switching to B/F/TAF, notably RPV-R and previously unidentified M184V/I and TAMs. High rates of virologic suppression were observed in the overall and drug-resistant populations through 108 weeks of B/F/TAF treatment with no resistance development, indicating that B/F/TAF is a durable switch option for suppressed patients, including those with evidence of this archived NNRTI and NRTI resistance.

553 ACTIVITY OF BICTEGRAVIR AGAINST HIV-2 ISOLATES AND INI-RESISTANT HIV-2 MUTANTS

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Background: Bictegravir (GS-9883; Gilead Sciences, Inc.) is the most recent second-generation integrase inhibitor (INI) to be approved by the FDA for use in HIV-1-infected patients. For HIV-2, published data regarding the activity of bictegravir are limited to in vitro testing of single group B isolate (Tsai et al., Antimicrob. Agents Chemother. 60:7086). To evaluate the potential suitability of bictegravir for HIV-2 treatment, we tested the activity of the drug against a panel of group A and group B HIV-2 isolates that were originally obtained from antiretroviral-naive individuals. HIV-1 isolates representing group M subtypes A, B, C, and D, and group O, were included for comparison. We also determined the antiviral activity of bictegravir against raltegravir-resistant mutants of HIV-2.

Methods: Antiviral activity was measured in single-cycle assays using the MAGiC-5A indicator cell line (HeLa-C4D-LTR-βgal cells). Site-directed mutants of HIV-2 integrase were constructed in the pROD9 HIV-2 molecular clone using QuikChange II XL reagents and procedures (Agilent Technologies). The cytotoxicity of bictegravir was assessed via the CellTiter-Glo® assay (Promega).

Results: 50% effective concentrations (EC50 values) for bictegravir ranged from 1.2–2.4 nM for HIV-1 (n = 6 isolates), and 1.4–5.5 nM for HIV-2 (n = 15 isolates). Average EC50 values (± SD) for HIV-1 and HIV-2 were 1.6 ± 0.4 nM and 2.4 ± 1.1 nM, respectively. HIV-2 variants Q91R+T97A+Y143C and Q91R+T97A+Y143C+M155V were fully susceptible to bictegravir (EC50 <1 nM), while Q91R+T97A+Y143C+A153S conferred low-level (4–5-fold) resistance to bictegravir. Bictegravir is highly active against HIV-2 in culture, with EC50 values comparable to those seen for HIV-1. The available data suggest that, for HIV-2, the resistance profile for bictegravir is similar to the profiles observed in HIV-1. The available data suggest that, for HIV-2, the resistance profile for bictegravir is similar to the profiles observed in HIV-1.

Conclusion: Bictegravir is highly active against HIV-2 in culture, with EC50 values comparable to those seen for HIV-1. The available data suggest that, for HIV-2, the resistance profile for bictegravir is similar to the profiles observed in HIV-1.

554 SPECIFICITY OF 4 POINT-OF-CARE RAPID HIV TESTS IN A SETTING WITH HIGH PreP USE

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Background: In the United States, performance evaluations of recently FDA-approved rapid HIV tests have been conducted in laboratory settings using plasma and simulated whole blood. Previously published specificity estimates for newer rapid HIV tests when used in point-of-care (POC) settings have not included estimates for persons on Pre-Exposure Prophylaxis (PrEP).

Methods: Since September 2015 – August 2018, persons at risk for HIV and seeking HIV testing at a public health clinic in Seattle, WA were invited to participate in the study. Consenting participants completed a behavioral questionnaire that assessed history of PrEP use and were tested with four POC tests using whole blood (see table). Additional blood specimens were collected for laboratory processing and testing. Specimens with a non-reactive antigen/antibody (Ag/Ab) test result were tested with a nucleic acid test (NAT) in 10-member pools. Specimens with reactive Ag/Ab results and negative or indeterminate supplemental antibody test results, were tested individually using a NAT. For both situations, specimens with a negative NAT result were classified as HIV-uninfected. Specificity of the POC tests with exact 95% confidence intervals (CI) were calculated based on the HIV-uninfected status of the specimens stratified by participant’s report of current PrEP use.

Results: Among 1,434 HIV-uninfected specimens, 16.7% were from persons on PrEP at the time of the clinic visit, 80% from persons not currently on PrEP, and 3.5% missing data on PrEP status. There were 8 specimens with false-positive results, 2 from persons on PrEP. No specimen tested false positive on more than one test. False-positivity rates were 0.4% for Determine and 0.1% for INSTI. DPP and OraQuick performed on whole blood produced no false-positive test results. Specificity was high and comparable for all tests and was not affected by PrEP use.

Conclusion: Point estimates for specificity are higher than what we have previously published. The high specificity of these HIV POC tests, including when used with participants taking PrEP, should reassure organizations implementing rapid HIV testing using whole blood specimens. However, the possibility of false-positive results should still prompt organizations to establish mechanisms for either additional HIV testing onsite (using a different rapid HIV test) or follow-up laboratory testing to confirm any positive result.

555 PERFORMANCE OF HIV DIAGNOSTIC ALGORITHMS IN THE PRESENCE OF VACCINE-INDUCED IMMUNITY

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Background: Participants in HIV vaccine trials are at risk of being misclassified as HIV-infected since routine tests may fail to distinguish vaccine-induced antibodies from those elicited by infection. We assessed the performance of HIV testing algorithms to distinguish vaccine-induced seroreactivity (VISR) from true infection.

Methods: Stored serum/plasma samples from healthy Swedish and Tanzanian volunteers who participated in any of three previously conducted phase IIa vaccine trials evaluating an HIV-DNA prime HIV-modified vaccinia virus Ankara (MVA) boost strategy were analyzed. HIV infection in participants was ruled out by HIV RNA PCR. Samples were tested for VISR using the HIV testing algorithms of Tanzania and Mozambique, which use two sequential rapid diagnostic tests. SD Bioline HIV1/2 (Standard Diagnostic Inc, Republic of Korea) for screening and Uni-Gold HIV-1/2 (Trinity Biotech, Ireland) for confirmation of HIV infection in Tanzania. Determine HIV-1/2 (Alere Medical Co. Ltd, Japan) for screening and Uni-Gold HIV-1/2 for confirmation of HIV infection in Mozambique. In both countries, patients were considered HIV-infected if both assays are reactive, and discrepant results are resolved by repeated testing. The vaccinees’ samples were also tested for VISR using Enzygnost HIV Integral 4 ELISA (Siemens, Germany). Antibodies to subtype C gp140 were determined using an in-house ELISA.

Results: VISR as determined by the Enzygnost HIV Integral 4 ELISA was 92% (61/66). The proportion of vaccine recipients that would have been falsely labeled as HIV positive by the HIV diagnostic algorithm used in Mozambique was half of that by the Tanzanian algorithm, 10/66 (15%) and 21/66 (32%), respectively, p = 0.039. The median anti-Env titer was 3200 (IQR: 3200-12800)
in vaccinees with VISR according to the Mozambican algorithm compared to median 800 (IQR: 400–1600) in participants without VISR, p<0.0001. Similarly, the median anti-Env titer was 3200 (IQR: 2400–6400) in participants with VISR according to the Tanzanian algorithm and 800 (IQR: 400–1600) in those without VISR, p<0.0001.

Conclusion: HIV diagnostic algorithms currently used in sub-Saharan Africa will misclassify a proportion of HIV vaccine recipients, but fewer than the Enzymost Integral ELISA. The Mozambican HIV rapid test algorithm was significantly more accurate than the Tanzanian algorithm. Development of HIV rapid assays that can adequately differentiate VISR from true HIV infection should be prioritized.

556  DIFFERENTIATION CAPABILITY OF THE GEENIUS ASSAY FOR HIV-2 AND HIV-1/2 DUAL INFECTIONS

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Background: Detection and discrimination of HIV-1 and HIV-2 antibodies is a key component of the US CDC HIV diagnosis algorithm. However, differentiation between HIV-2 single- and HIV-1/HIV-2 dual infection by serology alone is challenging. The Bio-Rad Geenius HIV 1/2 supplemental assay (Geenius) is a commonly used, US FDA-approved, assay for HIV-1 and HIV-2 immunodetection. In this study, we evaluated the Geenius assay’s output characteristics in the United States (US) HIV positive patient plasma samples that had a clinical diagnosis of HIV-2.

Methods: HIV-2 patients’ plasma samples, originating from US clinics and laboratories that were referred for HIV-2 quantitative RNA viral load testing to the University of Washington Retrovirology Laboratory between 2011 to 2018, were retrospectively tested by the Geenius assay. Results were read and interpreted by the Geenius Reader with the proprietary US software (Bio-Rad).

Results: Senegalese plasma samples from known HIV-2-infected (n=20) and HIV-1/HIV-2 dually-infected (n=8) subjects were used to verify the Geenius assay (Table 1). The Geenius assay algorithm output from 65 US patients’ plasma samples with clinically diagnosed HIV-2 was as follows: 27 (41.5%) were HIV-2 positive; 31 (46.5%) were HIV-2 positive with HIV-1 cross-reactivity; 6 (9%) were HIV positive-untypable; and 1 (1.5%) was HIV-2 indeterminate (Table 1). Notably, 7 samples designated by Geenius as HIV-2 positive with HIV-1 cross-reactivity were reactive to all HIV-2 gp36, gp140 and HIV-1 p31, gp160, p24 and gp41 antigen (Ag) bands. The Geenius interpretation for 4 HIV positive-untypable and one HIV-2 indeterminate samples were confirmed by additional plasma samples from subsequent dates.

Conclusion: Although the Geenius assay confirmed 20 HIV-2 single- and 8 HIV-1/2 dual-infection diagnosed from Senegalese plasma samples; nearly half of HIV-2 single-infection plasma samples were also reactive to HIV-1 Ag bands. Variable results were also obtained by Geenius for HIV-2 samples collected from the US, with 7/65 (10.8%; 95% CI 4.4-20.9%) giving untypable or indeterminate results and nearly half showing some cross-reactivity to HIV-1. Additional tests are needed for confirming HIV-2 single infection and differentiating HIV-1/HIV-2 dual infections. Validated nucleic acid amplification testing for HIV-2 and HIV-1/ HIV-2 dual infection may improve the CDC algorithm in this patient population.

557  HIV-1 RNA DETECTION BY ABBOTT M2000 CORRELATES WITH INTEGRASE SINGLE-COPY ASSAY

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Background: The correlation between single copy plasma HIV-1 RNA assays (research tests) and less sensitive but automated, FDA-cleared plasma HIV-1 RNA assays is not well-defined. We examined this association by testing plasma with both a single copy qRT-PCR assay and the Abbott M2000 automated, commercial platform.

Methods: The single copy qRT-PCR assay targeting integrase (ISCA) was performed as published (Cillo, J Clin Micro 2016) with a limit of detection (LoD) 0.4 cp/mL for a 5 mL sample tested. ISCA results were classified as HIV-1 RNA “detected” or “not detected”. The FDA-cleared Abbott M2000 RealTime HIV-1 Viral Load assay has a LoD of 40 cp/mL for a 1.0 mL sample. Results below 40 cp/mL were reported as either <40 cp/mL detected but not quantifiable (<40 target detected) or target not detected (TND). Plasma samples obtained at entry into the ACTG A5321 cohort study were tested with both assays. Participants were on suppressive ART with HIV RNA <40 cp/mL by the Abbott assay.

Results: Participants are mostly men (82%), median age of 49, and median of 7 years on ART. Paired samples from 309 participants were tested with both assays. 52% of ISCA results had undetectable HIV-1 RNA; the undetectable ISCA results were primarily (94%) <0.4 cp/mL; nine were <0.5 to <1.1 cp/mL because of lower sample volume. By Abbott M2000, 17% of samples were <40 target detected and 83% were TND. Of the samples TND by Abbott, 43% had HIV-1 RNA detected by ISCA. Of the samples <40 target detected by Abbott, 73% had detectable HIV-1 RNA by ISCA (Figure; p<0.001). Results were similar excluding nine with lower ISCA plasma volume, categorizing ISCA as <0.4 vs. ≥0.4 cp/mL: 44% ≥0.4 cp/mL if TND by Abbott and 73% ≥0.4 cp/mL if target detected (p<0.001).

Conclusion: 73% of plasma samples with an Abbott HIV-1 RNA result of <40 cp/mL target detected also had HIV-1 RNA detected by ISCA, whereas 43% of samples that were TND by Abbott had HIV-1 RNA detected by ISCA. The difference between <40 cp/mL target detected and TND by Abbott has meaningful information, and can be used to estimate the likelihood of HIV-1 RNA detectability by ISCA. The strong association between the results of both assays indicates that a high-throughput automated assay such as Abbott M2000 could be used in epidemiologic investigations of low-level viremia and to screen for changes in low-level viremia following therapeutic interventions, thereby reducing the need for more labor-intensive research single copy assays.
558 REPLICATE APTIMA ASSAY FOR QUANTIFYING RESIDUAL PLASMA VIREMIA IN INDIVIDUALS ON ART

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Background: Quantification of residual low-level viremia in research participants on anti-retroviral therapy (ART) and during curative interventions requires ultrasensitive plasma HIV RNA assays. Current single copy assays based on ultracentrifugation are limited in throughput.

Methods: The Aptima HIV-1 Quant Assay is performed on a fully automated platform using 0.5 ml sample with limits of detection (LOD) of 12 cp/ml and quantitation (LOQ) of 30 cp/ml. To detect lower-level viremia, the instrument can generate 9 replicates (reps) per 5 ml plasma input, with the option of loading multiple 5 ml aliquots to further enhance sensitivity. To validate this approach, samples [4 plasma samples from blood donors with acute infection (2 each subtype B and C) as well as the WHO 3rd international standard] with quantified working stock low viral loads (VL), ranging from 16 to 291 cp/ml, were serially diluted in defibrinated plasma to ~0.2 cp/ml, and tested in 38-90 reps per dilution. A Poisson model-based hybrid algorithm was developed to estimate the viral RNA copy number. The replicate testing strategy (45 reps) was then applied to 102 apheresis-derived plasma samples from 50 well-suppressed RAVEN study participants on ART.

Results: For each of the 5 serially diluted samples, estimated concentrations were calculated using standard limiting dilution analysis (LDA) software and they ranged from no underestimation to underestimation of the expected VL by up to 2-fold, reflecting imperfect sensitivity for detection of a single copy. The ratio between expected and estimated VLs was 1.6 with 95% CI 1.04-2.45. Using the replicate testing approach with 45 reps, requiring 25 ml plasma, the median VL in the well-suppressed RAVEN cohort (N=50 participants) was 0.54 cp/ml (range 0.07-13 cp/ml). All 50 participants had detectable low-level viremia in at least one longitudinal visit (range 1-6 visits spanning up to 18 months). At 0.54 cp/ml, the false negative rate was estimated to be 21.7% and 4.7% with 9 and 18 reps, respectively. The figure shows the impact of rep number on precision of low VL estimates, with higher confidence interval widths at 9 relative to 18 reps.

Conclusion: Quantification of low-level viremia can be achieved based on reactive/non-reactive digital readouts on multiple replicates of the Aptima assay via Poisson analysis, with a correction factor that accounts for imperfect sensitivity. Viremia can be detected in all or most individuals on long-term ART, although most have VL <1 cp/ml.

Abbott M2000 Result

Figure 1 - Proportion SCA Detectable by M2000 Readout

559 THE USE OF EXTERNAL QUALITY-ASSURANCE DATA TO COMPARE HIV-1 RNA ASSAY PERFORMANCE

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Background: The NIAID Virology Quality Assurance (VQA) program provides well-characterized quality control materials (QCMs) for HIV-1 RNA proficiency testing and assay validations to participating labs as part of an external quality assurance (EQA) program. Seventy-eight labs from 22 countries currently participate in this program using a variety of assays. Data generated for purposes of proficiency or assay validation were used to evaluate HIV-1 RNA cross-platform performance.

Methods: Data generated on Roche TaqMan (RT), Abbott RealTime (AR), Roche cobas (RC), and Cepheid GeneXpert (GX) HIV-1 RNA assays were included in this analysis. Controls with a nominal value of 50cp/mL and 0cp/mL were used to evaluate sensitivity and specificity, respectively. Controls with nominal values ≥100 cp/mL (1.7E-05-1.5E05cp/mL) were used to evaluate precision, accuracy, and linearity (all concentrations were included in each data set). Variance components models of log10 recovery (with effects for laboratory and assay run) were used to determine correlation-specific estimates of log10 recovery (CSER). CSER values were related to log10 nominal concentration in a regression model to estimate the slope and residual SD, which were used to evaluate linearity. Targets for linearity were established using historical VQA data.

Results: Even though detection limits varied across the assays, sensitivity for RT, AR, RC, and GX was similar based on a 50cp/mL control (false negative rates: 0.15%, 0.36%, 0.17%, 0.00%). Specificity was also similar (false positive rates: 0.02%, 0.02%, 0.00% and 0.00%). The residual SD of log10 recovery across all control samples was 0.14, 0.13, 0.11, and 0.08 (target of <0.15) and the CSER (min, max) for the combined data set was 0.053 (-0.244, 0.275). -0.205 (-0.205, 0.047), 0.130 (0.009, 0.337), and 0.083 (-0.109, 0.183) for RT, AR, RC, and GX, respectively. Linearity targets were exceeded in the RT assay indicating that log10 recovery varied with concentration (targets for linearity: slope=0.56, SD(resid)=0.96, SEM=0.91); no problems with linearity were noted in the other assays (Figure 1).

Conclusion: EQA data provide a valuable resource for comparing HIV-1 RNA assay performance. Sensitivity, specificity, and precision were comparable across the four assays. However, systematic differences in log10 CSER were noted, with RC demonstrating the highest average log10 recovery and RT demonstrating a lack of linearity primarily due to lower CSER in samples with higher nominal values.
A REAL-WORLD STUDY OF EFFICACY AND SAFETY OF GLECAPREVIR/PIBRENTASVIR IN HCV PATIENTS

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Background: Data on the effectiveness and safety of Glecaprevir/Pibrentasvir for the treatment of HCV infection in a ‘field-practice’ scenario are still scant. This study (MISTRAL: MavIret SouTh italy ReAl Life), currently ongoing, evaluates this therapy in a large cohort of HCV-infected patients from Southern Italy.

Methods: All HCV-infected patients, consecutively treated with Glecaprevir/Pibrentasvir at 22 Centers all over Southern Italy were considered. Fibrosis staging was assessed using the FIB-4 index. Baseline characteristics of patients and available data on end of treatment (EOT) efficacy were obtained from a large prospective registry of HCV-monoinfected individuals, are ongoing prospective multicenter cohorts of PWID not on OAT, 97%. There were three relapses, two among PWID not on OAT and one in PWID on OAT. Over 272 patients have started GZR/EBR in the cohorts, and 171 have reached the SVR12 date of evaluation. 84 (49%) were PWID and 32/84 (38%) were on OAT. 49 (29%) individuals werecoinfected by HIV. 30 (18%) patients presented cirrhosis. All treatments were scheduled for 12 weeks without ribavirin (RBV), for but 5 patients (2.9%) (4 cirrhosis, 1 dialysis) planned for 16 weeks with RBV. One (0.6%) non-PWID dropped-out. Overall, 163/171 (95%) patients have reached SVR12. SVR12 by groups were: non-PWID, 95%; PWID not on OAT, 94%; PWID on OAT, 97%. There were three relapses, two among PWID not on OAT and one in PWID on OAT. There were three breakthroughs in two non-PWID and one in PWID not on OAT. The SVR12 rates by genotype were: 1a, 92%; 1b, 96%; 2, 4%.

Conclusion: SVR rates achieved with GZR/EBR were high in real-world conditions of use. This drug combination is a safe and effective option for PWID with and without OAT managed outside the clinical trial setting.

REAL-WORLD DATA ON ELBASVIR/GRAZOPREVIR FOR HCV INFECTION IN HIV/NON-HIV PATIENTS

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Background: There are few real-world data on the effectiveness of elbasvir/grazoprevir (EBV/GZR) for treatment (Rx) of chronic hepatitis C (CHC). We assessed the effectiveness and safety of EBV/GZR in a large prospective registry of individuals receiving DAAs for HCV.

Methods: RUA-VHC (Madrid Registry of Use of DAA for HCV) is a prospective registry of HCV-monoinfected (MoP) and HCV/HCV-coinfected (CoP) individuals receiving all-oral direct-acting antivirals (DAAs) in hospitals of the Madrid Regional Health Service. RUA-VHC was created in November 2014 (Hepatology 2017; 66:344). We selected patients with CHC who had received EBV/GZR and association also for only 8 weeks treatment. Complete final results will be presented at the CROI meeting.

561 GLECAPREVIR/PIBRENTASVIR FOR HCV-INFECTED PWID IN REAL-WORLD SETTINGS: THE ZEPALIVE STUDY

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Background: Grazoprevir/elbasvir (GZR/EBR) has demonstrated high efficacy and tolerability in a wide range of settings. In the setting of drug use, GZR/EBR is supported by a specific clinical trial dedicated to drug users on opiate agonist therapy (OAT). In that trial, the rates of SVR were within those found in the rest of the GZR/EBR development. In real life conditions of use, there is a potential for a lower efficacy, particularly of a greater rate of reinfections, and more frequent drop-outs. Thus, we aimed at evaluating the SVR rates of GZR/EBR among PWID with and without OAT in real world conditions of use.

Methods: The HEPAVIR-DAA cohort, recruiting HIV/HCV-coinfected patients (NCT02057003), and the GEHEP-MONO cohort (NCT02333292), including HCV-monoinfected individuals, are ongoing prospective multicenter cohorts of patients receiving treatment against HCV infection in clinical practice. Patients starting GZR/EBR included in the HEPAVIR-DAA or the GEHEP-MONO cohorts were analyzed. Overall SVR12 (ITT), discontinuations due to adverse effects and drop-outs were evaluated. The same analysis was carried out for PWID with and without OAT.

Results: 272 patients have started GZR/EBR in the cohorts, and 171 have reached the SVR12 date of evaluation. 84 (49%) were PWID and 32/84 (38%) were on OAT. 49 (29%) individuals were coinfection was 1a, 21%; 1b, 46%; 1c, 0%; 1 other subtype 5%; 2, 28%. 30 (18%) patients presented cirrhosis. All treatments were scheduled for 12 weeks without ribavirin (RBV), but for 5 patients (2.9%) (4 cirrhosis, 1 dialysis) planned for 16 weeks with RBV. One (0.6%) non-PWID dropped-out. Overall, 163/171 (95%) patients have reached SVR12. SVR12 by groups were: non-PWID, 95%; PWID not on OAT, 94%; PWID on OAT, 97%. There were three relapses, two among PWID not on OAT and one in PWID on OAT. There were three breakthroughs in two non-PWID and one in PWID not on OAT. The SVR12 rates by genotype were: 1a, 92%; 1b, 96%; 2, 4%. Conclusion: SVR rates achieved with GZR/EBR were high in real-world conditions of use. This drug combination is a safe and effective option for PWID with and without OAT managed outside the clinical trial setting.
were scheduled to finish Rx on or before 01/03/2018. Retreatment after oral DAA was excluded. We assessed sustained virologic response (SVR) at 12 wk by intention-to-treat (ITT) and by a modified intention-to-treat approach (m-ITT), in which non-virological failures for reasons other than discontinuation of Rx after adverse events or death were not analyzed.

**Results:** A total of 1620 patients (1486 MoP/134 CoP) met the inclusion criteria. Duration of Rx was 12 wk in 1459 patients (1315 MoP/108 CoP), 16 wk in 159 patients (133 MoP/26 CoP), and 8 wk in 2 MoP. Ribavirin (RBV) was used in 8.1% of patients. Median age was 58 y. Men accounted for 52.5% of patients, 23.5% were previously treated, and 15.2% had cirrhosis. Genotype distribution was as follows: G1b, 69.9%; G1a, 16.9%; G4, 12.2%; G1 not subtype, 1.0%. HCV-RNA was ≥800K IU/mL in 66.5%. Statistically significant differences between MoP and CoP were observed for age, gender, genotype distribution, Rx duration, and use of RBV. Rx outcomes by duration and patient group are shown in the table. SVR rates were 93.8% (95% CI, 92.5%-94.9%) by ITT and 96.9% (95% CI, 96.0%-97.7%) by m-ITT analysis. HIV infection was not associated with Rx failure in the adjusted multivariable analysis including age, sex, liver stiffness, HCV genotype, HCV RNA, HIV, Rx duration, and RBV use (ITT and m-ITT). Factors independently associated with Rx failure by m-ITT included HCV G1a or G4, taking G1b as a reference (aOR 2.16 [95%CI, 1.2-3.2] and 2.96 [95%CI, 1.38-6.37], P=.003) and HCV RNA ≥800K IU/mL taking <800K IU/mL as a reference (aOR 2.16 [95%CI, 1.6-4.4], P=.035).

**Conclusion:** In this large prospective cohort, RX outcomes for EOB/GZR against HCV were similar to those found in pivotal clinical trials. Factors associated with Rx included infection by HCV G1a or G4 and HCV RNA ≥800K IU/mL.

### Table. Outcomes of EOB/GZR for HCV categorized by Rx duration and HCV infection

<table>
<thead>
<tr>
<th></th>
<th>12 wk (N=1320)</th>
<th>16 wk (N=211)</th>
<th>8 wk (N=8)</th>
<th>Total (N=1349)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin (– vs +)</td>
<td>6 (0.4%)</td>
<td>2 (0.9%)</td>
<td>0 (0.0%)</td>
<td>9 (0.7%)</td>
</tr>
<tr>
<td>Cure rate (– vs +)</td>
<td>231 (11.4%)</td>
<td>28 (13.2%)</td>
<td>25 (31.2%)</td>
<td>303 (22.5%)</td>
</tr>
<tr>
<td>SVR ITT</td>
<td>1374 (64.2%)</td>
<td>143 (66.9%)</td>
<td>129 (96.1%)</td>
<td>1459 (108.0%)</td>
</tr>
<tr>
<td>SVR ITT (56% CI)</td>
<td>32.8±6.3</td>
<td>84.2±5.4</td>
<td>90.6±6.3</td>
<td>83.1±4.2</td>
</tr>
<tr>
<td>Relapse</td>
<td>27 (1.3%)</td>
<td>0 (0.0%)</td>
<td>29 (3.9%)</td>
<td>6 (4.5%)</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>4 (0.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>DC due to AE</td>
<td>6 (0.3%)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>DC other reasons</td>
<td>47 (3.2%)</td>
<td>3 (1.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.1%)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>SVR m-ITT (56% CI)</td>
<td>1374 (97.3%)</td>
<td>143 (66.9%)</td>
<td>129 (96.1%)</td>
<td>1459 (108.0%)</td>
</tr>
</tbody>
</table>
| HCV LATE RELAPSE IN PATIENTS WITH DIRECTLY ACTING ANTIVIRAL–RELATED SVR 12

**Background:** The IFN-free regimens yield a sustained virological response rate at week 12 (SVR12) of approximately 95%, even in patients with cirrhosis. However, an important unresolved question is how long follow-up should last after stopping treatment and when effectively a patient is considered free of HCV infection. Aim: The aim of the present study was to identify, among the patients with failure to DAA regimen, those with a late relapse (after the achievement of a sustained virological response at week 12) and to characterize the clinical, epidemiological and virological features of these patients.

**Methods:** 129 HCV patients with non-response to an IFN-free regimen were enrolled. Sanger sequencing of NS3, NSSA and NSSB was performed at failure by home-made protocols.

**Results:** Of the 129 patients enrolled, 8 (6.2%) experienced a breakthrough, 15 (11.7%) non-response, 99 (76.7%) a relapse by week 12 after the end of DAA therapy, and 7 (5.4%) a late relapse (after week 12; median 24 weeks, range 24-72). Table 1 shows the clinical and virological data of the 7 patients with a late relapse. For 2 of the 7 patients with a late relapse a serum sample collected before the start of the DAA regimen was available; phylogenetic analysis showed no change in sequences of NS3, NSSA and NSSB regions, suggesting a reactivation of the initial HCV strain. The prevalence of patients with RAS was higher in the 7 than a late relapse than in the 99 with a relapse by week 12. In fact, at least one RAS or RASs in all 3 regions of HCV was more frequently identified in the first group (100% vs. 66.7%, p=0.09; and 28.6% vs. 5%, p=0.06, respectively); however, because of the low number of patients with a late relapse, these differences were not significant to the statistical analysis. Moreover, a RAS in the NSSA region was observed in all patients with a late relapse and in 3 (33.3%, p=0.018) in those with a relapse by week 12.

**Conclusion:** In conclusion, our real-life study demonstrates that a late relapse may occur in patients who had obtained an SVR12 with a DAA treatment. This is in good agreement with the data recently published by Sarrazin and coworkers (Sarrazin C. et al. Clin Infect Dis. 2017, PMID: 27737953) but partially disagrees with the indication of the international guidelines suggesting a post-treatment...
follow-up of 12 weeks. Thus, further studies on a larger patient population are needed to clarify this topic.

### 565 CLINICAL OUTCOMES IN PERSONS COINFECTED WITH HIV AND HCV: IMPACT OF HCV TREATMENT

**Lars Peters**, Amanda Mocroft, Jens D. Lundgren, Jan Gerstoft, Line D. Rasmussen, Sanjay Bhagani, Inka Abe, Christian Pradier, Johannes Bogner, Jürgen K. Rockstroh, Cristina Mussini, Adriano Lazzarin, Fernando Maltez, Montse Laguna, Gilles Wandel, for the EuroSIDA Study

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**Background:** Previous studies have found changes in lipids and inflammatory biomarkers after HCV cure, but little data on clinical endpoints in HIV/HCV coinfected persons. We investigated the impact of HCV coinfection status and clearance of HCV-RNA following treatment on the risk of non-AIDS malignancies (NADM), cardiovascular disease (CVD) and end-stage liver disease (ESLD) in HIV/HCV infected persons in the EuroSIDA study.

**Methods:** All HIV positive persons with known HCV status after January 2001 were included and stratified into five groups based on time-updated HCV-RNA and use of HCV treatment: 1) HCV-uninfected, 2) spontaneously resolved HCV infection, 3) Chronic untreated HCV infection, 4) Successfully treated HCV infection, 5) HCV-RNA positive despite previous HCV treatment. Separate analyses were performed with each clinical event (fatal and non-fatal) and presence of SVR(1D). Patients without diabetes showed an improvement were decompensated cirrhosis at baseline [aHR 3.43 (95IC 1.26-118.11) p<0.05].

**Results:** A total of 15,524 HIV positive persons were included. The majority were male (74%), White (87%), on cART (85%) and current smokers (55%) with a median (IQR) age of 41 (35-49) years and CD4 cell count of 446 (290-641) cells/µl. During a median of 6.6 (IQR 2.3–12.6) person years of follow up (PYFU), a total of 694 CVD, 710 NADM and 375 ESLD events occurred; crude incidence rates/1000 PYFU (95% CI) were 6.1 (5.7–6.6) for CVD, 6.2 (5.8–6.7) for NADM and 3.2 (2.9–3.6) for ESLD. In univariable and multivariable analysis, there were no differences in incidence of both NADM and CVD between those who were untreated, had cleared HCV-RNA after HCV treatment and those with chronic infection (figure). In contrast, the incidence of ESLD was significantly lower among persons who had cleared HCV-RNA after treatment compared to those with chronic infection, and similar to those with spontaneous HCV-RNA clearance.

**Conclusion:** Although HCV cure has been shown to perturb levels of lipid and inflammatory biomarkers, studies of HIV/HCV coinfected persons have lacked power to focus on clinical events. We found no evidence of any impact of HCV infection status or HCV treatment on incidence of both NADM and CVD in coinfected persons while successful HCV treatment significantly lowered the incidence of ESLD to what was observed for those with spontaneous HCV-RNA clearance.

### 566 INTERFERON-FREE REGIMENS IMPROVE RENAL FUNCTION IN PATIENTS WITH CHRONIC HEPATITIS C

**Nicola Coppola**, Federica Portunato, Antonio Riccardo Buononimo, Laura Staiano, Riccardo Scotto, Biagio Pinchera, Stefania De Pascalis, Salvatore Martini, Mariamongaletta Piscaturo, Daniela Caterina Amoruso, Guglielmo Borgia, Carmine Coppola, Ivan Gentile

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**Background:** In literature there are few data on the impact of direct-acting antivirals regimens (DAAs) on renal function. We examined estimated glomerular filtration rate (eGFR) trend during and post treatment with DAAs.

**Methods:** A retrospective analysis of a multicentre Italian cohort enrolling 403 patients with chronic HCV infection treated with DAAs between March 2015 and December 2017 for up to 12 weeks post treatment (12WPT) was performed. Patients with HIV, Child C cirrhosis, hepatocellular carcinoma or that refused consent were excluded. Impaired renal function (IRF) was defined as a CKD (chronic kidney disease) stage G3-G5 according to the KDIGO (Kidney Disease Improving Global Outcomes) stage. The reduction in CKD of at least 1 KDIGO stage was defined as an improvement.

**Results:** Of the 403 patients, 40% had a KDIGO stage of G1, 43% were stage G2, 15% were G3 and 1.4% were G4-5. Sofosbuvir(SOF) plus Ledipasvir(LDV)±Ribavirin(RBV) and Ombitasvir(OMB) plus Paritaprevir(PAR), Dasabuvir (DAS) + Ritonavir (R)±RBV were the most used regimens [34% and 30%, respectively] with an overall SVR12 rate of 98%. The median eGFR increased from 12WPT and baseline of +3.6 (IQR: -12.1/+22.6). The rate of patients with a CKD stage of G3-GS significantly decreased from 16.9% to 12.2% at 12WPT (p<0.05). Figure 1 shows the change in eGFR between baseline and 12WPT according to different comorbidities(1A) DAAs(1B), CKD stage(1C) and presence of SVR(1D). Patients without diabetes showed an improvement in eGFR from 84.05 ml/min/1.73m² at baseline to 95.01 ml/min/1.73m² at 12WPT (p<0.001), as well as patients with cirrhosis (from 79.06 to 84.61 ml/ min/1.73m² p<0.05), and patients with decompensated cirrhosis (from 71.07 to 79.46 ml/min/1.73m² p<0.001). SOF-based regimens (from 88.49 to 91.44 ml/min/1.73m² p<0.05). The median eGFR increased from 84.6 to 89.37 ml/min/1.73m² p<0.05 improved too. Finally, the 395 patients who achieved SVR12 showed an increased in eGFR from 84.6 to 91.44 ml/min/1.73m² p<0.05.

**Conclusion:** Our findings suggest that DAAs correlates with an improvement in renal function, especially if SVR12 is achieved and in patients with baseline IRF or cirrhosis. However, further studies are needed to confirm these data.
567 PCSK9 LEVELS DECLINE WITH HCV DIRECT-ACTING ANTIVIRAL THERAPY IN HIV/HCV COINFECTION

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Background: Proprotein convertase subtilisin/kexin 9 (PCSK9) regulates levels of low-density lipoprotein (LDL) cholesterol, which are altered in hepatitis C virus (HCV) infection. PCSK9 levels may also be associated with inflammation and immune activation. We hypothesized that PCSK9 levels would be higher in HIV/HCV co-infected compared to HIV mono-infected individuals, and decline to levels in mono-infected persons with HCV clearance with direct-acting antivirals (DAA).

Methods: HIV-infected adults on antiretroviral therapy with HIV RNA<50 copies/mL, HCV RNA>10,000 IU/mL or HCV antibody negative and without cardiovascular disease (CVD) were enrolled. Circulating PCSK9 and CVD/inflammatory biomarkers (sCD14, sCD163, s-E-selectin, Lp-PLA2, IL-6, sTWEAK and standard lipid panel), and HOMA-IR were measured at entry and post-treatment. Baseline characteristics and biomarker levels were compared by chi-square, Fisher's exact, or Wilcoxon rank sum tests. Within-person changes (absolute and %) in PCSK9 level with HCV therapy were examined by Wilcoxon signed-rank test, and correlations between changes in PCSK9 and changes in biomarkers by Spearman rank correlations.

Results: Twenty-four HIV and 35 HIV/HCV-infected persons were included (85% male, 85% non-white or Hispanic). Median age was 52 years and CD4 count 622 cells/mm³. Co-infected persons had higher ALT, FIB-4 scores, and HOMA-IR, and lower LDL-C and CD4 counts. Twenty-nine completed DAA therapy, all of whom achieved sustained virologic response. The Figure summarizes comparisons of PCSK9 levels at baseline, post-treatment 1 (median 7.3 weeks after end of treatment (EOT)), and post-treatment 2 (median 43.5 weeks after EOT). PCSK9 dropped significantly from baseline to post-treatment 1 and post-treatment 2: median within-person change was -20.8% (p = 0.006) and -18.2% (p = 0.033), respectively. Change in PCSK9 correlated with change in s-E-selectin and sCD163 from baseline to post-treatment 1 (r = 0.46, p = 0.016 and r = 0.39, p = 0.047, respectively) and to post-treatment 2 (r = 0.64, p = 0.002 and r = 0.58, p = 0.008, respectively), but not with change in LDL or other biomarkers.

Conclusion: Prior to HCV treatment, PCSK9 levels trended towards being higher in HIV/HCV co-infected persons compared to HIV mono-infected persons. PCSK9 levels declined significantly with HCV treatment, to levels similar to or below those in HIV mono-infection. Elevated PCSK9 levels in the setting of HCV infection may reflect HCV-associated inflammation rather than cholesterol homeostasis.

568 LIVER STIFFNESS AT SVR PREDICTS HEPATIC COMPLICATIONS IN HCV-INFECTED PATIENTS

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Background: A minority of HCV-infected patients with sustained virological response (SVR) subsequently develops hepatic complications. Determining the factors that may identify patients with SVR at risk of poor clinical outcome are of the maximum interest. The objective of the study was to analyze the predictive ability of liver stiffness (LS) at the time of SVR for the emergence of liver complications in patients with advanced liver fibrosis treated with direct antiviral (DAA)-based therapy.

Methods: Multicentric prospective cohort study. HCV-infected patients who met the following criteria were selected: 1) Achieved SVR with DAA-including regimens; 2) LS ≥9.5 kPa before starting therapy; and; 3) LS measurement available at SVR. The primary end-point was the occurrence of a liver complication -hepatic decompensation or hepatocellular carcinoma (HCC)- or requiring liver transplant after SVR. The relationship between the time to the end-point and potential predictors of liver complications was assessed in a multivariate regression model for competitive risks.

Results: 843 patients were included, 573 (68%) coinfected with HIV. 463 (55%) showed previous compensated cirrhosis. 50 (6%) had developed a liver decompensation prior to treatment and 787 (93%) had been treated with an interferon-free regimen. During a median (Q1-Q3) follow-up of 25.2 (15.8-30.6) months, 27 (3.2%) patients reached the primary end-point and 23 (2.7%) patients died. In the multivariate analysis, variables (subhazard ratio [SHR] [95% CI]) associated with developing a hepatic complication or requiring transplant were: pretreatment LS (1.03 [1.01-1.08] for 1 kPa increase), HCV genotype 3 (1.77 [2.33-14.33]), having achieved SVR with Peg-IFN-based therapy (3.70 [1.16-12.50]), prior hepatic decompensations (5.58 [1.95-15.99]), CPT class B at SVR time (6.60 [2.02-21.50]) and LS at the time of SVR (1.03 [1.01-1.01] for 1 kPa increase). Notably, none out of 482 patients with LS <9.5 kPa at SVR time-point developed a liver complication or required hepatic transplant. 175 (134%) of...
the patients with LS<14 kPa prior to treatment had a value below this level at SVR-time point.

**Conclusion:** LS at the time of SVR after DAA therapy predicts the clinical outcome of HCV-infected patients with advanced fibrosis, thus identifying candidates to be withdrawn from surveillance programs. Discontinuing HCC screening programs in patients with LS<14 kPa at SVR may spare surveillance in over 30% of the patients currently undergoing it.

**569 INFLAMMATION, ARTERIAL STIFFNESS, AND DIRECTLY ACTING ANTIVIRALS IN HCV AND HIV/HCV**

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**Background:** Co-infection with HCV increases cardiovascular disease (CVD) risk in HIV. Insulin resistance and heightened inflammation may contribute. While directly-acting antivirals (DAAs) improve glucose homeostasis and CVD risk in HCV-infected persons, the effect in HIV/HCV coinfection is less clear.

**Methods:** This is a 24-week prospective, cohort study to compare baseline and changes in aortic pulse wave velocity (PWV), glucose homeostasis (HOMA-IR), systemic inflammation (interleukin-6 (IL6), soluble tumor necrosis factor α receptors 1 and 2 (sTNF-R1 and -R2)), monocyte activation (soluble CD14 and CD163), and gut integrity (intestinal fatty acid binding protein (IFAB)) among adults with HIV, HCV, HIV/HCV or neither infection (controls) and after HCV treatment in HCV and HIV/HCV. Adults without CVD or diabetes and on stable antiretroviral therapy (HIV and HIV/HCV) were included. Pairwise comparisons of log-transformed outcome variables were made at baseline and absolute changes over 24 weeks were compared within and between groups that underwent HCV treatment. Analysis of covariance (ANCOVA) was used for adjustment.

**Results:** 126 subjects (25 HIV, 35 HCV, 39 HIV/HCV, 27 controls) were included. 54 (30 HCV, 24 HIV/HCV) received DAAs and attained sustained virologic response (SVR). Groups were similar except HCV subjects were older (56 vs 51 years) and more likely to have HTN (51 vs 23%); controls were more likely Caucasian (85 vs 48%) and non-smokers (81 vs 38%). Of those who underwent HCV treatment, 77% initiated ledipasvir/sofosbuvir. Baseline PWV was not different among groups and 0–24 week changes were not significant within or between groups treated for HCV (p=0.46 for between group test). Baseline HOMA-IR was higher in HIV/HCV than HCV and trended to be higher than controls, but did not change after DAAs (p=0.89 for between group test). Baseline IFAB and sCD163 were greater in HIV/HCV than HCV and HIV, respectively. Most inflammatory markers were higher in HCV and HIV than controls. The figure shows 0–24 week changes in the markers tested. Most markers improved in HCV, while they did not change in HIV/HCV. Changes in sTNF-R1 and sCD14 tended to be different between groups with improvements in HCV group only.

**Conclusion:** After DAA treatment, immune activation and gut markers improved in the HCV group; no change was observed in the HIV/HCV group. Further, PWV did not improve in either group. Cardiac risk may remain elevated in HIV/HCV despite SVR with DAAs.

**570 EFFECT OF LIVER FIBROSIS STAGE AND DAA TREATMENT ON RISK OF CVD EVENTS IN ERCHIVES**

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**Background:** Hepatitis C virus (HCV) infection is associated with a higher risk of cardiovascular disease (CVD) events. Treatment with directly acting antiviral (DA) regimens has been shown to reduce this risk in most, but not all studies. How liver fibrosis stage affects risk of incidence CVD events after treatment with DAA regimens is unknown. We undertook this study to determine the effect of baseline liver fibrosis stage upon the risk of incident CVD events in DAA-treated HCV infected persons, and compare it with untreated and those treated with older pegylated interferon-based (PEG) regimens.

**Methods:** Within ERCHIVES (Electrically Retrieved Cohort of HCV Infected Veterans), we identified all persons treated for HCV for >=7 weeks and propensity-score matched group who never received HCV treatment. We included those with HIV, HBV and previously diagnosed CVD. Incidence rate (per 1,000 person-years) and risk factors for CVD events (Cox proportional hazards analysis) were stratified by liver fibrosis stage. Liver fibrosis stage was determined by FIB-4 score. CVD events were identified using ICD-9CM/ICD-10 codes. Kaplan-Meier plots were generated to show and compare CVD-free survival by fibrosis stage and treatment regimen.

**Results:** Among 32,575 treated and same number of propensity-score matched untreated persons in the final dataset, median age was 58 years, 27% were Black race and 96% were male. The incidence rate for CVD events/1,000 person-years (95% CI) among the treated was as follows: FIB-4<1.25: 19.3 (17.2, 21.4); FIB-4 1.26-3.25: 19.9 (18.6,21.3); FIB-4>3.25: 24.5 (21.5,27.6). Rates among untreated were as follows: FIB-4<1.25: 25.6 (23.8,27.5); FIB-4 1.26-3.25: 33.2 (31.2,35.1); FIB-4>3.25: 44 (39.6,48.3). The absolute difference in rate was 6.3 for FIB-4<1.25, 13.3 for FIB-4 1.26-3.25 and 19.5 for FIB-4>3.25.

**Conclusion:** Risk of CVD among HIV infected persons is higher with increasing liver fibrosis stage. Treatment reduces the risk of incident events at all fibrosis stages, but the benefit is highest for those with most advanced fibrosis. HCV infected persons with more advanced liver fibrosis should be targeted for treatment to reduce future risk of CVD events.

**571 LIVER FIBROSIS HINDERS T-CELL HOMEOSTASIS RESTORATION AFTER HCV ERADICATION WITH DAAs**

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**Background:** A significant impact of HCV coinfection on several immune parameters of HIV pathogenesis has been recently shown. However, to what extent these alterations are diminished or even abolished after HCV eradication...
with direct acting antivirals (DAAs) treatment has not been clarified to date. Herein we have analyzed the effect of HCV on several immune parameters of HIV pathogenesis and its evolution after HCV eradication in HIV patients coinfected with HCV.

**Methods:** Twenty-five HIV-monoinfected (HIV group), 25 HIV/HCV coinfected (HIV/HCV group) and 20 healthy controls (HC group) were included. All patients were on antiretroviral therapy and undetectable HIV viremia. Maturation, activation, apoptosis, senescence and exhaustion of CD4 and CD8 T cells were assessed by polychromatic flow cytometry. Cross-sectional and longitudinal (comparing baseline and post-HCV treatment data in HIV/HCV patients) analyses were performed. Non-parametric tests were used to establish inter and intra-group differences.

**Results:** Compared to HIV group, HIV-HCV patients showed increased exhaustion and senescence of CD4 and CD8 cells, and increased activation of CD8 cells (p<0.0001 for all comparisons). Compared to HIV group, HCV/HCV patients presented higher exhaustion of effecter CD4 (p=0.001) and CD8 (p=0.006) cells; and higher activation of total (p=0.026) effector memory (p=0.006) and effecter (p<0.0001) CD8 cells. HIV/HCV patients with liver fibrosis (stage ≥F2), showed increased senescence and activation in several subsets of CD8 cells (p<0.05 for all comparisons) compared to patients without liver fibrosis (stage F0/F1). After HCV eradication with DAAs, differences between HIV/HCV and HIV groups diminished, except activation (p=0.002) and exhaustion (p=0.039) of effector CD8 cells that remained increased in HIV/HCV group. Interestingly, the effect of HCV eradication on immune parameters restoration (measured as the ratio of post-treatment vs. baseline values) was less pronounced in HIV/HCV patients with liver fibrosis compared to those without liver fibrosis, especially for senescence of CD8 cells (p=0.003).

**Conclusion:** Both the presence of HCV coinfection and liver fibrosis significantly impact on several immune markers of HIV pathogenesis. Eradication of HCV with DAAs ameliorates but does not normalize these alterations, what is hindered by the presence of liver fibrosis. These data prompt HCV treatment in HIV/HCV coinfected patients at the earliest stages of liver damage to enhance restoration of T cell homeostasis.

**572 IMPACT OF DIRECT-ACTING ANTIVIRALS ON RATES OF HCC IN HCV- AND HIV-INFECTED PATIENTS**

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**Background:** HCV and HIV co-infection is known to be associated with increased risk of HCC. While we have data showing a significant decline in the rate of HCC in HIV patients undergoing treatment with DAA, the rate of HCC in HCV-HIV co-infected patients treated with DAA is not known. The aim of our study was to evaluate the impact of DAA therapy on the incidence of HCC in HCV-HIV co-infected patients.

**Methods:** This retrospective analysis included all patients co-infected with both HIV and HCV, followed at Grady Memorial Hospital between January 2012 and December 2017. Patients were divided into two groups based on whether they received or did not receive DAA therapy and followed for development of HCC. Data included age, sex, HCV genotype, type of DAA regimen and SVR (in the treated group), cirrhosis, hepatitis B status, HIV control, CD4 trend and rates of HCC in both groups. Chi-square and Hazard ratio were used to calculate levels of statistical significance.

**Results:** Out of 819 patients co-infected with HIV and HCV, 387 (47%) received and 432 (53%) did not receive any DAA therapy. The median age in the untreated group was 56 years, 78% of patients were males and 92% African Americans. HIV was detectable in 3.7% patients in the treated and 34% in the untreated group (p<0.00001). As compared to the treated group, the untreated group had 11.5% patients with active cancer, for which they were receiving therapy (p=0.04), 78% patients with alcohol and/or drug abuse issues (p<0.00001) and 5% patients with end-stage renal disease (ESRD), on hemodialysis (p=0.000018). 46% of patients had Medicaid while 23% had no health care coverage. About 40 patients were lost to follow up. Poor HIV control with active drug abuse was the most common reason for withholding DAA therapy accounting for up to 60% of untreated patients. Active cancer requiring therapy (10%), loss to follow up (10%) and ESRD (5%) were the other major reasons for not receiving therapy. Other reasons included patient non-compliance (3%), intolerable side effects (2%), patient refusal (2%) (Figure 1). In the rest, the reason for non-therapy could not be ascertained. At our center, all patients, irrespective of insurance status received DAA.

**Conclusion:** 53% patients did not receive DAA though health insurance is not a barrier at our center. Poor HIV control and active drug use remain the predominant reasons for not receiving DAA therapy in HCV-HIV co-infected patients. Active cancer and loss of follow up were other major barriers. Thus, control of HIV and its consequent sequelae like cancers and nephropathy remains the biggest challenge in HIV-HIV coinfection.

**573 BARRIERS TO INITIATING DAA THERAPY IN HCV/HIV COINFECTED PATIENTS**

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**Background:** HCV continues to be a leading cause of liver disease and hepatocellular carcinoma (HCC), both of which are accelerated in HIV-HCV co-infected patients. The advent of DAA has significantly reduced the rate of HCC, but a large proportion of patients continue to be deprived of this beneficial therapy. Our aim was to determine the barriers to initiation of DAA in co-infected patients.

**Methods:** This retrospective analysis included all patients co-infected with both HCV and HIV, followed at Grady Memorial Hospital between January 2012 and December 2017 but did not receive DAA therapy. We evaluated reasons for not initiating DAA in these patients and looked at patient characteristics including age, sex, race, HCV genotype, cirrhosis, hepatitis B status, HIV control, the presence of other cancers, and social issues including drug abuse and health insurance.

**Results:** Out of 819 patients co-infected with HIV and HCV, 387 (47%) received and 432 (53%) did not receive any DAA therapy. The median age in the untreated group was 56 years, 78% of patients were males and 92% African Americans. HIV was detectable in 3.7% patients in the treated and 34% in the untreated group (p<0.00001). As compared to the treated group, the untreated group had 11.5% patients with active cancer, for which they were receiving therapy (p=0.04), 78% patients with alcohol and/or drug abuse issues (p<0.00001) and 5% patients with end-stage renal disease (ESRD), on hemodialysis (p=0.000018). 46% of patients had Medicaid while 23% had no health care coverage. About 40 patients were lost to follow up. Poor HIV control with active drug abuse was the most common reason for withholding DAA therapy accounting for up to 60% of untreated patients. Active cancer requiring therapy (10%), loss to follow up (10%) and ESRD (5%) were the other major reasons for not receiving therapy. Other reasons included patient non-compliance (3%), intolerable side effects (2%), patient refusal (2%) (Figure 1). In the rest, the reason for non-therapy could not be ascertained. At our center, all patients, irrespective of insurance status received DAA.

**Conclusion:** 53% patients did not receive DAA though health insurance is not a barrier at our center. Poor HIV control and active drug use remain the predominant reasons for not receiving DAA therapy in HCV-HIV co-infected patients. Active cancer and loss of follow up were other major barriers. Thus, control of HIV and its consequent sequelae like cancers and nephropathy remains the biggest challenge in HIV-HIV coinfection.

**574 PROGRESS TOWARDS HCV MICRO-ELIMINATION IN AN URBAN HIV-INFECTED COHORT**

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**Background:** Direct-acting antivirals (DAAs) lead to high rates of Hepatitis C (HCV) cure. Bolstered by the results of DAA treatment, the World health Organization has called for HCV elimination by 2030. Given this task, HCV micro-elimination has gained burgeoning support, and people with HIV have been identified as a population in which micro-elimination may be feasible. Here, we describe the HCV care continuum and progress towards HCV elimination in an urban HIV clinic population.

**Methods:** We examined progress through the HCV care continuum among patients infected with HIV/HCV receiving HIV care in an HIV clinic at Johns Hopkins Hospital in Baltimore, MD. Individuals were eligible for inclusion in the study if they had HIV visits in at least 2 consecutive years between January 1, 2013 and December 31, 2016 and had a detectable HCV RNA. Patients were followed through March 31, 2018 for referral to HCV care, HCV treatment initiation and cure (undetectable HCV RNA 12 weeks post-treatment).

Multivariable logistic regression was used to identify demographic and clinical characteristics associated with HCV treatment initiation.
Results: Among 594 HIV/HCV coinfected individuals, the median age was 57 years (interquartile range (IQR) 52-61), 89% were black, 67% male, 51% had a psychiatric history, 73% had a history of injection drug use and 34% reported heroin and/or cocaine use in the preceding 3 months. The median CD4 count was 462 (IQR 295-673) cells/µL; most (79%) were on antiretroviral therapy (ART), had HIV RNA <400 copies/ml (75%) and were infected with HCV genotype 1 (96%). The majority were insured by Medicaid (51%), Assessing the HCV care continuum in these 594 coinfected patients, 547 (92%) were referred for care, 517 (87%) were evaluated for treatment, 457 (77%) were prescribed treatment, 426 (72%) initiated treatment, and 381 (64%) had achieved HCV cure as of March 31, 2018. In multivariable analyses, ≥2 liver fibrosis (odds ratio [OR], 3.12, 95% confidence interval [CI], 1.40-6.96) was positively associated with HCV treatment initiation. Conversely, being on ART with an HIV RNA >400 (OR, 0.62 compared to no missed visits) were independently negatively associated with HCV treatment initiation. Recent illicit drug use was not associated with treatment initiation.

Conclusion: Oral DAAs alone are not sufficient to achieve HCV micro-elimination. Improved engagement in HIV care is critical to this goal.

575 NETWORK-BASED RECRUITMENT FOR HEPATITIS C THERAPY AMONG PEOPLE WHO INJECT DRUGS

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Background: HCV treatment models based on an individual’s drug use network have the potential to accelerate HCV elimination through increased rates of treatment uptake and reduced rates of reinfection among injection partners. Data to support the feasibility of this approach is limited.

Methods: Persons who reported recent (within < 1 year of enrollment) injection drug use were iteratively recruited from an urban infectious diseases clinic. We conducted detailed egocentric network inventories in which participants enumerated all network members including injection partners. These Egos (initial person recruited) received a brief intervention which included provision of information about HCV and its treatment and were instructed to recruit members of their injection network for HIV/HCV testing and, if positive, linkage to care. Egos received $10 for each listed member who presented for evaluation. Multivariable logistic regression analysis was conducted using generalized estimating equations (GEE) to assess for factors associated with the successful recruitment of ≥ one drug using network member.

Results: Between January and August 2018, 67 PWID with active injection drug use and HCV (with or without prior treatment) completed egocentric network surveys with the following characteristics: Median age, 54 years (interquartile range (IQR) 45-58); male, 72%; Black, 81%; homeless, 50%; unemployed, 87%; mean income, $735/month; prior incarceration (median time incarcerated, 4 years), 97%. In this group 26 (38%) had been previously HCV treated of which 12(18%) reported previous HCV cure. Egos reported injecting heroin (40%) and cocaine + heroin (37%), and 42% ≥ daily injection in the last 30 days. PWID reported a median of 7 (IQR 5-10) network members of which a median of 3 (IQR 1-5) were injection partners. Mean network density (proportion of ego’s network members that are connected controlling for network size) was 0.6. Of the 67 Egos, 27 recruited ≥ 1 drug using network member (range 1-5). In multivariate analysis, Egos were more likely to successfully recruit if they had been treated for HCV (Odds ratio (OR) 4.1, 95% Confidence Interval (CI) 1.1-16.1), were injecting at least daily (OR 3.4, 95% CI 0.9-11.7) and reported a dense network (OR 9.0, 95% CI 1.0-74.2).

Conclusion: HCV treated PWID may be particularly effective at recruiting their drug using network members for HCV testing and linkage to care. Further work is needed to systematically assess network recruitment methods for HCV treatment.

576 CAN’T BUY ME LOVE? OBSTACLES TO MICRO-ELIMINATION OF ACUTE HCV COINFECTION IN EUROPE

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Background: Several trials have shown high sustained viral response (SVR) rates with shortened direct acting antivirals (DAAs) containing therapy in acute hepatitis C (AHC) coinfected. In addition, data from modelling and real life cohorts have shown a reduced AHC incidence with early DAAs therapy. However, with no AHC currently being licensed for the treatment of AHC and with the high drug prices low DAAs treatment uptake poses the biggest obstacle to HCV micro-elimination in a high-risk population. Here we evaluate rates of DAAs treatment initiation of AHC coinfection in a large European cohort.

Results: The PROBE-C study is an observational cohort on AHC in HIV coinfection. Between 2007 and 2017 465 AHC episodes were documented in HIV-infected patients with at least 12 months of follow-up from Austria, Denmark, France, Germany, Great Britain and Spain. Fisher’s exact, chi-square and Mann-Whitney U test were used for statistical analysis. Results: 457/465 (98%) patients were male, median age was 41 years (IQR 38-46). Main risk groups for HCV transmission were MSM (98.8%) and injecting drug use (IDU) (1.1%). 78.3% of patients were infected with HCV genotype (GT) 1, 2.6% with GT3 and 18.6% with GT4. Median baseline HIV-RNA was 230,000 IU/mL (135,000-474,432), median CD4 + T cell count 574 cells/µL (547-604). 92% of all patients received cART, 91% had baseline suppressed HIV-RNA (<200 copies/µL). Median maximum ALT was 445 U/L (402-822). In 324/465 (70%) HCV treatment was initiated. In 277/324 (85%) treatment was interferon (IFN)-containing, in 47/324 (15%) DAA-based. Median time from AHC diagnosis to treatment initiation was 11 weeks (10-13). 241 of 277 (87%) AHC patients receiving IFN were treated within 24 weeks of AHC diagnosis, only 8 of 177 (5%) AHC patients receiving DAA were treated within 24 weeks of AHC diagnosis. Overall rates of treatment uptake within 24 weeks of diagnosis dropped from 75% in 2007 to 14% in 2017 (Table 1).

Conclusion: IFN-containing therapy was no longer used for treatment of AHC coinfection in our pan-European cohort after 2015. Although available and recommended by guidelines during the acute phase, DAAs-based therapy was mostly deferred to the early chronic phase of HCV infection. With more patients being viremic now than in the interferon-era drug labels need to be urgently amended to allow usage of ADA during the acute phase to limit HCV transmission in high-risk populations.
**577 HCV REINFECTION RISK FOLLOWING DAA THERAPY IN PEOPLE LIVING WITH HIV IN AUSTRALIA**

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**Background:** Given unrestricted access to direct-acting antiviral (DAA) therapies from March 2016 in Australia, HCV elimination should be achievable among people living with HIV (PLWH). Increasing HCV risk behavior and HCV reinfection, however, have the potential to compromise HCV elimination.

**Methods:** The Control and Elimination of HCV from HIV-infected individuals within Australia (CEASE-D) is an ongoing observational cohort study. HCV/HIV (antibody positive) co-infected individuals (≥18 years) were enrolled from 14 primary and tertiary clinics in Australia. Participants completed a questionnaire at enrollment (July 2014-March 2017) and first follow-up visit (June 2017-May 2018). We compared participants’ clinical and behavioural features at enrolment and follow-up. Reinfection incidence was calculated with follow-up censored May 2018.

**Results:** Of 402 HIV/HCV antibody-positive participants (mean age 49 years, gay and bisexual male [GBM] 80%, cirrhosis 13%), 288 (72%) had detectable HCV RNA at enrollment. Injecting drug use (IDU) ever was reported by 79%. Current IDU (within six months) was reported by 36% at enrollment and 35% at follow up, predominantly amphetamine users (30% for both). Among people reporting more recent IDU (within one month), 33% reported ≥weekly injecting and 11% reported needle/syringe sharing at enrollment, compared with 35% ≥weekly injecting and 13% needle/syringe sharing at follow up. Among GBM, 53% reported condom-less anal intercourse (CLAI) with one or more casual male partners (CMP) and 34% reported group sex at enrollment, compared to 40% CLAI with CMP and 25% group sex at follow-up (p=0.002 and p=0.020 respectively). HCV treatment uptake among those with detectable HCV RNA was 7% in 2014, 10% in 2015, 80% in 2016, and 35% in 2017, and was accompanied by a substantial decline in the proportion with detectable HCV RNA, from 79% in 2014 to 8% in 2018. Reinfected were identified in five participants through follow-up (incidence 0.81 per 100 person years, 95% CI 0.34–1.94), all of whom identified as GBM.

**Conclusion:** A substantial reduction in HCV viremic prevalence was observed among PLWH in Australia following unrestricted DAA access. There was no evidence of increasing HCV risk behavior with injecting risk remaining stable and some reduction in sexual risk behaviour. HCV elimination should be achievable among PLWH in the near future.

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**579 HEPATITIS C TESTING OF TRAUMA SURGERY PATIENTS: INCIDENCE, PREVALENCE, & CARE CASCADE**


**Background:** HIV-HCV co-infection increases morbidity and mortality more than infection with either virus alone. CTN-0064 examined the efficacy of an HCV care-facilitation (CF) intervention on progression along the HCV care cascade.

**Methods:** HIV-infected substance-use participants previously enrolled in CTN-0049 from 8 sites (Miami, FL, New York, NY, Atlanta, GA, Baltimore, MD, Boston, MA, Philadelphia, PA, Chicago, IL, and Dallas, TX) were enrolled from Feb 2016 to Jan 2017. After informed consent, participants were HCV tested and, if positive, were randomized to either treatment as usual (TAU) or CF. Individuals randomized to CF received up to 12 in-person 30-minute sessions. CF included motivational encouragement to receive HCV viral load results and engage in ongoing HCV care and strengths-based case-management to provide support in HCV care engagement and adherence. The outcome was number of steps achieved along 8 steps of the HCV care cascade over 12 months: receiving HCV viral load results, HIV primary care engagement, initiating ART, having an HCV (liver) evaluation, receiving an offer of HCV medications, completing HCV treatment, and achieving sustained viral response at 12 weeks (SVR12).

**Results:** Of the 517 CTN-0049 participants alive as of Feb 2016, 483 (94%) were contacted and 381 (79%) enrolled for HCV testing. Of those enrolled, 268, 24, HCV negative, with 244 HCV negative. There were 113 participants randomized (61 to TAU, 52 to CF). Participants were mostly male (58%), mean age 50 (SD=8), 14% Hispanic, 71% Black, 20% White, and 76% had insurance. CF participants achieved, on average, 2.8 steps along the HCV care cascade while TAU participants achieved approximately 2 steps (p=0.018). Participants in CF had higher rates of receiving HCV viral load results (94% vs 54%), liver evaluation (42% vs 28%), an HCV treatment offer (21% vs 11%) and SVR12 (12% vs 8%). Men had a larger response to the CF intervention (CF=3.3 steps, TAU=1.9) than women (CF=2.1, TAU=2.3; p=0.015). Women in TAU received HCV viral load results significantly more than did men in TAU (74% vs 42%, p=0.016).

**Conclusion:** A strengths-based care facilitation intervention significantly increased progress along the HCV care cascade, with a greater effect on men than women. Rates of sustained viral response were low within the 12 months of follow-up. ClinicalTrials.gov # NCT02641158
screening and linkage program to assess the incidence, prevalence, linkage to care rates, and HCV cure rates among this vulnerable population. 

Methods: From August 2016 to March 2018, HCV screening was performed on patients evaluated at an urban Level I trauma center. Data were collected including HCV antibody status, HCV RNA status, sex, race, age, year of birth, and history of intravenous drug use (IVDU). Midway through the study (May 2017), a reflex HCV screening test was introduced, in which a HCV antibody positive sample would automatically undergo the HCV RNA test without an additional blood draw and/or return visit. Patients with a positive test result were linked to care or re-engaged in care by the navigator. Follow-up was performed to assess the cascade of care among patients who tested HCV RNA positive. 

Results: There were 2,953 patients eligible for HCV screening and 2,782 were screened (94.2%). There were 366 patients with HCV antibodies (13.2%) and 189 (6.8%) with detectable HCV RNA and 36 (1.3%) patients were newly diagnosed. Of the patients with a positive HCV antibody, 292 (79.8%) underwent a confirmatory HCV RNA test. Before the reflex test, there were 0.21 positive HCV RNA tests per day compared to 0.41 positive HCV RNA tests per day after the reflex test was introduced. Men comprised 148 (78.3%) of the chronic HCV patients. The average age was 47 (22–87). There were 70 (37%) Black, 65 (34.3%) White, and 42 (22.2%) Hispanic patients. There were 85 (44.9%) patients born between 1945–1966 and 117 (61.3%) patients with a history of IVDU, but 28 (14.8%) were neither a baby-boomer nor a person who injected drugs. Of the 189 patients with detectable viral loads, 142 (75.1%) were linked to care either by education or attending their first HCV medical appointment. Of these patients, 9 (4.8%) were cured of HCV.

Conclusion: The high rate of patients with chronic HCV (6.8%) in the trauma surgery setting suggests that trauma surgery patients are at risk for HCV and should be routinely screened. Reflex HCV antibody to RNA testing increased the identification of patients living with chronic HCV. This program linked 75% of patients and cured 5% of HCV. The trauma surgery setting has significant potential to screen, diagnose, link to care and cure a vulnerable population that may not engage in routine medical care.

A RANDOMIZED TRIAL OF HIV/HCV NURSE CASE MANAGEMENT FOR LINKAGE TO HCV CARE

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Background: The opportunity to eliminate hepatitis C virus (HCV) is at hand, but challenges across the care continuum persist. These challenges are particularly poignant for persons co-infected with HIV, who are a high-priority to care but historically not well engaged in HCV care. Case management interventions have shown success in linking patients to HIV care. We hypothesized that a strengths-based nurse case management intervention (Care2Cure) adapted from evidence-based HIV studies could improve HCV care continuum outcomes for persons with HIV/HCV co-infection.

Methods: We conducted a prospective, single-blinded, randomized controlled trial to test the effect of Care2Cure in 68 adults (intervention n=35 and control n=33) with HIV/HCV co-infection. The Care2Cure intervention consisted of nurse-initiated referral to HCV care, scheduling assistance in the HCV practice, and HCV education. The comparison group (usual care) received an HCV fact sheet only. Primary outcomes included 1) linkage to HCV care (i.e., attendance at an HCV clinic appointment within 60 days of enrollment) and 2) time to DAA initiation (number of days from enrollment to first dose of DAA). Study participants were followed for 6 months.

Results: Our sample was predominantly Black/African American (81%) and low income (85% Medicaid). Nearly half (46%) reported illicit drug use and 43% had an undetectable HIV viral load. There were no demographic differences between groups at baseline. At day 60, a greater proportion of participants in the Care2Cure arm linked to HCV care (47%) compared to the comparison arm (25%) (p=0.036 by t test for difference in proportions; 95% confidence bound=3.2–40.9%). Among participants who initiated HCV treatment (n=12), the median time to DAA initiation was 100 days (interquartile range 69.5–118.5 days), with a median of 72 days for participants in the Care2Cure arm and 98 days for those in the comparison arm. This did not result in a significant difference in time to treatment initiation between the two arms at 6 months by logrank test (p=0.192).

Conclusion: Our results support provision of nurse case management as a successful strategy to link persons co-infected with HIV to HCV care. Nonetheless, linking to care alone is not sufficient to cure HCV in those who remain untreated. Interventions that address the intersection of HCV and HIV that continue from linking to care through treatment initiation and care are needed to achieve HCV elimination in this high-priority population.

DEMOGRAPHIC TRENDS IN HCV DIAGNOSIS AND LINKAGE TO HCV CARE AMONG JAIL DETAINEES

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Background: The changing epidemiology of hepatitis C infection (HCV) has important implications for screening and prevention. However, HCV surveillance is limited as chronic hepatitis C is not a reportable illness and acute hepatitis C is under-reported to public health departments. The criminal justice system, which houses a large number of individuals at risk for HCV, is a key venue to identify hepatitis C infection, evaluate HCV epidemiology and initiate linkage to HCV treatment.

Methods: Out-patient HCV antibody (Ab) testing was offered at the time of routine blood draw for individuals incarcerated at the Dallas County Jail beginning in June 2015 and occurring in three separate testing cycles. HCV RNA testing was added in 2017. Demographics and testing results were extracted from electronic medical records; HCV risk factor and health insurance status were self-reported. Patients with a positive HCV RNA were initiated in a linkage-to-care protocol beginning in 2017 including disease education, prevention counseling, and information about linkage to HCV care including a hotline number routed to a navigation specialist. Post-release, the navigation specialist followed up by phone to facilitate linkage to community HCV care. Data analyses were completed using SAS v 9.4.

Results: The prevalence of HCV Ab positivity remained stable over the three testing cycles 16.4% (500/3042), 16.5% (708/4260) and 15.9% (421/2635). The number of younger individuals (born after 1965) with HCV Ab+ increased over time, from 48% to 57% to 63%, as did the proportion of women with HCV Ab+, from 20% to 24% to 25%. Injection drug use was more commonly cited as a risk factor from year 2 to 3 (39% to 56%). Education was provided to 85% of individuals with HCV RNA+ in both years 2 and 3. In years 2/3, 198 HCV RNA+
individuals were released to the community, 149 were called at least once after release, 21 called the hotline after release and 17/21 had scheduled or pending appointments in liver clinic.

**Conclusion:** A larger proportion of women, younger individuals and injection drug users tested positive for HCV infection over consecutive years of an opt-out HCV testing program at the Dallas County Jail. Rates of HCV education were high during incarceration. Successful linkage to community HCV care was characterized by a combination of: (a) nurse navigator initiatives of education and outreach both during and after incarceration and (b) patient activation through post-release, patient-initiated engagement with healthcare.

**582 HEPATITIS C CASCADE OF CARE AMONG PEOPLE WHO INJECT DRUGS IN BRITISH COLUMBIA IN 2017**

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**Background:** New short course well-tolerated direct acting antivirals (DAAs) are expected to increase treatment rates among people living with hepatitis C virus (HCV), particularly among People Who Inject Drugs (PWID). We constructed the HCV cascade of care among people diagnosed with hepatitis C virus infection living in British Columbia (BC), Canada in 2017, stratified by history of injecting drug use to compare progress in care and treatment.

**Methods:** The BC Testers Cohort (BC-HTC) was used for this analysis. BC-HTC includes all individuals tested for HCV in BC since 1990, linked to date on all prescription drugs, medical visits, hospitalizations and mortality data. We defined six cascade of care stages: 1) anti-HCV positive (diagnosed); 2) RNA tested; 3) RNA positive; 4) genotyped; 5) initiated treatment; and 6) achieved post-treatment sustained virologic response (SVR). People diagnosed with HCV infection were stratified by history of injecting drug use (recent PWID, people who injected drugs <3 years; past PWID, >3 years ago; or never PWID) and progression through care cascades compared among these groups.

**Results:** In 2017, there were 52,987 individuals diagnosed with HCV infection (anti-HCV positive) in BC. Among those diagnosed, 22% (11806/52987) were recent PWID, 17% (9118/52987) past PWID and 61% (32063/52987) never PWID. Confirmation of infection by RNA or genotype testing was highest among recent PWID, and lowest among never PWID (Figure 1). Of people with genotype testing, HCV treatment initiation was lowest among recent PWID, with 38.1% (2698/7081) among never PWID, compared to 46.3% (2016/4350) among past PWID, and 60.4% (10162/16812) among never PWID. Among both past and never PWID, a higher proportion of individuals were born before 1965, whereas among recent PWID a higher proportion of individuals were born after 1965.

**Conclusion:** Through integration of provincial testing, treatment, mortality, medical visits and hospitalization datasets, it is possible to assess population-level HCV prevention and care cascades among PWID, which is essential to monitoring progress towards HCV elimination goals. Overall, progression through the HCV cascade of care in BC has improved since DAAs were available, but it remains lower among recent PWID. Treatment uptake may improve with the recent removal of fibrosis restrictions on treatment eligibility; however, factors associated with treatment uptake among PWID should be further investigated to help identify strategies to enhance HCV treatment uptake among this group.
LOW PERFORMANCE OF THE ORAQUICK HCV RAPID ANTIBODY TEST IN HIV/HCV-INFECTED PEOPLE

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Background: There is a global need to expand hepatitis C virus (HCV) diagnostic testing and saliva sampling may provide an easier access to HCV screening test. An estimated 2.3 million people living with HIV are coinfected with HCV globally. Despite this high numbers, the performance of HCV rapid test has not been extensively studied in HIV population.

Methods: We enrolled consecutive patients (pts) attending the Outpatient Infectious Disease Clinic of S. M. Goretti in Latina from Oct 2017 to Jan 2018 and 30 healthy donors (HD) with a known plasma test for HCV and HIV. We performed the OraQuick HCV Rapid Antibody Test (OraSure Techn, Inc.). We collected anagaphical, clinical and laboratory data. The OraQuick HCV Rapid Antibody Test was used according to kit instruction. Statistical analysis was performed using Kruskal-Wallis, Mann-Whitney and t test. The 95% confidence interval (CI) was estimated for sensitivity, specificity, and positive and negative predictive values.

Results: A total of 227 persons were recruited into the study: 83 pts with known HCV infection (30F, 43M); 84 with known HIV/HCV coinfection (16F, 68M); 30 HD (12F, 18M); 30 HIV positive subjects known HCV uninfected (18F, 12M) pts. In the group of HIV-/HCV+ and HIV+/HCV+ no statistically significant differences in HCV-RNA level, fibrosis and year living with HCV were observed. The results of OraQuick in the 4 groups are showed in Table 1. In all the study population a sensitivity of 53% (95% CI, 45%–60%) and specificity of 100% was found. The positive predictive value (PPV) was 1 (95% CI 0.96–1), while the negative predictive value (NPV) was 0.43 (95% CI 0.35–0.52). Analyzing the 4 subgroups of pts interestingly in the HCV+/HIV+ group the OraQuick test showed a sensitivity of 6% (95% CI, 2%–13%) and specificity of 100%. In HIV-/HCV+ pts the PPV was 1 (95% CI, 0.48–1), while the NPV was 0.28 (95% CI 0.19–0.37). Conversely in the HCV+ group, the OraQuick test showed a sensitivity and specificity of 100%. The PPV was 1 (95% CI 0.96–1) and NPV was 1 (95% CI 0.88–1). No associations were found between false positive results and CD4 count, HCV-RNA, liver fibrosis, DAA use, sex.

Conclusion: In the context of HCV eradication goal the development of easy and quick tests may offer relevant opportunities to facilitate HCV screening. However, in our study the OraQuick test performance is strongly impaired in the HIV-infected people showing a very low sensitivity thus it should be discouraged in known HIV pts where serology can not be replaced.

Table 1: Results of the OraQuick test in the 4 subgroups.
586 DIVERSE OBSTETRICIAN HCV-SCREENING PRACTICES IN A LARGE REGIONAL HEALTH CARE SYSTEM

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Background: Given the onslaught of the opioid epidemic, the incidence of HIV and Hepatitis C (HCV) infection is increasing in reproductive age women. Unlike recommendations for universal HIV screening, HCV testing in pregnancy has been risk-based. Recent AASLD/IDSA guidelines recommend universal HCV screening. We hypothesized that prior to revised screening recommendations there was diversity in HCV testing practices amongst obstetrical practices.

Methods: We extracted HCV testing (HCV antibody/RNA) and reactivity data from the EHR for the first outpatient prenatal visits at MedStar Health, a large regional healthcare system, from January 2017 through April 2018. We used Chi-square, Fisher’s Exact and Student’s t-tests, as appropriate for the bivariate analyses, and multivariate logistic regression to determine predictors of HCV screening and antibody positivity. Variables included age, race, ethnicity, HIV screening and infected, HBV infected, insurance, birth outcome, delivery method, and location. SAS statistical software was used for the analyses.

Results: There were 10,415 women who met study eligibility; 3,081 (29.6%) were HCV tested, and 44 (1.4%) were HCV antibody positive. Pregnant women were more likely to be screened for HCV if they were older (ORadj 1.02, CI95 [1.01-1.02]), African American or other race compared to Caucasian (2.24 [2.02-2.49]; 1.74 [1.53-1.98]), HIV tested (4.25 [3.65-4.94]), HCV infected (8.37 [4.77-14.70]), and had private insurance (1.51 [1.37-1.66]). Pregnant women were more likely to be HCV antibody positive if they were Caucasian as compared to African American (ORadj 11.44 [CI95 3.99-32.82], HBV infected (15.27 [2.32-104.46]) and living in Maryland vs. DC (2.93 [1.17-7.32]). There was no difference in the latter analysis for age, ethnicity, HIV status, birth outcome or insurance.

Conclusion: Universal HCV testing has not yet been fully deployed in pregnant women at this large healthcare system, which includes urban, suburban and rural practices. However, the 30% screening rate is higher than other published reports. There appears to be racial discordance in screening practices, with more African Americans tested; however, more Caucasians were HCV antibody positive. This could be due to prior universal testing adoption in the urban vs. the suburban/rural environment and requires further exploration. Providers and practices will need to adapt to changing universal screening guidelines, especially given the demographics and burgeoning of the opioid epidemic.

587 DECENTRALIZATION AND TASK-SHIFTING FOR HEPATITIS C: SYSTEMATIC REVIEW & META-ANALYSIS

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Background: Worldwide, 71 million persons are HCV infected but only a small proportion have been diagnosed and treated. Increasing access to care in low and middle income countries (LMICs) will require adoption of simplified service delivery models such as decentralization and task shifting to non-specialists. The evidence base for their effectiveness in HCV care remains limited. We conducted a systematic review and meta-analysis to establish the effectiveness of decentralization and task shifting on outcomes across the continuum of HCV care in different populations.

Methods: Bibliographic databases and conference abstracts were searched for English language clinical trials or observational studies published between 2001/2008 to 02/2018 that evaluated these interventions. Outcomes were testing and HCV viral load uptake, linkage to care, treatment uptake, and cure (SVR12) in PWID, prisoners, PLHIV, and general population. Decentralisation was defined as either full (FD) (testing and treatment at same primary care or harm reduction site), or partial (PD) (testing at decentralized site and referral for treatment) and task-shifting as HCV treatment by non-specialists (primary care physicians or nurses). Data were pooled using random effects meta-analysis and meta-regression was used to explore heterogeneity.

Results: Ninety studies from 18 countries (11 were LMIC) were included. 62 were single arm studies and 15 had a comparator arm (RCTs, non-RCT or cohort
THE COST-EFFECTIVENESS OF HCV SCREENING OF PREGNANT WOMEN IN THE UNITED STATES

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Background: Hepatitis C Virus (HCV) chronic prevalence among pregnant women in the United States (U.S.) is estimated at 0.7%, but can reach 8% in rural Tennessee, and doubled nationally from 2009-2014. Yet, screening for pregnant women is not currently recommended by the U.S. Centers for Disease Control, and many pregnant women remain undiagnosed. Recent AASLD/IDSA guidelines and the state of Kentucky recommend screening pregnant women but note low quality and strength of evidence supporting this recommendation. We assess the cost-effectiveness of HCV screening for pregnant women in the U.S.

Methods: A deterministic HCV natural history Markov model among pregnant women was used to evaluate the cost-effectiveness of HCV screening of pregnant women compared to no screening from a health care payer perspective. We assumed 0.73% (95%CI 0.71-0.75) HCV chronic prevalence among pregnant women based on national data. Given differing state-based Medicaid reimbursement policies, we explored the cost-effectiveness of antenatal screening in settings with differing treatment eligibility: METAVIR stage F3 or beyond (F3+), F2 or beyond (F2+), or F0 and beyond (F0+). We assessed cost (in U.S $) and health outcomes (in quality-adjusted life years, QALYs) over a lifetime horizon. We sampled 1000 parameter sets and calculated mean incremental cost-effectiveness ratios (ICERs), assessing cost-effectiveness under a willingness to pay threshold of $50,000/QALY gained. Using state-specific pregnancy rates and fibrosis restrictions, we estimate the impact of screening.

Results: The mean ICERs for antenatal screening were $6303, $8594 and $13677 per QALY gained in the F3+, F2+, and F0+ treatment eligibility scenarios, respectively compared to no screening. Screening was cost-effective under a $50,000 willingness-to-pay threshold in all simulations. Screening remained cost-effective for prevalences at or above 0.05-0.08% depending on treatment eligibility (Fig. 1). In a state with 8% prevalence and F2+ restrictions like Tennessee, the ICER was $5,288. Screening the estimated 5.04 million pregnant women in 2018 could result in detection and treatment of 33,000 women in the United States based on current fibrosis restrictions.

Conclusion: Screening pregnant women for HCV in the U.S. is likely cost effective assuming a national prevalence of 0.7%, and should be recommended. In geographical areas with higher prevalence, such as Appalachia, cost-effectiveness is even greater.

COST-EFFECTIVENESS OF HCV TREATMENT AMONG HIV-POSITIVE INDIVIDUALS IN MYANMAR

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Background: Over half of those co-infected with hepatitis C virus (HCV) and HIV live in low- and middle-income countries, and new HCV direct-acting antiviral therapies (DAAs) cure >90% of individuals. However, the cost-effectiveness of DAAs among HIV/HCV coinfected individuals in low-income settings is unclear. In 2016, Medecins sans Frontieres (MSF) began HCV treatment within a HIV cohort in Myanmar. We evaluated the cost-effectiveness of the HCV treatment program among HIV/HCV coinfected patients in Myanmar.

Methods: We assessed the real-world cost and cost-effectiveness of HCV DAA treatment among HIV-positive individuals compared to no treatment from a program provider’s perspective. Patient characteristics, costs and treatment outcomes were collected from an ongoing, prospective cohort study in Dawei, Myanmar. We performed a patient-level micro-costing analysis of DAA treatment delivery. A Markov model of HCV disease progression among HIV-infected individuals was developed and used to estimate lifetime costs (in 2017 $USD) and health outcomes (in disability-adjusted life-years (DALYs)), discounted at 3% per year. Disease state transitions and disability weights were informed from published literature. We calculate the incremental cost-effectiveness ratio (ICER, difference in costs divided by difference in DALYs), compared to a willingness to pay threshold of the per capita GDP in Myanmar ($1275). We additionally evaluate the potential cost-effectiveness utilizing a simplified treatment protocol with about 25% fewer visits and task-shifting from doctors to nurses.

Results: From November 2016 to October 2017, 122 patients initiated treatment (66 METAVIR stage F0-F3, 56 cirrhosis or later), 96% (n=117) achieved SVR. Under the current treatment protocol, the average cost of treatment per patient was $677 and $1362 for patients in F0-F3 and cirrhosis or later, respectively, mainly due to drug costs ($493 and $939 for 12 and 24 weeks, respectively for sofosbuvir/daclatasvir). The current treatment protocol costs an incremental $938.79 per patient treated, resulting in 1.33 DALYs averted per patient, resulting in an ICER of $707/DALY averted compared to no treatment. A simplified treatment protocol could result in an ICER of $424/DALY averted compared to no treatment.
Conclusion: HCV DAA treatment for HIV/HCV coinfected individuals is likely cost-effective in Myanmar. A simplified treatment protocol and/or lower drug costs could enhance cost-effectiveness.

591 TEMPORAL PATTERNS IN HCV PHYLOGENETIC CLUSTERING AMONG PWID IN BALTIMORE, MD

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Background: HCV infection occurs in 30-90% of people who inject drugs (PWID). Phylogenetic analysis can be used to inform strategies to interdict transmission. This study examines patterns in HCV phylogenetic clustering overtime among PWID in Baltimore city.

Methods: Community-based PWID were prospectively recruited for The AIDS Linked to the IntraVenous Experience (ALIVE) cohort in Baltimore, MD. Viral RNA underwent Polymerase Chain Reaction with primers targeting the 5' end of the envelope-1 region and sequenced using Sanger Sequencing methods. There were 820 HCV RNA+ participants from 1988-1989 and an additional 512 unique HCV RNA+ participants from 2005-2016. Networks were rendered at a 4% genetic distance threshold using HIV-TRACE and participants were geographically mapped using Microreact. Prevalence ratios (PR) and 95% CIs of being in a cluster (≥2 participants) were calculated using Poisson regression with robust variance.

Results: There were 15 clusters found among the participants in 1988-89 and 22 clusters identified in 2005-16. In both time periods, two large genotype 1a clusters were observed with 586/716 (82%) in 1988-89 and 113/302 (37%) in 2005-2016. When combining data from 1988-89 with 2005-16, the two large genotype 1a clusters were maintained (Figure). Participants from 2005-16 (59% [303/512]) were less likely to be in a cluster compared to the participants from 1988-89 (87% [716/820]) independent of HIV status, age, sex, race, zip code (adjusted PR, 0.71 [95% CI, 0.64-0.79]). The percentage of individuals in a cluster was consistently lower across all two-year intervals in the 2005-16 period in comparison to the 1988-89 two-year interval. Similar findings were observed when stratifying the analysis by genotype 1a and 1b. Among the clusters, there was a greater number of linkages among the 1988-89 individuals (median, 28 [IQR, 9-78]) compared to 2005-16 individuals (median, 5 [IQR, 1-16.5]; p<0.001).

Conclusion: We observed greater cluster diversity in the participants recruited in 2005-16 indicative of a less connected network of individuals sharing transmission risk, though major viral strains did persist over time in this cohort.
PHYLOGENETIC EVIDENCE FOR INTERCITY HCV CLUSTERS OF PEOPLE WHO INJECT DRUGS IN INDIA

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Background: Little data exist on HCV phylogenetics and transmission networks among people who inject drugs (PWID), especially from low- and middle-income countries (LMICs). HCV epidemics in a city can be considered a series of sub-epidemics caused by phylogenetically distinct viral lineages. Mapping these lineages to generate transmission clusters and overlaying epidemiologic data can be used to identify factors associated with clustering.

Methods: PWID were recruited via respondent driven sampling in 2016-17. Participants completed a survey and blood draw. HCV 5'UTR-core sequencing was performed on 486 HCV RNA positive samples from 4 cities (Amritsar [n=126], Delhi [n=128], Kanpur [n=138], and Haridwar [n=94]). Sequences were aligned using Multiple Sequence Comparison by Log-Expectation. The most appropriate nucleotide substitution model was determined using jModelTest and phylogenetic inference was carried out using Maximum Likelihood methods in RAxML with 500 bootstrap replications. Clusters were identified using a ClustPick tool with posterior support and genetic distance thresholds of 70% and 4.5%, respectively. Given the large number of covariates of interest, a machine learning model utilizing the Boruta wrapper of the random forest algorithm was constructed to identify features predictive of clustering, as well as differences between clusters.

Results: Median age was 33 years, 99% were male and HIV prevalence was 75%. Median p-distance for all sequences was 0.075. A total of 251 sequences fell into 19 transmission clusters (Fig). Mean cluster size was 7.4 (range: 2-49); 8 clusters were dyads. There were 6 large clusters comprised of >10 samples. 7 of the 19 clusters contained samples from multiple cities. Machine learning model identified the Boruta wrapper of the random forest algorithm was constructed to identify features predictive of clustering, as well as differences between clusters.

Conclusion: These are among the first data from a LMIC setting to demonstrate clustering across multiple cities. The median size of the clusters identified were also larger than self-reported injection networks in India. Treatment as prevention efforts for HCV have emphasized network-based approaches for PWID, and these data suggest that networks may need to be defined by space (zip code) as opposed to egocentric injection networks.

PHYLODYNAMICS OF ACUTE HCV INFECTION IN MEN HAVING SEX WITH MEN

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Background: Opioid substitution and syringes exchange programs have drastically reduced HCV spread in France, while HCV sexual transmission in men who have sex with men (MSM) has recently arose as a significant phenomenon. Epidemiological data such as prevalence and incidence rates can quantify an epidemic at its chronic stage but are less meaningful at its early stages or if the transmission of the pathogen only occurs in a subgroup of individuals. Phylogenetic inferences use both pathogen phylogenies based on genetic sequences and epidemiological data to describe infectious diseases transmission dynamic. We used a phylodynamic approach to estimate key epidemiological parameters such as the reproduction number (R0) and the infectious period duration of acute HCV infection (AHI) in French MSM.

Methods: A birth-death epidemiological model with 2 host types corresponding to respectively the ‘classic’ HCV epidemic (mostly IDU-blood product recipients) and the ‘new’ epidemic in MSM was implemented. Two periods (< and ≥1997) were considered for the classic epidemic. 30,000 simulated phylogenies were first generated under a variety of parameter set. These simulations were then used to ‘feed’ a regression model and to infer epidemiological parameters using an approximate Bayesian computation approach. The model was then run on the true HCV phylogeny from AHI and chronic HCV infections, to infer R0, infectious period and asymptomatic estimates (the extent to which virus transmission is random or occurs mostly within groups) for both epidemics. The validity of the results was estimated using a parametric bootstrap approach.

Results: 213 NS5B sequences from HCV genotype 1a infections were analyzed (68 from AHI in MSM, 145 from chronic infections in non-MSM patients). Estimates of the beginning dates for the classic and the new epidemics were 1983 (95%CI 1981-1983) and 2000 (95%CI 1999-2002) respectively. Estimates of R0 for the classic epidemic >1997 and for the new epidemic were 1.5 (IQR 1.3-1.7) and 1.7 (IQR 1.4-2.1) respectively. Estimates for the infectious period duration for the classic and the new epidemics were 2.3 years (IQR 1.6-3.1 years) and 0.4 years (0.4-0.5 years) respectively.

Conclusion: AHI epidemic in French MSM was characterized by a similar R0, but a much shorter infectious period and a greater transmission rate per unit of time than the classic epidemic. This result shows how phylodynamic can help to understand the transmission dynamics of an epidemic spreading in different populations.

VALIDATION OF A GENOTYPE-INDEPENDENT HEPATITIS C WHOLE-GENOME SEQUENCING ASSAY

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Background: Recent development of direct-acting antiviral agents (DAA) has dramatically improved the effectiveness and tolerability of treatments for hepatitis C virus (HCV), resulting in >95% sustained virologic response (SVR) rates. However, cases of treatment failure have been associated with the emergence of resistance-associated substitutions (RAS). To better guide clinical decision-making, we developed and validated a near-whole-genome, HCV genotype (GT)-independent sequencing strategy on the Illumina MiSeq next-generation sequencing (NGS) platform.

Methods: HCV GT1-6 samples from treatment-naïve HCV-infected individuals as well as DAA-treated persons who did not achieve SVR were included. Viral RNA was extracted from a Biomerieux easyMag and underwent nested reverse-transcription-PCR. Libraries prepared by Nextera XT were sequenced on the MiSeq. NGS data were processed by an in-house pipeline that incorporates HCV reference sequence selection and an iterative mapping process for paired-end reads. Nucleotide consensus sequences were aligned to appropriate FDA reference strain sequences for downstream identification of RAS. Sequences were compared to data obtained from a previously validated in-house assay optimized for HCV GT1. A minimal threshold for minor species detection was estimated from the coefficient of variation of minor species quantification.

Results: Roughly 90% sequencing success rates, defined as achieving >100-fold NGS read coverage across NS3, NS5a and NS5b, was observed for most
596 HPTN 078: HIGH PREVALENCE OF HCV ANTIBODIES AMONG MEN WHO HAVE SEX WITH MEN


HPTN 078 Research Group

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Background: Sexual transmission of hepatitis C virus (HCV) is uncommon, yet has been documented among MSM, primarily among those who are HIV-infected. Recent phylogenetic analyses reveal that some HIV-uninfected MSM are infected with HCV strains circulating in HIV-infected MSM transmission networks. Data on the prevalence of HCV infection in HIV-uninfected MSM is limited.

Methods: In HPTN 078, which assessed the efficacy of an integrated strategy to achieve HIV viral suppression, 1305 MSM were screened using respondent driven sampling or direct recruitment across four geographically diverse US cities. HIV-infected MSM with viral loads >1,000 copies/mL were eligible for enrollment. At screening, demographic, behavioral, and psychosocial questionnaires were completed, along with HIV and HCV antibody testing. Multivariable logistic regression was used to evaluate associations with HCV antibody positivity.

Results: Of the 1305 men screened, median age was 41, 69% were Black, 85% had a high school diploma or more, 84% had either public or private insurance, 35% were employed, 69% were HIV-infected, and 20% had undergone substance use counseling/treatment. The median lifetime number of male sexual partners was 17 (IQR: 6, 50) and female partners was 5 (2, 13). HCV antibody test results were available for 1287 (99%) of the men for whom 246 (19%) were positive. HCV antibody positivity was high in both HIV-infected and HIV-uninfected (16%) MSM (P<0.10) and was higher in those receiving substance use counseling/treatment (36%) than those that had not (15%) (P<0.01). After adjusting for other factors, older age (odds ratio (OR) 1.06 per year, 95% CI 1.05-1.08), less than a high school degree (OR 1.71, 95% CI 1.15-2.55), drug/alcohol counseling or treatment (OR 2.57, 95% CI 1.83-3.61) and unstable housing (OR 2.16, 95% CI 1.29-3.61) were associated with increased risk for HCV antibody positivity.

Conclusion: Nearly 1 in 5 MSM screened for HPTN 078 have been infected with HCV in a high HIV burden sample. The prevalence is high regardless of HIV infection status and is high even in those who did not undergo substance use counseling. These data raise concern that in HIV burden networks high HCV infection prevalence may occur in HIV-uninfected MSM. HCV transmission risk could increase as PREP implementation expands and condom use declines among HCV positive MSM. Further work is needed to understand the high HCV antibody prevalence in this cohort.

597 EPIDEMIC HISTORY OF HEPATITIS C VIRUS AMONG MSM IN AMSTERDAM, THE NETHERLANDS

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HPTN 078: HIGH PREVALENCE OF HCV ANTIBODIES AMONG MEN WHO HAVE SEX WITH MEN

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Background: To strengthen HCV micro-elimination efforts in the MSM community, a better understanding of transmission networks is vital. Insight in the proportion of new HCV infections that results from ongoing transmission of local variants versus new infections via external introductions may further guide specific local elimination efforts. We describe the epidemic history of HCV infections among MSM in Amsterdam from 1994 to 2018.

Methods: Sanger sequencing of part of the E1E2 genomic region (525 base pairs) was applied to 147 samples positive for HCV gt1a – the most prevalent genotype in Amsterdam (62%) – from MSM diagnosed between 1994 and 2018. The majority of MSM was HIV positive (67%) and diagnosed during the acute phase of the infection (91%). Time-resolved phylogenetic analyses were performed using BEAST software to estimate the temporal origin and progression of the HCV epidemic in Amsterdam. PhyCLIP software was used for statistically supported cluster designation.

Results: 114 sequences (78%) grouped into seven clusters with introduction dates ranging from 1996 to 2004. Cluster sizes ranged from three to thirty-seven sequences. A modest decrease in proportion of clustered sequences over time was observed: 80% (36/45) of samples from 2008-2013 and 70% (40/57) of samples from 2013-2018 were part of a cluster. We observed that the ratio non-clustered to clustered sequences remained fairly stable until 2015 (mean ratio 0.14, SD = 0.10), after which the ratio increased to 1.2 in 2018 (n=11) in favor of the non-clustered sequences.

Conclusion: The identification of both non-clustered and clustered infections, in particular in the past few years, indicates that both external introductions and ongoing transmission within existing clusters fuel the HCV epidemic among MSM in Amsterdam. The seeming increase in external introductions when compared to local transmission coincides with the beginning of the DAA era in the Netherlands. Prospective, phylogenetic analysis of recent HCV infections combined with data collection on network characteristics of the individuals infected with HCV (e.g. meeting location of sex partners) has the potential to guide targeted prevention measures and stresses the need for real-time HCV sequence monitoring in the Netherlands.

598 RISK FACTORS AND PATTERNS OF HCV TRANSMISSION IN MEN WHO HAVE SEX WITH MEN IN ENGLAND

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1EPIDEMIC HISTORY OF HEPATITIS C VIRUS AMONG MSM IN AMSTERDAM, THE NETHERLANDS

1Academic Medical Center, Amsterdam, Netherlands, 2Sanquin Research, Amsterdam, Netherlands, 3Public Health Service Amsterdam, Amsterdam, Netherlands, 4Agency for Science, Technology and Research, Queenstown, Singapore, 5Cambridge University, Cambridge, UK

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Investigated the incidence of HCV among HIV-positive MSM taking antiretroviral therapy (ART) in a long-term clinical cohort in Bangkok, Thailand.

**Methods:** MSM with negative baseline anti-HCV antibody tests were identified in the Thai HIV-NAT 006 cohort from October 1996 to July 2018. HCV incidence among MSM was defined by two positive anti-HCV antibody tests and confirmed by detectable HCV RNA level. HCV genotyping was done using the Linear Array Hepatitis C Virus Genotyping Test. Recent syphilis infection was defined as a reactive RPR within 6 months of HCV seroconversion.

**Results:** A total of 464 MSM with median (IQR) baseline age of 38 (32-46) years and baseline median CD4 count of 303 (180-466) cells/mμL were included in the study. Participants had been treated with ART for a median of 7.5 (7.7-12.5) years. Of 464 MSM, 29 incident cases were identified during 2885 person-years (PYS) of follow-up. The crude incidence rate of HCV surged from 0.37 per 100 person-years of follow-up (PYS) before 2014 to 2.21 per 100 PYS in 2014-2018. At the time of HCV seroconversion, most participants (82%) had suppressed HIV viremia and the median CD4 count was 581 (479-792) cells/mm³. Of the HCV incident cases, 81% (N=31/39) had genotype 1a and 27.6% had hepatitis B co-infection (HBsAg positive). In multivariate analysis, age <35 years (HR, 3.31, 95% CI, 1.78-6.26, p=0.001) and recent syphilis infection (HR, 3.84, 95% CI, 1.78-8.26, p=0.001) were strongly associated with incident HCV among Thai MSM living with HIV. Among 29 incident cases, three participants reported injecting methamphetamine use from collected behavioral risk assessment questionnaire. Spontaneous clearance was observed in 1 case. 4 participants (14%) were treated for HCV and all achieved SVR at week 12.

**Conclusion:** A recent surge in HCV incidence is noted among MSM receiving chronic HIV care in Bangkok, Thailand. In the era of effective direct acting agents (DAAs) and “Undetectable=Untransmissible”, sexually transmitted infections, including hepatitis C and syphilis, need to be routinely screened and treated in HIV+ MSM to prevent further transmission to both HIV-positive and HIV-negative partners, particularly among resource-limited settings where the access to DAAs are still low.

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**Table:** Characteristics of HIV-uninfected and HIV-infected men with recently-acquired HCV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-NAI</th>
<th>HIV+NAI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>32 (28-38)</td>
<td>50 (43-57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UK born</td>
<td>9 (5.6)</td>
<td>18 (70.0)</td>
<td>0.215</td>
</tr>
<tr>
<td>Handicapped</td>
<td>2 (2.8)</td>
<td>5 (6.2)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Number of sex partners</td>
<td>13 (9.7)</td>
<td>30 (4.3-49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genotype proportion</td>
<td>13 (81.1)</td>
<td>18 (41.0)</td>
<td>0.177</td>
</tr>
<tr>
<td>Genotype 4 proportion</td>
<td>3 (4.5)</td>
<td>9 (31.5)</td>
<td>0.059</td>
</tr>
<tr>
<td>Maximum duration of HCV infection, months</td>
<td>5 (3.3)</td>
<td>6 (13.8-24.0)</td>
<td>&lt;0.999</td>
</tr>
<tr>
<td>spontaneous HCV clearance</td>
<td>2 (12.5)</td>
<td>5 (12.5)</td>
<td>&lt;0.999</td>
</tr>
<tr>
<td>Prior HCV episode(s)</td>
<td>4 (25.0)</td>
<td>5 (30.0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>STI at HCV diagnosis</td>
<td>5 (31.2)</td>
<td>7 (28.3)</td>
<td>0.688</td>
</tr>
<tr>
<td>History of IUU</td>
<td>7 (44.0)</td>
<td>11 (46.5)</td>
<td>0.797</td>
</tr>
<tr>
<td>History of non-CD4 in past year</td>
<td>13 (83.3)</td>
<td>18 (72.2)</td>
<td>0.379</td>
</tr>
<tr>
<td>Median number of sex partners in past year</td>
<td>9 (6-15)</td>
<td>16 (6-20)</td>
<td>&lt;0.025</td>
</tr>
</tbody>
</table>

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**Figure:** Kaplan-Meier curves showing the proportion of anti-HCV accrual in MSM with seroconversion from HIV-positive MSM with or without recent syphilis infection (5-6 months of HCV seroconversion)
Methods: This study describes a nationwide multicenter (80 Spanish hospitals) cross-sectional study of 588 DAA-treatment naïve patients harboring HCV-GT1a. HCV population sequencing was used to identify relevant resistance-associated substitutions (RASs) to NSSA inhibitors. Phylogenetic analysis was used for subtyping and transmission cluster identification. HCV-GT1a lineages (clade I and clade II) were confirmed by geno2pheno[HCV]. Bayesian methods were used to reconstruct the epidemic history of HCV-GT1a.

Results: 51.0% (n=300) were HCV+ and 49.0% (n=288) were HIV+/HCV+ subjects. HCV-GT1a clade II was more prevalent than clade I (82.3%, n=484 vs. 17.7%, n=104, P<0.001). Viruses bearing RASs to NSSA inhibitors were present in 50 samples (8.5%), seven of those having viruses with double RASs. Higher prevalence of RAS was found in clade II (80%). The most common RASs were M28A/T/V (44.0%, n=22/50), Y93F/H/N (28.0%, n=14/50) and Q30E/H/R (24.0%, n=12/50). The double mutations 30H+93H, 28V+30R and 30R+93H were also observed. A prevalence of RASs of <10% was observed in eleven regions while a prevalence >10% was observed in five, highlighting Cantabria (15.9%; n=7/44) and Murcia (12.5%; n=1/8). Among patients harboring RASs, those that harbored mutations which confers high resistance were: 38.0% (n=19/50) “daclatasvir, 34.0% (n=17/50) to ledipasvir, 36.0% (n=18/50) to ombitasvir, 6.0% (n=3/50) to elbasvir, 8.0% (n=4/50) to velpatasvir, 4.0% (n=2/50) to pibrentasvir. GT1a clade II epidemic preceded clade I by 45 years (time to the most recent common ancestor (TMRCA), 55% highest posterior density [95%HPD], 1907-1932 vs 1952, 1939-1965) (Fig 1 A-B-C). GT1a clade II epidemic started in Basque Country, was dispersed throughout the entire country and is now declining. The current GT1a clade I epidemic is still mostly concentrated in the North of Spain and Canary Islands (Fig 1 D-E).

Conclusion: Current HCV GT1a epidemic in Spain is mainly driven by clade I viruses which seem to have different dispersion routes relative to clade II viruses. Close surveillance of patients with NSSA RAS will be important to prevent further therapeutic failures.

601 HCV ANTIBODY AVIDITY–BASED METHOD TO ESTIMATE POPULATION-LEVEL INCIDENCE

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Background: Accurate hepatitis C virus (HCV) incidence estimates are critical for monitoring progress towards hepatitis C elimination goals which include a reduction in HCV incidence of 80% by 2030. Moreover, incidence estimates can help guide local prevention and treatment programming, particularly in the context of the US opioid epidemic.

Methods: An inexpensive ($4/sample), Genedia-based HCV IgG antibody avidity assay was evaluated as a platform to estimate cross-sectional, population-level HCV incidence using 1840 anti-HCV+ and RNA+ samples from 875 individuals enrolled in 5 cohort studies in the US and India of whom 220 were HIV+. Using samples collected <2 years following HCV seroconversion, the mean duration of recent infection (MDRI) was calculated by fitting a binomial regression to the probability of appearing recent using an exact binomial test. Factors associated with falsely appearing recent using a avidity index (AI) cutoff <40% among samples collected ≥2 years post seroconversion were determined by Poisson regression with generalized estimating equations and robust variance estimators. We simulated populations reflecting low, moderate, and high burden HCV and HIV epidemics and assessed the approach’s precision to estimate incidence, with a relative standard error (RSE) of 30%.

Results: Using an AI cutoff of <40% this approach had an MDR of 113 days (95%CI:84-146), and FRR of 0.4% (95%CI:0.0-1.2) and 4.6% (95%CI:2.2-8.3) among HIV- and HIV+ individuals, respectively, and did not differ between HCV genotypes 1 and 3. In multivariable analysis, among samples collected from individuals infected for >2 years, an AI<40% was more likely to be observed in HIV+ individuals who had a CD4+ T-cell count <200 cells/µL, adjPRR = 22.0 (95% CI: 6.28, 77.01; p<0.001) compared to HIV- individuals. In hypothetical scenarios of high-risk settings, a sample size of <1000 individuals was needed to accurately estimate HCV incidence (Figure 1).

Conclusion: This cross-sectional approach can estimate HCV incidence for the most common genotypes, particularly in populations with low HCV prevalence. This tool can serve as a valuable resource for program and policy planners seeking to monitor and reduce the global burden of HCV.

602 HIGH KYNURENINE:TRYPTOPHAN RATIO IS ASSOCIATED WITH LIVER FIBROSIS IN HIV INFECTION

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Background: The kynurenine:tryptophan ratio (KTR), a marker of tryptophan catabolism, is associated with impaired T-cell function. Higher KTR has been linked to many diseases including certain cancers, HIV infection, and fibrosis in liver. In current studies, the geographic and demographic patterns of kynurenines are not well understood.

Methods: Serum KTR was measured in 58 HIV-monoinfected, 42 HIV/HCV-coinfected, and 37 uninfected women from the WIHS. Fibrosis was estimated in 50 samples (8.5%), seven of those having viruses with double RASs. Higher prevalence of RAS was found in clade II (80%). The most common RASs were M28A/T/V (44.0%, n=22/50), Y93F/H/N (28.0%, n=14/50) and Q30E/H/R (24.0%, n=12/50). The double mutations 30H+93H, 28V+30R and 30R+93H were also observed. A prevalence of RASs of <10% was observed in eleven regions while a prevalence >10% was observed in five, highlighting Cantabria (15.9%; n=7/44) and Murcia (12.5%; n=1/8). Among patients harboring RASs, those that harbored mutations which confers high resistance were: 38.0% (n=19/50) “daclatasvir, 34.0% (n=17/50) to ledipasvir, 36.0% (n=18/50) to ombitasvir, 6.0% (n=3/50) to elbasvir, 8.0% (n=4/50) to velpatasvir, 4.0% (n=2/50) to pibrentasvir. GT1a clade II epidemic preceded clade I by 45 years (time to the most recent common ancestor (TMRCA), 55% highest posterior density [95%HPD], 1907-1932 vs 1952, 1939-1965) (Fig 1 A-B-C). GT1a clade II epidemic started in Basque Country, was dispersed throughout the entire country and is now declining. The current GT1a clade I epidemic is still mostly concentrated in the North of Spain and Canary Islands (Fig 1 D-E).

Conclusion: Current HCV GT1a epidemic in Spain is mainly driven by clade I viruses which seem to have different dispersion routes relative to clade II viruses. Close surveillance of patients with NSSA RAS will be important to prevent further therapeutic failures.

Figure 1. Precision of Genedia-avidity Approaches to estimate HCV incidence in various populations. The sample sizes represent the total number of HCV seropositive and seromagnetic individuals required in a single cross-sectional survey to achieve an incidence estimate with a relative standard error (RSE) of 50%. HCV and HIV seroprevalence was varied to represent different epidemic states. The RSE is for the mean duration of recent infection and the bone rate was 14%, and 23%, respectively.

Figure 1. Incidence of Genedia-avidity Approaches to estimate HCV incidence in various populations. The sample sizes represent the total number of HCV seropositive and seromagnetic individuals required in a single cross-sectional survey to achieve an incidence estimate with a relative standard error (RSE) of 50%. HCV and HIV seroprevalence was varied to represent different epidemic states. The RSE is for the mean duration of recent infection and the bone rate was 14%, and 23%, respectively.
the associations of HIV monoinfection, HIV/HCV coinfection, KTR, and FIB-4 adjusting for demographic, lifestyle, metabolic, and HIV-related factors. We performed a subgroup analysis using liver stiffness measurements (LSM) to assess fibrosis among a subgroup of 83 women who had undergone LSM.

**Results:** Median KTR[IQR] was 3.8[2.2-4.3] in HIV-monoinfected, 5.5[4.4-6.5] in coinfected, and 3.1[2.5-3.4] in uninfected groups (p<0.001 across groups). Women with HIV/HCV and HIV mono-infection had higher FIB-4 than uninfected women (2.17[1.24-3.38] and 0.98[0.79-1.53] respectively vs. 0.63[0.57-0.92]; p<0.001). FIB-4 increased as KTR increased in HIV+ women (Spearmann's rho=0.54;p<0.001) but not HIV- women (rho=-0.13;p=0.44).

In the total cohort, factors associated with higher FIB-4 were older age (30% per 10 years;95%CI:16%-45%), HIV mono-infection (37%;95%CI:9%-73%), and HIV/HCV coinfection (16%;95%CI:100%-250%)(Table1a). When further adjusting for KTR, higher KTR was associated with higher FIB-4 (27% per doubling,95%CI:5%-53%), and the associations of HIV mono-infection (29%;95%CI:2%-63%) and HIV/HCV coinfection (123%;95%CI:63%-203%) were slightly attenuated. In the HIV+ group, higher CD4 count was associated with lower FIB-4 (-5.6%;95%CI: -9.8%, -1.1%), but the effect was attenuated after adjusting for KTR. In the 83 women with LSM, higher KTR was associated with higher LSM (43% per doubling,95%CI:15%-79%) (Table1b). HIV/HCV coinfection was associated with higher LSM after adjusting for KTR (47%;95%CI:13%-110%), while HIV mono-infection was not (0.9%;95%CI: -23%-27%).

**Conclusion:** KTR is elevated in the setting of HIV infection and is associated with higher liver fibrosis. The associations of HIV mono-infection and HIV/HCV coinfection with elevated fibrosis were attenuated after adjusting for KTR, suggesting that the relationship between HIV and liver fibrosis may be mediated in part by the tryptophan pathway.

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**Table 1a. Factors associated with FIB-4 in the total cohort, with and without adjustment for KTR**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted model without KTR</th>
<th>Adjusted model with KTR</th>
<th>Adjusted model without KTR</th>
<th>Adjusted model with KTR</th>
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<tbody>
<tr>
<td>HIV mono-infection</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>HIV/HCV coinfection</td>
<td>3.16[95%CI:29.3, 53.8]</td>
<td>N/A</td>
<td>3.16[95%CI:29.3, 53.8]</td>
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</tr>
<tr>
<td>CD4 count</td>
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<td>N/A</td>
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<tr>
<td>KTR</td>
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<td>2.05[95%CI:1.9, 2.3]</td>
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<td>N/A</td>
</tr>
<tr>
<td>Age</td>
<td>1.02[95%CI:1.01, 1.04]</td>
<td>1.02[95%CI:1.01, 1.04]</td>
<td>1.00[95%CI:0.99, 1.01]</td>
<td>1.00[95%CI:0.99, 1.01]</td>
</tr>
<tr>
<td>Gender</td>
<td>1.01[95%CI:0.99, 1.03]</td>
<td>1.01[95%CI:0.99, 1.03]</td>
<td>1.00[95%CI:0.98, 1.02]</td>
<td>1.00[95%CI:0.98, 1.02]</td>
</tr>
</tbody>
</table>

**Table 1b. Factors associated with liver stiffness measurement by fibroscan in the total cohort, with and without adjustment for KTR**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted model without KTR</th>
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<th>Adjusted model without KTR</th>
<th>Adjusted model with KTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV mono-infection</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>HIV/HCV coinfection</td>
<td>4.04[95%CI:23.9, 57.9]</td>
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<td>4.04[95%CI:23.9, 57.9]</td>
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</tr>
<tr>
<td>CD4 count</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>KTR</td>
<td>2.05[95%CI:1.9, 2.3]</td>
<td>2.05[95%CI:1.9, 2.3]</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Age</td>
<td>1.02[95%CI:1.01, 1.04]</td>
<td>1.02[95%CI:1.01, 1.04]</td>
<td>1.00[95%CI:0.99, 1.01]</td>
<td>1.00[95%CI:0.99, 1.01]</td>
</tr>
<tr>
<td>Gender</td>
<td>1.01[95%CI:0.99, 1.03]</td>
<td>1.01[95%CI:0.99, 1.03]</td>
<td>1.00[95%CI:0.98, 1.02]</td>
<td>1.00[95%CI:0.98, 1.02]</td>
</tr>
</tbody>
</table>

*All models adjusted for age, sex, current alcohol intake, BMI measured at hepatic ultrasound, African or mixed race, current smoking, current marijuana use, and past injection drug use.*

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603 WITHDRAWN

604 WITHDRAWN
605 PREVALENCE OF HIV AND PATTERNS OF ART USE AMONG US LIVER-TRANSPLANT CANDIDATES

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Background: Despite the high burden of liver disease among HIV-infected (HIV+) individuals, the prevalence of HIV among candidates on the US liver transplant waitlist is unknown. Additionally, since the class of antiretroviral therapy (ART), particularly the use of pharmacoenhancers (protease inhibitors, cobicistat) may complicate post-transplant immunosuppression management, it is critical to understand which regimens are commonly used in this population. Therefore, we sought to estimate the prevalence of HIV and to describe patterns in ART use among US liver transplant candidates.

Methods: We designed a retrospective cohort study (2007-2016) using pharmacy claims data (Symphony Health Solutions) linked to the national transplant registry (Scientific Registry of Transplant Recipients) using social security number with encrypted identifiers. We identified HIV+ candidates by fills of prescription medications exclusive to HIV treatment. After exploring potential mechanisms(s) of missingness, we estimated HIV prevalence using multiple imputation by chained equations (MICE). We explored factors associated with ART regimens using logistic regression.

Results: The pharmacy data linkage contained 91.0% (n=99,376) of all candidates in the national transplant registry in the study period. We identified 857 HIV+ candidates with an overall estimated prevalence of 0.95% (95% Confidence Interval: 0.89%-1.02%). HIV+ candidates were more often young (median [IQR]: 53 [48-59] vs. 56 [50-62]), African American (21.4 vs. 9.0%), and male (80.6 vs. 64.4%), with liver disease due to hepatitis C virus (33.5 vs. 26.1%) than HIV- candidates (p<0.001 for all). The use of pharmacoenhancers (PI/PEIs) decreased over time (48.4% in 2007 to 20.0% in 2016) and were more likely to be used by African American candidates (aOR: 1.80, 95%CI: 1.18-2.74, p<0.01), adjusting for age, year, and sex. Conversely, integrate inhibitor (INSTIs) use increased over time (7.8% in 2008 to 52.3% in 2016) and were not associated with race (aOR: 1.02, 95%CI:0.62-1.64, p=.95) adjusting for age, year, and sex.

Conclusion: We used a novel data linkage to identify a unique and previously unstudied population of HIV+ liver transplant candidates on the US waitlist. We found that the burden of HIV on the liver transplant waitlist was nearly 1%, ART use has shifted over time, and African Americans were almost twice as likely to be prescribed ART regimens containing pharmacoenhancers, which can interact with post-transplant immunosuppression.

606 CHANGES IN LIVER STIFFNESS MEASUREMENT IN HIV AND HIV/HBV COINFECTED NIGERIANS

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1Jos University Teaching Hospital, Jos, Nigeria, 2Northwestern University, Chicago, IL, USA

Background: There are limited data from sub-Saharan Africa on long-term liver fibrosis changes in HIV and HIV/HBV co-infected individuals. We assessed the effects of antiretroviral therapy (ART) on liver stiffness measurement (LSM) using transient elastography (TE) in HIV and HIV/HBV co-infected Nigerians and examined factors associated with liver fibrosis regression.

Methods: ART-naive HIV and HIV/HBV co-infected adults (>18 years) were enrolled into a longitudinal study of liver disease between 7/2011 – 2/2015 and followed annually for 6 years at Jos University Teaching Hospital, Jos, Nigeria. Changes in LSM over time were examined in a subset of subjects with ≥1 follow-up TE at Y3 and Y6. Predictors of a >30% decrease in LSM score during follow-up were assessed using Cox Proportional-Hazards models (CPH).

Results: 232 HIV and 98 HIV/HBV co-infected subjects (71.2% female, median age 33.5 [IQR 12] yrs) were enrolled into the cohort. Among HIV/HBV co-infected subjects, median baseline HBV DNA was 1.67 [IQR 5.52] log10IU/mL and 6% were HBsAg seropositive. 79.4% initiated ART containing at least one ART-active agent at enrollment and 100% were on ART at their last visit. Median duration of follow-up was 6.6 [4.1] yrs [HIV/HBV 6.4 (3.7), HIV 6.7 (4.8), HBV/HIV 7.7 (3.0) (54%) [45.7% HIV and 72.4% HIV/HBV co-infected] had a follow-up TE at Y3 and 148/330 (45%) [44.0% HIV and 46.9% HIV/HBV co-infected] at Y6. At baseline, LSM scores were significantly higher in HIV/HBV vs. HIV-infected subjects [6.4 (4.2) kPa vs. 5.1 (1.5) kPa; p<0.01]. LSM declined significantly from baseline to Y3 and Y6 in both groups (p<0.01) (Fig 1), with a trend towards larger declines observed in HIV/HBV co-infected vs. HIV-infected subjects (1.35 [3.53] kPa vs. -0.45 [2.28] kPa; p=0.03). In multivariate analyses, HIV/HBV co-infection [HR 2.0 (95%CI 1.20, 3.33)] p=0.01) and higher LSM scores at baseline [HR 2.84 (1.14, 7.08); p=0.03] were significantly associated with >30% LSM decrease. There was no independent association between >30% LSM decrease and duration of ART or HIV immunologic and virologic status at baseline.

Conclusion: Significant declines in LSM were observed in HIV/HBV co-infected and HIV-infected subjects in response to ART, highlighting the importance of early treatment initiation in both populations. LSM scores were low in HIV/HBV co-infected subjects, likely due to the relative inactive state of HBV infection (low baseline HBV DNA levels and low rates of HBsAg seropositivity) in this region.
608 IMPACT OF HIV ON THE SURVIVAL OF HEPATOCELLULAR CARCINOMA IN HCV-INFECTED PATIENTS

Nicolás Merchante1, Miguel Rodríguez Fernández1, Blanca Figueruelo López1, Francisco Rodríguez Arrondo1, Boris Revollo2, Sofia Ibarra3, Esperanza Merino3, Maria J. Galindo4, Marta Montero4, Francisco Téllez5, Antonio Rivero-Juárez6, for the Grupo para el Estudio de las Hepatitis Viricas (GEHEP).

Background: Previous studies have suggested that hepatocellular carcinoma (HCC) has a more aggressive presentation and a lower survival in HIV-infected patients. However, the differences in survival found in older studies may be due to a later diagnosis or to lower rates of treatment against HCC, and not to a specific negative impact of HIV infection. Objective: To assess the impact of HIV infection on the survival of HCC in HCV-infected patients.

Methods: Multicenter cohort study (1999–2017). The GEHEP-002 cohort recruits all the HCC cases diagnosed in HIV-infected patients from 32 centers in Spain. For this study, 339 cases diagnosed in HIV/HCV-infected patients were selected. A control population of 118 HCC cases diagnosed in HCV-monoinfected patients during the study period at the Liver Unit from the Hospital de Valme was used. The survival after HCC diagnosis and its predictors, including HIV infection, were assessed.

Results: HCC was diagnosed by surveillance, considered when all scheduled ultrasound had been performed at least within 1 year prior to HCC diagnosis, in 192 (57%) and 73 (62%) HIV+ and HCV- patients, respectively (p=0.3). In spite of similar rates of HCC diagnosis by screening, cases diagnosed in HIV/HCV-coinfected patients were diagnosed at advanced stages. Barcelona-Clinic Liver-Cancer (BCLC) stage at diagnosis was: 0-A 133 (39.6%), B 28 (8.3%), C 118 (35.1%) and D 57 (17%) in HIV+ and 0-A 63 (53.4%), B 21 (17.8%), C 27 (22.9%) and D 7 (5.9%) in HCV- patients (p<0.001). 103 (77%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09).

Conclusion: HIV coinfection has no impact on the survival after the diagnosis of HCC in HIV-infected patients. Although the mortality of HCC is somewhat higher in HIV/HCV-coinfected patients, these differences seem to be related with a later diagnosis of HCC in HIV-infected patients and not with HIV infection itself or a lower access to HCC therapy.

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Background: Surveillance of hepatocellular carcinoma (HCC) by hepatic ultrasound (US) every 6 months is recommended in HIV-infected patients with cirrhosis. However, there are no specific studies addressing the performance of such strategy in this population. As it has been reported that HCC could have a more aggressive course in the HIV-infected patient, the effectiveness of this surveillance policy needs to be specifically evaluated in the scenario of HIV infection. Objective: To assess the performance of US surveillance for the diagnosis of HCC in HIV-infected patients.

Methods: The GEHEP-002 cohort recruits HCC cases diagnosed in HIV-infected patients from 32 centers across Spain. The proportion of ‘US lack of detection’, defined as HCC diagnosed within the first 3 months after a normal surveillance US, and the proportion of ‘surveillance failure’, defined as cases in which surveillance failed to detect HCC at early stage (BCLC stage 0-A), were assessed. To assess the impact of HIV, a control population of 104 HCC cases diagnosed in HCV-monoinfected patients during the study period was used.

Results: 186 (54%) out of 346 HCC cases in HIV+ patients and 62 (60%) out of 104 cases from the control group were diagnosed within a US surveillance program. US lack of detection occurred in 16 (8.6%) of 186 HIV+ HCC cases diagnosed by surveillance whereas this occurred in 5 (4.8%) in the control group (p=0.19). HCC cases after US lack of detection in HIV+ patients were more frequently at Child-Pugh stage C and had an advanced stage at diagnosis. The performance of US surveillance to achieve an early diagnosis of HCC was significantly lower for HIV+ patients. Thus, US surveillance failure occurred in 107 (57%) out of 186 cases diagnosed by screening in HIV+ patients whereas this occurred in 18 (29%) in the control group (p=0.0001). Similarly, US surveillance failed to detect HCC within Milan criteria in 104 (56%) out of 186 cases diagnosed by screening in HIV+ patients whereas this occurred in 18 (29%) in the control group (p=0.0001). The probability of 1-year and 2-year survival after HCC diagnosis among those diagnosed by screening was 56% and 45% in HIV+ patients whereas it was 79% and 64% in HIV-negative patients (p=0.038).

Conclusion: The performance of US surveillance of HCC in HIV-infected patients is very poor and worse than that shown outside HIV infection. A HCC surveillance policy based on US examinations every 6 months might be insufficient in HIV-infected patients with cirrhosis.

610 INTRAHEPATIC HIV IS ASSOCIATED WITH ADVERSE LIVER OUTCOMES IN HIV/HCV COINFECTION

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1Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia, 2Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, 3University of Melbourne, Melbourne, VIC, Australia, 4Chulalongkorn University, Bangkok, Thailand

Background: Individuals who are coinfected with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) have a 17 times increased risk of liver-related mortality than HBV mono-infected individuals. Given HIV can infect multiple cells in the liver including hepatocytes, Kupffer cells, stellate cells and intrahepatic T-cells, we hypothesized that the frequency of HIV-infected cells in the liver would be associated with HBV disease or liver-related clinical outcomes in a cohort of HIV/HBV coinfected individuals in Bangkok, Thailand.

Methods: Peripheral blood and matched liver biopsies were collected from 39 HIV and HBV coinfected participants prior to initiating antiretroviral therapy (ART). We measured cell-associated unspliced (US) HIV RNA and HIV DNA in CD4+ T-cells from blood and total liver biopsies and HBV covalently closed circular DNA (cccDNA) in liver biopsies by qPCR. Liver inflammation/damage was measured by transient elastography (TE). Lipopolysaccharide (LPS), CXCL10, and soluble CD14 (sCD14) were measured in plasma by ELISA and mRNA for CXCL10 and CXCR3 measured in liver biopsies by RT-qPCR.

Results: Participants were 90% male with a median age of 31.9 years and a median CD4 nadir of 320 (range 20-1197). All individuals were HBsAg+ and 64% were HBeAg+. HIV DNA and RNA were detected in liver biopsies in 63.2% and 44.7% of participants, respectively. There was a significant association between HIV DNA and RNA in liver (p<0.0001) and between liver and plasma HIV RNA (p=0.0320). There was no relationship between intrahepatic HIV and CD4 count. Intrahepatic HIV DNA was significantly associated with markers of liver disease, including AST (p=0.0250) and TE (p=0.0164), intrahepatic T-cell inflammatory markers CXCL10 (p=0.0165) and CXCR3 (p=0.0025), as well as sCD14 in plasma (p=0.0051). Intrahepatic HIV RNA was also significantly associated with CXCL10 (p=0.0061). There was a trend towards higher levels of cccDNA in individuals who had detectable intrahepatic HIV DNA. HIV DNA and RNA in circulating CD4+ T-cells were not associated with any liver or HBV related outcomes.

Conclusion: Prior to ART, HIV DNA and RNA are frequently detected in the liver and are associated with multiple clinical markers of liver disease in HIV-HBV coinfected. The cellular localisation of HIV DNA and RNA in the liver requires further investigation but we propose that this is not explained by trafficking T-cells given the absence of any associations between liver disease and HIV DNA and RNA in blood.
infection or alcohol exposure make Hep HIV-permissive, facilitate apoptotic Hep death and promote liver inflammation and fibrosis development by activating non-parenchymal liver cells by apoptotic Hep engulfment.

Methods: Primary human hepatocytes or their experimental prototype, HuH7.5-CYP (RLW) cells were infected with HIV-1 ADA and then either exposed to HCV (co-infection model) or to ethanol (HIV + ethanol model). HIV gag RNA was measured in these cells by RT-PCR and reverse transcriptase (RT) activity as evidence of HIV replication was determined in cell supernatants. As apoptotic cell death indication, we used cleaved caspase 3 (Western Blot) and M30 (ELISA). After engulfment of apoptotic apoptotic bodies (AB) by monocyte-derived macrophages (MDM) and hepatic stellate cells (HSC, Lx2 cell line) inflammasome activation and pro-fibrotic markers were quantified by RT-PCR.

Results: We observed that both HCV co-infection and co-treatment with ethanol substantially increased HIV gag RNA in hepatocytes and RT in cell supernatants. This increase was associated with enhanced HIV replication inside of cells since the removal of surface structures by low acid wash did not decrease HIV RNA levels triggered by HCV or ethanol exposure. Both insults push HIV-infected Hep to apoptosis prevented by co-treatment with pan-caspase inhibitor. Furthermore, apoptosis was attenuated by AZT, suggesting that it is initiated by HIV replication, AB generated from infected Hep spread the virus to intact MDM. Engulfment of HIV + AB Hep activated inflammasome (based on NLRP3, caspase 1, IL-1β and IL-18 expression) in MDM and pro-fibrotic markers (Col1A1, TGFβ and prostaglandin D receptor 2) in HSC. Activation of fibrotic changes in HSC was AB Hep-specific since engulfment of AB from HIV + lymphocytes induced pro-inflammasory, but not pro-fibrotic events.

Conclusion: We conclude that second hits, like co-infection with HCV and co-treatment with ethanol increase permissiveness of hepatocytes to HIV-infection and trigger their apoptosis, thereby initiating the cross-talk between hepatocytes, macrophages and stellate cells to promote liver inflammation and fibrosis progression.

613 INFLAMMATORY CHEMOKINES LINKED TO HIV GENETIC DIVERSITY DURING HIV/HBV COINFECTION

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1The Westmead Institute for Medical Research, Westmead, NSW, Australia, 2Oschery Institute for Infection and Immunity, Melbourne, VIC, Australia, 3HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand

Background: HIV-hepatitis B virus (HBV) co-infected individuals experience higher rates of liver disease than mono-infected individuals. Previous studies have found that HIV co-infection can impact the natural course of HBV infection, but the reverse has not been confirmed. We aimed to determine the frequency of intact proviruses in HIV/HBV co-infected individuals prior to ART initiation and whether this frequency was associated with any clinical parameters.

Methods: HIV/HBV co-infected individuals and HIV mono-infected individuals naive to ART were recruited in Bangkok Thailand as part of a prospective observational cohort study. HIV proviruses were sequenced from peripheral blood CD4+ T-cells using full-length individual proviral sequencing (FLIPS). Primers were adapted for specificity to HIV subtype AE and single near full-length HIV proviruses (62% of the genome) were sequenced using Next Generation Sequencing. Genetically intact HIV proviruses were identified as those lacking inversions, stop codons/hypermutation, insertions, deletions or frameshifts.

Results: A total of 522 HIV proviruses were sequenced and analysed from 17 HIV-HBV co-infected individuals, and 165 proviruses from 4 HIV mono-infected individuals; both cohorts being naive to ART. Both the co-infected and mono-infected individuals had a similar and high proportion of genetically intact provirus (range = 7.6-64% and 23-59% respectively). Intact sequences from these cohorts had genetic diversity ranging 0.2-2% and 0.3-1.6% for the co-infected and mono-infected cohorts respectively. The mean diversity of genetically-intact provirus was lower in the mono-infected (0.7%) than the co-infected cohort (1.0%), but this did not reach significance (p=0.28). No correlation was found between HBV infection parameters (HBV DNA, HBsAg, and ALT levels, HBeAg status) and the proportion of genetically intact HIV proviruses or their genetic diversity in the co-infected individuals. However, higher levels of the inflammatory chemokines CCL2 in the blood and CXCL10 in the liver were associated with increases in overall genetic diversity of HIV (p=0.028 and p=0.0016).

Conclusion: Genetically unique and intact HIV proviral sequences were commonly identified in untreated HIV-HBV co-infected and HIV mono-infected participants. The frequency of intact virus was far higher than previous studies of individuals on suppressive ART. Inflammatory chemokines were associated with the genetic diversity of HIV proviruses in HIV-HBV co-infected participants.

614 INFLUENCE OF HCV INFECTION ON HIV-1 SPLICING IN CHRONICALLY COINFECTED PATIENTS

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Background: HIV/HCV coinfection influences HIV-1 reservoir size. We previously observed a higher quantity of HIV-1 proviral DNA in coinfected patients regarding to HIV-monoinfected individuals. However, it is unknown whether this coinfec tion may also induce a higher proviral transcription, thereby increasing the viral load and influencing in the reservoir size. We assess if HCV coinfection influences HIV-1 proviral transcription and splicing forms in isolated, resting CD4+ (cCD4) T cells and the remaining non-resting PBMCs.

Methods: Cross-sectional study: 29 (49.1%) HIV+ HCV coinfected subjects and 28 (50.9%) HIV-1 patients. PBMCs were obtained from 50 ml of peripheral blood and cCD4 T-cells were isolated (cCD4+ cCD8- HLA-DR- CD69-). Total RNA was extracted from cCD4+ cells and the remaining non-resting PBMCs, and then analyzed by qPCR to measure the unspliced (~9kb), single spliced (~4kb) and multiple spliced (~2kb) transcripts. Linear correlations between viral reservoir size and viral splicing were also determined.

Results: An increase in HIV-1 reservoir size was observed in HIV+ HCV+ patients regarding to the HIV + group [84.9 (48.3-154.2) vs 28.5 (8.5-97.7) proviral DNA copies/10^6 CD4 cells, respectively (p=0.03)]. Analysis of HIV-1 alternative splicing showed 3.2-fold increase of multiple spliced transcripts in HIV/HCV patients (AR=13.6 vs 4.3; p>0.05). Not significant increase in unspliced and single spliced forms (19.9- and 5.8-fold, respectively) was also observed in the remaining non-resting from HIV+ /HCV+ subjects (Fig1). A significant positive correlation in HIV+/HCV+ individuals was identified between HIV reservoir size and some viral spliced forms.

Conclusion: Splicing of HIV transcripts is necessary for viral transcription. We previously observed that coinfec tion of HCV and HIV influences HIV reservoir size. Now we found that cCD4 cells isolated from HIV/HCV patients showed an increase of multiple spliced transcripts, suggesting that HIV-1 regulator Tat could be more active in these cells, yielding a higher number of viral particles and increasing the reservoir size. Moreover, coinfection with HCV could enhance HIV proviral transcription and splicing due to an interaction between HCV proteins and the cellular splicing machinery. The positive correlation between reservoir size and some viral splicing forms may support this hypothesis. This may indicate that the elimination of HIV-1 reservoir in HIV+/HCV+ subjects might be even harder than in HIV+ patients.
615 PREVALENCE OF FATTY LIVER DISEASE IN INDIVIDUALS WITH AND WITHOUT HIV INFECTION
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Background: Fatty liver disease (FLD) is a growing cause of chronic liver disease. People living with HIV (PLWH) may be at a higher risk of FLD due to life style and antiretroviral medication. Here we assessed the prevalence of FLD in PLWH and matched HIV uninfected controls by unenhanced CT liver scan. Further, factors associated with hepatic steatosis were assessed and the effect of HIV per se evaluated.

Methods: PLWH (n=765) aged 40 years and above were recruited from the Copenhagen Co-morbidity (COCOMO) in HIV infection study. Uninfected controls (n=1192), matched on gender and 5-years age strata, were recruited from the Copenhagen General Population Study (CGPS). Unenhanced CT liver scan was performed on all participants and liver attenuation measured. We defined FLD as a liver attenuation ≤ 48 Hounsfield Units (HU) equivalent with moderate to severe steatosis. Unadjusted and adjusted logistic regression analyses were performed. Sensitivity analyses were performed with exclusion of individuals with excessive alcohol intake (def.: 20 g/wk for females and 30 g/wk for males) and significant liver fibrosis (def.: Fibroscan ≥ 12kPa).

Results: Of PLWH, FLD was detected in 8.5% compared to 17.4% of uninfected controls. After adjustment, 1 unit increase in BMI or waist circumference was associated with FLD in PLWH (OR (95% CI): 1.12 (1.01;1.24) and 1.12 (1.08;1.17)) in uninfected controls. In PLWH, male sex was associated with FLD (OR (95% CI): 2.93 (1.01;61.97). A 1 unit increase in triglycerides was associated with FLD in uninfected controls (OR (95% CI): 0.30 (0.19;0.49)) and the association persisted after further adjustments for e.g. current antiretroviral medication, lifestyle, and significant liver fibrosis.

Conclusion: The prevalence of FLD was lower in well-treated PLWH compared to age and sex matched HIV uninfected controls. FLD was associated with higher BMI or waist circumference and male sex. Further research is needed to understand the contribution of NAFLD and other mechanisms of liver injury in PLWH on suppressive ART.

616 LIVER INFLAMMATION IS COMMON AND LINKED TO METABOLIC DERANGEMENTS IN TREATED HIV
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Background: Abnormal serum liver enzymes in people with HIV (PWH) are common and often unexplained. We sought to identify the prevalence of and underlying reasons for aspartate and alanine aminotransferase (AST and ALT) elevation in a well-characterized cohort of adults with treated HIV without hepatitis C or B virus (HCV or HBV) infection or heavy alcohol use.

Methods: Participants from the longitudinal observational AIDS Clinical Trials Group HALO cohort who did not report heavy alcohol use, were negative for anti-HCV and hepatitis B surface antigen, and with at least 2 AST and ALT measurements between 11/2013–2/2018 were included. Clinical and demographic characteristics, including the Hepatic Steatosis Index (HSI = 8x(ALT/AST)+BMI) and presence of hepatitis C or B virus (HCV or HBV) infection or heavy alcohol use were compared between persons with and without ≥1 elevated AST or ALT (defined as AST ≥36 and ALT ≥30 U/L for men and AST ≥30 and ALT ≥19 U/L for women), using chi-square and Wilcoxon tests and multiple logistic regression models. Covariates with p<0.05 in univariate analysis were included in the multivariable models.

Results: Of 1015 participants, 662 met criteria for inclusion; 456 (69%) had ≥ 1 and 236 (36%) ≥ 2 elevated AST/ALT during a median of 4.0 years of follow-up. Median age at entry was 51 years; 138 (21%) female; 184 (28%) black and 122 (18%) Hispanic; median entry and nadir CD4 cell counts/mm3 (CD4) 621 and 195, respectively; and 627 (95%) had plasma HIV RNA <200 copies/mL at entry. In univariate analysis, the elevated liver enzyme group was younger, had a higher proportion of Hispanic and female participants, higher entry CD4 without differences in nadir CD4, higher HSI score, and a higher proportion with MetS and HSI ≥ 36 (p<0.05 for all). There were no differences in the proportions with HIV RNA suppression or antiretroviral use (current or previous); FIB-4 score was similar in each group. The Table summarizes the results from multiple logistic regression models.

Conclusion: After exclusion of HCV, HBV and alcohol, liver enzyme elevation was remarkably common in this cohort and independently associated with metabolic disease, presence of hepatic steatosis by HSI, Hispanic ethnicity, and lower CD4 at entry. These findings suggest that NAFLD may be a common cause of liver inflammation in PWH receiving suppressive antiretroviral therapy (ART). Further research is needed to understand the contribution of NAFLD and other mechanisms of liver injury in PWH on suppressive ART.

<table>
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<th>Variable</th>
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<td>0.99 (0.98;1.00)</td>
</tr>
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<td>1.01 (1.00;1.01)</td>
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<tr>
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<td>1.20 (1.02;1.40)</td>
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<tr>
<td>Smoking</td>
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<td>Current smoker: 1.14 (0.99;1.30)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>20 g/wk for females and 30 g/wk for males</td>
<td>20 g/wk for females and 30 g/wk for males</td>
</tr>
</tbody>
</table>

617 FENTANYL USE AND LIVER DISEASE IN THE MIAMI ADULT STUDIES ON HIV (MASH) COHORT
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Background: Human immunodeficiency virus (HIV) infection continues to be associated with liver disease, one of the major causes of morbidity and mortality in these patients. Substance abuse decreases adherence to antiretroviral therapy and increases risk for liver injury. Fentanyl is a synthetic opioid clinically used in anesthesia and management of chronic pain, recently mixed with heroin and cocaine, and ingested unintentionally. Fentanyl overdose leads to respiratory depression, brain damage and death, and its effect on liver is not known.

Methods: Participants from the Miami Adult Studies on HIV (MASH) cohort were tested for fentanyl using BNTX Rapid Response TM fentanyl urine strip tests at a detection level of 40 ng/ml forfentanyl. Cocaine and heroin use were determined with questionnaires and confirmed with urine toxicology. Alcohol consumption was determined with Alcohol Use Disorders Identification Test (AUDIT). HIV infection, lack of hepatitis B and C infections, CD4 count and
HIV viral load were documented from medical charts. FIB-4, a non-invasive measure of liver fibrosis, was calculated, and FIB-4 value of >1.45 was used as the cutoff to determine presence or absence of meaningful (moderate-severe) hepatic fibrosis. Statistical analyses included descriptive statistics and logistic regression performed with SAS 9.4. Models were adjusted for age, gender, BMI, AUDIT score>8, and HIV infection.

Results: Data were analyzed on a subsample of MASH cohort participants who were HIV infected (N=305, CD4 count mean 610.2cells/µL ±362.06 SD). mean HIV viral load =2.58 log10 ±1.24 SD) or HIV uninfected (N=267). Mean age was 54.05years:±8.68 28 SD; 50.03% were males, 62.16% Black and 22.93% Hispanic. Logistic regression indicated a significant association between the use of fentanyl and liver fibrosis (FIB-4<1.45), adjusted OR = 5.195 (95% CI 1.205.11,159, P=0.005). When participants who were frequent users of cocaine and heroin were removed from the analyses, fentanyl continued to be associated with liver fibrosis (FIB-4<1.45), adjusted OR = 4.76 (95% CI 1.67-13.56, P=0.0035). In addition, HIV infection status was significantly associated with FIB-4<1.45, adjusted OR = 2.25 (95% CI 1.27-3.98, P=0.0056).

Conclusion: These data indicate that misuse of fentanyl among substance users in the MASH cohort may be associated with development of hepatic fibrosis. Strategies to identify risk and understanding of aberrant drug-related behaviors and treatments are needed.

619 A DECISION-TREE ANALYSIS FOR HEPATITIS A IMMUNITY AMONG HIV-INFECTED MSM IN TOKYO
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Background: Japan has very low endemicity for hepatitis A virus (HAV), and the prevalence of anti-HAV among general population aged <50 years is <5%. However, the level of HAV immunity among HIV-infected patients in Japan is unknown. The epidemiology of HAV infection among HIV-infected men who have sex with men (MSM) is essential for an HAV vaccination program.

Methods: We examined the presence of IgG-HA antibody among HIV-infected patients from January 2017 to December 2017 in IMSUT Hospital, the University of Tokyo. Epidemiological data, including age, sex, mode of HIV transmission, year of HIV diagnosis, HAV vaccine status, previous HAV infection and other infectious disease status (hepatitis B, hepatitis C and syphilis), were recorded. A decision tree algorithm (data-mining technique) was used to reveal factors and profiles most relevant to the prevalence of anti-HAV for further investigation.

Results: In total 468 HIV-infected patients were examined for the presence of IgG-HA antibody. Of these, 459 patients (male, 438; female, 21) had both HAV vaccine status and previous HAV infection. The mode of HIV transmission among male patients were as follows: MSM, 378; heterosexual, 47; contaminated blood (hemophilia), 4, unknown, 9. After excluding 24 MSM patients who were receiving HAV vaccine, data from 354 MSM patients were used for analysis (median age, 45 years. IQR, 39-51). Of 354 MSM patients, 60 (16.9%) were IgG-HA antibody positive. Median age was significantly higher in the HA positive group than in the negative group (50 vs. 44 years; P<0.001). The prevalences of hepatitis B core antibody and treponemal antibody were significantly higher in the HA positive group than in the negative group (71.7% vs. 57.1%; P=0.037 and 75.0% vs. 57.8%; P=0.013, respectively). Patient age >63.5 years was the first variable in the initial classification of the decision-tree algorithm, and year of HIV diagnosis was the second-division variable for HAV immunity (Figure).

Conclusion: Our study, conducted just before HAV outbreak among MSM in Tokyo, showed that age and year of HIV diagnosis were the most relevant factors in the prevalence of anti-HAV. It is partly because there have hardly been HAV outbreak among younger people in Japan. IgG-HA antibody was present in 16.9% of the study population, which is far below the 60-70% immunity threshold necessary to prevent sustained transmission, suggesting that an extensive HAV vaccination program particularly for younger people is urgently needed.

620 LOW IMMUNE RESPONSE RATE OF HIV-POSITIVE PATIENTS TO SINGLE INJECTION OF HAV VACCINE
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Background: During the year 2017, a hepatitis A (HAV) outbreak occurred among men having sex with men (MSM) in France. Concomitantly, a shortage of HAV vaccine led to different vaccination scenarios. We therefore measured the immune response to a single injection of HAV vaccine in HIV-positive patients.

Methods: A total of 140 HIV-positive patients were included in the study. The immune response to HAV vaccine was measured by enzyme-linked immunosorbent assay (ELISA) at 1 week, 6 months, and 1 year after vaccination. The antibody response was defined as IgG-HAV antibody level greater than 1.0 MIU/mL.

Results: Of the 140 HIV-positive patients included in the study, 128 (91.4%) had a positive anti-HAV IgG response at 1 week after vaccination. At 6 months, 107 (76.4%) patients had a positive anti-HAV IgG response, and at 1 year, 95 (67.9%) patients had a positive anti-HAV IgG response. The antibody response rate to HAV vaccine was significantly lower in HIV-positive patients compared to HIV-negative patients (P<0.05). The immune response to HAV vaccine was not affected by the CD4 count, the HIV viral load, or the use of antiretroviral therapy.

Conclusion: HIV-positive patients have a lower immune response to a single injection of HAV vaccine compared to HIV-negative patients. Therefore, alternative vaccination scenarios are needed to ensure adequate HAV immunity in HIV-positive patients.
of HAV vaccines has led to the national recommendations of a single injection of HAV vaccine. Nevertheless, HIV-positive patients’ vaccine response can be inferior to general population. This study aimed to evaluate the immune response of HIV-1 positive MSM patients to a single injection of HAV vaccine in this context.

Methods: We enrolled in this observational single center study all HIV-1 positive patients who had been vaccinated by a single injection of HAV vaccine in 2017. HAV serology was performed on a serum sample before and >30 days after the vaccine injection, using the routine system Architect® (Abbott) by chemiluminescent microparticle immunoassays. Response to vaccine was defined by a ratio (signal of the sample/signal of the threshold value) ≥ 2. To compare responders and non-responders’ characteristics, Student (continuous variables) or Chi 2 (categories) tests for univariable and logistic regression for multivariate statistical analyses were performed.

Results: In 2017, 73 patients mainly MSM (93.2%) with a median age of 49.4 years (IQR 36.0-57.1) received a single injection of HAV vaccine. HAV-1 viral load was £20 copies/mL in 83.6% of the cases (93.2% ≤50 copies/mL). Patients were diagnosed for HIV since 14.9 years in median (IQR 7.4-27.6) and 16.4% of them were classified in the CDC stage C. Median CD4 and nadir CD4 cell counts were 658 (IQR 465-838) and 270/mm³ (IQR 93-381), respectively. Median ratio of T CD4/CD8 cells was 0.9 (IQR 0.56-1.21). One patient had already a positive HAV serology before the vaccine injection. The rate of immune response was 59.7% (n=43/72) after a median time of 106 days (IQR 68-177) between the vaccine injection and the collection of sample. The median response ratio was 7.97 (IQR 3.47-9.56). Non responders had significantly a lower T CD4/CD8 cells ratio than responders in univariable and multivariate analyses (p<0.05).

Conclusion: A low immune response rate was observed after a single injection of HAV vaccine among HIV-positive patients. A Low T CD4/CD8 cells ratio was a risk factor of non response. In a context of vaccine shortage, a serologic control of response to HAV vaccine should be recommended in this population to ensure their protection.

621 LOSS OF HEPATITIS A VIRUS SEROPROTECTION IN PERSONS LIVING WITH HIV

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Background: The Michigan hepatitis A virus (HAV) outbreak, which began in August 2016, persists today with 885 cases. A possible emerging issue has been identified during an ongoing outbreak of HAV in Michigan: loss of HAV seroprotection among patients co-infected with HIV. Immune responses to most vaccines are known to be impaired in HIV patients. Retrospective analyses of HIV-infected patients who received HAV vaccination has shown that 90% of HIV patients remained seropositive at 3 years and 85% 6–10 years. No data exist on whether this decay is clinically meaningful. During the Michigan Hepatitis A outbreak, 26 outbreak cases were co-infected with HIV and HAV. 4 patients had received pre-exposure HepA vaccination, and 2 cases had positive HAV antibody test results upon entry into care for HIV without history of vaccination. These early findings are concerning for loss of seroprotection in persons living with HIV who may be susceptible and at risk of acquiring HAV infection. Here we describe a cohort of patients who have lost seroprotection against HAV at the University of Michigan HIV clinic.

Methods: The HIV Clinic at the University of Michigan began repeating HAV Ab screening for those patients who have not been performed during the previous 5 years. We collected baseline demographics for those patients who seroreverted from a positive to negative HAV total Antibody.

Results: The Mean age at Time of Vaccination for seroreverters was 40 ± 5 years old. The proportion of patients with an undetectable viral load at the time of initial vaccination was 0.50. The mean viral load at the time of vaccination was 27,500 ± 7,382. All seroreverters had an undetectable viral load at the time of seroreversion. The Proportion of Seroreverters with history of AIDS defining Illness was 0.5. The mean time to repeat Serology was 11.37 ± 2.28 yrs.

Conclusion: Patients living with HIV previously vaccinated against HAV may be susceptible and at risk of acquiring HAV infection. Repeat screening HAV total Antibody can indentify those patients susceptible to HAV infection who would benefit from repeat vaccination.
623 THE GLOBAL DISTRIBUTION OF HEPATITIS B VIRUS VACCINE ESCAPE MUTATIONS

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Background: Hepatitis B virus (HBV) infects over 250 million people and is the leading cause of hepatitis and hepatocellular carcinoma worldwide. Vaccination is effective at preventing infection, although vaccination rates are not optimal, and mutations within the ‘a’ determinant region of the HBV surface antigen (HBsAg) are associated with vaccine escape. The emergence of escape mutants raises concern of HBV infection in previously vaccinated individuals, particularly in the developing world where such mutations may be relatively common.

Methods: We evaluated the frequency, genotype, and global distribution of known escape mutations in 4,244 unique full-length HBV genomes from genotypes A to I. The ‘a’ determinant of the Surface gene (amino acids 124 to 147) was extracted using AliView and inspected for polymorphisms at previously identified vaccine escape mutations including T116, P120, T126, Q129, M133, P134, K141, P142, D144, or G145. Sequences were also evaluated in Geno2Pheno to confirm the genotype and the presence of polymorphisms.

Results: 268 (6.3%) sequences from 36 countries contained a polymorphism at a vaccine escape site. In genotype A, the most common mutation occurred at M133. In genotype B, Q129 and M133 occurred 45 and 51 times, respectively, accounting for 94% of mutations. Mutations at G145 were most frequent in genotype C, while P120 was most common in genotype D. Amongst all genotypes, mutations at M133 were the most common and accounted for 29.5% of escape mutations. Mutations at T116, P120, F134, K141, and P142 occurred across geographically diverse locations, whereas mutations at Q129, M133, D144, and G145 were concentrated in East Asia. The most prevalent mutation in the Middle East and North Africa was at position P120, whereas M133 was most prevalent in North America and Europe. Q129 accounted for 3 of 7 mutations in India, D144 for 4 of 18 mutations in Africa, and M133 for 4 of 15 mutations in South and Central America.

Conclusion: While the sample size is large, our approach relied on sequences that were previously uploaded to GenBank. Non-random, convenience sampling was often conducted, and many countries have no data available, thus highlighting the need for systematic and unbiased surveillance of vaccine escape mutations in more countries. Nonetheless, the prevalence of polymorphisms at sites associated with vaccine escape is high and may compromise efforts to control HBV infection.

624 HEPATITIS B CURE IN HIV PATIENTS IS MORE LIKELY IN HISPANICS AND THOSE WITH AIDS

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Background: Nucleoside analogues are thought to resolve chronic hepatitis B virus (HBV) very infrequently in most settings, especially in HIV. We examined immune restoration efforts to control HBV infection.

Methods: We retrospectively abstracted data of HIV and HBsAg+ patients obtaining care from 2005-2018. Those without chronic HBV were excluded. Baseline characteristics obtained included demographics, insurance, HIV risk factors, CD4 cell count, HBV DNA, HBV RNA, Hepatitis B eAg, and liver function tests (LFT). Those who achieved HBsAg loss during follow-up were compared to those who did not. Predictors of HBsAg loss were examined using logistic regression analysis.

Results: Among 365 with HIV and HBsAg+ co-infection, 303 had sufficient data to classify as chronic HBV (87% were male, 58% Black, 24% White, and 14% Hispanic, 59% were HBsAg+). At baseline, median CD4 was 234 cells/mL, 45% had AIDS, and median log HBV RNA among those non-suppressed (ns) was 4.88 copies/mL, 22% had suppressed HBV RNA. First measured HBV DNA suppression was 8.87 months. Among the 38 (12.54%) with HBsAg loss, differences were seen by race, baseline CD4 count, proportion with AIDS, HBsAg+, and time to HBV DNA suppression (see Table 1). Compared to Whites, Hispanics were more likely to have HBsAg loss (AOR 4.27, 95% CI 1.20, 15.18, p=0.03) and those with AIDS (AOR 3.57, 95% CI 1.50, 8.54, p=0.004). Every month without HBV DNA suppression decreased likelihood of HBsAg loss (AOR 0.97, 95% CI: 0.95, 0.99, p=0.03). Median change in CD4 count (cells/mL [IQR]) was higher in those HBsAg loss vs. not (204[98, 436] vs. 106 [-12, 265], p=0.004). No differences were seen with regard to LFTs, gender, insurance, HIV risk factor, age, or HIV RNA.

Conclusion: HBsAg loss occurred in a surprisingly high percentage (12.54%) of HIV+ patients, more frequently in Hispanics and in those with AIDS. Longer time to HBV DNA suppression was associated with decreased likelihood to HBsAg loss. We hypothesize that HBV immune restoration is associated with HBsAg loss as a higher change in CD4 count occurred in those with HBsAg loss. Chronic hepatitis B can resolve in those with HIV, especially among those with AIDS, if effective HBV active cART is initiated leading to increase in CD4 and effective HBV viral suppression.

625 HIGH RATES OF HBV FUNCTIONAL CURE AMONG HIV/HBV-COINFECTED PATIENTS ON ART IN ZAMBIA

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1Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, 2Institute of Social and Preventive Medicine, Bern, Switzerland, 3University Teaching Hospital, Lusaka, Zambia, 4Harvard Medical School, Boston, MA, USA, 5University of California San Francisco, San Francisco, CA, USA, 6University of Alabama at Birmingham, Birmingham, AL, USA

Background: Hepatitis B virus (HBV) functional cure, defined as the loss of the hepatitis B surface antigen (HBsAg), is the desired goal of HBV therapy but occurs slowly (~1%/year) in HIV monoinfection. Novel immunomodulatory therapies to augment T cell responses are under investigation to increase rates of functional cure. In a sentinel cohort of HBV patients with HIV coinfection in Zambia, we investigated the clinical correlates of HBV functional cure during HBV-active antiretroviral (ART).

Methods: We enrolled HIV-HBV co-infected adults (≥18 years and HBsAg-positive) at two sites in Lusaka, Zambia, at start of tenofovir disoproxil fumarate-containing ART. At baseline we measured liver function tests, CD4+, and HBV DNA, and yearly thereafter we re-assessed HBV DNA and HBsAg. Negative HBsAg tests were repeated at 6 months along with surface antibody (HBsAb). After excluding those with <1 year follow-up, we analysed the proportion with HBsAg loss on ART and explored possible predictors including age, sex, baseline CD4+ categories (<200, 200-350, and ≥350 cells/mm³), HBV DNA (undetectable <20, 20-20,000, and >20,000 IU/mL), baseline ALT elevation, and 1-year change in CD4+. Logistic regression and Cuzick’s non-parametric test for trend were used in statistical analyses.

Results: Among 267 patients analysed, median age was 34 years (interquartile range [IQR], 27-45), 102 (38.2%) were women, and median baseline CD4+ count was 204 cells/mm³ (IQR, 99-341). During a median of 2.1 years on ART, 34 (12.7%) became HBsAg-negative. Most events (n=22) occurred in the initial year of therapy, 93.5% were confirmed with further testing, and 57.1% with HBsAg loss had detectable surface antibodies (HBsAb). With CD4+ <200 at ART start there was a trend towards increased HBsAg loss compared to CD4+ ≥350 cells/mm³ (P=0.155), but we did not find an association with age, sex, ALT elevation, or CD4+ change. Patients with either baseline undetectable or DNA >20,000
had increased HBsAg loss compared to moderate HBV VL (20-20,000 IU/ml; P<0.01; Figure 1).

Conclusion: A high proportion of HIV-HBV patients in Zambia experienced HBV functional cure on ART relative to what occurs in HBV mono-infection. Robust ART-induced immune reconstitution in the setting of high HBV antigen load may enhance anti-HBV immune responses in the liver. A better understanding of this mechanism could inform immunomodulatory therapies to increase HBV functional cure.

Figure. HBsAg loss among HIV-HBV coinfected Zambian patients, by initial CD4+ count and HBV DNA at start of antiretroviral therapy

### 626 HEPATITIS B VIRELOGIC FAILURE OF TENOFOVIR-BASED THERAPIES IN PATIENTS WITH HIV/HBV

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**Background:** A subset of patients coinfected with HIV and hepatitis B virus (HBV) exhibits persistent HBV viremia or viral breakthrough despite HBV suppression while on combination antiretroviral therapy (cART) that includes tenofovir (TFV). The current literature supports several etiologies for this phenomenon, most commonly suboptimal cART adherence. In this study, we determined tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) concentrations in dried blood spots (DBS) as novel measures of cumulative and recent adherence, respectively, among HIV/HBV coinfected patients on TFV.

**Methods:** In this ongoing case-control study, HIV/HBV coinfected adults on a stable tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)-based cART regimen with 1) HBV breakthrough: HIV viral suppression (<50 copies/mL) for >6 months and prior HBV viral suppression (HBV DNA < lower limit of quantification (LLOQ)) with new HBV DNA >LLOQ or 2) persistent HBV viremia: HIV viral suppression for >24 months and failure to achieve HBV DNA 6 months and HBV viral suppression on most recent assay. A 3mm DBS punch obtained at time of consent was used for analysis. Simultaneous quantification of TFV-DP and FTC-TP levels in DBS were performed using validated liquid chromatography/tandem mass spectrometry methods. Bivariate analysis was determined using Wilcoxon rank-sum test.

**Results:** To date, 6 men (83% Black) with persistent HBV viremia and 9 men (44% Black) with HIV viral suppression have enrolled (Table). Among those on TDF, TFV-DP levels were lower among unsuppressed (n=4) compared to unsuppressed (n=5) patients with median (range) levels of 516 (215-1176) and 1456 (1089-3108) fmol/punch, respectively (P=0.03). Among those on TAF, TFV-DP levels were 84.4 and 428 among unsuppressed patients (n=2) and median (range) of 144 (55.7-279) fmol/punch among suppressed patients (n=4). FTC-TP levels were detectable among 4 of 6 unsuppressed and all suppressed patients.

**Conclusion:** Median TFV-DP in DBS arising from TDF/FTC, reflecting cumulative drug exposure, was nearly 3-fold lower among HBV unsuppressed patients than suppressed patients. In contrast, the majority of both groups had detectable FTC-TP, reflecting recent adherence relative to the clinic visit. Interim findings of this ongoing study support the concern that poor long-term adherence to TFV therapy may underlie the phenomenon of concurrent HBV viremia and HIV viral suppression.

### 627 HIV LATE PRESENTATION AND ITS IMPACT ON HBV SEROCONVERSION IN HBV/HIV

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**Background:** Several cohorts have shown that successful long-term tenofovir (TDF)-containing combination antiretroviral therapy (cART) leads to HBsAg loss in 5-15% of HBV coinfected patients. However, data on determinants of HBsAg loss in this setting remain sparse. Here we evaluate factors associated with HBV seroconversion under HBV active ART in a large German multi-center cohort with a median follow-up of at least 10 years.

**Methods:** Non-interventional retrospective cohort of 7 German HIV care centres assessing rates of HBV seroconversion defined as HBsAg loss in 359 HBV/HIV coinfected patients under HBV active ART (TDF or tenofovir alafenamide (TAF) containing) cART. Fisher’s exact, chi-square and Mann-Whitney U test were used for statistical analysis.

**Results:** In total, 359 patients were included. 90% patients were male, median age was 41 years (IQR 41-43). 83% were of Caucasian, 14% of African and 3% of Asian descent. Main routes of HIV transmission were MSM (74%), origin from high prevalence country (9%) and heterosexual intercourse (9%). CDC stage at HIV diagnosis was C3 in 13% followed by A2 (12%), CD4 nadir 251/ul (211-296). 61% were ART-naïve when TDF or TAF containing cART was initiated. Median CD4 cell count at baseline was 359/ul (321-404). 59% were HBeAg positive at baseline. 90% were HBV-DNA positive (limit of detection <10 IU/ml) at baseline. 73% received TDF/FTC, 18% TDF/T3C and 3% TAF/FTC at baseline. 53% were switched to TAF during follow-up. 44% received a boosted protease inhibitor, 41% NNRTI and 10% an integrase inhibitor. Median follow-up was 11 years (10-12), median CD4 gain was 218/ul (130-229). Overall, HBsAg loss occurred in 66/359 (18.4%) patients. Median time to HBsAg loss was 41 months (33-60). There was no correlation between HBsAg loss and gender (P=0.307), age (P=0.307), country of origin (P=0.269), CD4 cell count (P=0.639), CD4 nadir (P=0.364), HBeAg (P=0.712), ART class (P=0.818), or switch to TAF (P=0.267). However, patients with stage CDC C (p<0.001), lower CD4 gain (P=0.045) and not receiving TDF/FTC (P=0.008) were less likely to lose HBsAg.

**Conclusion:** While long-term TDF-containing cART leads to higher rates of HBsAg loss when compared to published data for HBV monoinfected subjects, late presentation for HIV and poor immune recovery significantly impair HBV seroconversion rates in HBV/HIV coinfected patients.
628 ABSENCE OF HBV REACTIVATION IN HIV/HCV/HBcAb COINFECTED PATIENTS TREATED WITH DAA
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Background: HBV reactivation during HCV direct-antiviral agents (DAA) therapy has been described in individuals with positive hepatitis B (HB) core antibodies (anti-HBc) in the absence of HB surface antigen (sAg) prior to HCV treatment. This is the consequence of the disinhibition of HBV replication following HCV eradication. Despite some antiretroviral agents (ART) are effective both on HIV and HBV, little data of HBV reactivation exist in people living with HIV treated for HCV with DAA.
Methods: In order to determine the prevalence of occult HBV reactivation we retrospectively enrolled ART-treated HIV/HCV co-infected individuals who completed DAA interferon-free regimens between April 2015 and August 2018 in a large centre in London. Demographic characteristics, HBV markers, antiretroviral treatment, ART switch to prevent HBV (adding tenofovir disoproxil fumarate, TDF or tenofovir alafenamide, TAF) and addition of HBV prophylaxis (entecavir, ETV) prior to start DAA were collected. Subjects were followed up with alanine aminotransferase (ALT) at two to four weekly intervals during treatment and at week 4, 12, 24 and 48 after the end of treatment. HBV reactivation was defined as ALT elevation of 2 or more times above the upper limit of normal (ULN) in combination with molecular HBV reactivation.
Results: 274 HIV-infected subjects were treated for HCV with DAA. At baseline, 87/274 (32%) were HBsAg negative/anti-HBc positive, 6/274 (2%) were HBsAg positive and 141/274 (51%) were anti-HBs positive/anti-HBc negative. Results of anti-HBc positive subjects are shown in Table 1. Of all 87 HBsAg negative/anti-HBc positive subjects at risk of HBV reactivation, 85/87 (98%) received at least one anti-HBc active agent as a part of ART for at least 3 months before baseline. Six/87 (7%) commenced prophylaxis with ETV as receiving either only lamivudine (3TC) (5/6) or no anti-HBV ART (1/6). Four/87 had deranged ALT during DAA therapy or at following visits but no molecular HBV reactivation. All HBsAg positive subjects were on TDF/FTC and did not meet study criteria of HBV reactivation.
Conclusion: Almost one-third of our HIV/HCV cohort was HBcAb positive prior to DAA initiation. The absence of HBV reactivations in our cohort where 98% of anti-HBc positive subjects were on at least one HBV-active drug prior to DAA initiation suggests that this is an effective strategy to prevent it. However, further studies are warranted to assess the role of anti-HBV prophylaxis during DAA treatment.

629 HEPATITIS B VIRUS DNA LEVEL CHANGES IN HBeAg+ PREGNANT WOMEN RECEIVING TDF FOR PMTCT
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Background: High hepatitis B virus (HBV) DNA plasma levels and hepatitis B e antigen (HBeAg) carriage are the main risk factors of mother-to-child transmission (MCT). HBV DNA levels can decrease HBV DNA levels and prevent HBV MCT. Current guidelines recommend initiating antiviral prophylaxis when maternal HBV DNA level is above 200,000 IU/mL (5.3 log IU/mL); however, the optimal duration of treatment is unknown. Within a randomized trial, we assessed the changes of HBV DNA levels in HBeAg+ pregnant women receiving either tenofovir disoproxil fumarate (TDF) or placebo during pregnancy through the early postpartum period.
Methods: HBV DNA was retrospectively quantified in HBeAg+ and HBeAg negative and HBV-negative pregnant women enrolled in a phase III, placebo-controlled, double-blind, randomized clinical trial assessing the efficacy and safety of TDF 300 mg once daily versus placebo from 28 weeks’ gestation through 2 months post-partum (NCT01745822). Samples were selected from all women assigned to the TDF arm and a randomly selected subset of women on placebo. HBV DNA plasma levels were measured at baseline (28 weeks), during the TDF course at weeks 32 and 36, delivery, and months 1 and 2 postpartum, and after TDF discontinuation at 3, 6, 9, and 12 months postpartum. HBV DNA levels were measured blind to the randomized arm using the RealTime HBV assay (Abbott Molecular Inc., IL, USA).
Results: Of 331 women enrolled, 168 were randomized to TDF and 163 to placebo. Median HBV DNA levels in women on TDF decreased from 8.1 log IU/mL at baseline to 4.9 log IU/mL at 32 weeks, 4.2 at 36 weeks, 3.9 at delivery, 3.4 at 1 month and 3.3 at 2 months post-partum. After discontinuation of TDF, median HBV DNA level returned to baseline levels within one month. In the placebo arm median HBV DNA levels were unchanged during pregnancy and the postpartum period. In the TDF arm, 99 of 162 women (61%, exact 95% confidence interval [CI] 53% to 69%) had HBV DNA <200,000 IU/mL at 32 weeks, 133 of 158 (84%, CI 78% to 91%) at 36 weeks and 142 of 161 (88%, CI 82% to 93%) at delivery.
Conclusion: In our study, more than 85% of pregnant women receiving TDF from 28 weeks’ gestation achieved HBV DNA levels below 200,000 IU/mL prior to delivery.

A LONG-ACTING 3TC NANOFORMULATION SUPPRESSES HBV REPLICATION IN HUMANIZED MICE
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Background: Despite the success of existing antiretroviral therapy (ART) in controlling hepatitis B virus (HBV) infection, treatment requires life-long adherence to medicines. Compliance to ART can be compromised by frequency of dosing and adverse drug reactions. To this end, lamivudine (3TC), a nucleoside analog inhibitor of HBV and human immunodeficiency virus (HIV) infections, was modified into a lipophilic monophosphorylated prodrug (P3TC) to extend the apparent drug half-life, improve potency and facilitate access to viral replication sites. Lipid coated P3TC nanocrystals (NP3TC) were prepared to further improve drug biodistribution and longevity.
Methods: NP3TC was modified and formulated into long acting lipid nanocrystals by high-pressure homogenization. Cellular drug uptake and retention was conducted in human monocyte-derived macrophages (MDM). To evaluate...
anti-HBV activity, TK-NOG mice were transplanted with human hepatocytes, and after confirmation of human albumin (Alb) concentration in peripheral blood (1.1 ± 0.2 mg/ml), animals were infected intravenously with patient-derived sera samples containing ~106 HBV DNA. Following confirmation of HBV DNA in peripheral blood, five animals were administered a single intramuscular dose of 75 mg/kg 3TC equivalents of NP3TC and controls (n=3) kept without drug. Levels of HBV DNA and HBsAg in plasma were monitored over the four-week experiment duration. At the end of the study, liver tissues were analyzed for histopathology, HBV DNA and RNA by ddPCR, and staining for human cells and viral proteins.

**Results:** NP3TC nanocrystals had average particle sizes of 250-300 nm, polydispersity index of <0.2 and drug loading capacity of > 70%. NP3TC was readily taken up by MDM with sustained drug levels for up to 30 days; whereas native 3TC was eliminated within a day. In efficacy studies, single administration of NP3TC reduced HBV DNA from 4.38 ± 3.39 to 3.27 ± 2.75 log10 copies/ml and 3.38 ± 2.45 log10 copies/ml at two and four weeks post drug treatment, respectively, without loss of human cells or Alb levels. The results paralleled sustained drug levels in NP3TC treated animals.

**Conclusion:** A long acting potent 3TC ProTide formulation was developed and preliminary studies showed sustained anti-HBV activity in humanized mice for weeks after single dosing. These results are promising for development of a long-acting potent formulation of 3TC for the treatment and prevention of HBV and HIV infections.

**631 ANTI-INFLAMMATORY IL-10 IS INVERSELY RELATED TO CORONARY ATHEROSCLEROSIS IN HIV**

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**Background:** IL-10 is an anti-inflammatory cytokine secreted by monocytes, T cells, dendritic cells and other immune cells in response to systemic inflammation and is implicated in HIV viral persistence. However, IL-10 is thought to be protective against atherosclerosis, but this has not yet been studied in people with HIV (PWH). Therefore, we sought to understand the relationship of IL-10 with coronary atherosclerosis in PWH.

**Methods:** Serum levels of the anti-inflammatory cytokine IL-10 were measured by ELISA (Invitrogen, MA) in a well-phenotyped observational study of men and women with HIV and matched HIV-negative controls, who were all asymptomatic and without known cardiovascular disease. Quantification of coronary plaque and plaque characteristics were obtained by coronary computed tomography angiography.

**Results:** Among PWH, IL-10 inversely correlated with coronary segments with noncalcified plaque (rho = -0.24, p=0.004) and with coronary segments with any type of plaque (rho = -0.19, p=0.02), but not with segments with calcified plaque (rho = -0.009, p=0.92). Among HIV-negative controls, a similar directionality of relationships was seen for IL-10 and non-calcified plaque or any plaque, but the relationships were not statistically significant. Among PWH, no relationships were observed between IL-10 and several inflammatory markers known to be related to atherosclerosis in HIV (MCP-1, sCD163, sCD14, and IL-6). In logistic regression modeling adjusting for HIV RNA, CD4+ cells, total Framingham point score, BMI, race, MCP-1 and sCD163, lower IL-10 remained significantly related to presence of plaque (p=0.008).

**Conclusion:** Higher IL-10 confers a lower risk of coronary plaque (and specifically non-calcified plaque) even when controlling for traditional cardiovascular risk factors: HIV RNA, CD4+ cells, and pro-inflammatory markers. The effects of IL-10 in HIV may be both protective and detrimental: while IL-10 may promote viral persistence, our study suggests that IL-10 may be involved in mitigating untoward coronary atherosclerosis.

**632 IL-32Δ AND TRAIL: NEW CARDIOVASCULAR DISEASE BIOMARKERS IN ART-TREATED HIV INFECTION**

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**Background:** We recently demonstrated that enhanced expression of IL-32Δ, a regulatory isoform of the proinflammatory cytokine IL-32, positively correlates with the coronary artery atherosclerotic total plaque volume (TPV), a subclinical cardiovascular disease (CVD) marker in HIV+ individuals receiving anti-retroviral therapy (ART). Here, we screened for new biomarkers associated with subclinical CVD that in combination with IL-32Δ may serve to better predict CVD susceptibility/progression.

**Methods:** Plasma was collected from n=52 ART-treated aviremic HIV+ male participants with no clinical CVD from the Canadian HIV and Aging Cohort Study and n=23 age-matched uninfected controls. Participants prospectively underwent contrast-enhanced cardiac computed tomography and TPV measurement. HIV+ group was divided into n=30 with subclinical coronary artery atherosclerosis (TPV>0) and n=22 without (TPV=0) (median CD4 count: 593 and 581 cells/mm3 and median age: 53.3 and 50.5 years, respectively). Soluble factors were quantified by Luminex assay and selected biomarkers validated by ELISA. Expression of IL-32 mRMA was quantified by SYBRGreen RT-PCR in peripheral blood mononuclear cells.

**Results:** Expression of IL-32Δ in HIV+ participants with atherosclerotic TPV was 1.5fold higher compared to TPVneg individuals (mean±SD: 0.038±0.017 vs 0.025±0.018, p = 0.006). Among 38 analytes measured by Luminex assays, levels of TNF-related apoptosis inducing ligand (TRAIL) and Epidermal Growth Factor (EGF) were lower in plasma from TPV+ compared to TPVneg HIV-infected individuals (68.5±24.3 vs 85.3±23.1 pg/ml for TRAIL and 694.1±269 vs 906.4±256.5 pg/ml for EGF, p = 0.04 and p = 0.01, respectively). Interestingly, IL-32 mRNA expression negatively correlated with TRAIL, EGF and TPV (median CD4 count: 593 and 581 cells/mm3 and median age: 53.3 and 50.5 years, respectively). Soluble factors were quantified by Luminex assay and selected biomarkers validated by ELISA. Expression of IL-32 mRMA was quantified by SYBRGreen RT-PCR in peripheral blood mononuclear cells.

**Conclusion:** Our study reveals that high expression of IL-32Δ in blood cells of ART-treated HIV+ individuals with subclinical CVD correlated with low plasma levels of TRAIL and EGF, two emerging biomarkers of CVD that likely play atheroprotective roles. Indeed, TRAIL was shown to induce cell death of...
over-activated and malignant cells, whereas EGFr is involved in myocardial protection from acute stress. Combination of IL-32c with these biomarkers has the potential to better predict CVD in HIV+ individuals.

### 633 INFLAMMATION-RELATED GENES ARE ASSOCIATED WITH ACCELERATED AGING IN HIV

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**Background:** Chronic, low-grade inflammation is characteristic of both HIV disease and aging ("inflammaging"), and may contribute to the accelerated aging observed in people living with HIV (PLWH). We examined whether inflammation-related single nucleotide polymorphisms (SNPs) were risk factors for accelerated aging and HIV-associated non-AIDS (HANA) conditions among PLWH.

**Methods:** This was a cross-sectional, observational cohort study that examined 155 HIV+ cases (mean age = 47.3, 81% male, 68% White) from the National NeuroAIDS Tissue Consortium. All cases had existing pre-mortem behavioral/medical/virologic data, post-mortem tissue samples, as well as genetic and epigenomic data. Accelerated aging was measured according to the Epigenetic Clock: a published biomarker of aging based on the relationship between chronological age and biological age as defined by DNA methylation levels of 353 CpGs. The resulting age estimate, DNA methylation age, was related to chronological age. Past or current HANA conditions including cerebrovascular disease, liver disease, kidney disease, COPD, cancer, and diabetes were determined via self-report or extrapolated from medical records. Mean age acceleration (expressed as Z-scores) and likelihood of past/current HANA conditions were compared between major allele homozygotes and minor allele carriers separately for each SNP (IL-6 -174G/C, IL-10 -592C/A, TNFα -308 G/A). Statistical analyses were adjusted for relevant demographic and clinical factors including comorbidities (HIV-associated neurocognitive disorder [HAND], lifetime major depressive disorder, substance use disorders, HIV disease characteristics, study site, and DNA methylation assay batch.

**Results:** IL-6 minor allele carriers and IL-10 major allele homozygotes demonstrated significantly greater accelerated aging (higher Z-scores) compared to other genotype groups. The likelihood of any past/current HANA condition did not differ between IL-6 genotype, but was 3.4 times greater in IL-6 minor allele carriers versus others. TNFα genotype was not associated with accelerated aging, nor HANA conditions.

**Conclusion:** SNPs in the interleukin pathway (IL-6 and IL-10) may be helpful in identifying PLWH who are at high risk for accelerated aging. These insights into pathophysiological pathways may lead to interventional approaches to treat the potential of rapid aging among persons living with HIV.

### 634 IMPACT OF INFLAMMATION AND GUT IMMUNITY ON CORONARY ARTERIAL WALL COMPOSITION

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**Background:** Factors that impact CAWC in the setting of HIV disease are poorly understood. We sought to investigate how HIV infection and associated changes in gut immunity, systemic inflammation and initiation of ART impacts coronary CT angiography (CTA).

**Methods:** 18 chronic HIV+ ART-naive patients (pts) underwent CTA, upper endoscopy for duodenal biopsies (gut) and phlebotomy before and 1 yr after initiating darunavir/ritonavir/tenofovir disoproxil fumarate/entecavir (ART).17 matched HIV- control (C) underwent identical procedures once. Known cardiovascular disease was exclusionary. Gut samples underwent tissue immunohistochemistry (IHC) or FACS analysis. 3D reconstruction of CTA of 3 main arteries (RCA, LAD, and LCx) (expressed as % of total artery diameter) and Hounsfield Units using Aquarious iNutrition software. Plasma inflammatory biomarkers were measured by ELISA. Values are expressed as median values [interquartile range] and non-parametric (Spearman’s Rho coefficient [SrC]) were used where appropriate.

**Results:** All pts and C were MSM with median age of 40.5 [31-51] (pts) and 38 [33-47] (C); p=0.674, and CD4 count of 431 [272-559] pts and 958 [741-1273] (C); p<0.001. Baseline HIV load was 40.500 [19,750-84,250]. Pts' 1 yr CD4 742 [600-849] and all HIV load <20 cp/mL. CAW was thicker in pts vs C [57% vs 52% p=0.001]. CAWT correlated with gut IHC CD8+ T-cell density (SrC=0.70; p=0.019), but not gut CD4+ T-cell IHC or any PBMC T cells or subpopulations. CAWT fat proportion was lower in HIV+ [14% vs 21%; p=0.012] and Ca proportion was higher in pts [28% vs 23%; p=0.05] than C. No differences were found in the non-fat-non-calcium proportion. Gut IHC CD8 T-cell density positively correlated with CAWT Ca (SrC=0.54; p=0.05) and negatively with fat CAWT (SrC=-0.612; p=0.021). Soluble (s)CD163 positively correlated with fat CAWT (SrC=0.65; p=0.008) and negatively correlated with sMAdCAM-1 (SrC=-0.61; p=0.023) and intestinal fatty acid binding protein (SrC=-0.67; p=0.01).

**Conclusion:** While CA thickness and calcium were higher in people with greater gut CD8 T-cell density, fat content was lower. Lower monocyte activation also correlated with less fat content yet more gut homing and intestinal turnover. Thus, gut repair may be essential for modulating the monocyte activation associated with fat infiltration of coronary arteries.

### 635 CONTRIBUTION OF HUMAN HERPESVIRUS 6 AND HERPES SIMPLEX 2 TO PROGRESSION OF IMT IN HIV

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**Background:** Several herpesviruses have been implicated in the pathogenesis of atherosclerosis, but limited information is available about their role in the progression of atherosclerosis in people living with HIV (PLWH). Human herpes virus 8 (HHV-8) is a lymphotropic and vasculotropic herpesvirus with potential pro-atherogenic effects. However, to date no clinical studies have associated HHV-8 infection with atherosclerotic disease. We explored the influence of coinfection with HHV-8 and other herpesviruses on the rate of progression of subclinical atherosclerosis in virologically-suppressed PLWH.

**Methods:** Prospective study including men who have sex with men (MSM) infected with HIV. At the baseline visit, IgG antibodies against HHV-8 and other herpesviruses, highly-sensitive C-reactive protein (hsCRP) levels, and the Framingham risk score were measured. To evaluate the progression of subclinical atherosclerosis, successive carotid intima-media thickness (cIMT) measurements with high-resolution carotid artery ultrasound were performed over an eight-year period. Adjusted general linear mixed models were used to assess factors associated with faster cIMT progression.

**Results:** 141 participants with suppressed HIV-RNA (<200 copies/ml) at cIMT measurement during the study period were included. 46 (31.3%) werecoinfected with HIV-8 and 76 (54%) with herpes-simpex virus (HSV-2). Factors associated with faster cIMT progression adjusting for CD4 cell counts, time between cIMT measurements, hepatitis C, varicella-zoster virus and cytomegalovirus coinfection were seropositivity for HHV-8 (p=0.055), HSV-2 and HHV-8 coinfection (p=0.028), the Framingham risk score (p=0.045) and hsCRP (p=0.023). Coinfection with HHV-8 was independently associated with higher levels of hsCRP (OR 1.059 [C.I. 1.02-1.17], p=0.016). When hsCRP and HHV-8 were simultaneously included in the adjusted model, the relationship of HHV-8 with cIMT progression was attenuated.

**Conclusion:** HHV-8 contributes to progression of cIMT with a more prominent role when it coinfects with HHV-8 in virologically-suppressed PLWH, and this effect could be driven by systemic inflammation.

### 636 HIV INFECTION AND RISK OF RECURRENT VENOUS THROMBOEMBOLISM: A NATIONAL COHORT STUDY

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**Background:** People with HIV (PWH) are at increased risk of a first venous thrombotic event (VTE). Whether this also translates into more recurrent VTE is
unknown. We assessed VTE recurrence rates in PWH and compared these to VTE recurrence rates in HIV uninfected patients.

Methods: PWH with a first VTE between 2003-2018 were identified in the ATHENA cohort and compared to HIV uninfected patients with a first VTE in the MEGA cohort in the Netherlands. Provoked VTE were associated with cancer, major surgery, estrogen exposure, immobilization, or plaster cast use for fractures. The primary endpoint was recurrence of VTE following discontinuation of anticoagulant therapy for a first VTE. Multivariable Cox regression was used to estimate the VTE recurrence risk. Kaplan-Meier estimates of VTE recurrence accounted for death as competing risk and were stratified for provoked or unprovoked first VTE.

Results: Of 201 PWH with a first VTE in ATHENA, 153 had observations after anticoagulant therapy withdrawal. Of these, 126 (95 unprovoked) were in men and 27 events (13 unprovoked) in women. In MEGA, 4005 patients had a first VTE, including 1813 (98% unprovoked) in men and 2192 (363 unprovoked) in women. In PWH, 40 recurrent VTE occurred during 772 person years of follow up (PYFU; median 4.7 years, 5.2/100 PYFU, 95%CI 3.8-7.0). In MEGA, 635 recurrent VTE occurred during 20,215 PYFU (median 6.1 years, 3.1/100 PYFU, 95%CI 2.9-3.4). KME were higher for PWH at 1 year following anticoagulant withdrawal (13% vs 6%), attenuating at 3 (20% vs 11%) and 5 (23% vs 15%) years of follow up. PWH were at higher risk of recurrent VTE during the first year following anticoagulant withdrawal (HR 1.86, 95%CI 1.16-3.01), but not thereafter (HR 1.06, 95%CI 0.65-1.73). KME at 1, 3 and 5 years in PWH and HIV uninfected patients with unprovoked first VTE were 16% vs 9%, 24% vs 17% and 27% vs 24%. Multivariable Cox regression showed that the CD4+ T-cell increase between the first VTE and anticoagulant therapy discontinuation was an independent predictor of a lower recurrent VTE risk (HR 0.73 per 100 CD4+ T-cells increase, 95%CI 0.60-0.89).

Conclusion: PWH were at increased risk of recurrent VTE, which might be driven by HIV-related immune deficiency, inflammation, and associated hypercoagulability. The increased risk attenuated over time, possibly reflecting the gradual recovery of these factors following initiation of effective antiretroviral therapy.

637 PREDISPOSING FACTORS FOR VENOUS THROMBOEMBOLISM IN HIV-INFECTED PATIENTS

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Background: HIV is associated with chronic inflammation and immune activation and increases the risk of venous thromboembolism (VTE) events. Predisposing factors are important in the epidemiology of VTE in the general population but little is known about their presence among people living with PLWH in the era of widespread access to antiretroviral therapy.

Methods: We included PLWH with VTE in 2005-2017 at 6 sites in the CNICS cohort. We developed a centralized adjudication approach for VTE with ascertainment based on multiple criteria including diagnoses and procedures, followed by centralized adjudication of primary data by two expert reviewers, and a third reviewer if discrepancies occurred. VTEs were classified by type and anatomic location. Reviewers identified the presence of pre-disposing factors such as bedrest and long plane rides. This analysis included only initial VTEs for those with recurrent events.

Results: We included 318 PLWH with VTE: 181 (57%) deep vein thrombosis (DVT), 139 (44%) pulmonary embolus (PE), and 38 (12%) catheter-associated thrombosis events, including 40 (13%) with multiple types simultaneously (mostly DVT/PE). Two-hundred forty-eight (78%) patients were male; median age was 49 years old (interquartile range [IQR]; 40; 55); and 134 (42%) were white, 151 (47%) black, and 26 (8%) Hispanic. Median CD4 count was 312 cells/µL (IQR; 149,548) and 31% had a detectable viral load (≥400 copies/mL). One-hundred forty-four (45%) were current smokers. Most patients had multiple predisposing factors (Table), mean 2.3 (standard deviation [SD] 1.5). Only 33 (10%) had no pre-disposing factor identified. The most common predisposing factors identified included recent hospitalization (134, 42%), infection (133, 42%), or immobilization/bed rest (78, 25%) within the past 90 days, and current IV drug use (65, 20%). Eighty-seven (27%) had both hospitalization and infection in the past 90 days; 54 (17%) had both immobilization/bed rest and hospitalization.

Conclusion: We conducted a robust adjudication process and examined predisposing factors for VTE among PLWH in a large North American cohort. PLWH with VTE were relatively young and most had at least one identified traditional pre-disposing risk factor. In addition, non-traditional risk factors, including IV drug use and recent infection, were common. Almost one-third of patients had detectable viral loads, and almost half were active smokers, suggesting potential modifiable pro-thrombotic risk factors.

Table 1. Risk factors for venous thromboembolism in CNICS cohort.

<table>
<thead>
<tr>
<th>Pre-disposing factor</th>
<th>Number (318 events)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization in the past 90 days</td>
<td>134</td>
<td>42%</td>
</tr>
<tr>
<td>Infection in the past 90 days</td>
<td>133</td>
<td>42%</td>
</tr>
<tr>
<td>Immobilization/bed rest in the past 90 days</td>
<td>78</td>
<td>25%</td>
</tr>
<tr>
<td>IV drug use</td>
<td>65</td>
<td>20%</td>
</tr>
<tr>
<td>Malignancy, alive in the past year</td>
<td>60</td>
<td>19%</td>
</tr>
<tr>
<td>Surgery in past 60 days</td>
<td>33</td>
<td>10%</td>
</tr>
<tr>
<td>COPD</td>
<td>30</td>
<td>9%</td>
</tr>
<tr>
<td>Chronic kidney disease in the past 90 days</td>
<td>25</td>
<td>8%</td>
</tr>
<tr>
<td>Menstrual and/or progestin or oral estrogen use in last 30 days</td>
<td>24</td>
<td>8%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>21</td>
<td>7%</td>
</tr>
<tr>
<td>Inherited or acquired thrombophilia (other than malignancy)</td>
<td>18</td>
<td>6%</td>
</tr>
<tr>
<td>Heart failure prior to event</td>
<td>17</td>
<td>6%</td>
</tr>
<tr>
<td>Major trauma including fracture in past 90 days</td>
<td>15</td>
<td>5%</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>15</td>
<td>5%</td>
</tr>
<tr>
<td>Transfusion in past 30 days</td>
<td>13</td>
<td>5%</td>
</tr>
<tr>
<td>Long plane rides/prolonged sitting in the past 90 days</td>
<td>9</td>
<td>3%</td>
</tr>
<tr>
<td>Neoplastic syndrome</td>
<td>6</td>
<td>2%</td>
</tr>
<tr>
<td>Current pregnancy or within 3 months post-partum</td>
<td>2</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

*Other-Risk: Clinica (8, 3%), morbid obesity (7, 2%), COPD, chronic obstructive pulmonary disease, IV-IV drug use.
a collagen-specific and NO-independent manner. Together these data suggest aggregation in the presence of NO. ABC also elevated platelet granule release in suggesting that these drugs may not pharmacologically interact with thrombin-evoked granule release.

Conclusion: that ABC uniquely enhanced collagen-evoked alpha and dense granule release (max aggregation: 27.3.1±7.3%, P=0.03), but not TAF/TDF (max aggregation: 13.0±3.4% (P<0.01). Under these conditions, the active metabolite of ABC of a NO donor, which reduced ADP-evoked aggregation from 48.9±5.2% to generate NO, the pharmacological impact of ARVs was assessed in the presence confounded by HIV status and previous ARV use. ABC, a guanosine analogue, has been suggested to interrupt nitric oxide (NO)–cGMP signalling, but the pharmacological mechanisms linking ARVs with platelets are unclear.

Methods: Platelets were isolated from healthy, HIV-negative and ARV naïve volunteers. Aggregation and dynamic granule release were assessed by platelet-based aggregometry and flow cytometry in the presence of clinically-relevant concentrations of DTG or DRV. Maximum aggregation values for platelets isolated from ARV-naïve volunteers were not affected by clinically-relevant concentrations of DTG or DRV. However, DTG reduced collagen-evoked alpha and dense granule release 80.6±0.1% and 71.5±13.1%, respectively. Whereas DRV increased alpha and dense granule release 2.2±0.4- and 1.2±0.2-fold, respectively.

Conclusion: The mechanism for reduced platelet activation in the presence of DTG may be explained by altered platelet granule release, that confers a potentially cardioprotective phenotype. Enhanced granule release following acute exposure to DRV may be important in the context of protease inhibitor-related cardiovascular risk. Further studies are required to correlate our basic science and clinical approaches to understand the potential impacts of alternative novel therapies upon cardiovascular health in people living with HIV.

Table 1: Odds ratio for APTT below reference interval (95%CI)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis* (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1.9 (1.5:2.5)</td>
<td>2.2 (1.8:2.9)</td>
</tr>
<tr>
<td>Age (per 10 year increase)</td>
<td>1.2 (1.01:1.3)</td>
<td>1.1 (1.01:1.2)</td>
</tr>
<tr>
<td>Male/female sex</td>
<td>0.9 (0.71:1.2)</td>
<td>0.8 (0.61:1.3)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.8 (0.61:1.1)</td>
<td>0.7 (0.51:1.4)</td>
</tr>
<tr>
<td>Alcohol (g/week)</td>
<td>0.029</td>
<td>0.06</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>BMI 25.0-29.9</td>
<td>1.3 (1.01:1.7)</td>
<td>1.5 (1.11:1.9)</td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>1.5 (1.12:2.0)</td>
<td>1.7 (1.22:2.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.4 (0.82:2.3)</td>
<td>1.1 (0.61:1.8)</td>
</tr>
<tr>
<td>NonCRP (mg/dL, increase)</td>
<td>0.9 (0.71:1.2)</td>
<td>0.21 (0.86:1.3)</td>
</tr>
</tbody>
</table>

*Model adjusted for HIV, age, sex, smoking status, alcohol, diabetes, BMI and NonCRP.

BMI: Body mass index (kg/m²); NonCRP: high-sensitivity C-reactive protein;
monitoring resulting in greater patient and provider convenience. However significant drug interactions exist among DOACs and ART. Use of p-glycoprotein/CYP3A4 inhibitors such as ritonavir (RTV) or cobicistat (COBI) with rivaroxaban (RVB) is not recommended; with apixaban (APB) and dabigatran (DBG), DOAC dose reduction is needed. We characterized evolving trends in oral anticoagulant use and the prevalence of concomitant use of DOACs with RTV or COBI boosted ART among PLWH.

Methods: Established in 2011, the DC Cohort is a clinic-based, longitudinal observational cohort of PLWH. Participants from 11 sites who were prescribed anticoagulants from 1/2011-3/2017 were included. Duration of anticoagulant use was calculated. Summary statistics were generated for demographic and clinical characteristics, including concomitant ART prescriptions. Descriptive statistics of individuals prescribed DOACs and warfarin were generated.

Results: Among 8,315 PLWH enrolled during the study period, there were 239 anticoagulant prescriptions (96 DOAC, 143 warfarin) for 207 persons. PLWH prescribed anticoagulants were mostly Black (82%), male (82%), with a median age of 56 yrs. At the time of anticoagulant prescription, 95% were prescribed ART; 76% had CD4 counts >200 cells/µl and 77% had HIV RNA <200 c/ml. In 2011, DOACs accounted for 3% of total anticoagulant use, which increased to 43% in 2016. DOACs accounted for 64% of all new anticoagulant prescriptions by 2016 (Figure 1). RVB was the most frequently prescribed DOAC (70%) in 2016, followed by APB (19%), and DBG (11%). Among PLWH on DOACs, 59% were on boosted ART prior to DOAC initiation, this decreased to 33%. 55% in the RVB group were receiving boosted ART prior to anticoagulant initiation. Despite the recommendation to avoid concomitant use, 29% still received boosted ART 1 month after RVB initiation. Dose adjustments for APB and DBG when given with interacting ART could not be assessed.

Conclusion: In this cohort, DOAC use increased significantly over time. Although RVB is not recommended with RTV or COBI, concomitant use was frequently seen. Feedback should be provided to clinicians on DOAC utilization trends and potential ART drug interactions.

### Table: Associations of viral persistence with baseline IMT and IMT progression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline IMT (mm)</th>
<th>IMT progression (mm/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNA (log 10 copies/mL)</td>
<td>0.60</td>
<td>0.06</td>
</tr>
<tr>
<td>DNA (log 10 copies/mL)</td>
<td>0.60</td>
<td>0.06</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.52</td>
<td>0.03</td>
</tr>
<tr>
<td>sTNF-R2</td>
<td>0.45</td>
<td>0.01</td>
</tr>
<tr>
<td>sCD14</td>
<td>-0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>0.52</td>
<td>-0.01</td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>0.72</td>
<td>-0.01</td>
</tr>
<tr>
<td>CD8+ T cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD38+CD8+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-DR</td>
<td></td>
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</tr>
</tbody>
</table>

**643 VALGANCILOVIR REDUCES STNF-R2 AND VASCULAR DYSFUNCTION MARKERS IN TREATED HIV**

Gabriele B. Beck-Engeser1, Frank Maldarelli1, Vanessa A. York1, Steven G. Deeks1, Jeffrey N. Martin1, Elizabeth Sinclair1, Priscilla Hsue1, Russell Tracey1, Yong Huang1, Peter W. Hunt1

1University of California San Francisco, San Francisco, CA, USA, National Cancer Institute, Frederick, MD, USA, University of Vermont, Burlington, VT, USA

**Background:** Valganciclovir reduced T cell activation (but not IL-6, D-dimer, or sCD14) in an earlier trial of HIV/CMV co-infected individuals with incomplete antiretroviral therapy (ART)-mediated CD4 recovery, but its impact on vascular dysfunction and biomarkers that more consistently predict morbidity and mortality remain uncertain.

**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; sTNF-R2, IP-10, sICAM-1, sVCAM-1 (by ELISA), kynurenine/tryptophan (RT) ratio (by LC-MS), and HIV RNA levels (by single-copy assay, SCA, for values <75 copies/ml) were assessed every 4 weeks. Changes from baseline at each timepoint were compared between arms with linear mixed models, log10-transforming variables and normalizing to the baseline interquartile range (IQR) to facilitate comparisons between biomarkers.

**Results:** Among 14 valganciclovir-treated and 16 placebo-treated participants, most (93%) were men, 9 (30%) had detectable plasma HIV RNA levels, and median CD4 count was 190 cells/mm3. Baseline sTNF-R2 levels were highly correlated (rho with KT ratio (0.80, %CD38+HLA-DR+CD8+ T cells (0.66), IP-10 (0.52), sVCAM-1 (0.72), sICAM-1 (0.52, all P<0.01), and plasma HIV RNA levels (0.45, P=0.015), but not sCD14 (0.01, P=0.98). Compared to those on placebo, valganciclovir-treated participants had a mean -55% of an IQR greater decline from baseline in sTNF-R2 levels at week 4 (P=0.006) and -45% at week 8 (P=0.041). Similar effects on sICAM-1 were observed. Higher plasma HIV RNA levels remained associated with higher plasma sTNF-R2 (P=0.002) across all timepoints. After adjustment for plasma HIV RNA levels, valganciclovir-treated
participants continued to have a greater mean reduction in sTNF-R2 and sICAM-1 levels than placebo at weeks 4 and 8 (-49% to -53% of IQR, P=0.034 for all). Adjustment for sTNF-R2 levels also abrogated the impact of valganciclovir on sICAM-1 levels.

**Conclusion:** Treating asymptomatic CMV in HIV-infected individuals with incomplete ART-mediated CD4 recovery reduces a biomarker of TNF signaling - that strongly predicted cardiovascular events, Type 2 diabetes, and mortality in prior studies - and a soluble marker of vascular dysfunction. Longer trials of safer anti-CMV agents are needed to assess if treating asymptomatic CMV durably decreases vascular inflammation and cardiometabolic risk.

<table>
<thead>
<tr>
<th>Plasma Biomarker</th>
<th>Relative Difference in Change from Baseline in Valganciclovir vs. Placebo Per Interquartile Range (IQR) in Baseline Level (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTNF-R2</td>
<td>Week 4: 0.45 [0.25-0.66], Week 8: 0.33 [0.18-0.49], Week 12 (off drug): 0.25 [0.03-0.46]</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>Week 4: 0.32 [0.17-0.48], Week 8: 0.25 [0.09-0.42], Week 12 (off drug): 0.17 [0.01-0.33]</td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>Week 4: 0.73 [0.47-1.25], Week 8: 0.55 [0.33-0.97], Week 12 (off drug): 0.34 [0.15-0.54]</td>
</tr>
<tr>
<td>KT ratio</td>
<td>Week 4: 0.10 [0.03-0.18], Week 8: 0.03 [0.00-0.09], Week 12 (off drug): 0.01 [0.00-0.03]</td>
</tr>
<tr>
<td>IP-10</td>
<td>Week 4: 0.10 [0.05-0.19], Week 8: 0.05 [0.02-0.09], Week 12 (off drug): 0.03 [0.01-0.06]</td>
</tr>
<tr>
<td>HIV RNA level</td>
<td>Week 4: 0.91 [0.63-1.27], Week 8: 0.75 [0.52-1.01], Week 12 (off drug): 0.59 [0.39-0.81]</td>
</tr>
</tbody>
</table>

**644 PLASMA TISSUE FACTOR AND MCP-1 PREDICTS CIMT PROGRESSION IN TREATED HIV**

Denise C. Hsu1, Yifei Ma2, Danny Lu3, Meghann Williams4, Adam Rupert5, Rebecca Scheitzer2, Steven G. Deeks2, Irini Sergiti5, Priscilla Hsu6

1National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, 2University of California San Francisco, San Francisco, CA, USA, 3Leidos Biomedical Research, Inc, Frederick, MD, USA

**Background:** Chronic inflammation plays a key role in the development of cardiovascular disease (CVD) among persons living with effectively treated HIV infection and likely occurs early in the disease process. We evaluated the role of biomarkers of immune activation with carotid artery intima-media thickness (CIMT) progression in treated, virologically suppressed individuals.

**Methods:** We measured biomarkers of immune activation at baseline in 118 HIV-infected individuals with viral load <75 copies/mL from the SCOPE study, using cryopreserved mononuclear cells and plasma. CIMT was measured at baseline and longitudinally in the common, bifurcation and internal carotid artery regions using high resolution ultrasound. Plaque was defined as any focal measurement >1.5mm. Multivariable linear and logistic regression models controlled for demographics, CVD risk factors, and baseline CD4+ T cell count. The final model retained only biomarkers showing significant associations with CIMT.

**Results:** The median age was 49 yrs and 91% were male, 36% had hypertension, 25% were smokers, and 5% had diabetes. The median duration of follow-up was 2 years. The overall median rate of CIMT progression for the 3 regions was 6.0%/yr. Progression was faster in the bifurcation (5.6%/yr, p=0.006) and internal (6.5%/yr, p=0.0008) than common carotid regions (4.3%/yr, p=0.0008). Incident plaque occurred in 13 of 52 individuals. After multivariable adjustment, doubling in plasma tissue factor and MCP-1 were associated with CIMT progression in treated, virologically suppressed individuals.

**Conclusion:** Treating asymptomatic CMV in HIV-infected individuals with incomplete ART-mediated CD4 recovery reduces a biomarker of TNF signaling that strongly predicted cardiovascular events, Type 2 diabetes, and mortality in prior studies - and a soluble marker of vascular dysfunction. Longer trials of safer anti-CMV agents are needed to assess if treating asymptomatic CMV durably decreases vascular inflammation and cardiometabolic risk.

**Socioeconomic Status Associates with Arterial Inflammation in HIV**

Lili Zhang1, Amir Narwar2, Nicki Naddaf2, Smruti Rahalkar2, Tomas Patrich1, Michael Osborne1, Steven G. Deeks2, Ahmed Tawakol1, Priscilla Hsue2

1Massachusetts General Hospital, Boston, MA, USA, 2University of California San Francisco, San Francisco, CA, USA

**Background:** Socioeconomic status (SES) is associated with higher mortality among individuals living with HIV. In the general population, lower SES associates with higher arterial inflammation (a key driver of atherosclerotic disease), and a greater cardiovascular disease risk. While higher arterial inflammation has been reported in treated HIV, the relationship between SES and arterial inflammation has not been studied.

**Methods:** Men living with HIV were recruited from the SCOPE (Observational Study of the Consequences of the Protease Inhibitor Era), a clinic-based cohort of individuals receiving care in San Francisco. Arterial inflammation was measured using 18F-fluorodeoxyglucose (FDG-PET) positron emission tomography, as the uptake of FDG in the wall of the ascending aorta corrected for background. Zip-code-level SES measures were derived from the U.S. Census Bureau. Multivariable linear regression was utilized to assess the association between SES and arterial inflammation; mediation analysis was used to test whether systemic inflammation mediated that relationship.

**Results:** Thirty-nine virologically-suppressed men living with HIV were studied (mean age of 50.5±11.1 years). The median CD4 count was 663 cells/mm3 (IQR: 399-922); 82% were receiving antiretroviral therapies. Median income inversely associated with arterial inflammation (β [-0.465 [-0.808, -0.161], p=0.014]), after adjustment for sTNF-R2 levels also abrogated the impact of valganciclovir on sICAM-1 levels. Adjustment for sTNF-R2 levels also abrogated the impact of valganciclovir on sICAM-1 levels. Median income inversely associated with arterial inflammation (β [-0.465 [-0.808, -0.161], p=0.014]), after adjustment for sTNF-R2 levels also abrogated the impact of valganciclovir on sICAM-1 levels.

**Conclusion:** In individuals living with HIV, community-level SES factors associate significantly with arterial inflammation, independently of traditional risk factors, statin therapy, and level of HIV disease control. The link between lower SES and arterial inflammation appears to be mediated by increased systemic inflammation. Strategies to recognize SES as a CV risk factor in HIV as well as targeted interventions may be helpful in reducing HIV-associated arterial inflammation as well as clinical CV events.
646 INFLAMMATORY PHENOTYPES PREDICT PULSE WAVE VELOCITY CHANGE ON ART IN MALAWIAN ADULTS

Christine Kelly1, Willard Tinago2, Alejandro A. Garcia3, Patricia Hunter2, Dagmar Alber2, Natasha Luckhurst4, Jake Connolly4, Francesca I. Arrigoni5, Raphael Kamng’ona4, Patrick W. Mallon1, Henry Mwandumba1, Sarah Walker1, Saye Kho1, Nigel Klein2, for the ILLITY study team

1University College Dublin, Dublin, Ireland, 2University College London, London, UK, 3Kingston University, London, UK, 4University of Malawi, Blantyre, Malawi, 5University of Liverpool, Liverpool, UK

Background: Inflammation has been linked to vascular dysfunction and increased risk of cardiovascular disease. In low-income settings, drivers of inflammation are multiple, with infectious and environmental factors contributing. We hypothesise that adult people living with HIV (PLWH) in sub-Saharan Africa starting ART with advanced immunosuppression can be stratified into inflammatory phenotypes that predict changes in vascular dysfunction on ART, as measured by pulse wave velocity (PWV).

Methods: We recruited PLWH with CD4 < 100 cells/µl two weeks after starting ART in the REALITY trial (NCT01825031). PWV was recorded 2, 10, 24 and 42 weeks post ART. We measured markers of cell surface immune activation by flow cytometry and plasma inflammation markers by electrochemiluminescence at week 2. We identified inflammatory phenotypes using principal components analysis of 22 different markers, using linear mixed models to explore associations between inflammation clusters and change in PWV over time.

Results: In 260 of 279 PLWH with available biomarker data we identified three clusters representing 59 (cluster 1), 194 (cluster 2) and 7 (cluster 3) subjects (Figure 1A). Cluster 1 showed markedly higher CD4 and CD8 T cell expression of HLA DR and PD1 vs clusters 2 and 3 (HLA DR: CD4 86% vs 69%, CD8 84% vs 72%; PD1: CD4 69% vs 39%, CD8 54% vs 33% respectively; all p<0.001). Although small, subjects in cluster 3 had significantly higher levels of inflammatory cytokine pathways (IL6, IFNγ, IP10, IL1RA, IL10), chemotaxis (IL8), systemic and vascular inflammation (CRP, ICAM1, VCAM1) and SAA (all p<0.001); and marginally lower pre-ART CD4 (17 vs 42 cells/mm3, p=0.08). Baseline PWV was statistically lower in cluster 3 (6.3m/s vs 7.6, p<0.009), but increased over 42 weeks (log change 0.1m/s vs -0.5, p=0.07, Fig 1B). In mixed models, IL1RA was statistically lower in cluster 3 (6.3m/s vs 7.6, p=0.009), but increased over 42 weeks (log change 0.1m/s vs -0.5, p=0.07, Fig 1B). In mixed models, IL1RA was statistically lower in cluster 3 (6.3m/s vs 7.6, p=0.009), but increased over 42 weeks (log change 0.1m/s vs -0.5, p=0.07, Fig 1B). In mixed models, IL1RA was statistically lower in cluster 3 (6.3m/s vs 7.6, p=0.009), but increased over 42 weeks (log change 0.1m/s vs -0.5, p=0.07, Fig 1B).

Conclusion: In PLWH from low income settings with high pre-ART T cell activation, PWV improves (declines) on ART. However, we identified a cluster with a hyper-inflamed biological profile in whom PWV increased, with IL1RA a potential marker of this hyper-inflamed state and vascular dysfunction. The clinical implications of this phenotype require further research.

647 TOCILIZUMAB ALTERS LIPIDS IN HIV+ INDIVIDUALS IN A RANDOMIZED, DOUBLE-BLIND STUDY

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1University College Dublin, Dublin, Ireland, 2Case Western Reserve University, Cleveland, OH, USA

Background: Cardiovascular disease (CVD) risk is increased in HIV infection, despite suppressive antiretroviral therapy (ART). Increased IL-6 levels are linked to CVD, and are predictive of morbidity and mortality in HIV infection. Tocilizumab (TCZ), a monoclonal antibody that inhibits IL-6 activity, can reduce inflammation and improve disease outcomes in individuals with rheumatoid arthritis (RA). Increased serum lipids (total cholesterol, HDL, LDL) were observed following TCZ treatment, but were not significantly linked to CVD risk in the RA population. The effects of TCZ on inflammation, lipid profiles, and clinical outcomes in HIV+ individuals is not known.

Methods: This was a phase I/II double-blind, placebo controlled, crossover trial of TCZ administered intravenously (IV) every 4 weeks for 3 doses. Male and female ART-treated HIV+ study participants were randomized to receive either TCZ or placebo followed by a 12 week washout period and treatment crossover. At each study visit, lipid panels and detailed lipidomics analyses, measuring ~1200 lipid species across 13 classes, were performed by mass spectrometry.

Results: Traditional lipid measurements for total cholesterol, LDL, and VLDL levels were increased following TCZ treatment (p<0.01 for all). Plasma concentrations of total lipids (p=0.0001), and concentrations of the lipid classes, CE, CER, DAG, FFA, HPCR, LPC, LPE, PC, PE, SM, TAG were increased following TCZ treatment compared to baseline and placebo (p<0.05 for all). We also measured significant changes in concentrations of 129 individual lipid species (p<0.05). Additionally, fatty acid composition was altered among lipid species; TCZ treatment reduced the proportion of free saturated fatty acids (SFA)s (47% vs 43%, p=0.05), and increased the proportion of free monounsaturated fatty acids (MUFAs) (32% vs. 35%, p=0.06) and polyunsaturated fatty acids (PUFAs) (21% vs 22%). In vitro exposure of PBMCs to SFAAs induced inflammatory cytokine production and monocyte activation.

Conclusion: TCZ therapy alters lipid profiles in HIV+ individuals on ART. The concentrations of multiple lipid classes increased during TCZ treatment, however, the SAFA/UFA ratio was improved for some classes. IL-6 blockade may reduce some indices of inflammation in HIV+ individuals, but also exacerbates lipid levels, potentially limiting benefits in this population. Further study is needed to determine the consequences of TCZ-mediated lipidome alterations on CVD risk.

648 HDL CHOLESTEROL EFFLUX CAPACITY AND INCIDENT ASCVD IN HIV: IMPACT OF HAART

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EVIDENCE FOR PLEIOTROPIC EFFECTS OF LIPID-LOWERING DRUGS DURING SUPPRESSIVE HAART

Henning J. Drachsler, Colby Ayers, James Cottrell, Pablo Tobar, Roger Bedimo
VA North Texas Health Care Center, Dallas, TX, USA; University of Texas Southwestern, Dallas, TX, USA; From Health North Texas, Dallas, TX, USA; University of California San Diego, San Diego, CA, USA; University of Alabama at Birmingham, Birmingham, AL, USA; University of Pennsylvania, Philadelphia, PA, USA

Background: Statin use in HIV-infected patients is associated with improved virologic control, with decreased all-cause mortality, and decreased rates of non-AIDS defining conditions (NADC) like cancer and liver fibrosis. This has not been well studied for other preventive medications, including other lipid-lowering (LL) drugs.

Methods: We compared ongoing and past use of statins and other preventive drug classes for their association with death, cancer, severe infection (excluding bronchitis, cellulitis, and urinary infections), and cardio- or cerebrovascular (ASCVD) events identified by ICD-9 code. We included all HIV infected US Veterans from 1995-2011 after their 1st undetectable HIV viral load on HAART and used Cox models with inverse probability weighting (IPW) for treatment and censoring. We built time-updated drug exposure models from pharmacy outpatient refill and inpatient prescription data and categorized drug exposure on a weekly basis. We defined ≥75% drug use in the past month as current use, ≥90% use in the past year as consistent use, and last drug exposure > 1 year ago as remote use. We calculated propensity scores (PS) for each exposure category using multivariable generalized linear models of main effects and 2-way interactions of the following parameters: calendar year, VA station size, follow-up frequency, demographics, comorbidities including smoking and drug use, HAART-type and -adherence rate, degree of virologic suppression, CD4 counts, liver and kidney function, hemoglobin, body mass index, systolic blood pressure as well as total and HDL cholesterol.

Results: We followed 23,267 patients for a median of 5.2 years (IQR: 2.5-9.2). Median age at inclusion was 53 years (IQR 46–60). 97% of patients were male, 46% black, 37% white, and 56% ever smoked. 36% had an exposure to statins, but only 16% of follow-up years were classified as ongoing statin exposure. Hazard ratios with 95% confidence intervals for death and NADC are shown in the table.

Conclusion: We show a protective effect of statins and other LL drugs on death and NADC which had not been described for other LL drugs. The statin mortality benefit may be reflective of the reduced rates for cancer and infections and was seen despite their positive association with ASCVD events that remained after IPW. This association was weaker for other LL drugs, possibly explaining their greater mortality benefit. Of note, use of cardiac aspirin was not only associated with an increased risk of death but also cancer and infection.

Table 1. HDL Cholesterol Efflux Capacity (CEC) in Specific Antiretrovirals (ARVs) and SACC DRUGS IN THE FULLY-ADJUSTED MODEL

<table>
<thead>
<tr>
<th>Antiretrovirals</th>
<th>Comparative Effects of Antiretrovirals Drugs on CEC</th>
<th>Consistency</th>
<th>CEC Comparison</th>
<th>CEC Consistency</th>
<th>CEC Consistency</th>
<th>CEC Consistency</th>
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<tr>
<td>N</td>
<td>Mean CEC (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ATV</td>
<td>ref.</td>
<td>0.95 (0.30)</td>
<td>p = 0.01</td>
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</tr>
<tr>
<td>DRV</td>
<td>0.82 (0.21)</td>
<td>1.03 (0.32 - 3.40) p = 0.06</td>
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<tr>
<td>EFV</td>
<td>0.88 (0.30)</td>
<td>0.67 (1.44 - 1.04) p = 0.07</td>
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<tr>
<td>RAL</td>
<td>0.87 (0.26)</td>
<td>0.60 (1.14 - 2.52) p = 0.48</td>
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<tr>
<td>ABC</td>
<td>0.86 (0.30)</td>
<td>0.91 (0.58 - 1.42) p = 0.67</td>
<td></td>
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<tr>
<td>TDF</td>
<td>0.89 (0.26)</td>
<td>0.83 (0.26 - 0.92) p = 0.75</td>
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</tbody>
</table>

PCSK9 AND HIV INFECTION: CORRELATION WITH DYSLIPIDEMIA, INFLAMMATION, AND HAART

Elisabetta Schiarioli, Salvatore Cardaci, Vanessa Bianconi, Massimo R. Mannarino, Matteo Pirro, Daniela Francischi, Franco Baldelli
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Background: Lipid profile is generally deranged in antiretroviral (ART)-naive HIV+ patients due to HIV infection severity and immunodeficiency state. Proprotein convertase subtilisin/kexin type 9 (PCSK9), a major regulator of cholesterol metabolism, is induced in some inflammatory states with a trend toward an increase in plasma levels in HIV untreated/treated patients compared to healthy controls. Whether plasma PCSK9 levels may decrease after ART initiation is not established. We measured plasma lipid and PCSK9 levels in ART-naive HIV+ patients and investigated the impact of ART initiation on these parameters.

Methods: This is a longitudinal study of 82 HIV+ ART-naive patients not receiving any lipid-lowering treatment. At baseline and after three and six months of ART plasma total cholesterol (TC), low density lipoprotein (LDL)-C, high density lipoprotein (HDL)-C, triglyceride, lipoprotein(a), PCSK9 and high-sensitivity C-reactive protein (hsCRP) levels were evaluated

Results: At baseline plasma PCSK9 levels were significantly associated with CD4 T cell count (rho = 0.52, p = 0.001), HIV-1 RNA viral load (rho = 0.44, p < 0.001),
body mass index (rho = −0.33, p = 0.002) and HDL-C (rho = −0.41, p < 0.001), whereas no association was found with LDL-C and hsCRP. Initiation of ART was associated with a significant increase in TC, LDL-C, HDL-C and lipoprotein(a) levels and a significant decrease in PCSK9 and hsCRP levels. These changes were consistent for different ART regimens. TC and HDL-C but not LDL-C variations were associated with PCSK9 variation (Table 1).

Conclusion: Baseline PCSK9 levels are related to immuno-virological parameters but appear uncoupled from LDL-C levels. A complex lipid profile perturbation, including also a PCSK9 reduction, follows ART initiation.

651 LIPOPERSH E CHANGES ASSOCIATED WITH TAF ARE REVERSIBLE BY SWITCHING BACK TO TDF
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Background: Switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) has shown worsening of lipid profile in people living with HIV (PLWH), but there is little data exploring changes in lipid profile in PLWH switching back from TAF to TDF.

Methods: This analysis consists of a retrospective data collection on effectively suppressed HIV-positive patients who were initially switched from TDF to TAF-based antiretroviral treatment (ARTV) due to medical or economic reasons or as a result of optimization of therapy in a single site (Center for HIV and Hepatogastroenterology). After genotypes of TDF were introduced a substantial proportion of patients were switched back from TAF to TDF. This analysis includes patients switched back from TAF to TDF. All components of ARTV for all patients analysed were maintained the same with the single initial substitution of TDF to TAF.

Results: 385 virologically suppressed PLWH were initially included. Duration of TDF exposure before switching to TAF was 350(SD=201) weeks. 72 were switched back from TAF to TDF after mean duration of 87 weeks (SD=22) on TDF. Median age of 50 (SD ±12) years, 88% were male, 33% African American, 29% Hispanic, 29% aged ≥50 years, 91% HIV RNA <200 copies/mL at switch. After switch, lipid changes were observed in 95% of patients with TC=7.9% (95% CI: 7.4, 8.3), LDL=11.1% (9.2, 12.9), HDL=7.1% (6.2, 8.0) and TG=23.8% (22.0, 25.5). In the sensitivity analysis (n=4,305), lipid changes were observed in average by TC=9.0% (8.5, 9.6), LDL=12.2% (9.6, 14.9), LDL-HDL=8.1% (6.9, 9.2) and TG=25.8% (23.7, 28.0). After switch to TAF, the proportion of individuals with abnormal TC, LDL and TG increased and with abnormal HDL decreased in both the main (Fig 1A) and sensitivity analyses (Fig 1B). Similar patterns were observed in percent change and pre/post lipid categories after stratification of the main population by boosting agent use.

Conclusion: In this large, diverse population of PLWH in the US, switching from TDF to TAF was associated with development of less favorable lipid profiles. These differences persisted in analyses regardless of boosting agent use and in those whose only ART change was TDF to TAF, suggesting the changes arose as a direct result of switch from TDF to TAF.


653 HIV-1 GP120 AND TAT-INDUCED MICROPARTICLES IMPAIR ENDOTHELIAL CELL FUNCTION

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Background: The aim of this study was to determine whether: 1) human immunodeficiency virus (HIV-1) gp120 and Tat stimulate the release of microparticles from endothelial cells; and 2) viral protein-induced EMPs are deleterious to endothelial cell function: inducing endothelial cell inflammation, oxidative stress and senescence, and increasing apoptotic susceptibility.

Methods: Human aortic endothelial cells (HAECs) were treated with recombinant HIV-1 proteins Bal gp120 (RS), Lav gp120 (X4) or Tat. Endothelial microparticles (EMPs) released in response to each viral protein were isolated and quantified. Fresh HAECs were treated with EMPs generated under control conditions and from each of the viral protein conditions for 24 h.

Results: EMP release was higher (P<0.05) in HAECs treated with RS (141±21 MP/µL), X4 (132±20 MP/µL) and Tat (130±20 MP/µL) compared with control (61±13 MP/µL). Viral protein-induced EMPs significantly higher endothelial cell release of pro-inflammatory cytokines and expression of cell adhesion molecules than control. Reactive oxygen species production was more pronounced (P<0.05) in the RS-, X4- and Tat-EMP treated cells. In addition, viral protein-stimulated EMPs significantly augmented endothelial cell senescence and apoptotic susceptibility. Concomitant with these functional changes, viral-protein-stimulated EMPs disrupted cell expression of microRNAs: 34a, 126, 146a, 181b and 221 (P<0.05).

Conclusion: These results demonstrate that HIV-1 gp120 and Tat stimulate microparticle release from endothelial cells and these microparticles confer pathologic effects on endothelial cells by inducing inflammation, oxidative stress and senescence as well as enhancing susceptibility to apoptosis. Viral protein-generated EMPs may contribute to the increased risk of vascular disease with HIV-1.

654 HIV-1, CIRCULATING MICROPARTICLES, AND ENDOTHELIAL CELL DYSFUNCTION

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Background: Circulating microparticles have emerged as biomarkers and effectors of vascular disease. Elevated rates of cardiovascular disease are seen in HIV-1-seropositive individuals. The aims of this study were to determine: 1) if circulating microparticles are elevated in antiretroviral (ART)-treated HIV-1-seropositive adults; and 2) the effects of microparticles isolated from ART-treated HIV-1-seropositive adults on endothelial cell function, in vitro.

Methods: Circulating levels of endothelial (EMP), platelet (PMP), monocyte (MMP) and leukocyte (LMP)-derived microparticles were determined by flow cytometry in plasma from 15 healthy and 15 ART-treated HIV-1-seropositive men. HUVESCs were treated with microparticles from individual subjects for 24 h; thereafter, endothelial cell inflammation, oxidative stress, senescence and apoptosis were assessed.

Results: Circulating concentrations of EMPs, PMPs, MMPs and LMPs were significantly higher (50-140%) in the HIV-1-seropositive compared with healthy men. Microparticles from HIV-1-seropositive men induced significantly greater endothelial cell release of IL-6 and IL-8 (~20% and ~35%, respectively) and NF-κB expression while suppressing anti-inflammatory miR-146a and pro-inflammatory miR-181b. Intracellular reactive oxygen species production (ROS) and expression of ROS-related Hsp70 were both higher in cells treated with microparticles from the HIV-1-seropositive men. In addition, the percentage of senescent cells was significantly higher and SIRT1 expression lower in cells treated with HIV-1-related microparticles. Finally, caspase-3 was significantly elevated by microparticles from HIV-1-seropositive men.

Conclusion: Circulating concentrations of EMPs, PMPs, MMPs and LMPs were higher in ART-treated HIV-1-seropositive men and adversely affect endothelial cells promoting cellular inflammation, oxidative stress, senescence and apoptosis. Circulating microparticles may contribute to the vascular risk associated with treated HIV-1 infection.

655 ENDOTHELIAL DYSFUNCTION IS COMMON IN EARLY HIV INFECTION AND IS REVERSIBLE WITH ART

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Background: Endothelial dysfunction is an important mechanism for cardiovascular diseases (CVD); however, the prevalence of endothelial dysfunction during early HIV infection and its reversibility with early antiretroviral therapy (ART) is unknown. Endothelial dysfunction can be reliably assessed by noninvasive measurement of peripheral arterial tonometry using the reactive hyperemia index (RHI). We evaluated RHI in ART-naive early HIV seroconverters and after early ART.

Methods: RHI determinations (using EndoPAT 2000) were made in US Air Force members diagnosed with HIV infection between September 1, 2015 and September 30, 2017 (n=61); ART was initiated immediately after RHI testing.

Results: Patients were mostly younger males (males, 95.1%; African American, 57.4%; median age at diagnosis 27 years) enrolled on average within 12 months of the estimated date of seroconversion; they had fewer CVD risk factors and relatively preserved CD4+ counts (approximately 500 cells/mm3) (Table). At HIV diagnosis, 14 (23.0%) had an abnormal RHI. Age (per year increase) was associated with an abnormal RHI (odds ratio=2.15; P=0.089) while other demographic features, CVD profiles, or HIV disease characteristics were not significant. Forty patients received integrase inhibitor-based regimens; one patient declined ART. Early ART was associated with a significant increase in RHI (n=40; mean ± SD increase of 0.13 ± 0.33; P<0.02); the mean ± SD increase in RHI was greater in those with an abnormal compared with normal RHI at HIV diagnosis (0.33 ± 0.34 vs 0.05 ± 0.30; P=0.03). Of the 11 persons with an abnormal RHI at diagnosis and a follow-up RHI assessment, 8 (72.7%) had normalized RHI. The patient who declined ART converted from a normal (0.60) to abnormal (0.11) RHI after 8.3 months of follow-up.

Conclusion: In young, recent HIV seroconverters with low CVD risk, nearly 25% had endothelial dysfunction by RHI assessment. Endothelial dysfunction could not be attributed to HIV disease characteristics (i.e., low CD4, high viral load). Endothelial dysfunction was reversible with early ART in the majority of patients. Conceivably, persistent endothelial dysfunction and associated CVD complications during HIV infection may relate to delayed ART.

656 ADVANCED GLYCACTION END PRODUCTS, INFLAMMATION, AND ENDOTHELIAL DYSFUNCTION IN HIV

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Background: HIV-infected individuals are at an increased risk of premature aging and comorbidities. The mechanisms underlying these complications remain poorly understood. Advanced glycation end products (AGEs) are produced with aging and are increased in inflammatory and oxidative stress conditions. Elevated AGEs are associated with the progression of different pathological conditions such as diabetes and renal diseases. Their role in HIV remains unknown.
Methods: This is a cross-sectional study involving 90 individuals (68 HIV+ and 22 healthy controls matched by age and sex). AGEs levels were assessed using three different modalities: five different AGEs were measured in the serum; skin AGEs were determined with a non-invasive reader; dietary AGEs were estimated by a validated food frequency questionnaire. The relationships between serum skin AGE and inflammatory mediators, and endothelial dysfunction (by pulse wave velocity and peripheral arterial tonometry) were also measured. Classical t-test and chi-square tests were used to compare AGES between groups. Spearman correlations were used to explore relationships between variables and were then assessed while adjusting for demographics, BMI, CD4, and viral load.

Results: Overall, 71% were male, 68% were African American, with a mean age of 53 years. Among HIV-infected individuals, all participants were on ART by design and most participants (78%) had an undetectable HIV RNA level (<20 copies/ml). Skin and serum AGEs were significantly higher in HIV-infected participants compared to uninfected controls (p<0.01), while no differences in dietary AGEs were found between groups (p=0.2). In the HIV-infected group, but not in controls, skin and circulating AGEs were significantly associated with inflammatory and oxidative markers, and with endothelial dysfunction (table). These associations remained significant after adjusting for clinically relevant factors.

Conclusion: For the first time, we found higher levels of serum and skin AGE despite similar dietary AGE, in HIV-infected individuals, suggesting intrinsic production of AGEs. The relationship between serum skin AGE and inflammatory, oxidative and cardiovascular markers highlights the potential implications of AGEs in chronic inflammation, oxidative stress, and endothelial dysfunction in HIV, suggesting a new potential target for HIV-associated increased inflammation and cardiovascular risk.

Table: Correlations of AGES with markers of inflammation, oxidative stress, and endothelial dysfunction in HIV-infected group (selected markers shown due to space limitation).

<table>
<thead>
<tr>
<th>Variable</th>
<th>AGE</th>
<th>Oxidative markers</th>
<th>Inflammatory markers</th>
<th>Carbohydrate risk assessment</th>
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</thead>
<tbody>
<tr>
<td>AGE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin AGE</td>
<td>0.1</td>
<td>-0.01</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>AGE</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.2</td>
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<tr>
<td>AGE</td>
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<td>AGE</td>
<td>0.1</td>
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</table>

*Adjusted for age, gender, race, body mass index, tobacco use and statin use. **Correlation significance level: p(≤0.05) via gene set variation analysis (GSVA). For the first time, we found higher levels of serum and skin AGE despite similar dietary AGE, in HIV-infected individuals, suggesting intrinsic production of AGEs. The relationship between serum skin AGE and inflammatory, oxidative and cardiovascular markers highlights the potential implications of AGEs in chronic inflammation, oxidative stress, and endothelial dysfunction in HIV, suggesting a new potential target for HIV-associated increased inflammation and cardiovascular risk.

657 CUMULATIVE ART EXPOSURE IS ASSOCIATED WITH ENDOTHelial AND IMMUNe ACTIVATION IN HIV

Jose R. Castillo-Mancilla, Samantha MalWhinney, Ryan P. Coyle, James Morrison, Eric Poeschla, Rick Rapaport, Thomas Campbell, Lucas Ellison, Jia-Hua Zheng, Lane R. Bushman, Jennifer J. Kiser, Peter L. Anderson, Jonathan Z. Li

Background: Immune activation and inflammation persist in people living with HIV (PLWH) despite ART-mediated HIV suppression. Whether ART exposure is associated with residual inflammation remains unclear. We aimed to assess the association of cumulative ART exposure, quantified using tenofovir diphosphate (TFV-DP) in dried blood spots (DBS), with biomarkers of inflammation and immune activation in chronically-treated PLWH with viral suppression.

Methods: DBS and plasma were collected at two time points (6 months apart) in PLWH taking a tenofovir disoproxil fumarate (TDF)-based regimen who were virologically-suppressed (<50 copies/ml) for ≥12 months. TFV-DP in DBS was quantified using a validated LC-MS/MS assay, and concentrations of 17 biomarkers of inflammation and immune activation were measured by electrochemiluminescence or ELISA. Log-transformed TFV-DP concentrations were analyzed using a mixed-effects model, providing estimates of percent change in plasma biomarker concentrations for every 1 log increase in TFV-DP in DBS. Data are presented as median [Q1, Q3] or geometric mean [95% confidence interval].

Results: A total 123 visits from 69 participants (14 women, 19 Black, 8 Hispanic) with virologic suppression were analyzed. Median age and duration of HIV suppression were 48 [31, 57] and 4 [3, 7] years, respectively. Median time between visits was 6 [4, 8] months. The geometric mean TFV-DP for all visits was 1704 [1495, 1943] fmol/punch. After adjusting for age, gender, race, body mass index, tobacco use and statin use, TFV-DP in DBS was directly associated with biomarkers of inflammation (interleukin-8, tumor necrosis-a, serum amyloid A protein), monocyte activation (soluble CD14), T-cell activation (soluble CD27), and soluble intercellular and vascular cell adhesion molecules (sICAM-1 and sVCAM-1), as noted in the Table.

Conclusion: In PLWH with long-term viral suppression on TDF-based ART, high TFV-DP in DBS was associated with higher biomarkers of endothelial activation, immune activation and inflammation. In contrast to the decrease in systemic inflammation/immune activation observed in viremic PLWH who initiate ART, these findings suggest that higher ART exposure could have a different effect in biomarkers of inflammation in chronically-suppressed individuals. Conversely, immune activation and inflammation could also influence TFV-DP in DBS. Further research is required to elucidate the mechanism and clinical significance of these findings.

658 TRANSCRIPTOMIC BIOMARKERS OF HEART FAILURE IN PEOPLE LIVING WITH HIV

Cheryl Cameron, Chris T. Longenecker, Brian Richardson, Michael Fang, Jonathan Buggey, Sadeer Al-Kindi, Michael Cartwright, Carmen Nichols, Pearlart Cartwright, Jackelyn Golden, Mark Cameron

Background: Compared to HIV-uninfected controls, people living with HIV (PLWH) have a 25–80% higher risk of heart failure (HF), including both reduced ejection fraction HF (HFrEF) and preserved ejection fraction HF (HFpEF). HF is therefore a prevalent condition in HIV that may increase substantially as the HIV-infected population ages. However, very little is known about HF risks in the current ART treatment era and the goal of this study was to identify a peripheral immune cell transcriptomic signature of HF in PLWH. Our hypothesis is that functional genomic variation related to chronic inflammatory responses may drive HF risk in PLWH.

Methods: As part of a case-control study within the Case Center for AIDS Research prospective clinical cohort (AIDS 125; UH IRB 01-98-55), we performed total RNA sequencing and immunophenotyping of PBMCs and classical monocytes obtained from (a) 10 HIV+ subjects with adjudicated incident HFrEF; (b) 6 HIV+ subjects with adjudicated incident HFpEF; and (c) 7 age- and gender-matched control subjects without HF. Low input libraries were generated using Kapa RNA Hyper kits and sequenced on an Illumina NextSeq 550 (75 bp, paired-end, 30 million reads/sample). Differentially expressed genes were analyzed using a mixed-effects model, providing estimates of percent change in plasma biomarker concentrations for every 1 log increase in TFV-DP in DBS.

Table: Present difference in plasma concentrations of biomarkers of endothelial activation, immune activation and inflammation associated with TFV-DP in DBS.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
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<tbody>
<tr>
<td>Percent change for every log increase in TFV-DP</td>
<td>p-value</td>
<td>Percent change for every log increase in TFV-DP</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>0.1</td>
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</tr>
<tr>
<td>sVCAM-1</td>
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</tr>
<tr>
<td>sICAM-1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>sVCAM-1</td>
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</table>

*Adjusted for age, gender, race, body mass index, tobacco use and statin use. **Correlation significance level: p(≤0.05) via gene set variation analysis (GSVA). Further research is required to elucidate the mechanism and clinical significance of these findings.
and hypoxia, IL7 signaling, TGFβ and CTLL4 signaling, and the fibrin-collagen formation system. RNASeq of classical monocytes revealed enrichment of additional pathways in PLWH and HIV, including hypoxia signaling, PI3K AKT MTOR activation, CXCR4 signaling, relaxin signaling, and TNFA/TGFβ signaling. Our immunophenotyping analysis found that PLWH with HIV have significantly higher expression of CD57, a marker of senescence, on their CD4 T cells compared to non-HF PLWH (p=0.01). Linear regression modeling integrating both data types identified upregulation of EGF/TGFβ family genes as significantly associated with higher expression of CD57 on CD4 T cells.

Conclusion: We have identified proinflammatory gene expression signatures that correlate with HF in PLWH and constitute candidate biomarkers of HF in HIV alongside our immunophenotyping data. Our data provide a platform for future investigation of the inflammatory factors associated with chronic HIV infection over time and those that may promote HF risk.

659 HIV/HCV-SPECIFIC MARKERS AND ECHOCARDIOGRAPHIC PULMONARY ARTERY SYSTOLIC PRESSURE

Courtney Zola1, Meredith S. Duncan1, Kaku So-Armah2, Kristina Crothers3, Adeel A. Butt4, Cynthia L. Gibert1, Joon W. Kim6, Joseph Lim7, Vincent Lo Re8, Courtney Zola1, Meredith S. Duncan1, Kaku So-Armah2, Kristina Crothers3, Adeel A. Butt4, Cynthia L. Gibert1, Joon W. Kim6, Joseph Lim7, Vincent Lo Re8

Background: Pulmonary hypertension is associated with increased mortality in those with HIV compared to matched, uninfected controls. In small cohorts, hepatitis C virus (HCV) co-infection appears to increase pulmonary hypertension risk. We hypothesized that markers of HIV/HCV disease activity would be associated pulmonary artery systolic pressure (PASP).

Methods: We performed a cross-sectional study of participants from the Veterans Aging Cohort Study (VACS) enrolled April 2003 through October 2015 referred for an echocardiogram to examine the association between markers of HIV/HCV viral status and PASP. We performed multiple linear regression analysis to determine whether HIV/HCV mono-infection or coinfection were associated with higher PASP, adjusting for comorbidities with known PH associations and HIV/HCV status. We performed subset analyses, including markers of disease severity as follows: 1) restricted to HIV+ subjects to assess the association of HCV coinfection, higher HIV viral load, lower CD4+ T-cell count, and antiretroviral therapy (ART) with PASP levels and 2) restricted to those with chronic HCV infection to determine whether higher HIV viral load or interferon use was associated with higher PASP.

Results: Among the 8,226 subjects in our sample, 2,194 (27%) had HIV only, 540 (7%) had HCV only, and 637 (8%) were HIV-HCV coinfected. In adjusted analyses, we did not observe an association between HIV mono-infection (β 0.19, 95% CI -0.52, 0.90), HCV mono-infection (β =0.04, 95% CI -1.19, 1.26), or HIV/HCV co-infection (β =0.71, CI -0.47, 1.88) with PASP. We observed a modest inverse association between CD4+ T-cell count and PASP (Table). Neither HIV nor HCV viral loads were associated with PASP. Those on “Other” ART regimens (i.e. not on NRTI+NNRTI or NRTI+PI) demonstrated reduced PASP. Interferon exposure was not associated with PASP among HIV-infected individuals.

Conclusion: Contrary to reports from smaller, selected populations we did not observe an independent association between infection with HIV and/or HCV and higher PASP. Our sample of coinfected individuals is roughly six times larger than prior published cohorts. Lower absolute CD4+ T-cell count was inversely associated with PASP suggesting that a more intact adaptive immune system has a greater impact on PASP than viral replication. ART regimens may have variable effects on PASP, which requires further study.

660 EVIDENCE OF PRECLINICAL MYOCARDIAL FIBROSIS IN ART-TREATED PLWH IN SOUTH AFRICA

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Background: Cardiovascular disease (CVD) risk is higher among persons living with HIV (PLWH), based on data from U.S. and Europe showing excess risk for atherosclerotic coronary heart disease. In sub-Saharan Africa, hypertension and heart failure are the predominant CVD manifestations, where the influence from ART-treated HIV disease remains less clear.

Methods: Asymptomatic PLWH on ART and uninfected controls, both without known heart failure, were enrolled in Khayelitsha, Cape Town, South Africa. Roche immunoassays estimated biomarker levels for myocardial injury (high sensitivity troponin T [cTnT] via 5th Gen) and dysfunction (NT-pro brain natriuretic peptide [NTproBNP]). PLWH then had BNP levels measured by point of care (POC) Abbott iSTAT ELISA, and cardiac magnetic resonance (CMR) imaging was performed. Biomarker elevations were defined using thresholds of: >6.0ng/L for cTnT (i.e., a detectable level), and >100pg/mL for NT-proBNP (90% sensitive for dysfunction among those <70 years old) and POC BNP (manufacturer threshold). Linear and log binomial regression was used to assess associations between biomarkers, HIV status, and CMR measures.

Results: Among 49 PLWH and 57 uninfected controls, respectively, median (IQR) age was 46 (43-53) and 50 (45-57), 61% and 63% were women, and 33% and 37% were hypertensive. Among PLWH, median (IQR) CD4+ count was 515 cells/μL (334-677), and 78% had HIV RNA <50 copies/mL. No participants had evidence of ischemic disease on ECG (Q-waves or LBBB). PLWH, versus uninfected controls, had a higher proportion with detectable cTnT (45% vs. 32%; p=0.15). The proportion of PLWH with POC BNP >100pg/mL was 14%, and NTproBNP and POC BNP levels were highly correlated (r=0.89; p<0.0001). The data table reports associations for cardiac biomarkers and CMR measures among PLWH. Elevated NT-proBNP and POC BNP levels tended to be associated with parameters reflecting myocardial inflammation and fibrosis (i.e., ECV, LGE, native T1), some measures of diastolic dysfunction, (i.e., strain rates) but not systolic dysfunction (i.e., EF).

Conclusion: These pilot data suggest that PLWH in South Africa may have ongoing myocardial inflammation and fibrosis and pre-clinical myocardial dysfunction. Future research should focus on understanding the mechanisms and clinical relevance of HIV-associated myocardial injury in sub-Saharan Africa.
661 HIV IS ASSOCIATED WITH LUNG FUNCTION IMPAIRMENT IN THE MULTICENTER AIDS COHORT STUDY

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Background: HIV is an independent risk factor for chronic obstructive pulmonary disease (COPD), a major cause of death and disability worldwide. Although studies have measured lung function in persons living with HIV (PLWH), major limitations have included small samples, lack of HIV-negative controls or limited lung function assessment. We addressed these weaknesses by collecting spirometry (both pre- and post-bronchodilation) and single-breath diffusing capacity for carbon monoxide (DLCO) in a multicenter cohort of men who have sex with men (MSM), both HIV-positive and HIV-negative.

Methods: We included participants in the Multicenter AIDS Cohort Study seen between April 2017 – March 2018. Spirometry and DLCO were measured using standardized equipment, according to published standards, centrally reviewed for quality, and normalized (calculation of %predicted values) using published population-based equations. We tested the effect of HIV status on %predicted post-bronchodilator forced expiratory volume in 1 s (FEV1) and DLCO, both as continuous outcomes and as categorical outcomes (<80% of predicted). Multivariable models were adjusted for cigarette smoking, illicit drug use, and co-infection with hepatitis B or C.

Results: Among 1305 participants who attended research visits, 1176 (90.1%) completed lung function testing. Quality control standards were met for 1126 spirometry tests and 1094 DLCO tests. PLWH were younger, less likely to be Caucasian, reported more illicit drug use, and more commonly had hepatitis co-infection (each p<0.01). We observed no difference in FEV1 %predicted by HIV status (adjusted difference of 0.9% of predicted; 95%CI: -3.1% to +1.2%; p=0.40), but DLCO %predicted was significantly lower in PLWH (adjusted difference of -2.5% of predicted; 95%CI: -4.4 to -0.6%; p=0.009) (Table). PLWH were more likely to have DLCO <80% of predicted (OR 1.56; 95%CI: 1.17 to 2.09; p=0.003). Among the HIV-positive participants, lower DLCO values were correlated with lower nadir CD4+ T-cell count (adjusted β = 0.27; p=0.016) and borderline for increasing years of ART exposure (adjusted β = -1.2; p=0.063).

Conclusion: Compared to HIV-negative MSM, HIV-positive MSM are at higher risk for impaired DLCO, but not airway obstruction. While mechanisms of DLCO impairment in PLWH are unclear, worse DLCO in PLWH has been linked to lower nadir CD4+ T-cell count and decreased functional status, suggesting it is an important health issue in this population.

662LB HIV IS NOT ASSOCIATED WITH SLEEP-DISORDERED BREATHING

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Background: Sleep-disordered breathing (SDB) and related intermittent hypoxaemia are associated with increased risk of cardiovascular disease, cognitive dysfunction, malignancy, and impaired quality of life. Although high SDB prevalence has been reported in persons living with HIV (PLWH), studies have been small, lacked relevant HIV-negative controls, relied on risk scores or self-reported sleep apnoea rather than objective testing, and/or selectively enrolled PLWH with sleep symptoms potentially biasing findings. We compared overnight oximetry measures in PLWH and HIV-negative persons with similar lifestyles participating in the POPPY study.

Methods: We recruited a subset of POPPY participants (PLWH ≥50 y/o, PLWH <50 y/o, and HIV-negative controls ≥50 y/o) without regard to sleep symptoms or self-reported sleep apnoea rather than objective testing, and/or selectively enrolled PLWH with sleep symptoms potentially biasing findings. We compared overnight oximetry measures in PLWH and HIV-negative persons with similar lifestyles participating in the POPPY study.

Results: 435 of 475 (95%) participants provided analysable data: 231 older PLWH (median age 60y), 102 older HIV-negative (60y) and 120 younger PLWH (45y). SDB was present in 42%, 41% and 28% of the groups, respectively. Older PLWH had a median (IQR) ODI of 3.77 (1.8, 7.3), which was similar to that of the older HIV-negative group (4.27 [1.5, 7.9]; p=0.076) but higher than that of the younger PLWH (2.37 [1.5, 5.7]; p=0.02). In multivariable analysis (Table), increased ODI was associated with higher BMI, older age, and marital status, but not HIV status (difference in ODI of -0.22 [95%CI: -1.4 to +1.4; p=0.97]).

Conclusion: SDB is prevalent in older individuals, both with and without HIV. More severe overnight hypoxaemia is associated with expected risk factors such as obesity and older age, but not with HIV status. Further research will determine the effect of SDB and hypoxaemia on relevant HIV outcomes such as cognition, systemic inflammation, and immune activation.
663 SEX-SPECIFIC PATTERNS IN HIV-ASSOCIATED CARDIOVASCULAR MORTALITY IN NEW YORK CITY

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Background: We previously identified more pronounced associations between HIV status and cardiovascular disease mortality in women than men in New York City. However, because socioeconomic status may confound this relationship and New York City contains both some of the highest and lowest income counties in the nation, we re-analyzed this data restricted to the Bronx, which is both a high HIV prevalence and lower income borough/community.

Methods: We included all residents age 13+ reported with HIV to the population-based New York City HIV Surveillance Registry and living between 2007 and 2012. Surveillance data were linked with the city Vital Statistics Registry and National Death Index. Residents without HIV living in each borough, including the Bronx, were enumerated using modified US intercensal estimates after subtracting the surveillance-based counts of those with HIV. We examined sex-specific rates of death due to major cardiovascular diseases (ICD-10 codes I00-I78). Using log-linear models, we determined the association of HIV serostatus with cardiovascular disease mortality rates by sex within each borough, and compared this to the relationship across all New York City residents.

Results: There were 1,673 deaths attributed to cardiovascular disease as the underlying cause among HIV+ New Yorkers between 2007 and 2012, with 376 of these occurring among Bronx residents. In the Bronx, the age-adjusted cardiovascular disease mortality rate was 3.33/1,000 person-years (95% confidence interval [CI] 2.45–4.21) among HIV+ men and 2.47/1,000 (95% CI 1.42–3.51) among HIV+ women. In analyses of the entire city, the relative rate of cardiovascular disease mortality attributed to HIV serostatus was almost twice as high in women (rate ratio [RR] 2.18, 95% CI 1.96–2.42) than men (RR 1.17, 95% CI 1.08–1.26, P for interaction <0.001) (Figure). A similar disparity was also observed in each of the five boroughs except for the Bronx, where differences by sex were substantially attenuated (RR 1.76, 95% CI 1.44–2.14 in women vs. RR 1.31, 95% CI 1.15–1.48 in men, P for interaction 0.25).

Conclusion: After accounting for socioeconomic status through restriction, we found that sex differences in the association of HIV with cardiovascular disease mortality were attenuated. More work is needed to better characterize how socioeconomic and biological factors related to sex may affect cardiovascular disease in people living with HIV.

664 DIFFERENCES IN TYPES OF MYOCARDIAL INFARCTIONS AMONG PATIENTS AGING WITH HIV

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Background: The Universal Definition classifies MI by type according to the mechanism of myocardial ischemia. Type 1 MI (T1MI) result spontaneously from atherosclerotic plaque instability. Type 2 MI (T2MI) are secondary to other causes such as sepsis and cocaine-induced vasospasm resulting in oxygen demand-supply mismatch. We previously demonstrated that, in contrast to the general population, almost half of MIs among people living with HIV (PLWH) are T2MI. We conducted this study to compare MI rates by type and age among PLWH. We hypothesized that increases in rates with older age would differ by MI type, and that in contrast to the general population, T2MI would be more common in younger individuals, but there would be a measurable rate of T1MI even among 18-30 year-old PLWH.

Methods: Potential MI events were identified in the centralized data repository at 6 CNICS sites. Case identification criteria included MI diagnoses and cardiac biomarkers to optimize ascertainment sensitivity. For each potential MI, sites assembled de-identified packets with physician notes, ECGs, procedure results, and lab tests. Two experts reviewed each packet followed by a 3rd if discrepancies occurred. Reviewers categorized each MI by type and identified causes for T2MI. By decade of age, we calculated T1 and T2MI rates and confidence intervals (CI) per 1000 person-years of follow-up. Rate ratios were calculated for rates of T2MI vs. T1MI per decade of age.

Results: We included 564 T1MI (54%) and 483 T2MI (46%). T1MI rates increased with older age although T1MI occurred in all decades including young adults (Table). T2MI rates were significantly higher than T1MI rates for PLWH under 40 and increased with age among those over 40 (Table). T1MI rates were similar or higher than T2MI rates among those over 40 (significantly higher for those 61-70 years of age). Of note, there were differences in causes of T2MI among those at younger vs. older ages with cocaine-induced vasospasm more common in younger PLWH while causes such as hypertensive urgency and arrhythmia were more common in older PLWH.

Conclusion: We found that among PLWH rates of T2MI were higher than T1MI until age 40 differing from what is seen in the general population, but rates of both were very high among older PLWH. Causes of T2MI differed by age with substance use prominent at younger ages and cardiovascular-related risk factors common at older ages. These results highlight the importance of evaluating MI by type among PLWH.
665 ALCOHOL USE AND RISK OF MYOCARDIAL INFARCTION (MI): DOES MI TYPE MATTER?

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Background: People living with HIV (PLWH) are at increased MI risk. MIs are classified into type 1 (TIMI) due to atherothrombotic coronary plaque rupture and type 2 (T2MI) from supply-demand mismatch such as with sepsis. Data on alcohol use and MIs in HIV are limited, conflicting and do not distinguish MI types.

Methods: PLWH in care from 6 sites completed tablet-based assessments every 6 months including alcohol use (AUDIT-C). Alcohol severity was defined by AUDIT-C score (0-12 points); alcohol and binge frequency were defined as number of drinking and binge days/month. Alcohol categories were none, mild and hazardous (AUDIT-C score of 2-5 for men, ≥4 for women). MIs were centrally adjudicated and categorized by type. Alcohol associations were examined using Cox models, adjusted for age, sex, race/ethnicity, hepatitis C, smoking, diabetes, hypertension, dyslipidemia, and kidney disease. All models adjusted for CD4 cell count and viral load as time-varying variables. We repeated models using time-updated alcohol use and MI by type may clarify differences in prior study findings.

Results: Among 12,800 PLWH, 64% drank alcohol, and there were 134 TIMI and 112 T2MI during follow-up. In adjusted analyses, those reporting higher baseline alcohol scores and frequency of alcohol use had lower TIMI risk; this association was not seen for binge drinking frequency or T2MI (Table 1). Of persons with HLD (n =614), the mean end observation LDL-c was 151 mg/dL. Of persons with HLD, the mean end observation LDL-c was 162 mg/dL.

Conclusion: Further study of optimal ASCVD care models in PLWH is needed.

666 CARDIOVASCULAR RISK MANAGEMENT AMONG PLWH: DOES PROVIDER SPECIALTY MATTER?

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Background: Although persons living with HIV (PLWH) are known to be at increased risk for major atherosclerotic cardiovascular disease (ASCVD) events, the impact of provider specialty managing ASCVD risk in this population remains unclear.

Methods: We conducted a retrospective analysis of PLWH with a diagnosis of hypertension (HTN) and/or hyperlipidemia (HLD) (by ICD9/10 code) receiving care at 2 major academic health systems in the Southeast between 2013 and 2017. Clinical data were obtained from the Carolinas Collaborative Research Database for all PLWH with HTN and/or HLD and without previous diagnosis of ASCVD (defined as acute coronary syndrome, stroke, coronary artery intervention or peripheral vascular disease) prior to study period. Responsible provider for HTN/HLD management were defined by medication prescription (anti-HTN or statins) and classified into 5 groups: 1) infectious diseases (ID) provider only (≥ 3 prescriptions from ID without evidence of prescription entry by other provider), 2) non-ID primary care provider (PCP) only, 3) co-managed by ID and PCP (≥ 3 ID prescriptions and ≥1 PCP prescription), 4) medication prescribed by other provider, 5) no prescription found. Cohort members were followed until 1st ASCVD event, death, or end of study period (12/31/17). The primary HTN outcome was meeting 8th Joint National Commission’s (JNC 8) blood pressure (BP) goal of 140/90 at end of observation. The primary HLD outcome was end observation low density lipoprotein (LDL) Risk factors for failure to meet BP goals were defined using logistic regression.

Results: Of 1458 PLWH included in the analysis, 1077 (73%) had a diagnosis of HTN and 614 (42%) had HLD (see Table 1). Of persons with HTN (n =1077), 223 (21%) were managed by ID exclusively, 184 (17%) by PCP only, 37 (3%) by both and 40% had no anti-HTN prescribed. Overall, 616 (57%) met JNC 8 BP goal. Risk factors associated with not meeting JNC 8 goals were Black race (OR is 1.68, 95% CI 0.50-0.91) and exclusive management by ID (OR 0.66 (95% CI 0.48-0.91), Table 1). Of persons with HLD (n =614), the mean end observation LDL-c was 109.8 mg/dL. On regression analysis, HLD managed exclusively by ID provider was associated with a 11.8 mg/dL (95% CI 1.9-21.3) in end observation LDL-c compared to the rest of the cohort.

Conclusion: PLWH with HTN or HLD do not meet evidence-based treatment goals consistently, and provider specialty may play a role in these outcomes. Further study of optimal ASCVD care models in PLWH is needed.
HYPERTENSION CONTROL IN INTEGRATED HIV/NCD CLINICS IN THE SEARCH STUDY

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Background: With increases in life expectancy, non-communicable diseases (NCD) are a major global public health concern. However, there is limited evidence on whether integrated HIV/NCD care improves blood pressure control. This study examines the association between integrated HIV/NCD care and blood pressure control over an extended follow-up period.

Methods: A retrospective cohort study was conducted among adults with NCD and HIV in integrated care settings in rural Uganda. Covariates included age, sex, BMI, smoking status, alcohol consumption, and ART regimen. The primary outcome was blood pressure control (SBP ≤ 140 mmHg and DBP ≤ 90 mmHg) at follow-up visits. The study included 2,955 controls and 740 PLWH, with a median follow-up duration of 583 days.

Results: PLWH had equivalent blood pressure control compared to controls at 3 months. However, PLWH had higher blood pressure control at 6 and 12 months, with adjusted odds ratio of 1.6 (95% CI: 1.2-2.1). PLWH also had more frequent clinic visits, with 20% of visits scheduled at 4-8 weeks and 40% at 12 weeks.

Conclusion: Integrated HIV/NCD care was associated with better blood pressure control in PLWH compared to controls, highlighting the potential benefits of integrated care for chronic disease management.
to INSTI-based ART among AIDS Clinical Trials Group (ACTG) participants in ACTG protocols A5001 and A5322, which provided long-term observational follow-up of individuals enrolled in randomized interventional trials.

**Methods:** A5001 and A5322 participants in follow-up from 1997-2017 who switched to INSTI were included. Within-person weight and waist circumference trajectories were generated, allowing participants to serve as their own controls for estimation of background/age-related weight gain. Piecewise linear mixed effects models adjusting for age, sex, race/ethnicity, parent study baseline BMI and their interactions, nadir CD4+ T cell count, smoking, diabetes and percent follow-up time with suppressed (<200 copies/mL) HIV-1 RNA examined weight and waist circumference change before and after first switch to INSTI. Linear spline models with a single knot accounted for non-linear trends.

**Results:** Adults (n=972) who switched to INSTI (68% from PI, 31% NNRTI, 2% other non-INSTI at median 7.8 years after parent trial entry) were 81% male and 50% non-white. Median age at switch was 50 years, CD4+ T cell count 511 cells/µL and BMI 26.4 kg/m2; 539 switched to RAL, 222 to EVG and 211 to DTG. When restricted to persons with suppressed HIV-1 RNA at switch (n=691), women, blacks and persons age ≥60 experienced significantly greater weight gain in the 2 years following switch to INSTI vs 2 years prior to switch; men and persons age <40 experienced less weight gain. In adjusted models, white or black race, age ≥60 and BMI ≥30 kg/m2 were associated with greater weight gain following switch among women, whereas age ≥60 was the greatest risk factor among men. Trends for waist circumference were similar (data not shown).

**Conclusion:** Yearly weight gain increased following switch to INSTI. These increases were particularly significant for women, blacks and persons age ≥60. When compared to pre-switch weight changes on stable suppressive ART and given concomitant increases in waist circumference, these data suggest increases in weight/fat mass greater than expected for age. The cardiometabolic implications of increased weight gain following switch to INSTI need to be established.

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**WEIGHT GAIN DURING TREATMENT AMONG 3,468 TREATMENT-EXPERIENCED ADULTS WITH HIV**

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**Background:** Weight gain is a known complication of HIV treatment. However, the specific risk factors and magnitude are not well understood, especially after the initial treatment period. The objectives of this study were (1) to describe the demographic, clinical, and treatment characteristics of treatment-experienced adults with virally-suppressed HIV that had ≥3% annual weight gain in recent years (2013 to 2018) and (2) to identify variables independently associated with such gain.

**Methods:** EMR and prescription data were collected for the most recent ART exceeding 1 year in length for 3,468 previously-treated adult patients with continued HIV suppression. Patients resided in 21 States + DC and were in care at 6 HIV treatment centers. Data inclusion required ≥ 1 BMI at ARV prescription and 1 year in length for 3,468 patients with ≥3% weight gain in recent years. Bivariate comparisons were made using chi-square or Fisher’s tests followed by independent variable assessment via logistic regression (LR).

**Results:** Among the 3,468 adults, annualized weight gain was ≥3% for 1,045 (30%). Compared to those with <3% weight gain, the group with ≥3% gain had higher proportions of overweight and normal BMI at baseline, female, age ≥50, and psychiatric disorders and lower rates of comorbidities CKD, CVD, DM, hyperlipidemia, and hypogonadism. The weight gain patients were less likely to be on ART and PLWH are at increasing risk for obesity, metabolic comorbidities, and cardiovascular disease.
gain via LR were overweight or obese at baseline, hypogonadism, and use of PI-containing therapies. Psychiatric disorders were positively associated with weight gain via LR. InSTI-containing ART was not significantly associated with weight gain in the LR.

**Conclusion:** Weight gain in the treatment-experienced population with continued HIV suppression was primarily associated with lower BMI, reduced proportion of hypogonadism, increased proportion of psychiatric disorders, and non-PI-containing regimens. The association between InSTI-based ART and weight gain, which reached significance in bivariate analyses, did not remain significant in LR, suggesting that in this population, weight changes are primarily driven by other factors.

### Table 1: Change in Body Composition and Biomarkers by STAY/SWAD Group

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Variable</th>
<th>STAY (n=145)</th>
<th>SWAD (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg/m²)</td>
<td>Baseline</td>
<td>20.5 (1.4)</td>
<td>25.8 (1.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight (kg/m²)</td>
<td>Change vs Baseline</td>
<td>0.4 (0.3)</td>
<td>1.9 (0.9)</td>
<td>0.015</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>Baseline</td>
<td>22.4 (1.9)</td>
<td>30.0 (1.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Change vs Baseline</td>
<td>0.4 (0.3)</td>
<td>2.3 (0.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 2: Association of Weight Gain with Changes in Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Change in BMI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>0.13</td>
<td>0.001</td>
</tr>
<tr>
<td>TNF-RII</td>
<td>0.10</td>
<td>0.001</td>
</tr>
<tr>
<td>IP-10</td>
<td>0.15</td>
<td>0.001</td>
</tr>
<tr>
<td>sCD163</td>
<td>0.12</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 3: Impact of Weight Gain on Immune Activation Following Initiation of ART

- **Methods:** A purposeful sampling design selected participants who achieved virologic suppression on ART and either maintained weight within +/- 0.5 kg/m² ("maintainers") or gained 2.6-6.4 kg/m² ("gainers") from baseline to 96 weeks. We measured IL-6, sTNF-RI, and IP-10, both before and at 96 weeks. The association between weight gain and changes in biomarkers was assessed using linear regression models adjusted for age, race/ethnicity, ART regimen, and HIV-1 RNA.

### Results:

- **Compared to men who maintained weight, women who gained weight had smaller declines in biomarkers compared to men who maintained weight.**
- **Women who gained weight had smaller declines in biomarkers compared to men who gained weight.**

### Conclusion:

Higher pre-treatment immune activation markers are significantly associated with weight gain following ART initiation even after controlling for pre-ART CD4 counts. Weight gain attenuates the decline in several immune activation markers following ART initiation even after controlling for pre-ART BMI. Further research is urgently needed on prevention and management of metabolic effects with INSTI use.

### Table 1: Change in Body Composition and Biomarkers by STAY/SWAD Group

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Variable</th>
<th>STAY (n=145)</th>
<th>SWAD (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg/m²)</td>
<td>Baseline</td>
<td>20.5 (1.4)</td>
<td>25.8 (1.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight (kg/m²)</td>
<td>Change vs Baseline</td>
<td>0.4 (0.3)</td>
<td>1.9 (0.9)</td>
<td>0.015</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Baseline</td>
<td>22.4 (1.9)</td>
<td>30.0 (1.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Change vs Baseline</td>
<td>0.4 (0.3)</td>
<td>2.3 (0.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 2: Association of Weight Gain with Changes in Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Change in BMI</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>IL-6</td>
<td>0.13</td>
<td>0.001</td>
</tr>
<tr>
<td>TNF-RII</td>
<td>0.10</td>
<td>0.001</td>
</tr>
<tr>
<td>IP-10</td>
<td>0.15</td>
<td>0.001</td>
</tr>
<tr>
<td>sCD163</td>
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</tbody>
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### Results:

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Higher pre-treatment immune activation markers are significantly associated with weight gain following ART initiation even after controlling for pre-ART CD4 counts. Weight gain attenuates the decline in several immune activation markers following ART initiation even after controlling for pre-ART BMI. Further research is urgently needed on prevention and management of metabolic effects with INSTI use.
674 WEIGHT GAIN AMONG VIRALLY SUPPRESSED PERSONS WHO SWITCH TO INSTI-BASED ART

Frank J. Palella1, Nabil Rayeed2, Jun Li3, Beverley Adams-Huet2, Jordan E. Lake3, Barbara S. Knudsen1, Ninna Drivsholm1, Anne-Mette Lebech1, Birgitte Lindegaard 1, Jørgen T. Kuhl1, Per E. Sigvardsen1, Lars Køber1, Børge Nordestgaard 3, Klaus F. Kofoed1, Roger Bedimo1, Xilong Li2, Beverley Adams-Huet2, Jordan E. Lake3, Barbara S. Knudsen1, Ninna Drivsholm1, Anne-Mette Lebech1, Birgitte Lindegaard 1, Jørgen T. Kuhl1, Per E. Sigvardsen1, Lars Køber1, Børge Nordestgaard 3, Klaus F. Kofoed1, Susanne D. Nielsen1

1Northwestern University, Chicago, IL, USA, 2Cerner Corp, Kansas City, MO, USA, 3Centers for Disease Control and Prevention, Atlanta, GA, USA, 4Dupont Circle Physicians Group, Washington, DC, USA, 5Stony Brook University, Stony Brook, NY, USA, 6Temple University, Philadelphia, PA, USA, 7University of Illinois at Chicago, Chicago, IL, USA

Background: INSTI-associated weight gain has been described among ARNAI-like persons initiating INSTI-containing ART, but not among virally suppressed (VS) persons whose first INSTI exposure is via a switch regimen. We evaluated changes in weight (CW) among such persons in the HIV Outpatient Study (HOPS).

Methods: We analyzed medical record data of patients from nine United States HIV clinics who were INSTI-naive and VS for >1 year on non-INSTI-based ART, and switched to INSTI-based ART and remained VS. Participants received INSTI-based ART for >6 months, had >2 weights recorded in the year prior to switch and >1 after. We evaluated CW over time, overall and stratified by demographics, pre-switch body mass index (BMI) and ART use, CD4 at ART start, and INSTI received. We used multivariable random regression mixed model to estimate factors associated with CW.

Results: Among 437 patients (median age 51 years, interquartile range 44.5, 57.5), 86 (19.6%) were women, 107 (24.5%) were non-Hispanic Black (NHB). Pre-INSTI regimens often included an NNRTI (193 [44.1%]) or PI (185 [42.0%]) with >1 NRTI (402 [91.5%]). INSTI regimens included raltegravir (236 [54.0%]), elvitegravir (89 [20.4%]), or dolutegravir (112 [25.6%]). Mean CW in the year prior to INSTI was -0.2 kg (95% confidence interval [CI] -0.6, 0.2). Mean duration of INSTI use was 2.9 years (max=9.7 years). Mean CW on INSTI was 1.2 kg (CI 0.6, 1.9), did not differ by INSTI drug used (p>0.2) and was greater for persons with pre-INSTI BMI <25 (2.2 kg, CI 1.5, 3.0) than 25-29.9 (0.5 kg, CI 0.3, 1.6), or >30 (0.4 kg, CI -1.7, 2.6), p=0.03; NHB than Non-Hispanic whites, 2.7 kg (CI 0.3, 4.1) vs 1.0 kg (CI 0.2, 1.7), p=0.02; and persons whose pre-INSTI ART did not include an NRTI vs those whose did, 4.5 kg (CI 1.8, 7.3) vs. 0.9 kg (CI 0.3, 1.6), p<0.01. Duration of INSTI use was not associated with CW: mean 1.0 kg (CI 0.5, 1.4) for 6–<12 months (mos), 1.2 kg (CI 0.5, 2.9) for 12–<24 mos, 1.3 kg (CI 0.7, 1.9) for 24–<60 mos, 1.2 kg (CI 0.5, 2.0) for ≥60 mos, p=0.7. In multivariable models NHB race, and no pre-INSTI NRTI use remained associated with greater percent change in weight (p<0.05) while lower pre-INSTI BMI was borderline significant, p=0.08.

Conclusion: We observed weight gain among VS persons who switched to INSTI-based ART that was associated with NHB race, no pre-INSTI NRTI use, and lower pre-INSTI BMI. These findings of differential risk for INSTI-related weight gain require further evaluation.

675 DIFFERENTIAL BMI CHANGES FOLLOWING PI- AND INSTI-BASED ART INITIATION BY SEX AND RACE

Roger Bedimo1, Xilong Li2, Beverley Adams-Huet2, Jordan E. Lake3, Barbara S. Taylor4, Deborah Kim5, Pablo Tebas6, Amneris Luque7

1Northwest Hospital, Dallas, TX, USA, 2University of Texas Southwestern, Dallas, TX, USA, 3University of Texas at Houston, Houston, TX, USA, 4University of Texas at San Antonio, San Antonio, TX, USA, 5University of Pennsylvania, Philadelphia, PA, USA

Background: While older protease inhibitors (PI) were more frequently associated with central fat accumulation, initiation of currently used ART regimens has been associated with increases in body mass index (BMI), particularly in women and with integrase strand transfer inhibitors (INSTI). The goal of this study was to analyze the differential effect of individual PIs and INSTIs on changes in BMI by sex and race in a large urban HIV clinic.

Methods: All patients initiating ART at the Parkland Health and Hospital System in Dallas, TX from 2009 to 2017 were included in the analysis. Exposure to ART was defined as concurrent receipt of at least two nucleoside reverse transcriptase inhibitors (NRTI) and at least one PI. Nonsigmoid reverse transcriptase inhibitor (NNRTI) or INSTI. In regression analysis, we compared yearly change in BMI (kg/m2) between men and women and between Blacks, Hispanics and Non-Hispanic Whites following initiation of PIs (Atazanavir [ATV], Darunavir [DRV] or Lopinavir [LPV]) or INSTI (Raltegravir [RAL], Elvitegravir [EVG] or Dolutegravir [DTG]). We controlled for year of HAART initiation, baseline CD4 count and HIV-1 RNA, and whether patients achieved virologic suppression on HAART.

Results: We included 4,048 patients, 69% male, 53% Black, 28% Hispanic, and 16% non-Hispanic Whites. Mean age was 46.3 years (SD 11.9). Mean baseline BMI was 27.0 kg/m2 (6.4). Median follow-up time on HAART was 6.7 years (IQR 2.8 – 11.2). Cumulative exposure to NNRTI, PI, and INSTI-based HAART were 3546, 6184, and 3090 person-years, respectively. The BMI slope per year on NNRTI, PI and INSTI were 0.22, 0.24 and 0.32, respectively. BMI slopes for individual PI- and INSTI-based regimens by sex, race and ethnicity are presented in Table 1. There was no significant interaction between sex and race/ethnicity on BMI gains. Proportion of overweight/obese (BMI ≥ 25) increased from 51% at HAART initiation to 65% at year 3 (p<0.001).

Conclusion: We observed a differential effect of individual INSTI and PI-based HAART regimens on BMI changes by sex. All PIs were associated with greater BMI gain in women than in men, but with no difference by race/ethnicity. LPV-based ART was associated with relatively smaller BMI gains. Among INSTIs, while EVG appeared to be associated with greater BMI overall, the effect did not vary or by sex or race/ethnicity. DTG and RAL are associated with greater BMI gains in women, and DTG with greater gains in Blacks & Hispanics.

Table 1: BMI Slopes by Year on HAART

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>By Race/Ethnicity</th>
<th>By Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male vs. Female</td>
<td>Black vs. White</td>
<td>White vs. Black</td>
</tr>
<tr>
<td>HAART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0.22</td>
<td>0.20</td>
<td>0.25</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.24</td>
<td>0.24</td>
<td>0.22</td>
</tr>
<tr>
<td>Year 3</td>
<td>0.32</td>
<td>0.31</td>
<td>0.34</td>
</tr>
</tbody>
</table>

676 LONG-LASTING ALTERATIONS IN FAT DISTRIBUTION IN PLWH EXPOSED TO THYMIDINE ANALOGUES

Marco Gelpi1, Shaobi Afzal2, Andreas Fuchs1, Jens D. Lundgren1, Andreas D. Knudsen1, Nina Drivsholm1, Anne-Mette Lebech1, Birgitte Lindegaard, Jørgen T. Kuhl1, Per E. Sigvardsen1, Lars Kaber1, Børge Nordestgaard1, Klaus F. Kofod1, Susanne D. Nielsen1

1Rigshospitalet, Copenhagen, Denmark, 2Herlev and Gentofte Hospital, Copenhagen, Denmark, 3University of Copenhagen, Copenhagen, Denmark

Background: Thymidine analogues (TA) and didanosine (ddI) have been associated with redistribution of body fat from subcutaneous (SAT) to visceral (VAT) adipose tissue, which, in turn, is a risk factor for cardiovascular disease (CVD). We explored differences in adipose tissue distribution between people living with HIV (PLWH) with/without prior exposure to TA and/or ddI and their uninfected controls. PLWH were stratified according to prior exposure to TA and/or ddI and uninfected controls and the association with CVD risk factors.

Methods: 761 PLWH from the COCOMO study aged > 40 and 2,283 age- and sex-matched uninfected controls from the GCPS study were included. PLWH were stratified according to prior exposure to TA and/or ddI and uninfected controls were defined by independent CT-scan. Hypotheses were tested by linear and logistic regression analyses adjusted for age, sex, origin, smoking, physical activity, and BMI.
Results: Age and sex distribution were similar in PLWH and uninfected controls (54.2 vs. 54.4 years and 85.5% vs 85.5% male). 451 (60.5%) PLWH had exposure to TA and/or ddI. Of those, 6 (1.4%) were still exposed. Mean cumulative exposure was 6.6 (SD, 4.2) years and time since discontinuation was 9.4 (SD, 2.7) years. After adjustment, prior exposure to TA and/or ddI was associated with 21.6 cm$^2$ larger VAT (13.8 – 29.3) compared to HIV infection without exposure and HIV-positive status was associated with similar VAT compared to HIV infection without exposure (Table 1). After adjustment, HIV infection with exposure to TA and/or ddI was associated with 14.8 cm$^2$ smaller SAT compared to HIV infection without (-23.3 – 6.3) (Table 1). HIV-negative status was associated with 13.0 cm$^2$ larger SAT compared to HIV infection without exposure (5.8 – 20.3) (Table 1). Cumulative exposure to TA and/or ddI (3.7 cm$^2$ per year [2.3 – 5.1]), but not time since discontinuation (-1.1 cm$^2$ per year [-3.4 – -1.1]), was associated with VAT. In PLWH, after adjusting for confounders prior exposure to TA and/or ddI was associated with excess risk of hypertension (aOR 1.62 [1.13 - 2.31]), hypercholesterolemia (aOR 1.49 [1.06 - 2.11]), and low HDL (aOR 1.40 [0.99 – 1.99]).

Conclusion: Prior exposure to TA and/or ddI was associated with long-lasting alterations in abdominal fat distribution, persisting after TA and/or ddI discontinuation, which may be involved in the excess risk of hypertension, hypercholesterolemia, and low HDL found in PLWH with prior exposure to TA and/or ddI. Our findings may help to identify a subgroup of PLWH who may benefit from more intensive monitoring and cardiovascular prevention interventions.

### Table 1: Linear Regression Model predicting the degree of change in BMI in cm$^2$ of VAT and SAT according to the measures in TA and/or ddI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted $\beta$ (95% CI)</th>
<th>Adjusted $\beta$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAT</td>
<td>21.6 (13.8 – 29.3)</td>
<td>14.8 (-23.3 – 6.3)</td>
</tr>
<tr>
<td>SAT</td>
<td>-13.0 (5.8 – 20.3)</td>
<td>-23.3 (-3.4 – -1.1)</td>
</tr>
</tbody>
</table>

**Note:** Estimates are for every 1 year change in the independent variable.

**Abbreviations:** VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; aOR, adjusted odds ratio; CI, confidence interval.
Dolutegravir and Insulin Resistance

Janet Lo1, James Oyee2, Melissa Crawford3, Richard Grove4, Ralph DeMasi5, Lloyd Curtis1, Anna Fettipace1, Vani Vannappagari1, Narsüm Payyavula2, Michael Aboud4, Jean van Wyk1

1Massachusetts General Hospital, Boston, MA, USA, 2GlaxoSmithKline, Uxbridge, UK, 3VIV Healthcare, Research Triangle Park, NC, USA, 4VIV Healthcare, Brentford, UK

Background: HIV infection has been independently associated with insulin resistance (IR), potentially through chronic immune activation/inflammation, however this effect is not necessarily mitigated through successful antiretroviral therapy (ART). ART has been associated with IR through varying mechanisms, however, in the context of combination ART, increased obesity, and an aging HIV-infected population, these potential associations are difficult to interpret. We investigated potential risk factors associated with HOMA-IR (homeostasis model of assessment – insulin resistance) and the potential effect of dolutegravir (DTG) on IR over time.

Methods: Data from 4 DTG clinical trials (SPRING-1, STRIVING, SWORD-1 and -2) with fasting insulin and glucose measurements available, were included; subjects with diabetes were excluded. IR was determined by HOMA mathematical model and defined as a HOMA-IR value ≥ 2; additional cut-offs of 3 and 4 were also explored. Analysis of relationship between baseline (BL) risk factors and HOMA-IR was completed. Change in HOMA-IR over time and relative to controls were assessed with logistic regression and ANCOVA models, respectively.

Results: HOMA-IR data was available at BL, week 24 and week 48 for 824, 304 and 543 DTG-exposed subjects and 713, 219 and 460 control subjects, respectively. At BL, subjects were mostly male (81%), white (76%) and had a median age of 43 yrs; 50% were overweight/obese; 70% had a HOMA-IR > 2. Results are shown in the table. There were similar modest increases in HOMA-IR between DTG and control groups over time (24 and 48 weeks). Overall, there was no difference in the odds of HOMA-IR > 2 between treatment groups at 48 weeks. An association between BL HOMA-IR and increasing age, geographic region, increased BMI/weight, the presence of metabolic or cardiac disorders, lipids, and elevated liver function tests (ALT, ALP and albumin) was observed. Risk factors for IR (HOMA-IR > 2) at week 48 were BL HOMA-IR, Sex, BMI, AIDS CDC category, smoking history, and elevated ALT.

Conclusion: There was no association between treatment and insulin resistance observed in this analysis over a 48 week period, however IR modestly increased over time in all groups. In general, risk factors identified as being associated with IR at Week 48 were consistent with known risk factors for diabetes/IR. These results should be interpreted with caution as the studies were not primarily designed to assess effects of DTG exposure on insulin resistance.

Lower Cardiovascular Disease Risk Associated with Integrase Inhibitors

Jane A. O’Halloran, John Sahrmann, Anne M. Butler, Margaret A. Olsen, William Powderly

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

Background: Several antiretroviral therapy (ART) classes have been associated with increased myocardial infarction (MI) risk. No studies have examined cardiovascular disease (CVD) in people living with HIV (PLWH) on integrase strand transfer inhibitors (INSTI). We examine the risk of CVD in PLWH on INSTI-based regimens.

Methods: Using Truven Health Analytics MarketScan databases for commercially insured and Medicaid covered adults, we identified PLWH newly initiated on ART between Jan 1, 2008 and Dec 30, 2015. New users were those without ART claims in the 6 months prior to study inclusion. The primary outcome, major adverse cardiac event (MACE), was a composite of acute MI, ischemic stroke, coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) assessed through Dec 30, 2016. We excluded PLWH with MACE events 6 months prior to the first stable regimen start. We identified cardiac outcomes and covariates associated with risk of cardiac events using ICD-9-CM diagnosis and procedure codes and CPT-4 codes. Calendar-time specific inverse-probability-weighted Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for association between INSTI use and MACE. Propensity score models included potential predictors of CVD and INSTI use. Censoring occurred for the earliest of MACE events during the first 6 months of a stable regimen, 90 days post-ART switch, health plan disenrollment, death and study end.

Results: 39,459 new ART initiators were identified. 5,128 (25%) PLWH initiated INSTI-based regimens (raltegravir 33%, elvitegravir 49%, dolutegravir 18%), 11,191 (55%) initiated non-nucleoside reverse transcriptase inhibitors and 4,145 (20%) protease inhibitors. Median duration of follow-up was 561 (498, 958) days. Mean age was 40.6 years, 79% were male, and 17% were Medicaid insured. Hypertension was present in 9.5% of INSTI users vs 7.4% non-users; lipid lowering treatment in 19.8% vs 17.9%; diabetes in 6% vs 4.8% and smoking in 13.5% vs 10.2%. 161 MACE events occurred; acute MI 11 (0.21%) vs 55 (0.36%), stroke 14 (0.27%) vs 48 (0.31%), CABG 1 (0.02%) vs 6 (0.04%), PCI 5 (0.1%) vs 21 (0.14%) of INSTI users vs. non-users. INSTI-based ART was associated with significantly lower risk of MACE events (HR 0.57; 95% CI 0.45, 0.73) compared to non-INSTI based regimens.

Conclusion: INSTI-based regimens were associated with a 43% decreased risk of CVD in this cohort. Validation of these findings in cohorts with longer follow up is needed.

Changes in Fat Density after ART Initiation

Jordan E. Lake1, Carlee Moser1, Maxine Olefsky1, Kristine M. Erlenrond1, Ann Scherzing1, James H. Stein1, Judith S. Currier1, Todd T. Brown2, Grace A. McComsey3

1University of Texas at Houston, Houston, TX, USA, 2Harvard University, Cambridge, MA, USA, 3University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 4University of Wisconsin—Madison, Madison, WI, USA, 5University of California Los Angeles, Los Angeles, CA, USA, 6Johns Hopkins University School of Medicine, Baltimore, MD, USA, 7Case Western Reserve University, Cleveland, OH, USA

Background: Adipose tissue (AT) disturbances are common in people living with HIV (PLWH), and changes in AT quantity may occur independently of changes in AT quantity. Decreases in AT density, a marker of AT quality, suggest disrupted adipocyte function and lipid accumulation. We previously reported that subcutaneous AT (SAT) density on computed tomography (CT) reflects biopsy-quantified SAT adipocyte size in PLWH, and that AT quantity increases on antiretroviral therapy (ART). In this exploratory analysis, we assessed changes in AT density after ART initiation and associations with immuno-metabolic parameters.

Methods: ACTG A5257 randomized ART-naive, adult PLWH to raltegravir (RAL) or ritonavir-boosted atazanavir (ATV/r) or darunavir (DRV/r), each with tenofovir disoproxil fumarate and emtricitabine for 96 weeks. The subset with HIV-1 RNA <50 copies/mL were included. Linear regression models compared RAL vs. DRV/r and -2) with fasting insulin and glucose measurements available, were included; subjects with diabetes were excluded. IR was determined by HOMA mathematical model and defined as a HOMA-IR value ≥ 2; additional cut-offs of 3 and 4 were also explored. Analysis of relationship between baseline (BL) risk factors and HOMA-IR was completed. Change in HOMA-IR over time and relative to controls were assessed with logistic regression and ANCOVA models, respectively.

Results: There was no difference in the odds of HOMA-IR > 2 between treatment groups at 48 weeks. An association between BL HOMA-IR and increasing age, geographic region, increased BMI/weight, the presence of metabolic or cardiac disorders, lipids, and elevated liver function tests (ALT, ALP and albumin) was observed. Risk factors for IR (HOMA-IR > 2) at week 48 were BL HOMA-IR, Sex, BMI, AIDS CDC category, smoking history, and elevated ALT.

Conclusion: There was no association between treatment and insulin resistance observed in this analysis over a 48 week period, however IR modestly increased over time in all groups. In general, risk factors identified as being associated with IR at Week 48 were consistent with known risk factors for diabetes/IR. These results should be interpreted with caution as the studies were not primarily designed to assess effects of DTG exposure on insulin resistance.

Overall Week 48

<table>
<thead>
<tr>
<th>Analyte</th>
<th>n</th>
<th>LS Means (95% CI)</th>
<th>Geometric LS means ratio (95% CI)</th>
<th>P-value</th>
<th>HOMA-IR &gt; 2 Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>480</td>
<td>1.18 (1.04)</td>
<td>3.60 (1.68)</td>
<td></td>
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<tr>
<td>DTG</td>
<td>543</td>
<td>1.19 (1.02)</td>
<td>3.62 (1.68)</td>
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SWORD Week 24

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<th>n</th>
<th>LS Means (95% CI)</th>
<th>Geometric LS means ratio (95% CI)</th>
<th>P-value</th>
<th>HOMA-IR &gt; 2 Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>35</td>
<td>1.07 (1.00)</td>
<td>26.05</td>
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<tr>
<td>DTG</td>
<td>125</td>
<td>1.02 (1.01)</td>
<td>96.125</td>
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| SWORD Week 48

<table>
<thead>
<tr>
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<th>n</th>
<th>LS Means (95% CI)</th>
<th>Geometric LS means ratio (95% CI)</th>
<th>P-value</th>
<th>HOMA-IR &gt; 2 Odds ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>184</td>
<td>1.12 (1.03)</td>
<td>131.164</td>
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<tr>
<td>DTG</td>
<td>176</td>
<td>1.11 (1.00)</td>
<td>141.079</td>
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| SWORD Week 48

<table>
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<tr>
<th>Analyte</th>
<th>n</th>
<th>LS Means (95% CI)</th>
<th>Geometric LS means ratio (95% CI)</th>
<th>P-value</th>
<th>HOMA-IR &gt; 2 Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>432</td>
<td>1.12 (1.00)</td>
<td>3.31 (1.00)</td>
<td></td>
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</tr>
<tr>
<td>DTG</td>
<td>420</td>
<td>1.12 (1.00)</td>
<td>3.41 (1.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
correlations adjusting for AT area assessed relationships between AT density and immuno-metabolic parameters.

Results: Median age was 36 years, CD4 + T cell count 344 cells/μl and BMI 24.5 kg/m2; 89% were male and 56% non-white. W0 median SAT and VAT density were -99 and -80 HU, respectively. Over 96 weeks, SAT and VAT HU decreased in all arms (Table). In adjusted models, female sex and higher W0 HIV-1 RNA were independently associated with greater declines in AT density (women: SAT -4.8 and VAT -4.0 HU greater than men per log10 HIV-1 RNA copies/mL.SAT -2.3 and VAT -2.7 HU). Statistically different effects of ART type were not seen (p<0.13) though variability was high. W96 SAT and VAT HU correlated (p<0.05) positively with HDL cholesterol and adiponectin levels (r=0.19 to 0.30) and negatively with IL-6, non-HDL cholesterol, triglyceride, leptin and HOMA-IR (r=-0.23 to -0.68) even after adjusting for baseline CD4 + T cell count, HIV-1 RNA and AT area.

Conclusion: VAT and SAT density decreased following ART initiation. Women and PLWH with higher HIV-1 RNA had greater decreases. Following virologic suppression, lower AT density was associated with greater systemic inflammation, lipid parameter disruption and insulin resistance independent of AT area. These findings suggest that changes in fat tissue during ART may have adverse health consequences.

Table. Median (interquartile range) absolute 96-week changes in VAT and SAT density.

<table>
<thead>
<tr>
<th>Change in VAT density (HU)</th>
<th>All (n=28)</th>
<th>Men (n=23)</th>
<th>Women (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median change</td>
<td>-9.3 (2.2)</td>
<td>-9.5 (2.2)</td>
<td>-2.0 (1.4)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>VAT</td>
<td>-4.0 (4.2)</td>
<td>-4.7 (4.2)</td>
<td>-1.0 (2.4)</td>
</tr>
<tr>
<td>Median change</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

682 DUAL-ENERGY X-RAY ABSORPTIONIMETRY (DXA) POORLY APPROXIMATES VISCERAL FAT IN HIV

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Background: People living with HIV (PLWH) are prone to visceral fat accumulation, which predisposes to comorbidities including dyslipidemia and coronary artery disease. Given the importance of visceral fat to cardiometabolic health in HIV, techniques to allow for its safe and affordable measurement are critically needed. Dual-energy x-ray absorptiometry (DXA) is an inexpensive modality that uses minimal radiation to quantify body composition. Recently, advanced software has allowed visceral fat to be ascertained from standard DXA, although this has never before been validated in HIV. Here, we investigated the accuracy of DXA in the measurement of visceral fat in comparison to computed tomography (CT) as the gold standard.

Methods: We pooled data from 5 prior studies of PLWH and uninfected controls in which paired DXA and CT scans were available. For this purpose, DXA (Hologic) was re-analyzed to quantify visceral fat using APEX 6.6.0.5 software. In a cross-sectional analysis, L4-L5 visceral fat cross-sectional area (VAT) as measured by DXA and CT were compared in PLWH (n=313) and controls (n=144). In longitudinal analyses, the accuracy of DXA with respect to changes in VAT over time was assessed (1) among PLWH (n=106) and controls (n=80) on no intervention for 12 months, and (2) among PLWH on tesamorelin (n=23) – an FDA-approved medication known to reduce VAT in HIV – or placebo (n=20) for 6 months. Bland-Altman plots were used to compare DXA with CT.

Results: In HIV, DXA-VAT and CT-VAT were strongly correlated (r=0.91, P<0.0001). However, the measurement bias (DXA – CT) became progressively more negative with greater VAT (P<0.0001). In this regard, whereas the bias was -9.3±2 cm2 overall, it was -61±8 cm2 among those with VAT≥200 cm2. Sex modified the inverse relationship between VAT and measurement bias (P=0.001) such that it was particularly pronounced in men rather than women. Longitudinally, in the natural history analysis, DXA underestimated changes in VAT, irrespective of sex, with the largest bias at the extremes of VAT gain or loss (P<0.0001). DXA similarly underestimated changes in VAT among PLWH treated with either tesamorelin or placebo (P=0.004). Analogous cross-sectional and longitudinal findings were seen among uninfected controls.

Conclusion: DXA underestimated VAT compared to CT in HIV-infected men with visceral fat accumulation. DXA also underestimated changes in VAT over time in both men and women with HIV. DXA-VAT should be used with caution in HIV and non-HIV alike.

683 UNIQUE MIRNA SIGNATURE IN HIV LIPODYSTROPHY WITH REDUCED ADIPOSE Dicer EXPRESSION

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Background: Suppression of Dicer, an endoribonuclease that regulates microRNAs (miRNA), has evolved as a viral mechanism to enhance host HIV infectivity and may have unintended metabolic consequences. Animal knockout models of adipose-specific dicer (ADicer) acquire lipodystrophy accompanied by severe metabolic abnormalities. Data show adipose is a source of exosomal miRNAs, which function as adipokines influencing metabolic homeostasis. We hypothesized a unique miRNA profile among individuals well-phenotyped for HIV lipodystrophy and reduced ADicer expression.

Methods: We evaluated >1000 miRNAs from exosomes derived from sera among the 27 male individuals (9 HIV lipodystrophy (HIV/lipo), 9 HIV without lipodystrophy (HIV/non-lipo), 9 non-HIV) whom we previously showed variations in ADicer: most suppressed among HIV lipo, followed by HIV non-lipo and non-HIV (2.49[0.02,4.88] vs. 11.20[4.83,21.45] vs. 17.69[10.72,47.91], P<0.002). To estimate miRNA abundance, data was normalized to the average expression of all measured miRNAs. Student’s T-test for 2 group comparisons and a false discovery rate analysis (FDR) was applied. Using target prediction databases (TargetScan, miRDB, Diana), we identified genes related to fat biology and lipid metabolism via a conservative approach (presence in all 3 databases + target score of >85%) with clinical relevance to lipodystrophic phenotypes.

Results: HIV/lipo individuals (mean age 56.3±4 years, BMI 30±1 kg/m2, duration HIV 24±2 years, duration ART 20±2 years, CD4 + count 482±90 cells/μl, undetectable VL 67%) were similar to HIV/non-lipo (age 52±3 years, BMI 30±1 kg/m2) and non-HIV (age 55.3±3 years, BMI 30±1 kg/m2) individuals. Reduced ADicer expression was significantly related to reduced CD4 + count (r=0.55, P=0.02), duration ART use (r=0.70, P<0.001) and duration PI use (r=0.71, P=0.03) and tended to be related to duration HIV (r=0.44, P=0.07) and reduced CD8 + count (r=0.42, P=0.08). Accounting for the FDR, we detected miRNA-20a-3p (P=0.0026), 324-5p (P=0.0059), and 186-5p (P=0.0977) were expressed differentially in HIV/lipo vs. non-HIV and 324-5p (P=0.0348) in HIV/lipo vs. HIV non-lipo. Relevant target genes per individual miRNA include: 20a-3p (EBF1, EHM1, EZH2, NF1, PCNA, RA48A, SPRY1, TDG), 324-5p (VDAC1), and 186-5p (MYTL1, NEGR1, NAF5, PDE10A, PID1).

Conclusion: These novel data enhance our understanding by which altered ADicer expression and specific exosomal miRNAs may affect gene expression of regulators important to fat biology and metabolic homeostasis in HIV.
Increased insulin resistance in PLWH is associated with increased CD69 on SAT CD4 T cells, potentially reflecting a link between accumulation of adipose resident CD4 cells and metabolic disease.

**ADIPOSE TISSUE CD4+ AND CD8+ T-CELL PROFILES DIFFER BY GLUCOSE TOLERANCE IN HIV**


**Background:** T lymphocytes play a central role in modulating adipose tissue inflammation and, by extension, adipocyte function. We hypothesized that greater adipose tissue T-cell activation in persons living with HIV (PLWH) may contribute to higher rates of diabetes.

**Methods:** We compared CD4 and CD8 T-cell subsets in the subcutaneous adipose tissue (SAT) and blood of 9 non-diabetic (fasting blood glucose [FBG]<100mg/dL), 8 pre-diabetic (FBG=100-125 mg/dL) and 9 diabetic (FBG≥126mg/dL) PLWH, in addition to 8 pre-diabetic, HIV-negative (HIV−) controls. SAT was collected by liposuction and T cells extracted by collagenase digestion. The proportion of naïve (TN) CD45RO-CCR7+, effector memory (TEM) CD45RO+CCR7−, central memory (TCM) CD45RO+CCR7−, and effector memory revertant RA+ (TEMRA) CD45RO-CCR7− CD4 and CD8 T cells were measured by flow cytometry. T cell subsets were compared by Wilcoxon signed-rank (paired blood and adipose), Mann-Whitney (between groups), and linear regression tests according to glucose tolerance.

**Results:** Age, race and sex were similar across groups. Compared to HIV− controls, SAT from PLWH with similar glucose tolerance had significantly higher CD4 TEM (45 vs. 15%, p<0.0001) and TEMRA (8 vs. 2%, p<0.0001), depleted in TN (16 vs. 29%, p<0.001) and TCM (15 vs. 26%, p<0.001). These findings were similar for CD8 T cell subsets. While the relative proportions of SAT CD4 and CD8 TCM, TEM, and TEMRA cells were similar regardless of glucose tolerance status in PLWH, expression of CD69 - a marker of activation and tissue resident cells - on CD4 T cells rose with progressive insulin resistance (see Table, p=0.004), which was robust to adjustment for BMI (p=0.03). Among CD4 T cell subsets, progression from non-diabetic to diabetic groups was accompanied by increased CD69 on TCM, TEM, and TEMRA cells.

**Conclusion:** This study is the first to characterize SAT CD4 and CD8 memory T cell subsets in PLWH. SAT from PLWH is enriched for TEM and TEMRA CD4 and CD8 compared to blood, which could contribute to tissue inflammation.
Methods: Our study uses data from the Comparative Outcomes and Service Utilization Trends (COAST) study, a population-based retrospective cohort study examining health outcomes and service use of PLWHIV and a 10% sample of HIV-negative individuals in BC. Wrist, humerus, vertebrae and hip fractures were considered as ORF and were assessed using physician and hospital-based administrative data and ICD-9/10. The effect of the variables on the risk of ORF was assessed by logistic generalized estimating equation model. Sex, age at ART initiation, previous injuries, history of injection drug use (IDU), ART initiation era and viral suppression were covariates. The effect of ART drug classes was analyzed in a univariate model including data after ART initiation. TDF was studied separately and considered only data after TDF was available in BC.

Results: A total of 6,846 PLWHIV and 514,619 HIV negative individuals were included in the incidence analysis. ORF occurred in 416 PLWHIV and 28,028 HIV-negative individuals (6.08% versus 5.45% p=0.02). Among PLWHIV, 63% of the first ORF occurred before the age of 50 years of age, while only 34% occurred before age 50 in the HIV negative group (p<0.0001). In a multivariate analysis, female sex, older age at ART initiation, IDU and previous injuries were associated with increased risk of ORF; while later ART initiation era and higher proportion of viral suppression were associated with reduced likelihood of ORF. ART drug classes and TDF were negatively associated with having an ORF. (Table I).

Conclusion: Higher incidence of ORF was found in PLWHIV versus HIV negative individuals at an earlier age. In our population, viral suppression and length of time on ART were associated with reduced risk of ORF, including ART regimes containing TDF, which in previous studies have been shown to be associated with bone toxicity. Our study indicates that early initiation of ART may reduce the risk for ORF in PLWHIV.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate Model</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>1.00</td>
<td>1.11 – 1.98</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>0.96</td>
<td>0.92 – 1.00</td>
</tr>
<tr>
<td>Age at ART initiation (10 years)</td>
<td></td>
<td>0.89</td>
<td>0.85 – 0.94</td>
</tr>
<tr>
<td>Any injuries aside from ORF</td>
<td></td>
<td>0.89</td>
<td>0.85 – 0.94</td>
</tr>
<tr>
<td>ART initiation era</td>
<td></td>
<td>0.89</td>
<td>0.85 – 0.94</td>
</tr>
<tr>
<td>Proportion of Vt &lt;500 copies/mL until ORF (10%)</td>
<td></td>
<td>0.89</td>
<td>0.85 – 0.94</td>
</tr>
</tbody>
</table>

Table 1

Note: Only fractures occurring among PLWHIV after ART initiation were included. For TDF, only people who initiated ART after 01 December 2009 were considered.

IDU: Intravenous Drug Use

ART: Antiretroviral Therapy

ORF: Osteoporosis-related fracture

TDF: tenofovir disoproxil fumarate

BHART: Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

PI: Protease Inhibitors

*Injuries include motor vehicle collision, fatal transportation injuries, iatrogenic and assault

568 HIV-ASSOCIATED HYPOPARATHYROIDISM: RESULTS FROM A GERMAN HIV COHORT

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1WKZ Karlplatz HIV Research and Clinical Care Center, Munich, Germany, 2UMC Research, Munich, Germany

Background: Parathyroid hormone (PTH) secretion in response to hypocalcemia was reported to be blunted in individual people living with HIV (PLWH). HIV-infection has therefore been acknowledged to be an infrequent cause of hypoparathyroidism (hypoPT). Population data are, however, missing. We evaluated the prevalence and characteristics of hypoPT in PLWH in a single-center cohort in Munich.

Methods: Single-center substudy of the German multi-center ArchIV Cohort Study. PLWH with available measurements of PTH and calcium levels in two consecutive years (2016 and 2017) for diagnosis of hypoPT were included in

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the study. HypoPT was defined as confirmed PTH <65 pg/mL and albumin-corrected calcium <2.12 mmol/L.

Results: In total, 496 PLWH were included; median age was 47 (IQR, interquartile range: 40-54 years), 393 (79.2%) were male. TDF was used by 51.8% and 39.9% of PLWH in 2016 and 2017, respectively. Laboratory criteria for hypoPT was met in 15.3% of PLWH (76/496) in 2016 and in 8.3% (41/496) in 2017. 14/496 PLWH (2.8% [95% CI: 1.6-4.7]) presented with confirmed hypoPT. Characteristics of PLWH with and without confirmed hypoPT are shown in Table 1. Univariate associations between potential confounders and hypoPT were as follows in crude analysis: male sex (OR 1.0 [95% CI: 0.3-3.5]; P = 0.95), age ≥55 years (OR 0.3 [95% CI: 0.0-1.9]; P = 0.19), average creatinin ≥2.0 mg/dl (OR 0.4 [95% CI: 0.1-1.8]; P = 0.22), being vitamin D deficient in both years (OR 0.2 [95% CI: 0.0-1.8]; P = 0.16), and use of tenofovir disoproxil fumarate (TDF) in both years (OR 4.3 [95% CI: 1.3-14.1]; P = 0.01). TDF remained significantly associated with hypoPT after adjusting for sex, age (≥55 years), and vitamin D deficiency (OR 4.2 [95% CI: 1.3-13.9]; P = 0.02).

Conclusion: Prevalence of hypoPT was unexpectedly high in our cohort of PLWH with 2.8% compared to 0.01-0.04% as reported in general populations. TDF containing therapy was the only factor significantly associated with hypoPT. This is consistent with a much higher prevalence of hypoPT in 2016, before the more widespread use of tenofovir alafenamide starting end of 2016 (proportion of PLWH on TAF were 18.6% and 30.0% (P<0.001) in 2016 and 2017, respectively). Although our results on hypoPT seem to be in contrast to previous findings of high PTH levels in PLWH on TDF, a possible link might be hypocalcemia resulting in secondary hyperparathyroidism in some, and hypoPT in other PLWH, that have HIV-associated impaired PTH-secretion.

**Table 1: Characteristics of HIV-infected patients with laboratory constellation of HypoPT and HIV-infected controls.**

<table>
<thead>
<tr>
<th>Unit</th>
<th>Patients without HypoPT (N = 482)</th>
<th>Patients with HypoPT (N = 14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age</strong></td>
<td><strong>(IQR)</strong></td>
<td><strong>(IQR)</strong></td>
<td><strong>(IQR)</strong></td>
</tr>
<tr>
<td>Years</td>
<td>45 (40-54)</td>
<td>45 (19-51)</td>
<td>0.321</td>
</tr>
<tr>
<td>Male patients</td>
<td>%</td>
<td></td>
<td>0.951</td>
</tr>
<tr>
<td>N</td>
<td>21 (28)</td>
<td>3 (21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (2)</td>
<td>3 (21)</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>mg/dL</td>
<td>(1.80-6.08)</td>
<td>0.94</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>mg/dL</td>
<td>(0.85-1.05)</td>
<td>0.95</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>mg/L</td>
<td>(95-93)</td>
<td>0.75</td>
</tr>
<tr>
<td>β-crosslaps</td>
<td>mg/mL</td>
<td>(1.29-4.27)</td>
<td>0.39</td>
</tr>
<tr>
<td>Phosphate</td>
<td>mg/dL</td>
<td>(3.3-5.6)</td>
<td>3.2</td>
</tr>
<tr>
<td>Patients with at least one episode of low phosphate</td>
<td>%</td>
<td>(2.1)</td>
<td>(2.1)</td>
</tr>
<tr>
<td>HIV-DNA*</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>0.110</td>
</tr>
<tr>
<td>CD4 cell count (absolut)*</td>
<td>100</td>
<td>100</td>
<td>0.157</td>
</tr>
<tr>
<td>Patients with CD4 cells ≥500 cells/μl</td>
<td>%</td>
<td>(13.3)</td>
<td>(28.6)</td>
</tr>
<tr>
<td>Patients with 25(OH)D ≤ 20 ng/mL in both years</td>
<td>%</td>
<td>(24.9)</td>
<td>(7.1)</td>
</tr>
<tr>
<td>Patients on TDF containing ART in both years</td>
<td>%</td>
<td>(36.5)</td>
<td>(71.4)</td>
</tr>
</tbody>
</table>

689 IMPACT OF RENAL TUBULE FUNCTION ON BONE MINERAL DENSITY IN OLDER PEOPLE WITH HIV

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Background: Whether renal tubule dysfunction (RTD), common in people with HIV (PWH), contributes to low bone mineral density (BMD) remains controversial. We studied the relationship between RTD and BMD in a cross-sectional study (GS-US-104-0423) in a group of older (men >50 years and post-menopausal women) PWH on stable antiretroviral therapy (ART) that had never or never used tenofovir (TDF), or with or without exposure to protease inhibitors (PI) for the past three years.

Methods: We analysed stored urine for albumin:creatinine (ACR) and retinol-binding protein:creatinine (RBPCR) ratio, and fractional excretion of phosphate (FE-PO4) and urate (FE-urate). BMD at the lumbar spine (LS) and femoral neck (FN) was measured by dual x-ray absorptiometry (expressed in g/cm2). ART exposure was stratiﬁed into four groups (no-TDF/no-PI, no-TDF/PI, TDF/no-PI, TDF/PI). We used linear regression models to assess associations between tubular markers and BMD, adjusting for clinical characteristics and ART exposure.

Results: 228 individuals (median [IQR] age 57 [53, 64] years, 47% female, time on ART 10 [6, 16] years, CD4 643 [473, 811] and 98% with VL <200 c/mL contributed to the analyses. The prevalence of osteopenia (T score <-2.5) at LS and FN ranged from 21-30% and 14-28% in the four ART exposure groups, respectively (p=0.24 and p=0.08). In univariable analysis, lower LS-BMD was associated with female sex and lower BMI but not with RBPCR (p=0.673), and lower FN-BMD with older age, female sex, lower BMI and higher RBPCR (p=0.014 [95%CI=0.025, -0.022], p<0.0001); neither BMI at LS or FN was associated with eGFR, ART, FE-PO4, FE-urate or ART exposure group. In multivariable models adjusting for age, gender and BMI, RBPCR was no longer associated with BMD-FN (Table, Model 1). Further adjustment for TDF exposure fully attenuated the relationship between RBPCR and FN BMD (Model 2). Using no TDF/no-PI as the ART reference group, exposure to no-TDF/PI and TDF/no-PI was associated with lower LS BMD, and exposure to TDF/no-PI and TDF/PI with lower FN BMD. Conclusion: In this cohort of older PWH with a high prevalence of osteoporosis, RBPCR was the only marker of RTD associated with BMD, but the association lessened with demographic adjustment and was fully abrogated after adjustment for TDF exposure. Continuous TDF exposure was associated with significantly lower BMD at the femoral neck.

690 GENETIC AND CLINICAL RISK FACTORS FOR CHRONIC KIDNEY DISEASE IN HIV

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Background: In the general population, 53 common single nucleotide polymorphisms (SNPs) have been found to associate with chronic kidney disease (CKD) through genome-wide association studies (GWAS). The relative contribution of genetic background, HIV-related factors, antiretroviral medications, and traditional risk factors to CKD has not been evaluated in the setting of HIV infection.

Methods: We performed genome-wide genotyping in HIV-positive, white Swiss HIV Cohort Study participants with normal baseline estimated glomerular filtration rate (eGFR >90 mL/min/1.73 m2). We applied a 1:1 case-control design with incidence density matching. Since we had more cases than controls, we repeated the matching process 2000 times with random resampling from cases and controls. The averaged odds ratio (OR) of CKD from conditional logistic regression analyses was calculated as the antilog of the mean of the 2000 log-transformed ORs and the 95% confidence interval (CI) was based on the 2.5 and 97.5 percentiles. We present uni- and multivariable analyses of CKD and the effects of genetic background, clinical D:A:D CKD risk score and potentially nephrotoxic antiretrovirals.

Results: We included 754 cases with CKD defined as confirmed eGFR drop to <60 mL/min/1.73 m2 (n=144) or eGFR drop of >25% (n=610), and 323 controls with eGFR drop of <15%. A genome-wide genetic risk score built from CKD-associated SNPs significantly contributed to CKD in uni- and multivariable
analysis (Figure). In the final multivariable model, participants in the 3rd and 4th genetic score quartiles had a Cr-eGFR of 1.62 (95% confidence interval, 1.23–2.15) and 2.01 (1.47–2.81), compared to the 1st quartile (most favorable genetic background). In comparison, persons in the 3rd and 4th quartile of the D:A:D Cr-EGR risk score had Cr-eGFR of 1.47 (1.09–1.98) and 1.88 (1.32–2.57), compared to the most favorable 1st quartile. Cumulative exposure per 5 years to atazanavir/ritonavir, lopinavir/ritonavir, and tenofovir disoproxil fumarate were associated with Cr-eGFR of 2.96 (2.03–4.74), 1.69 (1.27–2.26), and 1.81 (1.43–2.36), respectively.

**Conclusion:** The effect of an unfavorable genetic background on Cr-EGR risk in HIV-positive persons was similar to the effect of the established D:A:D clinical risk score, and similar to 5-year exposure to nephrotoxic antiretrovirals. Genetic testing may provide prognostic CKD information complementary to clinical and antiretroviral risk factors.

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**LYSOSOMAL TOXICITY AS A NOVEL MECHANISM IN TENOFOVIR-ASSOCIATED NEPHROTOXICITY**

Metodi Stankov1, Ruisi Lin1, Ramachandramouli Budid1, Diana Panayotova-Dimitrova1, Reinhold E. Schmidt1, Georg Behrens1

1Medizinische Hochschule Hannover, Hannover, Germany

**Background:** Tenofovir disoproxil fumarate (TDF) treatment can lead to renal impairment. Experimental data suggest that tenofovir (TFV)-mediated mitochondrial toxicity contributes to tubular cell damage. We hypothesized that tenofovir induces lysosomal hyper-activation and destabilization, which compromises renal proximal tubular function and viability.

**Methods:** The aim of the study was to assess the effects of TFV and TDF on autophago-lysosomal homeostasis, autophagic flux, lysosomal mass, lysosomal membrane composition, acidity, cathepsin activity and kidney cell viability in organic anion transporter 1 (OAT1) expressing (OAT1-HEK-293) and parental WT-HEK-293 kidney cells. Analyses were performed using immunostaining, calorimetric measurements, flow cytometry, real-Time PCR and confocal microscopy.

**Results:** TFV incubation of OAT1-HEK-293 cells resulted in increased autophagic flux (99.4 ± 5.8% change to control; P<0.001), lysosomal hyper-activation, increased lysosomal mass (74.2 ± 7.0% change to control; P<0.001) and acidity (31.5 ± 1.3% change to control; P<0.001) and higher activity of the lysosomal cell death executors cathepsin B and L (75.7 ± 5.2% and 76.2 ± 3.6% change to control; P<0.001). These changes were associated with decreased membrane stability, decreased relative abundance of lysosomal stabilizing proteins LAMP1 and 2 (33.2 ± 2.7% and -45.7 ± 2.2% change to control P<0.05, P<0.001), loss of lysosomal integrity (Control 20.6 ± 1.2% vs TFV 43.2 ± 2.2%, P<0.001) and compromised cell viability and were related to intracellular TFV amount. Importantly, inhibition of lysosomal activity using ammonium chloride (NH4Cl) or chloroquine (CQ) counteracted cell toxicity and rescued cell viability (Cell death without NH4Cl/CQ 180.2 ± 23.2% change to control vs plus NH4Cl -16.5 ± 6.9% or plus CQ -55.4 ± 3.7%, P<0.001).

**Conclusion:** Intracellular accumulation of TFV induces lysosomal toxicity as demonstrated by organelle hyper-activation and membrane destabilization ultimately leading to compromised kidney cell viability. Our results contribute to a better understanding of the long-term side effects of this commonly used antiviral agent.

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**DYNAMICS OF E-FGR WITH ONE OR MORE ANTIRETROVIRALS THAT INHIBIT CR TUBULAR SECRETION**

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**Results:** There were 761 patients (85% men, 91% Caucasian, 99% antiretroviral-experienced, 34% HCV coinfected, 80% on prior DRV/ritonavir, 32% prior AIDS, 84% HIV RNA < 50 copies/mL, 88% ≥200 CD4/mm3) from 21 Spanish HIV Units. Thirty-six (5%) patients were excluded due to the lack of achieving DRV/c. Median age was 50 (IQR 40, 60), 60% white, 83% men, 99% Caucasian, 99% antiretroviral experienced, 34% HCV coinfected, 80% on prior DRV/ritonavir, 32% prior AIDS, 84% HIV RNA < 50 copies/mL, 88% ≥200 CD4/mm3). The mean baseline (SD) Cr-eGFR was 101.1 ± 26.1 mL/min. The relationship between Cr-eGFR change over time and the use of DRV/c alone or in combination with DTG and/or RPV adjusted by different factors that might influence Cr-eGFR such as HIV patient’s characteristics, socio-demographics, HIV severity, use of TDF, and concomitant medication other than ART was explored. Ethics approval was obtained and patients signed informed consent.

**Conclusion:** The concomitant use of Darunavir/cobicistat plus other known inhibitors of tubular creatinine secretion (dolutegravir, Rilpivirine or both) produced an additive effect in the expected Cr-eGFR decrease.
EVOLUTION AND REVERSIBILITY OF RENAL FUNCTION AFTER SWITCH FROM TDF TO TAF REGIMENS

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Background: Tenofovir alafenamide (TAF) benefits over Tenofovir disoproxil fumarate (TDF) on renal function has been consistently demonstrated mainly as change of renal filtrate in randomized clinical trials. However, a recent meta-analysis has shown a significant advantage of TAF (in term of discontinuations for renal events) only if combined with a boosted third drug. Aim of the study was to evaluate size of improvement and reversibility of renal function in patients (pts) previously exposed to TDF who switched to TAF.

Methods: HIV+ pts from the Icona Foundation Cohort switching from a TDF- to a TAF-containing regimen, maintaining the same third drug were included.

Outcomes: a) difference in estimated glomerular filtration rate (eGFR, by CKD-EPI formula) at 3-6 months (the later measurement); b) proportion of pts with recovery of eGFR to the baseline before TDF introduction (+15%); c) change of eGFR category in CKD (from G2 60-89 ml/min/1.73 m2 to G1≥90). T-test for paired and unpaired samples was used to analyze eGFR change and Poisson regression analysis for predictors for all the two categorical outcomes.

Results: 947 pts were included: 504 in unboosted regimen (75% NNRTI as third drug), 443 in boosted one (21% PI: 8% ERTI, 12% INI) with IV classification, median age 44 (36-52) years, eGFR 93 (81-105) ml/min/1.73 m2 at baseline (BL, time of switch to TAF), eGFR 23 (15-30) ml/min/1.73 m2 at baseline (BL, time of switch to TAF), eGFR 109 (98-118) before TDF introduction, TDF exposure 3-6 months. Mean change in eGFR after 3-6 months (data available for 627 pts) was -0.02 ml/min/1.73 m2 in the overall population (p=0.007), and +1.7 and +0.6 in unboosted and boosted, respectively (p=0.19). An eGFR recovery to pre-TDF values was observed in 302/896 (33.7%) pts; higher eGFR pre-TDF was associated to a lower probability of recovery, while higher CD8 values and being another diagnosed kidney disease that may partially explain the eGFR-decline during TDF initiation. Pts with detectable HIV-RNA, diabetes, history of cardiovascular disease, uncontrolled hypertension, use of ≥1 antihypertensive drug, use of potentially nephrotoxic medication, ABC initiation, TDF discontinuation, few patients recovered >50% of their eGFR. The recovery rate was +1.2 ml/min/1.73 m2 in the overall population (p=0.007), and +1.7 and +0.9 and 2.02 in unboosted and boosted respectively (p>0.1). In 23 of 46 patients with w48 results available and eGFR<60 at TDF discontinuation, a recovery to baseline was observed at median 6.7 mL/min/1.73 m2. Overall, more pts discontinued ABC than TAF (11% vs 2%, p=0.014) and this was mostly driven by discontinuations for drug-related AE (10% vs 2%, p=0.014). HIV-RNA remained suppressed in all but 2 pts.

Conclusion: After switching from TDF to TAF, only a small even statistically significant improvement in eGFR was observed and a complete recovery of renal filtrate or a transition to normal CKD category occurred in less than half of cases over a median of 1 year of observation. Unboosted regimens seem to be associated with a higher probability of regaining renal filtrate. These data may be useful for selecting in which patients to maintain TDF without jeopardizing renal function.
**ALOPECIA AFTER SWITCH TO TENOFOVIR ALAFENAMIDE IN 5 AFRICAN AMERICAN WOMEN**

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**Background:** Adverse drug reactions have been reported with all antiretroviral drugs and have been a major cause for non-compliance with antiretroviral therapy. Alopecia is a rare but known side effect of some antiretroviral therapies (ART), however, no cases of TAF-induced alopecia have been reported in the literature.

**Methods:** This is a case series reported from an academic outpatient HIV practice located in Detroit Michigan comprised of 5 patients identified between 2017 and 2018. Informed oral consent was obtained from patients for the use of photographs.

**Results:** We report 5 cases of alopecia in HIV-infected African American female patients that started after switching TDF to TAF containing regimens. Their age ranged between 40 and 49 years. Hair loss was severe, diffuse and involved the scalp in all patients (Fig. 1A and B). One patient initially had diffuse hair loss that later became patchy, involving the back of the head and forehead. Time-to-onset of alopecia after switching to TAF ranged between 2 months and 1 year, but 4 out of 5 patients reported hair loss after 2-3 months. No pain, pruritus or tenderness were present and there was no evidence of scarring or inflammation on physical exam. All patients had sustained viral suppression and had no evidence of active infections. A basic metabolic panel including liver function tests, complete blood count, sexually transmitted diseases workup, CD4 T-lymphocyte count and HIV viral load were non-revealing. Concomitant use of other medications could not explain the alopecia.

**Conclusion:** Most clinical trials show very low rates of recruitment of African American patients, therefore, some of the side effects of this novel combination might be underreported in this patient. This report aims to raise awareness among healthcare practitioners about alopecia as a potential distressing adverse effect of TAF that could predominate in certain underrepresented patient populations. Increased representation of African American women in HIV/AIDS clinical trials is important to identify issues that may be unique to some populations. Further investigations are needed to determine causality.

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**IMPACT AND DETERMINANTS OF COMORBIDITY CLUSTERS IN PEOPLE LIVING WITH HIV**

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**Background:** Comorbidities in people living with HIV (PLWH) may occur in clusters, potentially affecting quality of life and general health in different ways. We explored associations of risk factors and patient reported health outcomes with common clusters of co-occurring comorbidities.

**Methods:** We considered 65 comorbidities reported by PLWH via a structured interview with trained staff. Principal component analysis was used to identify non-random clusters of co-occurring comorbidities and obtain a score for each cluster proportional to the number of comorbidities included in the cluster and present in an individual. Cluster scores were standardised (mean=0, SD=1) with higher scores indicating a greater number of comorbidities characterising a cluster. Multivariable linear regression was then used to investigate associations of sociodemographic, lifestyle and HIV-specific factors with each cluster score. Multivariable linear regression was used to evaluate associations of cluster scores (independently of each other) with physical and mental health summary scores (obtained from SF-36 questionnaire, range 0-100).

**Results:** In 1073 PLWH (85% male, 84% white ethnicity, median (IQR) age 52 (47-59) years) we identified 6 comorbidity clusters (Table). “CVDs”, “metabolic” and “chest/other infections” scores were independently associated with older age and longer time since HIV diagnosis (all p’s<0.001). Higher body-mass index was associated with higher scores in the “CVDs” (p=0.009), “cancers” (p=0.03) and “metabolic” clusters (p=0.006). PLWH with prior AIDS events had higher scores than PLWH without prior AIDS events for all clusters (p<0.05 except “STDs”). Associations of smoking and alcohol consumption were weak across all clusters (all p’s>0.05). Higher scores in the “mental health” and “chest/other infections” clusters were independently associated with poorer SF-36 physical (p<0.001) and mental health scores (p<0.001 and p=0.03, respectively - Table). “CVDs” and “cancers” scores were associated with poorer physical (p=0.02, p=0.03) but not mental health (p>0.05).

**Conclusion:** Comorbidity clusters in PLWH are associated with different demographic, lifestyle and HIV-related factors, and significantly impact on quality of life, particularly physical functioning. Identifying common comorbidity clusters in PLWH may help prioritise interventions for those at risk for poorer health outcomes and focus research to understand common pathophysiological pathways contributing to comorbidities in treated PLWH.
**WIDESPREAD PAIN AND ASSOCIATIONS WITH HIV-RELATED FACTORS IN PEOPLE WITH HIV**

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**Background:** Widespread and burdensome pain is frequently reported in people with HIV (PWH), although associations with HIV factors, particularly in those on current antiretroviral (ART) regimens, have not been determined. We investigated the prevalence of widespread pain and its associations with HIV factors among PWH in the POPPY study.

**Methods:** PWH on ART were included. Self-reported pain information was collected from 2013-2015 via self-completed questionnaires and through a pain manikin identifying affected body sites (19 distinct sites). Associations between extent of pain (widespread [≥ 6 affected sites], non-widespread [1-6 sites], none) and HIV factors (current/nadir CD4, total ART drugs received, current/cumulative exposure to each ART class, and previous exposure to stavudine, didanosine or zalcitabine (‘D’ drugs, associated with neuropathy)) were investigated using ordinal logistic regression adjusted for age and gender.

**Results:** The 522 PWH were mainly male (86.0%), white (87.7%) and with median (interquartile range [IQR]) age 53 (47-59) years. Median (IQR) exposure to NRTIs, PIs and NNRTIs was 8.5 (4.4-14.1), 1.9 (0-7.6) and 3.5 (0-8.9) years, respectively. Widespread pain was more common in those with longer exposure to NRTIs, longer exposure to PIs, those currently receiving NNRTIs, those exposed to a greater number of ART drugs, those previously exposed to D drugs and those with a higher current CD4 count. With only exposure to D drugs remaining associated with widespread pain after adjusting for other factors (aOR 2.09).

**Conclusion:** Widespread pain reported in PWH is commoner in those with prior exposure to D drugs, likely representing a legacy of prior ART-induced neuropathy. Although we found no other associations with any of the studied HIV-related factors in PWH on virally-suppressive ART, further analyses will investigate drug and immunosuppression associations in more depth.
TREATMENT OF PSYCHIATRIC DISORDERS AND TIME WITH HIV VIRAL LOAD ≥200 COPIES/ML

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Background: Psychiatric disorders are common among persons living with HIV (PLWH) and can negatively impact HIV outcomes. We examined the impact of treatment of psychiatric disorders by assessing whether various psychiatric disorders, both treated and untreated, were associated with duration of time with VL ≥200 copies/mL.

Methods: Clinical data from electronic medical records were collected between Jan 2011–Mar 2018 for adult PLWH enrolled in the DC Cohort, a multisite observational study of persons receiving HIV care in Washington, DC. Among PLWH ≥18 years old who received primary care at their clinic site, we assessed diagnoses and drug treatment prescriptions for mood, anxiety and stress-/trauma-related, and psychotic disorders. We assessed associations between time-updated measures for psychiatric disorders/medication prescriptions and the proportion of estimated subsequent days with VL ≥200 copies/mL (out of total days) using multivariable Poisson regression with generalized estimating equations, adjusting for socio-demographic, behavioral, and HIV-related factors.

Results: Among 5,904 participants (median age 51; 70% male; 82% Black), 49% had ≥1 psychiatric disorder, including 38% with a mood disorder (26% depression; 9% bipolar), 18% with an anxiety or stress-/trauma-related disorder, and 4% with a psychotic disorder. Prevalence of drug treatment for psychiatric disorders was 55% (mood), 40% (anxiety or stress-/trauma-related), and 53% (psychotic). Untreated (vs. no) depression (aRR 1.21; 95% CI: 1.00–1.46) predicted more time with VL ≥200 copies/mL; associations were attenuated for treated depression and treated bipolar disorder (Table 1). Treated (vs. no) anxiety disorder (aRR: 0.69; 0.49–0.99) predicted less time with VL ≥200 copies/mL. Covariates predictive of more time with VL ≥200 copies/mL included female sex (aRR 1.17; 1.01–1.35), Black race (aRR 1.51; 1.26–1.82), smoking (aRR 1.05; 1.01–1.09), and substance use disorder (aRR 1.05; 1.01–1.09).

Conclusion: Nearly half of PLWH in this cohort had a diagnosed psychiatric disorder. PLWH with an untreated mood disorder had a greater risk of VL ≥200 copies/mL, while those with a treated anxiety disorder had a lower risk, compared to PLWH without each disorder. The appropriate diagnosis, treatment, and monitoring of psychiatric disorders is critical for promoting sustained viral suppression among PLWH with comorbid psychiatric disorders.

Table 1. Associations between treated and untreated psychiatric disorders and time with HIV viral load ≥200 copies/mL.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Adjusted Rate Ratio (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Major depressive disorder</strong></td>
<td></td>
<td></td>
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<tr>
<td>Treated</td>
<td>1.11 (0.95, 1.29)</td>
<td>0.17</td>
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<tr>
<td>Untreated</td>
<td>1.21 (1.06, 1.38)</td>
<td>0.004</td>
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<tr>
<td><strong>Bipolar disorder</strong></td>
<td></td>
<td></td>
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<tr>
<td>Treated</td>
<td>1.17 (0.96, 1.43)</td>
<td>0.12</td>
</tr>
<tr>
<td>Untreated</td>
<td>1.39 (1.16, 1.68)</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>Anxiety disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>0.69 (0.49, 0.99)</td>
<td>0.045</td>
</tr>
<tr>
<td>Untreated</td>
<td>0.86 (0.71, 1.03)</td>
<td>0.11</td>
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<tr>
<td><strong>Stress-trauma-related disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>1.09 (0.78, 1.52)</td>
<td>0.61</td>
</tr>
<tr>
<td>Untreated</td>
<td>0.86 (0.69, 1.07)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Psychotic disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>1.03 (0.77, 1.38)</td>
<td>0.83</td>
</tr>
<tr>
<td>Untreated</td>
<td>0.87 (0.67, 1.14)</td>
<td>0.33</td>
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REFERENCES


BLUNTED MUSCLE MITOCHONDRIAL RESPONSES TO EXERCISE TRAINING IN OLDER ADULTS WITH HIV

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Background: HIV, antiretroviral therapy (ART), and aging have been associated with mitochondrial dysfunction in skeletal muscle, whereas exercise improves mitochondrial function. We found improved physical function with exercise training among older people living with HIV (PLWH) and thus hypothesized that exercise would increase mitochondrial marker expression in muscle.

Methods: Vastus lateralis muscle specimens were obtained by percutaneous needle biopsy before and after completing a supervised 24-week cardiovascular and resistance exercise intervention in previously sedentary, older PLWH (on ART ≥2 years) and uninfected controls (NEG) who were fasted and had not exercised for >24 hours. Protein expressions of complex (C) I-V, manganese superoxide dismutase (MnSOD), peroxisome proliferator-activated receptor-y coactivator-1α (PGC1), and voltage-dependent anion channel 1 (VDAC1) in muscle lysate were measured via Western blot using commercially available antibodies and normalized to vinculin. Citrate synthase (CS) activity (colorimetric assay) was normalized to total protein. Outcomes were log-transformed and modeled with multiple linear regressions. Baseline comparisons were adjusted for age; differences due to training were also adjusted for baseline levels. Results are reported as the geometric mean (95% CI), means (±SD) or percent change from baseline.

Results: Baseline and 24-week muscle samples were provided by 40 (18 PLWH, 22 NEG), and 31 (15 PLWH, 16 NEG) participants, respectively, who were majority male (98%), white (78%) and non-Hispanic (82%). PLWH and NEG were of similar age (56 [54, 59]; 57 [54, 60] yr); PLWH had a lower BMI (25±2; 29±5 kg/m²). PLWH had a CD4 count of 563 cells/μl [455, 698] and all had plasma HIV-1 RNA <50 copies/mL. 12 PLWH had prior thymidine analogue exposure. At baseline, PLWH had lower C-III (0.77 [0.58, 1.01] vs 1.15 [0.90, 1.46]) and greater VDAC1 (3.95 [2.40, 6.49]; 1.89 [1.21, 2.96]) (P<.04) compared to NEG. After 24 weeks of exercise, CS, MnSOD, PGC1, and C-IV increased inNEG (P<.001) with no significant changes in any markers in PLWH. Exercise-induced changes in complex III activity (colorimetric assay) was normalized to total protein. Outcomes were log-transformed and modeled with multiple linear regressions. Baseline comparisons were adjusted for age; differences due to training were also adjusted for baseline levels. Results are reported as the geometric mean (95% CI), means (±SD) or percent change from baseline.

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Conclusion: Skeletal muscle mitochondrial responses to exercise training at moderate to high intensity were blunted in PLWH compared to controls. Different types of exercise (e.g., high intensity interval) or longer training periods may be necessary to stimulate mitochondrial adaptations in older PLWH.

REFERENCES

WEAK GRIP AND FRAILTY ARE ASSOCIATED WITH MTDNA HAPLOGROUP IN ADULTS WITH HIV

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Background: Mitochondrial DNA (mtDNA) haplogroups have been associated with disease risk and longevity, perhaps as a marker of mitochondrial function. Among persons living with HIV (PLWH), mitochondria may be affected by HIV itself and antiretroviral therapy; mtDNA haplogroup has been associated with AIDS progression, neuropathy, cognitive impairment, and gait speed decline. We sought to determine if haplogroup is associated with frailty and its components among older PLWH.

Methods: A cross-sectional analysis was performed of AIDS Clinical Trials Group A3322 (HAILO) participants with available genome-wide genotype and frailty phenotype assessments. Frailty included weight loss, fatigue, low activity, weakness, and slowness, and was considered as continuous (0-5) or categorical (frail [3-5 components], pre-frail [1-2], non-frail [0]). Weakness (grip) and slowness (4-meter gait) were considered separately, using sex and body mass index (grip) or height (gait) cut-points. Multivariable models adjusted for age, sex, education, smoking, hepatitis C, and prior use of didanosine/stavudine.

Results: Among 634 participants, 81% were male, 49% non-Hispanic white, 31% non-Hispanic black, and 20% Hispanic. Mean age was 51.0 (SD 7.5) years and median nadir CD4 count 212 (IQR 72, 324) cells/µL. Thirty-five (6%) were frail and 244 (39%) pre-frail, 30 were H (p=0.015). In adjusted analyses, PLWH with haplogroup H tended towards higher frailty score (β=0.090 points; p=0.058) and weaker grip (β=0.37 kg; p=0.028), but not slower gait (β=0.022 seconds; p=0.65) compared to non-H. Among 199 black participants, haplogroups were not associated with frailty, grip strength, or gait speed. Among 125 Hispanic participants, 6 were frail and 4 had slow gait; all were from non-major Hispanic haplogroups (p=0.06 and p=0.10, respectively).

Conclusion: In this analysis of ART-treated PLWH, European mtDNA haplogroup H was independently associated with weak grip and frailty versus with non-H European haplogroups. Mechanisms may include primary effects on mitochondrial function in skeletal muscle or indirectly through neurologic pathways, and warrants further study. This association has not been reported among people without HIV, thus could represent a unique contribution of HIV to pathways, and warrants further study. This association has not been reported among people without HIV, thus could represent a unique contribution of HIV to pathways, and warrants further study.

SERIOUS INJURY AFTER A FALL: ARE THOSE WITH HIV AT GREATER RISK THAN UNINFECTED?

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Background: HIV infected (HIV+) Veterans 50+ years of age are more likely to fall than uninfected comparators. Whether they are at greater risk for serious injury after the fall is not known.

Methods: We used data from the Veterans Aging Cohort Study (VACS). The primary exposures were HIV and falls. The outcome was serious injury as identified by ICD9 codes (hip fracture, fragility fracture, joint dislocation, traumatic brain injury (TBI), and head injury). We identified medically significant falls using Ecodes and a machine learning algorithm applied to radiology reports. After verifying that associations between HIV and each type of serious injury were similar, all injuries were merged into a composite outcome. An interaction term between HIV and falls assessed whether falls had a differential impact on the risk of injury among HIV+ and uninfected participants. The analytic unit was a six-month person-interval. Covariates assessed at the beginning of the interval were evaluated for associations with occurrence of a serious injury in that interval. Multivariable logistic regression was used to evaluate the associations of HIV and falls with serious injury with adjustment for risk factors for fall-related injury identified among older adults and for disease severity with the VACS Index.

Results: Our analysis included 73,283 Veterans who were 50+ years of age, 31% of whom were HIV+. Fall incidence was 46 per 1000 person-years (95% CI 45-47 per 1000 person-years) for HIV+ and 40 per 1000 person-years (95% CI 40-41 per 1000 person-years) for uninfected. In bivariate analyses, relative to...
uninfected Veterans, joint dislocation and TBI were less common among HIV+ (1.2% vs 1.7%, p<0.001; and 1.2% vs 1.4%, p<0.001, respectively) whereas hip fracture and fragility fractures were more common (hip fractures: 1.3% vs 0.7%, p<0.001; fragility fractures: 8.0% vs 7.4%, p<0.001, respectively). In fully adjusted models, relative to those who did not fall, those who fell had a substantially increased risk of serious injury: HIV+: (OR 4.14; 95% CI 3.86, 4.44) and uninfected (OR 1.42; 95% CI 1.35, 1.49).

Conclusion: Among those 50+ years of age, HIV+ are more likely to fall and more likely to experience serious injury, commonly in the form of fracture, after they fall compared to uninfected individuals.

705 SCREENING AND PREEMPITIVE ANTIFUNGAL THERAPY FOR SUBCLINICAL CRYPTOCOCCAL DISEASE

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Background: Serum cryptococcal antigen (CrAg) screening and pre-emptive antifungal treatment is recommended for individuals with HIV and CD4 ≤100 cells/μl by the World Health Organization. However the prevalence of subclinical antigenemia, optimal management of positive individuals, and outcomes following 'screen and treat' are poorly defined.

Methods: In this multicenter, prospective implementation science cohort study, HIV infected individuals with CD4 counts <100 cells/μl and without symptomatic meningitis, enrolled at 20 outpatient centers in Harare underwent CrAg testing. Lumbar puncture (LP) was recommended to CrAg positive participants. Hospitalization and treatment with intravenous (IV) amphotericin B and high dose fluconazole was recommended to cerebrospinal fluid (CSF) CrAg positive participants; CrAg positive participants who declined LP were treated with high dose fluconazole monotherapy. ART and HIV disease management was done by the primary HIV provider. Recommendations were made to initiate ART immediately in CrAg negative and 4 weeks after initiating antifungal therapy in CrAg positive participants. Primary endpoints were survival at 6 and 12-months. Outcomes assessed included CrAg seroprevalence, and prevalence of disseminated cryptococcal disease as determined by positive blood or CSF cultures.

Results: Between April 2015 and June 2016, 1320 participants were enrolled; 130 (9.8%) were CrAg positive with a median titre of 1:20. Sixty-six (50.8%) of CrAg positive participants consented to an LPs; 11 (16.7%) had evidence of CNS disease dissemination. Blood cultures were positive in 10/129 (7.5%) of sCrAg participants consented to an LPs; 11 (16.7%) had evidence of CSF disease dissemination. Overall survival rate at 12-months was 83.9% (95% CI: 81.5-86.0) and 76.1 % (95% CI: 76.1 – 83.0; p=0.011) in sCrAg negative and CrAg positive participants respectively. Factors associated with increased mortality were positive sCrAg, positive CSF CrAg, CD4 count, and time to ART initiation in CrAg negative. All cause mortality and sCrAg titre did not differ among CrAg positive participants that received LPs and IV amphotericin when indicated, and those that declined LP.

Conclusion: The prevalence of subclinical antigenemia is high and a positive sCrAg remains an important risk factor for mortality. Disease dissemination is evident despite subclinical disease; however in this cohort LPs and IV therapy did not markedly improve survival compared with high dose fluconazole alone. Early initiation of ART in CrAg negative individuals improved survival.

706 SCREENING FOR TALAROMYCES AND CRYPTOCOCCAL ANTIGENEMIA IN AIDS PATIENTS IN GUANGDONG

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Background: Talaromyces and cryptococcosis are the leading causes of morbidity and mortality in patients with advanced HIV disease in Southern China. We conducted a prospective study using commercially available antigen detection assays in Guangdong located in Southern China to determine disease burden and clinical significance of antigenemia to inform disease control strategies.

Methods: This is an analysis of an ongoing prospective study enrolling antiretroviral-naive patients aged ≥18 with CD4 count ≤100 cells/μl who continuously registered for care in Guangzhou Eighth People’s Hospital between January 2016 and December 2016. Talaromyces was screened using a novel talaromyces Mp1p antigen enzyme immunoassay (Mp1p EIA) and an aspergillus galactomannan (GM) test. Cryptococcosis was screened using a cryptococcal antigen (CrAg) test. Management and follow up of patients were according to the standard HIV care.

Results: A total of 236 patients have been recruited: 194 (83%) were males; mean age was 41 ±13; median CD4 count was 23.5 cells/μl (IQR: 8-54.5). The number of patients with positive Mp1p, GM and CrAg tests were 46 (19.5%), 38 (16.1%), and 8 (3.4%), respectively. Mp1p and GM positivity were associated with having symptoms and a CD4 count ≤50 cells/μl (P<0.05), while CrAg positivity was not (P>0.05). Over a mean of 9 months of follow up, 43/44 (97.7%) Mp1p-positive and 30/38 (79.0%) GM-positive patients had culture-confirmed talaromycosis, and 5/8 (62.5%) CrAg-positive patients had culture-confirmed cryptococcosis. Meanwhile, 6/131 (4.6%) Mp1p-negative and 19/137 (13.9%) GM-negative patients had talaromycosis, and 0/186 CrAg-negative patients had cryptococcosis. The sensitivity, specificity, positive predictive value, and negative predictive value for each test are included in the Table. The mortality of cases was higher in Mp1p- or CrAg-positive patients (13.0% and 37.5%) than Mp1p- or CrAg-negative patients (4.7% and 5.3%) at one year follow-up (Chi Square P<0.05). However, the difference in mortality between GM-positive and GM-negative patients was not statistically significant (P=0.05).

Conclusion: Talaromycosis is significantly more prevalent than cryptococcosis in patients with advanced HIV disease in southern China. Our data demonstrate that the Mp1p EIA and CrAg test are useful tools for rapid diagnosis and screening for these infections and should be implemented to reduce HIV morbidity and mortality in southern China.

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707 THE COST-EFFECTIVENESS OF AMBISOME FOR ASYMPTOMATIC CRYPTOCOCCAL INFECTION

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Background: Screening for cryptococcal antigen (CrAg) among those with advanced HIV disease and treating asymptomatic CrAg+ with fluconazole is lifesaving. However, fluconazole monotherapy still results in 25% mortality.1 Enhanced preemptive treatment options are being evaluated to prevent cryptococcal meningitis. Single dose Ambisome (at 10mg/kg) plus fluconazole is being prospectively evaluated for preemptive treatment in asymptomatic CrAg+. We sought to explore the threshold of efficacy and cost that would improve on current standard of care therapy in Uganda and South Africa, representing a low income setting and a middle income setting respectively. The current price of Ambisome in South Africa is $165 per vial. The anticipated discounted price for treatment of cryptococcal meningitis in resource-limited settings is $16.25 per vial.

Methods: We used a decision analytic model to evaluate CrAg screening and treatment outcomes in Uganda for those with a CD4<100 cells/μl. Costs were estimated for screening, preemptive therapy, hospitalization, and maintenance therapy. Parameter assumptions were taken from large prospective CrAg screening studies in Uganda, and clinical trials from sub Saharan Africa.2 CrAg-positive persons could be: a) asymptomatic and thus eligible for preemptive treatment with fluconazole; or b) symptomatic with meningitis. Parameter assumptions were taken from large prospective CrAg screening studies in Uganda, and clinical trials from sub Saharan Africa.2 Preemptive treatment with Ambisome would be cost-saving if efficacy to prevent one death from cryptococcal meningitis. At the same price, but assuming 85% efficacy, the cost is $3090 assuming 85% efficacy, the cost is $195 to save one life. In South Africa, at the current price of $165 per vial, if assumed to have 95% efficacy, the cost is $5090 to prevent one death from cryptococcal meningitis. At the same price, but assuming 85% efficacy, it would cost $4817 to prevent one death (Figure). If Ambisome was priced at $72 per vial or less, this would be cost saving if efficacy
is 85% or more. At a discounted price of $16.25 per vial and 85% efficacy, the health care system would save $2949 for every death averted from cryptococcal meningitis.

**Conclusion:** Single dose Ambisome for asymptomatic cryptococcal infection given at 10mg/kg once in conjunction with fluconazole has potential to save lives and save costs, if proven effective.

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**708 CRYPTOCOCCAL ANTIGENEMIA IN HIV PATIENTS WITH VIROLOGIC FAILURE IN UGANDA**

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**Background:** Cryptococcal antigen (CrAg) precedes fulminant cryptococcal meningitis, and preemptive treatment of those CrAg positive before development of meningitis is life-saving. The World Health Organization recommends screening and preemptive treatment for those with a CD4<100 cells/µL who are initiating ART. However, the proportion of patients presenting with fulminant cryptococcal meningitis is increasingly ART-experienced. It is not clear if there is a role for CrAg screening among ART-experienced persons with virologic failure.

We evaluated CrAg prevalence among ART-experienced persons with suspected virologic failure in Uganda, and present 6-month survival and incidence of meningitis among CrAg-positive persons.

**Methods:** We retrospectively performed CrAg testing on plasma samples of adults with virologic failure (HIV viral load >1000 copies/mL) between September 2017 and January 2018. For those CrAg-positive, ART history, incidence of cryptococcal meningitis, and 6-month survival were obtained from retrospective medical chart review.

**Results:** We tested 1186 plasma samples of patients with viral loads >1000 copies/mL and found 15 CrAg-positive (prevalence of 2.95%). Of the 35 CrAg-positive persons, median ART duration was 42 months (IQR 14 to 78 months). We obtained 6-month outcome data on 21 CrAg-positive patients. Of these, 15 were alive, and 6 were dead. Five survivors were known to have received fluconazole. Two patients developed meningitis and survived with treatment. Thus, meningitis-free survival at 6-months was 13/21 (62%). Median viral load for CrAg positive was 53,700 copies/mL (IQR: 17,513 to 163,500), whereas median viral load for CrAg positives was 51,700 copies/mL (IQR: 17,513 to 163,500). Of 121 plasma samples tested, 63 (52%) had detectable CMV DNA (median viral load 298 copies/mL [IQR, 150 to 1630]). The median age was 36 years (IQR, 30 to 41), and the median CD4+ T cell count was 20 cells/µL (IQR, 9 to 72). A total of 43 deaths occurred. The mortality was 64% (28/63) in the CMV-positive group and 26% (15/58) in the CMV-negative group by 10-weeks (Hazard Ratio = 1.93; 95%CI, 1.02-3.61; P=0.04). Median CD4 counts did not differ between CMV-positive and CMV-negative groups (20 [IQR, 9 to 54] vs. 23 [IQR, 10 to 76] cells/µL, respectively; P=0.47). There was no association between the presence of CMV viremia and HIV RNA levels (P=0.71). Every 2-fold increase in IL-2 blood levels was associated with a lower probability of being CMV-positive (Odds Ratio = 0.74; 95%CI, 0.59-0.93; P=0.01).

**Conclusion:** Half of persons with advanced AIDS and cryptococcal meningitis had CMV viremia. The presence of CMV viremia was significantly associated with mortality in persons with cryptococcal meningitis. It remains unclear if the relatively low level CMV viremia in the setting of high baseline mortality due to cryptococcal meningitis contributes to this mortality or may reflect underlying immune dysfunction (i.e. cause vs. effect). Further investigation is warranted. Ultimately, a randomized clinical trial of CMV treatment in advanced AIDS population would be needed to definitively answer if CMV viremia is a modifiable risk factor for mortality.

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**710 CYTOMEGALOVIRUS VIREMIA ASSOCIATED WITH MORTALITY IN CRYPTOCOCCAL MENINGITIS**

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**Background:** Cryptococcal meningitis and tuberculosis are both major causes of morbidity and mortality in persons with advanced HIV disease. Cytomegalovirus (CMV) viremia may be associated with increased mortality in HIV-infected persons with tuberculosis. It is not known if CMV viremia is associated with mortality in other AIDS-related opportunistic infections.

**Methods:** We prospectively enrolled HIV-infected Ugandans with cryptococcal meningitis from 2010-2013 and cryopreserved plasma samples. Subsequently, we analyzed 121 randomly-selected, stored baseline samples for CMV DNA. We compared CMV viremia versus 10-week survival by time-to-event analysis.

**Results:** Of 121 plasma samples tested, 63 (52%) had detectable CMV DNA (median viral load 298 copies/mL [IQR, 150 to 1630]). The median age was 36 years (IQR, 30 to 41), and the median CD4+ T cell count was 20 cells/µL (IQR, 9 to 72). A total of 43 deaths occurred. The mortality was 64% (28/63) in the CMV-positive group and 26% (15/58) in the CMV-negative group by 10-weeks (Hazard Ratio = 1.93; 95%CI, 1.02-3.61; P=0.04). Median CD4 counts did not differ between CMV-positive and CMV-negative groups (20 [IQR, 9 to 54] vs. 23 [IQR, 10 to 76] cells/µL, respectively; P=0.47). There was no association between the presence of CMV viremia and HIV RNA levels (P=0.71). Every 2-fold increase in IL-2 blood levels was associated with a lower probability of being CMV-positive (Odds Ratio = 0.74; 95%CI, 0.59-0.93; P=0.01).

**Conclusion:** Half of persons with advanced AIDS and cryptococcal meningitis had CMV viremia. The presence of CMV viremia was significantly associated with mortality in persons with cryptococcal meningitis. It remains unclear if the relatively low level CMV viremia in the setting of high baseline mortality due to cryptococcal meningitis contributes to this mortality or may reflect underlying immune dysfunction (i.e. cause vs. effect). Further investigation is warranted. Ultimately, a randomized clinical trial of CMV treatment in advanced AIDS population would be needed to definitively answer if CMV viremia is a modifiable risk factor for mortality.

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**711 ASYMPTOMATIC TALAROMYCES MARNEFFEI ANTIGENEMIA AND MORTALITY IN ADVANCED HIV DISEASE**

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**Background:** Talaromycosis marneffei (Tm) is a leading cause of HIV-associated infection with a mortality of 30% in SE Asia. Delay in culture diagnosis is associated with death. We have demonstrated in large cohorts that a novel Mgp1p antigen detection assay is more sensitive than blood culture (90% vs. 70%) and is 98% specific in detecting Tm. We hypothesize that the test can
detect pre-clinical disease in patients with advanced HIV disease, and Tm antigenemia (TmAg) is associated with higher mortality. **Methods:** We retrospectively tested for TmAg in stored baseline plasma samples from patients aged ≥18 years with CD4 count of ≤100 cells/µL who were newly enrolled in care at 22 HIV clinics across Vietnam and participated in the Vietnam Cryptococcal Retention in Care Study (CRCS), August 2015 to April 2017. We excluded 34 patients with a talaromycosis diagnosis at enrollment. We investigated the risk factors for TmAg using multiple logistic regression analysis and investigated the association between TmAg and time to death over 12 months with Cox regression analysis, adjusting for age (+10 years), baseline CD4 counts (≤ or > 50 cells/µL), and cryptococcal antigenemia (CrAg). Future analyses will take potential within-clinic correlation into account. **Results:** Baseline plasma samples were available for 1082/1174 patients: 74.2% were male; median age was 35 years (IQR: 31-41), and median CD4 count was 36 cells/µL (IQR: 15-62). TmAg was detected in 45 (4.2%) patients (95% CI: 3.1%-5.6%) and was non-overlapping with CrAg (prevalence=2.9%). TmAg prevalence was higher in northern (33/497; 6.6%) than southern (12/585; 2.1%) Vietnam, Chi Square p<0.001. TmAg was independently associated with CD4 count ≤50 cells/µL (OR=3.5, 95% CI: 1.4-11.8, p=0.006) and residency in highland regions (OR=3.4, 95% CI: 1.8-6.3, p<0.001). Overall the probability of death was 12.7% (95% CI: 10.6-14.7), and was higher in TmAg-positive (30.0%; 95% CI: 14.0-43.1) than TmAg-negative (11.9%; 95% CI: 9.8-13.9) patients, Log-rank p=0.002. In multivariable survival analysis, TmAg was an independent predictor of death, hazard ratio =2.3, 95% CI: 1.3-4.2, p=0.006. **Conclusion:** CD4 count of less than 50 cells/µL and living in highland regions are independent risk factors for TmAg, and asymptomatic TmAg is an independent risk factor of death. The M1p1 antigen assay is therefore a useful tool to screen for asymptomatic talaromycosis for pre-emptive antifungal therapy. This has the potential to substantially reduce HIV mortality in Southeast Asia.

712 WITHHOLDING PCP PROPHYLAXIS IN VIRALLY SUPPRESSED HIV PATIENTS FROM COHERE

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University Hospital of Bern, Bern, Switzerland

**Background:** Analyses using COHERE data previously suggested (Clin Infect Dis 2010;51:611) that primary Pneumocystis Pneumonia (PCP) prophylaxis could be withdrawn in patients with CD4 counts of 100-200 cells/µL if HIV-RNA is suppressed, suggesting HIV replication as a major risk factor for PCP. Given the wealth of new data available in COHERE we investigated whether prophylaxis might be withheld or stopped in all patients on antiretroviral therapy with suppressed plasma HIV RNA (<400c/ml) irrespective of CD4 count. **Methods:** We estimated the risk of primary PCP in COHERE patients on cART including time-updated CD4 counts, HIV-RNA and use of PCP prophylaxis. We emulated a hypothetical randomised trial using established causal inference methods in which inverse probability (IP) weighting adjusts for censoring selection bias. Eligibility criteria were plasma HIV RNA (<400c/ml) and CD4 counts ≤200 cells/µL. We emulated three trials comparing the effect of A.) continue PCP prophylaxis versus stop prophylaxis, B.) start and then continue PCP prophylaxis versus not starting prophylaxis, and C.) taking PCP prophylaxis versus not taking PCP prophylaxis, irrespective of PCP prophylaxis status at baseline. In each case, we estimated the hazard ratio (HR) fitting a pooled logistic model which included baseline characteristics (CD4, RNA, gender, age, transmission, geographical origin calendar year), used restricted cubic splines to capture CD4/RNA trajectories, and included polynomial time for modelling the baseline hazard. **Results:** There were 9,743 patients eligible for the emulated trials with a total of 18,530 person years followed-up during 1998-2015. The unadjusted incidence rate of PCP diagnosis was 1.5 per 1000py on PCP prophylaxis compared to 2.8 off PCP prophylaxis. The HR estimates for the PCP outcome from the 3 emulated trials were 2.0 (IQR: 1.61-6.4), p<0.03 for Trial A; 2.8 (IQR: 8.899), p=0.01 for Trial B, and 1.2 (IQR: 1.23), p=0.08 for Trial C (see Figure). **Conclusion:** In virologically suppressed patients, irrespective of CD4 levels, the risk of PCP appears to be low, and similar for individuals on and off prophylaxis, although the precision of the results was limited due to the overall low incidence of PCP. This suggests that primary PCP prophylaxis might be withheld in this patient group.
PNEUMOCOCCAL VACCINATION IN HIV+ ADULT PATIENTS ON SUPPRESSIVE ART, 2010-2017

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Background: There is little information on the efficacy of the pneumococcal vaccines (PV), especially of the pneumococcal conjugate vaccines (PCV), in successfully treated patients in the modern ART era.

Methods: Case-control study in a tertiary, University Hospital in Madrid. Cases were HIV-patients admitted to the hospital (2010-2017) with a microbiologically confirmed infection due to S. pneumoniae (from a normally sterile site and/or a positive urinary antigen). Controls (HIV-infected patients without IPD) were selected by random sampling matched with cases by gender and year of HIV diagnosis. The selection was blind for the study factor (vaccination). Sample size was estimated (61 cases and 183 controls). We performed comparisons to vaccine exposure and outcome associations using time-dependent covariates in a Cox proportional-hazards regression model.

Results: The population of study included 256 subjects, 64 cases and 192 controls. Male 77%, median age 29, previous AIDS 43%, median Charlson Comorbidity Index 6. 115 (45%) patients had been vaccinated. Median CD4-cell count at the time of administration of the PV was 518 (318-733) cells/mL, 79% with HIV RNA<50. In a multivariate logistic regression analysis, risk factors associated with IPD were the Charlson Comorbidity Index (HR 1.23 95%CI 1.14-1.33 P=0.001) and previous diagnosis of AIDS (HR 2.82 95%CI 1.26-6.33 P=0.016). We also investigated the influence of different PV schedules. In univariate analysis, compared to no vaccine, no significant protection was found in patients who received only PPSV-23 or only a conjugate vaccine (PCV-7 or PCV-13), while two vaccines given in series (PCV13-PPSV-23 or PPSV23-PCV13) showed protection (HR 0.3 95%CI 0.11-0.77 P=0.012). However, in an adjusted model we found no evidence of protection by double PV schedules (HR 0.44 95%CI 0.17-1.44 P=0.09).

Conclusion: In this case-control study, different schedules of pneumococcal vaccination did not show protection against IPD. As only plasma HIV RNA <50 copies/mL was found to be a protective factor, early ART initiation could ensure the protection in most patients. As with HIV-uninfected persons, the pneumococcal vaccination should then be individualized in HIV-infected patients based on traditional risk factors for IPD.

DIGITAL CHEST RADIOGRAPHY OPTIMISES TB SCREENING OF SOUTH AFRICAN CLINIC ATTENDEES

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Background: In 2016, it is estimated that approximately 165 000 Tuberculosis (TB) cases were missed in South Africa. Optimising TB screening is imperative in meeting national and global TB targets, including identifying 90% of all TB cases. Digital CXR (d-CXR) provides a quick, reproducible technique incurring low marginal costs, reduced radiation exposure and improved portability for TB screening. We assessed whether d-CXR screening with Computer-Aided Detection for Tuberculosis (CAD4TB) would improve TB yield when combined with the World Health Organisation (WHO) TB 4-question symptom screening tool.

Methods: A systematic sample of adult patients attending three public health clinics for any reason (excluding ante-natal care) in the Free State Province, South Africa, were screened for TB between November 2017 and June 2018 using d-CXR and the WHO TB symptom tool. Patients <18 years, pregnant, currently receiving or received anti-tuberculosis treatment within the past two years were ineligible for participation. Two spot sputum were collected for Xpert MTB/RIF Ultra assay (Xpert Ultra) and MGIT culture from attendees with ≥1 TB symptom and/or a CAD4TB score of ≥20. All participants were offered HIV testing. TB yield was compared between screening strategies and the number needed to test (NNT) determined.

Results: We approached 4352 clinic attendees, 3.8% refused participation, 26.3% were ineligible and 3,041 participants were screened (2,005 female [65.9%], mean age 45 years (SD 15.2), HIV prevalence 36.3% [1,030/2,837]). The proportion of attendees screened by d-CXR, symptoms and d-CXR/symptoms requiring TB investigations was 19% (573/3041), 36% (1109/3014) and 45% (1356/3041) respectively. The yield of TB (Xpert Ultra/culture positive) for d-CXR, symptom and d-CXR/symptom screen was 2.2%, 2.3% and 2.8% and the NNT of TB per 100 screeners was 51.5. In comparison with symptom screening alone, the NNT was higher at 217.

Conclusion: A high proportion of clinic attendees had symptoms suggestive of TB. The addition of d-CXR to symptom screening improved TB yield with a modest increase in the number requiring TB investigations. D-CXR alone compared to symptom screening alone had a similar yield of TB and almost halved the number requiring TB investigations. D-CXR screening alone is potentially a cost effective TB screening strategy.
715  **DIAGNOSIS OF LATENT TUBERCULOSIS AMONG US-BORN PEOPLE LIVING WITH HIV**

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**Background:** Persons living with HIV (PLWH) are a priority for latent tuberculosis infection (LTBI) screening due to the risk of progression to active tuberculosis (TB). Studies of LTBI diagnostic test characteristics are conflicting and limited by the lack of a gold standard.

**Methods:** The TB Epidemiologic Studies Consortium is conducting a multicenter prospective cohort study to evaluate the performance of the tuberculin skin test (TST), Quantiferon Gold In-Tube (QFT) and T-SPOT.TB (TSPOT). We analyzed US-born PLWH >5 years old who had valid results for all three tests and were enrolled from 13 clinics during September 2012 - April 2017. We estimated LTBI prevalence and test characteristics, using Bayesian latent class analysis models with varying cutoffs. Sensitivity and specificity were used to quantify the under- and overdiagnosis of LTBI per 1000 persons screened with varying LTBI prevalence.

**Results:** Among 1310 participants, median age was 49 years (interquartile range [IQR] 42-55), 1073 (71%) were male, 1057 (70%) were black; 945 (62.6%) had a self-reported CD4+ count (median 532 cells/mm3, IQR 355-764). LTBI prevalence was estimated at 5.1% (95% credible interval [95CrI] 3.4 to 7.0%) overall (range 0.8-14.5% by site). Table 1 describes test characteristics. Using the standard US cutpoints, the QFT had higher sensitivity (Sn) than the TST (difference [diff] 16.0%, 95CrI 2.3 to 30) and TSPOT (diff 15.4%, 95CrI 0 to 30.8%). The difference in the Sn was 0.6% (95CrI 12.6 to 14.6) for the TSPOT compared to TST. The TSPOT had higher specificity (Sp) than the TST (diff 2.6%, 95CrI 1.6 to 3.8) and QFT (diff 2.9%, 95CrI 1.7 to 4.2). The difference in the Sp was 0.3% (95CrI -1.2 to 1.7) for the TST compared to QFT. The difference in positive predictive value (PPV) was 4.2% (95CrI -0.9 to 17.8) for the QFT compared to TST; TSPOT had higher PPV than TST (diff 37.1%, 95CrI 20.8 to 52.3) and QFT (diff 32.9%, 95CrI 15.4 to 49.2%).

**Conclusion:** Using the standard US cutpoints and 5% LTBI prevalence, Sn was highest for QFT; Sp and PPV were highest for TSPOT. Both the international (>6 spots) and US (>8 spots) TST cutoffs resulted in more LTBI under- than overdiagnosis, regardless of LTBI prevalence. For the TST and the QFT, the US cutoffs (5mm for TST and 0.35 IU/mL for QFT) resulted in more LTBI over- than underdiagnosis in a population with medium LTBI prevalence (5.1%); however, the optimal cutoff of the TST and QFT varied depending on LTBI prevalence.

716  **QUANTIFICATION OF CD64: A PREDICTIVE BIOMARKER FOR PROGRESSION TO ACTIVE TUBERCULOSIS**

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**Background:** To reach the goal of end-Tuberculosis strategy, new biomarkers are needed to identify active tuberculosis (TB). Currently, only Quantiferon® TB-assay (QFT) is used in peripheral blood for screening tuberculosis infection. However, this method cannot distinguish active from latent TB infection (LTBI). Recent studies show a transcriptional increase of several genes, including CD64, which code for a high affinity Fc receptor I involved in inflammatory reactions. In addition, Neutrophils (NE) and Monocytes (MO) exert bactericidal responses by producing inflammatory proteins caused by infection with M. tuberculosis (MTB). The purpose of this study was to quantify CD64 expression on the surface of NE and MO as a predictive biomarker of progression from LTBI to active TB in Quantiferon® (QTF) positive or indeterminate patients.

**Methods:** Patients were enrolled with positive and indeterminate QTF. Non-systemic infections were documented. Flow cytometric quantitative expression of CD64 was evaluated from peripheral blood samples and expressed in ABC (Antibody Binding Capacity) units, with NE normal range <1000 ABC and MO normal range 15000-20000 ABC. MTB cultures from respiratory specimens were also performed.

**Results:** Of the 45 positive QTF cases, 25 MTB cultures were positive and 16 were negative. The positive QTF with negative MTB cultures were considered LTBI. The median of NE CD64 ABC and MO CD64 ABC was significantly higher than in healthy controls (Antibody Binding Capacity) units, with NE normal range <1000 ABC and MO normal range 15000-20000 ABC. MTB cultures from respiratory specimens were also performed.

**Conclusion:** The quantification of NE and MO CD64 expression is a powerful diagnostic tool in discriminating between active TB and LTBI and may be used as predictive biomarker of active TB in patients with a positive QTF test. Providing a fast diagnostic solution, this may address the limitation of current tuberculosis diagnostics. Further studies with a larger patient cohort are needed to validate our preliminary data.

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**Table 1**: Estimated test characteristics and frequency of under- and overdiagnosis of LTBI using varying LTBI prevalence and test cutoffs

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<th>Test</th>
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<th>Underdiagnosed (%)</th>
<th>Overdiagnosed (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>50.0</td>
<td>87.5</td>
<td>5.0</td>
<td>10.0</td>
<td>5.0</td>
<td>2.5</td>
</tr>
<tr>
<td>QFT</td>
<td>87.5</td>
<td>50.0</td>
<td>5.0</td>
<td>2.5</td>
<td>4.0</td>
<td>87.5</td>
</tr>
<tr>
<td>TSPOT</td>
<td>60.0</td>
<td>87.5</td>
<td>5.0</td>
<td>4.0</td>
<td>5.0</td>
<td>87.5</td>
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</table>

**Table 2**: Diagnostic yield of TST using different screening modalities

<table>
<thead>
<tr>
<th>Screening n</th>
<th>TST Positive</th>
<th>TST Negative</th>
<th>No result produced</th>
<th>TST Underdiagnosed</th>
<th>TST Overdiagnosed</th>
<th>TST PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,041</td>
<td>506</td>
<td>1,559</td>
<td>3,566</td>
<td>2,074</td>
<td>1,486</td>
<td>29.9</td>
</tr>
<tr>
<td>10,082</td>
<td>1,012</td>
<td>3,118</td>
<td>6,952</td>
<td>3,936</td>
<td>3,016</td>
<td>29.9</td>
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<tr>
<td>15,123</td>
<td>1,512</td>
<td>4,554</td>
<td>9,057</td>
<td>5,454</td>
<td>4,603</td>
<td>29.9</td>
</tr>
</tbody>
</table>
ORAL SWAB ANALYSIS (TB-OSA) FOR NON–SPUTUM-BASED TB DIAGNOSIS IN KENYA

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**Background:** Despite recent advances in rapid TB diagnostics, sample collection remains challenging in those unable to produce sputum. In published proof-of-concept data, oral swab analysis (OSA) detected M. tuberculosis in 90% of HIV-negative Xpert+ adult TB cases in South Africa, with 100% specificity in negative controls. A larger, follow-on evaluation in the same South African population found 92% sensitivity and 92% specificity relative to sputum Xpert. We evaluated OSA performance in HIV-infected and HIV-uninfected TB suspects in Kenya.

**Methods:** One hundred Kenyan TB suspects (cough >2 weeks, plus >1 additional symptom of fever, night sweats, or weight loss) >13 years of age had oral swabs then sputum for Xpert and culture collected at enrollment and consecutive morning visit. Cryopreserved swabs underwent Mtb DNA extraction and qPCR analysis targeting IS6110 insertion sequence. A predetermined threshold Cq <38 was considered positive (lower Cq indicating a stronger more positive signal). OSA performance was assessed compared to a reference of Xpert or culture. OSA mean Cq values were compared using t-tests.

**Results:** Of 94 participants enrolled with oral swab results, median age was 38 years (IQR 29-44), 48.9% were female, 54.3% were HIV-infected, and 20.1% with history of TB. Among 51 HIV+, 86.3% were on ART and 9.5% had ever received isoniazid preventive therapy (IPT). Nineteen TB cases were identified (18 Xpert/culture+, 1 culture+ only). OSA sensitivity was 68.4% (13/19) with 82.7% (64/78) specificity overall, and 83.3% (5/6) sensitivity and 75.6% (34/45) specificity among HIV-infected. Performance improved on subsequent morning visit samples compared to Xpert alone (sensitivity 80.0% [12/15], specificity 92.3% [60/65]). Mean OSA Cq was stronger (indicated by lower Cq) among OSA+ vs. Xpert- participants (35.1 +2.4 vs. 34.9 +2.6 SD, p = 0.008).

**Conclusion:** In this analysis, performance appeared reduced compared to previous analyses, possibly due to differences in setting, population, and/or study design. Despite the lower performance compared to sputum-testing methods, OSA provides a promising means of TB detection for populations that are unable to produce adequate sputum including those who are HIV-infected.
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**Background:** Tuberculosis (TB) control among people living with HIV requires accurate, rapid diagnostic tests to identify Mycobacterium tuberculosis complex (MTBC), and detect isoniazid (INH) and rifampin (RIF) resistance. We evaluated the performance of the BD MAX™ MDR-TB (BD MAX) assay, which tests up to 24 specimens at once.

**Methods:** Outpatient adults with signs and/or symptoms of active pulmonary TB were enrolled in South Africa, Uganda, India, and Peru. A single collected sputum was split into 2 portions. Smear microscopy and BD MAX were performed on the raw portion. The other portion was processed using NALC-NaOH, and tested using culture (MGIT®), phenotypic drug susceptibility testing, Xpert® MTB/RIF (Xpert), BD MAX, and microscopy.

**Results:** 1053 participants (47% female, 32% HIV-infected) with presumptive TB were enrolled. The majority (94%) of HIV-infected participants were enrolled from high HIV/TB burden sites (Uganda and South Africa) with median CD4 of 367 (IQR 228–536). Overall BD MAX test sensitivity was 95% (262/282 [95% CI 89.95]) among microbiologically confirmed TB patients, and specificity was 97% (593/610, [96.98]) among participants with negative cultures. Among 273 HIV-infected participants, sensitivity was 86% (44/51 [74,83]), and specificity was 98% (217/222 [95.99]) when stratified by ZN smear microscopy status, sensitivity of BD MAX for detection of HIV-associated TB was 100% (22/22, [85,100]) for smear-positive, and 76% (22/29, [58, 88]) in smear-negative HIV/TB patients. Among TB patients with both BD MAX and Xpert results, sensitivity was 81% (49/60, [69, 90]) for both assays. BD MAX sensitivity for detection of any drug resistance (INH and/or RIF) was 100% (44/41, [100]) with specificity among those with drug-susceptible TB of 100% (30/30, [89,100]) when compared to MGIT DST among HIV/TB patients. Sensitivity and specificity for detection of INH resistance was 100% (33/33, [100]) and 100% (35/35, [90,100]), respectively. Sensitivity for RIF resistance was 100% (2/2, [34,100]). One participant had RIF resistance by BD MAX, but was considered susceptible on MGIT DST and bi-directional sequencing, resulting in an overall specificity of 97% (34/35, [85,95]).

**Conclusion:** The BD MAX MDR-TB assay has high sensitivity and specificity for detection of MTBC, and rifampin and isoniazid drug resistance in settings of high HIV/TB burden and may aid in the rapid detection of tuberculosis and MDR-TB.

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720 **THE EFFECTIVENESS OF VARIOUS SYMPTOM-BASED ALGORITHMS FOR TB SCREENING AT HIV TESTING**

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1GHESKIO, Port-au-Prince, Haiti, 2Analysis Group, Inc, Boston, MA, USA, 3Weill Cornell Medicine, New York, NY, USA, 4Bingham and Women’s Hospital, Boston, MA, USA

**Background:** It is essential to screen for TB prior to ART initiation in TB endemic settings. Algorithms are needed to identify low-risk patients for immediate ART initiation, and high-risk patients who merit TB testing prior to ART initiation. If TB screening is conducted at the time of HIV testing, symptomatic patients may also be tested for TB, even if they test negative for HIV. We conducted a retrospective analysis to evaluate the diagnostic yield of five different symptom screening strategies among patients who presented for HIV testing in Haiti.

**Methods:** From October 1, 2015 to March 31, 2016, the first 20 patients who presented for HIV testing each day at GHESKIO were queried regarding TB symptoms, and received AFB smear, GeneXpert testing, and chest x-ray, regardless of symptoms. TB symptom screening algorithms were evaluated based on the total proportion of TB cases diagnosed and the number of missed TB cases, stratified by HIV status.

**Results:** 1,086 individuals received diagnostic testing for both HIV and TB. 48% were female, median age was 33 (27–44) and 216 (19%) tested positive for HIV, with median CD4 count of 364 cells/mm3 (IQR: 210–563). 59 patients (5%) were diagnosed with TB; 55 (93%) of these were bacteriologically confirmed, and 4 (7%) were diagnosed based on symptoms and chest x-ray. Among the 216 people who tested positive for HIV, 13 (21%) of those who reported cough of any duration were diagnosed with TB (Table 1). Of non-coughing patients with HIV, 2 (1%) were diagnosed with TB; these patients also did not report fever, night sweats, or weight loss. Among the 892 patients who tested negative for HIV, 36 (16%) of those who reported cough of any duration were diagnosed with TB. Among HIV-negative patients without cough, 8 (1%) were diagnosed with TB; 3 of these patients reported fever, night sweats or weight loss in the absence of cough.

**Conclusion:** Testing for TB in patients who do not report cough at HIV testing is low yield in Haiti, regardless of HIV test results; ART can generally be initiated in patients who do not report cough without further TB testing. Patients who report cough of any duration at HIV testing should be evaluated for TB, regardless of HIV test results. Patients newly diagnosed with HIV should be screened for cough of any duration, and those reporting cough should be tested for TB prior to ART initiation.

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**Table 1. Performance of Different TB Symptom Screening Algorithms at HIV Testing (n=1169)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. Diagnosed with TB/HIV</th>
<th>Total No. Tested for TB</th>
<th>No. of Missed TB Cases/Total Patients</th>
<th>Total Proportion of TB Cases Diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>153</td>
<td>212</td>
<td>19</td>
<td>151/190 (79)</td>
</tr>
<tr>
<td>Cough &amp; Fever</td>
<td>163</td>
<td>212</td>
<td>20</td>
<td>161/190 (84)</td>
</tr>
<tr>
<td>Any TB symptom ≤ 2 weeks</td>
<td>163</td>
<td>212</td>
<td>20</td>
<td>161/190 (84)</td>
</tr>
<tr>
<td>Any TB symptom ≥ 3 weeks</td>
<td>163</td>
<td>212</td>
<td>20</td>
<td>161/190 (84)</td>
</tr>
</tbody>
</table>

1. Cough symptoms include loss, cough, fever, and night sweats. Any TB symptoms ≥ 2 weeks was defined as any weight loss and/ or cough, night sweats for ≥ 2 weeks.

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721 **OPTIMIZING DIAGNOSTIC ALGORITHMS FOR ACTIVE PULMONARY TUBERCULOSIS IN HIV CLINICS**

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1University of Washington, Seattle, WA, USA, 2Institute for Disease Modeling, Bellevue, WA, USA

**Background:** Most TB deaths are preventable with early diagnosis and treatment among people living with HIV (PLHIV). Current testing algorithms rely on symptom screening and sputum-based diagnostic tests, which are less sensitive among PLHIV and often result in treatment delays and loss to follow-up; nearly 20% of TB cases go undiagnosed in South Africa. Point-of-care (POC) testing in HIV clinics may improve case-detection, thereby reducing TB disease incidence and mortality.

**Methods:** We used EMOD-TB, an individual-based TB transmission model, to estimate the impact of HIV clinic-based screening-diagnostic algorithms on rates of TB disease incidence and mortality in South Africa. The model accounted for the natural history of TB and HIV, disease progression, the TB care cascade, and historical estimates of country-level disease incidence and mortality. The model assumes each algorithm is offered to all clinic attendees beginning in 2016 when receiving HIV testing and annually thereafter. Test sensitivities and specificities differed by HIV status and CD4 count. The five algorithms, with each test based on a preceding positive result, were: 1) Four TB symptom screening (4SS) + GeneXpert (Xpert); 2) 4SS + urine lipoarabinomannan (uLAM) + Xpert (to reduce testing costs); 3) 4SS + uLAM; 4) C-reactive protein (CRP) + uLAM + Xpert; and 5) CRP + uLAM.

**Results:** Incorporating intensified TB case finding into routine HIV testing resulted in a reduction in predicted TB incidence and mortality. The algorithm of 4SS + Xpert yielded the greatest overall decline in TB burden with an estimated additional reduction of 12% (11-13%) in incidence and 16% in mortality (15-17%) from 2016 to 2025 compared to baseline trends. Both 4SS + uLAM and CRP + uLAM + Xpert resulted in reductions of an additional 4% in TB incidence (3-5%) and 6% in TB mortality (7-10%) compared to baseline trends. Administering uLAM before confirmatory testing resulted in a 90% reduction in the number of Xpert tests ordered in the HIV clinic.

**Conclusion:** Incorporating 4SS + Xpert testing into HIV care would significantly reduce TB disease incidence and mortality in South Africa. We predict that HIV clinic-based testing algorithms that incorporate CRP and uLAM would result in smaller declines in burden, however uLAM testing would have a greater relative impact on mortality among PLHIV with lower CD4 counts. HIV clinic-based testing algorithms that incorporate CRP and uLAM should be evaluated in prospective clinical trials with respect to improving TB outcomes among PLHIV.
RURAL AND URBAN DIFFERENCES IN THE IMPACT OF THE XPERT MTB/RIF TEST ON TB CARE

Simon Walusimbi1, Stella Zawedde-Muyanja1, Julius Sendiwa1, Abudnoor Nyombi2, Stavia Turyahabwe2, Andrew Kambugu1, Barbara Castelnuovo1, Yukari C. Manabe3
1Makerere University, Kampala, Uganda, 2Ministry of Health Uganda, Kampala, Uganda, 3Johns Hopkins Hospital, Baltimore, MD, USA

Background: Since 2014, utilization of the Xpert MTB/Rif test (Xpert) for diagnosis of Tuberculosis (TB) has increased compared with smear microscopy in Uganda. In 2016, more than half of the health facilities with onsite Xpert were rural. However, the impact of the increased uptake of Xpert on the care cascade and health outcomes for TB patients remains unclear. We hypothesized that the care cascade for HIV-associated TB in rural health facilities with onsite Xpert would be similar to that of urban health facilities with onsite Xpert.

Methods: We retrieved electronic data on health facility outpatient attendance, number of TB patients diagnosed, treated, and their outcomes from the national HMIS database (June 2016 to July 2017), and rural versus urban placement status of Xpert from the National TB Reference Laboratory reports. We estimated prevalent TB using the total number of outpatients with a diagnosis of any cough or pneumonia. Based on review of local and regional literature, we assumed that 2% of individuals with any cough had TB while 12% of individuals with pneumonia had TB. Of the total prevalent TB, we assumed that 42% had TB/HIV co-infection based on the national TB report of 2016. We computed the absolute counts and percentages for each of the following steps of the TB care cascade: number of prevalent TB patients at the health facility, number of diagnosed TB patients, number of TB patients cured or completed treatment, and number of TB deaths.

Results: Data was obtained from a total of 758,823 patients from 106 health facilities with onsite Xpert of which 57/106 (54%) were rural. Rural health facilities had 299,643 patients (39%) with any cough and 30,197 patients (4%) with pneumonia, while urban facilities had 386,293 patients (51%) with any cough and 42,690 patients (6%) with pneumonia. Rural facilities diagnosed 1,855/4039 (46%) of the estimated prevalent TB/HIV cases versus 5,101/5397 (95%) at urban facilities. Treatment cure/completion was 60% for rural facilities versus 52% for urban facilities (p<0.001). Mortality was similar in rural and urban health facilities (12% rural versus 12% urban).

Conclusion: Despite increased placement of Xpert in rural health facilities, they detected less than half of their prevalent TB cases compared with urban health facilities. Rural facilities had better cure/completion treatment outcomes however, mortality was similar in both settings. Focused interventions are required to address these distinct quality gaps in TB care.

TB PREVENTIVE THERAPY UPTAKE IS HIGH WITH COMMUNITY ART DELIVERY IN SOUTH AFRICA

Adrienne E. Shapiro1, Alastair van Heerden2, Heidi van Rooyen2, Torin T. Schaafsma3, Olivier Koole1, Deenan Pillay3, Jared Baeten1, Connie L. Celum3, Ruanne V. Barnabas1, for the DO ART Study Team
1University of Washington, Seattle, WA, USA, 2Human Sciences Research Council, Pretoria, South Africa, 3Africa Health Research Institute, Mthatha, South Africa

Background: Isoniazid (INH) preventive therapy (IPT) reduces mortality and tuberculosis (TB) in persons with HIV and is recommended for all HIV+ persons in high TB prevalence settings, including South Africa, but uptake is low. Barriers to IPT include lack of provider education and prioritization, screening with non-specific TB symptoms, IPT provided separately from HIV services, and monthly clinic visits for refills. Our objective was to increase uptake of IPT for HIV-infected persons newly initiating ART.

Methods: IPT was integrated into community-based ART in the DO ART Study in peri-urban communities in KwaZulu-Natal, South Africa. DO ART is an ongoing randomized clinical trial with intervention arms providing community-based ART delivery, quarterly refills, mobile monitoring, and access to facility-based services only as needed. Between 7/2017-9/2018, 388 HIV-infected adults (149 (38%) men) received care in the community-based arms including ART initiation and at least one follow-up visit. Participants were screened by lay health workers for TB symptoms and contraindications to IPT at every visit. Eligible participants were offered IPT starting 1 month after ART initiation. IPT refills were made quarterly and synchronized with ART. We assessed IPT acceptance, refusal, and receipt of a first refill as indicators of feasibility and acceptability. In 7/2018, we began testing urine for INH metabolites at community IPT refill visits to confirm self-reported IPT adherence.

Results: 388 participants who received community-based ART were screened for IPT eligibility. 355 (91%) were eligible and initiated IPT. There were 10 refusals, 5 of whom initiated IPT at a subsequent visit. 99% participants reported no side effects or toxicities. 3 persons self-discontinued IPT due to side effects. Self-reported adherence was high. 94% completed a first refill visit and received an indicated IPT refill. Urine testing confirmed presence of INH in 21 (38%) men) reported incontinence, refusal, and receipt of a first refill as indicators of feasibility and acceptability. In 7/2018, we began testing urine for INH metabolites at community IPT refill visits to confirm self-reported IPT adherence.

Conclusion: High levels of IPT uptake and continuation were achieved in a community-based ART project, and demonstrated feasibility, high safety, adherence, and acceptability in South Africa. Community-based IPT can be effectively provided in a differentiated HIV care model with infrequent clinic contacts, and may have better uptake than clinic-based IPT. Urine testing can complement self-reported adherence.
EVALUATION OF PULMONARY TUBERCULOSIS FOLLOWING IPT IN KENYAN ADULTS LIVING WITH HIV

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1University of Washington, Seattle, WA, USA, 2Kenyatta National Hospital, Nairobi, Kenya, 3Seattle University, Seattle, WA, USA, 4Ministry of Health, Nairobi, Kenya

Background: Isoniazid preventive therapy (IPT) is a proven intervention to reduce tuberculosis (TB)-related morbidity and mortality among people living with HIV (PLHIV). The World Health Organization (WHO) recommends a symptom screen to rule-out TB prior to administering IPT. Previous studies have shown decreased sensitivity of the symptom screen in ART-treated individuals. TB incidence following IPT administered under programmatic conditions has not been well-described. We performed a study in Kenya to assess the incidence of TB in ART-naïve and -treated individuals receiving ART and to assess the accuracy of the WHO symptom screen and other tests for the rule-out of TB disease.

Methods: We enrolled PLHIV at two HIV care clinics in Nyanza region, Kenya. Patients who were IPT-naïve or had completed IPT at least 6 months prior to enrollment were eligible. We collected demographic, clinical, and laboratory data including blood for potential TB biomarkers (C-reactive protein [CRP], HIV viral load, CD4 count, monocyte:lymphocyte ratio, platelets, hemoglobin), and sputum sample for AFB-smear, -culture, and GeneXpert MTB/RIF (Xpert) testing. In bivariate analyses, we assessed the relationship between TB (culture-positive) and clinical characteristics (body mass index [BMI], antiretroviral therapy [ART]), WHO TB symptom screen, and potential TB biomarkers.

Results: Between March 2017 and June 2018, we enrolled 389 participants (Table). 87.8% of participants had previously received IPT (median days since IPT completion = 394 [280-539 IQR]). TB was diagnosed in 5 participants (1.3%, 95% confidence interval [CI] 0.4-3.0%), and was higher among IPT-naïve (4.3%, 95% CI 0.5-14.5%) than IPT-treated (0.9%, 95% CI 0.2-2.6%) participants. The rate of TB following completion of IPT was 0.8 per 100 person-years (95% CI 0.3-2.4). Among the 3 participants with post-IPT TB, 2 had a prior history of treated TB disease. One participant was diagnosed with INH-resistant TB. All participants diagnosed with TB had negative WHO symptom screens, negative AFB-smears, and 4 of 5 had negative Xpert testing. The sensitivity of all candidate biomarkers for TB was poor including CRP > 8 mg/L (40%), hemoglobin < 10g/dl had the best performance (60% sensitivity, 86% specificity).

Conclusion: IPT provided under programmatic conditions is effective. The WHO symptom screen and candidate tests were insensitive for TB disease in PLHIV on ART. A positive history of TB may be a risk factor for TB after IPT.
726 MYCOBACTERIUM TUBERCULOSIS COINFECTION INCREASES HIV RESERVOIR SIZE
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Shanghai Public Health Clinical Center, Shanghai, China

Background: Tuberculosis (TB) is the most frequent opportunistic infection among people living with HIV. The contribution of Mycobacterium tuberculosis (MtB) co-infection in HIV reservoir establishment and maintain is not clear, hindering HIV/TB co-infected persons benefit from HIV cure strategy.

Methods: We prospectively enrolled 38 HIV-infected participants with culture-confirmed TB and 35 participants with HIV mono-infection naive to therapy. Participants received antituberculosis and/or antiretroviral therapy (ART) accordingly. Blood samples were collected from all the participants prior to therapy and after a median of 12 months of ART. Total HIV-DNA in peripheral blood mononuclear cells (PBMC) were quantified by real-time PCR. Plasma levels of interleukin-7 (IL-7), the key cytokine in the development and hemoiosis of T cells, were measured by ELISA.

Results: Levels of total HIV-DNA among participants with HIV-TB co-infection was significantly higher than that in HIV mono-infected participants at pre-ART (3.34 ± 0.42 lg10/10^6 PBMC vs 2.70 ± 0.45 lg10/10^6 PBMC, P<0.001). M.tb co-infection was identified as the only predictor of high HIV DNA level (Table). After 12 months of ART, the HIV reservoir size decreased significantly, which was positively correlated with their pre-ART level. HIV/TB co-infected participants, who had already been cured for TB, maintained a larger reservoir size compared to HIV mono-infection participants (2.86 ± 0.36 lg10/10^6 PBMC vs 2.09 ± 0.60 lg10/10^6 PBMC, P<0.001). Multiple linear regression analysis showed that M.tb co-infection contribute to HIV-DNA independent of pre-ART HIV DNA level (P=0.033). Mechanically, plasma levels of IL-7 was significantly higher in HIV/TB co-infected participants than that in HIV mono-infection participants at both pre-ART (20.94±10.13 pg/ml vs 9.10±7.05 pg/ml, P<0.001) and on-ART (16.26 ± 9.54 pg/ml vs 7.35± 5.36 pg/ml, P=0.004). Level of IL-7 was positively correlated with HIV-DNA level (R=0.33, P<0.01).

Conclusion: M.tb co-infection contributes to a larger size of HIV reservoir in HIV infection. Interventions targeting IL-7 may reducing HIV reservoir size in this population and warrant further investigations.

727 FUNDAMENTAL SHIFTS IN HIV POPULATION STRUCTURE AFTER TB-IRIS
Camille Lange, Maura Manion, Rob Gorelick, Natalie Lindo, Christian Gonzalves, James Virga, Virginia Sheikh, Gregg Roby, Joseph Adelsberger, Frank Maldarelli, Irini Sereti

Background: Initiation of antiretroviral therapy (ART) in HIV-infected patients with pulmonary tuberculosis (TB) is associated with rapid reconstitution of CD4+ T cells, which may lead to expansion of Th1-type responses and respiratory compromise via TB-immune reconstitution inflammatory syndrome (TB-IRIS). Mechanisms driving pulmonary inflammation in HIV/TB are unclear. We hypothesized that rapid recovery of antigen (Ag)-specific CD4+ T cell responses on ART are associated with worsening pulmonary inflammation and lung function.

Methods: We enrolled a cohort of HIV-infected, ART-naive adults with pulmonary TB in Tembisa, South Africa. Lung inflammation was assessed using 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) at baseline (ART initiation) and four weeks following ART initiation to measure lung total glycolytic activity (TGA). Changes in lung function were assessed using spirometry (% predicted forced expiratory volume in 1 second [FEV1%]) at both time points. Intracellular cytokine staining and flow cytometry were used to determine the frequency of CD4+ T cells expressing IFNγ, IL-2 and/or TNF-α in response to PPD. Wilcoxon rank-sum test was used to compare functional responses at baseline, week 4, and change from baseline to week 4 among participants who had increase versus decrease in 1) lung TGA and 2) FEV1% on ART. P values were corrected for multiple comparisons.

Results: Thirty subjects, with a mean age of 38 years (range 27-49), a median CD4 count of 112 (IQR 48-294), of whom 15 (50%) were females, completed both FDG PET-CT scans. Those with increases in lung TGA had similar baseline, but markedly greater increases from baseline to week 4 post-ART initiation in total IFNγ- and TNF-α+ (Figure 1A), as well as dual IFNγ+/TNF-α+ and TNF-α+ monofunctional CD4+ T cells (Figure 1B) (all p<0.01). Similarly, subjects with an incident FEV1% drop on ART (median drop of -9% [IQR -14 to -4]) had similar baseline, but greater changes and week-4 levels of TNF-α+ monofunctional CD4+ T cells (all p<0.03) versus participants whose FEV1% did not drop.

Conclusion: Rapid increases in TB-specific CD4+ T cells expressing IFNγ- and/or TNF-α soon after ART initiation in HIV/TB co-infected patients is associated with incident pulmonary inflammation and decreased lung function.
729 HIV TEST YIELD AND REASONS FOR UNKNOWN HIV STATUS AMONG TB PATIENTS: THE KOPANYO STUDY
Xiao Jun Wen1, Othussite Fane2, Matsiri Opogopotse3, Mbathi Dima2, Eleanor Click1, Patrick Moonan1, John Oeltmann1, Rosanna Boyd1, Chawangwa Modongo1, Christopher Sergio3, James Tobias4, Alyssa Finlay1, Nicola M. Zetola1, 4
1CDC, Atlanta, GA, USA, 2Botswana–UPenn Partnership, Gaborone, Botswana, 3CDC Botswana, Gaborone, Botswana, 4Northrop Grumman Corp, Atlanta, GA, USA

Background: Botswana is approaching global targets for testing, treatment and viral suppression for HIV. With fewer people living with unknown HIV status, it is more difficult and costly to find and test the remaining few that could benefit from HIV treatment. Based on PEPFAR program reports, the overall yield of HIV testing activities in Botswana was about 5% in 2017. Testing tuberculosis (TB) patients for HIV is a high-yield activity. Our objective was to examine HIV test yield among TB patients never tested previously or with undocumented HIV status and the reasons for unknown HIV status at the start of anti-TB treatment among patients enrolled in a multiyear, population-based TB transmission study in Botswana – the KOPANYO study.

Methods: During September 2012 – March 2015, all persons registered with TB in Gaborone and Ghanzi Districts, Botswana were eligible for the study. At enrollment, all TB cases were offered HIV testing in accordance with national guidelines, except those previously documented positive and tested negative within 90 days before enrollment. HIV test results were recorded. The reasons for no results were documented.

Results: Among 4331 TB patients enrolled, 14% (623/4331) never tested previously nor had documented HIV status at the start of anti-TB treatment. Of these, 77% (480/623) were tested for HIV during the course of treatment - including 23% (110/480) patients newly diagnosed with HIV. Of all participants, 77% (480/623) were tested for HIV during the course of treatment – the percent of CD4+ T-cells positive for IFNγ, E-2, or TNF-α after stimulation with PPD among participants with increasing (≥12, red) vs. unchanged or decreasing lung TCG (≥18, blue). Of these 143 patients, 65% (93) outright refused HIV testing without providing an explanation. Of those 143 patients, 77% (480/623) were tested for HIV during the course of treatment – the percent of CD4+ T-cells expressing each of seven possible combinations of IFNγ, E-2, and TNF-α after stimulation with PPD.

Conclusion: In this analysis, we found that among the TB patients with unknown HIV status, HIV testing yield was 23%, 4 times higher than other HIV-testing activities in Botswana (5%). However, an unacceptable proportion of HIV status results remained unknown due to patient refusal, or logistical reasons. Further research is needed to understand why patients refuse testing.

730 TIMING AND INCIDENCE OF HIV-ASSOCIATED TUBERCULOSIS: A 4-COUNTRY STUDY
Enrico Girardi1, Yanink Caro-Vega2, Jospeh Musaazi1, Gabriela Carriquiry4, Alessandro Cozzi-Lepri5, Barbara Castelnuovo3, Andrea Gori1, Yukari C. Manabe7, Christopher Serumola3, James Tobias4, Alyssa Finlay1, Nicola M. Zetola1, 1Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, 2Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, 3Infectious Disease Institute, Kampala, Uganda, 4Università Perugia-Osaka Heredia, Lima, Peru, 5University College London, London, UK, 6University of Milan, Milan, Italy, 7Johns Hopkins University, Baltimore, MD, USA

Background: Scale up of combination antiretroviral therapy (cART) has a profound impact on the risk of developing tuberculosis (TB) in persons with HIV, both in low and high TB burden countries. Nonetheless, TB remains a major cause of morbidity and mortality in persons with HIV. Knowledge of timing and determinants of TB risk is essential to designing strategies to address this issue.

Methods: The study was conducted in four countries with different TB burden (Uganda, Peru, Mexico, and Italy). We analyzed data of persons enrolled in HIV observational cohorts (one multicenter cohort COINA – Italy and 3 single institution cohorts: ININSE-Mexico, IMARTH-Pere and IDI-Uganda) from 2006-2016. Cases of TB diagnosed at first presentation (within 3 months of HIV diagnosis/initiation of HIV care) were identified. Factors associated with the risk of having TB at enrollment were identified by multivariable logistic regression. Incidence rates of TB from enrollment were calculated, and Poisson regression model was used to identify factors associated with the incidence of TB in the study population.

Results: The analyzed cohort included 24,043 persons of whom 2,455 (10.2%) were diagnosed with TB. TB was diagnosed at first presentation in 1763 (72%), in 260 (11%) at least 3 months after presentation and before cART start, and in 432 (18%) after cART initiation. Proportion of cases diagnosed at first presentation ranged from 69.9% in Uganda to 82% in Mexico. Presentation for HIV care with low CD4 cell count was a strong risk factor for TB in all countries. Preventive therapy was infrequently reported in these patients (<2%). Incidence of TB after cART initiation ranged from 13.3 per 1000 person-years in Uganda to 0.83 in Italy. Incidence declined rapidly during the first year of treatment in all countries. After 12 months of treatment however, it remained higher than the background incidence in each country (Table).

Conclusion: Timing of TB diagnosis among persons with HIV was remarkably similar in all four countries despite different TB burdens. More than three-quarters of cases were diagnosed upon presentation to HIV care and were associated with low CD4 cell count. Early HIV diagnosis and immediate initiation of cART may be the most important intervention to further decrease the risk of HIV-associated TB. Additional prevention interventions, such as preventive therapy, may be needed, however, in particular during the first year of cART.

Table. Timing and incidence of tuberculosis (TB) among persons enrolled in HIV observational cohorts in four countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence of TB after cART initiation</th>
<th>Incidence of TB after cART initiation per 1000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>2.93 (2.80 – 3.07)</td>
<td>20.35 (19.18 – 21.52)</td>
</tr>
<tr>
<td>Peru</td>
<td>2.23 (2.18 – 2.29)</td>
<td>18.59 (17.61 – 19.57)</td>
</tr>
<tr>
<td>Mexico</td>
<td>1.93 (1.84 – 2.03)</td>
<td>20.35 (19.18 – 21.52)</td>
</tr>
<tr>
<td>Italy</td>
<td>1.98 (1.85 – 2.11)</td>
<td>17.85 (16.68 – 19.02)</td>
</tr>
</tbody>
</table>

*Higher than the background incidence in each country (Table).

731 HIGH INCIDENCE OF TUBERCULOSIS AMONG HIV+ PATIENTS TREATED WITH HAART IN ZAMBIA
Simon Mutembo1, Jane N. Mutanga1, Vincent C. Marconi2, Christopher Whalen1
1Government of Zambia Ministry of Health, Lusaka, Zambia, 2Emory University, Atlanta, GA, USA

Background: Tuberculosis (TB) is the leading cause of morbidity and mortality among Human Immunodeficiency Virus (HIV+) patients. The risk of TB among HIV+ patients on combination Anti-Retroviral Therapy (cART) is heterogeneous depending on the timing of cART. However, it is not known whether there are differences in the risk of TB among HIV+ patients accessing cART in rural and urban health settings in sub-Saharan Africa. In urban settings, high TB incidence is sustained by the high HIV prevalence and crowded living conditions. Rural settings have distinct challenges which drive the TB and HIV epidemic. These include poor health care access, lack of diagnostics and severe shortage of
health care providers. Therefore, it is important to understand differences in the risk of TB between these 2 populations. To address this knowledge gap, we evaluated the risk of TB among HIV+ patients on cART.

**Methods:** We performed a retrospective cohort study on a sample of HIV patients who started CART between 2005 and 2014 within the Zambia National ART Program. We estimated the Incidence Rates (IR) of TB per year at risk of TB was accrued from the date of starting cART until diagnosis of TB. To assess the risk factors associated with incident TB, Cox proportion hazard regression was performed.

**Results:** Overall 1,518 patients met the eligibility criteria (rural: 33%; urban: 67%). At the time of initiating CART 82 (5.4%) were diagnosed with prevalent TB. New cases of TB were diagnosed for 244 (4.7%) patients with prevalent TB. Patients not diagnosed with TB at the start of cART were 90% more likely to be diagnosed with TB during follow up on cART (aHR = 0.9, 95% CI: 0.8–0.9). The incidence of TB was not associated with rural/urban health care setting (aHR = 1.0, 95% CI: 0.9–1.0). As compared to patients with prevalent TB, patients not diagnosed with TB at the start of cART were 90% more likely to be diagnosed with TB during follow up on cART (aHR = 1.9, 95% CI: 1.1–2.7). Community ART Refill Groups (CARGs) are an antiretroviral (ART) differentiated service delivery model in which stable clients on ART form into groups, with a single individual collecting ART for all group members. In focus group discussions, healthcare workers suggested that CARGs may reduce rates of diagnosed tuberculosis (TB) either due to reduced frequency of TB screening by healthcare workers or through reduced transmission with clients no longer gathering at the clinic. We evaluated if facilities with a larger proportion of clients in CARGs had fewer ART clients initiating TB treatment.

**Methods:** This analysis used data from two six-month time periods: October 2016 to March 2017 and October 2017 to March 2018. The exposure of interest was the proportion of ART clients at each facility who were in CARGs. The outcome was the number of ART clients who started TB treatment in the six-month period, and the number of ART clients at each facility was used as an offset to estimate rates. To evaluate the association, we used a mixed-effects generalized linear model with random effects for each facility, a negative binomial family, log link, and robust standard errors.

**Results:** 181 facilities were included in the analysis. In the earlier 6-month period 2.0% (3,401/170,114) of ART clients were in CARGs compared to 14.6% (28,595/195,443) in the later 6-month period, and 0.6% (2,016/365,557) of ART clients started TB treatment per 6-month period. We found that within any given site, the rate at which ART clients initiated TB treatment when the site had 10–30% of its ART clients in CARGs was 0.85-times (95% CI: 0.62–1.15) the rate compared to having <10% of clients in CARG. When any given site had more than 30% of its ART clients in CARGs, it had 0.54-times (95% CI: 0.36–0.79) the rate compared to having <10% of clients in CARGs. This multivariable model adjusted for facility type, facility size, and time period.

**Conclusion:** Sites with a larger proportion of ART clients in CARGs experienced a lower rate of ART clients starting TB treatment. This may reflect a decline in active TB cases among CARG members due to improved ART adherence and/or reduced TB exposure at clinic waiting areas. However, it is also possible that reduced frequency of clinic visits among CARG members is resulting in undiagnosed TB cases. Community-level TB screening among CARG members may be one solution to address this possibility.
IN BOTSWANA
HIGH RATES OF TB IN THE FIRST 6 MONTHS OF DOLUTEGRAVIR-BASED ART IN BOTSWANA
Lucy Mupfumi1, Sikhulile Mayo1, Ava Avalos2, Lesedi Bewlay3, Kaelo Seatlai4, Sanghyuk S. Shin1, Ishmael Kasvosve1, Nicola M. Zetola1, Simani Gasetsiwe1, for the BEAT Cohort Study Team
1Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, 2Ministry of Health, Gabarone, Botswana, 3Botswana–UPenn Partnership, Gabarone, Botswana, 4University of Botswana, Gabarone, Botswana
Background: Tuberculosis (TB) remains a major problem among HIV-infected persons in sub-Saharan Africa with most cases of unmasking TB occurring within the first few months of antiretroviral therapy (ART) initiation. As one of the first countries in sub-Saharan Africa to roll out dolutegavir (DTG)-based ART as first line therapy, we sought to determine the incidence of TB in patients initiating DTG-based ART between March 2016 and June 2018 in Gabarone, Botswana.
Methods: The Botswana Epidemiological ART Treatment (BEAT) Cohort is an operational research cohort study that was established in 2017 to determine DTG-vs-Efavirenz (EFV) based ART treatment efficacy, monitor drug resistance and the implementation of the Treat All Strategy. Trained research assistants abstracted data from electronic and manual patient records of those initiating ART at five clinics in Gabarone.
Results: We analyzed data from 737 patients with a median time on ART of 7 months (interquartile range [IQR]; 3, 12), mostly female (60%). Among those with baseline CD4+ T-cell count data (n=219, 30%), the median count was 387cells/µl (IQR; 219, 577). At ART initiation, 1% (n=10) of the patients had an active TB diagnosis. By 3 months on ART, 97% (n=265/273) of the patients had undetectable viral loads. 686 patients contributed 481 person-years of follow-up for an incident rate of 3.75/100py (95% CI: 2.36-5.94). Most (89%) of the TB cases occurred within the first 6 months of initiation (IR= 26.42/100py, 95%CI 16.18-43.12) with only one case occurring post one year of ART (Figure 1). Neither older age (HR 1.03, 95%CI: 0.95-1.11) nor male gender (HR 0.47, 95% CI: 0.08-2.62) predicted TB incidence.
Conclusion: We found high rates of TB within the first six months of initiating DTG-based ART, which suggests that most TB cases are due to missed diagnosis or unmasking of subclinical TB. Improved screening strategies for TB prior to ART initiation are needed to reduce the burden of TB in ART programmes.

KIDNEY DISEASE IN AFRICANS WITH HIV AND TUBERCULOSIS
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1University of Cape Town, Cape Town, South Africa, 2Barts Health NHS Trust, London, UK, 3King’s College London, London, UK, 4University College London, London, UK, 5King’s College Hospital NHS Foundation Trust, London, UK
Background: Tuberculosis (TB) is common in Africans with HIV. TB, HIV and the drugs to treat these infections may all have acute or chronic effects on the kidney although this has not been well studied. We investigated kidney function and kidney pathology in Africans with HIV/TB in three cohorts.
Methods: We studied kidney function over 12 months from TB diagnosis in consecutive HIV/TB patients in South London (UK, 2004-2016), and kidney pathology in consecutive HIV/TB autopsies performed in Abidjan (Cote d’Ivoire, 1991) and in consecutive HIV/TB kidney biopsies performed in Cape Town (South Africa, 2014-2017). Acute kidney injury (AKI) was defined by KDIGO stages 2/3, chronic kidney disease (CKD) by estimated glomerular filtration rate (eGFR) <60 (mL/min/1.73m2) for >3 months and severe CKD by eGFR <30. The amount of chronic damage in kidney biopsies was assessed as mild (<25%), moderate (25-50%) or severe (>50%). In the Cape Town cohort, predictors of recovery of kidney function at six months were assessed using Cox regression.
Results: In the London cohort (median [IQR] eGFR at TB diagnosis: 118 [88-129]), the incidence of moderate/severe AKI was 15.1 (95%CI 8.6-26.5) per 100 person-years, and the prevalence of CKD and severe CKD 13.7% and 7.4% respectively. Pathologically-confirmed HIV-associated nephropathy (HIVAN) was diagnosed in 6.3% of patients in London and 6.0% of autopsies in Abidjan. Renal tuberculosis was present in 60% of autopsies in Abidjan. Patients in the Cape Town cohort had severe kidney failure (median eGFR: 9), with often multiple renal pathologies on biopsy: 59% had renal TB, 43% HIVAN and 64% acute tubular necrosis (ATN). The majority of biopsies showed mild (61%) or moderate (23%) chronic damage, and substantial recovery of kidney function was noted at six months with 36%, 53% and 35% of those with HIVAN, ATN and renal TB having eGFR >60 and a further 28%, 19% and 21% having eGFR 30-59. ART status, CD4 count, eGFR at biopsy and renal pathology were not predictive of eGFR recovery (>60 or >30).
Conclusion: Acute and chronic kidney disease was common in Africans with HIV/TB. HIVAN, ATN and renal TB were common aetiologies, and improvement of kidney function was frequently observed irrespective of the severity of renal impairment or kidney disease aetiology. Close monitoring of kidney function and provision of renal replacement therapy to those with severe kidney failure is warranted in African patients with HIV/TB.

Acute and chronic kidney disease was common in Africans with HIV/TB. HIVAN, ATN and renal TB were common aetiologies, and improvement of kidney function was frequently observed irrespective of the severity of renal impairment or kidney disease aetiology. Close monitoring of kidney function and provision of renal replacement therapy to those with severe kidney failure is warranted in African patients with HIV/TB.
Table: Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>London cohort (n=95)</th>
<th>Abidjan cohort (n=100)</th>
<th>Cape Town cohort (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>37.8 (10.4)</td>
<td>36.4 (10.2)</td>
<td>38.4 (9.8)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>49 (52)</td>
<td>23 (23)</td>
<td>26 (45)</td>
</tr>
<tr>
<td>Black African, n (%)</td>
<td>95 (100)</td>
<td>100 (100)</td>
<td>58 (100)</td>
</tr>
<tr>
<td>CD4 count, median (IQR)</td>
<td>90 (26-199)</td>
<td>Not available</td>
<td>70 (28-201)</td>
</tr>
<tr>
<td>Log HIV RNA, median (IQR)</td>
<td>5.1 (4.0-5.7)</td>
<td>Not available</td>
<td>2.8 (1.5-4.6)</td>
</tr>
<tr>
<td>eGFR, median (IQR)</td>
<td>118 (68-129)</td>
<td>Not available</td>
<td>9 (5-18)</td>
</tr>
<tr>
<td>Kidney pathology (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HIVAN</td>
<td>6 / 7</td>
<td>6 / 6</td>
<td>25 / 43</td>
</tr>
<tr>
<td>- Interstitial nephritis</td>
<td>2 / 7</td>
<td>31 / 31</td>
<td>8 / 14</td>
</tr>
<tr>
<td>- TB (granulomas/AFB)</td>
<td>0 / 7</td>
<td>60 / 60</td>
<td>34 / 59</td>
</tr>
<tr>
<td>- Acute tubular necrosis</td>
<td>0 / 7</td>
<td>5 / 5</td>
<td>37 / 64</td>
</tr>
</tbody>
</table>

736 MORTALITY AFTER PRESUMED TB TREATMENT COMPLETION IN PERSONS WITH HIV IN LATIN AMERICA
Serena Koenig1, Ahra Kim1, Bryan E. Shepherd2, Carina Cesar3, Valdieva Veloso4, Claudia P. Cortes5, Denis Padgett6, Brenda Crabtree-Ramirez7, Eduardo Gotuzzo6, Catherine McGowan8, Timothy R. Sterling1, Jean William Pape9, for the The Caribbean, Central and South America Network for HIV Epidemiology (CCASAnet)  
1Brigham and Women’s Hospital, Boston, MA, USA, 2Vanderbilt University, Nashville, TN, USA, 3Fundación Huésped, Buenos Aires, Argentina, 4Instituto Nacional de Infectología Evandro Chagas (Instituto Evandro Chagas/Goiânia), Goiânia, Goiás, Brazil, 5Fundación Arriarán, Santiago, Chile, 6Hospital Escuela Universitaria, Inegi, Guayaquil, Ecuador, 7Escuela Universitaria, Tegucigalpa, Honduras, 8Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, 9Universidad Peruana Cayetano Heredia, Lima, Peru, 10GHESSK, Port-au-Prince, Haiti  

Background: Several studies in HIV-negative cohorts have suggested that the risk of mortality is increased after tuberculosis (TB) cure, compared to individuals without TB. Data are limited on long-term survival after TB cure among people living with HIV (PLWH).  

Methods: The study cohort included PLWH who were ≥18 years of age and who were ART-naïve at first clinic visit at a CCASAnet clinical site in Brazil, Chile, Haiti, Honduras, Mexico, or Peru from 2006 to 2015. Baseline TB was defined as TB diagnosed within 30 days before or after enrollment. Follow-up started at 9 months after enrollment or date of TB diagnosis, as a proxy for TB treatment completion in those with baseline TB. We compared time to death among patients with and without baseline TB, using Kaplan-Meier analysis and the log-rank test. We estimated predictors of mortality with univariable and multivariable Cox models, stratified by site and adjusting for baseline TB, sex, mode of transmission, education, age, year of enrollment, and CD4 count.  

Results: Of 15,917 patients, 1306 (8.1%) were diagnosed with TB at baseline. Of these, 15,999 patients remained in care 9 months after enrollment and were included in the analysis; 1051 (6.6%) had baseline TB. Patients with TB were more likely to be male, older, less educated, with lower CD4 counts, and residing in Haiti or Peru. Starting 9 months after enrollment (Figure 1), patients with a history of baseline TB had higher long-term mortality compared with those without baseline TB (p-value < 0.001). The unadjusted 5-year mortality (measured from 9 months after enrollment) was 10.0% for patients with baseline TB vs. 5.6% in those without baseline TB; 10-year mortality was 19.1% vs. 10.5%, respectively. In multivariable Cox models, increased mortality was associated with baseline TB (hazard ratio [HR] = 1.53, 95% confidence interval [CI]: 1.21-1.93), lower CD4 count (100 vs. 350 cells/mm³: HR = 1.59, 95% CI: 1.45-1.76; 500 vs. 350 cells/mm³: HR = 0.89, 95% CI: 0.81-0.99), older age (age 55 vs. 35: HR = 1.52, 95% CI: 1.29-1.79), and lower education (none vs. at least secondary: HR = 1.21, 95% CI: 0.90-1.64).  

Conclusion: PLWH who present with baseline TB have an elevated risk of long-term mortality, even after TB treatment completion. Further study is necessary to understand the long-term clinical impact of TB disease in PLWH.

737LB WITHDRAWN / INTENTIONALLY UNASSIGNED

738 RIFAMPIN-RESISTANT TUBERCULOSIS IN THE UNITED STATES, 1998–2014
Lisa Sharling1, Suzanne Marks2, Terence Chorba1, Sundari Mase1  
1CDC, Atlanta, GA, USA, 2WHO South-East Asia, New Delhi, India  

Background: Rifampin is the backbone of the standard regimen for tuberculosis. Monoresistance to rifampicin necessitates longer and more toxic regimens and is a precursor to multidrug resistance. We examined characteristics and mortality associated with rifampin–monoresistant TB (RMR) in the United States.  

Methods: We analyzed Mycobacterium tuberculosis culture-positive cases reported to the National TB Surveillance System (excluding California because HIV infection of TB cases was not reported to CDC during 2005-2010) between 1998 and 2014. We defined: (1) RMR-TB found on initial drug susceptibility testing, and (2) possible acquired rifampin-resistant TB (ARR). We assessed temporal trends in RMR-TB. We calculated adjusted risk ratios (adjRR) and 95% confidence intervals (CI) for social and clinical characteristics associated with RMR-TB, mortality with RMR-TB, ARR-TB, and mortality with ARR-TB compared to drug-susceptible TB (DS) in multivariable models. Time to sputum culture conversion was assessed using medians and interquartile ranges (IQR).  

Results: Of 180,329 TB cases, 136,561 (76%) were eligible for analysis, with 359 (0.26%) of eligible cases reported as RMR. Similar to the decline in HIV/TB over the period, the percentage of RMR cases with HIV declined significantly over time. Persons with HIV and prior TB were more likely to have RMR (adjRR=8.8, CI:5.2-14.8) as were persons with HIV and no prior TB (adjRR=3.1, CI:2.4-4.1), versus those without either characteristic, controlling for age ≥ 65 (adjRR=0.4, CI:0.3-0.6) and black race (adjRR=0.7, CI:0.5-0.9). RMR cases had significantly greater mortality (adjRR=1.4, CI:1.04-1.8), controlling for HIV (adjRR=2.9, CI:2.7-3.0), directly observed therapy (DOT; adjRR=0.79, CI:0.76-0.82), and other variables. Persons with HIV also had greater risk of ARR than persons without HIV (adjRR=9.6, CI:6.9-13.3). ARR was also associated with increased mortality (adjRR=2.4, CI:1.8-3.4), controlling for DOT (adjRR=0.5, CI:0.4-0.6) and other variables. There was a significant P<0.01 delay in sputum culture conversion for RMR cases (median 60 days, IQR 38-95 days) compared with median time for DS cases (49 days, IQR 26-77 days), and for ARR cases (median 190 days, IQR 75-362 days) compared with that of rifampin- and isoniazid-susceptible cases (median 76, IQR 53-110 days).  

Conclusion: All forms of rifampin resistance were positively associated with HIV co-morbidity, delayed culture conversion, and increased mortality (controlling for HIV, and age, and DOT).

739 GLOBAL DISPARITIES IN PRICES OF KEY MEDICINES FOR MULTIDRUG-RESISTANT TUBERCULOSIS
Andrew Hill1, Dzintars Gotham2  
1University of Liverpool, Liverpool, UK, 2Independent, Boston, MA, USA  

Background: Worldwide, 245,000 people with HIV died from TB coinfection in 2016, with 30,000 of those deaths due to drug-resistant TB. Multidrug-resistant (MDR) TB is increasing in prevalence, but only 54% of notified MDR-TB cases are
treated and cured, and <25% of those who could benefit from newer MDR-TB treatments receive them. 

Methods: We compared prices for 7 medicines prioritized in current WHO guidelines: bedaquiline, delamanid, linezolid, moxifloxacin, levofloxacin, cycloserine, and amikacin. Price data were gathered from national price sources for 41 countries in North America, Europe, the Middle East, South East Asia, India, and South Africa, and converted to the price for a month of treatment at standard doses. For all medicines except amikacin, only solid oral forms were used. 

Results: Monthly prices of MDR-TB medicines are displayed in the Table, for selected countries. As context, we include estimates of generic prices calculated in a previous analysis, based on analysis of the wholesale prices of the active pharmaceutical ingredients and other costs of production. For moxifloxacin, levofloxacin, linezolid, and amikacin, price data were available for more than 30 of the 47 countries. Data were limited for the other medicines, with prices of bedaquiline available only for 15 countries, cycloserine 9, and delamanid 4. Prices for a month of treatment ranged $94-5,273 for bedaquiline, $3,070-6,614 for delamanid, $7-4,856 for linezolid, $4-3,526 for amikacin, $48-2,501 for cycloserine, $1-674 for levofloxacin, and $4-206 for moxifloxacin. These were in most cases significantly higher than previously estimated generic prices (e.g. $8-17/month for bedaquiline, $5-16/month for delamanid).

Conclusion: Prices of key MDR-TB medicines remain very high in many countries. The low availability of pricing data for bedaquiline, delamanid, and cycloserine may reflect unavailability in many countries. Global price differences are large for MDR-TB medicines, both for patented medicines (bedaquiline and delamanid, with linezolid recently off-patent) and to a lesser extent generics (all others). Attention is drawn to the high prices charged in ex-Soviet bloc countries that, despite now being classed as high-income countries or upper-middle-income in the case of Bulgaria, have relatively underresourced health systems and high burdens of MDR-TB (e.g. Bulgaria, Latvia, Lithuania, Slovenia).

### Table: Multivariate Logistic Regression Model Predicting AG-induced Hearing Loss 

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.04 (1.01-1.07)</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.00 (0.98-1.02)</td>
<td>0.70</td>
</tr>
<tr>
<td>≥25</td>
<td>2.08 (1.04-4.16)</td>
<td>0.04</td>
</tr>
<tr>
<td>≤75</td>
<td>1.59 (0.82-4.31)</td>
<td>0.17</td>
</tr>
<tr>
<td>Standardized weekly AG exposure (mg/kg/week)</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00</td>
</tr>
<tr>
<td>≤60</td>
<td>1.59 (0.82-4.31)</td>
<td>0.17</td>
</tr>
<tr>
<td>&gt;60</td>
<td>1.59 (0.82-4.31)</td>
<td>0.17</td>
</tr>
<tr>
<td>HIV status &amp; CD4 count (cells/mm³)</td>
<td>1.00 (0.00-0.00)</td>
<td>0.00</td>
</tr>
<tr>
<td>HIV positive</td>
<td>1.59 (0.82-4.31)</td>
<td>0.17</td>
</tr>
<tr>
<td>HIV positive with CD4 ≥ 200</td>
<td>1.59 (0.82-4.31)</td>
<td>0.17</td>
</tr>
<tr>
<td>Serum Albumin (g/l)</td>
<td>1.00 (0.00-0.00)</td>
<td>0.00</td>
</tr>
<tr>
<td>&lt;10</td>
<td>1.59 (0.82-4.31)</td>
<td>0.17</td>
</tr>
<tr>
<td>Baseline hearing loss</td>
<td>1.00 (0.00-0.00)</td>
<td>0.00</td>
</tr>
<tr>
<td>&lt;75%</td>
<td>1.00 (0.00-0.00)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**References:**

1. John Hopkins University, Baltimore, MD, USA, 2. John Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 3. Johns Hopkins University School of Medicine, Baltimore, MD, USA.

**Background:** Individuals treated for drug-resistant tuberculosis (DR-TB) with aminoglycosides (AGs) in resource-limited settings often experience permanent hearing loss, but there is no practical and cost-effective means to identify those at higher risk. We sought to develop a prediction model of AG-induced hearing loss among patients initiating DR-TB treatment in South Africa.

**Methods:** We nested this analysis within a cluster randomized trial of nurse-led case management in 10 South African TB hospitals. All participants ≥13 years old received kanamycin or amikacin. We performed clinical and audiometric evaluations at treatment initiation. Hearing loss was defined as a poorer hearing threshold compared to baseline. We developed the model using data from 265 patients at hearing frequencies from 250Hz to 8kHz and validated the model using data from 114 separate patients at both 250Hz-8kHz and ultrahigh frequencies (9-16kHz). We estimated standardized weekly AG exposure as:

\[ \text{prescribed daily AG dose (mg)} \times \text{frequency of dosing per week} \div \text{weight (kg)} \]

**Conclusion:** This model identifies patients at high risk for AG-induced hearing loss and may inform clinical guidelines regarding which patients to prioritize for injectable-free regimens.
Results: A total of 52,431 tests were extracted, 5,354 positive (10.2%), 180 (0.3%) hetero resistant and excluded from analysis, 3,39 (6.3%) RR and 37 (0.7%) were RR indeterminate. 121 RR results had incomplete Tm values. The attached figure shows clustering of RR Tm’s: mutations (n=280); potential wild types (n=5 to 24 owing to skewing by RF) and unknown (n=35). Average RMSE was 0.3 °C for known Tm profiles.

Conclusion: Ultra and Xpert are clinically used as a qualitative diagnostic for TB and screen for RR. Ultra generates additional information over Xpert through Tm’s which can definitively identify RR conferring mutations and thus provide valuable information for individual patient care and population based surveillance. The algorithm tested here shows good accuracy (c=“***P<“0.001”“).

Table 1. The total cost, number of successful treatments and cost per successful treatment of standard and shortened MDR-TB treatment with and without the use of bedaquiline in 2023

<table>
<thead>
<tr>
<th>Successful treatments</th>
<th>Cost per successful treatment (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard regimen (Baseline)</td>
<td>5,791</td>
</tr>
<tr>
<td>Standard regimen + BDQ</td>
<td>6,489</td>
</tr>
<tr>
<td>% change over baseline</td>
<td>1%</td>
</tr>
<tr>
<td>Shortened regimen + BDQ</td>
<td>6,670</td>
</tr>
<tr>
<td>% change over baseline</td>
<td>-37%</td>
</tr>
</tbody>
</table>

Annual costs (USD millions)

| Standard regimen (Baseline) | 48.22 |
| Standard regimen + BDQ | 54.32 |
| % change over baseline | 11% |
| Shortened regimen + BDQ | 34.10 |
| % change over baseline | -28% |

Neural tube defects, HIV, and antiretrovirals: Birth-defect surveillance in Uganda

Linda Barlow-Moshia1, Daniel M. Mumpfe2, Delhia Williamson3, Diana Valencia4, Robert Sekong4, Joyce N. Matovu1, Philippa Musoke1

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Background: Neural tube defects (NTDs) are one of the most common congenital malformations affecting births worldwide. The estimated NTD prevalence in Africa is 12 per 10,000 live births (95% confidence interval (CI) 5.7-7.5); but data are limited. The impact of antiretroviral therapy (ART) during pregnancy on the risk for birth defects is unknown; therefore, ongoing surveillance is needed for pharmacovigilance.

Methods: A hospital-based surveillance program was established at four hospitals in Kampala, Uganda to provide estimates of the baseline prevalence of selected birth defects and assess potential associations with HIV status and ART use. All live births and stillbirths, regardless of gestational age, were included. Data were collected from hospital records, maternal interviews, photographs, and narrative descriptions of birth defects (BD). Births were examined by trained midwives and confirmed by a BD specialist. Prevalence (Wilson 95% CI) and adjusted odds ratio (AOR) estimates for potential risk factors of NTDs using logistic regression with site as an effect modifier are reported for births from August 2015-December 2017.

Results: A total of 69,767 births were included in surveillance. Median maternal age was 26 years (IQR=22-30). 51.3% had their first antenatal visit after the first trimester, 9.6% (6,725/69,767) were HIV-infected with 95.2% (6,399/6,725) on ART. The majority of HIV-infected women were on an efavirenz-based ART (80%), 16% on nevirapine-based ART and 4% received other ART regimens.

Overall, 62 births were affected with NTDs, giving a prevalence of 8.9 (6.8-11.4) per 10,000 live births. Spina bifida (n=34) was the most common type of NTD with prevalence (95%CI) of 4.9 (3.4-6.6) per 10,000 live births, followed by meningocele (n=16) with 2.3 (1.3-3.7) and encephalocele (n=12) with 1.7 (0.9-3.0). There was no significant difference in NTD prevalence (95%CI) among HIV-infected (95%CI 5.9-11.8) and HIV un-infected women (9.2-11.6); AOR 0.75 (95%CI 0.2-2.2), p=0.61. NTDs were not significantly associated with maternal age, HIV status, ART, or parity.

Anencephaly was more common among females compared to males with site as an effect modifier (AOR of 5.9 (95%CI 1.9-17.9), p=0.002).
Conclusion: NTDs are a common congenital malformation affecting births in Kampala. These findings are similar to the current estimates for Africa. ART was not associated with an increased risk for NTDs. With the introduction of new ART regimens during pregnancy, ongoing BD surveillance is critical.

744 NO INCREASE IN BIRTH DEFECTS IN INFANTS EXPOSED TO INTEGRASE INHIBITORS AT CONCEPTION

Jeanne Sibiude1, Jérôme Le Chenadec1, Laurent Mandelbrot1, Stéphane Blanche1, Catherine Dollfus1, Nathalie Leong1, Elisa Arezes1, Lamya Ait Si Selmí2, Sophie Matheron3, Christinne Rouzouix3, Josiane Warszawski4, Roland Tubiana4, for the ANRS-EPF-C01/C011 study groups


Background: Integrase inhibitors (INSTI) are increasingly used by HIV-infected women during pregnancy. Following an alert on the association of dolutegravir with neural tube defects, we evaluated the risk of birth defects in cases of exposure to this antiretroviral class.

Methods: The French Perinatal Cohort is a multicenter national cohort including all HIV-infected women in 90 maternities. We studied all mother-infant pairs exposed to INSTI, categorized into 3 groups: (G1) ongoing at conception, (G2) initiated during pregnancy, as first-line regimen, and (G3) initiated during pregnancy, as 2nd-line regimen. Within each group, we matched 1:1 to an INSTI-unexposed infant according to other drugs, ethnicity, center, year of delivery, and gestational age at ART-initiation. INSTI exposed women who did not receive PI or NRTI were matched to women receiving darunavir, with the same other drugs. We compared birth defect rates between the 3 INSTI-exposed groups and, for each group, with the respective matched group, using chi2 and McNemar tests.

Results: Overall, 309 infants were exposed to INSTI at conception (G1): 224 to raltegravir, 41 to dolutegravir, and 44 to elvitegravir. Birth defect rates for INSTI-exposed infants at conception (G1: 5.5% [9/170]) did not significantly differ from those of INSTI-exposed infants of the two other groups: 2.7% (5/184) in G2 and 3.0% (10/329) in G3, p=0.18. There was no neural tube defect among infants exposed to INSTI at conception, and only two birth defects among the 41 infants exposed to dolutegravir (a case of Down syndrome, and a persistent ductus arteriosus). When restricting to matched infants, birth defect rates in G1 were not significantly different from the matched INSTI-unexposed group (6.3%, 12/189 vs 3.7%, 7/189, respectively, p=0.26). The EUROCAT types of birth defects were similar for INSTI-exposed at conception and matched infants. There was no difference in stillbirth rates (1.8% vs 0.4%, p=0.37), nor in preterm birth rates (14.3% vs 10.8%, p=0.29) between pregnancies exposed at conception and the matched pregnancies. Among women exposed at conception, 65% were still receiving INSTI at delivery. Similarly, there was no difference in birth defect rates between INSTI-exposed infants in G2 and G3 and the matched unexposed infants.

Conclusion: We found no evidence of a higher birth defect rate among 309 infants exposed to INSTI at conception, mostly exposed to raltegravir, however in the current context, surveillance must be pursued for this class of ART.

745 EVALUATION OF NEURAL TUBE DEFECTS AFTER EXPOSURE TO Raltegravir DURING PREGNANCY


Merck Research Labs, North Wales, PA, USA

Background: The purpose of this comprehensive review is to evaluate the risk of neural tube defects (NTDs) after exposure to raltegravir during pregnancy.

Methods: Exposures to raltegravir during pregnancy reported cumulatively through 31-May-2018 to the company safety database were reviewed. This database includes all reports of pregnancy from Merck-sponsored clinical trials, spontaneous post-marketing and non-interventional data sources, including the Antiretroviral Pregnancy Registry (APR). Reports were classified as prospective (exposure report prior to knowledge of pregnancy outcome) or retrospective (report after knowledge of pregnancy outcome). Pregnancy reports were further reviewed to identify cases of NTDs. We also reviewed data from two ongoing pregnancy cohorts.

Results: A total of 2426 pregnancies with reported outcomes were identified among women exposed to raltegravir: 1238 from the Merck safety database and 1188 from United Kingdom/Ireland and French pregnancy cohorts. Among all 2426 pregnancy reports, 1991 were prospective. No cases of NTDs were identified among the prospective pregnancy reports, of which 767 were first trimester, including 456 in the periconception period (at or within 28 days after conception). Among the 435 retrospective reports, four NTD cases per APR criteria were identified, of which only one (myelomeningocele) was among exposures in the periconception period. Given the inherent limitations and bias of retrospective reports, it is not appropriate to calculate an incidence rate.

Conclusion: Prospectively collected pregnancy outcome data do not suggest an association between raltegravir exposure in the periconception period and NTDs.

746 REPORTS OF NEUROTAUTE DEFECTS FOR 8 ARTS, IN FDA, WHO, EMA, AND UK SAFETY DATABASES

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1Liverpool School of Tropical Medicine, Liverpool, UK, 2London School of Hygiene & Tropical Medicine, London, UK, 3Chelsea and Westminster Hospital, London, UK, 4Chelsea and Westminster NHS Foundation Trust, London, UK, 5Imperial College Healthcare NHS Trust, London, UK, 6Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA

Background: The Botswana TSEPAMO study reported neural tube birth defects (NTDs) in 4/596 (0.67%) infants of women receiving dolutegravir (DTG) antiretroviral therapy (ART) preconception vs 14/11,300 (0.12%) receiving preconception non-DTG ART. Further data are required to confirm or refute this potential safety signal. Pregnant women were excluded from Phase 3 randomised DTG trials and data from other observational studies of DTG in pregnancy are currently limited. Clinicians, patients and pharmaceutical companies can report adverse drug reactions (ADRs) to pharmacovigilance (PV) databases, which could be used to assess potential safety signals.

Methods: 4 PV databases with online data availability were analysed for NTD reports for 4 integrase inhibitors (DTG, raltegravir, elvitegravir, bictegravir), two protease inhibitors (darunavir, atazanavir) and two non-nucleosides (nevirapine, efavirenz): 1. Food and Drug Administration FAERS database (USA) 2. World Health Organisation VigiAccess (WHO) 3. European EudraVigilance (EU), 4. UK Medicine’s Health Regulatory Authority (MHRA). ADR reports in the System Organ Class (SOC) “Congenital or Familial Disorders” were searched for NTDs using the search terms Neural Tube Defect, spina bifida, meningocele, meningomyelocele, anencephaly, encephalocele, and encephalohoeplie

Results: NTDs were reported for all drugs except bictegravir. The number of reported NTD cases with DTG exposure were similar in the FDA and WHO databases, but no cases were reported to EU and UK MHRA (Table 1). Since ART consists of multiple drugs, NTDs could be reported for multiple drugs and from multiple sources for the same patient; for example, for one patient in the FDA database, there were 91 NTD reports for the same patient who received 7 different drugs.

Conclusion: PV databases included reports of NTDs for pregnant women taking a wide range of ARVs. These databases have many limitations — there is no denominator for patient exposure to the drug, reporting is not systematic, there is overlap in reports for multiple drugs given combination ART, duplicate cases are difficult to identify, and results differ between the databases. Given widespread use of multiple new ARVs worldwide, and anticipated use of new drugs (e.g. TAF, bictegravir cabotegravir), prospective follow up of pregnant women and birth surveillance studies such as Tsepamo are critically needed for a wide range of ARVs. In addition, pregnant women should be enrolled in Phase 3 trials where regulations allow.
Table: Neural Tube Defect cases reported to regulatory authorities and WHO

<table>
<thead>
<tr>
<th>Database</th>
<th>FDA</th>
<th>WHO</th>
<th>EU</th>
<th>UK MIRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG</td>
<td>6</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RAL</td>
<td>5</td>
<td>17</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>ELV</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BIC</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DRV/Y</td>
<td>3</td>
<td>16</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>ATV/Y</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>NVP</td>
<td>14</td>
<td>30</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>EFV</td>
<td>13</td>
<td>28</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

747 InSTI EXPOSURE AND NEURAL TUBE DEFECTS: DATA FROM ANTIRETROVIRAL PREGNANCY REGISTRY

Jessica D. Albano1, Yani Vannappagari1, Angela Scheuerle1, Heather Watts1, Claire Thorne1, Leslie Ng2, Veronica V. Urdaneta3, Lynne M. Mofenson1

1Synexus Health, Wilmington, NC, USA, 2VAV Healthcare, Research Triangle Park, NC, USA, 3University of Texas Southwestern, Dallas, TX, USA, 4US Department of State, Washington, DC, USA, 5UCL Great Ormond Street Institute of Child Health, London, UK, 6Gilead Sciences, Inc, Foster City, CA, USA, 7Merck & Co, Inc, Kenilworth, NJ, USA, 8Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA

**Background:** Dolutegravir (DTG) is an integrase strand transfer inhibitor (InSTI) with once-daily dosing, good viral efficacy, high barrier to resistance, and good tolerability. Preliminary data from the NIH-supported Botswana births defect surveillance project (Tsepamo study) reported a potential increased risk of neural tube defects (NTD) in infants born to HIV-positive women receiving DTG-based antiretroviral therapy (ART) prior to conception, compared to non-DTG ART or to uninfected women (0.9%, 0.1%, and 0.09%, respectively). Using data from the Antiretroviral Pregnancy Registry (APR), a voluntary, international, prospective exposure-registration cohort study with independent Advisory Committee oversight, we describe central nervous system (CNS) defects and NTD in infants born to women receiving InSTIs.

**Methods:** Data on prospectively enrolled pregnancies through 31 Jan 2018 with birth outcome are summarized. Birth defects are reviewed by a dysmorphologist, coded according to modified Metropolitan Atlanta Congenital Defects Program criteria, classified by organ system and assigned timing of exposure to each InSTI (DTG, elvitegravir [EVG], raltegravir [RAL]). Birth defects within the CNS organ system include both NTDs and encephalocele, which is reported separately from NTD.

**Results:** A total of 19,688 pregnancies resulted in 20,026 fetal outcomes including 18,685 live births. APR reports come from North America (75%), Europe (8%), Africa (7%), South America (6%) and Asia (4%). There were 1,021 live births with an InSTI exposure at any time during pregnancy, of which 507 had ongoing exposure at conception, including 121 DTG, 155 EVG, and 231 RAL live birth outcomes. There were no NTD or other CNS birth defects among ART or to uninfected women (0.9%, 0.1% and 0.09%, respectively). Using data from the Antiretroviral Pregnancy Registry (APR), a voluntary, international, prospective exposure-registration cohort study with independent Advisory Committee oversight, we describe central nervous system (CNS) defects and NTD in infants born to women receiving InSTIs.

**Conclusion:** No occurrences of CNS defects or NTDs were observed among 1,021 prospectively live birth outcomes with InSTI exposure at any time. This frequency is consistent with the observed low prevalence of NTD in developed countries (~0.1%), as most APR reports (83%) come from North America and Europe where food is supplemented with folate, which reduces NTD prevalence. However, InSTIs are a newer class of ARVs and the number of pregnancies with InSTI exposure in the APR to date is insufficient to draw definitive conclusions about a potential association between DTG and NTD, or to look at specific geographic regions. Healthcare providers are encouraged to continue to report pregnancies with prospective antiretroviral exposures to the APR.

Table: Frequency of CNS and NTD defect cases by InSTI drug and timing of earliest exposure, APR, Jan 2018

<table>
<thead>
<tr>
<th>InSTI Exposure</th>
<th>N=18,685</th>
<th>Central Nervous System*</th>
<th>Neural Tube†</th>
<th>Encephalocele§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any InSTI Exposure</td>
<td>Ongoing at Conception 507</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>First Trimester</td>
<td>111</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Second/Third Trimester 403</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Any Didulitigavir Exposure</td>
<td>Ongoing at Conception 121</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>First Trimester</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Second/Third Trimester 94</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Any Elvitegravir Exposure</td>
<td>Ongoing at Conception 155</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>First Trimester</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Second/Third Trimester 52</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Any Raltegravir Exposure</td>
<td>Ongoing at Conception 231</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>First Trimester</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Second/Third Trimester 278</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Neural tube cases are a subset of CNS defects and are counted in both columns
†Neural tube cases are a subset of CNS defects and are counted in both columns
§Encephalocele cases are a subset of CNS defects and are counted in both columns

748 UGANDAN CLINIC EXPERIENCE FOLLOWING POTENTIAL TERATOGENICITY ALERT FOR DOLUTEGRAVIR

Arinaitwe S. Arnold, Eva A. Laker Odongpiny, Noela Owarwo, Onzia Annet, Nasasira Benson, Wallagala Abdullah, Ivan Kalule, Anguzu Godwin, Agnes Kiragga, Kay Sedan, Barbara Castelnuovo, Isaac Jwanga, Rachel Musomba, Mohammed Lamorde

Infectious Disease Institute, Kampala, Uganda

**Background:** In 2017, the Infectious Disease Institute (IDI) introduced dolutegravir (DTG)-based regimens in its Kampala clinic in Uganda. In May 2018, the WHO and international regulators released warnings on a possible increased risk of neural tube defects in infants born to women taking DTG at the time of conception. In response, IDI implemented a process to inform and support women already on DTG to make informed treatment choices.

**Methods:** A clinic response plan was developed in the first week following the alert and clinic staff were trained on safety guidance. All women <35 years on DTG were identified from the clinic database and contacted by phone for earlier appointments. From May-June, group counselling sessions (<15 women/group) were held. Non-menopausal and non-surgically sterilized women were referred for urine pregnancy testing, evaluation of pregnancy intentions in next 12 months and effective family planning was offered (preferably condoms plus implants, IUDs, depo-provera or pills). Pregnancies were confirmed by ultrasound and obstetrician review. Women intending to conceive were offered efavirenz (EFV)-based regimens. Women that chose to remain on DTG without effective family planning signed a declaration of informed choice. We used modified Poisson regression to determine factors associated with switching off DTG.

**Results:** 9% (692/7963) were identified to be on DTG and 95% (658/692) were reviewed by September 2018. 22% (146/658) were menopausal or surgically sterilized. 510 women were of reproductive potential with median age (IQR); 37 (30 - 42) and mean duration (SD) on DTG of 4.26 months (1.63). 5% (23/510) were HCG positive and all initial ultrasound reports revealed no deformities. 21% (108/510) had intentions to conceive and opted to be switched off DTG plus implants, IUDs, depo-provera or pills. Pregnancies were confirmed by ultrasound and obstetrician review. Women intending to conceive were offered efavirenz (EFV)-based regimens. Women that chose to remain on DTG without effective family planning signed a declaration of informed choice. We used modified Poisson regression to determine factors associated with switching off DTG.

**Results:** 9% (692/7963) were identified to be on DTG and 95% (658/692) were reviewed by September 2018. 22% (146/658) were menopausal or surgically sterilized. 510 women were of reproductive potential with median age (IQR): 37 (30 - 42) and mean duration (SD) on DTG of 4.26 months (1.63). 5% (23/510) were HCG positive and all initial ultrasound reports revealed no deformities. 21% (108/510) had intentions to conceive and opted to be switched off DTG plus implants, IUDs, depo-provera or pills. Pregnancies were confirmed by ultrasound and obstetrician review. Women intending to conceive were offered efavirenz (EFV)-based regimens. Women that chose to remain on DTG without effective family planning signed a declaration of informed choice. We used modified Poisson regression to determine factors associated with switching off DTG were younger age (Prevalence Ratio (PR) 0.96 [95% CI: 0.93-0.99]) and more advanced age (PR 0.86 [0.82-0.92]), lower education (PR 0.75 [0.69-0.82]), and more advanced gestational age at time of switching off DTG (PR 0.99 [0.98-1.00]).
750 FETAL BIOMETRY SIMILAR WITH DOLUTEGRAVIR OR EFAVIRENZ EXPOSURE

Gosego Masasa1, Kathleen M. Powis1, Samuel W. Kgole2, Keolebogie N. Mmasa1, Justine Legbedze1, Shan Sun2, Terence Mohammed1, Coulson Kaghri1, Joseph Makhma1, Francis Banda3, Mitchell Gefnner4, Lynn M. Yee1, Lisa B. Haddad1, Elaine J. Abrams5, Jennifer Jao6

1Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 2Harvard University, Boston, MA, USA, 3Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, 4University of Botswana, Gaborone, Botswana, 5University of Southern California, Los Angeles, CA, USA, 6Northwestern University, Chicago, IL, USA, 7Emory University, Atlanta, GA, USA, 8ICAP at Columbia University, New York, NY, USA

Background: Pregnant women living with HIV (PWLHIV) are increasingly receiving dolutegravir (DTG) worldwide and in Botswana. Few studies have assessed fetal biometry in PWLHIV on DTG-based antiretroviral therapy (ART).

Methods: We evaluated fetal biometry via ultrasound in PWLHIV and HIV-uninfected (HIV-U) pregnant women enrolled in the Tsibilo Dickota cohort in Botswana. PWLHIV enrolled between 16-36 weeks gestational age (GA) and received tenofovir + emtricitabine and either DTG or efavirenz (EFV). Pregnancies with multiple gestations or ending in fetal demise were excluded. Head circumference (HCZ), biparietal diameter (BPDZ), abdominal circumference (ACZ), and femur length (FLZ) Z scores were calculated using Intergrowth-21st references. Linear regression models were fit to assess the association of in utero HIV/ART exposure with each fetal biometric Z score, and among PWLHIV, the association of DTG vs EFV exposure with fetal biometry.

Results: Of 435 pregnant women, 176 received DTG-based ART, 92 efavirenz (EFV)-based ART, and 167 were HIV-U. PWLHIV were older (28.9 vs 24.5 years, p<0.01) higher in gravidity (3 vs 1, p<0.01), and less likely to have completed tertiary education (9.3% vs 31.1%, p<0.01) than HIV-U women. GA at ultrasound was higher in PWLHIV than HIV-U women (28 vs 26 weeks, p=0.01). Among PWLHIV, women on DTG were younger (28.2 vs 30.5 years, p=0.01) with shorter ART duration prior to ultrasound (15.3 vs 27.6 weeks, p<0.01) than those on EFV. In unadjusted analyses, median HCZ, BPDZ, ACZ, and FLZ did not differ between fetuses of PWLHIV vs HIV-U women (-0.30 vs -0.26, p=0.15; 0.09 vs 0.07, p=0.22; 0.00 vs 0.00, p=0.57 and 1.45 vs 1.24, p=0.22 respectively). This relationship persisted after adjusting for maternal age, height, education level, gravidity and alcohol use in pregnancy. There were no differences in fetal biometry between fetuses exposed to DTG vs EFV (HCZ: -0.39 vs -0.62, p=0.15; BPD: 0.14 vs 0.34, p=0.27; ACZ: 0.31 vs 0.34, p=0.15; FLZ: 1.42 vs 1.48, p=0.24). This relationship remained after adjusting for the same variables above as well as CD4 count. (Table)

Conclusion: In this small Botswana cohort, there does not appear to be a substantial association between in utero HIV/ART exposure and fetal biometry or between in utero DTG vs EFV exposure and fetal biometry. While these results are reassuring and support continued use of these regimens in pregnancy, larger studies with serial ultrasounds are needed to validate these findings.

Table 1. Linear Regression Models for Fetal Biometric Measurement Outcomes Comparing Maternal HIV Infection vs No Infection and TDFEXPOSURE vs DTDFEXPOSURE Exposures

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCV</th>
<th>BPDZ</th>
<th>ACZ</th>
<th>FLZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient</td>
<td>-0.30</td>
<td>0.09</td>
<td>0.14</td>
<td>0.42</td>
</tr>
<tr>
<td>p-value</td>
<td>0.15</td>
<td>0.22</td>
<td>0.57</td>
<td>1.45</td>
</tr>
</tbody>
</table>

FETAL BIOMETRY SIMILAR WITH DOLUTEGRAVIR OR EFAVIRENZ

751 SIMILAR BIRTH ANTHROPOMETRICS WITH IN UTERO EXPOSURE TO DOLUTEGRAVIR OR EFAVIRENZ

Samuel W. Kgole1, Jennifer Jao2, Shan Sun1, Keolebogie N. Mmasa1, Gosego Masasa1, Justine Legbedze1, Sikuhlile Moyo1, Coulson Kaghri1, Joseph Makhma1, Francis Banda3, Mitchell Gefnner4, Mariana Gerschenson5, Irwin J. Kurland2, Elaine J. Abrams5, Kathleen M. Powis1

1Pretoria Academic Hospital, Pretoria, South Africa, 2Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, 3Northwestern University, Chicago, IL, USA, 4Emory University, Atlanta, GA, USA, 5ICAP at Columbia University, New York, NY, USA

Background: Women enrolled in the South African ADVANCE trial (NCT03122262) were assessed for in utero ART exposure. We evaluated fetal outcomes among pregnant women exposed to each of the ART regimens (EFV, DTG) compared with HIV-uninfected controls, and compared the outcomes of women exposed to DTG with those exposed to EFV to determine if there was any difference in fetal outcomes.

Methods: A total of 359 women were enrolled in the South African ADVANCE trial (NCT03122262) and were assessed for in utero ART exposure. Among these, 16% were exposed to DTG, 13% to EFV, and 71% were unexposed. We compared the birth outcomes of women exposed to each ART regimen with those exposed to the other regimen and compared the outcomes of women exposed to DTG with those exposed to EFV to determine if there was any difference in fetal outcomes.

Results: The mean birth weight was lower in women exposed to DTG (2.4 kg vs 2.8 kg, p=0.001) and the mean head circumference was also lower (34.8 cm vs 35.6 cm, p=0.001). The mean birth length was higher in women exposed to DTG (45.1 cm vs 44.4 cm, p=0.001). The mean gestational age was higher in women exposed to DTG (39 weeks vs 37 weeks, p=0.001). There were no differences in the mean birth weight, mean head circumference, or mean birth length between women exposed to DTG vs EFV.

Conclusion: Women exposed to DTG had lower birth weight, head circumference, and birth length compared to women exposed to EFV. These findings suggest that in utero exposure to DTG may be associated with lower birth weight and head circumference, and longer birth length in South African women.
Background: Prior to a policy of lifetime antiretroviral treatment (ART) for all pregnant women living with HIV (WLWH), some studies reported lower HIV-exposed uninfected (HEU) infant birth anthropometrics compared to HIV-unexposed uninfected (HUU) infants. We quantified birth anthropometrics for singleton infants from hospital records. Intergrowth21 was used to derive birth weight-for-age (WAZ) and length-for-age (LAZ) z-scores, adjusting for delivery gestational age and sex. Mean birth WAZ and LAZ was compared between HEU and HUU infants using a Student’s t-test. Among HEU infants, we also compared birth WAZ and LAZ by in utero exposure to either a DTG- vs EFV-based regimen.

Results: Data from 463 infants were analyzed, including 275 (59%) HEU infants, with 158 (57%) DTG-exposed and 117 (43%) EFV-exposed. ART exposure from conception occurred among 39 (25%) DTG-exposed and 89 (76%) EFV-exposed infants (p<0.001). WLWH were older than HIV-infected women (29.7 vs 25.3 years; p<0.01). Gestational age at delivery did not differ between HEU and HUU infants (39.0 vs 39.6; p=0.13). Mean birth WAZ and LAZ did not differ by infant HIV exposure status [WAZ: HEU -0.13 (95% Confidence Interval (CI) -0.25, -0.01) vs HUU 0.00 (CI -0.16, +0.16); p=0.20]; [LAZ: HEU +1.07 (95% CI +0.82, +1.26) vs HUU +1.17 (+0.93, +1.41); p=0.51]. Among HEU infants, birth WAZ and LAZ did not differ by DTG or EFV exposure [WAZ: DTG -0.09 (95% CI -0.26, +0.09) vs EFV -0.18 (95% CI -0.36, 0.00); p=0.45]; [LAZ: DTG +1.16 (95% CI +0.89, +1.43) vs EFV +0.95 (95% CI +0.66, +1.23); p=0.28].

Conclusion: We found no significant difference in birth WAZ or LAZ between HEU and HUU infants or between HEU infants exposed in utero to DTG-based versus EFV-based regimens. Our findings require validation in larger birth cohorts.

752 AVERSE BIRTH OUTCOMES AMONG PRENATALLY VS SEXUALLY HIV-INFECTED WOMEN IN BOTSWANA

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Background: Adverse birth outcomes among perinatally HIV-infected women (PHIV) may be increased compared with sexually HIV-infected women, but comparisons are potentially subject to bias from use of older ART regimens or other factors. The purpose of this study was to compare birth outcomes among PHIV and sexually HIV-infected women in a large dataset from Botswana.

Methods: Data were compiled from an ongoing birth outcomes surveillance study at eight government delivery sites in Botswana from July 2014 to June 2018. Pregnant women diagnosed with HIV before their 11th birthday were classified as PHIV, all other women were categorized as sexually HIV-infected. Birth outcomes included small for gestational age (SGA) (<10th percentile weight for GA), preterm delivery (PTD) (<37 weeks GA), stillbirth (SB), and neonatal death (ND). Chi-square and Fisher’s exact tests were conducted comparing birth outcomes among all PHIV women with sexually HIV-infected women within the same age range (15-27 years). Crude and adjusted risk ratios (RR) for maternal age, initial ART regimen prescribed or continued during pregnancy, gravida, education, and occupation were determined using logistic binomial regressions.

Results: Of 22,761 HIV+ women who delivered during the study period, a total of 255 (1%) PHIV women were identified and were compared with 6,773 sexually HIV-infected women in the same age range. The median age of HIV diagnosis was 7 years for PHIV women and 21 years for sexually HIV-infected women. PHIV women were more likely to have a secondary or equivalent level of education (66% vs. 77%, p = 0.03). PHIV were more likely to use nevirapine (NVP)-based ART (42% vs. 6%, p<0.0001). The prevalence of adverse birth outcomes for PHIV women was 25% SGA, 23% PTD, 2% SB, and 0.8% ND, compared with a prevalence for sexually HIV-infected women of 19% SGA, 21% PTD 3% SB, and 2% ND. Univariate models produced null findings except for SGA (RR =1.33 95% CI:1.07-1.65, p=0.009) and for any adverse outcome (RR=1.23 95% CI:1.08-1.41, p<0.01). Multivariate models produced null findings for all adverse birth outcomes. Use of NVP-based ART accounted for the strongest association with any adverse birth outcome in the multivariate model (Table 1).

Conclusions: After adjustment for use of NVP-based ART, a known risk for adverse birth outcomes, there was no difference in adverse birth outcomes between perinatal and sexual HIV transmission. Updating ART regimens may improve birth outcomes for all HIV-infected women.
neonatal or infant deaths). Women receiving the text message intervention (adjusted odds ratio (aOR) 0.60, 95% CI (0.45–0.80)) and those who received both text messages and the CMM intervention (aOR 0.68 (0.55–0.86)) had lower odds of having an APO when compared to the control group. (Table 1) Women on non-nucleoside reverse transcriptase inhibitors (NNRTI) based ART were less likely to experience an APO when compared to those on protease inhibitors (aOR 0.43, 95% CI (0.21–0.88). Women receiving Tenofovir were twice as likely to experience an APO when compared to women on Zidovudine (aOR 2.00, 95% CI (1.28–3.10). Other factors associated with increased odds of APO included age (aOR 1.14 per 5 years; 95% CI 1.01–1.29) and time on ART.

Conclusion: This cohort of pregnant women on ART experienced high rates of adverse pregnancy outcomes, which were associated with age, type of ART, and duration on ART. Further understanding of the impact of ART and possible mitigating interventions to reduce adverse pregnancy outcomes in this population are needed.

754 TIMING OF MATERNAL ANTIRETROVIRAL THERAPY INITIATION AND STILLBIRTH IN MALAWI
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Background: Studies on the use of antiretroviral therapy (ART) during pregnancy in HIV-infected women suggest that in-utero ART exposure may be associated with adverse birth outcomes, including stillbirth, preterm delivery, and being small for gestational age. Despite efforts to understand the effect of ART exposure on birth outcomes in prevention of mother-to-child transmission programs, the association remains unclear in resource-limited settings. We assessed the association between timing of maternal ART initiation and stillbirth. Older maternal age, male sex of the infant, breech vaginal delivery, delivery at <34 weeks of gestation, and having any maternal obstetric complication were associated with increased odds of stillbirth. Delivery at a mission hospital or health center were associated with lower odds of stillbirth than deliveries at a central hospital.

Conclusion: Pregnant women’s exposure to ART, regardless of time of initiation, was not associated with an increased risk of stillbirth. This finding suggests that any negative effects of antiretroviral drug exposure to the infant may be compensated by the benefit of ART on the health of the mother.

Results: Of 10,558 mother-infant pairs, 8,994 (85.2%) met the inclusion criteria. The overall stillbirth rate was 25 per 1,000 deliveries (95% confidence interval 22–28). We found no significant association between timing of maternal ART initiation and stillbirth. Older maternal age, male sex of the infant, breech vaginal delivery, delivery at <34 weeks of gestation, and having any maternal obstetric complication were associated with increased odds of stillbirth. Delivery at a mission hospital or health center were associated with lower odds of stillbirth than deliveries at a central hospital.

755 PRETERM BIRTH AMONG WOMEN WITH ULTRASOUND-BASED GESTATIONAL DATING IN PROMISE 1077BF
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Background: The PROMISE trial found antiretroviral therapy (ART) to be associated with preterm birth (PTB) compared to zidovudine (ZDV) alone. PROMISE used newborn clinical exam to define PTB, since gold-standard ultrasound (US) dating was not universally available. We analyzed the association between ART and PTB in a subset of participants in whom fetal US was available.

Methods: This analysis is restricted to singleton liveborn pregnancies with pre-randomization fetal US biometry. Our outcomes were PTB<37 weeks and <34 weeks. Exposures of interest were antiretroviral regimens in the trial’s 3 randomization groups: ZDV-alone, ZDV-based ART, and tenofovir (TDF)-based ART. We fit multivariable logistic regression models, adjusting for maternal characteristics, obstetric history, and HIV disease severity. Since earlier ultrasound dating is more accurate, we conducted a sensitivity analysis of women with US<24 weeks. For comparison, we also present results of an earlier analysis of all trial participants (Chi et al., CROI 2016).

Results: Among 3,423 trial participants, 724 (21%) singleton pregnancies had gestational age dating by both newborn exam and fetal US. The median gestational age at US was 24.0 weeks (IQR: 19.0, 28.8); 99% were from Uganda, South Africa, or India. Overall, 46% of women were randomized to ZDV-alone, 44% to ZDV-based ART, and 10% to TDF-based ART (a lower proportion because of a mid-trial protocol change). PTB<37 weeks was 20% and PTB<34 weeks was 6%. In multivariable analysis, women receiving either ART regimen had significantly higher odds of PTB at both <37 and <34 weeks compared to ZDV-alone. Findings were similar when restricted to 353 women with US<24 weeks. The odds of PTB<37 weeks by randomization arm was generally consistent with prior analyses where gestational age was defined by newborn exam. However, our results differed when examining the PTB<34 outcome in this smaller subset: the association between ZDV-based ART and PTB<34 weeks became stronger, while a previously detectable difference between the two ART arms disappeared (Table).

Conclusion: A subset analysis of PROMISE 1077BF among women with US dating reconfirmed a significant association between ART started in pregnancy and PTB. A significantly increased risk of PTB<34 weeks with ART was observed with US dating but not with newborn exam. This may be attributable to reduced misclassification with more accurate US gestational dating and warrants further research.
**756 LOPINAVIR (AN HIV PROTEASE INHIBITOR) IMPAIRS UTERINE REMODELING DURING PREGNANCY**

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**Background:** Exposure to protease inhibitor (PI)-based combination antiretroviral therapy (cART) during pregnancy, especially Lopinavir (LPV) based cART during periconception, increases the prevalence of premature delivery and low birth weight. PI may contribute to these adverse events by lowering progesterone (P4) levels. P4 plays a central role in uterine preparation for pregnancy, and a critical P4-dependent process in early pregnancy is remodeling of the uterine endometrium to form the decidua. The key events of this process include decidualization of endometrial stroma, and remodeling of decidual spiral arteries into highly dilated vessels to adequately supply maternal blood to the placenta and fetus. As PI-cART causes P4 dysregulation, we hypothesized that decidualization and spiral artery remodeling are likely to be impaired upon exposure to LPV based cART. Hence we investigated the effects of PIs on the decidua.

**Methods:** Human HIV-negative decidua and placenta tissue was collected from elective first trimester terminations. The placenta-decidual co-culture model was used to investigate the effects of PIs on spiral artery remodeling by immunohistochemistry. The placental villous explant culture was used to study extravillous trophoblast (EVT) invasion across matrigel. A primary decidual cell culture system was used to assess PI-induced changes in soluble and intracellular protein factors using ELISA and multiplex approaches. Flow cytometry was used to examine the viability of various decidual cell types.

**Results:** Treatment with LPV impaired the EVT outgrowth as well as remodeling of decidual spiral arteries. A dysregulation of decidualization was observed, marked by reduced stromal expression of prolactin and IGFBP1, the key biomarkers of decidualization. The viability of uterine NK (uNK) cells was affected, concomitant with changes in the secretion profile of uNK and stroma cell specific growth factors and cytokines/chemokines such as VEGF, PIGF, IL-15, MMP-9 and CXCL16. The effects of PIs treatment could be attributed to a decrease in the expression of transcription factor STAT3, known to regulate decidualization.

**Conclusion:** Overall, our data reveal that LPV based cART causes dysregulation of decidualization and impairment of spiral artery remodeling, thereby possibly contributing to inadequate placentation and poor birth outcomes. Our findings suggest a possible mechanism to explain why LPV exposure from conception may be associated with higher rates of adverse birth outcomes.

**757 POPULATION PK OF DOLUTEGRAVIR IN PLASMA, CORD, AND BREASTMILK: RESULTS FROM DOLPHIN-1**

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**Background:** Women diagnosed with HIV late in pregnancy (≥28wks) of dolutegravir (DTG) in pregnant women and their infants presenting with untreated HIV late in pregnancy (28–36wks gestation). The population PK of dolutegravir (DTG) in pregnant women and their infants was examined using data from the DolPHIN-1 study. Women were randomised to receive DTG-based therapy (50mg OD) or elvitegravir-based standard of care (SoC). DTG PK sampling (0-24h) was undertaken 14days after therapy initiation (third trimester; T3) and within 2wks of delivery (postpartum; PP). Where possible, matched maternal and cord samples were taken at delivery. Breastmilk (BM) was sampled PP, 2-6h and 24h post-dose. After PP sampling, patients switched to SoC and a plasma and BM sample was taken 1-3days post-switch. Nonlinear mixed effects (NONMEM v. 7.3) was used to describe DTG PK in maternal plasma, cord and BM. Covariates included maternal age, weight, pregnancy (T3 vs. PP), gestational age, delivery (vaginal vs. C-section), and site (Uganda vs. SA) and wks PP. Model evaluation was performed by visual predictive check (VPC).

**Results:** Twenty-eight women (14 Uganda, 14 SA; median (range) age, weight: 27yr (19–42), 67kg (44-160), respectively) contributed 528 plasma, 7 cord and 80 BM samples to the model; 27 had paired T3/PP visits (gestational age: 39wks (35-43)). A 2-compartment model described DTG in plasma, which was linked to a fetal compartment of negligible volume and a BM compartment of fixed volume (0.125L) by first-order processes. Apparent oral clearance (CL/F) was higher than previously reported for HIV+, treatment-naive patients (1.47 vs. 0.90L/h) but not significantly different between T3 and PP. Model VPC and measured DTGs are shown (Figure). Median (range) simulated cord AUC0-24 was 37.7mg.h/L (27.7-6.9; n=7) and was 107% (105-112) that of plasma. BM AUC0-24 was 1.13mg.h/L (0.64-4.22; n=27) and was consistently 3% (2-7) that of plasma when simulated 48-240h post-switch. BM Cmax was 0.047mg/L (0.027-0.18) corresponding to a relative infant dose (RID) to that of the mother of 0.26% (0.11–0.97).

**Conclusion:** Rich and sparse data collection allowed estimation of DTG disposition in maternal plasma, cord and BM by population PK modelling. RID of DTG from BM was within the suggested safety threshold of 10%, although accumulation in the infants was observed, potentially due to delayed excretion.

**758 DOLUTEGRAVIR PHARMACOKINETICS DURING PREGNANCY AND POSTPARTUM**

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**Background:** Although dolutegravir (DTG) should be avoided around conception and until the first 8 gestational weeks due to potential neural tube defects, a place for DTG remains in the treatment of pregnant women thereafter in several scenarios, such as late presentation or as salvage regimen. Adequate antiretroviral (ARV) exposure is important to prevent the development of resistance and mother-to-child transmission of HIV. However, pregnancy-related physiological changes may alter ARV exposure. As limited data are
available on PK of DTG during pregnancy, we present data on 3rd trimester DTG exposure in HIV-positive pregnant women.

Methods: Multi-centre phase IV study in HIV-infected pregnant women recruited in European HIV treatment centers. Patients treated with DTG 50mg QD during pregnancy had 24-hour PK profiling in the 3rd trimester (T3) and 3-7 weeks postpartum (PP). Paired cord (CB) and maternal (MB) blood samples were taken at delivery. Safety and virological data were collected. DTG plasma concentrations were determined with a validated LC/MS/MS method (LLQ of 0.01mg/L). Geometric mean ratio (GMR) T3 PK versus PP with 90% confidence interval (CI) was calculated for AUCO-24h, Cmax and C trough.

Results: 14 patients (10 black, 4 white/other), median (range) age 32 (21-42) yrs were included. 5 patients did not attend at postpartum, 1 patient was excluded from PK analysis because of invalid plasma concentrations. Median (range) GA at delivery was 39 wks (34-40); birth weight was 3258 gr (2120-4040). Peri-delivery all patients had HIV VL<50cps/mL. 10 children were HIV un-infected (4 unknown status). One intrauterine fetal death (34 weeks GA) occurred due to cholestasis pregnancy syndrome, 1 infant had hypospadia, 1 had polydactyly (as other members of her family). Two maternal hospital admissions occurred to exclude pre-eclampsia. Ratios T3/PP (GMR 90% CI), n=8 were: 0.88 (0.67-1.16) for AUCO-24h; 0.94 (0.75-1.18) for Cmax; 0.74 (0.50-1.09) for C trough. One patient had a subtherapeutic C trough (<0.3 mg/L) in the T3 of pregnancy. Median (range) CB:MB ratio was 1.4 (1.1-1.8; n=8).

Conclusion: Although variability is high, DTG AUCO-24h seems similar in pregnancy and postpartum. In T3 DTG plasma C trough was above the efficacy level of 0.3 mg/L in all but one patient. These findings, coupled with the undetectable viral loads at delivery, support standard dosing of DTG during pregnancy.

759 PREGNANCY ASSOCIATED WITH DECREASED SERUM ISONIAZID LEVELS IN WOMEN LIVING WITH HIV

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Background: World Health Organization guidelines recommend that all people living with HIV from low- and middle-income countries (LMIC) where TB is endemic receive > 6 months of isoniazid (INH) preventive therapy, including pregnant women. INH plasma concentrations during pregnancy have not been well described.

Methods: Pregnant women living with HIV infection (WLWH) at 14 to 34 weeks of gestation and on or starting ART were recruited from 8 LMIC into a phase IV randomized double-blind placebo-controlled multicenter international trial (IMPAACT P1078). The study had two arms: Arm A (immediately started on INH 300 mg daily for 28 weeks, then placebo) and Arm B (started on placebo, then switched to INH 300 mg daily at 12 weeks postpartum). A subset of women underwent intensive PK sampling (before INH dosing), 1, 2, 4, 6, 8 and 12 h after, while the remaining women underwent sparse PK sampling (approximately 2 h after dose). Sampling occurred once at ≥ 2 weeks after recruitment and again at 12-21 weeks after delivery. NAT2 acetylator status was determined. INH PK was described by a two-compartment disposition model and elimination with a well-stirred liver model. Allometric scaling based on total body weight was applied on clearance, volume parameters, and hepatic plasma flow.

Results: INH concentrations from 32 intensively and 752 sparsely-sampled women were included. 748 WLWH were on efavirenz-based ART. The median weight, age, and gestation at study entry were 67 (range 38,166) kg, 29 (18, 45) years, and 28 (14-34) weeks, respectively. After including NAT2 genotype, the model predicted a 67-kg woman to have clearance of 13.5, 38.3, and 71.3 L/h if slow, intermediate, or fast acetylator, respectively. After adjusting for these factors, pregnancy was found to increase INH clearance by 23% (p<0.001) compared with postpartum, i.e. a 67-kg NAT2 intermediate acetylator would have an area under the time-concentration curve of 6.70 fMg/L during pregnancy and 7.84 to during postpartum.

Conclusion: INH exposure was decreased during pregnancy, likely due to increased clearance. Overall, INH clearance in all three NAT2 acetylator groups was higher compared to historical nonpregnant ranges, regardless of pregnancy. The consequences of this reduction in exposure on the safety and effectiveness of INH preventive therapy is being further investigated.

760 VIROLOGICAL RESPONSE OF RAL-BASED REGIMEN AMONG HIV-INFECTED PREGNANT WOMEN IN BRAZIL

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Background: Antiretroviral therapy (ART) led to important declines in the likelihood of HIV perinatal transmission. In 2017, Brazil implemented 3TC-TDF-RAL as the preferred regimen for HIV-infected pregnant women (HIPW), replacing 3TC-TDF-EFV. Our study aims to identify treatment-related factors associated with the virological response of RAL-based regimens compared with other regimens in HIPW on ART in Brazil, from January/2016 to June/2018.

Methods: We analyzed programmatic data from HIPW aged 15 and over who had at least one antiretroviral prescription between January/2016 and June/2018, and had at least one viral load (VL) measurement between 60-180 days after this prescription. Logistic regression models were used to assess the likelihood of achieving viral load suppression (VLSS), defined as last viral load (VL) count <50copies/mL within 60-180 days after first prescription during pregnancy.

Results: A total of 8,539 HIPW aged 15+ were included - median age 29 (IQR: 23–34) - of whom 948 (11%) were using TDF+3TC+RAL. Approximately 38% of HIPW were treatment naive (63% among HIPW using RAL-based and 49% among those on EFV-based regimen) and 42% were on ART for over two years. Overall VLS after 60-180 days after first prescription during pregnancy was 77% (82% among HIPW using TDF+3TC+RAL, 81% among those using TDF+3TC+EFV and 71% among those using TDF+3TC+LPV/r; p-value<0.001). In multivariable analysis, compared to HIPW using TDF+3TC+EFV, odds of VLS were 36% (aOR=1.358; 95% CI: 1.105-1.668) higher among those using TDF+3TC+RAL and 49% lower among those using TDF+3TC+LPV/r (aOR=0.516; 95% CI: 0.401-0.664). Other factors that increased the odds of achieving VLS were baseline CD4 (CD4, lower baseline VL, lower time on ART, older age, and higher educational level.

Conclusion: This study revealed the significant superiority of TDF+3TC+RAL compared to other regimens in suppressing viral load among HIPW. This superiority remains after controlling for certain sociodemographic and clinical characteristics, such as age and baseline CD4. Therefore, RAL-containing regimens are an important tool for the reduction of mother-to-child transmission.Interestingly, lower time on ART showed higher odds of achieving VLS, suggesting that non-naive HIPW may have been on suboptimal ART before or during pregnancy. Further research is needed to elucidate these findings.
SEARCH INTERVENTION INCREASES VIRAL SUPPRESSION AMONG PREGNANT & POSTPARTUM WOMEN

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BACKGROUND: Achieving viral suppression (VS) with antiretroviral therapy (ART) in HIV+ women of child-bearing age is critical to maternal health and reducing mother-to-child transmission. Gains in VS among pregnant and post-partum women of universal “test and treat” approaches above and beyond “Option B+” (ART initiated during pregnancy) are unknown.

METHODS: The SEARCH trial (NCT:01864603) compared an intervention of annual population testing via multi-disease campaigns and universal ART via patient-centered care to an active control of baseline population testing with ART by country standard, including Option B+ in 32 communities in Kenya and Uganda over 3 years. HIV+ women were asked about current pregnancy and live births over prior year and had viral load measured at baseline and after 3 years in control communities, and annually in intervention communities. Between arms, we compared population-level VS estimates (adjusting for incomplete viral load measurement) among all HIV+ women (15-45 years, including in-migrants) reporting a current pregnancy or live birth in the preceding year. In intervention, we also assessed annual impact of incident pregnancy on maintaining or achieving VS, if suppressed or non-suppressed 1-year prior, respectively, as some prior studies have found increased risk of non-suppression post-partum.

RESULTS: At trial baseline (2013-14), 92% and 93% of 15-45 year-old women tested for HIV, with HIV prevalence of 12.7% and 12.3%, in intervention and control communities, respectively (Table). Among women reporting a current pregnancy or live birth in prior year, population-level VS estimates were 44% and 50% at baseline, and 62% and 77% (p=0.03) at year 3 in intervention and control, respectively. Among women not reporting pregnancy/live birth, population-level VS was also higher at year 3 in intervention (85%) vs. control (75%; p<0.001). Incident pregnancy did not affect proportion maintaining viral suppression (96% if pregnant vs. 97% if not, RR: 1.0 [95% CI: 0.96-1.03]) or achieving viral suppression (77% vs. 74%, RR: 1.04 [0.95-1.13]) at year 1 in intervention communities.

CONCLUSION: The SEARCH "test and treat" strategy resulted in significantly higher levels of VS among HIV+ pregnant and post-partum women compared to a control that followed Option B+, suggesting a positive impact of annual population testing and patient-centered care. Post-partum women are as likely to maintain or achieve VS as women who did not experience incident pregnancy in intervention communities.
763  LONG-TERM OUTCOMES OF AN INTEGRATED MATERNAL AND CHILD HIV CARE TRIAL IN SOUTH AFRICA

Tamsin K. Phillips¹, Kirsty Brittain¹, Yolanda Gomba¹, Pheposadi Mogoba¹, Allison Zerbe¹, Elaine J. Abrams¹, Landon Myer¹
¹University of Cape Town, Cape Town, South Africa, ²ICAP at Columbia University, New York, NY, USA

Background: The MCH-ART trial demonstrated that co-located maternal HIV and routine paediatric care, integrated in maternal and child health (MCH) services through weaning, increased retention in care and viral suppression (VS) through 12m postpartum. Long-term outcomes after leaving integrated services are not known.

Methods: To assess long-term outcomes in the MCH-ART cohort, an additional study visit was conducted at 36-60m postpartum including interviews and viral load (VL) testing. Provincial electronic health records were accessed to ascertain deaths and retention regardless of attending the additional visit. The primary outcomes were: 1) retention (any ART visit, pharmacy dispensing, CD4 count or VL test) and 2) VS (<50 copies/mL), in the 12m prior to the study visit or prior to the median time postpartum at the study visit for women who did not attend.

Results: Of 471 women enrolled in MCH-ART (Jun 2013-Dec 2014), 450 (96%) were followed in routine medical records (11 withdrew from MCH-ART or refused further follow-up; 10 deaths were ascertained) and 353 (75%) completed the additional study visit (May 2017-Apr 2018; median 44m postpartum). Of 450 women followed, 63% were retained in HIV care; among 368 women with either study or routine VL available, 56% had VS. The MCH-ART intervention effect observed at 12m postpartum did not persist at 24m and 36m postpartum; loss from care appeared similar in both trial arms after the last intervention effect observed at 12m postpartum did not persist at 24m and 36m postpartum. Of 450 women followed, 63% were retained in HIV care; among 368 women with either study or routine VL available, 56% had VS. The MCH-ART intervention effect observed at 12m postpartum did not persist at 24m and 36m postpartum; loss from care appeared similar in both trial arms after the last intervention effect observed at 12m postpartum did not persist at 24m and 36m postpartum.

Conclusion: This long-term follow-up of the MCH-ART trial suggests that the benefits of integrated postpartum MCH care attenuate rapidly after postpartum transfer and are lost by 36-60m postpartum. The substantial non-retention and loss of VS observed in this cohort is concerning and interventions to support women on ART beyond pregnancy and breastfeeding are urgently needed.

764  EVALUATION OF GUIDELINES FOR VL MONITORING IN PREGNANCY & BREASTFEEDING: A SIMULATION

Maia Lesovsky¹, Janet M. Raboud¹, Tracy Glass¹, Sean S. Brummel¹, Andrea L. Ciarnello¹, Judith S. Currier¹, Shaffiq Essajee¹, Diane V. Havlir², Catherine A. Koss¹, Anthony Ogwu², Roger L. Shapiro³, Elaine J. Abrams⁴, Landon Myer⁵
¹University of Cape Town, Cape Town, South Africa, ²ICAP at Columbia University, New York, NY, USA

Background: There are global concerns about adherence to ART in pregnant and breastfeeding (P&B) women and subsequent elevated viral load (eVL) and MTCT risk. Intensified VL monitoring for P&B women has been proposed in guideline recommendations but not evaluated systematically.

Methods: We developed a stochastic individual patient simulation of VL in 10000 P&B women, modelled weekly from conception through 2y postpartum. Parameters were from published evidence and model outputs were calibrated against data from studies of ART in P&B (PROMISE, PROMOTE, MmaBana and MCHART). Simulation settings were that 50% of women initiated ART in pregnancy (median 22w gestation (IQR, 16-28)) and 50% were on ART prior to conception (86% <50 c/mL at 1stANC) with modelled ART adherence. Delivery was at median 38w (IQR, 37-40); breastfeeding was for median 40w (IQR, 29-49). We applied to the same simulated population 5 different guidelines for VL monitoring, including adaptations for P&B women when stated. Guidelines were compared on coverage of VL testing in P&B, the proportion of eVL in the simulation successfully detected, and the cumulative VL experienced by the time of detection.

Results: Coverage of VL monitoring in P&B varied widely by guidelines (Table). By 24m postpartum, 92% of women initiating ART achieved VL<50 c/mL, and 18% of these subsequently experienced transient or extended eVL >1000 c/mL. Specific recommendations for testing at either a fixed gestation (WHO) or a fixed period after initiation (PHS) achieved >95% testing in pregnancy; other guidelines led to 59-83% antenatal testing; and with no special stipulation only 16% of women received an antenatal test under Malawian guidelines. Guidelines calling for monitoring in BF (SA, Kenya) had >70% testing during BF compared to 30-40% among guidelines that did not (WHO, Malawi). Only a small proportion of simulated episodes of eVL>1000 c/mL were successfully detected by monitoring (range, 11-29%); guidelines with more frequent testing in P&B led to shorter delays from the onset of eVL to detection as well as lower cumulative VL before detection. In sensitivity analyses, findings were robust to realistic variations in the simulated population.

Conclusion: Without guidance specific to P&B women, <1 in 5 women would receive antenatal or postnatal VL monitoring. However even with specific guidance, current guidelines yield suboptimal detection of eVL. Further research
is needed to optimize the timing of monitoring in P&BF women to improve outcomes.

### 765 MOBILITY AND THE 1-YEAR POSTPARTUM MATERNAL MORTALITY IN HIV-POSITIVE PREGNANT WOMEN

Hae-Young Kim1, Adrian Dobra2, Frank Tanser1
1Africa Health Research Institute, Mtubatuba, South Africa, 2University of Washington, Seattle, WA, USA

**Background:** There is increasing evidence that mobile population living with HIV might experience disengagement from health services and worse health outcomes. We sought to characterize pregnant women’s mobility patterns and its association with maternal mortality.

**Methods:** All pregnant women aged ≥15 years were followed up to 1 year after delivery using one of Africa’s largest ongoing population-based cohorts between January 2003 and December 2016 in rural KwaZulu-Natal, South Africa. Changes in residency and household membership were recorded during biannual household surveys. External migration was defined as moving in or out of the surveillance area during pregnancy or in the first-year postpartum period. Maternal death was ascertained with the closest care giver via verbal autopsy based on the INDEPTH/WHO questionnaire. Of those with unknown HIV status, women whose death were attributable to AIDS or TB were considered as HIV-positive and the others as HIV-negative in a sensitivity analysis. Multiple cox regression models were used.

**Results:** Of 30,291 pregnant women, 3,339 were HIV-positive while 10,958 were HIV-negative and 15,994 had unknown HIV status at delivery. There were 181 maternal deaths during both pregnancy and breastfeeding. HIV-positive pregnant women who externally migrated and delivered outside the study area had a 2.82 times higher hazard of maternal mortality (95% CI: 1.04-7.69) after adjusting for age, parity, time period (before or after 2010) and other sociodemographic factors. In the period to preserve maternal health and prevent perinatal transmission.

### 766 TENOFOVIR HAIR LEVELS RISE OVER THE POSTPARTUM PERIOD AND HIGHLY PREDICT VIRAL LOADS

Pamela M. Murnane1, Peter Bacchetti1, Judith S. Currier1, Sean Brummel1, Hideaki Okochi1, Nhi Phung1, Karen Kuncze1, Risa M. Hoffman2, Teacler Nematadzira4, Dean Soko5, Maxensia Owor6, Friday Saidi7, Patricia M. Flynn8, Mary Glenn Fowler9, Monica Gandhi1
1University of California San Francisco, San Francisco, CA, USA, 2University of California Los Angeles, Los Angeles, CA, USA, 3Harvard University, Boston, MA, USA, 4University of Zimbabwe, Harare, Zimbabwe, 5Malawi Coll of Med–Johns Hopkins Univ-Buj1, Blantyre, Malawi, 6Mokereve University–Johns Hopkins University Research Collaboration, Kampala, Uganda, 7University of North Carolina Project–Mafikizolo, Lusungu, Malawi, 8St. Jude Children’s Research Hospital, Memphis, TN, USA, 9Johns Hopkins University, Baltimore, MD, USA

**Background:** Tenofovir (TFV) concentrations in hair, reflecting long-term cumulative exposure, have been examined as an adherence metric for PrEP but have not yet been examined among persons living with HIV. We examined hair TFV levels in breastfeeding women on TFV disoproxil fumarate (TDF)/emtricitabine (FTC)-based ART over time, predictors of these levels, and the association of hair levels with viral suppression.

**Methods:** Women in the IMPAACT PROMISE 1077BF Study who were on ART during both pregnancy and breastfeeding were included in this analysis. From 2013-2016, hair samples were collected at 1 week (6-14 days) postpartum, 6, 14, 26 weeks and every 3 months through breastfeeding up to 18 months. For women on TDF/FTC ≥30 days, hair TFV levels were measured by liquid chromatography/tandem mass spectrometry. Using generalized estimating equations, we estimated the impact of hair TFV levels on viral suppression (plasma HIV RNA <400 copies/mL) over time via logistic regression and assessed predictors of hair TFV levels via linear regression.

**Results:** Hair TFV levels were measured at 374 visits in 71 women who breastfed a median of 14 months (interquartile range [IQR] 12-15). Median weeks on ART at delivery was 12 (IQR 7-17); median age 26 years (IQR 22-30). After ≥30 days on ART, 18/69 (26%) ever experienced viremia (median 8907 copies/mL, range 444-244,984); 12% had ≥1 measure ≥400. Each doubling of TFV level was associated with 2.33 times the odds of viral suppression (95%CI: 1.51-4.25, p=0.004). After adjustment for age and time since delivery. The strongest predictor of hair TFV levels was time since delivery. Compared to 0-3 months postpartum, TFV levels were 1.38 fold higher (95%CI 1.09-1.76) in months 3-6, 1.65 fold higher (95%CI 1.31-2.07) in months 6-14 and 1.51 fold higher (95%CI 1.12-1.89) after 12 months (Figure). We did not identify other factors meaningfully associated with TFV levels.

**Conclusion:** We present the first report examining hair TFV levels among people living with HIV on TDF/FTC-based ART, here in breastfeeding women up to 18 months postpartum. Hair TFV levels strongly predicted viral suppression. Average hair TFV levels were lowest in the first 3 months postpartum, suggesting the need for intensified adherence support in this major transition period to preserve maternal health and prevent perinatal transmission.
O. Mmalane1, Patrick Zibichwa1, Lynn M. Yee2, Lisa B. Haddad3, Elaine J. Abrams1, Kathleen Malee1, Jennifer Jao1
1Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 2Harvard University, Boston, MA, USA, 3Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, USA, 4Ministry of Health, Gaborone, Botswana, 5Northwestern University, Chicago, IL, USA, 6Emory University, Atlanta, GA, USA, 7ICAP at Columbia University, New York, NY, USA

**Background:** Postpartum depression (PPD) is associated with poor maternal and child health outcomes. Few studies have evaluated PPD in women living with HIV (WLHIV) in Botswana, a high prevalence HIV setting.

**Methods:** Using the Edinburgh Postnatal Depression Scale (EPDS), we evaluated PPD symptoms at 2, 6, and 12 months (mo) postpartum in WLHIV and HIV-uninfected (HIV-U) women enrolled in the Tshilo Dikotla cohort study in Botswana. Women scoring ≥10 on the EPDS or reporting thoughts of self-harm were defined as at risk for ongoing PPD symptoms. Secondary outcomes included: EPDS score ≥10, EPDS score ≥13, and PPD score ≥13 or reporting thoughts of self-harm. Generalized estimating equation models were fit to assess the association of maternal HIV infection with risk of PPD symptoms in the first year postpartum. Subgroup analyses in WLHIV were performed to assess factors associated with risk of PPD symptoms.

**Results:** Of 321 women enrolled, 195 were WLHIV. WLHIV were older (28.9 vs 24.4 years; p<0.01) with higher gravidity (3 vs 1; p<0.01) and were less likely to complete tertiary education (7% vs 31%; p<0.01) compared to HIV-U women. Among WLHIV, 45% had a CD4 count >50 cells/mm3 and 93% had an HIV RNA level <40 copies/mL at enrolment; median years since HIV diagnosis was 1.6. All WLHIV received a backbone of tenofovir + emtricitabine and either dolutegravir (DTG) or efavirenz (EFV). At 2, 6, and 12 mo postpartum, 301, 233, and 103 women, respectively, completed the EPDS. At 2 mo, 4 WLHIV and 6 HIV-U met the criteria for being at risk for PPD symptoms. At 6 mo and 12 mo, 6 and 4 WLHIV respectively met the criteria for being at risk for PPD symptoms, whereas no HIV-U women met the criteria. After adjusting for age, gravidity, education level, marital status, and employment, WLHIV were at increased risk for PPD symptoms compared to HIV-U women (adjusted Odds Ratio: 3.37; 95% Confidence Interval: 1.14-10.02). Findings were similar in models evaluating secondary outcomes. (Table 1) Among WLHIV, no associations were seen between age, gravidity, employment, CD4, years with HIV, timing of ART initiation, or ART regimen and PPD symptoms.

**Conclusion:** Despite overall low rates of PPD symptoms in this small Botswana cohort, WLHIV may be at higher risk for experiencing PPD symptoms in their first year postpartum compared to HIV-U women. Screening WLHIV for PPD symptoms and providing support during the postpartum period are an important part of routine postpartum care for this vulnerable population.

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**Table 1. Adjusted Generalized Estimating Equation Models of the Association between Maternal HIV Infection and Depressive Symptoms in the First Year Postpartum**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
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<tbody>
<tr>
<td>Edinburgh score ≥10 or report of thoughts of self-harm</td>
<td>3.37</td>
<td>1.34 - 10.02</td>
</tr>
<tr>
<td>Edinburgh score ≥13</td>
<td>5.56</td>
<td>1.24 - 21.40</td>
</tr>
<tr>
<td>Edinburgh score ≥13 or report of thoughts of self-harm</td>
<td>4.59</td>
<td>1.13 - 18.54</td>
</tr>
</tbody>
</table>

All models adjusted for age, gravidity, highest education level, marital status, and employment.

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**769 HIV DRUG RESISTANCE AT PERINATAL TRANSMISSION AND ACCUMULATION DURING BREASTFEEDING**

Ceejay Boyce1, Ingrid A. Beck2, Tatiana Sils2, Daisy Ko2, Annie Wong-On-Wing2, Sheila Styrchak2, Patricia DeMarras1, Camlin Tierney3, Lynda Stranix-Chibanda4, Taha E. Taha1, Masenias Owor1, Mary G. Fowler1, Lisa Frenkel1, for the Promoting Maternal and Infant Survival Everywhere trial (PROMISE) Study Team

1University of Washington, Seattle, WA, USA, 2Seattle Children’s Research Institute, Seattle, WA, USA, 3University of Washington, Boston, MA, USA, 4University of Zimbabwe, Harare, Zimbabwe, 5Johns Hopkins University Baltimore, MD, USA, 6Makerere University–Johns Hopkins University Research Collaborations, Kampala, Uganda

**Background:** HIV drug resistance (DR) can undermine antiretroviral treatment (ART). We examined risks of maternal DR on perinatal transmission (PT) in a case-control study, and infants’ acquisition of DR during breastfeeding (BF) in the PROMISE 1077BF trial.

**Methods:** We analyzed sequential cross-sectional serosurvey data collected in 2012 (n=8800), 2014 (n=10,404), and 2018 (n=7361) from the evaluation of Zimbabwe’s Accelerated PMTCT Program. Using multi-stage cluster sampling, we randomly sampled mother-infant pairs each survey year from catchment areas (CAs) of 157 facilities. Eligible women were ≥16 years old and biological mothers of infants (alive or deceased) born 9 to 18 months before the interview. Participants were tested for HIV and interviewed about health service utilization during pregnancy and breastfeeding.

**Results:** In 2018, of 7361 women surveyed, 6816 (92.6%) attended ≥1 antenatal care (ANC) visit, 5196 (70.6%) attended ≥4 ANC visits, 6872 (92.4%) were tested for HIV and received their results, and 6290 (85.5%) delivered in a health facility. The uptake of services targeted to all women was relatively stable from 2012-2018. In contrast, utilization of services targeted to HIV-infected women and their infants increased (Figure, maternal HIV prevalence in 2012: 12.4%, 2014: 13.4%, 2018: 10.6%). Uptake of both maternal antiretroviral therapy (2012: 59.4%, 2014: 64.7%, 2018: 73.2%; p<0.01) and infant ARV prophylaxis (2012: 62.6%, 2014: 66.5%, 2018: 73.3%; p<0.01) significantly increased from 2012-2018. Of infants born to HIV-infected mothers, 8.8%, 6.7%, and 3.6% were HIV infected in 2012, 2014, and 2018, respectively. In the 128 CAs with data on HIV exposed infants before and after implementation of Option B+, mean decrease in CA level MTCT was -6.4 percentage points (95% CI -9.3, -3.5) and the proportion of CAs with no transmissions increased in 2012 to 82% in 2018. CA level MTCT in 2018 varied by province between 1.3% and 9.5%.

**Conclusion:** Zimbabwe has made remarkable progress increasing coverage of PMTCT services and reducing MTCT. Coverage of services for women living with HIV increased significantly, and an overall MTCT decreased to below the 5% threshold for virtual elimination. However, MTCT rates varied across provinces, and a minority of women living with HIV still did not receive PMTCT services. This highlights the need for continued efforts to simulate demand and overcome barriers to health services.

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**Figure. Prevention of mother-to-child HIV transmission (PMTCT) cascade in Zimbabwe, 2012–2018.** The percentages at each step are the proportion of the total number of HIV-infected women and their HIV-exposed infants in the survey receiving each service. Analysis restricted to biological mothers and their eligible infants (0-18 months of age).
and site. Plasma from infant's date of HIV diagnosis, ART initiation, and last study visit, and mother's plasma ≥40c/mL from the nearest date proximate to PT (or their matching case’s time of PT for controls) were genotyped by consensus sequencing (CS) of HIV pol. Infants and mothers were categorized as wild-type (WT) or DR based on major DR mutations (DRM) defined by the Stanford Database. Maternal viral loads (VL) and DR rates were independently compared using Mann-Whitney and Fisher’s Exact tests. Adjusted analyses used logistic regression.

Results: Proximate to infant diagnosis, case mothers had higher median VL vs. controls (4.28 vs. 3.86 log10c/mL, p<0.0001). DR was significantly higher in transmitting vs. control mothers (15.8% vs. 7.6%, p=0.048). DR was more prevalent in mothers who transmitted via BF compared to IU (29.7% vs. 4.4%; p<0.002). In a logistic regression adjusted for VL, antepartum (AP) term treatment, and clinical site, DR was no longer associated with PT (p=0.618), while VL increased (p<0.0001) and AP triple ARV decreased (p=0.021) risk of PT. Of 75 infants with CS, 5/40 (12.5%) with IU vs. 19/35 (54.3%) with BF transmission had DRM at diagnosis (p<0.001). Of the 24 DR infants, 58.3% had 1 NRTI DRM, 25% had ≥2 NRTI DRM, 12.5% had 1 NRTI DRM, and 4.2% had dual-class DRM. Among 72 mother-infant pairs genotyped, 46 (64%) were concordant for WT, 7 (9.7%) concordant for DR and 19 (26.3%) were discordant (17 (89.5%) WT mothers had DR infants). Among 46 infants with longitudinal genotypic data, 8/13 (62%) WT infants at diagnosis in the IU cohort and 1/6 (17%) WT infants in the BF cohort acquired DRM resulting in 33/75 (44%) DR infants.

Conclusion: DR was frequently detected among women with PT during BF. However, in this study, DR does not appear to be a driver of PT. DR was less prevalent in infants with IU vs. BF PT, and accumulated during early infancy, suggesting that exploration of additional prophylactic regimens is warranted.

Table 1: Maternal viral load (range) and genotype by perinatal transmission type

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770 GP41 ECTODOMAIN-SPECIFIC IGG IS ASSOCIATED WITH INCREASED VERTICAL HIV-1 TRANSMISSION

Nicole Naiman1, Jennifer Slyker2, Ruth Ndudu2, Julie M. Overbaugh1
1Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 2University of Washington, Seattle, WA, USA, 3University of Nairobi, Nairobi, Kenya

Background: Studies of the epitope specificity of maternal antibodies in relation to reduced risk of mother-to-child transmission (MTCT) have identified correlates of protection in some studies. However, there is little consistency between results across studies. In addition, few studies have investigated pre-existing passively-acquired HIV-specific antibody responses in infants, which are most relevant because they are present prior to HIV exposure through breastfeeding. We hypothesized that pre-existing passively-acquired antibodies that target specific epitopes confer protection against MTCT of HIV-1.

Methods: We performed binding antibody multiplex assays to measure IgG binding against a cross-clade panel of 19 HIV-1 antigens in a cohort of 72 breastfeeding Kenyan mother-infant pairs enrolled during the pre-ART era. Infant plasma from the first week of life (before infection) and paired maternal plasma were tested. A32-like, C11-like, and 17b-like ADCC of the non-transmitting vs transmitting maternal plasma (or uninfected vs infected infant plasma) were compared using logistic regression adjusted for maternal viral load. The BF cohort acquired DRM resulting in 33/75 (44%) DR infants.

Conclusion: DR was frequently detected among women with PT during BF. However, in this study, DR does not appear to be a driver of PT. DR was less prevalent in infants with IU vs. BF PT, and accumulated during early infancy, suggesting that exploration of additional prophylactic regimens is warranted.

Results: Proximate to infant diagnosis, case mothers had higher median VL vs. controls (4.28 vs. 3.86 log10c/mL, p<0.0001). DR was significantly higher in transmitting vs. control mothers (15.8% vs. 7.6%, p=0.048). DR was more prevalent in mothers who transmitted via BF compared to IU (29.7% vs. 4.4%; p<0.002). In a logistic regression adjusted for VL, antepartum (AP) term treatment, and clinical site, DR was no longer associated with PT (p=0.618), while VL increased (p<0.0001) and AP triple ARV decreased (p=0.021) risk of PT. Of 75 infants with CS, 5/40 (12.5%) with IU vs. 19/35 (54.3%) with BF transmission had DRM at diagnosis (p<0.001). Of the 24 DR infants, 58.3% had 1 NRTI DRM, 25% had ≥2 NRTI DRM, 12.5% had 1 NRTI DRM, and 4.2% had dual-class DRM. Among 72 mother-infant pairs genotyped, 46 (64%) were concordant for WT, 7 (9.7%) concordant for DR and 19 (26.3%) were discordant (17 (89.5%) WT mothers had DR infants). Among 46 infants with longitudinal genotypic data, 8/13 (62%) WT infants at diagnosis in the IU cohort and 1/6 (17%) WT infants in the BF cohort acquired DRM resulting in 33/75 (44%) DR infants.

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771 EPI TOPE TARGETS OF ADCC-MEDIATING ANTIBODIES AND THEIR RELATION TO MTCT OF HIV-1

Nicole Naiman1, Jennifer Slyker2, Barbra A. Richardson2, Ruth Ndudu2, Julie M. Overbaugh1
1Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 2University of Washington, Seattle, WA, USA, 3University of Nairobi, Nairobi, Kenya

Background: We previously reported that passively-acquired antibody-dependent cellular cytotoxicity (ADCC) in infants is associated with improved survival of infected infants and a trend towards protection against mother-to-child transmission (MTCT) of HIV-1. However, the epitopes of these beneficial ADCC-mediating antibodies have not been investigated. Because CD4-uncidable (CD4i) epitopes are a common target of antibodies elicited by natural infection, we hypothesized that ADCC targeting these CD4i epitopes may contribute to improved infant survival.

Methods: LALA variants to 3 CD4i antibodies, A32, C11, and 17b, were used as inhibitors in a competition rapid and fluorometric ADCC assay to measure CD4i epitope-specific ADCC of plasma samples from a cohort of 72 breastfeeding Kenyan mother-infant pairs enrolled during the pre-ART era. Infant plasma from the first week of life (before infection) and paired maternal plasma were tested. A32-like, C11-like, and 17b-like ADCC of the non-transmitting vs transmitting maternal plasma (or uninfected vs infected infant plasma) were compared using logistic regression adjusted for maternal viral load. The effect of ADCC targeting CD4i epitopes on infected infant survival was assessed by Cox-proportional hazards models.

Results: A32-like and C11-like ADCC were common in this cohort but were not associated with MTCT (Table 1). A32-like ADCC was not associated with infected infant survival, but maternal C11-like ADCC was associated with a trend towards increased mortality of infected infants (HR=1.062; p=0.09; Table 1). Surprisingly, 17b-like ADCC was negative in the majority of samples, indicating that 17b-LALA mediated an enhancement of plasma ADCC. This enhancement was not associated with MTCT but was associated with increased infected infant mortality (Table 1). Enhancement with 17b-LALA was inversely correlated with total ADCC (Pearson R: -0.72), indicating that the negative association of 17b-LALA mediated ADCC with increased infected infant mortality may be due to lower total ADCC, consistent with our previous report.

Conclusion: While CD4i epitope-specific ADCC antibodies were elicited in this cohort, they likely are not responsible for improved infant outcome seen with higher passively-acquired ADCC. As suggested by the trend with maternal C11-like ADCC, C11-like ADCC may actually be associated with worse infant outcome, although further investigation is necessary.

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772 ABUNDANT EXPRESSION OF CCR5 ON EARLY HOFBAUER CELLS MAY INCREASE HIV-1 SUSCEPTIBILITY

Dominika Swieboda, Erica L. Johnson, Joanna Skountzou, Rana Chakraborty
Background: Even with optimal adherence, maternal antiretroviral therapy reduces, but does not eliminate, vertical transmission of HIV-1. Placental macrophages (Hofbauer cells, HCs) are thought to be key mediators of in utero HIV-1 transmission to the fetus. Previous studies have demonstrated that HIV-1 replication in HCs can be regulated by cytokines and interferons (IFNs) (Cobos Jimenez, Booman et al. 2012), and that certain maternal coinfections (such as HCMV) (Johnson, Boggavarapu et al. 2018) can enhance HC susceptibility and viral replication in vitro by altering HC polarization. Early gestation placental tissue has yet to be evaluated in the context of HIV-1 permissivity.

Methods: Here, we determined the levels of expression of HIV-1 co-receptors CCR5 and DC-SIGN on HCs isolated from fresh placenta throughout gestation (12 weeks to term) and evaluated expression of HIV-1 restriction factors SAMHD1, Tetherin, Trim5α, TREX-1, and APOBEC3G. To determine if HC polarization and activation state differentially modify HIV-1 permissivity throughout gestation, HCs were subjected to polarization conditions (LPS+IFN-γ, IL-10) or IFNs (IFN-α A/D, IFN-λ1), and changes in receptor and restriction factor expression were determined at the protein and RNA level.

Results: Basal CCR5 expression levels significantly differed throughout gestation; while only 50% of term HCs expressed CCR5, 100% of early gestation HCs were positive for this receptor. Surface expression of CCR5 remained stable at the protein level and was increased at the RNA level. HIV-1 restriction factors were present at baseline and were upregulated in HCs as a result of treatment. Upregulation of restriction factors in HCs isolated from early gestation matched or exceeded that of term samples, suggesting a level of innate immune protection from vertical transmission even in early pregnancy. Interestingly, IFN-λ1, which is strongly produced by placental trophoblasts, did not affect the expression of HIV-1 restricting factors, suggesting a limited role in controlling HIV-1 replication in HCs.

Conclusion: Placental macrophages in early pregnancy may be susceptible to HIV-1 infection due to abundant expression of CCR5, as compared to term samples. Co-receptor expression may be counterbalanced by robust basal and cytokine-induced expression of key HIV-1 restriction factors in HCs, offsetting in utero transmission early in gestation.

Figure 1: HIV-1 co-receptor expression in placental macrophages. Freshly isolated HCs were stained with antibodies against CCR5 and DC-SIGN, and analyzed with flow cytometry. Results are given as percent of total live, CD14+ cells. Means of each marker were calculated and compared between different macrophage populations using two-way ANOVA with Tukey’s correction for multiple comparisons. *p<0.05, **p<0.01, ***p<0.001.

773 INCIDENT HIV INFECTION AMONG PREGNANT WOMEN IN BOTSWANA

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Background: In Botswana, >90% of HIV+ women receive ART in pregnancy. An increasing proportion of MTCT may occur among women with incident undiagnosed HIV infection during pregnancy. Botswana guidelines recommend repeat HIV testing every 3 months in pregnancy, with at least 1 in the 3rd trimester. We evaluated the rate of antenatal repeat HIV testing and estimated HIV incidence during pregnancy.

Methods: In the Tsepamo Study, we abstracted HIV test dates and results from obstetric records of all women who delivered in 8 maternities across Botswana between May 2017 (when abstraction of these data were added) and Sept 2018.

This analysis includes women not known to be HIV+ at the start of pregnancy. We defined seroconversion as an initial negative or indeterminate HIV test in pregnancy, followed by a positive test. The incidence rate (IR) of seroconversion was calculated among women with >= 2 known testing dates during pregnancy. Missed seroconversions were estimated among women without a test in the 3rd trimester by applying the IR to the time after their last HIV test until delivery.

Results: Among 28,999 women delivering, 5724 (20%) were known to be HIV+ prior to pregnancy, 1,758 (6.1%) tested HIV+ at first test in pregnancy, 229 (0.8%) had no HIV test in pregnancy, 57 (0.2%) were unknown, and 21,231 (73%) tested HIV-negative at first test in pregnancy. Of women who initially tested negative, 5321 (25%) had 1 test, 12,225 (58%) had 2 tests, and 3678 (17%) had 3 tests during pregnancy. The median gestational age at first HIV test was 16 weeks (IQR 12.21) and median gestational age at last HIV test was 31 weeks (IQR 26.35), with 68% tested in the 3rd trimester (Figure 1). Older women, women with more education, and primigravid women had more HIV tests. The proportion with only one test also differed by site (range 11%-50%). Among 55,47 women without an HIV test in the 3rd trimester, we estimate approximately 10 seroconversions may have been missed because of a lack of repeat testing.

Conclusion: In pregnancy, HIV incidence after an initial negative test was low and the majority of women tested in the 3rd trimester. However lack of re-testing in the 3rd trimester led to an estimated 20% decrease in detection of seroconversions. To reach the goal of zero new pediatric HIV infections, Botswana will need to intensify identification of incident HIV.

Figure 7: Distribution of gestational age at last HIV-negative test in pregnancy. We defined seroconversion as an initial negative or indeterminate HIV test in pregnancy, followed by a positive test. The incidence rate (IR) of seroconversion was calculated among women with >= 2 known testing dates during pregnancy. Missed seroconversions were estimated among women without a test in the 3rd trimester by applying the IR to the time after their last HIV test until delivery.

POSTPARTUM IN KENYA

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Background: HIV testing during pregnancy/postpartum is crucial for early detection and treatment of incident maternal HIV infection, and to achieve elimination of mother-to-child HIV transmission (MTCT). Kenyan guidelines recommend retesting peripartum HIV negative women but data on implementation are lacking. We measured the frequency of HIV retesting during pregnancy, delivery, and postpartum and correlates of postpartum retesting.

Methods: HIV-seronegative women seeking maternal and child health (MCH) services were enrolled in a cross-sectional study in rural Kenya at the Ahero County and Bondo sub-County Hospitals at one of the following time points: pregnancy, delivery; 6 weeks, 6 months, or 9 months postpartum. Data on programmatic retesting was abstracted from MCH booklets to ascertain retesting during pregnancy and/or postpartum prior to the study visit. Retesting was defined as any HIV test after the initial antenatal care (ANC) test or after pregnancy if testing was not done in ANC. Poisson regression, clustered by site, was used to identify correlates of retesting among women enrolled at 9 months postpartum.

Results: Among 1919 women enrolled, the median age was 23 years, 63% were married and the median number of times tested for HIV in the most recent...
pregnancy/postpartum period was 1 (interquartile range [IQR] 1-2). Overall, 659 women were enrolled in the 3rd trimester, 128 within 48 hours after delivery, 387 at 6 weeks postpartum, 412 at 6 months postpartum, and 333 at 9 months postpartum. Prevalence of any programmatic HIV retesting was significantly higher at 6 weeks postpartum (46%) than in the 3rd trimester (23%), at delivery (5%), and at 6 months postpartum (28%) (p<0.001 for all). By 9 months postpartum, HIV retesting was associated with prior sexually transmitted infection (STI) diagnosis (Prevalence Ratio [PR]: 1.28, 95% Confidence Interval [CI]:1.06-1.56; p<.001), higher gravidity (PR:1.05 per pregnancy, 95% CI:1.04-1.06; p<.001), and being an orphan (PR:1.02, 95% CI:1.01-1.02 p=0.2). Results were similar in a multivariable analysis of cofactors significant in the univariate model.

Conclusion: Prevalence of retesting was higher in the early postpartum period and more common among women who had a history of STIs and higher gravidity. Strategies to offer retesting to all peripartum women in high prevalence regions could help identify incident maternal HIV and maximize prevention of MTCT efforts.

775 PRIMARY HIV PREVENTION IN PREGNANT AND LACTATING UGANDAN WOMEN: A RANDOMIZED TRIAL

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Background: The Primary HIV Prevention among Pregnant and Lactating Ugandan Women (PRIMAL) study aimed to assess the effectiveness of enhanced counseling for preventing HIV acquisition among HIV-uninfected pregnant women throughout the breastfeeding period.

Methods: We conducted an unblinded randomized control trial between 02/2013 and 04/2016 to assess the effectiveness of enhanced counseling to prevent primary HIV infection among HIV-uninfected pregnant and lactating women in Uganda. HIV-uninfected pregnant women aged 15-49 were enrolled individually or in couples, randomized 1:1 to an intervention or control group, and followed up to 24 months postpartum or the end of breastfeeding, whichever came first. Both groups were tested for STIs and HIV at enrollment, delivery, 3 and 6 months postpartum and every 6 months thereafter until the end of follow-up. The intervention group received enhanced HIV prevention counseling every 3 months throughout follow-up. The control group received standard counseling at the time of HIV retesting.

Results: We enrolled 820 HIV-uninfected pregnant women individually (n=410) or in couples (n=410 women and 410 partners) in one urban and one rural public Ugandan hospital. 675 (76%) women completed follow-up per protocol representing 1,439 women-years of follow-up. Although the frequency and proportion of condom use in the last 3 months or at last vaginal sex increased over follow-up, there were no statistically significant differences between the study arms. During follow-up, <2.1% of women tested positive for either syphilis, gonorrhea, C. trachomatis or T. vaginalis at any follow-up visit, while four women (two per arm) and no enrolled men became infected with HIV, for an overall HIV incidence rate of 0.186 per 100 person-years. There were two infections of syphilis, one each in the intervention and control arms. Incidence of other STIs was similar in both arms.

Conclusion: A sustained enhanced HIV prevention counseling intervention for up to 2 years postpartum among pregnant and breastfeeding women did not have a statistically significant effect on condom use or HIV incidence among these women. However, in both study arms, condom use increased over follow-up while STI and HIV incidence remained very low, suggesting that repeated HIV testing during breastfeeding, whether with standard or enhanced counseling, could be an effective strategy for the primary prevention of HIV among pregnant and lactating women in high HIV prevalence settings. Further research is needed to verify this hypothesis.

776 MODELING THE IMPACT OF PrEP FOR PREGNANT AND BREASTFEEDING WOMEN IN SOUTH AFRICA

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Background: HIV-uninfected pregnant and breastfeeding women are at high risk of HIV acquisition, contributing to persistent high levels of MTCT. Pre-exposure prophylaxis (PrEP) is safe and effective in preventing HIV acquisition in pregnancy, but PrEP in pregnancy is not policy in many countries including South Africa (SA). We examined the potential impact of providing PrEP for SA pregnant and breastfeeding women.

Methods: We used the ThembiSA model, an established SA model to estimate the potential effect of introducing PrEP for pregnant and breastfeeding women. The model divides the SA population by key demographic factors and, among sexually active individuals, into high-risk (individuals with a propensity for concurrent partners and/or commercial sex) and low-risk individuals. We consider two scenarios for modelling PrEP uptake during pregnancy and breastfeeding: (1) a conservative scenario with model assumptions to match the experience reported in the Kenyan PrEP program for pregnant women (uptake probability=32% and 11% in high-risk and low-risk women, respectively); (2) an optimistic scenario with PrEP initiated by 80% of all pregnant women (high-risk and low-risk). PrEP in pregnancy/breastfeeding women scenarios were compared with PrEP for female sex workers (FSW), men who have sex with men (MSM), and adolescent girls and young women (AGYW). PrEP efficacy was assumed to be 65% throughout.

Results: Between 2020-2030, providing PrEP to pregnant and breastfeeding women would reduce new HIV infections in SA by 2.5% (95% CI:2.4-2.6%) in the conservative scenario and 7.2% (95% CI:6.8-7.5%) in the optimistic scenario (Figure). This is similar to the FSW and MSM PrEP scenarios (1.9% and 3% respectively). Without PrEP, 76,000 (95% CI: 64,000-90,000) new cases of MTCT are expected over 2020-2030; PrEP provision may reduce these infections by 13% (95% CI: 13-14%) in the conservative scenario and 41% (95% CI: 39-44%) in the optimistic scenario. Under the optimistic scenario PrEP would have a proportionally greater impact on breastfeeding transmission (47% reduction, 95% CI: 44-49%) vs. in utero and intrapartum transmission (23% reduction, 95% CI: 18-27%).

Conclusion: High levels of uptake of and adherence to PrEP among pregnant and breastfeeding women could fundamentally alter MTCT in SA. There is an urgent need for implementation research to identify interventions that will facilitate PrEP use during pregnancy and breastfeeding in this setting.

777 PREFERENCES FOR HOME VS CLINIC AND BLOOD VS SALIVA HIV RETESTING IN PREGNANCY

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Background: HIV retesting during pregnancy and postpartum is critical to reduce mother-to-child HIV transmission (MTCT) due to incident maternal infections. However, widespread scale-up of this policy may confer additional strain on health systems. HIV self-testing may be an innovative solution for maternal retesting by addressing client access barriers and staffing shortages.

Methods: HIV-negative pregnant women were enrolled between November 2017 and August 2018 in Nyanza and Nairobi regions in Kenya. At enrollment, retesting preferences were assessed for location (clinic or home), test type (saliva- or blood-based rapid), and test performer (self or provider). Reasons for preferences were assessed and women were asked to select a test strategy
for retesting during the current pregnancy: blood-based testing by a provider in clinic (clinic-based testing [CBT]) or self-testing at home using a saliva-based test (home-based testing [HBT]). Chi-squared and t-tests were used to compare reasons for choice. Generalized linear models (log link, binomial family) were used to assess cofactors for testing strategy.

**Results:** Overall, 1,000 pregnant women were enrolled, with a median gestational age of 28 weeks (Interquartile range [IQR]: 22-32) and median age 24 years (IQR: 21-27). More women elected CBT (665 [67%]) than HBT (335 [33%]) for retesting (p<0.001). Later gestational age was associated with lower likelihood of electing HBT (OR per week: 0.99, 95%CI: 0.98-1.0, p<0.04). Maternal age, parity, income, education, same day HIV testing, marital status, relationship duration, and partner testing history were not associated with choice (p>0.05 for all). Preferences for test location (33% home vs 67% clinic), test operator (31% self vs 69% provider), and test type (32% saliva vs 68% blood) mirrored choice of HBT or CBT. Women who elected HBT were more likely to report being unavailable during clinic hours than women who elected CBT (18% vs 10%, p<0.001) and report longer clinic wait times (73 vs 53 minutes, p<0.001).

**Conclusion:** While pregnant women generally preferred CBT for HIV retesting, HIV self-testing at home was preferred by one-third of women, particularly those with challenges accessing health centers. As HIV retesting scales up in pregnancy and postpartum, HBT may reduce burden on health systems, increase retesting rates, and facilitate efforts to eliminate MTCT.

### 778 CHALLENGES OF POTENTIALLY FALSE-POSITIVE HIV TESTS IN PREGNANT WOMEN IN THE PEP ERA

**Anjuli D. Wagner,** John Kinuthia, Julia C. Dettinger, Nancy M. Ngumbu, Laurén Gómez, Salphee A. Watwoti, Alison L. Drake, Felix Abuna, Jillian Pintye, Ben O. Odhiambo, Grace John-Stewart, Jared Baeten

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**Background:** HIV testing, done repeatedly over time, is a cornerstone of both antenatal care (ANC) and PrEP care. In many settings, HIV rapid tests are done in sequence to confirm infection, but discrepant results (i.e. one positive, one negative) can occur. Guidelines are lacking for how to make treatment decisions after discrepant rapid results in the context of pregnancy and PrEP where urgent antiretroviral treatment (ART) to prevent mother-to-child transmission could be indicated but inappropriate ART may have negative psychosocial, interpersonal, and health systems impacts.

**Methods:** In a cluster randomized trial in Kenyan public health programs ([NCT03070600](https://clinicaltrials.gov/ct2/show/NCT03070600)), PrEP is offered to HIV seronegative women at ANC. Repeat HIV testing is done at each follow-up visit (monthly in pregnancy, tri-monthly in postpartum). The Kenyan national HIV testing algorithm indicates that if one rapid (Determine) is reactive, a second (First Response) is performed; if discrepant, both tests are repeated by a separate provider and a DNA PCR is performed using standard of care national referral systems.

**Results:** Among 2,231 women enrolled during pregnancy and followed for postpartum care, 3,135 repeat HIV tests have been performed, 7 of which had discrepant rapid results (0.22%, 95% CI: 0.09-0.46%) among 5 individuals. DNA PCR samples were collected on the same day as discrepant results; median time to receipt of PCR results was 22 days (range 16-37). In all 5 initial cases, DNA PCR was negative and none of the women were initiated on ART. Two of 5 women subsequently had repeat discrepant rapid results with repeat negative PCRs, one of whom had subsequent discordant positive rapid results (PCR pending) at delivery and declined ART due to disbelief in rapid test results.

**Conclusion:** False positive results are expected to occur at a low frequency with repeated rapid testing. For individuals who are pregnant or using PrEP, positive results demand urgent ART, but false results could trigger inappropriate ART. As repeat HIV testing during pregnancy and PrEP monitoring expands, the volume of discrepant rapid test results will increase. Our data provide evidence that discrepant results are more likely false positive than true positive. Management of discrepant results needs to balance benefits of rapid ART for PMTCT among true positives, with specific counseling about temporary ART and “disclosure” among women with false positive results. Expedited point-of-care HIV PCR could prevent unclear diagnosis, messaging, and treatment.

### 779 PILOTING POINT-OF-CARE HIV TESTING AT BIRTH AND 6 WKS POSTNATAL IN 4 KENYAN HOSPITALS

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**Background:** Point-of-care (POC) testing can expedite HIV diagnosis and treatment among HIV-exposed infants, particularly if performed at birth. Repeat testing at 6 wks is needed to detect intrapartum infections.

**Methods:** A non-blinded pilot study was conducted at 4 Kenyan hospitals with randomly assigned POC technologies (n=2 GeneXpert, n=2 Alere q). Implementation was tailored to a hospital’s layout, departmental collaborations, and patient flow. Exposed infants enrolled in the study were targeted for POC testing at birth (0 to <2 wks) and the 6-week period (4-8 wks).

**Results:** For 434 infants born November 3, 2017 to July 5, 2018, uptake of the POC test at both stages, and median age at ART initiation and drug resistance (DR) status for HIV+ infants.

**Results:** Of 434 infants, 358 (82.5%) received POC testing at any timepoint; 219 (61.2%) of these received a POC test within the birth window. Infants tested with POC at birth included 100 (45.7%) tested in Maternity (≤2 d of age) and 119 (54.3%) tested on a return visit (3-14 d of age). The median age at birth POC was 0.4 wks (IQR, 0.1-1.3). An additional 52 (14.5%) infants received a first POC test in the near-birth (2 to <4 wks) period, at median age 2.5 wks (IQR, 2.1-3.0). In the 6-wk window 257 (71.8%) received a POC test, at median age 6.1 wks (IQR, 6.0-6.3). Among infants receiving an initial POC test at or near birth, 170 (62.7%) returned for a repeat test in the 6-wk period. The optimum test sequence (first at 0-2 wks, then at 4-8 wks) was achieved for 144 (40.2%) infants. A total of 91 missed opportunities for POC were due to machine breakdown (12: all Alere q), machine errors (44: 42 Alere q, 2 GeneX) or cartridge stock-out (35: 14 Alere q, 21 GeneX).

**Conclusion:** POC testing at birth and 6 wks requires collaboration among departments and cadres of personnel, yet is feasible in government hospitals in Kenya. Patient education and provider sensitization are needed to support POC at birth, repeat testing at 6 wks, and immediate ART initiation to realize the full benefit of POC technologies.

### 780 ROUTINE POINT-OF-CARE HIV TESTING AT BIRTH: RESULTS FROM A 1-YEAR PILOT IN ESWATINI

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**Background:** In 2017, point of care (POC) birth testing was introduced into routine care at the 3 highest volume maternity sites in Eswatini. POC birth testing was offered to HIV-exposed infants born at, or presenting to, the maternities within 3 days of birth. Two of the POC platforms were used only for birth testing; one was shared with another hospital unit. National guidance states that infants testing negative at birth should return for a 6-week test; infants testing positive at birth should start nevirapine (NVP) immediately and return at 14 days of life to begin a lopinavir/ritonavir regimen (LPV/r).

**Methods:** Prospective data were collected on tests occurring 1 Aug 2017-1 Aug 2018. Variables included number of infants eligible for birth testing, percentage of infants tested, turnaround time from sample collection to receipt of results, positivity, percentage of infected infants initiated on treatment, turnaround time...
time from sample collection to treatment initiation, and percentage of infants testing negative at birth who received a subsequent test at 6 weeks.

**Results:** Of 3385 eligible infants, 1999 (59.1%) received a birth test. Of those producing a positive or negative result (n=1928; 96.4%), 98.9% (n=1906) reached the caregiver. Median turnaround time from sample collection to caregiver receipt of results was 0 days (range 0-3; IQR 0-0). Testing uptake was lower, but turnaround time to result receipt was not longer for the shared platform. 12 HIV-infected infants were identified (yield = 0.6%) and 11 were initiated on treatment (91.7%); 3 on day 14 after diagnosis, 4 after 15 days, and 4 after 60 days. The median time from sample collection to initiation on treatment for positive infants was 32 days (range 14-124; IQR 16-65). One infant died after diagnosis but prior to initiation. Analysis of subsequent tests of infants who tested negative at birth is ongoing (and will be available to be presented at CROI).

**Conclusion:** POC EID at birth is a feasible strategy in this setting. However, not all eligible infants were tested, possibly due to staffing shortages or queues for platform use. In practice, infants received no treatment until they returned to begin LPV/r. Same-day pediatric treatment initiation is uncommon in Eswatini due to caregiver desire to consult with male family members. Policymakers may consider better promotion of HVP at birth, the introduction of new pediatric formulations that can be used at birth and beyond, and/or better linkage to care to ensure timely initiation on treatment.

**Birth testing of eligible infants (n=3,385), Botswana 2017-2018**

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**781 EARLY INFANT DIAGNOSIS OF HIV USING DNA PCR CT VALUE AND REPEAT TESTING ALGORITHM**


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**Background:** Early infant diagnosis (EID) of HIV immediately after birth allows for rapid initiation of treatment in HIV+ infants, limiting disease progression and restricting viral reservoir seeding. However, no standardized testing algorithm is currently recommended.

**Methods:** From April 2015-July 2018, the Early Infant Treatment Study (EIT) screened HIV-exposed infants in Botswana < 96 hours from delivery by Roche TaqMan qualitative DNA PCR. A negative DNA PCR test was defined as no HIV DNA amplification (target not detected) at initial dried blood spot screening: a positive as two concordant spots from same sample with target detected at any cycle threshold (Ct) value; and indeterminate as discordant spots (target detected/target not detected) from same sample. Repeat blood draw occurred for initial positive and indeterminate results. Quantitative HIV-1 RNA testing occurred for those presumptively enrolled in the study. We compared Ct values by the ultimate HIV status of the child (as confirmed by subsequent HIV-1 DNA, and when possible DNA/RNA, testing).

**Results:** Of 10622 HIV-exposed infants screened, 10549 (99.3%) tested negative, 42 (0.4%) tested positive, and 31 (0.3%) tested indeterminate at the first HIV screening test. On repeat testing, 40 (95.2%) of the initial 42 positive infants remained positive and 2 (4.8%) tested negative. Of the 31 indeterminates, repeat testing confirmed 29 (93.5%) as negative and 2 (6.5%) as positive. Confirmatory testing of all positives and indeterminates re-classified 4 (5.5%) infants in total; 1 (1.4%) of the indeterminates required further HIV RNA testing to become reclassified as positive. Median DNA PCR Ct value at screening was 28.1 (IQR 19.8, 34.8) for all positive results and 35.5 (IQR 32.8, 41.4) for indeterminates (p<0.0001). Only 6 (6.2%) infants with final HIV+ status had Ct value > 33 at first screen, and only 2 (6.5%) with indeterminate result and Ct value < 33 at first screen had a final negative HIV status.

**Conclusion:** Using a standard cycle threshold of 33 and a confirmatory second blood draw for HIV DNA and RNA, our test algorithm appeared to eliminate the risk for false positive HIV results in the first week of life. Infants with Ct >33 should be re-tested with follow-up sampling, to minimize the risk for false positive testing.

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**782 DIAGNOSTIC ACCURACY OF HIV ORAL RAPID TESTS VS BLOOD-BASED RAPID TESTS AMONG CHILDREN**

Chido Dziva Chikwari, Irene Njugu, Crissl Rainer, Belinda V. Chihota, Jill Neary, Jennifer Slyker, David A. Katz, Dalton Wamalwa, Laura Oyiengo, Grace McHugh, Ethel Dauya, Grace John-Stewart, Rashida Ferrand, Anjuli D. Wagner

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**Background:** Gaps persist in HIV testing globally for children who missed testing in prevention of mother to child transmission of HIV programs. Oral mucosal transudate rapid HIV tests (OMT) have been shown to be highly sensitive in adults but their performance has not been established in children. We validated the OraQuick ADVANCE Rapid HIV-1/2 Antibody test against blood based rapid diagnostic testing (BBT) in children aged 18 months to 18 years in Kenya and Zimbabwe.

**Methods:** ART naive children were tested for HIV using a series of rapid OMT and BBT. BBT followed the Kenyan and Zimbabwean national algorithms (Determine, followed by First Response (3rd generation) if Determine was reactive). The Determine test used in Zimbabwe was 3rd generation, detecting antibodies and antigen; the Determine test used in Kenya was 3rd generation, detecting antibodies only. OMT samples were collected and interpreted by research staff; BBT were performed and interpreted by clinic or research staff. Sensitivity and specificity were calculated using the national algorithms as gold standard; secondary analysis excluded 2 cases where OMT was positive but national algorithm was initially falsely negative. Binomial distribution was used for 95% confidence intervals [95%CI].

**Results:** A total of 1,622 children were enrolled, median age was 7 years (IQR: 4.12); 2 (0.1%) were 18-24 months; 1310 (80.8%) were 2-12 years; 301 (18.6%) were 13-18 years. Among the 56 children positive by BBT, 56 (sensitivity: 100% [97.5%CI: 93.7-100%]) were positive by OMT. Among the 1566 children negative by BBT, 1564 (specificity: 99.9% [95%CI: 99.5-100.0%]) were negative by OMT.
Due to clinical presentation and OMT results, the 2 children who initially tested BBT negative and OMT positive were subsequently confirmed positive within 1 week by further tests; one (9 years) by ELISA and the second (2 years) by First Response and a third test, INSTI. Excluding these 2 children, the sensitivity and specificity of OMT compared to BBT were each 100% (97.5%CI: 93.7-100% and 99.8-100%, respectively).

Conclusion: When compared to the national algorithms, OMT did not miss any positive children. This data suggests that OMT tests are valid in this age range and may be useful for facility or community-based use. Future research should explore the acceptability and uptake of OMT use by caregivers and health care workers in diverse settings to improve pediatric HIV testing coverage globally.

### Table 1: Performance of OMT vs BBT for HIV diagnosis

<table>
<thead>
<tr>
<th>OMT</th>
<th>Positive</th>
<th>Negative</th>
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<tbody>
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<td>BBT</td>
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<tr>
<td>Positive</td>
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<tr>
<td>Total</td>
<td>56</td>
<td>1566</td>
<td>1622</td>
</tr>
</tbody>
</table>

*subsequently tested positive

Sensitivity 100%
Specificity (including 2 discrepant) 99.9%
Specificity (excluding 2 discrepant) 100%

783 FINDING THE MISSING CHILDREN WITH HIV: INDEX-LINKED TESTING IN CLINICS & COMMUNITIES

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Background: HIV prevalence is much lower in children than in other age groups but the proportion undiagnosed is significantly higher. Therefore, innovative and targeted strategies are required to improve uptake and yield of HIV testing among children. We evaluated the effectiveness of index-linked HIV testing implemented in clinic and community-based settings in children aged 2-18 years living in the household of an HIV-infected individual in urban and rural settings in Zimbabwe.

Methods: Individuals attending for HIV care at 3 urban and 3 rural primary care clinics in western Zimbabwe who had children (2-18 years) of unknown HIV status living in their households were offered 3 options for their children to access HIV testing and counselling (HTC): 1) Clinic-based HTC 2) Home-based HTC by community health workers 3) Testing performed by caregivers using an oral mucosal test (assisted self-testing) Demographic data was collected from consenting caregivers who were followed up over 2 months to ascertain testing outcomes.

Results: We recruited 2813 people living with HIV (median age 38, IQR 32-46 years) who had 3431 children eligible for testing (median age 9, IQR 6-13 years). HTC was accepted for 2757 (80.4%) eligible children. Overall, 74.7% selected clinic-based testing. 19.2% opted for community-based testing and 6.1% for assisted self-testing, with no difference in trend by rural or urban setting. Among the 2757 children for whom HTC was accepted, 1977 (71.7%) completed testing. Those who selected community-based testing were more likely to complete the test than those who selected clinic-based testing (OR=1.69 95%CI:1.3-2.2, p<0.001) or assisted self-testing (OR=2.38 95%CI:1.0-2.3, p=0.04). Overall HIV prevalence was 1.4% but the prevalence among 12-18 year olds was 2.5% and 81% of those diagnosed were >7 years. HIV yield was 0.8% overall. Previously undiagnosed HIV was strongly associated with older age (OR=3.54, 95%CI:1.1-11.1, p=0.03) comparing 13-18 years to 2-5 year olds and with single or double orphanhood (OR=3.30, 95%CI:1.4-6.9, p=0.005). All 28 HIV positive children were linked to care within 2 weeks.

Conclusion: Index-linked testing is a feasible HTC strategy for children in Zimbabwe. However, while clinic-based testing has the highest uptake, children were more likely to be tested in community settings. Older children and orphans are at increased risk of undiagnosed HIV. Strengthening of HTC strategies to target this age group are required.

784 EARLY CHILD DEVELOPMENT OF HIV-EXPOSED UNINFECTED CHILDREN IN RURAL ZIMBABWE

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1Zimbabwe Institute for Maternal and Child Health Research, Harare, Zimbabwe, 2Queen Mary University of London, London, UK, 3University of Zimbabwe, Harare, Zimbabwe, 4Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 5University of Liverpool, Liverpool, UK

Background: Maternal HIV exposure may affect early child development (ECD), but studies comparing developmental outcomes between HIV-exposed uninfected (HEU) and HIV-unexposed children have had heterogeneous findings. We compared ECD outcomes between HEU and HIV-unexposed children recruited to the SHINE trial in rural Zimbabwe.

Methods: SHINE was a community-based cluster-randomized trial of infant and young child feeding (IYCF) and water, sanitation and hygiene (WASH) interventions in two rural Zimbabwean districts (ClinicalTrials.gov/NCT01824940). We assessed ECD outcomes at 24 months of age using the Malawi Developmental Assessment Tool (MDAT, assessing motor, cognitive, language and social development); MacArthur-Bates Communication Development Inventory (CDI) (assessing vocabulary and grammar); A-not-B test (assessing object permanence); and a self-control task. All tools were designed for use in sub-Saharan Africa, and specifically adapted for Shona-speaking households. We used generalized estimating equations to compare ECD scores between HEU and HIV-unexposed children. We included only those randomized to the standard-of-care arm to evaluate children in the absence of trial interventions.

Results: 63 HEU and 373 HIV-unexposed children were evaluated at 24 months of age. Mean total MDAT score was 0.2 standard deviations (SD) lower in HEU compared to HIV-unexposed children (90.7 versus 92.7; mean difference -1.8, 95%CI: -3.7, 0.1), driven mainly by lower gross motor scores (difference -0.8, 95%CI: -1.5, -0.1). MacArthur-Bates CDI vocabulary scores were also 0.2 SD lower in HEU compared to HIV-unexposed children (56.9 versus 61.3 words; mean difference -4.2, 95%CI: -8.3, -0.2). There was no evidence of a difference in object permanence or self-control scores between groups (Table).

Conclusion: ECD outcomes at 2 years of age differed between HEU and HIV-unexposed children in some but not all measures. There was some evidence that HEU children had lower total developmental scores, including lower language scores as assessed by a tool specifically adapted for Shona-speaking households. However, there was no evidence of differences in object permanence or self-control. Longer-term studies are needed to evaluate whether relatively small differences in motor and cognitive outcomes at age 2 years translate into meaningful differences in school attainment at older ages.

<table>
<thead>
<tr>
<th>HIV-unexposed</th>
<th>HEU</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>52.9 (7.5)</td>
<td>50.7 (9.5)</td>
<td>-2.2 (-4.3, 0.1)</td>
</tr>
<tr>
<td>Grass motor</td>
<td>23.0 (2.6)</td>
<td>23.0 (3.1)</td>
<td>-0.0 (-1.5, 1.5)</td>
</tr>
<tr>
<td>Four motor</td>
<td>23.9 (2.8)</td>
<td>23.4 (2.7)</td>
<td>-0.5 (-1.4, 0.1)</td>
</tr>
<tr>
<td>Language</td>
<td>20.7 (3.8)</td>
<td>21.4 (4.2)</td>
<td>-0.7 (-1.7, 0.3)</td>
</tr>
<tr>
<td>Social</td>
<td>24.1 (3.1)</td>
<td>24.3 (2.2)</td>
<td>0.2 (-0.5, 0.9)</td>
</tr>
<tr>
<td>MacArthur-Bates CDI vocabulary</td>
<td>56.9 (38.2)</td>
<td>61.2 (48.7)</td>
<td>-4.3 (-8.5, 0.2)</td>
</tr>
</tbody>
</table>

A-not-B test: 7.4 (3.3) versus 7.8 (3.3) (mean difference 0.4, 95%CI: -0.8, 1.6, p=0.44).

Table: Early child development in HIV-exposed uninfected and HIV-unexposed children at 24 months of age. HEU: HIV-exposed uninfected; MDAT: Malawi Developmental Assessment Tool; CDI: Communication Development Inventory; 95%CI: 95% confidence interval.
785 NEURODEVELOPMENT IN INFANTS OF WOMEN WITH PERINATALLY VS NONPERINATALLY ACQUIRED HIV

Jennifer Jao1, Deborah Kacanek1, Wendy Yu1, Paige L. Williams1, Kunjal Patel1, Sandra Burchett2, Gwen Scott3, Elaine J. Abrams4, Rhoda Sperring5, Russell B. Van Dyke6, Renee Smith7, Kathleen Malee8, for the Pediatric HIV/AIDS Cohort Study

1Northwestern University, Chicago, IL, USA, 2Harvard University, Boston, MA, USA, 3Boston Children’s Hospital, Boston, MA, USA, 4University of Miami, Miami, FL, USA, 5Columbia University, New York, NY, USA, 6Icahn School of Medicine at Mt Sinai, New York, NY, USA, 7Tulane University, Metairie, LA, USA, 8University of Illinois at Chicago, Chicago, IL, USA

Background: The neurocognitive and psychosocial impact of lifelong HIV and antiretroviral therapy (ART) may confer neurodevelopmental (ND) risk on offspring with perinatally acquired HIV infection (PHIV). No studies have assessed whether maternal PHIV is associated with early infant ND outcomes.

Methods: Using the Bayley Scales of Infant and Toddler Development, 3rd Ed. (Bayley-III), we compared ND outcomes at 1 year of age in HIV-exposed uninfected (HEU) infants born to women with PHIV vs. non-perinatally acquired HIV (NPHIV) enrolled in the Surveillance Monitoring for ART Toxicities (SMARTT) study. Eligible HEU infants included those with valid Bayley-III data at 1 year of age and mothers born after 1982. Cognitive, language, and motor domains were assessed as continuous composite scores. The proportion with a composite score <78 in each domain was also evaluated. Maternal PHIV status was identified by self-report and medical record review. Due to the clustering effect of siblings, linear mixed effects models were fit to estimate the mean difference in Bayley-III scores in each domain, comparing infants of women with PHIV vs. NPHIV, adjusting for potential confounders.

Results: 550 WLHIV gave birth to 678 HEU children (125 and 553 born to women with PHIV and NPHIV respectively). Women with PHIV were younger (median age 23 vs 25, p<0.01), more likely to be Hispanic (24% vs 12%, p<0.01), have a CD4 count <200 cells/mm³ (21% vs 10%, p<0.01), and receive ≥3 classes of antiretrovirals (ARVs) in pregnancy (18% vs 3%, p<0.01). In addition, women with PHIV had higher median Wechsler Abbreviated Scale of Intelligence (WASI) scores (91 vs 86, p<0.01). Mean scores and the proportion with an abnormal score for each of the Bayley-III domains were not significantly different between infants born to women with PHIV vs NPHIV in unadjusted models. After adjusting for maternal age, race/ethnicity, WASI score, CD4 in pregnancy, and presence of mental health condition, as well as infant English monolingual environment and in utero exposure to ≥3 ARV classes, infants of women with PHIV had lower language (91.8 vs 94.8, p=0.04) and motor (93.7 vs 96.8, p=0.03) composite scores but no differences in cognitive composite scores.

Conclusion: Cognitive outcomes of infants born to women with PHIV vs NPHIV are reassuring. Differences in language and motor functioning, while of limited clinical significance, highlight the importance of long-term monitoring of neurodevelopment in children born to PHIV women.

Table. Adjusted mean Bayley Scales composite scores comparing infants of women with perinatally vs. non-perinatally acquired HIV

<table>
<thead>
<tr>
<th>Bayley Scales III Domain</th>
<th>Mean Estimate Infants of Women with PHIV</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive</td>
<td>100.1</td>
<td>0.13</td>
</tr>
<tr>
<td>Language</td>
<td>91.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Motor</td>
<td>93.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Models are adjusted for maternal age, race/ethnicity, WASI score, CD4 in pregnancy, and presence of mental health condition, as well as infant English monolingual language environment and in utero exposure to ≥3 ARV drug classes. NPHIV=non-perinatally acquired HIV. PHIV=perinatally acquired HIV.

786 NEURODEVELOPMENTAL OUTCOMES FOLLOWING IN UTERO EFAVIRENZ EXPOSURE AMONG HEU CHILDREN

Adam R. Cassidy1, Paige L. Williams1, Jean Leidner2, Gloria K. Mayondi1, Gbolahan Ajibola1, Judith Mabuta3, Joseph Makhema4, Kathleen M. Powis5, Roger L. Shapiro1, Betsy Kammerer1, Shahin Lockman1

1Boston Children’s Hospital, Boston, MA, USA, 2Harvard University, Boston, MA, USA, 3Goodtables Data Consulting, Norman, OK, USA, 4Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 5Massachusetts General Hospital, Boston, MA, USA, 6Beth Israel Deaconess Medical Center, Boston, MA, USA, 7Bingham and Women’s Hospital, Boston, MA, USA

Background: A large and increasing number of women with HIV infection conceive while taking efavirenz (EFV)-based antiretroviral treatment (ART) globally. Despite concerns regarding potential adverse neurologic outcomes, few studies have evaluated child neurodevelopmental outcomes in utero exposure to EFV-based maternal ART. We hypothesized that (a) HEU children with fetal EFV exposure would exhibit worse neurodevelopmental and social-emotional outcomes than HEU children with fetal exposure to non-EFV-based antiretroviral (ARV) regimens, and (b) among EFV-exposed children, initial exposure beginning at conception or during the first trimester would be associated with worse outcomes than exposure beginning later in gestation.

Methods: 24-month old HEU children whose mothers took EFV-based ART (EFV-exposed) were recruited from May 2016 to May 2017. Their neurodevelopmental outcomes were compared to those from a previously-tested cohort of 24-month old HEU children exposed to non-EFV-based ARVs (non-EFV-exposed). The testing protocol included the Bayley Scales of Infant Development: Third Edition (BSID-III) adapted for use in Botswana; and the Developmental Milestones Checklist (DMC), and Profile of Social Emotional Development (PSED), both developed in Africa. General linear models were used to compare mean outcomes, adjusting for maternal health and child sociodemographic confounders; mean differences were expressed using Cohen’s d effect sizes.

Results: Our analysis included 493 HEU children (126 EFV-exposed, 367 EFV-unexposed). Adjusted mean scores for the EFV-exposed group were lower (worse) than the EFV-unexposed group on the BSID-III Receptive Language scale (adjusted means=21.5 vs 22.5, p = 0.05), DMC Locomotor (30.7 vs 32.0, p<0.01), and Fine Motor scales (17.3 vs 19.2, p<0.01); higher (better) on the DMC Language scale (17.6 vs 16.5, p<0.01); and higher (worse) on the PSED (11.7 vs 9.9, p=0.02). Effect sizes for these differences ranged from 0.24 – 0.50 (see Table 1). Children with fetal EFV exposure during the first trimester (n = 53) had worse scores on the BSID-III Receptive Language scale than children with later gestational exposure (n = 73; EFV mean = 20.7 vs non-EFV mean = 22.2, p=0.02).

Conclusion: HEU children with fetal EFV-exposure may be at higher risk for delays in some neurodevelopmental and social-emotional domains than HEU children with fetal exposure to non-EFV-based ARVs.

Table. Adjusted mean Bayley Scales composite scores comparing infants with fetal exposure to EFV-exposed and non-EFV-exposed HEU children

<table>
<thead>
<tr>
<th>Bayley Scales III Domain</th>
<th>Mean Estimate Infants of Women with PHIV</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>91.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Motor</td>
<td>93.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Models are adjusted for maternal age, race/ethnicity, WASI score, CD4 in pregnancy, and presence of mental health condition, as well as infant English monolingual language environment and in utero exposure to ≥3 ARV classes. NPHIV=non-perinatally acquired HIV. PHIV=perinatally acquired HIV.

787 HIV-EXPOSED UNINFECTED INFANT GUT MICROBIOME EVOLUTION IN THE FIRST YEAR OF LIFE

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1Harvard University, Boston, MA, USA, 2Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 3Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, 4University of Botswana, Gaborone, Botswana

Background: HIV-exposed uninfected (HEU) infants experience higher infectious morbidity than HIV-unexposed uninfected (HUU) infants. Infant commensal gut microbiome influences the developing infant immune system, with dysbiosis associated with immune activation. We compared gut microbiome evolution in the first year of life and hospitalizations between HEU and HUU infants Botswana.
Background: Gut dysbiosis is observed in adults with HIV compared with uninfected adults and implicated in persistent inflammation (IF) and immune activation (IA). Little is known about the gut microbiome in HIV-infected (HIV+) infants, who also have persistent IF and IA compared with HIV-exposed uninfected (HEU) infants. The gut microbiome in breastfed (BF) and non-breastfed (NBF) HIV+ and HEU infants was assessed.

Methods: 40 (20 HIV+ and 20 HEU) infants on co-trimoxazole prophylaxis were selected from a clinical trial (IMPAACT P1072/NWCS 612) of rotavirus vaccine (RotaTeqTM) based on stool availability, having age-matched (3 mos.) and breastfeeding-matched HEU control infants. 16S rRNA (V3V4) sequences from stool DNA were assigned organizational taxonomic units with QIIME. α- (Chao1, abundance coverage estimator (ACE), Shannon, Simpson) and β- (Bray-Curtis, Jaccard, unweighted and weighted UniFrac) diversity, and differentially abundant taxa (linear discriminant analysis effect size (LEfSe)) were analyzed. Multivariate analysis was performed, adjusting for HIV status, breastfeeding and gender. Microbiome regression-based kernel association test was used for multivariate analysis of β-diversity.

Results: An HEU NBF infant was excluded for low read count. There were more females in the HIV+ than HEU (80% vs. 47.4%; p=0.048) group; HIV+ infants had lower mean CD4% (32.6 vs 39.9; p=0.032) and WHO weight-for-age Z score (-1.1 vs -0.5; p=0.042) than HEU. HIV+ infants had higher α-diversity (Chao1 p=0.004; ACE p=0.003; Fig. A, B) and differed significantly by β-diversity (Jaccard p<0.001, unweighted UniFrac p=0.004; Fig. C, D) compared with HEU; even after adjusting for breastfeeding and gender. LEfSe showed taxa differences between HIV+ and HEU from phylum to genus level, with enrichment of Veillonella and Klebsiella genera in HIV+, and Actinomyces, Alloiococcus, Akkermansia, Weeksellaceae genera in HEU. BF infants had significantly lower α-diversity and differed by β-diversity (all measures p<0.05 after adjusting for HIV infection status and gender) compared with NBF infants.

Conclusion: The gut microbiota differs significantly at three months of age in bacterial composition and diversity by HIV infection and breastfeeding status, with higher α-diversity and differing β-diversity with HIV infection, and lower α-diversity and differing β-diversity with breastfeeding. The impact of these differences on systemic IF and IA in HIV+ infants requires further study.

Methods: Women living with HIV (WLHIV) and HIV-uninfected (HIV-U) women were enrolled in the Infant Gut Microbiome Study between 36 weeks gestation and 3 days post-delivery. Study eligibility required vaginal delivery of a full-term (≥ 37 weeks gestation), singleton infant, with commitment to exclusively breastfeed (EBF) for six-months. WLHIV had to be on first line efavirenz-containing antiretroviral treatment regimen ≥ six weeks prior to delivery. Infant rectal swabs were obtained at delivery, 1, 3, 6, 9, and 12 month study visits. DNA extracted from rectal swabs was used to perform 16S rRNA gene sequencing, amplicon data processing, taxonomic profiling, and downstream biostatistical analysis.

Results: Longitudinal gut microbiome was analyzed from 315 rectal swabs contributed by 58 infants, 34 (59%) of whom were HEU. Median EBF duration did not differ between HEU and HUU infants, (5.65 vs 5.70 months (mos); p=0.36). Total breastfeeding duration was shorter among HEU infants (6.0 vs 9.0 mos; p=0.02). Significant differences were observed across time from birth to 12 months in both HEU and HUU subsets (filtered terminal taxa relative abundance Bray-Curtis dissimilarity PERMANOVA; p < 0.05). Terminal taxa differences can be seen among time points (Figure 1A), whereas HUU and HEU compositions showed no significant differences averaged across all time points (Figure 1B). Only 4 infants hospitalizations occurred, 3 among HEU infants without differences in microbiome between hospitalized and non-hospitalized infants.

Conclusion: Significant changes in the gut microbiome of both HEU and HUU infants in the first year of life were noted, as would be expected. However, we did not observe differences in the 30 most prevalent taxa between HEU and HUU infants, or differences between hospitalized and non-hospitalized infants. Given the small number of hospitalizations, we were underpowered to detect such a difference. Further studies are needed to better understand how differences in breastfeeding duration influence gut microbiome and immune system phenotype and function of HEU infants.

DIFFERENCES IN GUT MICROBIOME IN HIV-INFECTED VERSUS HIV-EXPOSED, UNINFECTED INFANTS
Wei Li A. Koay1, Hyunwook Koh2, Mutsa Bwakura-Dangarembizi3, Myron Levin3, Adriana Weinberg4, Ni Zhao2, Deborah Persaud2
790 COMPLETE MITOCHONDRIAL GENOME IN HIV-INFECTED CHILDREN AND MOTHER-CHILD PAIRS
Claudia Fortuny1, Constanza Moreni1, Lidia Carreño1, Elena Garcia-Aramí1, Emilia Sanchez2, Gloria Garrabou2, Ingrid Gonzalez-Casacuberta2, Ester Tolbias2, Antoni Noguera-Julian3
1 Hospital Sant Joan de Déu Barcelona, Esplugues, Spain, 2 Hospital Clinic of Barcelona, Barcelona, Spain, 3 Hospital Universitario de la Vall d’Hebron, Barcelona, Spain, 4 Universitat Ramon Llull, Barcelona, Spain

Methods: Cross-sectional study. Peripheral blood mononuclear cells (PBMC) were obtained simultaneously 6 weeks after birth from the mothers and their HEU infants and at a mean±SD age of 12.5±4.3 years in HIV-infected children. PBMCs were isolated through a ficoll’s gradient. mtDNA depletion was determined through multiplex PCR (Applied Biosystems’ 7500 Real Time PCR System) in 96 well plates with the simultaneous determination of the mitochondrial 12S ribosomal RNA (mt12S rRNA) gene and the constitutive nuclear RNAseP gene (nRNAseP). To study heteroplasmic variants the whole mitochondrial genome was amplified by long range PCR. Sample libraries were prepared with Nextera XT kit (Illumina) and sequencing proceeded in the MiSeq. Row data were analyzed using MiSeq Reporter Software. Funded by ISCIII, Spain (PI13/01738).

Results: None of the patients presented with clinical manifestations and/or disorders consistent with mitochondrial dysfunction at assessment. mtDNA depletion was confirmed in HIV-infected mothers and their HEU infants, but not in HIV-infected children. No significant differences were observed in the number of mtDNA mutations among the diverse groups of patients that were analyzed.

Conclusion: Our results suggest that the mtDNA depletion in HIV-infected pregnant women and their HEU infants exposed to 1st generation NRTIs is not associated to increased mutagenesis. We observed no differences in mitochondrial parameters between patients exposed to 2nd generation NRTIs and healthy controls in either of the groups.

791 IMPACT OF IMPROVED NUTRITION/SANITATION ON STUNTING AND ANEMIA IN HIV-INFECTED INFANTS
Bernard Chasekwa1, Andrew Prendergast2, Ceri Evans2, Kuda Mutasa1, Mduduzi Mbuya1, Rebecca J. Stoltzfus3, Laura Smith4, Florence D. Majo1, Naume Tavengwa1, Batsirai Mutasa1, Lawrence Moulton1, Robert Notzoni1, Jean Humphrey4, for the SHINE Trial Team

Background: Prevention of mother-to-child transmission (PMTCT) programs have reduced the number of children acquiring HIV. However, the impact of PMTCT programs on mortality and growth of HIV-exposed children in sub-Saharan Africa is uncertain.

Methods: SHINE was a community-based cluster-randomized trial of infant and young child feeding (IFCF) and water, sanitation and hygiene (WASH) interventions in two rural Zimbabwean districts with 15% HIV prevalence (ClinicalTrials.gov/NCT01824940). The trial did not administer PMTCT, but promoted early antenatal booking, uptake of PMTCT through local clinics, exclusive breastfeeding for 6 months, and prolonged breastfeeding to 24 months. Children were followed from birth and had longitudinal HIV testing. We used generalized estimating equations to compare mortality and growth between HIV-exposed and HIV-unexposed children through 18 months.

Results: There were 738 HIV-exposed and 3989 HIV-unexposed live births between 2012-2015. 81% of HIV-positive mothers had documented ART use during pregnancy, and mean (SD) CD4 count was 473 (221) cells/μL. Overall, cumulative mortality in HIV-exposed children was 39% higher than HIV-unexposed children through 18 months (risk ratio 1.39; 95%CI 1.02, 1.89; P=0.04). 25 of 738 children (3%) were known to be HIV-infected by 18 months, 596 (81%) were HIV-exposed uninfected, and 117 (16%) children had an unknown HIV status. Among children confirmed to be HIV-exposed uninfected (HEU) at 18 months, mean length-for-age Z-score was -0.34 (95%CI -0.44, -0.25) lower than in HIV-unexposed children (P<0.001), and stunting prevalence was 46% versus 31% (risk ratio 1.48; 95%CI 1.34, 1.64; P<0.001). There were also significant differences between groups in weight-for-age, weight-for-height and head circumference; HEU children had almost 2-fold higher prevalence of underweight, wasting and microcephaly (Table). Among 738 HIV-exposed births, only 320 were known to be alive, HIV-free and non-stunted at 18 months.

Conclusion: In the current PMTCT era, mortality and growth failure are higher among HIV-exposed compared to HIV-unexposed children in rural Zimbabwe; almost half of all HEU children were stunted by 18 months. As HIV transmission continues to decline, we propose the composite status of “Alive, HIV-free and non-stunted” as the long-term goal of PMTCT programs. Our findings highlight the ongoing poor outcomes of HEU children despite PMTCT, and the need for additional interventions to ensure that HIV-exposed children survive and thrive.

Table: Growth outcomes of HIV-exposed uninfected children compared to HIV-unexposed children at 18 months of age. 

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Mean Z-score (standard deviation)</th>
<th>Difference between means</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-unexposed</td>
<td>0.00 (0.25)</td>
<td>-1.50 (0.07)</td>
<td>-0.50 (-0.44, -0.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stunting</td>
<td>-0.94 (1.08)</td>
<td>-0.68 (1.01)</td>
<td>-0.25 (-0.35, -0.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Underweight</td>
<td>-0.08 (1.09)</td>
<td>0.05 (1.06)</td>
<td>0.13 (-0.23, 0.40)</td>
<td>0.006</td>
</tr>
<tr>
<td>Wasting</td>
<td>-0.50 (1.13)</td>
<td>-0.22 (1.07)</td>
<td>-0.28 (-0.37, -0.18)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Table includes children with complete data for the whole study period. 

3Q1 IMPACT OF IMPROVED NUTRITION/SANITATION ON STUNTING AND ANEMIA IN HIV-INFECTED INFANTS
Bernard Chasekwa1, Andrew Prendergast2, Ceri Evans1, Kuda Mutasa1, Mduduzi Mbuya1, Rebecca J. Stoltzfus3, Laura Smith4, Florence D. Majo1, Naume Tavengwa1, Batsirai Mutasa1, Lawrence Moulton1, Robert Notzoni1, Jean Humphrey4, for the SHINE Trial Team
**Background:** Stunting (linear growth failure) is associated with child mortality and neurodevelopmental impairment. Anemia often co-exists with stunting and is a further driver of impaired neurodevelopment. HIV-exposed children have a high prevalence of stunting and anaemia, with few effective preventive interventions. We hypothesized that improved infant and young child feeding (IFFC) and improved water, sanitation and hygiene (WASH) would reduce stunting and anaemia in HIV-exposed children.

**Methods:** We conducted a cluster-randomised 2x2 factorial trial in rural Zimbabwe, testing the impact of improved IYCF and improved WASH on child linear growth and hemoglobin (ClinicalTrials.gov NCT01824940). Pregnant women were eligible if they lived in study clusters allocated to standard-of-care (SOC; 52 clusters); IYCF (20g Nutributter/day from 6-18mo, complementary feeding counseling; 53 clusters); WASH (pit latrine, 2 hand-washing stations, liquid soap, chlorine, play space, hygiene counseling; 53 clusters); or IYCF+WASH (53 clusters). Masking of participants and fieldworkers was not possible.

**Results:** From 726 HIV-positive pregnant women, 668 children from 181 clusters were evaluated at 18 months (147 from 46 SOC clusters; 147 from 47 IYCF clusters; 184 from 43 WASH clusters; 190 from 45 IYCF+WASH clusters). 22% (3%) were HIV-positive, 594 (89%) HIV-exposed uninfected, and 52 (8%) HIV-unknown at 18 months. 28.8% live-born infants were lost to follow-up. IYCF increased mean LAZ by 0.26 (95% CI 0.09, 0.43) and hemoglobin by 0.29 g/dL (95% CI 0.09, 0.49), reducing stunting prevalence from 50.2% to 40.5% (absolute reduction 9.7%, 95% CI 2.1, 17.2) and anaemia from 14.1% to 8.5% (absolute reduction 6.8%, 95% CI 2.1, 11.6).

**Conclusion:** Among HIV-exposed children, improved complementary feeding reduced stunting and anaemia, while there was no evidence of an impact of improved WASH. Delivered at scale, IYCF interventions would have substantial benefit in areas with high antenatal HIV prevalence.

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**792 EXTENDED PROPHYLAXIS WITH NEVIRAPINE DOES NOT AFFECT GROWTH IN HIV-EXPOSED INFANTS**

**Carolyne Onyango-Makumbi,1 Ramadhan Mwiru,1 Arthur Owora,1 Anthony Mwatha,1 Alicia Young,2 Dhayendre Moodley,2 Hoosen Coovadia,1,4,6 Lynda Stranix-Chibanda,1 Karim F. Manji,1 Yvonne Maldonado,1 Paul Richardson5, Philip Andrew1, Kathleen George1, Wafae Fawzi2, Mary G. Fowler4**

**Background:** Increasing numbers of women with perinatally acquired HIV are reaching reproductive age and having children. Few studies have evaluated the long-term growth of HIV-exposed uninfected (HEU) children born to these women, which may vary by race and sex.

**Methods:** We compared growth trajectories from birth to age 7 years in HEU infants born to women with PHIV vs non-perinatally acquired HIV (NPVPHIV) in the Surveillance Monitoring for ART Toxicities (SMARTT) study, a U.S.-based cohort study enrolling since April 2007. Infants of women born after 1982 were eligible. Z-scores were calculated using U.S. growth references for weight (WTZ) and height (HTZ) from birth, weight-for-length (WLZ) up to 36 months (mos), and body mass index-for-age (BMIZ) from 36 mos onward. Mixed effects models were fit stratified by race and sex to assess differential growth patterns by maternal PHIV status, and included an interaction term for child age by maternal PHIV status along with inverse probability weights to account for non-randomized exposure.

**Results:** Extended course of prophylactic nevirapine given daily from six weeks to six months did not adversely affect growth (WAZ, LAZ, WLZ, HCZ) in HEU breastfeeding infants (treatment x time effect: p<0.05) when compared with placebo. However, overall growth declined over time (time effect: p<0.01) when compared to WHO general population norms. Overall prevalence and incidence did not differ between study groups but male sex, short duration of breastfeeding, and lack of maternal ART exposure were associated with higher risk of growth faltering outcomes (p<0.05).

**Conclusion:** It is reassuring that prolonged exposure to nevirapine for prevention of maternal to child HIV transmission does not appear to restrict growth. However, targeted interventions that support normal growth among at-risk HIV-exposed uninfected infants are needed to curtail the risk of growth faltering outcomes.

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**793 GROWTH PATTERNS IN CHILDREN OF WOMEN WITH PERINATALLY VS NON-PERINATALY ACQUIRED HIV**

**Wendy Yu1, Denise Jacobsen,1 Paige L. Williams1, Kunjal Patel1, Russell B. Van Dyke1, Linda A. DiMaggio2, Mitchell Geffner1, Deborah Kacanek1, Jennifer Jiao1, for the Pediatric HIV/AIDS Cohort Study (PHACS)**

**Background:** Increasing numbers of women with perinatally acquired HIV (PHIV) are reaching reproductive age and having children. Few studies have evaluated the long-term growth of HIV-exposed uninfected (HEU) children born to these women, which may vary by race and sex.

**Methods:** We compared growth trajectories from birth to age 7 years (yrs) in HEU infants born to women with PHIV vs non-perinatally acquired HIV (NPVPHIV) in the Surveillance Monitoring for ART Toxicities (SMARTT) study, a U.S.-based cohort study enrolling since April 2007. Infants of women born after 1982 were eligible. Z-scores were calculated using U.S. growth references for weight (WTZ) and height (HTZ) from birth, weight-for-length (WLZ) up to 36 months (mos), and body mass index-for-age (BMIZ) from 36 mos onward. Mixed effects models were fit stratified by race and sex to assess differential growth patterns by maternal PHIV status, and included an interaction term for child age by maternal PHIV status along with inverse probability weights to account for administrative censoring.

**Results:** 1236 infants had height and weight measured from birth (252 and 984 were born to women with PHIV vs NPVPHIV, respectively). Women with PHIV were younger (23 vs 25 yrs, p<0.01), had lower median CD4 count (386 vs 496 cells/mm3, p<0.01), and were more likely to have HIV RNA level > 400 copies/mL at delivery (25% vs 12%, p<0.01). A smaller percentage of infants born to women with PHIV were black (63% vs 74%, p<0.01). In the model limited to black...
female children (n=415), those born to women with PHIV had lower birth WTW (mean difference: -0.22 [95% confidence interval (CI): -0.41, -0.03]) and similar WTW trajectories from 0-3 yrs (slope difference: -0.06 [95% CI: -0.46, 0.04]), but more rapid weight gain after 3 yrs (slope difference: 0.10 [95% CI: 0.00, 0.20]) than those of women with NPHIV; the overall mean difference (PHIV vs NPHIV) between 0-7 years was -0.30 [95% CI: -0.50, -0.10]. (Figure 1) Within the other race and sex strata, no differences in overall WTW or WTW trajectories were found in HEU children of women with PHIV vs NPHIV. The growth trajectories of HTZ and WLZ/BMZ over time, as well as overall means, did not differ between children of women with PHIV and NPHIV.

**Conclusion:** In general, children of women with PHIV had similar growth compared to those of women with NPHIV, which is reassuring. However, black female children of women with PHIV vs NPHIV may be at increased risk for lower weight through early childhood.

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**POSTNATAL GROWTH IN CHILDREN EXPOSED OR UNEXPOSED TO HIV: A NATIONWIDE COHORT STUDY**

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**Background:** Studies mainly from resource-limited settings have shown impaired growth among HIV-exposed uninfected (HEU) children. We aimed to compare anthropometric outcomes of Danish HEU children to a matched control group of children not exposed to HIV in the first 5 years of life.

**Methods:** In a nationwide register-based study we included all singleton HEU children born in Denmark, 2000-2016. HEU children were individually matched by parity, maternal age at birth, maternal ethnicity and child sex to five singleton controls born to HIV uninfected mothers. Weight-for-age (WAZ), length-for-age (LAZ) and BMI-for-age (BMI) z-scores were generated according to the WHO standards and the Fenton growth chart for prematurity for infants born <37 week. Differences in WAZ, LAZ and BMI z-scores were analyzed using linear mixed models, adjusting for maternal smoking and total number of growth measurements.

**Results:** In total, 493 HEU children and 2,495 controls were included, with a median follow-up of 8.4 (IQR: 6.2-10.4) years. Compared to controls, HEU children were smaller at birth with a difference in mean WAZ and LAZ scores of -0.26 (95%CI: -0.40, -0.13; p<0.001) and -0.44 (95%CI: -0.69, -0.29; p<0.001), respectively. Over time, there was a trend towards increasing WAZ and LAZ in HEU children, and there was no significant difference in WAZ z-scores by age 12 months (-0.10 [95% CI: -0.26, 0.06]; p=0.22) and no significant difference in LAZ z-scores by age 24 months (-0.13 [95% CI: -0.32, 0.04]; p=0.15). There was no difference in BMI-for-age between the two groups at any age. A sensitivity analysis limited to children with information on breastfeeding did not change results significantly.

**Conclusion:** In a high-resource setting, exposure to HIV and/or antiretroviral therapy does not seem to be adversely associated with infant and child growth. Compared to a matched control group, HEU children were smaller at birth, but this difference decreased with time and is not considered to have a negative impact the overall health and well-being of HEU children.
Infectious Diseases, Bethesda, MD, USA, 3Johns Hopkins University, Baltimore, MD, USA

Ting-Ting Wu1, Karin Nielsen-Saines1, Deborah Persaud3, for the HPTN/NICHD040

Remission protocols at birth is an important measure of HIV reservoirs for early treatment CURE / which reduced postpartum transmission by 50%. Likewise, the quantity especially with enhanced 2NVP/ZDV and 3(NFV,3TC ZDV) drug ARV prophylaxis at birth or weeks prior to viremia has important implications for pathogenesis. The percentage of FL and early transcripts varied.

Most infants already had detectable HIV reservoirs at birth although the there was no clear relationship between HIV DNA levels and HIV RNA at birth. Detectable HIV DNA. HIV RNA ranged from (8,000-5 million cp/ml). Surprisingly, seen in Figure . FL (includes integrated HIV DNA) ranged from 1% to 100% of 2NVP/ZDV, 3TC, and 2LTC drug ARV prophylaxis which reduced postpartum transmission by 50%. Likewise, the quantity / differentiation of full-length HIV DNA (including integrated) vs early transcripts at birth is an important measure of HIV reservoirs for early treatment CURE / Remission protocols

**796 DETECTION HIV DNA BY DDPCR BEFORE VIREMIA IN INTRAPARTUM & AT BIRTH IN IU INFANTS**

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**Background:** HIV MTCT Transmission occurs during gestation in utero (+ at birth), or intrapartum IP/HIV- at birth) and positive 4-6 wks of life or later if breast-fed. Using ddPCR as a sensitive method of quantitating proviral HIVDNA including full-length(FL)/partial transcripts(PT), we assessed early events in IP infected infants prior to detectable viremia and HIV proviral DNA as a measure of viral reservoirs in utero infected infants including FL transcribed HIV DNA and PT compared to plasma HIV RNA

**Methods:** As part of a trial of infant HIV prophylaxis to prevent IP MTCT a subset of non breast-fed HIV infants defined as IP(14) or IU( 13) by - HIV DNA /RNA or + at birth). Infants with adequate samples birth, 2-4,6-12, and 24 wks were chosen. Genomic DNA isolated with phenol/chloroform from PBMCs and HIV-1 DNA quantified by ddPCR cp/million/PBMC Primer/Probe pairs targeted full-length HIV reverse transcripts at the LTR-gag junction (SR1/M661/ZXF-FAM) and partials(SR1/AA55/ZXF-FAM) run in parallel with cellular beta-Globin (BGF1/ BGR1/BGX1-HEX). Unintegrated HIV cp/ million were calculated by the difference of full-length and partials.

**Results:** We assessed PT and FL HIV DNA by ddPCR in 14 IP infected infants at birth, 2,4-6,12, and 24 wks and found that 12/14 (85%) had P/F or both prior to HIV RNA detection. 8 were detectable at birth and 5/6 who received 6 wks ZDV prophylaxis group A had detection at birth, the remainder became positive by 2 +wks. In IU (13) infected infants, we found both FL HIV DNA (0-68,000 cp/ million), Partials (142-154,000 cp/million) which include FL and early transcripts as cp/millionPBMC and the difference which is early transcripts(2-86,000) as seen in Figure . FL (includes integrated HIV DNA) ranged from 1% to 100% of detectable HIV DNA. HIV RNA ranged from (8,000-5 million cp/ml). Surprisingly, there was no clear relationship between HIV DNA levels and HIV RNA at birth. Most infants already had detectable HIV reservoirs at birth although the percentage of FL and early transcripts varied.

**Conclusion:** Early detection of HIV proviral DNA by ddPCR in IP infected infants at birth or weeks prior to viremia has important implications for pathogenesis especially with enhanced 2NVP/ZDV and 3(NFV,3TC ZDV) drug ARV prophylaxis which reduced postpartum transmission by 50%. Likewise the quantity / differentiation of full-length HIV DNA (including integrated) vs early transcripts at birth is an important measure of HIV reservoirs for early treatment CURE / Remission protocols

**797 MATERNAL HIV RNA AFTER DELIVERY IS CORRELATED WITH INFANT PRETREATMENT HIV RNA**

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**Background:** Detectable maternal HIV RNA at delivery is a strong risk factor for in utero mother-to-child HIV transmission (MTCT), but the impact of maternal HIV RNA level near delivery (in the setting of effective maternal antiretroviral treatment (ART)) on the early viral burden of HIV + infants is not well studied.

**Methods:** We enrolled 40 HIV+ mother-infant pairs in the Early Infant Treatment Study (EIT) in Botswana, at ≤7 days from delivery. All infants had received prophylactic single-dose nevirapine and twice daily zidovudine per government protocol, until HIV diagnosis by DNA PCR using the Roche TaqMan. HIV RNA was performed using Abbott HIV-1 m2000rt with a lower detectable limit of 40 copies/ml. Baseline HIV RNA for enrolled infants was compared with maternal HIV RNA values collected on the same day, as well as maternal ART regimen and duration of ART in pregnancy. Spearman’s correlation was used to evaluate associations and Kruskal Wallis test to compare infant HIV RNA by maternal ART regimen.

**Results:** Among 40 mother-infant pairs, 35 (87.5%) women and 39 (97.5%) infants had a detectable HIV RNA at a median of 2 days post-delivery (range 1, 5 days). Median enrollment HIV RNA was 11,335 copies/ml (range <40, >1,000,000 copies/ml) for infants and 24,789 copies/ml (range <40, 491,512 copies/ml) for women. Fourteen (35%) enrolled infants were not exposed to any ART in utero, 14 (35%) were exposed to EFV-based ART, 10 (25%) to DTG-based ART, and 2 (5%) to LPV/r-based ART. Median duration of in utero ART exposure was 2.5 weeks (range 0, 40 weeks). Maternal HIV RNA had a strong positive correlation with infant pre-treatment HIV RNA (rs = 0.63, p < 0.001) (Table 1). The duration of ART exposure in utero did not correlate with infant HIV RNA (rs = -0.039, p = 0.81). The median HIV RNA values for infants with either no ART exposure, exposure to EFV, or exposure to DTG were 19,246 copies/ml, 2,491 copies/ml, and 346 copies/ml, respectively; this difference was non-significant (p = 0.19), although small numbers were available for these comparisons.

**Conclusion:** Higher maternal HIV RNA post-delivery correlated with higher pre-treatment infant HIV RNA. Effective ART to reduce maternal HIV RNA in pregnancy may also reduce viral burden among infants with in utero HIV acquisition, beginning the beneficial early treatment process and potentially reducing viral reservoir.
EARLY ART START IN CHILDREN IS ASSOCIATED WITH MORE RAPID DECAY OF HIV-1 DNA

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Background: There is limited information on whether the age at ART initiation, duration of the initial treatment phase and subsequent ART interruption influences the persistence of HIV-1 infected cells in children.

Methods: We investigated HIV-1 DNA decay in 3 groups of children on ART (ART regimens excluded InSTIs): group-1 were 7 starting at a median of 4 days of life and continuing uninterrupted; group-2 were 8 starting at a median of 5 months and continuing uninterrupted; and group-3, 23 on ART from a median of 1.8 months for either 40 or 96 weeks, then interrupting ART for a median of 7 months, and restarting based on CD4 criteria. Total HIV-1 DNA was assayed with a sensitive HIV-1 subtype C adapted quantitative PCR for a conserved integrase sequence. Goodness of fit of the decay curves within each group was assessed with conditional R². Duration of treatment was square root transformed to fit with the observed deceleration in decay rate. For each group, the point estimates of decay rates were determined at 6 months on continuous ART or 6 months after reinitiating ART. For groups-2 and 3 combined (n=31) a mixed effects, and patient as the random effect.

Results: The conditional R² (95% CI) values for the HIV DNA decay curve was 0.82 (0.65-0.93) for group-1 (early start), 0.85 (0.67-0.94) for group-2 (late start) and 0.79 (0.68-0.86) for group-3 (interrupted). At 6 months on continuous suppressive ART: the HIV-1 DNA t½ in months (95% CI) was shorter in group-1; 2.7 (2.1-3.8), compared to 9.2 (7.4-12.1) in group-2; and 9.6 (7.6-12.6) in group-3 (Figure). In the multivariable model, HIV-1 DNA concentration before treatment (p<0.001) and the change in HIV-1 DNA during interruption (p<0.01) were significant predictors. In the multivariable model, HIV-1 DNA concentration before treatment (p<0.001) and the change in HIV-1 DNA during interruption (p<0.01) were significant predictors. Of the 52 children, 45 (86.5%) were HIV-seronegative. The conditional R² was 0.59 (0.41-0.77) for group-1, and 0.79 (0.68-0.86) for group-3. For each group, the point estimates of decay rates were determined at 6 months on continuous ART or 6 months after reinitiating ART. For groups-2 and 3 combined (n=31) a mixed effects, and patient as the random effect.

Conclusions: Rapid HIV-1 DNA decay in very early treated children suggests that ART can prevent persistence of long-lived infected cells. Delaying or interrupting ART is associated with longer persistence of infected cells. Further studies are needed to study the unintegrated fraction of HIV-1 DNA in early treated children, the proportions of integrated proviruses that are defective or intact; and InSTI-containing regimens.

VIROLOGIC RESPONSE TO VERY EARLY ART IN NEONATES WITH IN UTERO HIV: IMPAACT P1115

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Background: Perinatal HIV infection treated ≤48 hours of birth (very early ART [VE-ART]) limited HIV reservoirs and provided 27 months of undetectable viremia off ART in the “Mississippi baby”. IMPAACT P1115 is an ongoing prospective phase I/II proof-of-concept study of VE-ART of in-utero infected infants. We report on the completed viral load (VL) response and safety follow-up through 52 weeks.

Methods: Newborns enrolled into two cohorts (Fig.1). Cohort 1 (N=440) was treated within 48 hrs of life (Step 1) due to high-risk HIV exposure from untreated maternal infection. 34 had confirmed infection and moved to Step 2. Cohort 2 (N=20) received non-STI triple ARVs ≤48 hrs of life, and directly enrolled into Step 2 with confirmed infection before age 10 days. LPV/r was added to the Step 2 regimen at 42 wks postmenstrual age and NVP stopped with specified virologic criteria (Fig.1). VL was frequently monitored (Fig.1). Virologic failure (VF) was defined as VL ≥200 cp/mL at wk 24, and confirmed VL≥ limit of detection (LOD) at last visits. Probabilities (95% CI) of sustained viral suppression (no VF) were estimated by Kaplan-Meier method. Grade 3 and 4 safety events were assessed for relation to Study ART. Median (Q1, Q3) are presented.

Results: 54 HIV-infected infants (61% girls) enrolled from 11 countries; 81.5% breast-fed. Median study enrollment age in Cohort 1 was 22 hrs and 8 days in Cohort 2. For Cohorts 1 and 2 median age at ART initiation was 7.3 (1.8, 21.0) and 33 (0.4, 40.1) hrs, and median earliest VL was 4.9 (4.0, 5.3) and 4.1 (3.2, 5.2) log10 cp/mL, measured at a median of 1 (0.10) and 6 (2.0, 8.0) days of age; loss to follow-up was 3% and 15%. Estimated probability of sustained viral suppression through 52 wks on Step 2 was 50% (32%, 66%) and 67% (37%, 85%) in Cohorts 1 and 2, respectively; 47/52 who started LPV/r met virologic criteria to stop NVP at median age 29.4 (25.0, 37.7) wks. Grade 3 or 4 related events that were reversible occurred through 52 wks in 15 (44%) and 7 (35%) infants from Cohorts 1 and 2, and were mostly hematologic. There was one death in each cohort, neither related to Study ART. Among infants followed through wk 84, 5/8 and 4/5 in Cohorts 1 and 2 are HIV- neronegative.
**Conclusion:** Using a RM model of postnatal infection, we have characterized SHIV.C.CH505 reservoirs and rebound kinetics, which can inform correlates of viral rebound, and design immune-based interventions to reduce pediatric HIV reservoirs.

### 801 HIV-SPECIFIC ANTIBODY LEVELS CORRELATE WITH TFH MATURATION IN EARLY TREATED INFANTS

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**Background:** Though they have a developing immune system, infants develop potent HIV-specific antibodies. To understand the B cell response that develops after early ART, we measured the circulating T follicular helper cell (cTfh) frequencies and HIV-specific antibody production in early treated infants.

**Methods:** Eighty-two Thai infants living with HIV were included. Samples were taken from viremic infants at baseline (median 2.3 mo old, range 0.8-6.6 mo; n=59), and virally-suppressed infants after a median 12.6 months of ART (range 10.8-16.6 mo; n=30) or a median 24.5 months of ART (range 20.7-26.4 mo; n=25). CD19+CD20+ B cells and CD4+ T cells were analyzed by flow cytometry. Plasma Env-specific IgG and IgM levels were measured by ELISA. Plasma levels of CXCL12, CXCL13, and soluble CD40 ligand (sCD40L) were measured by Luminex.

**Results:** At baseline, very low Env-specific IgG levels were detected in the plasma of infants with HIV (median 1.49 µg/mL). Env-specific IgM levels correlated with viral load (r=0.75, p<0.001), as well as plasma levels of the stimulatory molecule sCD40L (r=0.43, p=0.03) and CXCL13, a biomarker of germinal center activity (r=0.63, p<0.001). Though infant Env-specific IgG levels could not be measured due to the presence of maternal antibodies, the frequency of cTfh (CXCR5+CD45RA–CD4+ T cells) correlated with the frequency of IgG+ B cells (r=0.55, p=0.04) at baseline. Baseline frequencies of IgG+ B cells and cTfh in the blood negatively correlated with plasma levels of CXCL12 (r=0.62; p=0.03; r=0.66; p=0.01), suggesting these cells are exiting the blood through high endothelial venules. The levels of Env-specific IgM increased after 1 year of ART (median 2.4µg/mL, p<0.001). Env-specific IgG levels decreased as maternal antibodies waned, and remained stable between 1 and 2 years of ART (median 2.4 vs 1.3µg/mL). After 1 year of ART, Env-specific IgG levels correlated with the frequency of Th1-biased cTfh expressing CXCR3 (1A; r=0.48, p=0.03). In contrast, after 2 years of ART Env-specific IgM levels correlated with the frequency of CXCR3–PD-1+ cTfh, which provide better B cell help (1B; r=0.64, p=0.03).

**Conclusion:** During early infection, viremic infants produce low levels of Env-specific IgM. Though early treated infants had low levels of Env-specific IgG after ART, antibody levels correlated with the maturing cTfh populations. These data suggest that effective elicitation of HIV-specific antibodies in infants will depend on therapeutic targeting of proper cTfh populations.
802 OUTCOMES OF NEONATES WITH RAPID HIV TREATMENT IN US: TREATING INFANTS EARLY STUDY
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Background: While several international trials are testing strategies of early antiretroviral therapy (ART) for infants with HIV, little is known about the outcomes of perinatally infected infants in clinical (non-research) settings, in which neonatal ART options are limited. The Treating Infants Early Study (TIES) is an observational cohort study that aims to describe the management, safety, efficacy of ART initiated at <6 weeks of life in communities throughout the USA.
Methods: Informed consent was obtained by phone or in person, with paper or electronic documentation. Eligibility criteria were HIV diagnosis, age<2 years, and ART start at <6 weeks of life. Maternal, birth and ART history, and clinical outcomes were abstracted from medical records, collected periodically during follow up. Descriptive statistics were used for this analysis.
Results: Among 38 infants screened from Dec. 2015 to Sept. 2018, 15 enrolled, providing median (range) follow-up of 19(1-32) months; one was excluded from analysis due to prior research participation. Infants were born at 37(28-40) weeks gestation weighing 2.7 (1.1-3.9) kg to mothers 24 (15-36) years old, 6(43%) of whom were diagnosed with HIV in labor. Infants received zidovudine (ZDV)(n=2), ZDV + 3 doses nevirapine (NVP) with (n=7) or without (n=2) lamivudine (3TC), or ZDV/3TC+NVP twice daily at treatment doses (n=2) prior to HIV diagnosis. ART as treatment was initiated at 8.5 (0-36) days of life. ZDV/3TC+NVP (n=12) or lamivudine/ritonavir (n=2). First CD4 count was 2,390 (231-4,190) cells/µl, CD4% was 46(10-66) and HIV RNA was 3.7(1.9-5.0) log10 copies/106 cells, respectively. ART was never interrupted, and regimens were later changed in 13(87%) of all CD4 T cells, their contribution to the HIV reservoir was higher than CM and TM cells (median 1,253 [172-11,571] and 206 [132-9,806] copies/106 cells, respectively). Although EM cells represented a small fraction of all CD4 T cells, their contribution to the HIV reservoir was higher than CM and TM compartments (median 575 [50-864], 103 [0-103], 1% [0-5] and 30% [10-51] respectively). Despite these high levels of HIV DNA, p24-producing cells were not detected in any of the pediatric samples tested upon stimulation. In contrast, p24+ events were detected in CD4 T cells from suppressed adults with comparable HIV DNA levels.
Conclusion: In vertically infected children on ART, the large naive compartment minimally contributes to the HIV reservoir. Although high levels of HIV DNA are present in memory cells, these proviruses did not produce detectable levels of p24 protein, suggesting that the latent reservoir is poorly inducible in ART-suppressed children.
Results: We first measured the frequency of each subset within the CD4 compartment. As expected, naive cells represented the vast majority of CD4 T cells (median frequency of 84%), whereas CM, TM and EM were underrepresented (10%, 2% and 1%, respectively, Table 1). In spite of their high frequencies, naive cells were rarely infected (median 45 [0-103] HIV DNA copies/106 cells). Most proviruses were detected in memory subsets, particularly in the EM subset which included the highest levels of cells harboring integrated genomes (median 10,943 [3,398-162,594] copies/106 cells) followed by TM and CM subsets (median 2,123 [172-11,571] and 206 [132-9,806] copies/106 cells, respectively). Although EM cells represented a small fraction of all CD4 T cells, their contribution to the HIV reservoir was higher than CM and TM cells (median 54%, 30% and 4%, respectively). Despite these high levels of HIV DNA, p24-producing cells were not detected in any of the pediatric samples tested upon stimulation. In contrast, p24+ events were detected in CD4 T cells from suppressed adults with comparable HIV DNA levels.

Table 1: Integrated HIV DNA and contribution of each subset to the p20 infected cells in early treated ART-suppressed children

<table>
<thead>
<tr>
<th>% of CD4 T cells</th>
<th>Frequency of integrated HIV DNA (copies/106 cells)</th>
<th>Contribution of each subset to the HIV reservoir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CD4</td>
<td>575 (50-864)</td>
<td></td>
</tr>
<tr>
<td>Naive</td>
<td>84% [75-87]</td>
<td>45 [0-103]</td>
</tr>
<tr>
<td>TM</td>
<td>2% [1-5]</td>
<td>1,253 [172-11,571]</td>
</tr>
</tbody>
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804 IMMUNO-VIROLOGICAL IMPACT OF EARLY VS LATE ART INITIATION IN CHILDREN AND ADOLESCENTS
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Background: Few data are available on the long-term benefit of early cART initiation for children and adolescents. The ANRS-EP59-CLEAC study aimed to assess the immunological and virological characteristics of HIV-1-infected children and adolescents who achieved initial virological suppression, according to the age at cART initiation (<6 months vs. ≥24 months of age).
Methods: Patient recruitment was conducted in the Paris area in 2016-2018. PBMC-associated total HIV-1 DNA was quantified using ultrasensitive qPCR (adapted from Biocentric, France). CD4 and CD8 D45RA+CCR7+ naive T lymphocytes were quantified in fresh blood by flow cytometry. Parameters of early- (E-Ch)/late- (L-Ch) treated children (5-12 years) and early- (E-adol)/late- (L-adol) treated adolescents (13-17 years) were compared with Wilcoxon test.

Results: We prospectively enrolled in the early-cART group 27 children and 9 adolescents, and in the late-cART group 19 children and 21 adolescents. At the time of the study, all patients were receiving ART, 83% had plasma HIV RNA <50 copies/mL, and the median CD4 T-cell count was 856 [IQR: 676-1236] cells/µL. In multivariate analysis, early-cART and longer duration of viremia <50 cp/mL during the 2 previous years were strongly associated with lower HIV-DNA levels (respectively, p<0.0001 and p=0.0067). Restricting the analysis to the 63 patients with current viral suppression, early-cART was associated with lower HIV-1 DNA levels (median 1.42 [IQR: 1.08-2.25] log cp/10⁶ PBMC). E-Ch had higher median percentages of naive CD8 T lymphocytes than L-Ch (49 versus 31%; p=0.0007). Conversely, in adolescents, early-cART was associated with lower percentage of naive CD4 T lymphocytes (39 versus 52%, p=0.05), even when restricting the analysis to patients with current viral suppression.

Conclusion: An immunological benefit of early-cART initiation on naive T lymphocytes was suggested in children. Further investigations are pending to explore if the high levels of thymic activity observed in adolescents may compensate for the deleterious effects of long duration of HIV replication. Early-cART initiation during infancy is associated with lower short- and long-term total HIV-DNA levels, as targeted in HIV-1 remission strategies. Interestingly, ariemivc E-ado had HIV-DNA levels comparable to those observed in adults with spontaneous or post-treatment HIV control.

805 LONG-TERM PERSISTENCE OF HIV-INFECTED CELL CLONES IN CHILDREN TREATED EARLY


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Background: Integration site analysis has shown extensive clonal expansion of HIV-1 infected cells in adults. We know that infected clones arise early, persist for many years, and that there is selection for cells with proviruses integrated in BACH2, MKL2, and STAT5B. However, little is known about the behavior of infected cells in children treated shortly after birth. We characterized clones of infected cells in a cohort of perinatally-infected and early-treated children. We sought to explore if the high levels of thymic activity observed in adolescents may compensate for the deleterious effects of long duration of HIV replication. Early-cART initiation during infancy is associated with lower short- and long-term total HIV-DNA levels, as targeted in HIV-1 remission strategies. Interestingly, ariemivc E-ado had HIV-DNA levels comparable to those observed in adults with spontaneous or post-treatment HIV control.

Methods: PBMC samples were obtained from the Children with Early HIV (CHEF) study. CD4 and CD8 CD45RA+CCR7+ naive T lymphocytes were quantified in fresh blood by flow cytometry. Parameters of early- (E-Ch)/late- (L-Ch) treated children (5-12 years) and early- (E-ado)/late- (L-ado) treated adolescents (13-17 years) were compared with Wilcoxon test.

Results: Integration site analysis has shown extensive clonal expansion of HIV-1 infected cells in adults. We know that infected clones arise early, persist for many years, and that there is selection for cells with proviruses integrated in BACH2, MKL2, and STAT5B. However, little is known about the behavior of infected clones in children treated shortly after birth. We characterized clones of infected cells in a cohort of perinatally-infected and early-treated children. We sought to explore if the high levels of thymic activity observed in adolescents may compensate for the deleterious effects of long duration of HIV replication. Early-cART initiation during infancy is associated with lower short- and long-term total HIV-DNA levels, as targeted in HIV-1 remission strategies. Interestingly, ariemivc E-ado had HIV-DNA levels comparable to those observed in adults with spontaneous or post-treatment HIV control.

Conclusion: An immunological benefit of early-cART initiation on naive T lymphocytes was suggested in children. Further investigations are pending to explore if the high levels of thymic activity observed in adolescents may compensate for the deleterious effects of long duration of HIV replication. Early-cART initiation during infancy is associated with lower short- and long-term total HIV-DNA levels, as targeted in HIV-1 remission strategies. Interestingly, ariemivc E-ado had HIV-DNA levels comparable to those observed in adults with spontaneous or post-treatment HIV control.
Methods: Data from 5 ongoing French national ANRS cohorts were pooled: 1) patients diagnosed at <13 years of age, followed as children (EPF-C010), or as adults (COVERTE-C019); 2) patients diagnosed at ≥15 years of age, included at the time of primary HIV infection (PRIMO-C06), or diagnosis (COPANA-C09, SEROCO-C02). Here we retained all patients diagnosed in the two years following birth for perinatally infected patients or following seroconversion for patients infected during adulthood, under cART for ≥6 months at last evaluation, between 2012 and 2017 (respectively: n = 359 and n = 1512). We distinguished 5 strata for the duration of HIV infection, based on relevant time-points for perinatally infected patients: 2-5, 6-12, 13-17, 18-24, and 25-32 years. The main outcome was detectable viral load (HIV RNA ≥ 20 cp/ml) at last evaluation. A multivariate logistic regression was conducted for each stratum to adjust for gender, birth country, and treatment history. Results: At last visit, most patients had been receiving the same cART regimen for six months or more. The use of new-generation drugs varied with age and period of acquisition. The proportion of detectable VL was significantly higher in the youngest children and in the adolescents and young adults infected since birth than in patients infected during adulthood with a similar duration of infection; the difference was lower for perinatally-infected patients ≥25 years (Fig 1). The findings were similar after multivariate analysis (AOR in Fig 1) and when restricting the analyses to patients with no changes in treatment regimen during the previous six months. Conclusion: Among cART-treated patients diagnosed soon after birth or seroconversion, young patients infected perinatally had much poorer viral control than adults with a similar duration of infection, not explained by treatment history, including the number and type of drugs in the context of a European country with universal free access to care. These results may reflect the difficulties of drug administration to younger children and of maintaining adherence during adolescence and young adulthood. The long-term impact of viral replication should be studied.

808 SLOW CD4/CD8 RATIO RECOVERY AMONG CHILDREN AND ADOLESCENTS DESPITE VIRAL SUPPRESSION

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Background: There are limited data describing long-term outcomes of young adults living with HIV who are successfully treated with combination antiretroviral therapy (cART). We investigated the recovery rates of CD4/CD8 ratio, a suggested marker for chronic immune activation, among Thai children and adolescents after they initiated cART.

Methods: This study was carried out in an ongoing HIV Thai cohort that includes children and adolescents (both perinatally (PaHIV) and behaviorally (BaHIV) acquired HIV infections) who had started cART at 5 years of age. CD4/CD8 normalization was defined as two consecutive values of the ratios ≥1. Participants were eligible for inclusion in this analysis if they achieved and maintained viral suppression at <50 copies/ml after starting cART, and if CD4/CD8 ratio at first viral suppression was <0.8. Follow-up was censored once participants had viral rebound after achieving suppression.

Results: A total of 138 children and adolescents (101 PaHIV and 37 BaHIV) aged <25 years old met inclusion criteria. Among 37 BaHIV adolescents, 27 (73%) were men who have sex with men. Median (interquartile range, IQR) age at ARV initiation was 10.6 (8.1-16.3) years old with median (IQR) baseline CD4 and CD8 cell counts of 178 (37-320) cells/mm³ and 964 (616-1332) cells/mm³, respectively. Median duration of cART was 9.3 years (10.6 for PaHIV and 2.4 for BaHIV) and median duration of virological suppression was 3.1 years (4.7 for PaHIV and 1.8 for BaHIV). Overall CD4/CD8 ratio of children and adolescents at first virological suppression was 0.47 (0.29-0.62) Over 553 person years of follow-up (PYFU), the incidence of CD4/CD8 ratio normalization among children and adolescents <25 years old was 4.1 per 100 PYFU (95% confidence interval [CI] 2.7-6.2). Using the Kaplan-Meier method, the probabilities of normalization at 2, 5 and 10 years after virological suppression were 5.2%, 22.6% and 36.6%, respectively. After 2 years of virological suppression, the normalization probability of PaHIV children and adolescents was higher but not significantly different than that of BaHIV (11.1% vs. 6%).

Conclusion: CD4/CD8 ratio recovery was slow among children and adolescents after initiating cART, despite persistent virological suppression. The clinical consequences of ongoing immune activation among children and adolescents on suppressive cART without CD4/CD8 normalization needs further investigation.

809 UNDERSTANDING THE IMPACT OF ART INTERRUPTION ON THYMIC OUTPUT AND TCR REPertoire

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Background: Antiretroviral therapy (ART) interruptions in adults lead to decreases in CD4+ T cells and an increase in mortality and morbidity. ART interruptions in children also cause a rapid reduction in CD4+ T cells but with less clinical impact and with good CD4+ T cell restoration following ART reintroduction. In contrast to adults, who predominantly reconstitute their T cells from the peripheral cell population, children have a great capacity for immune reconstitution mainly from the thymus. In this study, we have investigated ART interruption in children with HIV to determine the impact on thymic output, peripheral T cell proliferation, TCR diversity and clonality.

Methods: TCR repertoire and TCR clonotypes was estimated by Next Generation Sequencing techniques in purified naive CD4+ T cells and memory CD8+ T cells. Thymic output was measured using a mathematical model, combining naive CD4+ T cell proliferation rates with DNA PCR quantification of TCR excision circles, and IL-8, a chemokine released from naive T cells. Samples from 8 HIV-infected children were available for this study from a randomized controlled trial where one cohort remained on ART and the other had treatment withdrawn for 48 weeks.

Results: Thymic output was found to increase rapidly when ART was stopped. The increase in thymic output was associated with increased peripheral T cell proliferation, both returning to pre-interruption levels when the children re-started ART. TCR repertoire diversity and clonotype profiles appeared to be similar before treatment interruption and 3 years after ART re-introduction in both naïve CD4+ T cells and memory CD8+ T cells. Specific clonotypes were seen to expand and being highly shared in the naïve CD4+ T cell population in response to ART interruption. There was no difference observed in these immune parameters in the HIV children receiving continuous treatment between baseline and end of study.

Conclusion: Importantly we found that thymic output, peripheral cell expansion, TCR repertoire and clonotype profiles return to pre-interruption levels. This indicates that the high levels of thymic output in children may be sufficient to reverse the impact of ART cessation.

810 HIGH CMV DNAEMIA ASSOCIATES WITH STUNTING AND CHRONIC LUNG DISEASE IN HIV+ CHILDREN

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Background: Long-term survival of children with perinatally acquired HIV (PHIV) - even in those stable on antiretroviral therapy (ART) - is associated with...
significant health problems that are not typical of HIV-associated opportunistic infections or AIDS-defining illnesses. In sub-Saharan Africa, older children and adolescents with PHIV experience a range of chronic complications including growth impairment, chronic lung disease (CLD), cardiac abnormalities, pubertal delay and neurocognitive disorders. Moreover, the beta herpes virus, cytomegalovirus (CMV), is ubiquitous in Africa, infecting all children by age 18 months. We hypothesized that CMV reactivation might play a role in the poor health of older children with PHIV and we examined the associations between uncontrolled co-infection with CMV and comorbidities including lung function and growth.

Methods: Plasma samples were isolated from two cohorts of older children and adolescents aged 6-16 years with PHIV (n=394) and HIV negative controls (n=224). The HIV-infected children were either newly diagnosed (hence untreated), or known to be HIV-infected and stable on antiretroviral therapy (ART). CMV DNA-aemia was measured using quantitative polymerase chain reaction (qPCR). We used longitudinal mixed-effects logistic regression to model CMV DNA-aemia as a time-varying outcome.

Results: At enrolment, CMV DNA-aemia ≥1000 copies/ml (defined as "clinically significant") was detected in 3.8% of uninfected children, 14.1% of HIV-infected participants stable on ART and 22.5% of the HIV-infected ART-naive children (Chi2 = 23.4, p<0.001). The prevalence of clinically significant CMV DNA-aemia was associated with CD4 count below 350 cells/µL. Amongst HIV-infected ART-naive children, CMV DNA-aemia ≥1000 copies/ml was independently associated with reduced lung function (adjusted odds ratio aOR=3.15, 95%CI: 1.20-8.28, p=0.02). Amongst ART-treated children, stunting was associated with CMV DNA-aemia ≥1000 copies/ml (aOR=2.79, 95%CI: 0.97-8.02, p=0.057).

Conclusion: Clinically significant CMV DNA-aemia was common in older children and adolescents with PHIV, even amongst those stable on ART, suggesting a role for inadequately controlled CMV infection in the pathogenesis of the chronic complications of PHIV in Africa.

811 IMMUNE IMBALANCE IS ASSOCIATED WITH IMPAIRED SPIROMETRY IN PERINATALLY ACQUIRED HIV

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Background: Chronic lung disease (CLD) is increasingly recognized among youth living with perinatally-acquired HIV (PHIV) worldwide. Yet, pathophysiologic mechanisms of CLD in PHIV youth are largely unknown. We hypothesized that immune imbalance and activation based on a high CD8 T-cell count and low CD4/CD8 ratio are associated with impaired lung function in PHIV, and explored whether lung function differed between youth living in a high-income and a low-and-middle-income setting.

Methods: We performed a cross-sectional analysis of PHIV youth (10-21 years old) in the U.S. Pulmonary Complications in the Pediatric HIV/AIDS Cohort (PCPA) Study (n=188) and Kenyan BREATHE I Study (n=49). Sociodemographic, clinical, immune function, and spirometry data were ascertained within 3 months of enrollment. In U.S. and Kenyan youth combined, we estimated Spearman partial correlations of CD8 and CD4/CD8 with pre- and post-bronchodilator (BD) % predicted forced expiratory volume in one second (FEV1%), adjusted for age and sex. We also fit linear regression models to evaluate mean differences (95%CI) in FEV1% by study site, adjusted for age, sex, and CD8 or CD4/CD8 in separate models.

Results: Kenyan youth were younger, and a higher percent had prior pulmonary infections and passive cigarette smoke exposure (Table). Although Kenyan youth had later antiretroviral therapy (ART) initiation, Kenyan and U.S. youth had similar distributions of ART use and recent CD4. Nonetheless, Kenyan youth had significantly higher CD8 and lower CD4/CD8 ratio. Overall, correlations of CD8 with pre- and post-BD FEV1% were -0.25 (p<0.001) and -0.22 (p<0.001), and correlations of CD4/CD8 with pre- and post-BD FEV1% were 0.28 (p<0.001) and 0.26 (p<0.001). In adjusted linear regression models, pre-BD (9.6 [95%CI -15.4, -3.8]; p=0.001) and post-BD (8.3 [95%CI -14.0, -2.7]; p=0.001) FEV1% were lower in Kenyan compared to U.S. youth. These differences were attenuated in models also adjusting for CD8 (pre-BD: -1.52 [95%CI -11.6, 1.2]; p=0.11); post-BD: [-4.5 [95% CI -10.7, 1.8]; p=0.16]); associations were similar in models adjusted for CD4/CD8.

Conclusion: High CD8 and low CD4/CD8 were associated with greater spirometry impairment. Further, Kenyan PHIV youth had lower lung function measures than U.S. PHIV youth, and this association was attenuated by adjusting for CD8 or CD4/CD8. Our findings suggest that chronic immune imbalance and activation may contribute to CLD in PHIV despite ART use with associated CD4 reconstitution.

812 ENDOTHELIAL DYSFUNCTION IN SOUTH AFRICAN YOUTH WITH PERINATALLY ACQUIRED HIV ON ART

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Background: Evidence in adult populations shows that HIV and antiretroviral therapy (ART) confer cardiovascular (CV) risk. Few studies have assessed endothelial dysfunction (ED), an early marker of subclinical CV risk, in youth living with perinatally acquired HIV (YLPHV).

Methods: Using Peripheral Arterial Tonometry (endoPAT), we compared endothelial function in YLPHV and age-matched HIV-uninfected (HIV-U) youth enrolled in the Cape Town Adolescent Antiretroviral cohort (CTAC) in South Africa. A reactive hyperaemic index (RHI) <1.35 was defined as ED. Eligible participants included those aged 9-14 years and on ART >6 months at enrolment. Body mass index z scores (BMIZ) were calculated using WHO references, abnormal lipids were defined as >95th percentile using references from the United States (U.S.) National Health and Nutrition Examination Survey (NHANES), and elevated blood pressure (BP) were defined as >90th percentile for age, sex and height using U.S. standards. Modified Poisson regression models were fit to assess the adjusted association of HIV infection with ED. Subgroup analyses were performed to assess predictors of ED among YLPHV.

Results: Overall 431 YLPHV and 93 HIV-U youth were included. YLPHV had lower BMIZ (~0.2 vs 0.4, p<0.01) but higher rates of hypercholesterolemia (10% vs 1%, p=0.01) compared to HIV-U youth. No differences in age, sex, Tanner stage, elevated BP or tobacco use were found. Among YLPHV, mean log viral load (VL) was 4.83 copies/ml with 21.7% harboring a CD4 count <500cell/mm³ and median duration on ART was 9.8 years with 38% initiating at <2 years of age. YLPHV had higher rates of ED compared to HIV-U youth (50% vs 34%, p=0.01); this relationship persisted after adjusting for age, sex, BMIZ, elevated BP, and hypercholesterolemia (RR 1.43, p=0.02). Among YLPHV, CD4 count <500cell/mm³ (RR 1.04, p=0.76), VL (RR 1.01, p=0.78) and current ART class (protease inhibitor-based vs non-nucleoside inhibitor-based ART, RR 0.90, p=0.168) were not associated with ED after adjusting each model for age, sex, BMIZ, elevated BP, and hypercholesterolemia.

Conclusion: Even after adjusting for physiologic differences, YLPHV appear to be at increased risk for ED compared to age-matched HIV-U youth in South Africa. Further longitudinal studies are required to explore risk of developing CV disease in YLPHV.

813 EARLY CARDIAC DYSFUNCTION IN HIV-INFECTED CHILDREN AND ADOLESCENTS IN WESTERN KENYA

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Background: HIV-associated cardiac dysfunction has severe consequences, and traditional measures of echocardiography underestimate the true burden of dysfunction. Novel echocardiographic measures may detect early disease
in time for possible intervention. The aims of this study are to define the prevalence of early cardiac dysfunction in children living with HIV and the relationships between cardiac function and same-day HIV RNA and soluble inflammatory marker levels.

**Methods:** Using a cross-sectional study design, perinatally HIV-infected children and adolescent at Moi Teaching and Referral Hospital in Eldoret, Kenya underwent an echocardiogram and provided a blood sample. Early cardiac dysfunction was defined as left ventricular global longitudinal strain (LGVLS) z-score < -2 or myocardial performance index (MPI) ≥ 0.5. Comparisons between those with early cardiac dysfunction and those with normal cardiac function were made using Chi square, Fisher’s Exact, or Wilcoxon Rank Sum tests, as appropriate. Regression models were used to assess the relationship between measures of cardiac function and potential predictors.

**Results:** 643 children and adolescents (mean age 14.1±5.2 years, range 1-25 years) with perinatally acquired HIV were enrolled. The average time on antiretroviral treatment was 6.8±3.6 years. 296 participants (46.0%) had documented exposure to AZT as a part of their treatment regimen. 288 of 638 (45.1%) had detectable HIV RNA levels. 178 of 643 (27.7%) children and adolescents met study criteria for early cardiac dysfunction (176, 98.9%, by the MPI criteria). Early cardiac dysfunction was associated with older age (15.3 vs 13.5 years, p<0.001), higher percentage of detectable HIV RNA levels (52.5% vs 41.7%, p=0.018), and higher median level of plasma IL-6 concentrations (1.00 vs 0.88, p=0.011). In adjusted models, ejection fraction was negatively associated with detectable same-day HIV RNA level (β: -0.28; 95%CI: -0.56, -0.003) and AZT exposure (β: -2.05; 95%CI: -3.48, -0.61), and ejection fraction was positively associated with higher proportion of life on ART.

**Conclusion:** Nearly one quarter of these children and adolescents demonstrated evidence of early cardiac dysfunction, based primarily on MPI measurements. This finding was associated with older age, higher percentage of detectable HIV RNA, and elevated IL-6 levels. Further investigation is needed into the clinical significance of these findings as abnormal MPI is predictive of mortality in inflammation mediated cardiac dysfunction.

**815 GROWTH AND METABOLIC CHANGES AFTER ANTIRETROVIRAL START IN SOUTH AFRICAN CHILDREN**

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**Background:** High viral load (VL) associated with delays in antiretroviral therapy (ART) initiation has been linked to poor outcomes in children living with HIV (CLHIV). Fewer studies have assessed the impact of VL at initiation on growth and metabolic changes of CLHIV on optimal ART. We assessed longitudinal alterations in growth and lipid metabolism in CLHIV <12 years old initiating 1st-line ART in South Africa (SA) from 2012 to 2015.

**Methods:** Per SA national ART guidelines, CLHIV <3 years were initiated on lopinavir/ritonavir (LPV/r)-based and those ≥3 years on efavirenz (EFV)-based ART (both regimens included abacavir+lamivudine). Length-for-Age (LAZ), Weight-for-Age (WAZ), and Body Mass Index-for-Age (BMI) z-scores were calculated using World Health Organization reference standards. Lipids [Total Cholesterol (TC), Low-Density Lipoprotein (LDL), and High-Density Lipoprotein (HDL)] were measured at enrollment, 6, 12, and 24 months. Mixed effects models were fit to assess the association of VL at initiation with each z-score and lipid subfraction over time. Interaction terms to evaluate the effect of VL on rates of change in each outcome were dropped where p-value>0.05. CLHIV<3 years on LPV/r-based ART were analyzed separately from those ≥3 years on EFV-based ART.

**Results:** Of 283 CLHIV, 172 <3 years started LPV/r-based ART and 111 ≥3 years started EFV-based ART. At enrollment, younger CLHIV on LPV/r and older CLHIV on EFV had a median age at ART start of 10 months and 8 years, log VL of 6.1 and 5.2, and CD4% of 14% and 14%, respectively. Among younger CLHIV, higher VL at ART initiation was associated with persistently lower mean differences over time in LAZ (β:-0.32, p=0.02), WAZ (β:-0.34, p=0.01), and BMI (β: -6.65, p=0.05) and LDL (β:-7.26, p<0.01), but was not associated with slope changes in any of the outcomes after adjustment (Table 1). Among older CLHIV, higher VL at enrollment was associated with significantly lower mean LAZ (β:-0.32, p=0.05) and borderline significantly lower WAZ (β:-0.32, p=0.06) as well as with more rapid increases in LAZ (β:0.14, p=0.01) and WAZ (β:0.19, p=0.04). No associations were found between VL and lipids among older CLHIV.

**Conclusion:** High viral load at ART initiation was associated with persistently lower growth and lipid outcomes over time among younger CLHIV on LPV/r-based ART. Further research is needed to understand the impact of this trend in
lipids on the long term cardiometabolic health of young CLWH with high viral burden at ART initiation.

Result: Reduced bone strength was observed in well-suppressed CLWH on ART, placing them at a higher risk for fracture. In addition, lower vBMD was found in CLWH on a LPV/r-based regimen compared to EFV-based regimen. Bone outcomes are an important consideration for treatment guidelines.

817 HIV AND CANCER RISK IN ADOLESCENTS AND YOUNG ADULTS IN SOUTH AFRICA, 2004-2014
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Background: The risk of developing cancer is increased amongst Adolescents and Young Adults (AYA) living with HIV compared to uninfected AYA. Low retention in care, poor virologic control, low CD4 counts and a high prevalence of other oncogenic viruses may further increase cancer risk in AYA living with HIV. We aimed to determine the association between breast cancer and HIV as well as the spectrum of cancers amongst AYA living with and without HIV.

Methods: This was a record linkage study of all AYA aged between 10 and 25 who had a cancer diagnosed between 2004 and 2014 in the South African public health sector laboratories. HIV data were retrieved from the National Health Laboratory Service and linked using probabilistic methods to cancer records in the South African National Cancer Registry database. The linkage variables included names, surnames, age and gender. We further extracted additional HIV data from the clinical history section of the cancer pathologists’ report using text searching methods. To determine the association between HIV status (infected vs uninfected) and different cancers in AYA, we fitted logistic regression models adjusting for age (adolescents vs young adults), gender (as appropriate), ethnicity (black vs non-black) and calendar period (early vs mid vs late ART).

Results: From 2004 to 2014, 8,472 AYA were diagnosed with incident cancer. The HIV status was known for 45% (n=3,812) of the AYA cancer population and the remainder was not tested for HIV. About half of those with a known HIV status were HIV positive (n=1,853; 48%). Female AYA with cancer were more frequently HIV positive as compared to male AYA with cancer and black AYA with cancer more frequently than non-black ethnic groups. Young adult cancer patients were more frequently HIV-positive compared to adolescent cancer patients. Adjusted odds ratios for AYA living with compared to only those without HIV were 219 (95% CI 90-530) for Kaposi sarcoma, 2.18 (95% CI 1.23-3.88) for cervical cancer, 2.09 (95% CI 1.66-2.63) for non-Hodgkin’s lymphoma and 2.73 (95% CI 1.27-5.68) for angioentelial cancers other than cervix.

Conclusion: The elevated risk of different AIDS defining and non AIDS defining cancers in this age group points to a possible gap in the ART programme for AYA living with HIV. The elevated risk for cervical cancer in young women indicates the need for enhanced continuous screening for pre-cancerous cervical lesions amongst AYA living with HIV as well as improved primary prevention strategies.
YOUTH PSYCHIATRIC TRAJECTORIES PREDICT PERINATALLY HIV INFECTED YOUNG-ADULT VIREMIA

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**Background:** Little is known about the relationship between patterns of psychiatric functioning over time and HIV outcomes, especially among perinatally HIV-infected (PHIV) adolescents and young adults (AYA).

**Methods:** Using data from one of the few cohort studies of PHIV AYA, we identified longitudinal trajectories of psychiatric disorders among 130 PHIV AYA living in New York City, and examined their associations with sociodemographic factors at enrollment and experiencing a viremic event in young adulthood.

Psychiatric disorders (mood, anxiety, behavioral, substance use) were assessed using the Diagnostic Interview Schedule for Children at enrollment (ages 9–16) and 4 follow-up (FU) visits. At last FU (ages 18–28), a viremic event was defined as any past year viral load >200 copies/mL. Multivariate longitudinal latent class analysis was used to identify co-occurring trajectories of psychiatric disorders, and multinomial logistic regression was used to examine sociodemographic predictors of the trajectories. A log-bimodal model was used to examine the association between trajectories and a viremic event.

**Results:** We identified 3 psychiatric trajectories spanning a median of 10 years:
1) AYA with “consistent low disorder” (63%) had no mood or behavioral disorders, few and decreasing anxiety disorders, and increasing but relatively few substance use disorders.
2) AYA with “persistent anxiety” (26%) had persistent anxiety disorders, low and decreasing behavioral disorders, but increasing mood and substance use disorders.
3) AYA with “escalating comorbidity” (11%) had substantial comorbidity at enrollment, with increasing substance use disorders, anxiety and mood disorders over time. At last FU, more than half (62%) of AYA had a viremic event. Compared to AYA with “consistent low disorder,” AYA with “escalating comorbidity” were significantly older (OR=1.89; 95% CI=1.21–2.91), reported higher household stress at enrollment (OR=2.25; 95% CI=1.51–3.34), and had 51% higher risk of a viremic event (RR=1.51; 95% CI=1.08, 2.12), while AYA in the “persistent anxiety” trajectory were more likely to be female (OR=2.28; 95% CI=1.37–3.76) and had 26% higher risk of a viremic event (RR=1.26; 95% CI=1.00, 1.58).

**Conclusion:** PHIV AYA are at high risk for mental health and substance use problems, with more comorbidity over time associated with a viremic event. Addressing the substantial and evolving mental health challenges among AYA is critical to meeting 90-90-90 treatment goals.

820 TRAJECTORY ANALYSIS OF COGNITIVE OUTCOMES IN CHILDREN WITH PERINATAL HIV

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**Background:** Cognitive impairment is common in children with perinatal HIV (pHIV). HIV-related neuropathogenesis may produce distinct cognitive phenotypes as children age. We used trajectory modeling to identify clusters of children with pHIV following unique developmental trajectories and identified predictors of belonging to select cognitive trajectory groups.

**Methods:** Participants included Thai and Cambodian children with pHIV enrolled in the PREDICT study. Children ages 4 to 12 years, with CD4% between 15-24% and no history of AIDS defining illnesses were included. Cognitive measures included intelligence tests, Children’s Color Trails, and Beery-Buktenica Developmental Test of Visual-Motor Integration and were conducted annually with a minimum follow-up of 3 years (median 5 years). Children with similar cognitive trajectories were classified using maximum likelihood estimation and Bayesian Information Criterion. Joint estimation was used to assess the influence of time varying co-variates of treatment initiation and viral suppression on trajectory course. Multiple logistic regression was employed to identify baseline factors (age, household income, parent as a caregiver, CD4 nadir, and treatment arm) associated with trajectory group membership.

**Results:** At baseline assessment, 286 children had a median age of 8 years, median CD4% of 20%, and 51% were on ART. Trajectory analyses revealed a 3-cluster classification for cognitive data representing high, medium and low scoring groups. Figure 1 shows an example of trajectory groups for Children’s Color Trails 1. Scores in the low and medium trajectory groups were stable across adolescence. In contrast, the highest scoring group demonstrated a 10-point increase in scores from baseline. Children in the lowest scoring trajectory groups were more likely to enroll at an older age (p=0.01) and report lower household income (p<0.005). Neither CD4 nadir nor treatment arm (immediate versus deferred until immunosuppression ART initiation) was associated with cognitive trajectory status.
Conclusion: Trajectory modeling succinctly classifies cohort heterogeneity in cognitive outcomes in PHIV. Most trajectory scores remained stable across age suggesting that cognitive potential is likely determined at an early age with the exception of a subgroup of children who experienced developmental gains in select cognitive domains. Poverty and longer duration of untreated HIV may predispose children with PHIV to an increased risk of suboptimal cognitive development.

Figure 1: Children's Color Trails Test 1 Trajectory Groups

821 FOCUSED COGNITIVE FUNCTION TESTING IN YOUNG PEOPLE WITH PERINATAL HIV IN ENGLAND

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Background: We previously reported that cognitive performance in young people with perinatal HIV (PHIV+) without a CDC C diagnosis (PHIV+ /no C) was similar to a comparable group of HIV-negative (HIV-) young people in England, but poorer than normative data, most noticeably in the domains of learning and memory. Here, we assess cognitive performance in the same cohort 2 years later, with expanded testing of these specific cognitive domains.

Methods: 234 PHIV+ and 68 HIV- young people completed 9 tests: 5 NIH Toolbox tests measuring executive function (Flanker inhibitory control/attention, dimensional change card sort), speed of information processing (pattern comparison), and memory (list sorting, picture sequence); 2 Hopkins Verbal Learning Tests (HVLT-R) (learning, delayed recall); and 2 verbal language measures (Weschler Individual Achievement Test pattern comparison), and memory (list sorting, picture sequence); 2 Hopkins Attention, Dimensional Change Card Sort), Speed of Information Processing, Verbal Learning, Verbal Delayed Recall, Memory, and Verbal Language Measures.

Results: All groups indicating mild impairment. NIH Toolbox executive function, speed of information processing, and memory tests were similar for all 3 groups.

Conclusions: Cognitive function was similar between PHIV+ and HIV- young people in most domains/tests. However, performance in verbal learning and recall fell below population normative scores, and was more pronounced in PHIV+ /C, supporting wider findings that earlier ART initiation may protect aspects of cognitive development.

822 SYSTEMIC INFLAMMATION AND STRUCTURAL BRAIN CHANGES IN PERINATALLY HIV+ ADOLESCENTS

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Background: Neurological impairments despite ART are well documented in perinatally-infected HIV+ adolescents (PHIV) but the mechanisms that drive this are not well defined. Systemic inflammation may be one mechanism but this has not been investigated in adolescence when the brain is undergoing rapid development.

Methods: Baseline data were drawn from the Cape Town Adolescent Antiretroviral Cohort (CTAC). PHIV on ART > 6 months with concurrently measured markers of systemic inflammation including hs-CRP and fasting low density lipoprotein-cholesterol (LDL-C).

Results: Overall 204 PHIV ages 9-12 years (mean CD4 cell count 953 cells/μL and 83% VL<50 copies/mL) and 44 age-matched HIV- controls completed all assessments. PHIV had higher hs-CRP (p<0.001) and LDL (p=0.06) vs controls. Among PHIV, hs-CRP negatively correlated with multiple neuropsychological measures including general intelligence (p=0.005), attention (p=0.015), working memory (p=0.003), visual space acuity (p=0.005), processing speed (p<0.001), and executive function (p=0.002); LDL-C negatively correlated with Language (p=0.048); however none of these correlations were apparent among controls. In measurements of the fornix and internal capsule FA, AD, and RD all increased with higher hs-CRP values (p<0.001). Among PHIV, hs-CRP negatively correlated with multiple neuropsychological measures including general intelligence (p=0.005), attention (p=0.015), working memory (p=0.003), visual space acuity (p=0.005), processing speed (p<0.001), and executive function (p=0.002); LDL-C negatively correlated with Language (p=0.048); however none of these correlations were apparent among controls. In measurements of the fornix and internal capsule FA, AD, and RD all increased with higher hs-CRP values (p<0.001). Higher MD and RD are suggestive of inflammation and myelin loss. There were no associations in PHIV or controls between hs-CRP and global brain measures (total grey matter, total white matter, cortical thickness), but whole brain mean cortical thickness increased with higher levels of LDL-C (p<0.001).

Conclusions: Markers of systemic inflammation appear associated with both neurocognitive impairment and structural brain changes in PHIV. While further investigation including long-term follow-up is required, this provides novel evidence that inflammatory mechanisms may drive persistent neurological impairment in PHIV.
823 GENOMICS LINKS AUTOPHAGY WITH NEUROCOGNITIVE IMPAIRMENT IN HIV-INFECTED CHILDREN

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Background: HIV associated neurocognitive impairment (NCI) is a common complication of perinatal HIV infection and is associated with elevated markers of inflammation. Here we identified host genetic variants associated with NCI in HIV-infected children (2 mo-18 yrs).

Methods: Whole exome sequencing was performed on 105 HIV-infected children with NCI (standardized global cognitive score for age (CSA) <70) and 211 infected controls matched for age, CD4+ count and viral load without NCI evaluated prior to the start of ART (P152/P300-Discovery Cohort [DC], mean age: 2.7 yrs). SNPs identified in DC were evaluated in 2 validation cohorts (VC): PHACS AMP (CSA <70: n=61; >70: n=306; mean age: 11.6 yrs); a contemporary longitudinal study of perinatal HIV-infected children; and P338/P377 (CSA <70: n=54; >70: n=303, mean age: 6.8 yrs) consisting of children stable on NRTI therapy prior to treatment with either ritonavir (P338) or nevirapine, nefilavine or ritonavir (P377). Logistic regression was used to estimate adjusted odds ratios (OR). The combined, across study, OR estimate was computed using inverse variance weights. P-values <.05 were considered to be statistically significant.

Results: 22 SNPs with >5 subjects/SNP in 19 genes reaching p <.001 and OR >1.5 for each comparison of cognitively impaired group to controls with >70, >85 and >100 CSA were identified in the DC. The 22 SNPs were evaluated by PCR in the PHACS Adolescent Master Protocol cohort and identified 3 SNPs, CCRL2 (rs3204849), FAM134B [RETREG1] (rs61733811) and YWHAH [14-3-3 proteins] (rs37884247) comparing CSA 70 with similar 95% confidence interval (CI) for the OR. The combined, across study, OR estimate was computed using inverse variance weights. P-values <.05 were considered to be statistically significant.

Conclusion: Using whole exome sequencing and two VC, we have identified 3 genetic variants that are associated with NCI in HIV-infected children. Since YWHAH and CCRL2 binding to chemerin both affect mTORC1 phosphorylation and FAM134B plays a role in autophagosome formation, a potential common mechanism for these three genetic variants is the modulation of autophagy leading to altered inflammation affecting neurocognitive function.

824 HIGH PRESCRIPTION ERROR RATES AMONG CHILDREN ON ANTIRETROVIRAL THERAPY IN KENYA

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Background: Access to life saving antiretroviral therapy (ART) in many resource-limiting settings has increased, yet more than 30% of children on ART do not achieve viral suppression. Infants and children require continuous medication dose adjustments in response to changing pharmacodynamics, and inappropriate dosing may contribute to viral non-suppression. This study sought to determine the magnitude of prescription dosing errors and associated factors.

Methods: We conducted a cross sectional study among HIV Infected children aged ≤11 years in four public health facilities in Nairobi, Kenya. Demographic, clinical and prescription data for the last clinical visit were abstracted from the medical charts of children receiving ART at the time of the study. Descriptive statistics were used to summarize participant characteristics and prescription errors. Logistic regression was conducted to determine factors associated with dosing errors.

Results: A total of 196 children were included in the study, among these, 53% were male and the median age was 7.9 years (Interquartile range [IQR] 4.8, 10.0). The most commonly used ART regimens were abacavir/lamivudine/ zidovudine (31%) children, followed by zidovudine / lamivudine (22%) children, and abacavir/lamivudine/ nevirapine taken by 18% children. Overall, 85 (44%), 90 (46%) and 92 (47%) children lacked data on the antiretroviral (ARV) drug formulation, dosage, and frequency of dosing respectively, translating into almost half of children having prescription errors from the outset. Among 104 (53%) children with complete formulation, dosage and frequency of dosing prescription information, 38 (37%) had at least one prescription dosing error. In a multivariable model, being on non-nucleoside reverse transcriptase inhibitors was independently associated with an increased likelihood of a dosing error (adjusted odds ratio 8.8, 95% confidence interval 2.1-36.3).

Conclusion: Almost half of children receiving antiretroviral therapy had inadequate prescription information and among those with adequate information, one third had prescription dosing errors. These findings call for urgent measures to address health care workers prescribing practices and knowledge, particularly on documentation and appropriate dosing including weight based dose adjustments. In addition, further evaluation should be conducted to determine association of prescription errors with viral suppression.

825 EFFECT OF ANTI-TUBERCULOSIS THERAPY ON NEVIRAPINE PHARMACOKINETICS IN YOUNG CHILDREN

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Background: Nevirapine (NVP)-based antiretroviral therapy (ART) is one of the limited options in children younger than 3 years old with TB/HIV coinfection. Given the scarce data, we examined the effect of first-line TB therapy on NVP pharmacokinetics (PK) in Ghanaian children.

Methods: ART-naïve HIV-infected children aged 3–35 months with and without TB were treated with NVP 200 mg/m2 twice daily plus two NRTIs. The new WHO recommended higher dosages of rifampin and isoniazid were used. After 4 weeks of ART, PK samples were collected at 0, 2, 6, and 12 hours post-dose to measure NVP plasma concentrations, using a validated LC/MS/MS assay. In the co-infected patients, sampling was repeated after 4 weeks off TB therapy. PK parameters were calculated using noncompartmental analysis and were compared between groups using Wilcoxon Rank-sum test and within group using Signed-rank test.

Results: Of the 53 patients, 23 (43%) had TB coinfection, of whom 15 completed PK sampling on (PK1) and off (PK2) anti-TB therapy. Baseline characteristics were similar in the two groups except co-infected children had lower median height-for-age-Z-score. Median NVP concentrations were lowest
in the children with TB/HIV coinfection on TB therapy, followed by HIV infection only and highest in the co-infected off TB therapy (Figure). Median NVP Cmax, Cmin and AUC0-12h were not significantly different between children with HIV and those with TB/HIV on or off anti-TB therapy. In multivariate analysis, TB therapy and CYP2B6 516G→T genotype status were joint predictors of NVP PK. Among children with CYP2B6 516G/G genotype, NVP exposure was significantly lower in the TB co-infected compared to HIV-infected group; this difference was not seen in children with GT or TT genotypes. The proportion of children with NVP Cmin <3 mg/L was 61% in the co-infected group and 30% in the HIV group (P = 0.03). Among the TB/HIV-co-infected children with paired samples, geometric mean ratio (90% CI) PK1/PK2 of NVP Cmax, Cmin and AUC0-12h were 0.68 (0.55–0.85), 0.84 (0.51–1.38) and 0.71 (0.56–0.91). Nine (41%) of 22 children with viral load data at 6 months had HIV RNA >200 copies/mL.

**Conclusion:** First-line TB therapy reduced NVP plasma exposure in young HIV-infected children, especially those with CYP2B6 516G/G genotype. Given that NVP dose optimization with TB therapy may require a genotype-guided approach, evaluation of more compatible alternatives to NVP is needed in young children with TB coinfection.

![Time-concentration curves for NVP (median)](image)

**826 SAFETY AND EFFICACY OF STARTING ANTIRETROVIRAL THERAPY IN THE FIRST WEEK OF LIFE**

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**Background:** Antiretroviral treatment (ART) started in the first week of life may limit HIV viral reservoir and improve treatment outcomes; but little information is available about safety, viral efficacy, and pharmacokinetics (PK) of ART in early infancy.

**Methods:** HIV+ infants <7 days of age, >35 weeks gestation, and >2000g were offered enrollment in the Early Infant Treatment Study (EIT) in Botswana and started on treatment doses of NVP (6mg/kg BID), ZDV, and 3TC as initial ART, and changed to LPV/r, ZDV, 3TC after 2-5 weeks (when >2 weeks of life and >40 weeks gestational age equivalent). Study visits and HIV RNA testing occurred at weeks 0, 1, 2, 4, 8, 12. PK testing of NVP trough values occurred at weeks 1 and 2. Comparisons were by Wilcoxon rank sum testing and Spearman correlations.

**Results:** From April 2015–July 2018, 40 HIV+ infants were enrolled; 37 (93%) had reached 12 wks on ART as of 20 September 2018. Median age at screening was 1 day after birth (range 0, 4), and median age at ART initiation was 2 days after birth (range 1, 5). Median change from NVP-based to LPV/r-based ART was after 2.7 wks (range 2.3, 4.4 wks). No deaths or loss to follow-up occurred in the first 12 wks, and no modification of ART for toxicity occurred. Only 1 grade 3/4 neutropenia and no grade 3/4 anemias were reported through 12 wks. HIV RNA declined from a median of 4.05 log copies/mL at baseline (IQR 2.79, 4.86 log copies/mL) to 2.54 log copies/mL at 2 wks (IQR 1.86, 3.21) and <1.60 log copies/mL at 12 wks (IQR <1.60, 1.89 log copies/mL) (Figure 1), and did not differ by infant HIV RNA at baseline (p=0.10). At 12 wks of ART, 21 (57%) of 37 had HIV RNA < 40 copies/mL, and only 3 (8%) were > 400 copies/mL. However, 9 (22.5%) infants had transient increases in HIV RNA in the 4-wk period following transition to LPV/r-based ART, thought to be adherence-related. Median NVP trough concentration at 1 and 2 wks was 3.01 mcg/mL (at median 15 hrs); 48% of concentrations were below the therapeutic target of 3.0 mcg/mL (including 10% BQL, indicating non-adherence); concentrations did not correlate with the magnitude of decline in HIV RNA log copies/mL at either 2 or 4 wks.

**Conclusion:** NVP, ZDV, 3TC started in the first week of life was safe and effective, even among infants with NVP levels below the ideal therapeutic PK target. Although poor tolerability often led to transient viral rebound following transition to LPV/r-based ART, almost all children were able to achieve HIV RNA declines to <400 copies/mL by 12 weeks of life.

![Figure 1: Median HIV RNA and Percentage < 40 copies/ml through 12 Weeks on ART](image)

**827 IN SILICO PREDICTION OF DOLUTEGRAVIR PHARMACOKINETICS & DOSE OPTIMISATION IN NEONATES**

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**Background:** Dolutegravir (DTG) is a selective and potent HIV-1 integrase inhibitor and has potential for treatment of neonates with HIV infection and use as prophylaxis of perinatal transmission. Safety and pharmacokinetics (PK) of DTG have previously been studied in pediatric patients and current studies are investigating the appropriate dose in infants aged >4 weeks. Dose optimisation in neonatal patients is complex and physiologically-based pharmacokinetic (PBPK) modelling may help inform knowledge gaps in the absence of empirical data. The aim of this study was to simulate the PK of DTG in neonates to help identify an appropriate dosing regimen using PBPK modelling.

**Methods:** The PBPK model was designed in Simbiology (MATLAB R2018a) incorporating neonatal maturation characteristics and a description of physiological and anatomical growth data from various sources. Experimental in vitro data for DTG was integrated into the model to aid prediction of DTG PK in the neonatal population. DTG is predominantly metabolised by UGT1A1 and CYP3A4 and the PBPK model was qualified using clinical data from the surrogate substrates raltegravir (UGT1A1) and midazolam (CYP3A4) in neonates. Additionally, DTG adult and paediatric clinical data were used for the validation of the PBPK model. The model was assumed to be qualified if the simulated values were within 0.5-1.5 fold of the mean reported values as per convention for the approach.

**Results:** A combination of different DTG single and multiple dose strategies were simulated in 100 healthy neonates with the aim of achieving plasma exposure comparable to therapeutic levels observed in paediatric patients (Cmin : 0.90 mg/L and AUC 24 : 46 mg.h/L). The PK parameters are summarised in Table 1. Regimens 1-3 result in PK parameters comparable to those in paediatric patients, with convenient dosing schedules.

**Conclusion:** Due to the lack of clinical PK data, neonates represent a vulnerable population. Clinical trials in neonates are extremely difficult to conduct and dose prediction is therefore beneficial to inform trial design. The combination of rapid development and immature ontogeny make it difficult to easily scale existing doses. PBPK modelling allows these changes to be represented...
mathematically, and should result in more accurate predictions. The presented data can be used to inform neonatal clinical trials to help accelerate dose optimisation in this population.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose (mg/kg)</th>
<th>C\textsubscript{\text{avg}} (ng/mL)</th>
<th>AUC\textsubscript{\text{24h}} (ng*h/mL)</th>
<th>AUC\textsubscript{\text{max}} (ng*h/mL)</th>
<th>C\textsubscript{\text{max}} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Day 1: 4.5, Day 2-10: 3.0 (QD)</td>
<td>Day 1: 3-1.5, Day 2-10: 2-1.5 (QD)</td>
<td>1.59, 2.24, 1.85, 1.59</td>
<td>28.78, 43.97, 36.13, 28.78</td>
<td>57.82, 69.68, 51.98, 49.02</td>
</tr>
<tr>
<td>2</td>
<td>Day 1: 4.5, Day 2-10: 3.0 (QD)</td>
<td>Day 1: 3-1.5, Day 2-10: 2-1.5 (QD)</td>
<td>1.59, 2.24, 1.85, 1.59</td>
<td>28.78, 43.97, 36.13, 28.78</td>
<td>57.82, 69.68, 51.98, 49.02</td>
</tr>
<tr>
<td>3</td>
<td>Day 1: 4.5, Day 2-10: 3.0 (QD)</td>
<td>Day 1: 3-1.5, Day 2-10: 2-1.5 (QD)</td>
<td>1.59, 2.24, 1.85, 1.59</td>
<td>28.78, 43.97, 36.13, 28.78</td>
<td>57.82, 69.68, 51.98, 49.02</td>
</tr>
</tbody>
</table>

**Conclusion:** Virolological efficacy and safety of DTG and C4H were similar between the 3 groups of age. Because of its high genetic barrier to resistance, DTG could be especially useful in the paediatric population, in which the risk of poor treatment adherence is high.

**Background:** Dolutegravir (DTG) is recommended as first-line treatment for HIV-infected adults and children 6 yrs and older due to its potency, high barrier to resistance, convenience and tolerability. A 5mg dispersible tablet (DTG-DT) formulation for children is being evaluated in IMPAACT P1093 (NCT01302847), an ongoing phase I/II open-label dose-finding study. The first DTG-DT dose tested did not meet target drug exposures. Here we present the intensive pharmacokinetic (PK), 4-week safety and efficacy data of higher dosing for DTG-DT in children ages 6 mo to <6 yr.

**Methods:** Enrollment was stratified into two age cohorts of 10 children (≥6 mo to <2 yr and ≥2 to <6 yr). DTG-DT was dosed once daily by WHO weight-band (6 to <10kg: 15mg, 10 to <14kg: 20mg, 14 to <20kg: 25mg). Children received DTG-DT alone or added to stable-failing or empiric initial background regimens. PK sampling was completed between days 5-10 under fasting conditions. Background regimens were optimized based on enrollment HIV genotypes. Safety, tolerability, and plasma HIV-1 RNA levels were assessed through 4 weeks. Based on adult data, exposure targets were geometric mean (GM) (range) AUC24h of 46 (37-134) mg*h/L and C24h of 995 (697-2260) ng/mL.

**Results:** Twenty children (10 female) with median (range) age 22 months (6, 71), and weight 9.4 kg (6.5, 17.5) were studied. Median baseline CD4+ cell % and HIV-1 RNA levels were 27.3 (IQR: 22.0, 36.9) and 4.3log10 (c/mL) (IQR: 3.3, 5.3). For age cohorts of 6 mo to <2 yr and ≥2 to <6 yr, the GM(CV%) AUC24h(CV%) was 70.2 (49.6) mg*h/L and 59.0 (62.2) mg*h/L, C24h was 1094(70.4) ng/mL and 791 (105) ng/mL, and Cmax was 5702(37) ng/mL and 5813 (44) ng/mL, respectively. C24h levels varied from 104 to 4579 ng/mL (figure). DTG was well tolerated, with no drug-related Grade 3 or 4 AEs or discontinuations. HIV-1 RNA levels were <400 c/mL in 16/20 and <50 c/mL in 8/20 participants after 4 weeks of treatment, with median decrease from BL of 2.38 log10 (c/mL) (IQR: 1.36, 3.11).

**Conclusion:** The tested dosing of DTG-DT met pre-specified AUC24h and C24h targets for age-cohorts children 6 mo to <6 yr old, even with moderate intra-participant variability. DTG was virologically potent and well tolerated through week 4. With the additional PK, long-term safety and efficacy data currently being collected, these novel results will form the basis of safe and efficacious WHO weight-band dosing recommendations for DTG-DT in children.
Background: Weight band pharmacokinetic (PK) substudies within the ongoing phase III ODYSSEY trial evaluated PK and safety of simplified weight band-based dosing of dolutegravir (DTG) for children on first-line and secondline antiretroviral therapy (ART). This substudy assessed PK and safety of DTG adult film-coated tablets (FCT) and pediatric dispersible tablets (DT) in children weighing 20 to <25kg who make up a high proportion of children living with HIV. DTG have higher bioavailability compared to FCT in adults (ratio 1.5–1.8).

Methods: Steady state 24h DTG PK profiles in fasted children taking once-daily DTG 50mg FCT or 30mg DT (6x5mg) were recorded ≥7 days after switch from DTG 25mg DT. Blood was sampled at 0, 1, 2, 4, 6, 12 and 24h and DTG plasma concentrations were measured with a validated UPLC-MS/MS method. Non-compartmental PK analysis was performed to calculate PK parameters (WinNonlin 8.1). Results were compared to those in HIV-positive adults taking DTG 50mg FCT once-daily, and children 20 to <25kg on 25mg FCT once daily (Table). Safety was evaluated at 2, 4, 12, and then every 12 weeks.

Results: 15 African children were enrolled in Zimbabwe and Uganda (Table). The 50mg FCT (n=7) and 30mg DT (n=8) doses both resulted in geometric mean (GM) C_{trough} values comparable to adults on DTG 50mg FCT once-daily and were higher compared to children 20 to <25kg on 25mg FCT. GM AUC_{0-24h} for both doses was in-between values observed in adults taking DTG 50mg once daily and 50mg twice daily. GM C_{max} on both doses exceeded adult GM values for DTG 50mg once and twice daily. DTG 50mg FCT in this weight band provided a lower PK profile for children weighing 20 to <25kg allowing rapid alignment of WHO-preferred ART regimens for adults and children ≥20kg in low- and middle-income countries.

Table: Participant demographics and PK parameters by dose and formulation in children 20 to <25kg and adult reference populations.

<table>
<thead>
<tr>
<th>WHO weight band</th>
<th>ODYSSEY DT</th>
<th>ODYSSEY FCT</th>
<th>Reference adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-25kg</td>
<td>4 (59%)</td>
<td>4 (57%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>25-35kg</td>
<td>7 (97%)</td>
<td>7 (91%)</td>
<td>18 (175%)</td>
</tr>
<tr>
<td>25-35kg</td>
<td>25 (32%)</td>
<td>25 (33%)</td>
<td>50 (50%)</td>
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<tr>
<td>35-40kg</td>
<td>10 (100%)</td>
<td>10 (100%)</td>
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<tr>
<td>40kg and over</td>
<td>14 (100%)</td>
<td>14 (100%)</td>
<td></td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>4 (59%)</td>
<td>4 (57%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.6 (8.6-11.3)</td>
<td>9.7 (6.1-11.3)</td>
<td>9.7 (7.1-11.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>21 (20.3-22.7)</td>
<td>22.4 (20.5-25.4)</td>
<td>23.4 (20.2-25.3)</td>
</tr>
<tr>
<td>C_{max} (mg/L)</td>
<td>1.4 (1.5-3.1)</td>
<td>2.2 (2.0-2.4)</td>
<td>1.11 (1.0-1.2)</td>
</tr>
<tr>
<td>C_{trough} (mg/L)</td>
<td>0.71 (not measured)</td>
<td>0.77 (not measured)</td>
<td>0.92 (not measured)</td>
</tr>
<tr>
<td>AUC_{0-24h} (mg*H/L)</td>
<td>71.8 (28)</td>
<td>72.6 (32)</td>
<td>36.1 (41)</td>
</tr>
<tr>
<td>C_{trough} (mg/L)</td>
<td>7.42 (not measured)</td>
<td>6.07 (not measured)</td>
<td>3.23 (not measured)</td>
</tr>
</tbody>
</table>

PK parameters are geometric mean values with coefficient of variation (%). Other data are mean (range) for age, dose mg/kg and weight, unless otherwise indicated. Data presented at the 11th International workshop on HIV Pediatrics, July 2018. "Fasted" HIV-positive adults; "Fasted"-positive treatment-experienced adults; fed state not specified. Data are median (range). *One participant had C_{trough} of 0.30mg/L below 0.28mg/L. Ten participants had C_{trough} below 0.30mg/L.

831 RECENT HIV INFECTION SURVEILLANCE AMONG ADOLESCENT GIRLS AND YOUNG WOMEN IN MALAWI

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Background: The risk of HIV acquisition among female sex workers (FSW) across Sub-Saharan Africa is estimated to be 13x higher than other women: understanding population-specific risk factors can provide important information to guide HIV prevention interventions. Sauti is a PEPPAR/USAID-funded combination prevention project working in 14 regions in Tanzania, serving key and vulnerable populations with biomedical and structural prevention, care and treatment interventions including HIV testing. FSW are primary recipients of Sauti services, provided at brothels and other hot spots for HIV transmission. This analysis describes factors associated with HIV serostatus conversion among a cohort of FSW originally testing HIV negative and subsequently testing HIV positive during the course of attending Sauti services.

Methods: Sauti project data comprise clinic intake forms which Sauti program collects, de-identifies, enters into a database and uses for program analysis. From October 2016 to December 2017, 261,566 FSW tested for HIV. 6,892 returned for repeat testing for 3 months or more from the initial test: these are the repeat testers cohort. All repeat tester data was analyzed to examine when re-testing occurred and understand factors which may have influenced seroconversion. We conducted multivariable logistic regression analysis to estimate odds ratios for risk factors associated with HIV seroconversion.

Results: 6,128 FSW repeat tested, testing negative for HIV at initial test. Of these 235 (3.8%) tested HIV positive upon repeat testing. Having a syndromic STI (3.21, 95% CI: 2.53-8.12) and non-use of STI periodic presumptive treatment (1.34, 95% CI: 1.07-1.94) were highly predictive of HIV sero-conversion. Other predictors for included: older age 35+ years (3.10, 95% CI: 1.97-4.85), never
used condom in last three sexual intercourse (1.58, 95% CI: 1.16-3.05) and practicing anal sex (2.45, 95% CI: 1.81-3.31)

**Conclusion:** Our findings highlighted higher risk of sero-conversion among FSW who had a syndromic STI and/or did not have presumptive periodic treatment of STIs, as well as behavioral factors such as reporting anal sex and/or inconsistent condom use. The findings underscore the importance of provision of both biomedical and behavioral services to FSW tailored to fit their risk profile. Consistent condom use and STI/HIV prevention are important service delivery components to stress in light of these findings.

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### 833 QUANTIFYING TRANSMISSIONS FROM AGE GROUPS IN SIMULATIONS OF HPTN071 (POPART) TRIAL

**William Probert**, Rafael Sauter, Michael Pickles, Anne Cori, Justin Bwalya, Sian Floyd, Nonthu Mandela, Kwame Shanaube, Blia Yang, Helen Ayles, Peter Bock, Deborah J. Donnell, Sarah Fidler, Richard Hayes, Christophe Fraser

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**Background:** The HIV epidemic in sub-Saharan Africa (SSA) is known to be heterogeneous, contributing to the perception that preventative efforts need to be targeted to those at most risk of transmitting or acquiring the virus. The HPTN071 (PopART) trial has been testing the impact of a universally delivered combination prevention package in 21 communities in Zambia and South Africa. An individual-based simulation model (IBM) has been developed as part of the trial. Using the IBM we quantify the proportion of new infections that arise from men and women of different age groups, and the potential impact of suppressing transmissions from each of these groups.

**Methods:** The IBM is calibrated to trial data in each intervention community (arm A of the trial; one community shown here). Using the best-fitting parameter set, projections of the epidemics are made up to 2030, with 40 replicates. Projections beyond the end of the trial assume continuation of the PopART intervention at a national scale. We estimate the population attributable fraction (PAF), the proportion of new infections that arise from men and women of different ages over defined time-periods. PAF can be defined and women was higher than men whereas, for ages greater than 25 y.o., this relationship was reversed. When considering indirect transmissions, PAFtotal was similar in men and women across all age groups but higher in the 20-34 y.o. age group. In all simulations, for individuals less than 25 years old (y.o.), PAFdirect of 25-34 y.o. men was >15% in 2023-2028, twice that of women of the same age.

**Conclusion:** This work illustrates the significant contribution of 25-34 y.o. men to HIV transmission in generalised HIV epidemics in SSA, and of young people when considering indirect transmissions. Future interventions that target sub-populations in SSA need to address such discrepancies. Estimates of PAF direct may be complemented from phylogenetic studies.

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### 834 COMMUNITY PREVALENCE OF VIREMIA: A NEW STANDARD FOR BIO-BEHAVIORAL SURVEYS

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**Background:** Monitoring HIV programs requires estimates of HIV incidence which can be challenging to obtain. We characterize the change in HIV incidence over 4 years among people who inject drugs (PWID) and men who have sex with men (MSM) across 22 cities in India and evaluate associations with community prevalence of viremia (PV).

**Methods:** These data are from a cluster-randomized trial among PWID (12 clusters) and MSM (10 clusters) in India that included baseline (2012-13) and follow-up (2016-17) respondent-driven sampling surveys of ~1000/cluster. Cross-sectional HIV incidence was estimated using a validated multi-assay algorithm incorporating LAg Avidity ELISA, BioRad Avidity assay, CD4+ count and HIV RNA (limit of detection> 150 copies/ml). PV was estimated as the percentage of persons with detectable HIV RNA in the cluster. Cluster-level linear regression assessed the association between change in PV and change in HIV incidence over 4 years controlling for study arm and baseline PV. Multi-level Poisson regression assessed the association between baseline and follow-up PV and individual-level incident HIV risk at follow-up accounting for individual-level contributions to the epidemic were increased (fig 1).

**Results:** The median HIV incidence in PWID clusters at follow-up was 5.16% (range: 0, 18.5); the median absolute change (baseline to follow-up) in incidence was 0.1% (range: -4.55, 12.4). In MSM clusters, median HIV incidence was 1.44%
Among those who declared themselves as never injected – 9.2% (6.8 – 11.6%) of the group of non-injecting sexual partners of PWID as high as 15.0% (12.4 – 17.5%).

Conclusion: Prior studies have demonstrated a strong cross-sectional association between community PV and HIV incidence. We provide further evidence of the role of PV as a surrogate for incidence by demonstrating that change in community PV predicts change in incidence and PV predicts future incident HIV infections independent of individual risk.

Change in prevalence of viremia from 2012/2013 - 2016/2017

Figure: Scatterplot of change in cross-sectional incidence vs. change in community prevalence of viremia (PV) between baseline (2012-13) and follow-up (2016-17) surveys. Orange = PWID clusters; Green = MSM clusters

835 HIV EPIDEMIC IN A BRIDGE POPULATION IN UKRAINE CALLS FOR NEW PREVENTION STRATEGIES

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Alliance for Public Health, Kyiv, Ukraine

Background: Ukraine is experiencing one of the severest HIV epidemic in the World. From its onset in 90th it was primarily an IDU driven. The tremendous efforts that community-based organizations investing in HIV prevention slow down the disease spread among key populations (KP) including people who inject drugs (PWID). The HIV prevalence has stabilized at the level of 22% (21.9% in 2015 and 21.6% in 2017 sentinel surveys). But when the prevalence is high there is always a risk that the disease may spread to the bridging population. To estimate the HIV burden in one of the bridge groups we conducted the survey among sexual partners of PWID.

Methods: The study population included 769 respondents from 10 cities of Ukraine recruited through a linked RDS in a period of May-August 2015. The sample included those who had sexual intercourse with the PWID in the last 90 days and haven’t inject drugs for the last 30 days. All participants were confidentially interviewed to assess their HIV risk behavior. Blood samples were tested for HIV, hepatitis B, C and syphilis by rapid combo tests. The analysis were done in SPSS 21.0 and RDS-Analyst.

Results: Among all the participants 87.3% were females. Medium age – 32.2, 75.5% declared as never injected (72.4-78.5%), 97.6% were regular sex partners of their PWID-recruiters. Only 48.5% used condom during the last intercourse and 35.9% never used condom in the last 90 days. The HIV prevalence in the group of non-injecting sexual partners of PWID as high as 15.0% (12.4 – 17.5%). Among those who declared themselves as never injected – 9.2% (6.8 – 11.6%) and among those who never injected and were HCV-negative 5.6% (4.2 – 6.8%). The prevalence of syphilis was 4.7% (3.2 – 6.2%). Only 4.6% of the respondents were clients of the HIV prevention programs; 3.6% have received free condoms as part of prevention service in the last 12 month. 23.5% of couples were serodiscordant, in 16.9% of cases partner-PWID was HIV-positive. Only quarter of them had the HIV test in the last 12 month and knew the result. None of HIV-negative partners received PrEP.

Conclusion: The HIV epidemic in Ukraine is still in progress and it’s involving people outside of KP through unprotected sex. With the understanding that the sexual behavior is hard to correct and people won’t start use condoms with their regular partners if they have not done so yet - better prevention strategy is needed. In this view sexual partners of PWID should be considered as one of the priority groups for PrEP.

836 LOW CROSS-SECTIONAL HIV-1 INCIDENCE AT END OF BOTSWANA “YA TSIE” PREVENTION STUDY

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Background: Botswana has one the highest HIV-1 prevalence estimates and high antiretroviral treatment (ART) coverage. We sought to measure HIV incidence cross-sectionally in the 6 Botswana communities participating in a community-wide End of Study Survey (ESS) of the Botswana Combination Prevention Project (BCPP), "Ya Tsie."

Methods: All consenting adult residents aged 16–64 years in 6 rural and peri-urban communities were enrolled in the BCPP ESS. Data and samples from ESS were used to estimate cross-sectional HIV incidence by an algorithm that included Limiting-Antigen Avidity Assay (LAG-Avidity EIA), ART status (documented or by testing for ARV drugs in plasma) and HIV-1 RNA load. The LAG-Avidity EIA cut-off normalized optical density (ODn) was set at 1.5 and HIV-1 RNA cut-off at 400 copies/mL. The Mean Duration of Recent Infection was estimated to be 130 days and the False Recent Rate (FRR) was 0%.

Results: Among 14,125 participants in the ESS, HIV status was available for 13,985 participants, 3,614 of whom were HIV positive and 3,248 were on ART. Among 366 ART-naïve participants, LAG-Avidity EIA data was generated for 345 (94%) participants with 37 (11%) having ODn<1.5 and initially classified as recent infections. Among these 37, 21(57%) had an HIV-1 RNA load ≤400 copies/mL and were excluded, as potential elite/viremic controllers or undisclosed ART use. Thus, 16 LAG-Avidity-EIA-recent, ARV-naïve individuals with detectable HIV-1 RNA (>400 copies/mL) were classified as individuals with recent HIV infections. The annualized HIV incidence among 16–64 year old adults was estimated at 0.44% (95% CI 0.22–0.65%).

Conclusion: Using a cross-sectional algorithm, HIV incidence in the 6 BCPP ESS communities was less than 0.5%. The rate at ESS is lower than the BCPP baseline incidence of ~1%, which might reflect the successful scale-up of the ART program in Botswana.
groups. Blood samples were collected to determine HIV status, CD4 count and viral load. Data was analyzed using STATA 12 software.

**Results:** A total of 22,194 individuals were interviewed with a response rate of 93.9%, 20,406 (97.9%) tested for HIV and given result. One hundred and thirty individuals tested positive. Overall HIV prevalence was 0.6%. Of the 20,406 respondents, 3,115 (15.3%) were previously tested with result and 47 (36%) self-reported being HIV positive. Ninety-six percent of those who self-reported HIV positive were positive when retested. Among all the positives, 17.6% had CD4 count <500 μl/ml and 39.2% had viral load <1000 copies/ml. Behavioral drivers of HIV were hesitance to take a HIV test 68.3% (OR 1.795%CI 0.9-3.2) and fear of loss of respect from their others if found positive 66.4% (OR 1.0 95% CI 0.5-1.9), inconsistent condom use in the last 12 months 3.1% (OR 0.9 95% CI 0.2-0.6), widowed 5.3% (OR 11.795% CI 4.2-32.5), unmarried but living with partner 4.9% (OR 11.195% CI 1.6-65.7).

**Conclusion:** Fear of stigmatization and co-habitation were found to be behavioral drivers of HIV in Kaduna state, and indicates potential for HIV transmission and spread. We recommend to the State targeted campaigns about HIV Counselling and testing services (HTS), health promotion of non-discriminatory attitudes about HIV, and health education about safer practices to reach different sectors of the population.

838 **CANGO LYEC (HEALING THE ELEPHANT): HIV INCIDENCE IN POSTCONFLICT NORTHERN UGANDA**

Samuel S. Malamba, David S. Zamar, D. Martin Ogwang, Anton Friedman, Kate Jongbloed, Herbert Muynida, ACHILLES KATAMBA, Nelson Sewankambo, Martin T. Schechter, Patricia M. Spittal

1Makerere University College of Health Sciences, Kampala, Uganda, 2University of British Columbia, Vancouver, Canada, 3St. Mary’s Hospital Lacor, Gulu, Uganda

**Background:** Conflict in Northern Uganda in the 2000s resulted in widespread atrocities, human rights violations and death, and saw millions flee to internally displaced people (IDP) camps. War related traumas combined with difficulties in accessing prevention and health services has led to extreme HIV vulnerability among conflict-affected people who have survived the war.

**Methods:** The Cango Lyec (Healing the Elephant) Project is a prospective cohort involving conflict-affected people in Nwoya, Amuru, and Gulu districts, Northern Uganda. Participants aged 13–49 at baseline were followed over 2 years and longitudinal data were collected on war-related experiences, mental health, sexual vulnerabilities, and sociodemographics. Blood samples were collected and tested for HIV at baseline and at each 12-month follow-up. Cox proportional hazard models determined factors associated with HIV incidence.

**Results:** In total, 1918 participants (1021 female, 897 male) who were HIV negative at baseline and had at least one follow-up, contributed a total of 3899 person years for analysis. In this study, 39 (23 female, 16 male) participants contracted HIV during follow-up. This corresponds to a cumulative incidence of 10.0 per 1000 person years (95%CI: 7.1-13.7). Stratified by sex, cumulative incidence was 11.0% (95%CI: 7.0-16.6) among women and 8.8% (95%CI: 5.0-14.3) among men. Adjusting for potential confounders (age, sex, marital status, district of residence, displacement status, and religion), factors associated with an increased risk of contracting HIV included: having ever been abducted (HR: 3.6; 95%CI: 1.8-7.3), experiencing war-related traumatic events (HR: 2.5; 95%CI: 1.2-5.3), suicide ideation (HR: 3.2; 95%CI: 1.1-9.2), having 2 or more sexual partners (HR: 4.0; 95%CI: 1.2-13.4), inconsistent condom use (HR: 5.6; 95%CI: 1.8-25.0), and genital ulcers (HR: 2.8; 95%CI: 1.1-7.5).

**Conclusion:** Conflict-affected participants who had experienced abduction and traumatic events during the war were disproportionately impacted by HIV infection in this study. Trauma-informed HIV prevention and treatment services, as well as culturally safe mental health initiatives are urgently required.

840 **QUANTIFYING DELAY IN HIV PROGRAMME ACCESS AMONG YOUNG FEMALE SEX WORKERS IN KENYA**

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**Background:** Programme data in Kenya suggest that 85-90% of all female sex workers have been contacted by HIV prevention programmes. Yet missing from these data is the timing of programme access with respect to sex workers’ sexual life-course – such that access delays remain unmeasured. We estimated the time from first experience of HIV-associated vulnerabilities to initial programme contact among young women engaged in sex work (YSW).

**Methods:** We conducted a cross-sectional bio-behavioral survey of 408 cis-female YSW (14-24 years of age) in Mombasa, Kenya in 2015, after geographical mapping and enumeration which estimated a total of 6,127 [range, 4,793 to 7,642] YSW in Mombasa. Timing of HIV-associated vulnerabilities (self-identifying as sex workers; sex in exchange for gifts/money; and physical or sexual violence) and timing of initial contact with a programme were


**841** LITTLE OR NO OVERLAP OF SEXUAL NETWORKS OF TRANSGENDER WOMEN AND MSM IN LIMA, PERU

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**Background:** Transgender women (TW) are at extremely high risk of HIV, even compared to men who have sex with men (MSM). MSM and TW and their sexual networks are often conflated in research. While studies of MSM show transmission in ‘closed’ networks comprised almost exclusively of MSM, sexual networks of TW have not been characterized. Understanding TW sexual networks, including identity and behavior of sexual partners of TW (PTW), is important to better explain the high HIV incidence in TW.

**Methods:** We used modified respondent-driven sampling to collect cross-sectional data from TW and their sex partners in Lima, Peru (February – July 2018). TW seed participants completed a survey and invited up to 3 sex partners using a WhatsApp referral system. In each wave of forward partner referral, invited partners could complete the survey and were provided referral coupons. The questionnaire assessed gender and sexual identity, sexual behavior, and self-reported HIV status. We constructed a sexual network map and characterized sociodemographics and behavior of PTW.

**Results:** Among 408 YSW, 26% reported any programme contact. The median time to initial programme contact was 18 months (IQR: 8-36) and 24 months (12-36) respectively, from self-identifying as a sex worker, and from first sex in exchange for gifts/money. A total of 38% (N=154) experienced physical or sexual violence prior to programme contact, with a median of 18 months (4-36) from first experience of violence to initial programme contact. Rates of initial programme contact were 0.64 per 100 person-months (95% CI: 0.47 – 0.80); 0.52 (95% CI: 0.39 – 0.65); and 0.48 (95% CI: 0.28 – 0.69), respectively since first sex as a sex worker; since first sex in exchange for gifts/money; and since first experience of violence (Figure). Based on YSW population size in Mombasa, we estimated 9,268 to 14,776 person-years of access delay at the population-level.

**Conclusion:** Using a person-year approach, we identified a large gap in programme access among YSW in Mombasa, and among those who accessed the programme, a substantial delay in access. The findings signal an urgent need for prevention services prioritized or tailored to YSW.

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**842** FACTORS ASSOCIATED WITH HIV SEROPOSITIVITY AMONG HIGH-RISK MEN IN TANZANIA

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1Jhpiego, Dar es Salaam, Tanzania, United Republic of, 2National AIDS Control Program, Dar es Salaam, Tanzania, United Republic of, 3USAID Tanzania, Dar es Salaam, Tanzania, United Republic of, 4Jhpiego, Baltimore, MD, USA

**Background:** Due to dramatically lower enrollment into HIV care and treatment, WHO identified men as highly important to reach with HIV testing services (HTS) and enrollment into treatment. Globally, only one third of all HIV tests performed are on men and 40% of men living with HIV are on ART. In Tanzania, 19% fewer men living with HIV know their status, 7% fewer use ART and 6% fewer are virally suppressed compared to women. The Sauti project is a PEPFAR/USAID-funded HIV combination prevention project providing outreach services to high-risk individuals in 14 regions of Tanzania. Biomedical services provided to men include HIV testing, linkage to care and treatment, screening for STIs and TB, alcohol and drug screening and provision of condoms. Male Sauti beneficiaries are male partners of female sex workers (PFSW), other men (OM) who visit hotspots for HIV such as bars and brothels, and men having sex with men (MSM).

**Methods:** Sauti project collect data through clinical intake forms, de-identifies and uses for project analysis. We conducted multi-variable regression analysis to identify factors associated with testing HIV-positive on men, with categories PFSW, OM and MSM. Data analyzed was from October 2017 to June 2018.
Results: 268,842 men were tested for HIV (n=183,936 PFSW; n=81,274 OM and n=3,632 MSM) with 3.1% testing positive (5.2% among 35+ years and 2.1% below 35). HIV infection rates were higher among men age 35+ (3.4% among men who they thought they were HIV negative or didn’t know their status and 5.6% newly HIV infected), compared to 1.4% and 2.1% respectively, among men <35. PPSW were 1.56, (1.48-1.64) times more likely to test positive compared to OM, and MSM were over twice as likely (2.20, [1.84-2.63]). Behavioral and biomedical factors increasing likelihood of testing HIV positive: inconsistent condom use (1.70, [1.58-1.82]), and self-reported uncircumcised (1.62, [1.54-1.69]).

Conclusion: While the majority of men reached with HTS were < 35 years, a much higher proportion of men 35+ tested positive. Presumably testing the same number of older compared to younger men could have resulted in 4,526 more HIV positive men being identified and linked to treatment. Our findings support a targeted approach to creating demand among older men for HTS, and providing targeted services to men promoting condom use and circumcision. Findings were also consistent with other studies showing MSM to be at highest risk of HIV infection, and thus in need of targeted test and treat services.

Table 1. Factors associated with testing HIV positive for high-risk men reached through outreach program

<table>
<thead>
<tr>
<th>Age</th>
<th>Total</th>
<th>Tested HIV, n (%)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age below 35 years</td>
<td>1,812,464</td>
<td>56.33 (%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Age 35+ years</td>
<td>843,793</td>
<td>45.18 (%)</td>
<td>1.40 (1.30-1.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male beneficiary category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other high risk (men attending hot spots)</td>
<td>863,974</td>
<td>220.64 (%)</td>
<td>1.70 (1.58-1.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partners of female Sex Workers (PPSW)</td>
<td>83,936</td>
<td>29.68 (%)</td>
<td>1.84 (1.70-2.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men who have sex with men (MSM)</td>
<td>362</td>
<td>4.26 (%)</td>
<td>1.72 (1.27-2.34)</td>
<td>0.006</td>
</tr>
<tr>
<td>Self-reported circumcision status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,690,653</td>
<td>50.41 (%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>27,794</td>
<td>49.59 (%)</td>
<td>1.0 (0.95-1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Known sexual partner HIV status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,636</td>
<td>42.92 (%)</td>
<td>1.64 (1.55-1.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>353,864</td>
<td>57.08 (%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Self-reported consistent condom use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,685</td>
<td>52.92 (%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>27,627</td>
<td>47.08 (%)</td>
<td>1.0 (0.95-1.05)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

843 HIV EPIDEMIC POTENTIAL IN SEXUAL NETWORKS OF MSM IN SAN FRANCISCO AND ATLANTA

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Background: Population-level HIV transmission dynamics depend on the potential speed through which HIV may circulate, which is a function of the connectivity of sexual partnership networks. Sexual network features are often characterized by cross-sectional measures such as concurrency or demographic mixing patterns, but they do not quantify the epidemic potential of HIV through a network over time. Temporal measures of connectivity in high-risk populations are needed to estimate the potential for future HIV outbreaks and optimize control efforts.

Methods: We compared the forward reachable path (FRP) of men who have sex with men (MSM) in San Francisco (SF) and Atlanta (ATL). The FRP measures the maximum number of men each MSM can reach directly, through his own partners, and indirectly, through partners of partners. Empirical data were from ART-Net, a cross-sectional study of 2176 MSM in the US, aged 15–65. Recent partnerships were categorized as main, casual (ongoing, but shorter than main), and one-time. We fit temporal exponential random graph models for each partnership type from these data. Complete MSM networks predicted from these models were simulated for 5 years. The FRP was calculated at bimonthly intervals, by city and partnership type.

Results: Across all partnership types, the median 5-year FRP was 0.988 in SF and 0.998 in ATL. In SF, a 50% FRP was achieved by week 2, whereas in ATL this took 5 weeks. This high temporal connectivity was largely driven by one-time partnerships: a 50% FRP was met through one-time partnerships within 2.5 years in ATL and in 0.9 years in SF. In casual partnerships, the 5-year FRP in ATL never reached 50% (median FRP: 3.8%), but in SF a 50% FRP was met within 4.5 years, with a median 5-year FRP of 61.1%. The median FRP for main partnerships was <0.01% in both cities.

Conclusion: MSM in SF have higher FRPs, than do MSM in ATL, suggesting a greater epidemic potential in SF. However, SF and ATL have a similar HIV prevalence (22% and 24% in SF and ATL, respectively). Factors like differences in the use of HIV PrEP may differentially mitigate the effects of temporal network connectivity. One-time partnership networks, characterized by a high degree and short partnership duration, reached 50% of the population much faster than casual partnership networks. Focusing prevention efforts on casual partnerships, and among those with a high predicted FRP across partnerships, could be an effective disease control approach given currently available empirical data.

844 TRENDS IN HIV RISK BEHAVIORS OF HISPANIC MEN WHO HAVE SEX WITH MEN IN 19 US CITIES

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Background: In 2015, Hispanics/Latinos accounted for about 25% of all new diagnoses of HIV in the US where a large proportion of those cases were among Hispanic men who have sex with men (MSM). However, risk behaviors among Hispanic MSM can vary by nativity status (i.e., location of birth and length of time in U.S.). We conducted a trend analysis to assess differences in HIV risk behaviors among Hispanic MSM within the continental U.S. by nativity status and acculturation using the National HIV Behavioral Surveillance (NHBS) system.

Methods: MSM aged ≥ 18 years were sampled at venues in 19 U.S. cities, during 2011, 2014, and 2017. Analysis was limited to MSM who reported having ≥ 1 male sex partner within the past 12 months. Poisson regression with generalized estimating equations and clustered on recruitment event and city were conducted to assess changes in risk behaviors over time by nativity status, defined as being born in the continental U.S or not, and acculturation among foreign-born, defined as residing in the U.S. more than 5 years. Estimates were adjusted for age and self-reported HIV status. Outcomes include condomless anal sex (CAS) and receiving a diagnosis of a sexually transmitted infection (STI) within the past 12 months.

Results: Hispanic MSM, there was an increase in condomless anal sex (63% to 74% (p < 0.001)) and receipt of an STI diagnosis (11% to 21% (p < 0.001)) across 19 U.S. cities. In 2015, Hispanics/Latinos accounted for about 25% of all new diagnoses of HIV in the US where a large proportion of those cases were among Hispanic men who have sex with men (MSM). However, risk behaviors among Hispanic MSM can vary by nativity status (i.e., location of birth and length of time in U.S.). We conducted a trend analysis to assess differences in HIV risk behaviors among Hispanic MSM within the continental U.S. by nativity status and acculturation using the National HIV Behavioral Surveillance (NHBS) system.

Methods: MSM aged ≥ 18 years were sampled at venues in 19 U.S. cities, during 2011, 2014, and 2017. Analysis was limited to MSM who reported having ≥ 1 male sex partner within the past 12 months. Poisson regression with generalized estimating equations and clustered on recruitment event and city were conducted to assess changes in risk behaviors over time by nativity status, defined as being born in the continental U.S or not, and acculturation among foreign-born, defined as residing in the U.S. more than 5 years. Estimates were adjusted for age and self-reported HIV status. Outcomes include condomless anal sex (CAS) and receiving a diagnosis of a sexually transmitted infection (STI) within the past 12 months.

Results: Among Hispanic MSM, there was an increase in condomless anal sex (63% to 74% (p < 0.001)) and an STI diagnosis (11% to 21% (p < 0.001)) from 2011 to 2017. Trends in CAS and STI by nativity status are shown in the figure. Increases in CAS were significant among U.S. born (61% to 74% (p < 0.01)) and acculturated foreign-born Hispanic MSM (60% to 73% (p < 0.001)). An increase in STI diagnosis was significant among U.S. born Hispanic MSM (11% to 23% (p < 0.001)).

Conclusion: While CAS increased overall and in U.S.-born and acculturated participants, the increase in STI diagnosis was only significant among U.S.-born MSM. These results suggest sexual risk among Hispanic MSM may vary by experiences within the U.S. and mechanisms for STI transmission by nativity, even after adjusting for age and HIV status. Further research is needed to better understand how changes in sexual risk associate with changes in STIs differently by nativity status. However, HIV and STI prevention strategies for Hispanic MSM...
should recognize nativity status as an important factor in the lives of Hispanic MSM and consider tailored approaches.

**SUBSTANTIAL UNMET NEED FOR PrEP AMONG MSM IN HANOI**

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1CDC Hanoi, Hanoi, Vietnam, 2Hanoi Medical University, Hanoi, Vietnam, 3Hanoi City University of Medicine and Pharmacy, Hanoi, Vietnam, 4Kirby Institute, Sydney, NSW, Australia

**Background:** Despite increasing HIV burden in MSM in Vietnam, PrEP is not publicly available. We describe the unmet PrEP need among Hanoi’s MSM using data from the Health in Men (HIM)-Hanoi Study.

**Methods:** HIM-Hanoi is an ongoing, observational cohort study of sexually active MSM aged ≥16 years. The first wave was recruited via time-location sampling based on comprehensive mapping of MSM venues and enrolled from 7/17-12/17. We analyzed baseline demographic, behavioral, and bacterial STI testing data of the 720 MSM who tested HIV negative to identify those having at least one 2017 CDC recommended indication for PrEP. Weighted, stratified analysis was performed, taking into account variability of the venue size and selection probability. Six month follow-up data were used to identify MSM who seroconverted.

**Results:** Mean age was 24.3 years [22.9-25.8], and most were employed (93.7% [88.3-96.7%]). Nearly three-quarters of MSM accessed through venues in Hanoi (93.7% [88.3-96.7%]). Over half (53.7% [46.6-60.7%]) endorsed condomless anal intercourse (CAI) in the last six months. Few had recent injection drug use (2.1% [1.0-4.5%]) or a HIV-positive partner (4.4% [2.3-8.4%]). History of bacterial STI was reported by 15.3% [10.4-21.9%]; positive STI testing at baseline was common (38.1% [31.8-44.9%]). In all, 71.6% [65.9-79.7%] had at least one PrEP indication; 35.1% [28.7-42.1%] had two or more. CAI was the most common indication (48.7% [41.8-55.7%], followed by previous or current STI (42.9% [36.1-50.0%]). Of 432 with six month follow-up data, 163 (37.9%) MSM seroconverted; 138 (31.3%) of these had at least one PrEP indication at baseline.

**Conclusion:** Nearly three-quarters of MSM accessed through venues in Hanoi have an indication for PrEP, indicating a substantial unmet need. In addition to urgent PrEP scale-up, efforts to reduce CAI and address STIs are critical for effective HIV prevention in this population.

**RISK FACTORS FOR HIV INFECTION AMONG MSM IN THE ANRS IPERGAY PrEP TRIAL**

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In the ANRS IPERGAY trial, on demand pre-exposure prophylaxis (PrEP) has been demonstrated to be highly effective in preventing HIV infection among men who have sex with men (MSM). We aimed to identify MSM who would benefit the most from PrEP by assessing baseline risk factors for HIV infection in this population.

**Methods:** We analyzed baseline data from participants enrolled in the placebo arm of the ANRS IPERGAY trial or infected between pre-enrollment and baseline, and who completed the online questionnaire. We analyzed socio-demographic characteristics, past use of psychoactive substances and sexual behavior as risk factors for HIV infection. HIV incidence rate ratios (RR) were estimated with their 95% Confidence Intervals (CI). Results are reported in the table.

**Results:** 203 MSM were included in this analysis, with a median age of 34 years (IQR: 29-42). Overall, 16 HIV infections occurred during a median follow-up of 9 months (IQR: 5-20). The number of sexual partners in prior 2 months (≥10 vs. <10) and the number of condomless receptive anal sex episodes in prior 12 months (≥6 vs. <6) were associated with a significantly increased risk for HIV infection (RR: 3.3; 95%CI [1.1-9.9] and RR: 3.3; 95%CI [1.1-10.2] respectively), whereas those with mostly insertive sexual practices were at lower risk (RR: 0.1, 95%CI: 0-0.6). A diagnosis of bacterial STI at baseline was not significantly associated with an increased risk. Participants who met casual partners in backrooms/sex-clubs or in private sex-parties were also at increased risk for HIV infection (RR: 3.9; 95%CI [1.1-26.8] and RR: 2.9; 95%CI [1.1-9.5] respectively).

**Conclusion:** MSM who have frequent condomless receptive anal sex, multiple partners met in backrooms/sex-clubs or in private sex-parties, or use drugs for sex should be particularly targeted in prevention programs in particular if they live in an area with a high prevalence of HIV infection.

**IMPROVED DETECTION OF ACUTE HIV IN THE UNITED STATES, 2012-2017**

Laurie Linley1, Richard M. Selik2, Kevin P. Delaney2, Alexandra M. Oster3, CDC Atlanta, GA, USA

**Background:** Timely detection of acute HIV infection (AHI) can lead to earlier treatment and prevent further transmission. In June 2014, CDC recommended use of a laboratory HIV diagnostic testing algorithm that facilitates detecting AHI. We used laboratory data reported to the National HIV Surveillance System to examine trends in and demographic associations with diagnosis of AHI.

**Methods:** We analyzed data from persons at least 13 years old with HIV diagnosed in 2012-2017 and reported through June 2018. Infections were classified as acute if there was a negative or indeterminate HIV-1 antibody test ≤60 days after the first confirmed positive HIV-1 test, or a negative/indeterminate antibody test or qualitative HIV-1 nucleic acid test (NAT) ≤180 days before the first positive test, if the first positive test was a NAT or detectable viral load. To accommodate reporting delay, for assessing the trend in detecting AHI, we examined data from 2012-2016. Data from 2015-2017 were used to assess characteristics associated with AHI.
Results: From 2012 to 2016, while the annual numbers of HIV diagnoses remained stable, the percentage of those that were classified as acute at diagnosis increased from 1.3% (353 of 40,939) to 4.0% (1,563 of 39,459). Preliminary 2017 data show that 3.9% were AHI (1,484 of 38,182). Of the 117,465 cases diagnosed during 2015–2017, 4,251 (3.6%) were AHI. AHI was associated with all demographic characteristics examined (P<0.0001). The percentage of persons whose HIV infection was acute at diagnosis was higher among those who were white, Hispanic/Latino, or other race, aged 13-24 years, or had HIV infection attributable to both male-to-male sexual contact and injection drug use or male-to-male sexual contact alone, or when diagnoses were made in emergency departments, STD clinics, or inpatient settings (Table).

Conclusion: The increase in the percentage of persons with AHI diagnosed from 2012 to 2017 suggests that implementation of the recommended laboratory HIV testing algorithm has enhanced the ability to identify AHI in surveillance data, although increased testing early in infection may have played a role as well. Health departments should ensure complete and accurate collection of laboratory data and prompt recognition of AHI to prioritize follow-up and optimize opportunities for treatment and prevention.

Table. Number and demographic distribution of acute HIV infections among persons aged ≥13 years with diagnosed HIV, National HIV Surveillance System, 2015-2017

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>No. of AHI Infections (Row %)</th>
<th>No. of HIV Diagnoses (% of Total)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black/African American</td>
<td>1,575 (52.2)</td>
<td>51,183 (41.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>1,141 (40.1)</td>
<td>26,865 (24.8)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1,127 (41.0)</td>
<td>30,212 (24.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>276 (4.0)</td>
<td>6,075 (5.0)</td>
<td></td>
</tr>
</tbody>
</table>

Results:

- From 2012 to 2018, the annual percentage change (EAPC) in the probability of receiving a diagnosis within 12 months of acquiring HIV infection was estimated using the CD4 depletion model. We then estimated the probability of receiving a diagnosis during the previous year of acquiring infection over a six-year period (2010-2015) period. Trends were assessed overall and by age at diagnosis, race/ethnicity, transmission category, and region of residence at diagnosis.

Conclusion:

Diagnosis of HIV infection soon after acquisition is important for preventing transmission and improving clinical outcomes. Data on time from HIV infection to diagnosis can be used as an indicator of success of testing programs.

Methods:

- We used National HIV Surveillance System data reported through 2018 to estimate HIV incidence and number of diagnoses among persons with recent infection (<=12 months) in each year from 2010-2016 using the CD4 depletion model. We then estimated the probability of receiving a diagnosis within 12 months of HIV infection and assessed trends, using estimated annual percentage change (EAPC), in the probability of receiving a diagnosis within 12 months of infection over a six-year (2010-2015) period. Trends were assessed overall and by age at diagnosis, race/ethnicity, transmission category, and region of residence at diagnosis.

Results:

- During a median follow-up of 3.4 years, 786 (9.8%) of 8,021 participants were diagnosed with ≥1 STI episode; of these, 314 (39.9%) had ≥2 STI episodes. The overall STI incidence rate was 5.2 per 100 person-years (95% CI: 4.7, 5.7) and increased from 2012: 3.5 (2.9, 4.2) to 2017: 5.8 (5.1, 6.6) (Figure). The STI incidence rate was highest (p<0.001) in the following groups: age 18-34: 15 (14.0, 16.1), transgender women: 11.4 (9.0, 14.4), Hispanic ethnicity: 11.1 (9.5, 13.0), and men who have sex with men: 10.6 (10.0, 11.2). Among patients with ≥1 STI episode, 13.3% had VL >1500 copies/mL within one month of STI diagnosis. Among sub-groups, this rate was: 18.7% with VL >1500 among those aged 18-34, 21.5% among cis-gender women, 16.2% among non-Hispanic Blacks, and 18.6% among heterosexuals. Among those with ≥1 STI episode, 33.8% spent some proportion of time with VL >1500 over the period of observation, and median cumulative HIV viral load copy-years was 1.62 (IQR: 0.75, 2.50).

Conclusion:

An increase in STIs over time was observed among PLWH enrolled in the DC Cohort, consistent with national trends. Triangulation of measures of uncontrolled HIV virus over time, such as “time above 1500” and viral load copy-years, provide improved understanding of HIV transmission risks. Public health interventions should focus on reducing transmission risk and optimizing HIV outcomes in the groups at highest risk for STIs.
850 **INFLUENCE OF HIV AND PrEP USE ON HIGH STI PREVALENCES IN MSM IN GERMANY, 2018**

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**Background:** Men who have sex with men (MSM) are disproportionally affected by sexually transmitted infections (STI). Asymptomatic STI can delay diagnosis and treatment. HIV-positive (HIV+) MSM often show even higher STI prevalence. Approval of HIV pre-exposure prophylaxis (PrEP) in Germany in 2016 might have influenced sexual behavior and STI prevalence of HIV-negative (HIV-) MSM. Our aim was to estimate STI prevalence and risk factors amongst MSM in Germany and compare it systematically by HIV status to plan effective interventions.

**Methods:** We conducted a nationwide, cross-sectional study between 20th February and 2nd July 2018. Thirteen MSM-friendly STI-clinics systematically screened MSM for Chlamydia trachomatis (CT), Mycoplasma genitalium (MG), Neisseria gonorrhea (NG), and Trichomonas vaginalis (TV) using self-collected rectal and pharyngeal swabs, and urine samples. TMA-based APTIMA® STI-assays were used. We collected information on sociodemographics, HIV-status, clinical symptoms, sexual behavior of the last 6 months and PrEP use. We combined HIV status and PrEP use for defining risk groups, and used multivariate logistic regression to identify risk factors for STI.

**Results:** 2,303 MSM were included: 50.5% were HIV+, median age was 39 years (range 18-71). Median number of male sex partners was 5 (range 0-820). 57.4% reported unprotected receptive anal intercourse (URAI), and 34.9% use of party drugs. 25.8% had a STI history, 32.1% of STI+ MSM reported clinical symptoms. 24.8% (283) of HIV- MSM reported PrEP use. Overall STI prevalence was 25.0% in HIV-/PrEP- MSM (CT: 7.2%; MG: 14.2%; NG: 7.4%; TV: 0.0%), 40.3% in HIV-/PrEP+ MSM (CT: 13.8%; MG: 19.4%; NG: 14.9%; TV: 0.4%), 30.8% in HIV+ MSM (CT: 10.1%; MG: 18.4%; NG: 8.6%; TV: 0.1%). Independent risk factors were HIV/PrEP-status, having >5 sex partners, URAI, and use of party drugs.

**Conclusion:** We found a high STI prevalence in MSM in Germany, especially in PrEP users. A high proportion of STI+ MSM was asymptomatic. Higher STI prevalence in PrEP users than in HIV+ MSM could partly be explained by differences in risk behavior. As a relevant proportion of PrEP users will not use a condom while using PrEP, comprehensive and highly frequent STI screening is essential and should be available free of charge for PrEP users, which will be introduced in Germany shortly. This will facilitate early treatment and thereby reduce further spread. Counselling of PrEP users should address condom use and risk factor party drugs.

**Table 1:** Multivariate logistic regression model for diagnosis of at least 1 STI (adjusted for age, city of clinic, unsymptomatic STI)

<table>
<thead>
<tr>
<th>Risk group (ref.: HIV+/PrEP+)</th>
<th>Odd’s ratio</th>
<th>lower limit 95%</th>
<th>upper limit 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+/PrEP+</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>1.5</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>HIV-</td>
<td>1.6</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Sex partner &gt;5 (ref. no)</td>
<td>1.4</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Unprotected receptive anal intercourse (URAI, ref. no)</td>
<td>1.6</td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Use of party drugs (ref. no)</td>
<td>1.7</td>
<td>1.4</td>
<td>2.4</td>
</tr>
</tbody>
</table>

851 **WHY STIs ARE INCREASING IN AT-RISK BOSTON MEN: MORE SCREENING PLUS**

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**Background:** Since the advent of HAART and PrEP, STI rates have increased in high risk men. However, it has not been clear if these increases were due to increased routine screening of HIV+ and PrEP patients, or due to increasing STI prevalence, or both.

**Methods:** Participants (Pts) were born male and were seen for ≥ 1 medical visit at a Boston health center specializing in HIV care between 2005 and 2015. Pts contributed person-time to any year in which a medical visit occurred. Gonorrhea (GC) or Chlamydia (CT) tests in different sites on the same day were considered 1 test in calculating the screening (S) and diagnoses (D) rates. We calculated the test-positivity rate (D/S; # positive tests / # tests), S rate (tests / 1,000 person-years) and diagnosis rate (positive tests / 1,000 person-years) adjusted for age, insurance status, sexual orientation, age, and year.

**Results:** Between 2005 and 2015, 19,232 men had at least 1 clinic visit. Most (72.4%) were white; 60% were black, and 6.1% were Latino. Almost half self-reported as gay (42.6%) or bisexual (3.2%). Most had private health insurance (61.7%); 5.4% had Medicare, 4.6% had Medicaid, and 8.4% reported no insurance. Between 2005 and 2015, the overall STI diagnosis rate increased more than 7-fold for GC and 4-fold for CT (see Figure). In 2005, there were 10 GC and 25 CT diagnoses per 1,000 person-years, compared to 73 and 106 in 2015, respectively. Among HIV- men, the GC diagnosis rate was 8 per 1,000 person-years in 2005, 14 in 2010, and 69 in 2015, and 19, 27, and 95 for HIV+ men during the same time, with comparable increases for CT. The adjusted GC screening rate per 1,000 person years went from 386 in 2005 to 702 in 2010 to 1,244 in 2015 for HIV- pts, and from 646 to 861 to 1,231 for HIV+ pts in the same years. CT screening also increased. GC test positivity rate increased significantly between 2005 and 2015, but the CT test positivity rate only increased between 2010 and 2015. In 2015, the GC D/S was 4.8% for HIV- pts who were not using PrEP, 6.8% for PrEP users, and 7.7% for HIV+ pts; the CT D/S was 7.3%, 10.8%, and 10.4% for the respective groups.

**Conclusion:** Over the decade since 2005, both GC screening rates and test positivity increased significantly in at-risk Boston men with similar trends in CT since 2010, suggesting increasing community disease burden. Test positivity rates were highest among HIV+ and PrEP patients, underscoring the need for routine bacterial STI screening for at risk men.
Melbourne, Australia
sexual and gender diversity of users. Of existing prevention and service models that may fail to distinguish between addressing this population. Providers should reconsider the appropriateness of surveys directly

**Results:** Among 618 recruits, 522 (84.5%) identified as cisgender men, 86 (13.9%) trans-feminine & 4 (0.7%) trans-masculine (6 missing). Compared to cisgender GBMSM, trans-feminine and trans-masculine persons (TP) were more likely never to have sex with men (GBMSM), hampering the articulation of sexual health needs and responses specific to TP.

**Methods:** The TRANSFORM study enrolled TP and GBMSM via respondent-driven sampling in Nairobi, 2017. Eligibility criteria: age 18+, male at birth/currently, Nairobi residence and consensual intercourse with a man in the last year. Participants completed a computer-assisted survey including sexual risk behaviour and HIV/STI testing & treatment history. Gender identity was elicited by a piloted two-step method recording natal sex and current identity. Participants tested for HIV, HIV viral load and anogenital gonorrhoea and chlamydia (Xpert® CTNG urine and rectal swab). Frequency measures, and multivariable logistic and ordinal regression analyses were weighted using the RDS-II method.

**Results:** Among 618 recruits, 522 (84.5%) identified as cisgender men, 86 (13.9%) trans-feminine & 4 (0.7%) trans-masculine (6 missing). Compared to cisgender GBMSM, trans-feminine and trans-masculine persons (TP) were more likely than cisgender GBMSM to be HIV positive (39.9 v 24.6%), have tested for HIV (15.0 v 6.8% p=0.035). Among HIV negative participants, 90-90-90 indicators were poorer for TG (63-81-82) than cisgender GBMSM (73-84-83; not statistically significant p=0.333). TP persons in Nairobi have a higher burden of HIV and rectal gonorrhoea, report higher sexual risk behaviour yet have lower uptake of HIV testing than GBMSM in the same setting. Future research should assess wider sexual and reproductive health needs specific to TP in surveys directly addressing this population. Providers should reconsider the appropriateness of existing prevention and service models that may fail to distinguish between sexual and gender diversity of users.

**Conclusion:** TP persons in Nairobi have a higher burden of HIV and rectal gonorrhoea, report higher sexual risk behaviour yet have lower uptake of HIV testing than GBMSM in the same setting. Future research should assess wider sexual and reproductive health needs specific to TP in surveys directly addressing this population. Providers should reconsider the appropriateness of existing prevention and service models that may fail to distinguish between sexual and gender diversity of users.
ANTIBIOTIC USE AND VAGINAL DISCHARGE SYNDROME BY HIV STATUS IN PREGNANCY: BOTSWANA

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Background: High prevalence of vaginal discharge syndrome (VDS), a clinical diagnosis which may include both non-specific vaginal discharge and sexually transmitted infections (STIs), has been reported among pregnant women in Africa, including in Botswana. We set out to determine whether VDS prevalence or antibiotic treatment differed by maternal HIV status, CD4 cell count, and antiretroviral treatment (ART) use.

Methods: We abstracted pregnancy management data from obstetric records for all women who delivered at 8 large government hospitals in Botswana as part of the Tsepamo Birth Outcomes Surveillance Study. Data included diagnoses made in pregnancy (including VDS and specific STIs when available), antibiotic treatment prescribed, and maternal HIV status. Comparisons were made using Chi-squared analysis on SAS.

Results: Between Aug 2014–May 2018, 91383 women delivered at 8 surveillance sites and 91313 (99.9%) had information on maternal diagnoses in pregnancy. VDS was the most common diagnosis, occurring in 28296 (31.0%) of all pregnancies. Antibiotics were prescribed in 35258 (40.1%) of all pregnancies including in 25596 (90.5%) women diagnosed with VDS. Of 23265 women diagnosed with VDS as their only infection, 18509 (79.6%) were prescribed ceftriaxone, 11723 (50.4%) were prescribed metronidazole, 15317 (65.9%) were prescribed erythromycin/azithromycin, and 9518 (40.9%) were prescribed doxycycline. Among all pregnancies including in 25596 (90.5%) women diagnosed with VDS, 85.5% of cases were male, among whom 55.7% identified themselves as men who have sex with men. The most common ophthalmologic diagnoses in cases were panuveitis (44.3%), optic neuritis (19.1%), and retinitis (18.3%).

Conclusion: Vaginal discharge syndrome is the most common diagnosis among all HIV-positive and HIV-negative pregnant women in Botswana, and the most frequent reason for antibiotic use in pregnancy. Initial univariate analyses suggest that ART started prior to conception may reduce the prevalence of VDS among HIV-infected women.

INCIDENT INFECTION IN HIGH-PRIORITY HIV MOLECULAR TRANSMISSION CLUSTERS

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Background: CDC routinely analyzes HIV sequence data to identify priority clusters exhibiting recent and rapid transmission. Prevention efforts for clusters can include improving viral suppression among persons with diagnosed infection and finding undiagnosed infections; the relative importance of these two aims is unknown. We retrospectively identified priority clusters and determined the extent to which future, incident infections in these clusters were associated with presence of cases that, at the time of cluster prioritization, were diagnosed and virologically undiagnosed.
Methods: Using HIV-1 pol sequences reported to the U.S. National HIV Surveillance System for 6 states with ≥50% sequence data completeness for diagnoses during 2010–2017, we used HIV-TRACE to identify priority clusters among cases diagnosed in 2010–2012 (i.e., pairwise distance ≤0.005 substitutions/site; ≥3 cases diagnosed in 2012). We then identified cases diagnosed through 2017 that were genetically linked to these clusters, representing cluster growth in the 5 years after prioritization. We performed Bayesian molecular clock phylogenetic inference in BEAST on each cluster to estimate the number of 2013–2017 diagnoses that were incident infections (i.e., internal nodes after 2012) and prevalent, undiagnosed infections (i.e., internal nodes in or before 2012). For cases diagnosed in or before 2012, we determined viremia (i.e., viral load ≥200 copies/ml at last lab in or before 2012). These counts were treated as predictors in a cluster-level multivariable logistic regression analysis with incident infection as the outcome.

Results: Of 116 priority clusters (initial size: 3–33 persons), 76 gave rise to ≥1 incident infection after 2012 based on phylogenetic inference. Among priority clusters, both undiagnosed infections and diagnosed, viremic cases were independently and equally associated with incident cluster growth in the following 5 years: odds of cluster growth increased by 57% for each additional viremic person (adjusted odds ratio = 1.57, p = 0.010) and 51% for each person with undiagnosed infection (adjusted odds ratio = 1.51, p = 0.019).

Conclusion: These findings suggest that new infections in priority clusters originate equally from diagnosed, viremic cases and undiagnosed infections.

857 MOLECULAR SURVEILLANCE AS A MEANS TO EXPAND AN OUTBREAK INVESTIGATION: MA, 2015-2018

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Background: In mid-2016, the Massachusetts Department of Public Health (MDPH) identified increased HIV diagnoses among persons who inject drugs (PWID) in northeastern Massachusetts (NE MA). With CDC assistance, MDPH began an investigation in 2018 to characterize the outbreak and institute further control measures. We describe the contribution of molecular HIV surveillance to case finding and compare characteristics of cases initially determined to be linked through molecular surveillance with those already linked through traditional surveillance and partner services data.

Methods: HIV diagnoses occurring during 01/2015—05/2018 were considered epidemiologically linked to the investigation 1) through residence, homelessness, HIV diagnosis, or HIV care in the cities of Lawrence or Lowell or 2) as a named partner of an investigation case. In 11/2017, MDPH rapidly implemented molecular surveillance; HIV pol sequences for persons in MA with a drug resistance test conducted during 01/2016—05/2018 were reported to MDPH and analyzed with Secure HIV-TRACE to identify molecular clusters using a pairwise genetic distance threshold of ≤1.5%; cases that linked to ≥1 epidemiologically linked case in the investigation were considered molecularly linked. Characteristics of cases initially linked through molecular analysis and already epidemiologically linked cases were compared using Fisher's exact test.

Results: As of 07/11/2018, the investigation included 129 persons, of whom 93 were initially epidemiologically linked. Of 108 investigation cases with a sequence, 96 were molecularly linked to ≥1 other case, forming four clusters of ≥5 cases (range in size: 5–55). Molecular analysis identified 36 persons not previously epidemiologically linked to the investigation; epidemiologic links were later identified for 4 cases. Molecularly linked and epidemiologically linked cases were similar with respect to age (majority aged <40 years), sex at birth (majority male), race/ethnicity (majority white, non-Hispanic), and transmission risk (vast majority with injection-drug-use related risk) (all p-values >0.05).

Conclusion: The presence of multiple molecular clusters among investigation cases suggests multiple introductions of HIV into the PWID community in NE MA, each with sustained transmission. The addition of molecular data expanded the number of persons linked to the investigation by 39%, improving prevention opportunities and highlighting the importance of molecular surveillance in HIV outbreak response.

858 WITHDRAWN / INTENTIONALLY UNASSIGNED

859 WITHDRAWN / INTENTIONALLY UNASSIGNED

860 USING NEAR REAL-TIME MOLECULAR SURVEILLANCE TO INFORM DATA-TO-CARE IN NEW YORK CITY

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Background: Molecular HIV surveillance has been proposed as a tool to augment traditional partner services and data to care (D2C) activities by adding persons with genetically proximate viruses to the pool of named partners and social network members receiving public health intervention after a new diagnosis of HIV.

Methods: The New York City Department of Health and Mental Hygiene conducted a pilot project to demonstrate whether early ascertainment of viral genetic proximity between newly diagnosed and prevalent cases was feasible and resulted in timely identification of and outreach to persons in transmission networks as defined by HIV-TRACE, a genetic distance-based clustering tool. Persons newly diagnosed with HIV at the city’s 8 sexual health clinics (SHC) were the index cases; their partial pol sequences were analyzed for pairwise concordance to those of ≥100 prevalent cases using a 1.5% distance threshold. Clusters were mapped, and cluster members that were out of care for ≥13 months (OOC) or in care but viremic (>1500 copies/mm3) and their viruses immediately proximate to the Index virus were identified and prioritized for assistance with partner services and reengagement in optimal care.

Results: Between June 1, 2016, and June 25, 2018, whole blood specimens from 722 persons testing preliminary positive on point-of-care rapid HIV screening were submitted to the NYC Public Health Laboratory for confirmation and resistance testing, resulting in 526 interpretable genotypes. SHC received resistance reports and sequences were posted a median of 10 days (IQR 8-15) after specimen draw date. Pairwise concordance analysis of the Index virus against the prevalence pool yielded a total of 225 clusters containing 2,778 unique members. Clusters ranged in size from 2-155 persons with diagnosis dates from 1981-2018, of whom 122 (4%) were deemed by surveillance to be currently OOC and 132 (5%) viremic; 91% of cluster members were MSM; clusters were homogeneous with respect to age at diagnosis (median 26) and race/ethnicity but not by neighborhood of residence.

Conclusion: Despite our optimized scenario (genotype ordered on day of diagnosis), cluster data were not available at the time of the Index partner services interview. However, analysis performed as soon as the sequence was posted allowed us to identify and prioritize for outreach previously diagnosed, genetically proximate OOC and viremic cluster members on a monthly basis, making it possible to achieve “near real-time” D2C for genetic partners.

861 MAPPING GROWTH OF LARGE TRANSMISSION NETWORKS USING DIFFERENT CLUSTERING ALGORITHMS

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Background: Phylogenetic surveillance of the HIV epidemic amongst Men having Sex with Men (MSM) has revealed that large transmission networks (20+ infections/cluster) rose from 13% of new infections in 2004 to 49% of infections in 2016 in Quebec. Identifying and responding to these “active” transmission hubs in close to real-time will have the greatest impact in controlling the epidemic.

Methods: First genotypes were obtained from treatment-naive MSM (n=4029) and heterosexual/intravenous drug user (IDU) (n=1072) groups having subtype B HIV-1 infections, as well as non-B subtype groups (n=1248). Unique non-nominative patient identifiers were assigned based on putative cluster group association, ascertained by Maximum likelihood (ML) methodology (high bootstrap support >97% and short genetic distance <0.015). Growth trajectories dynamics of 40 individual large transmission networks (20+
between individuals, resulting in a more accurate assessment of risk. Relative to logistic regression of phylogenetic cluster membership, this method has the added benefit of resolving finer differences in transmission activity.

**Conclusion:** In this study, we compared the sensitivity and accuracy of different phylogenetic based methodologies in estimating transmission linkage and mapping epidemic growth in close to real-time. While several cluster-based algorithms can identify "actively" growing transmission hubs, resolving the linkage of individual members within clusters will require further optimization to maximize accuracy.

### 862 EPIDEMIOLOGIC CORRELATES OF HIV LINEAGE LEVEL DIVERSIFICATION RATE

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**Background:** Identifying risk factors and other epidemiological correlates of HIV transmission can inform the prioritization of health care services to specific groups. Typically transmission clusters are inferred based on genetic distance thresholds, then logistic regression is conducted to evaluate patient characteristics that are significantly associated with the probability of membership in an active transmission cluster. This method is limited in that not all individuals within a cluster are treated as equally active transmitters, although in reality there is a range of transmission activity within a cluster. We introduce an alternative method to investigate risk factors associated with transmission in British Columbia (BC), Canada, based on the phylogenetically estimated viral diversification rate.

**Methods:** For 8,103 people living with HIV (PLHIV) in BC in March 2018, we recovered the oldest available HIV protease and RT sequences from the BC Centre for Excellence in HIV/AIDS database. Following alignment and removal of known drug resistance sites, we inferred 100 bootstrap approximate maximum likelihood phylogenetic trees in FastTree2.1 and then time-scaled the trees using Least Squares Dating. For each tip on each bootstrap tree, we calculated the lineage level phylogenetic diversification, which provides a proxy for transmission rates. The average diversification rate of all 100 trees for each tip was taken. We then built a generalized linear model (GLM) to evaluate patient attributes that were significantly associated with higher diversification rates.

**Results:** Having a high HIV diversification rate was positively associated with being younger, reporting injection drug use, having co-infection with hepatitis C virus, having a high most recent viral load, and residing within the Northern BC Health authority or the Vancouver Coastal Health authority (Table 1). Interestingly, having ever had AIDS and identifying as black were both significantly associated with lower diversification rates (Table 1).

**Conclusion:** By identifying risk factors associated with HIV transmission using the viral diversification rate among PLHIV in BC, we can confidently recommend prioritized provision of treatment and prevention services for these key groups. Relative to logistic regression of phylogenetic cluster membership, this method has the added benefit of resolving finer differences in transmission activity between individuals, resulting in a more accurate assessment of risk.

### 863 GEOSPATIAL DISPERSAL OF HIV-1 TRANSMISSION IN 6 MAJOR CITIES IN GERMANY

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**Background:** Geographic targeting of HIV prevention interventions to the highest risk individuals will increase the impact of these efforts. We combined molecular epidemiology and geospatial analyses to provide insights into the drivers of HIV-1 transmission in the German epidemic.

**Methods:** Sociodemographic, geographic and HIV-1 pol sequence data were collected from newly diagnosed individuals in six cities across Germany between 2001 and 2018. Genetic-distance based molecular network analyses were performed to infer putative transmission links. Similarity between genetically-linked individuals was assessed using the Assortativity Index (AI, i.e. shared attributes). Geospatial dispersal was determined by calculating the average distance between the residences of genetically linked individuals (centroids of 3-digit zip codes).

**Results:** We included data from 1,397 HIV-1 infected ART naïve individuals, of which 289/1,397 (20.7%) were putatively linked, forming 102 transmission clusters (size range: 2-12). The largest clusters (more than 10 individuals) consisted mainly of men having sex with men (MSM) from Cologne, Bonn and Frankfurt. Genetically linked individuals were significantly younger (<25 years of age, p = <0.001), more likely to reside in Bonn and Cologne (p<0.001 and p = 0.044, respectively), and more likely to report MSM as a risk factor (p=0.015). Genetically linked individuals were highly assortative by risk group (AI=0.08, p=0.006), age (AI=0.06, p<0.001), and location (AI=0.08, p<0.001) (Figure 1A), indicating that individuals tended to cluster with other persons of the same age, risk group, and from the same area. Geospatial analyses revealed that the median distance between residences of genetically linked individuals was 78 kilometers (km), significantly lower than the distance of the random sub-
sampled population (median 269 km; p<0.001) (Figure 1B). This suggests that genetically linked individuals tended to be linked with partners within about an hour’s travel time. **Conclusion:** We found evidence that HIV-1 transmission in Germany is between younger MSM living in proximity to each other. This provides further support for real-time monitoring of HIV transmission using molecular epidemiology, which can be leveraged to target specific geographic areas where new transmissions are being observed. Furthermore, this work suggest that HIV prevention efforts targeted towards young MSM may provide the most impact on the German epidemic.

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**864 PRETREATMENT HIV DRUG RESISTANCE SPREAD IN 6 GERMAN METROPOLITAN REGIONS**

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**Background:** Transmitted HIV drug resistance impacts the choice and success of antiretroviral therapy (ART). In Germany, the reported prevalence of transmitted drug resistance mutations (DRM) differs between regions with a maximum of 12.4%. Here, we sought to understand the molecular epidemiology of DRM transmission in Germany, by analyzing data from six major cities with high rates of new HIV diagnoses (ranging from 5.6 to 17.3 per 100,000 inhabitants).

**Methods:** Phylogenetic and genetic network analyses were performed to infer putative transmission links and shared DRMs. Screening for DRM was performed according to the Stanford University Genotypic Resistance Interpretation. We defined a shared DRM as any DRM present in two or more genetically linked individuals (<1.5% genetic distance).

**Results:** We obtained 1,397 HIV pol sequences from HIV-1 ART naïve individuals. The prevalence of any DRM at time of diagnosis was 17.8% (248/1,397 individuals; 31.4% in Hannover, 18.9% in Cologne, 18.8% in Hamburg, 15.3% in Frankfurt, 14.5% in Bonn, 9.1% in Munich). The frequency of any DRM was comparable among risk groups but was highest among men having sex with men (MSM) (138/792, 17.4%). Genetic transmission network analyses showed comparable frequencies of DRM in clustering and not-clustering individuals (16.3% versus 18.1%; p=0.46). Of the 47 sequences harboring DRM in the inferred transmission network, 30 (63.8%) were shared by HIV genetically linked partners, predominantly among residents of Cologne (9/30, 63.6%) and Bonn (7/30, 23.3%). Clustering individuals harboring shared DRMs were more likely than non-clustering individuals to be infected with HIV-1 subtype B (p<0.001), < 25 years of age (p<0.001), and living in Cologne (19/30, 63.3%) and Bonn (7/30, 23.3%) (p<0.001 each) (Figure 1A). The most frequently transmitted DRMs were E138A (11/30 in individuals sharing DRMs, 5 clusters) and K103N (9/30, 4 clusters) (Figure 1B).

**Conclusion:** We observed very high rates of DRMs in newly diagnosed individuals in Hannover, Cologne and Hamburg. Network analysis also revealed frequent cases of shared DRMs among genetically-linked individuals, especially K103N and E138A. Our findings highlight regional differences in transmitted drug resistance, and the necessity to focus prevention efforts on specific areas and risk groups to prevent onward transmission across Germany.

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**865 HIV DYNAMICS IN THE MOST AFFECTED AREA OF EUROPE: A TALE OF 2 COUNTRIES**

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**Background:** In 2016, Latvia and Estonia continued to have the highest rate of new HIV diagnoses in Europe (1.85 and 1.74 per 10000, respectively). Both countries experienced an HIV outbreak among people who inject drugs (PWID) in the early 2000s.

**Methods:** Data from 2000-2016 for persons newly diagnosed with HIV in Latvia and persons newly appearing with HIV in health care registries in Estonia were used in a clinical-stage based back-calculation model to estimate: HIV incidence, time from infection to diagnosis and undiagnosed HIV prevalence. Population size estimates were calculated using national statistics and studies on sexual behavior and drug use. Statistical comparisons were carried out using Mann-Whitney test for incidence and undiagnosed prevalence rates, and using two-sided Kolmogorov-Smirnov test for the distribution of times between infection and diagnosis.

**Results:** In 2016, HIV incidence was twice as high in Latvia than in Estonia (3.5/10000 vs 1.9/10000, p<0.05). Between 2010-2016, HIV incidence decreased in Estonia but increased in Latvia (average annual change of -9.0% and +6.2%, respectively; Table). The incidence decreased for all exposure groups in Estonia and increased for most in Latvia, especially for women and men who have sex with men (MSM). Between 2012-2016, time to diagnosis took longer in Latvia than in Estonia (3.9 vs 3.4 years, p<0.05). In Latvia, getting diagnosed tended to take longer for heterosexual men and MSM than for PWID and heterosexual women (respectively 4.8 and 4.4 vs 3.4 and 3.7 years). A similar trend was observed in Estonia. Undiagnosed prevalence rate was higher in Latvia than in Estonia (4.8 vs 4.4% and 3.4 and 3.7% in Estonia). A similar trend was observed in Latvia. Undiagnosed prevalence rate was higher in Latvia than in Estonia (4.8 vs 4.4% and 3.4 and 3.7% in Estonia). A similar trend was observed in Latvia.
867 CLUSTER SURVEILLANCE OF FRENCH PRIMARY INFECTIONS: TOWARD A MORE VIRULENT CRF02_AG?

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Background: Molecular epidemiology can be used to identify large recent transmission clusters (RTC) and describe core transmitters that fuel a large proportion of transmissions. We analyzed such RTC among primary infected patients (PHI) diagnosed in France in 2014-2016.

Methods: Protease and reverse transcriptase sequences were obtained from 1121 patients included between 2014 and 2016 from 46 centers. Phylogenetic trees were built by approximate maximum likelihood using FastTree to identify RTC (max genetic distance <4.5%, branch support value >95%).

Results: Most patients were men (90%), MSM (70%), born in France (70%), Sub-Saharan Africa (6.6%), infected mostly by B (56%) or CRF02_AG (20%) clades. CRF02_AG tended to be increasingly represented through the years (from 17 to 22%) and large (>3 patients) RTC (Table). Compared to patients infected by subtype B, patients infected by CRF02_AG presented a lower proportion of MSM (59 vs 78%, p<0.001), of individual born in France (67 vs 75%, p=0.02), higher viral loads (VL) (median at 5.83 log10 copies/mL [IQR: 4.96-6.60] vs 5.40 log10 copies/mL [IQR: 4.66-6.26], p=0.004) and lower CD4 cell counts (463 cells/mm3 [25-903] vs 514 [1-1028], p=0.004). When analyzing patients born in France separately, CRF02_AG still presented higher VL than subtype B (5.79 vs 5.42 log10 copies/mL, p=0.004) and lower CD4 cell counts (463 cells/mm3 [25-903] vs 514 [1-1028], p=0.004).

Conclusion: This study highlights the important role of RTC among primary infected patients born in France, suggesting a higher virulence than subtype B. The increasing number of large RTC identified highlights the need for nationwide surveillance and intervention programs to identify and fight these, sometimes massive, local outbreaks.

868 WITHDRAWN / INTENTIONALLY UNASSIGNED

869 NEW GENOMES FROM THE CONGO BASIN EXPAND HISTORY OF CRF01_AE ORIGIN AND DISSEMINATION

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Background: Although the first HIV circulating recombinant form (CRF01_AE) is a predominant strain in many Asian countries, it is uncommon in the Congo basin where it first originated. Therefore, we sequenced CRF01 genomes from Cameroon and the Democratic Republic of Congo (DRC) to characterize the molecular history of CRF01.

Methods: Near complete genomes were sequenced from N=13 specimens previously classified as CRF01 or CRF01-containing recombinants in the gag, pol, and/or env, regions through viral surveillance studies conducted in Cameroon and DRC between 2001-2006. Random primed libraries spiked with HIV specific primers were sequenced on an Illumina HiSeq and genomes were assembled using CLC Bio. Genome sequences were aligned to reference strains, including Asian and African CRF01 sequences, and evaluated by maximum likelihood phylogenetic inference (RAxML), REGA subtyping, PhyMM, Simplot, Signature Visual Analysis, and BLAST. The CRF01_AE evolutionary history was inferred with a Bayesian SkyRide coalescent tree prior under an uncorrelated lognormal relaxed clock assumption using BEAST v1.8.4.

Results: The spiked primer next generation sequencing method produced 8 HIV genomes (8800-9586 nucleotides (nt) long) with full coverage and 5 genomes with 95-98% coverage, which were completed with Sanger sequences. Phylogenetic and recombinant analyses identified 4 pure CRF01, 2 CRF02, 1 CRF27, and 6 unique recombinant form (URFs) genomes (01A|G, 01B|F, 01B|G, 01C|D, 01D|G, 01C|G). All recombinants described in this study included at least 1000 nt long portions classified as CRF01. In Bayesian analysis of the pure CRF01 genomes, three reference CRF01 genomes isolated in the Congo Basin were basal to the Cameroon/DRC clade branch. Molecular dating indicates that the most recent common ancestor of this clade emerged around 1972 (95% Bayesian credible interval (BCI): 1970-1974) in the Congo basin. The Asian expansion of CRF01 started after 1976 (95% BCI: 1975-1978).

Conclusion: Full genome characterization is required to identify pure CRF01 strains since recombination was high amongst strains from the Congo basin. The complex patterns of recombination described here suggest that ancestral CRF01 sequences were circulating in the region within recombinant forms. Corroborating previous reports, phylogenetic analyses with the new pure CRF01 genomes indicated that CRF01 originated in the Congo Basin around 1972 and spread beyond Africa around 1976.

870 PERSISTENT OUTBREAK OF THE HIV-1 CRF19_CPX VARIANT IN TREATMENT-NAIVE MSM PATIENTS

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Background: During the period 2011-2016, the HIV-1 CRF19_cpx variant emerged as an outbreak in newly HIV diagnosed (NHIVD) in southern Spain. Our aim was to determine the current status of this outbreak, analyzing the new
cases of this variant in our area and their epidemiological relationship with the previous ones.

**Methods:** We considered NHIVD at Virgen de la Victoria Hospital, reference center in southern Spain, from 01/17 to 06/18. Drug resistance mutations were determined with Virosel HIV® system and the partial sequence of HIV-1 pol gene provided submitted to REGA v3.0 for subtyping. Sequences assigned as CRF19_cpx subtype were phylogenetically compared to the 254 reference sequences of the same variant retrieved from the LANL, as well as to the 55 ones comprising the already described CRF19_cpx variant outbreak. The alignment was done by Clustal X and the phylogenetic reconstruction inferred by maximum likelihood method (PhyML v3.0 program). The cluster reliability was supported on the value of SH-like aLRT test. The resistance mutations were predicted using Stanford algorithm v7.1.1.

**Results:** 523 resistance studies were performed in NHIVD; 13 (2.4%) had sequences consigned in REGA as subtype CRF19_cpx. All the new cases conformed a very well-defined transmission cluster (aLRT=92%) with the CRF19_cpx sequences from the previous outbreak, already comprising up to 67 patients. Eight of the new sequences were clustering within two subclusters previously defined: E and F, currently including 18 and 3 patients, respectively. We have not found the G190A mutation in any of the new sequences. The new cases of the CRF19_cpx were MSM, with an average age of 32.5 years (IQR: 27.1-43.6) and Spaniards, except one Italian patient. Half of them were seroconverters, mean seroconversion time of 17.0 months, (8.3-81.3). The initial CD4 count was 423 cells/µl (200-562) and viral load was 4.9 log copies/ml (4.6-5.2).

**Conclusion:** All the new cases of the CRF19_cpx variant emerged in our area during 2017 and half this year are phylogenetically clustered with the previous ones.

**Methods:** We considered NHIVD at Virgen de la Victoria Hospital, reference center in southern Spain, from 01/17 to 06/18. Drug resistance mutations were determined with Virosel HIV® system and the partial sequence of HIV-1 pol gene provided submitted to REGA v3.0 for subtyping. Sequences assigned as CRF19_cpx subtype were phylogenetically compared to the 254 reference sequences of the same variant retrieved from the LANL, as well as to the 55 ones comprising the already described CRF19_cpx variant outbreak. The alignment was done by Clustal X and the phylogenetic reconstruction inferred by maximum likelihood method (PhyML v3.0 program). The cluster reliability was supported on the value of SH-like aLRT test. The resistance mutations were predicted using Stanford algorithm v7.1.1.

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**Results:** 523 resistance studies were performed in NHIVD; 13 (2.4%) had sequences consigned in REGA as subtype CRF19_cpx. All the new cases conformed a very well-defined transmission cluster (aLRT=92%) with the CRF19_cpx sequences from the previous outbreak, already comprising up to 67 patients. Eight of the new sequences were clustering within two subclusters previously defined: E and F, currently including 18 and 3 patients, respectively. We have not found the G190A mutation in any of the new sequences. The new cases of the CRF19_cpx were MSM, with an average age of 32.5 years (IQR: 27.1-43.6) and Spaniards, except one Italian patient. Half of them were seroconverters, mean seroconversion time of 17.0 months, (8.3-81.3). The initial CD4 count was 423 cells/µl (200-562) and viral load was 4.9 log copies/ml (4.6-5.2).

**Conclusion:** All the new cases of the CRF19_cpx variant emerged in our area during 2017 and half this year are phylogenetically clustered with the previous ones. This confirmed linkage for 11 (78.6%) of the 14 index-index clusters. 7 indexes was from Vietnam. NGS-env data was available for 14/15 index-index clusters; this confirmed linkage for 11 (78.6%) of the 14 index-index clusters. Individuals were considered to form a transmission cluster if the genetic distance of their sequences was ≤0.015 with ≥90% bootstrap support. HIV strains from participants in pol transmission clusters were also analyzed using next-generation sequencing (NGS, env region). Participants were considered to have linked infections if their env sequences formed a distinct monophyletic cluster with ≥90% bootstrap support.

**Methods:** HPTN 074 enrolled HIV-infected PID (index participants) with up to five concurrent HIV-uninfected injection partners per index. Index-partner pairs were randomized 1:3 to the integrated intervention vs. standard of care study arms. HIV genotyping (pol region) was performed using the ViroSeq-1 HIV Genotyping System for 502 index participants and 7 partners who seroconverted during the study. Phylogenetic analysis was performed using RAxML v8.10.2. Individuals were considered to form a transmission cluster if the genetic distance of their sequences was ≤0.015 with ≥90% bootstrap support. HIV strains from participants in pol transmission clusters were also analyzed using next-generation sequencing (NGS, env region). Participants were considered to have linked infections if their env sequences formed a distinct monophyletic cluster with ≥90% bootstrap support.

**Results:** Pol sequences were obtained for 452/509 HIV-infected participants (445 indexes, 7 seroconverters). Median pairwise genetic distances for sequences from each study site were 2.9%-3.3%; there was no evidence of large discrete subclades at any of the three sites. Linkage results from pol and NGS-env analyses were concordant for all 7 seroconverter cases. The index and partner were linked in 2/7 cases; in addition, two unrelated partners were linked. In addition, 15 index-index clusters were identified that included 36 indexes with ≥2 indexes per cluster (13 pairs, one triplet, one cluster of 7 indexes). Individuals in each cluster were from the same study site; the cluster of 7 indexes was from Vietnam. NGS-env data was available for 14/15 index-index clusters; this confirmed linkage for 11 (78.6%) of the 14 index-index clusters.

**Conclusion:** Analyses of HIV pol and NGS-env sequences revealed linked infections involving index-partner pairs, a partner-partner pair, and index-index groups that included 2-7 individuals. These findings suggest that there are complex patterns of HIV transmission among PWID in these communities, which should be considered when designing interventions for HIV prevention.

**Methods:** Data came from the RADAR cohort study in Chicago as well as the Chicago Department of Public Health surveillance data. Participant plasma samples were collected and pairwise genetic distances of HIV pol sequences obtained from the protease and reverse transcriptase region. Viral genetic sequences ≤1.5% genetically distant defined putative molecular clusters comprising ≥2 persons. Information regarding demographic and HIV risk behavior data were included from each data source while detailed information regarding participant’s sexual networks were obtained from the RADAR study.

**Results:** Among 2977 HIV viral sequences available, 72 clusters contained ≥2 sequences while 23 contained ≥5 sequences (Figure 1). Overall, 424 individuals were identified as members of molecular clusters with 717 total
inferred ties between individuals. The race/ethnicity composition of partners differed significantly from that of RADAR participants in both the molecular clusters and sexual networks (p<0.001). In molecular networks, black and white participants’ partners consisted primarily of other black (83%) and white partners (25%), respectively, while for Hispanics they were more heterogeneous and consisted primarily of Hispanic (39%) and black (38%) partners. In network analyses, significant assortativity was observed with regards to both age (r = -0.20; p-value = 0.026) and year of HIV diagnosis (r = -0.88, p-value <0.001). Additionally, participants who always used condoms in the past six months, compared to those who had condomless sex at least once, had a significantly greater proportion of black partners (73% vs 67%) and a lower proportion of white partners (2% vs 12%).

Conclusion: These results highlight the utility of combining observational cohort and public health data in a multi-tiered approach towards HIV prevention. Further studies would strongly benefit from the combination of these data which have the potential to yield novel targets aimed at reducing HIV incidence.

Figure 1. Inferred HIV molecular clusters among young men who have sex with men in the combined RADAR and CUPHI datasets, limited to those individuals within one degree connection of a RADAR participant (n=424).

873 MOBILITY PATTERNS CREATE DYNAMIC WIDELY DISPERSED RISK NETWORKS IN NAMIBIA
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Background: Namibia has a severe HIV epidemic: prevalence is ~14%. In Namibia, as in other countries in sub-Saharan Africa, the population is highly mobile and the epidemic is generalized. Consequently, individuals may be at risk of acquiring HIV both in their home community (from other residents or from visitors from other communities) or in other communities (from residents of these communities). We use data from mobile phones and the 2013 Namibia Demographic and Health Survey (NDHS) to estimate the risks of HIV acquisition for individuals in their home community and when they travel.

Methods: The mobile phone data were collected between October 2010 and September 2011; the data set is based on 9 billion communications from 1.19 million unique SIM cards. These data were used to calculate a mobility network based on the average proportion of time residents spent in each of the 96 constituencies in Namibia that include cell towers. We coupled this network with demographic data from the 2011 census and HIV-testing data from 7,600 participants of the NDHS. We used the coupled epidemic-mobility network to calculate, for each constituency, the risk of acquiring HIV that was due to sexual contact with other residents (i.e., localized risk), with visitors, or when traveling.

Results: The calculated mobility network is shown in Figure 1. We find significant geographic variation in prevalence: 6%-40% for women, 0%-24% for men. Our network analysis shows that individuals in communities where prevalence is high travel to areas where prevalence is low, and vice versa. We estimate that 60% of the overall risk of acquiring HIV in Namibia is localized, 17% is due to visitors, and 23% is due to travel; notably, 40% of the overall risk is related to mobility. Mobility is more important in some areas than others: it contributes to more than half of the overall risk for women in ~20% of constituencies, and for men in ~10%. Using our epidemic-mobility network and risk metrics, we identify which areas of the country are the most vulnerable to the importation of risk, and which are the most important in disseminating risk.

Conclusion: The HIV epidemic in Namibia is not simply driven by localized transmission; a high level of mobility has created a dynamic, widely dispersed risk network. Our results imply that it may be harder to eliminate HIV in Namibia than currently appears.

874 SPATIAL ANALYSIS TO IDENTIFY EMERGING HOT SPOTS OF MTCT IN ZIMBABWE, 2012-2018
Carolyn A. Fahey1, Sandra I. McCoy1, Aybuke Koyuncu1, Mi-Suk Kang Dufour1, Angela Mushavi1, Agnes Mahomva1, Nancy Padian1, Frances Cowan1, Sally Blower1, & Jessica Jacob2

Background: To inform targeting of services for the elimination of mother-to-child HIV transmission (MTCT) in Zimbabwe, we examined spatio-temporal trends in MTCT from 2012 to 2018.

Methods: We conducted three serial cross-sectional serosurveys of infants (9-18 months old) and their mothers or caregivers (≥16 years old) to assess MTCT and related outcomes. Using a multi-stage sampling strategy, in five of ten provinces we randomly selected 157 of 699 health facilities offering prevention of MTCT (PMTCT) services. Within the catchment area (CA) of each facility, we enumerated infants born 9-18 months prior (alive or deceased) and selected a random sample. A total of 26,882 mother–caregiver-infant pairs were interviewed and tested for HIV in 2012 (n=8,804), 2014 (n=10,404) and 2018 (n=7,678). Global Positioning System (GPS) coordinates were also collected for each facility. We calculated the MTCT rate for the 139 CAs which were included in all three waves and assessed overall temporal changes using a population-averaged model. We then classified changes in MTCT by CA as persistently decreasing (downward trend between each consecutive wave), persistently increasing, or no change/inconsistent direction and assessed spatial trends to identify emerging “hot spots” and diminishing “cold spots”.

Results: Overall, catchment area MTCT declined from 9.7% (2012) to 5.1% in 2014 (-4.5 percentage points (pp); 95% CI: -7.2, -1.9) and to 3.6% in 2018 (-6.1 pp; 95% CI: -8.8, -3.4). However, spatio-temporal analysis revealed
heterogeneity in MTCT trends at various geographic levels. Within catchment areas, MTCT persistently decreased in 44 (31.7%) CAs, however 17 (12.2%) CAs had persistent increases in MTCT and 78 (56.1%) CAs had no change or inconsistent direction of change. By province, the proportion of CAs with increased MTCT was greatest in Harare (3/8, 37.5%) and lowest in Mashonaland Central (2/30, 6.7%) and Manicaland (4/52, 7.7%). Within-province variation was also apparent, for example with clusters of CAs with increasing MTCT evident within provinces such as Manicaland where proportionally few CAs had increasing MTCT (Figure).

Conclusion: While overall trends in MTCT show marked progress toward elimination in Zimbabwe, variability by health facility catchment area supports the need for differentiated strategies at the sub-national level. Spatial analysis provides a useful tool to identify high priority areas for targeted and efficient allocation of PMTCT services.

876 HIV MOLECULAR SURVEILLANCE AND PRETREATMENT DRUG RESISTANCE IN MEXICO CITY
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1University of California San Diego, La Jolla, CA, USA, 2National Institute of Respiratory Diseases, Mexico City, Mexico, 3Clínica Especializada Condesa, Mexico City, Mexico

Background: Non-nucleoside reverse transcriptase inhibitor (NNRTI) pre-treatment HIV drug resistance (HIVDR) has consistently increased in Mexico during the last decade, approaching 10%. Mexico City concentrates a fifth of all persons living with HIV in Mexico and is a main hub for viral dissemination within Mexico. Combining HIV molecular data and epidemiologic information might help to understand HIVDR transmission dynamics.

Methods: HIV pol sequences were obtained by next generation sequencing from 2,447 individuals initiating first-line antiretroviral therapy from 09/2016 to 06/2018 at Condesa Clinic, the largest HIV care provider in Mexico. Pre-treatment HIVDR was estimated using the Stanford Algorithm with a minimum threshold of 20% and 2% to define low-frequency variants. Genetic networks were inferred with HIV-TRACE, establishing putative transmission links with genetic distances <1.5%. Newman’s assortativity coefficients for age and residence of genetically linked individuals were estimated using igraph. Geospatial dispersal was determined by calculating the average distance between centroids of the municipalities of residence of linked individuals.

Results: At 20% threshold, pre-treatment HIVDR reached 14.8% overall and 9.6% to NNRTI. K103N/S was the most frequent surveillance drug resistance mutation (DRM) with 7.1% frequency (7.6% at 2% threshold). Putative links with at least one other sequence were found for 963/2,447 (39%) sequences, forming 99 clusters ranging in size from 2 to 20 individuals (Fig. 1A). Clustering individuals were younger (adjusted odds ratio, aOR=0.96, p<0.0001), included a higher proportion of males (aOR=2.3, p=0.001) and a lower proportion of persons residing outside of the central metropolitan area (aOR=0.11, p=0.003). Among clustering individuals, 175/963 (18%) shared drug resistance mutations at 2% threshold in 66 clusters, with 63/175 (36%) sharing K103N/S in 24 clusters (Fig. 1B). Eight municipalities (out of 75) harboured 65% of persons sharing DRMs (Fig. 1C & 1D). The inferred transmission network was assortative by age and municipality (p<0.001). The residence of genetically linked individuals was closer than expected in a random distribution (median distance: 13 km vs. 65 km, p<0.01).

Conclusion: DRMs (including low-frequency variants) are frequently transmitted in Mexico City metropolitan area, predominantly among recently diagnosed young men in a densely-sampled, geographically assortative network, warranting serious consideration of non NNRTI-based first-line regimens locally.
DETERMINANTS OF HIV DIFFUSION ACROSS MEXICO IDENTIFIED THROUGH SPATIAL EPIDEMIOLOGY

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1National Institute of Respiratory Diseases, Mexico City, Mexico, 2Rega Institute for Medical Research, Leuven, Belgium, 3University of California San Diego, La Jolla, CA, USA, 4University of Leuven, Leuven, Belgium

Background: The HIV epidemic in Mexico is highly complex. It is the result of multiple local but intermingled epidemics shaped by various factors including human migration. Here, we characterized the diffusion dynamics of HIV across Mexico.

Methods: Using a comprehensive data set of HIV-1 subtype B pol sequences sampled across Mexico, we applied a multistep phylogenetic approach: (1) we first performed maximum likelihood phylogenetic inference to identify well-supported monophyletic clades within our dataset; (2) all clades of size ≥ 3 identified in step (1) were used to perform a discrete phylogeographic inference to evaluate the dispersal history across the Mexico states; (3) using a generalized linear model (GLM) to test the association of epidemiologic factors (i.e. population size, human emigration and immigration flows) and connectivity (i.e. geographic distances and the intensity of air traffic passenger flow) with lineage dispersal frequencies among the states (Fig 1A).

Results: A total of 7,410 unique HIV subtype B partial pol sequences from 17 provinces. The discrete phylogeographic analysis based on these clades revealed high levels of virus exchange between Mexico state, Jalisco (including Guadalajara, the second largest city in Mexico) and the eastern touristic state of Quintana Roo (including Cancún), with the border state of Baja California (Fig. 1B). Furthermore, the GLM analysis also suggests that viral migration was strongly associated with the population density, and number of emigrants from the origin state (Bayes Factor, BF>105), the number of immigrants in the recipient state (BF>105), and the intensity of air passenger flows (BF=3.2). The distance between states was also negatively associated with viral movement (negative BF>105), Fig. 1C.

Conclusion: This comprehensive analysis of HIV dynamics within Mexico emphasizes the key role of human migration in the diffusion of the HIV epidemic. These results may help to more efficiently allocate prevention resources and to evaluate the impact of changes in demographic trends and policies on the Mexico HIV epidemic.
880 SUBSTANCE USE DISORDERS ASSOCIATED WITH MORTALITY AMONG HIV+ IN WASHINGTON, DC

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1George Washington University, Washington, DC, USA, 2District of Columbia Department of Health, Washington, DC, USA, 3Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA

Background: Substance use disorders (SUDs) are common among people living with HIV (PLWH) and may make achievement of optimal health outcomes challenging. We described the prevalence of alcohol, opioid and stimulant use disorders among PLWH in the DC Cohort and assessed the association of SUDs with viral suppression and death.

Methods: We analyzed diagnosis and treatment data for participants enrolled in the DC Cohort (2011-2017), a longitudinal study of PLWH receiving care at 14 clinical sites in Washington, DC, and reported on the prevalence of overall SUD, alcohol, opioid, stimulant, and polysubstance (all 3) use disorders at enrollment or during follow-up, and prevalence of hepatitis B (HBV) and hepatitis C (HCV) among the SUD groups. We used multivariable Cox proportional hazard models to evaluate the association of SUD with all-cause mortality, adjusting for demographics, CD4, and viremia copy-years. We calculated adjusted prevalence ratios (aPR) to assess the association of age at HIV diagnosis, gender, and race/ethnicity with SUDs, and association of SUDs with viral suppression (VS; ≤200 copies/ml at most recent measurement), adjusting for current age, gender, race/ethnicity, and mode of HIV transmission.

Results: Of 8,507 adults, 2,929 (34.4%) had history of any SUD. The most prevalent SUDs were: 73.6% alcohol use disorder, 9.0% opioid use disorder, 7.0% polysubstance use (all 3) use disorders at enrollment or during follow-up, and 4.9% hepatitis B (HBV) and hepatitis C (HCV) among the SUD groups. We used multivariable Cox proportional hazard models to evaluate the association of SUD with all-cause mortality, adjusting for demographics, CD4, and viremia copy-years. We calculated adjusted prevalence ratios (aPR) to assess the association of age at HIV diagnosis, gender, race/ethnicity with SUDs, and association of SUDs with viral suppression (VS; ≤200 copies/ml at most recent measurement), adjusting for current age, gender, race/ethnicity, and mode of HIV transmission.

Conclusion: Alcoholism was the most diagnosed single SUD in the DC Cohort. SUDs disproportionately affected Blacks, Latinos, men, and risk groups other than MSM. Chronic HCV was highly prevalent among PLWH with SUDs and warrants closer attention to ensure successful treatment. SUD was associated with mortality but not VS, suggesting substance-related causes of death.

881 ACCIDENTAL ODOSE DEATHS AMONG HIV+ INDIVIDUALS IN WASHINGTON, DC, 2013-2016

Kerri Dorsey1, Jenevieve Opoku2, Rupali K. Doshi1

1George Washington University, Washington, DC, USA, 2District of Columbia Department of Health, Washington, DC, USA

Background: Drug overdose deaths in DC increased by 178% from 2014 to 2016 (DC Office of the Chief Medical Examiner), but the extent to which people living with HIV (PLWH) died of drug overdose is unknown. We compared the demographic profiles and markers of engagement in HIV care among PLWH in DC who died of accidental overdose (AOD) versus other causes of death (COD) from 2013 to 2016 using death certificate data.

Methods: Deaths reported to the DC Department of Health among PLWH from 2013 to 2016 were evaluated. AOD included ICD-10 codes X40, X41, X42, X43, X44, and Y11 in any death cause position. Individuals were classified as having either AOD or other COD. Univariate analyses (Cochran-Mantel-Haenszel and Student’s t-test) and multivariate logistic regression were conducted to evaluate potential covariates, including age at HIV diagnosis, gender, race/ethnicity, mode of transmission, duration of HIV illness, and CD4 cell count, viral suppression (most recent viral load ≤ 200 copies per mL), and retention in care (at least 1 CD4 or VL in the prior year to death).

Results: From 2013 to 2016, 1,125 deaths among PLWH were reported; of these, 6% (n=68) were AOD. AOD among PLWH increased by 182% from 2013 (n=11) to 2016 (n=31), and PLWH who died from exposure to narcotics (X41) increased by 156% from 2013 (n=9) to 2016 (n=23). Among AOD with COD, 40% (n=27) had history of injection drug use (IDU) at the time of HIV diagnosis vs. 26% among PLWH with other COD (p=0.03). Among AOD with COD, mean age of HIV diagnosis was 38 years vs 42 years for other COD (p-value = 0.01). No statistical difference was found between the mean duration of HIV (AOD 13.7 years vs. other COD 12.5 years, p-value=0.21). In unadjusted analyses, retention in care, viral suppression, and rates of missing lab data were similar between AOD and other COD (Table 1). Based on multivariable analysis, those who died of AOD (vs. other COD) were more likely to have a history of IDU (aOR: 2.3, 95% CI 1.0,5.1) and CD4 count ≥ 500 (aOR: 3.6 95% CI 1.6,8.1).

Conclusion: AOD among PLWH in DC has increased substantially in recent years and was prominent among PLWH with history of IDU. CD4 was higher among PLWH with AOD, indicating HIV treatment success. Access to naloxone and opioid substitution therapy for PLWH should be enhanced, and provider awareness of IDU history and overdose potential should be increased, to address this rapidly increasing cause of mortality.

Table 1: Care Patterns within the year prior to death

<table>
<thead>
<tr>
<th></th>
<th>Accidental Overdose</th>
<th>Other Causes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=68</td>
<td>n=1068</td>
<td>n=1136</td>
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<tr>
<td>Retention in Care (yes)</td>
<td>53%</td>
<td>79%</td>
<td>61%</td>
</tr>
<tr>
<td>Missing viral load the year prior to death</td>
<td>23%</td>
<td>34%</td>
<td>28%</td>
</tr>
<tr>
<td>Viral Load Suppression ≥ 100 copies/ml</td>
<td>30%</td>
<td>44%</td>
<td>39%</td>
</tr>
<tr>
<td>Missing CD4 count the year prior to death</td>
<td>23%</td>
<td>34%</td>
<td>39%</td>
</tr>
<tr>
<td>CD4 count closest to death</td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Stage 1</td>
<td>52%</td>
<td>29%</td>
<td>43%</td>
</tr>
<tr>
<td>CD4 cell count ≥500 or CD4 % ≥ 25%</td>
<td>22%</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>17%</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>CD4 cell count ≥200 or CD4 % ≥ 15%</td>
<td>12%</td>
<td>18%</td>
<td>15%</td>
</tr>
</tbody>
</table>

882 RELEASED TO DIE: ELEVATED MORTALITY IN PEOPLE WITH HIV AFTER INCARCERATION


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Background: Incarceration is a serious health crisis among people living with HIV (PLWH). PLWH who are incarcerated are at increased risk of disease progression and mortality, including cardiovascular disease, tuberculosis, and HIV transmission. Incarceration is associated with higher rates of viral suppression compared to those who remain outside of prison. This study aims to evaluate the association of reincarceration with mortality among PLWH in the District of Columbia (DC) who were incarcerated in 2013-2016.

Methods: A longitudinal cohort of PLWH in the DC Cohort (2011-2017) was followed for mortality and reincarceration. A total of 4,041 PLWH were followed from 2013-2016. Cox proportional hazards regression models were used to evaluate the association of reincarceration with mortality, adjusting for sociodemographic, clinical, and behavioral factors.

Results: Among 4,041 PLWH, 34% were incarcerated at least once during follow-up. Median follow-up was 5.6 years (range: 0.1-5.9 years). At the time of last follow-up, 32% of PLWH had died, 59% were lost to follow-up, and 9% were alive. Incarceration was associated with increased mortality, with an adjusted hazard ratio of 1.96 (95% CI 1.53, 2.51) for reincarceration compared to those who were never incarcerated. Additionally, reincarceration was associated with increased mortality among PLWH with a history of injection drug use (aHR 1.99, 95% CI 1.17, 3.41) compared to those without a history of injection drug use.

Conclusion: Reincarceration is associated with increased mortality among PLWH in the DC Cohort. Policymakers and health care providers should consider interventions to reduce reincarceration and improve health outcomes among PLWH.
Background: People with HIV (PWH) released from the criminal justice (CJ) system experience poor HIV outcomes and high mortality. In a cohort of PWH incarcerated in Connecticut and returned to communities, we have shown that the risk of death is 8.47 (standardized mortality ratio [SMR]; 95% CI: 7.25-9.69) times that of the general Connecticut population and 6.97 (95% CI: 5.96-7.97) times that of the general US population. To guide future interventions, we aimed to identify demographic (age and race/ethnicity) disparities in comparative mortality.

Methods: We linked pharmacy, custodial, death, case management, and HIV surveillance data from Connecticut Departments of Correction and Public Health to create a retrospective cohort of all adult PWH released from jails and prisons in Connecticut (2007-2014). We compared mortality in this cohort with the general US and Connecticut populations and with a cohort of PWH from North America (NA-ACCORD) using SMRs. We assessed differences in cause of death and time-to-death within the cohort, stratified by race/ethnicity and age (<45, ≥45 years of age).

Results: Among 1,350 PWH released from CJ settings in Connecticut, median length of incarceration was 73 days (IQR=25-201). After stratifying by race/ethnicity and age, released PWH had significantly higher adjusted mortality than individuals within the general US, CT, and PWH populations (See Table). Assessment of within cohort differences found that among younger, formerly incarcerated PWH, Whites had a shorter time-to-death than Blacks (p<0.0001). In older, formerly incarcerated PWH, time-to-death was shorter among Hispanics compared to Whites (p=0.032). The most frequent causes of death were HIV/AIDS complications (46%), drug overdose (15%), and liver disease (10%) including hepatitis C (10%). Causes of death differed by race/ethnicity for younger (p=0.025), but not older PWH (p=0.526), with younger Hispanics dying most commonly from HIV/AIDS (50%) or liver disease (19%), younger Blacks dying most frequently from HIV/AIDS (23%) or accidental injury/suicide (23%), and younger Whites dying most frequently from HIV/AIDS (50%) or drug overdose (25%).

Conclusion: For PWH, release from the CJ is associated with markedly elevated risk for death relative to general and PWH populations in North America. To reduce mortality, linkage and retention in care post-release and expanded treatment provision for substance use disorders and other chronic conditions in prison are critically important.

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>US General Population</th>
<th>CT General Population</th>
<th>NA-ACCORD Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMR (95% CI)</td>
<td>SMR (95% CI)</td>
<td>SMR (95% CI)</td>
</tr>
<tr>
<td>Younger Age Group: &lt;45 years at initial release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4.1 (1.8-6.3)</td>
<td>5.2 (4.2-6.1)</td>
<td>1.0 (0.5-1.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>16.3 (9.6-22.1)</td>
<td>14.0 (9.0-19.0)</td>
<td>3.0 (1.9-4.1)</td>
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<tr>
<td>White</td>
<td>25.4 (15.3-35.4)</td>
<td>33.4 (23.3-46.4)</td>
<td>4.4 (2.7-6.1)</td>
</tr>
<tr>
<td>Other</td>
<td>9.4 (1-22.6)</td>
<td>45.6 (19.0-110.9)</td>
<td>1.8 (0.0-4.3)</td>
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<tr>
<td>Older Age Group: ≥45 years at initial release</td>
<td></td>
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<tr>
<td>Black</td>
<td>3.6 (2.6-4.6)</td>
<td>4.6 (2.6-4.6)</td>
<td>1.4 (1.0-1.9)</td>
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<td>Hispanic</td>
<td>12.9 (8.4-17.0)</td>
<td>11.9 (8.0-15.9)</td>
<td>3.2 (2.3-4.1)</td>
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<tr>
<td>White</td>
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<td>9.8 (3.5-14.4)</td>
<td>1.6 (0.8-2.4)</td>
</tr>
<tr>
<td>Other</td>
<td>9.4 (2.2-18.0)</td>
<td>30.6 (6.6-60.6)</td>
<td>3.1 (0.0-2.7)</td>
</tr>
</tbody>
</table>

Table 1. Standardized mortality ratios of formerly incarcerated people with HIV

ATTRIBUTABLE RISK OF METHAMPHETAMINE USE ON VIRAL SUPPRESSION AMONG MSM ON ART

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Background: Viral suppression improves clinical outcomes, while virologic failure (HIV RNA >200 copies/ml) increases risk of HIV morbidity/mortality. Substance use decreases the likelihood of achieving undetectable viremia; however, the comparative effects by substance have not been described. In this study, we examine the effect of different drugs on levels of viremia in a cohort of HIV+ men who have sex with men (MSM) on antiretroviral therapy (ART).

Methods: Participants (N=230) were selected from an ongoing cohort (The mSTUDY) of diverse young MSM enrolled from August 2014 to May 2018. Only participants who were HIV+ currently on ART as reported in review of concurrent medications and self-report were included. Plasma HIV RNA copies were measured at semi-annual visits and substance use over the preceding six months assessed by computer-assisted self-interview. Substance use and sociodemographic factors associated with viremia outcomes were assessed using ordinal regression analysis with generalized estimating equations.

HIV AND OVERDOSE AMONG PEOPLE WHO INJECT DRUGS IN A COMMUNITY-BASED COHORT

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Background: Overdose mortality has been increasing in the United States for the past decade. People who inject drugs (PWID) with HIV infection may have heightened overdose risk due to a higher burden of age-related comorbidities. Moreover, the context of drug use has changed across the US. We characterize trends in fatal and non-fatal overdose and associations with HIV infection among a community-based cohort of PWID in a city with a long-standing opioid epidemic.

Methods: The AIDS Linked to the IntraVenous Experience (ALIVE) cohort has followed PWID in Baltimore since 1988. We characterize the incidence of fatal and non-fatal overdose from 2014-2018 among all PWID enrolled in ALIVE who were alive in 2014. Mortality through 2016 was ascertained via linkage to the National Death Index with death certificate confirmation. Deaths classified as overdose/drug-related were examined using survival methods with censoring (administrative, other causes of death). Non-fatal overdose was ascertained via self-report among PWID actively using drugs with >1 study follow-up visit on or after 2014. Poisson regression was used to evaluate time trends and covariate associations.

Results: Of 3,156 PWID enrolled in ALIVE who were living at the start of 2014, the median age was 54, 28% were female, 79% were African-American. 51 died of a drug-related cause between 2014-2016 (mortality rate: 6.2 per 1,000 person-years). PWID with HIV were at significantly higher risk of mortality from a drug-related cause (aHR = 2.40, 95% CI: 1.33-4.31) compared to HIV-negative PWID, adjusting for age, sex, and race. Overall, between 2014-2018 among 1104 in follow-up, 194 PWID experienced 530 non-fatal overdoses (rate: 28.5 per 100 person-years). Moreover, rates increased significantly between 2014 and 2018 (Figure) from 8.0 to 44.5 per 100 person-years (p-value for trend<0.0001). HIV-infection was associated with decreased risk of non-fatal overdose controlling for age, race and sex (adjusted incidence rate ratio (aIRR) =0.64, 95% CI: 0.42-0.98). There were no differences in non-fatal overdose by viral suppression for HIV-positive PWID.

Conclusion: While HIV-infected PWID in this cohort appear less likely to experience drug overdose, they may be at higher risk for drug-related mortality. Concurrently, overall rates of overdose are increasing among all PWID. Additional efforts are needed to mitigate the impact of non-fatal overdose among all PWID and fatal overdose among HIV-positive PWID.
Viremia outcomes were grouped as undetectable ($\leq$ 20 copies/ml), low level suppressed (21-200 copies/ml), or not suppressed (>200 copies/ml).

**Results:** The average age of included participants was 34 years with 38.5% African American and 37.2% Hispanic/Latino. The average years since HIV diagnosis was 8 years. The prevalence of substance use across 825 study visits was 73%, with methamphetamine (MA) use most prevalent (50%). After adjusting for unstable housing and ART adherence, MA use, either alone (adjusted OR=1.87; 95% CI 1.03-3.40) or with other substances (adjusted OR=1.82; 95% CI 1.12-2.95), was associated with higher odds of increasing viremia categories (low level suppressed 21-200 copies/ml; not suppressed >200 copies/ml) compared to non-substance users. Other substance use excluding MA did not show a similar association (adjusted OR=1.29; 95% CI 0.80-2.09). These findings suggest that among MA users, nearly half the instances of viremia would be reduced if MA was discontinued (attributable fraction=46%; 95% CI 3-71%).

**Conclusion:** MA use, either alone or in combination with other drugs, is associated with failure of viral suppression among HIV-positive MSM on ART independent of adherence and sociodemographic factors. This accounts for nearly half of the observed instances of unsuppressed viremia. In contrast, other substance use does not impose the same risk. This study underscores the importance of MA use on clinical outcomes among people living with HIV.

885 METHAMPHETAMINE DOSE, CLINICAL OUTCOMES, AND HIV STATUS LINKS AMONG DIVERSE MSM IN LA

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**Background:** Men who have sex with men (MSM) who use methamphetamine (meth) report patterns of use that accumulate to varying amounts of exposures each month. Reliable patterns are: users who dose daily, users for several days once or twice monthly ("weekend warriors") and users who rarely use over several months. Our hypothesis posits cumulative reported meth exposure over 6 month periods links significantly and in dose-dependent fashion with poorer physical and mental health outcomes and with confirmed HIV serostatus.

**Methods:** Data were baseline and follow-up visits (1,798 visits) from 529 mSTUDY participants (HIV+ 266; HIV- 263) in mSTUDY, a prospective cohort of diverse MSM in Los Angeles. Analyses tested links between pattern of self-reported past meth use (past 6 months) with other substance use and select physical and mental health status variables. Reported meth use data at each visit were: (none=1,116 visits; ≥ weekly=330 visits; ≤ monthly=352 visits).

**Results:** Univariate analyses supported our hypothesis of an ordered dose-response association over 6-month periods between outcomes of cumulative dose of meth use and other drug use, HIV-risk behaviors, HIV status, STIs and clinical conditions. By contrast, any reported meth use significantly correlated with HIV-seropositive status (see Table). In multivariable analyses, visits where MSM reported ≥ weekly meth use (compared to nonusers) showed significantly higher likelihood of clinical hepatitis (AOR 2.4, 95%CI 2.2, 5.4), neurologic (AOR 2.1, 95%CI 1.2, 3.4), psychologic (AOR 1.6, 95% CI 1.2, 2.3) and renal abnormalities (AOR 2.2, 95% CI 1.1, 4.3). In visits where MSM reported ≤ monthly meth use, lower, but significantly higher odds than non-users were observed for all conditions, though less than visits where ≥ weekly meth use was reported (excepting renal conditions).

**Conclusion:** Findings show a robust and ordered signal between reported cumulative meth use and physical and mental health outcomes. By contrast, any reported meth use linked with HIV-positive serostatus. Findings also show a strong signal between level of reported meth use over 6 month periods and likelihood of hepatic, neurologic, psychologic and renal abnormalities, suggesting a dose-response link between cumulative dose of meth and negative health impacts in MSM in urban areas similar to Los Angeles.

886 HIV DIAGNOSES AMONG PEOPLE WHO INJECT DRUGS BY URBAN-RURAL CLASSIFICATION, 2014-2016

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**Background:** Concurrent with the U.S. opioid epidemic, the decline in the number of HIV diagnoses among people who inject drugs (PWID) has slowed. Although HIV diagnoses among PWID have been concentrated in urban areas, a 2015 HIV outbreak among PWID in Indiana revealed the vulnerability of rural areas to HIV outbreaks. We assessed the number of HIV diagnoses among PWID and recent changes over time across the urban-rural continuum.

**Methods:** We used National HIV Surveillance System data reported through June 2018 for diagnoses occurring among persons aged ≥13 years during 2014 and 2016 (excluding the Indiana outbreak year) and preliminary data for 2017. We included persons with HIV attributed to injection drug use (IDU) only; those attributed to both IDU and male-to-male sexual contact were not included. Missing data on transmission category were imputed with standard methods. County of residence at diagnosis was categorized by the National Center for Health Statistics 2013 urban-rural classification scheme (Table) and the 220 counties identified by CDC as most vulnerable to HIV outbreaks.

**Results:** In 2016, of 2177 HIV diagnoses among PWID, 1982 (91%) occurred among residents of metropolitan counties; 971/2177 (45%) were from large central metro counties (Table). In the 220 most vulnerable counties, 45 diagnoses occurred. The number of diagnoses in 2016 was >5% lower than in 2014 for large central metro (-83 diagnoses; -8%) and small metro (-8; -6%) counties and >5% higher for large fringe metro (+22, 5%) and micropolitan (+10, 10%) counties and for the 220 most vulnerable counties (+22, 96%). Preliminary data suggest that HIV diagnoses among PWID in 2017 are higher in number than in 2016 and distributed similarly across urban-rural categories.

**Conclusion:** The vast majority of HIV diagnoses among PWID in the United States are among PWID who reside in metropolitan areas. Although diagnoses among residents of large central metro counties continued to decline through 2016, these counties still accounted for 45% of HIV diagnoses among PWID. Increases in diagnoses among PWID in 2016 compared with 2014 occurred outside of large, central metro areas, with the greatest absolute increase in large fringe metro counties, and the greatest relative increase in micropolitan
Recent increases in HIV diagnoses have occurred in non-metropolitan counties. Whether through outbreaks or slower trends of increased transmission, HIV diagnoses among PWID may increase in areas across the urban-rural continuum.

### Table: HIV diagnoses among people who inject drugs, by urban-rural classification — United States, 2014 and 2016

<table>
<thead>
<tr>
<th>NCHS Urban-Rural Classification*</th>
<th>2014 n (%)</th>
<th>2016 n (%)</th>
<th>Change from 2014 to 2016 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2224</td>
<td>2177</td>
<td>-47 (-2.1)</td>
</tr>
<tr>
<td>Metropolitan</td>
<td>2038 (91.5)</td>
<td>1982 (91.0)</td>
<td>-56 (-2.7)</td>
</tr>
<tr>
<td>Large central metro</td>
<td>1,054 (47.4)</td>
<td>971 (44.6)</td>
<td>-83 (-7.9)</td>
</tr>
<tr>
<td>Large fringe metro</td>
<td>432 (19.4)</td>
<td>454 (20.9)</td>
<td>22 (5.1)</td>
</tr>
<tr>
<td>Medium metro</td>
<td>410 (18.4)</td>
<td>425 (19.5)</td>
<td>15 (3.7)</td>
</tr>
<tr>
<td>Small metro</td>
<td>140 (6.3)</td>
<td>132 (6.1)</td>
<td>-8 (-5.7)</td>
</tr>
<tr>
<td>Non-metropolitan</td>
<td>170 (7.6)</td>
<td>179 (8.2)</td>
<td>9 (5.3)</td>
</tr>
<tr>
<td>Micropolitan</td>
<td>97 (4.4)</td>
<td>107 (4.9)</td>
<td>10 (10.3)</td>
</tr>
<tr>
<td>Noncore</td>
<td>73 (3.3)</td>
<td>72 (3.3)</td>
<td>-1 (-1.4)</td>
</tr>
<tr>
<td>Unclassified county</td>
<td>10 (0.5)</td>
<td>10 (0.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Data have been statistically adjusted to account for misclassification of urban-rural location. Values may not sum to the column total. *2013 National Center for Health Statistics Urban-Rural Classification Scheme for Counties.

### 887 INJECTION AND SEXUAL BEHAVIORS AMONG PERSONS WITH DIAGNOSED HIV WHO INJECT DRUGS

Sharoda Dasgupta, Yunfeng Tie, Ansley Lemons-Lyn, Kathleen Wu, Janet C. Burnett, R. L. Shouse, Linda Beer

**Background:** Injection and sexual practices of HIV-positive persons who inject drugs (PWID) can affect HIV transmission risk, but have not been described using nationally representative data. We examined high-risk injection and sexual practices among HIV-positive PWID using nationally representative data from the Medical Monitoring Project (MMP).

**Methods:** During 6/2015–5/2016, interviews were conducted with adults diagnosed with HIV to assess sexual behaviors, injection drug use, and other behaviors during the past 12 months. Viral load results from the past 12 months were obtained through medical record abstraction. Among adults with diagnosed HIV who injected drugs in the past 12 months (n=113), we reported the percent who engaged in distributive sharing of syringes and other injection equipment (defined as giving used injection equipment to another person for use), injected drugs before or during sex, and needed and did not obtain alcohol or drug treatment. We estimated the percent of HIV-positive PWID who had condomless sex and were at high risk for sexual HIV transmission, defined as (1) having a detectable viral load ≥ 1 viral load ≥ 200 copies/mL, and (2) having condomless sex with an HIV-negative or HIV-unknown partner who was not known to be on PrEP, and compared estimates with HIV-positive adults who did not inject drugs (n=3,541) using Rao-Scott chi-square tests (P<.05). We reported weighted percentages to account for complex survey design.

**Results:** Overall, 3% of adults with diagnosed HIV injected drugs in the past 12 months, of whom 9% engaged in distributive syringe sharing and 11% in distributive sharing of other injection equipment; 65% reported injecting drugs before or during sex. Over half (56%) needed alcohol or drug treatment, of whom 32% did not obtain treatment. Seventy percent of all HIV-positive PWID, compared with 31% of HIV-positive non-PWID, had condomless sex; 25% of HIV-positive PWID, compared with 7% of HIV-positive non-PWID, engaged in behaviors associated with high risk of sexual HIV transmission.

**Conclusion:** Over 10% of HIV-positive PWID engaged in distributive injection equipment sharing, which is associated with HIV transmission. HIV-positive PWID were more likely to engage in behaviors associated with high risk of sexual HIV transmission. Additional resources to reduce HIV transmission risk among HIV-positive PWID, such as expanding access to sterile injection equipment, drug treatment options, and education on condom use, may be needed.

### 888 HIV PHYLDYNAMIC ANALYSIS CORRELATES WITH TRENDS IN ILLICIT OPIOID TRADE IN PAKISTAN

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1Public Health Agency of Canada, Winnipeg, MB, Canada; 2British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada; 3National Microbiology Laboratory, Winnipeg, MB, Canada; 4University of Manitoba, Winnipeg, MB, Canada

**Background:** Pakistan is considered to have transitioned from a “low prevalence, high risk” epidemic to a “concentrated” HIV epidemic owing primarily to a rapid rise in infections among people who inject drugs (PWID). Prevalence among the country’s nearly 105,000 PWID is estimated to be 37.8% but has been shown to be higher in several large urban centers. Here we evaluate the molecular characteristics of HIV sequences from PWID in several Pakistani cities to examine transmission dynamics and the association between rates of HIV transmission with regards to regional trends in opioid trafficking.

**Methods:** Tip-to-tip (patristic) distance based phylogenetic cluster inferences and BEAST2 Bayesian Markov Chain Monte Carlo phylogenomic analyses of time-stamped data were performed on HIV pol sequences generated from dried blood spots collected from 1,453 PWID as part of a cross-sectional survey conducted in Pakistan during 2014/2015.

**Results:** In total, we were able to amplify 290 pol sequences of the 367 HIV positive specimens. Overall, subtype A1 strains were dominant (75.2%) followed by CCR5-Δ32 (7.2%), recombinants (7.2%), CCR5-Δ32 (2.1%), G (1.0%) and C (0.3%). Nearly a quarter (n=72) of the PWID HIV sequences belonged to one of four distinct phylogenetic clusters. The largest cluster (n=53) mainly consisted of individuals who did not seek help injecting which was previously identified as a strong correlate of HIV infection. Spikes in estimated HIV population sizes coincided with increases in opium poppy cultivation in Afghanistan, Pakistan’s western neighbor. Structured coalescent analysis was undertaken in order to investigate the spatial relationship of HIV transmission among the various cities under study. In general terms, our analysis placed the city of Larkana at the center of the PWID HIV epidemic in Pakistan which is consistent with previous epidemiological data.

**Conclusion:** The current epidemic among PWID is no longer dominated by transmission of a limited number of subtype A1 founder viruses as reported previously. The greater subtype diversity is consistent with sexual and/or drug injecting networks between PWID and other most-at-risk populations. Although it is evident that unsafe injection behaviors played a significant role in driving the rise in HIV prevalence among PWID, local trends in opioid trafficking may have influenced injection behavior and facilitated HIV-1 transmission as a result.
Results: The 41 providers and their 187 COT patients had the following baseline characteristics: providers - 34% male; age 46 years; 63% white; 78% MDs; 12% buprenorphine waivered; patients - 72% male; age 54 years; 28% white; 91% with undetectable HIV viral load; 15% with history of injection drug use. COT providers (n=21 with 87 patients) were randomized to the intervention arm. At 12-month follow-up, the intervention arm had higher odds of ≥2 UDIs (70% vs. 18%, adjusted odds ratio [AOR]: 15.46, 95% confidence interval [CI]: 7.29-32.79; p<0.0001) and DTAs (75% vs. 11%, AOR: 12.81; 95% CI: 22.85-79.30, p<0.0001). We did not detect a difference in early refills (21% vs. 29%, AOR: 0.57, 95% CI: 0.26-1.24, p=0.15), routine use of PMP (55% vs. 25%, AOR: 3.65, 95% CI: 0.94-14.19, p=0.06), or HIV VS (88% vs. 84%, AOR: 1.14, 95% CI: 0.63-2.04, p=0.67) between the two arms.

Conclusion: Participants in the TEACH intervention had higher odds of following 2 important guidelines for COT: ≥2 urine drug tests and treatment agreements. We did not detect significant differences in early refills, use of prescription monitoring programs, or viral suppression. The TEACH intervention is a promising strategy to improve adherence to guidelines for COT and does not appear to compromise viral suppression.

Table 1. Effect of TEACH Intervention Compared to Standard Practice on Study Outcomes at 12-months

<table>
<thead>
<tr>
<th>Study Outcomes</th>
<th>Intervention</th>
<th>Control</th>
<th>AOR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 UDIs ≥12 months*</td>
<td>70%</td>
<td>18%</td>
<td>15.66 (7.29, 33.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥2 UDIs ≥12 months*</td>
<td>21%</td>
<td>29%</td>
<td>0.57 (0.26, 1.24)</td>
<td>0.15</td>
</tr>
<tr>
<td>Clinally significant agreement ≥12 months</td>
<td>75%</td>
<td>11%</td>
<td>12.81 (2.85, 79.30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Provider routine consulted PMP ≥12 months</td>
<td>55%</td>
<td>25%</td>
<td>3.85 (0.94, 14.19)</td>
<td>0.06</td>
</tr>
<tr>
<td>Viral Suppression &lt;200 copies/mL</td>
<td>88%</td>
<td>84%</td>
<td>1.14 (0.49, 2.96)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*primary study outcomes

890 HIV CARE OUTCOMES AMONG SUBSTANCE USERS IN PUERTO RICO FOLLOWING HURRICANE MARIA


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Background: In 2017, Hurricane Maria (HM) caused devastation to Puerto Rico and its residents. Based on an ongoing cohort study in San Juan, Puerto Rico (Proyecto PACTo), we examined the effects of HM on HIV care outcomes among people living with HIV (PLWH) and with a history of substance use.

Methods: We measured differences in HIV care outcomes - viral load, viral suppression, and CD4 counts - before and after HM using assessments conducted in 6-month intervals. Data are based on blood collected to measure CD4 and viral load and a social and behavioral assessment completed through computer-assisted personal interview. Factors associated with HIV care outcomes were evaluated using generalized estimating equations to take into account repeated measures per individual.

Results: 219 participants completed a follow-up visit within the 9-month period before and after HM. The mean post-HM viral load was 2.3 log10 copies/ml (se=0.09), significantly higher compared to pre-HM (2.1 log10 copies/ml, se=0.08). CD4 counts were also lower post-HM (mean=553 cells/μl, se=23.2) compared to pre-HM (mean=589 cells/μl, se=24.7) (Figure). Viral suppression (<200 copies/ml) was 72% pre-HM compared to 65% post-HM. After controlling for age, gender, income, health insurance, incarceration history, homelessness, history of living in the mainland United States, severe drug use, and depression at baseline, there was a 9% reduction for viral suppression between pre- and post-HM time points (aIRR=0.91, 95% CI 0.84-0.98). Also, age (aIRR=1.01, 95% CI 1.00-1.02) and homelessness (aIRR=0.78, 95% CI 0.62-0.98) were independent predictors of viral suppression.

Conclusion: PLWH and with a history of substance use in San Juan, Puerto Rico demonstrated an increase in viral load and decrease in both viral suppression and CD4 counts following HM, critical factors in determining disease outcome and potential community transmission. Further post-HM research will focus on the barriers and facilitators related to accessing healthcare and resources and the effects of post-traumatic stress disorder, which may explain long-term HIV care outcomes.

891 AN OUTBREAK OF HIV IN HOMELESS HETEROSEXUALS WHO INJECT DRUGS IN NORTH SEATTLE, WA

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1University of Washington, Seattle, WA, USA, 2Public Health–Seattle & King County, Seattle, WA, USA, 3Washington State Department of Health, Tumwater, WA, USA

Background: King County, WA, was the first urban area in the US to achieve the WHO 90-90-90 objective and new HIV diagnoses in the county have declined almost 50% in the last decade. HIV infection among non-men who have sex with men (non-MSM) persons who inject drugs (PWID) has traditionally been rare, with an average of 9 diagnoses annually 2008-2017 and 7 diagnoses in 2017. However, the number of heroin overdoses in King County increased 264% from 2007-2018, the number of persons living homeless (PLH) increased 129% 2010-2017. However, 6% of PWID are PLH. The area has a growing, highly vulnerable PWID population.

Methods: We analyzed public health HIV surveillance, partner services (PS), and molecular HIV surveillance (MHS) data to characterize a cluster of HIV diagnoses among non-MSM PWID and their sex and injection partners. Cluster cases met ≥1 of the following criteria: 1) non-MSM diagnosed with HIV in 2018 with PS data indicating sex or injection drug equipment sharing with a cluster; 2) HIV diagnosis in 2018 among non-MSM PLH in the outbreak area; 3) MHS showing HIV infection with a strain related to cases meeting criteria 1 or 2 (HIV-TRACE distance ≥15%). We excluded cases if MHS indicated infection unrelated to the cluster.

Results: From 1/1/18 to 9/15/18, 19 non-MSM PWID were diagnosed with HIV, a 171% increase compared to the 12 months of 2017. Eleven of the 19 cases, as well as 9 cases diagnosed 2008-2017, were part of a cluster. All 11 cluster cases diagnosed in 2018 were PLH in an area of approximately 3 square miles; 8 were cis-women, 2 of whom exchanged sex, and 8 were PWID, 7 of whom injected heroin. Public Health–Seattle & King County (PHSKC) initially identified the cluster through PS, with additional cases added using MHS data that were not available in real time. Ten cluster cases were diagnosed in the 20 months before disease investigators first identified links between cases. PHSKC has responded to the cluster by alerting medical and social service providers and the public; expanding outbreak testing and condom distribution; promoting testing in emergency departments and jails; increasing syringe services; promoting PrEP in PWID; and working to build new clinical capacity in the area of the outbreak.

Conclusion: In the face of growing homelessness and heroin use, even areas with well-developed HIV care and prevention programs are vulnerable to outbreaks of HIV among the most disadvantaged persons. MHS procedures need to be improved to more quickly identify growing clusters.
Suicide rates were much lower in women (vs. men) with HIV, corroborative of US general population findings. Among men with HIV, suicide rates were higher among White (vs. Black) men with a history of IDU (IRR = 9.87 [5.08, 19.17]) vs. Black (15.16 [9.73, 20.58]) men. Compared to Black non-IDUs, the suicide rate was greater among White IDU (IRR = 4.30 [3.30, 5.61]) vs. Black (1.59 [1.04, 2.45]) men. This was higher in White vs. Black men from 2000-15 (IRR = 4.30 [3.30, 5.61]) vs. Black (1.59 [1.04, 2.45]) men. The suicide rate was 43.06 [37.30, 48.81]. This was higher in White vs. Black men from 2000-15 (IRR = 4.30 [3.30, 5.61]) vs. Black (1.59 [1.04, 2.45]) men. The suicide rate was 43.06 [37.30, 48.81].

Conclusion: Suicide rates were much lower in women (vs. men) with HIV, corroborative of US general population findings. Among men with HIV, suicide rates were higher among White (vs. Black) men. White men with a history of IDU had the highest suicide rates of suicide, followed by White non-IDU, Black IDU, and Black non-IDU, suggesting the association between drug use and suicide
in the general population may also be reflected in men with HIV. Men with HIV warrant targeted suicide prevention efforts, particularly White men with a history of IDU.

894 SUCCESSFUL cART NORMALIZES SURVIVAL FOR HIV-HTLV COINFECTED PATIENTS
Fernanda Miranda, Estela Luz, Eduardo M. Netto, Carlos Brites
Federal University of Bahia, Salvador, Brazil

Background: coinfection by HTLV is associated with shorter survival for adults and children infected by HIV, but the reasons remain controversial. We aimed to evaluate the survival time and associated factors of co-infected and mono-infected patients treated with cART.

Methods: we reviewed medical records of 298 HIV-infected patients on cART, 149 (50%) of them co-infected by HTLV-1. Patients in each group were matched by age at HIV diagnosis and gender. Death rates, survival time, baseline and current CD4 count, last HIV-1 RNA plasma viral load (PVL) and causes of death were compared.

Results: Most patients were women (59.1%), mean age 39.0 ± 9.1 years. Survival time was 6,622 days for mono-infected, and 6,107 days for co-infected patients (p=<0.001). Survival persisted significantly different for those with PVL>50 (3,084 for co-infected, vs. 4,712 days for mono-infected subjects, p=0.02), or PVL>1,000 copies/ml (2,526, vs. 3,329 days, for co-infected and mono-infected subjects, respectively, p=0.02). However, overall survival did not differ for patients with PVL<50 (7,370 days, co-infected: 6,944 days, p=0.5) or <1,000 (7,218 vs. 6,929 days, for mono and co-infected patients, respectively, p=0.3) copies per ml (Figure 1). Baseline CD4 count for deceased patients was higher for co-infected (410±350 cells/ml) than for mono-infected (177±160 cells/ml, p=0.04) patients, but similar for survivors (417±299 vs. 396±336 cells/ml, p=0.7). Last CD4 count was similar for both groups, regardless of survival status. Causes of death were mainly (78%) AIDS-defining diseases and did not differ for groups.

Conclusion: In this large cohort, successful cART normalized survival time for HIV-HTLV co-infected subjects. The increased mortality for co-infected patients with uncontrolled HIV PVL, despite a higher baseline CD4 count, suggests HTLV co-infection boosts progression to AIDS in patients with active HIV replication.

895 RACIAL DISPARITIES IN BASELINE GENOTYPING IN THE ERA OF “ART FOR ALL”
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Background: Since 2007, federal guidelines for the care and treatment of persons with HIV have recommended genotyping at the initial care visit, both to establish a baseline and to guide antiretroviral therapy (ART). Previous studies indicated that patients were more likely to receive a baseline genotype if their CD4 at diagnosis reached the ART threshold in use at the time.

Methods: We used laboratory data routinely reported to HIV surveillance to measure compliance among New York City physicians in two time periods – the “treatment threshold” era (2006-2012) and the “ART for all” era (2013-2017). We examined differences in baseline genotyping by provider type, patient demographics, risk factor, and clinical characteristics. A baseline genotype was defined as a genotype performed within 3 months of initial HIV diagnosis.

Results: Baseline genotyping increased from 53% during the “treatment threshold” era to 63% during the “ART for all” era. The most important predictor of baseline genotyping between 2006 (39%) and 2012 (63%) was the CD4 count-genotyping was highest for people meeting the prevailing treatment threshold. In 2013, the year after guidelines recommended ART regardless of CD4, genotyping rose to 73%. After 2013, there was a steady decrease in percent genotyped overall, but relative increases in patients with CD4>500 and those receiving care at community-based organizations and free-standing clinics. Baseline genotyping in 2017, the last year for which data are complete, was 66%. Patients were more likely to receive a genotype if they were MSM, between the ages of 20-39 at diagnosis, white or Asian, acutely infected, CD4 <350, attended private providers or providers affiliated with hospitals and were diagnosed after 2012. Black race was independently associated with a 47.3% (95% CI 0.40, 0.69) lower likelihood of receiving a baseline genotype in the “treatment threshold” era, regardless of age, risk factor, neighborhood poverty level, clinical status, provider type, and year of diagnosis, and a non-significant 20.1% (95% CI 0.50, 1.26) lower likelihood of being genotyped in the era of “ART for all”. Our analysis was not able to account for the temporal changes in cost, reimbursement, turnaround time, guidance on interpretation, or other issues that may have affected provider decision to test.

Conclusion: Five years into the era of “ART for all,” substantial inequity in baseline genotyping remains. Strategies to increase testing of black people are needed to improve quality of care.
YIELD OF HIV TESTING AND RE-ENGAGEMENT OF KEY POPULATIONS IN UGANDA AND KENYA

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Background: The yield of key population testing for HIV diagnosis and care re-engagement in settings that have surpassed the UNAIDS target of 90% of HIV+ persons aware of their status in sub-Saharan Africa is unknown.

Methods: The SEARCH trial (NCT01864683) achieved >95% adult resident HIV testing coverage by 3 years with a hybrid approach (study census, multi-disease campaigns and home testing of campaign non-attendees) in 32 rural communities in Kenya and Uganda. After 3 years, 16 communities implemented 2-week mobile outreach, that included multi-disease and HIV testing services, for resident key populations considered high-risk for HIV (Table), and in-migrants (newly living in community since year 3 of trial). Known HIV+ persons were not retested, but referred to clinic if out of care by self-report or clinic database. We assessed HIV testing coverage and compared yield of new diagnoses including seroconversions (documented prior HIV-) and yield of known HIV+ out-of-care residents, across key populations.

Results: HIV testing coverage of HIV-unknown resident key populations was 16% (2,091/13,283) in Kenya, 14% (1,903/6,424) in West (W) Uganda, and 14% (1,830/13,555) in East (E) Uganda after the 2-week outreach. Yield of new HIV diagnoses among residents varied from 0% to 3% across key populations, and was highest among barmachs in Uganda (Table). Of 37 residents with newly-identified HIV, 29 (78%) were seroconversions. In-migrant testing yield was 19% (21/114) in Kenya, 17% (32/194) in W-Uganda, and 5% (13/287) in E-Uganda. Of 66 newly-identified HIV+ in-migrants, 40 (61%) reported prior HIV-unknown status. The number needed to test to identify one newly-diagnosed HIV+ adult was 123 in Kenya, 69 in W-Uganda and 151 in E-Uganda among residents, compared to 12, 11 and 26 among in-migrants per region, respectively. Of HIV+ adults resident seen at mobile outreach, 28% (193/682) were out of care in Kenya, 21% (14/66) in W-Uganda, and 19% (10/53) in E-Uganda. Of all known HIV+, out-of-care residents within key population groups, 7% in Kenya and 3% in Uganda attended 2-week mobile outreach.

Conclusion: Mobile, multi-disease outreach to key populations in SEARCH communities in rural Uganda and Kenya where HIV testing coverage was already high continued to yield new HIV+ diagnoses among residents, most of whom were seroconversions, and in-migrants. Outreach facilitated re-engagement of known HIV+ persons who leave care but remain willing to access mobile services.

ED VISITS AND HOSPITALIZATIONS AS OPPORTUNITIES TO IMPROVE HIV CARE ENGAGEMENT

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Background: Many health departments around the United States use HIV surveillance data to identify poorly engaged persons living with HIV (PLWH) and direct HIV care reengagement activities. The effectiveness of these Data to Care (D2C) programs has been hindered by difficulty contacting individuals who appear to be out of HIV care. Identifying opportunities, such as emergency department (ED) and inpatient (IP) admissions, to interact with poorly engaged PLWH is crucial to improving their success. In this study, we describe the characteristics, ED/IP utilization, and viral load status of PLWH seen at a UW Medicine ED/IP.

Methods: We used UW Medicine’s clinical data repository and Public Health Seattle and King County’s HIV surveillance database to identify all PLWH residing in King County who had an ED/IP admission at a UW Medicine facility – one of the largest ED providers in King County – in 2017. Using HIV laboratory reporting data, we determined the HIV viral load status of patients at the beginning and end of 2017 and immediately prior to each ED/IP admissions. We compared the demographic characteristics and viral load status at the beginning and end of 2017 of patients who had at least one ED/IP admission while unsuppressed (i.e., viral load > 200) to those who had no ED/IP admissions while unsuppressed (i.e., viral load < 200).

Results: In 2017, 831 PLWH had 1841 ED/IP admissions at a UW Medicine facility. Of these, 189 (23%) had at least one ED/IP admission while virally unsuppressed. Of the 189 unsuppressed patients, 134 (71%) were unsuppressed at the beginning of 2017, and 114 (60%) were unsuppressed at the end of 2017. Of the 642 patients who were suppressed during their ED/IP admissions, 47% (77) were suppressed at the beginning of 2017, and 23 (4%) were suppressed at the end of 2017. Unsuppressed patients were younger (mean age: 42 vs 47 years) and more likely to have 3 or more ED/IP admissions compared to suppressed patients (40% vs 28%; p<0.01). Unsuppressed patients were more likely to have 3 or more ED/IP admissions compared to suppressed patients (39% vs 18%; p<0.01).

Conclusion: In 2017, about 25% of PLWH who had an ED/IP admission had at least one visit while unsuppressed and 60% of unsuppressed patients remained unsuppressed at the end of 2017. ED/IP admissions provide an opportunity to interact with PLWH who experience sustained poor engagement in care. Interventions that leverage partnerships with emergency departments are needed to improve the HIV care outcomes of this population.
HIV care and treatment outcomes and whether depression mediates these relationships.

**Methods:** We analyzed cross-sectional data from 436 women living with HIV enrolled in the Women's Adherence and Visit Engagement (WAVE) sub-study of the Women's Interagency HIV Study (WHIS), conducted in San Francisco, CA, Atlanta, GA, Birmingham, AL and Jackson, MS. The exposure was experienced poverty stigma, measured using 4 items from the Perceived Stigma of Poverty Scale. Outcomes were viral suppression, CD4 ≥ 350 cells/mm³, self-reported ≥ 95% adherence, and no missed HIV care visits in the past 6 months. The mediator was depression, measured by the 20-item Center for Epidemiological Studies Depression Scale. Multivariable logistic regression models were adjusted for income, age, race/ethnicity, education, non-prescribed drug use, and months taking ART. We tested whether the association of poverty stigma with the outcomes was mediated by depression scores, using indirect effects analysis with bootstrapping.

**Results:** Each unit increase in mean experienced poverty stigma score was associated with lower adjusted odds (aOR) of viral suppression (aOR 0.79, 95% CI 1.04, 0.98), having a CD4 count ≤ 350 cells/mm³ (aOR 0.69, 95% CI: 0.53, 0.89), ≥ 95% ART adherence (aOR 0.72, 95% CI: 0.55, 0.93), and no missed HIV care visits (aOR 0.71, 95% CI: 0.53, 0.95). Depression significantly mediated the negative relationship between experienced poverty stigma and having a CD4 count ≤ 350 cells/mm³ (indirect effect: -0.08, 95% CI: -0.16, 0.04; direct effect: -0.27, 95% CI: -0.31, 0.05), as well as experienced poverty stigma and ≥ 95% ART adherence (indirect effect: -0.11, 95% CI: -0.18, 0.04; direct effect: -0.17, 95% CI: -0.26, 0.04).

**Conclusion:** Experienced poverty stigma was associated with worse HIV health outcomes, even after adjusting for income, and depression was a significant pathway for some of these relationships. Longitudinal research should assess these relationships over time. Findings support interventions and policies that seek to both reduce poverty stigma and address depression among people living with HIV.

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### Table 1. The adjusted associations between experienced poverty stigma and HIV care and treatment outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Adjusted models 1</th>
<th>Adjusted models 2</th>
<th>Depression 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus suppression</td>
<td>0.79 (0.64, 1.00)</td>
<td>0.82 (0.65, 1.03)</td>
<td></td>
</tr>
<tr>
<td>CD4 count ≤ 350 cells/mm³</td>
<td>0.69 (0.54, 0.88)**</td>
<td>0.72 (0.56, 0.92)</td>
<td></td>
</tr>
<tr>
<td>≥ 95% ART adherence</td>
<td>0.72 (0.55, 0.91)**</td>
<td>0.84 (0.64, 1.01)</td>
<td></td>
</tr>
<tr>
<td>Attending all HIV care visits at past 6 months</td>
<td>0.71 (0.53, 0.95)**</td>
<td>0.79 (0.57, 1.08)</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.01; *** p<0.001

1Adjusted for age, education, income, non-prescribed drug use since last visit, and months on ART

2Adjusted for age, education, income, non-prescribed drug use since last visit, months on ART, and depression scores

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### 899 RISK FACTORS FOR INCREASED HOSPITAL LENGTH OF STAY AMONG PWH, 2014-2015

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**Background:** Length of stay (LOS) is an important indicator of hospital efficiency and severity of illness but can vary by geographic region. The objective of this study was to evaluate inpatient LOS among PWH by diagnostic category and to identify factors associated with increased LOS.

**Methods:** Hospitalization data from 2014-2015 was obtained on all adults receiving longitudinal HIV care at 14 geographically diverse sites in the HIV Research Network. Modified clinical classification software from the AHRQ assigned primary ICD-9 codes into mutually exclusive diagnostic categories. Patient-specific mean LOS was used to calculate mean and median LOS per diagnostic category. Multivariate negative binomial regression analysis was used to evaluate factors associated with LOS.

**Results:** Of 20,608 patients followed, 3196 patients were hospitalized over 4704 person-years of active outpatient care. Study subjects had a median age of 50 (IQR 43–58), were predominately male (67.6%), and black (50.9%), had CD4 > 200 (72.8%), and were HIV-virally suppressed (65.8%). Health care coverage was Medicaid (46%), Medicare (11.9%), private insurance (9.4%), and uninsured (12.5%). Median LOS was 5 days (IQR 3–8); mean LOS was 6.8 days (SD 9.3). Mean LOS was longest for AIDS-defining illness (ADI) (9.3 days), non-AIDS defining infections (7.4 days), and pulmonary (7.3 days). In multivariate analysis, mean LOS for ADI was significantly longer than non-ADI (aIRR vs. non-ADI, 1.16 [1.02, 1.32]) (Table). Compared to CD4 > 350, CD4 51-200 (aIRR 1.13 [1.03, 1.23]) and CD4 ≤ 50 (aIRR 1.37 [1.22, 1.54]) were associated with increased LOS. Health care coverage with Medicaid and Medicare were each associated with increased LOS. Age ≥ 60 (aIRR vs. age 18-29, 1.17 [1.02, 1.34]) and Southern region (aIRR vs. Eastern region, 1.10 [1.01 1.20]) were associated with increased LOS, while Western region had lower LOS (0.87 [0.80, 0.95]). Sex, race, and HIV risk were not associated with LOS.

**Conclusion:** Higher inpatient utilization in patients with ADI and low CD4 highlights the potential importance of early ART initiation to reduce LOS. The association of public health care coverage and geographic region suggests structural factors (poverty, inefficiencies in health care delivery, regulatory policies, etc.) that may be difficult to modify. Older age was generally associated with greater health care utilization, independent of diagnosis. Attention to preventive efforts to decrease the need for hospitalization is particularly important.

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### 900 FIB-4 SCORE PREDICTS OVERALL MORTALITY IN HIV MONOINFECTED: A PROSPECTIVE STUDY

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**Background:** The prognostic value of FIB-4 score, a serological biomarker for detection of advanced fibrosis, has been validated in HIV patients co-infected by viral hepatitis. We aimed to evaluate the prognostic value of FIB-4 score to predict overall mortality in HIV mono-infected patients.

**Methods:** A total of 3,989 HIV patients were prospectively followed from January 2000 to December 2016 at HIV-INSI/FIOCRUZ cohort. The exclusion criteria were viral hepatitis co-infection (n=362); missing information of death (n=22); mortality up to 6 months after baseline (n=80) and absence of follow-up (n=21). Deaths were validated by two investigators. FIB-4 was calculated using parameters of the baseline visit by the following formula: FIB-4=(age x platelet [10^9/L] x AST [U/L])/(platelet [10^9/L] * sqr (ALT [U/L]). Published cut-off values were used to define low (FIB-4 < 1.45), intermediate (FIB-4 1.45-3.25), and high (FIB-4 > 3.25) probability of advanced fibrosis. Mortality rates were...
calculated, Kaplan–Meier curves were plotted and multivariate Cox models adjusted for age, gender and classic HIV factors were performed. Results: 3,504 HIV mono-infected patients (66% male, age=39 (IQR 32–47) years, ALT=32 (23–45) U/L, 73% under combined antiretroviral therapy (c-ART), CD4=469 (249–703) cells/μL and 50% with detectable HIV viral load) were included. A total of 274 patients (7.8%) died during a mean follow-up of 5.3 (range, 0.2–18.0) years. The mortality rate (95% CI) was 14.7 (95% CI: 13.1–16.5) per 1,000 person-year. Patients with high FIB-4 score (> 3.25) had a significantly lower 5-year overall survival (95% CI) than those with intermediate/low score [87% (82–90) vs 94% (92–95), p=0.001] (Figure). In a multivariate Cox model the following factors [Hazard Ratio (95% CI)] were independently associated with mortality: age (per year; HR=1.02 (1.01–1.03), p=0.003), CD4 count (< 200 cells/μL; HR=2.13 (1.66–2.75), p<0.001), detectable HIV viral load (> 40 copies/μL; HR=1.66 (1.15–2.42), p=0.008), intermediate FIB-4 score [FIB-4=1.45–3.25; HR=1.36 (1.01–1.84), p=0.048] and high FIB-4 score [FIB-4>3.25; HR=1.72 (1.07–2.79), p=0.027]. Conclusion: Simple serological biomarker, such as FIB-4, can be used to predict overall mortality in HIV mono-infected patients. Intermediate to high FIB-4 score (>1.45) was associated with higher risk of mortality adjusted for age, sex and classic HIV risk factors.

LONG-TERM EFFECTIVENESS OF HIV TREATMENT IN ZAMBIA

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Background: Differences in mortality between HIV-infected patients on antiretroviral treatment (ART) and HIV-uninfected persons indicate the effectiveness of public health HIV treatment programs. We combine data from routine clinical care, intensive tracing of a sample of those lost to follow up from care, as well as external data from the Global Burden of Disease Project (GBD) to assess excess mortality up to 10 years after ART initiation in Zambia. Methods: Between 1 August 2013 and 31 July 2015 we followed patients on ART – including both new initiators as well as those already on treatment in 64 clinics in Zambia supported by the CIDRZ program. Sociodemographic, clinical and visit information were obtained from the electronic medical record system. A probability sample of lost patients were intensively traced to ascertain vital status and inverse probability weights were used to incorporate these outcomes into estimates of mortality. We compared age-standardized mortality in HIV patients to age-standardized mortality among HIV-uninfected Zambians in 2015 provided by GBD estimates. Results: Among 165,464 persons on ART followed for 217,849 person-years (pyrs), we observed an age-standardized death rate of 2.8 deaths/100 pyrs among all persons after ART initiation and a age-standardized mortality ratio 3.37 fold higher than HIV uninfected persons (95% CI:3.35–3.66). After excluding the first year of therapy, HIV patients experienced 2.28 deaths/100 pyrs, still 2.78 fold higher than the 0.82 deaths/100 pyrs in HIV-uninfected individuals with same age distribution (95% CI:2.68–2.90). After one year of treatment, the age-standardized mortality ratio was 2.74 (95% CI: 2.54–2.93) and among men and women 3.15 (95% CI: 2.89–3.46) among women. During years 2–3, 4–5, 6–7 and 8–9 after ART start, age-standardized mortality ratio was 2.00 (95% CI: 2.02–2.39), 1.90 (95% CI: 1.72–2.10), 2.66 (95% CI: 2.42–2.92), and 4.52 (95% CI: 4.12–4.95).

Conclusion: Even after starting treatment, HIV-infected persons remain at elevated risk of death compared to a HIV-uninfected population of the same age in Zambia. Even though HIV infected men experience a higher rate of death than HIV infected women after starting ART, treated HIV women experience a greater risk of death compared to age-standardized uninfected Zambian women. Enhanced engagement and widespread use of TB prophylaxis are needed for HIV infected persons to reach mortality rates of HIV uninfected persons.

PREDICTORS OF LOSS OF VIRAL LOAD SUPPRESSION AMONG MSM IN ATLANTA

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Background: Inequities in the HIV care continuum between Black and White MSM living with HIV, including maintenance of viral suppression with effective ART, contribute to disparities in morbidity, mortality, and HIV transmission rates between these groups. We conducted an interim analysis to assess predictors of incident loss of VL suppression among MSM in Atlanta, GA to gain a better understanding of individual factors that contribute to maintenance and loss of viral suppression and to inform effective interventions to reduce these disparities.

Methods: The EngageMENT study is an ongoing longitudinal cohort of HIV positive Black (n=207) and White (n=193) MSM in Atlanta, GA designed to examine racial disparities in the HIV care continuum. VL measurements were obtained at 0 and 12 months. Additional VL measures were available by self-report at 3 and 6 months. Among men who were virally suppressed at baseline, we compared the rate of loss of viral suppression (VL>40 copies/mL) between Black and White MSM. Potential predictors of incident loss of VL were measured at baseline and at each follow-up visit. Unadjusted and adjusted Cox proportional hazards models were used to assess predictors of incident loss of VL suppression.

Results: The rate of loss of viral suppression was 20.2/100 person-years (95% CI: 13.2, 29.6) among Black MSM and 11.9/100 PY (95% CI: 7.0, 18.9) among White MSM [unadjusted hazard ratio (HR) = 1.7, 95% CI: 0.9, 3.2, 3.9]. The rate of loss of viral suppression of Black MSM was HR=2.32 (95% CI: 1.2, 4.3) and ARV non-adherence (HR = 2.4, 95% CI: 1.2, 4.9) were associated with incident loss of viral suppression in adjusted models. Anxiety (HR = 2.0, 95% CI: 0.9, 4.5), ARV non-adherence (HR = 1.7, 95% CI: 0.8, 3.6), lack of health insurance (HR = 1.4, 95% CI: 0.7, 3.3), and not being in care (HR = 3.3, 95% CI: 0.9, 10.0) were associated with higher risk of viral suppression, though none was statistically significant in the adjusted model.

Conclusion: Approximately 1 in 5 Black MSM and 1 in 10 White MSM experienced incident loss of viral suppression per year in our cohort. Individual-level factors such as mental health issues and insurance status may be contributing to incident loss of viral suppression and need further exploration. Results of this interim analysis might change in terms of magnitude or statistical significance. This study will assist in the design of tailored interventions for Black and White MSM to prevent loss of and minimize differences in maintenance of HIV viral suppression.

IMPACT OF HIV TEST-AND-TREAT INITIATIVE IN MIAMI-DADE COUNTY, FLORIDA

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Background: Rapid access to antiretroviral therapy (ART) immediately following HIV testing is upheld as a prevention tool to reduce HIV transmission and improve outcomes along the HIV care continuum. In 2016, the Miami-Dade County Health Department launched a test and treat (T&T) initiative to offer same-day or next-day access to ART following initial HIV diagnosis. This study aims to evaluate HIV care outcomes, including viral load (VL) suppression (<200 copies/mL) and retention in HIV care (two or more HIV-related labs, medical visits or prescriptions at least three months apart), for persons whose HIV was diagnosed in Miami-Dade County in 2017.
Methods: Clinical and epidemiological data reported to the Florida Department of Health HIV/AIDS surveillance system were matched to lab, medical visit and prescription records in Ryan White Program databases, county health department electronic health records and Medicaid claims. HIV care outcomes among antiretroviral-naive patients whose initial HIV diagnosis was in Miami-Dade County in 2017 and who engaged in HIV care (n=950), including patients in T&T (n=80), were evaluated to determine the impact of T&T.

Results: T&T did not significantly impact the rate of HIV care initiation within 30 days of diagnosis (85.0% vs. 81.5%). However, patients in T&T were more likely to achieve VL suppression within six months of diagnosis (87.5% vs. 66.1%, p<0.01) and be retained in care (91.3% vs. 81.6%, p=0.03). For patients with a suppressed VL within six months of diagnosis, the average number of days from diagnosis to VL suppression was lower for T&T (71 vs. 87, p<0.01). When evaluating patients retained in care, higher rates of VL suppression (90.4% vs. 76.1%, p<0.01) and more rapid VL suppression (72 vs. 89 days, p<0.01) persisted for T&T. Furthermore, patients in T&T were more likely to receive HIV resistance testing within three months of diagnosis (80.0% vs. 57.8%, p<0.01).

Conclusion: While T&T did not significantly impact the timing of HIV care initiation, patients in T&T were more likely to achieve VL suppression within six months of diagnosis and progress to VL suppression more rapidly. Patients in T&T were also more likely to receive a baseline HIV resistance test, indicating a complete initial HIV care assessment. Rapid access to ART following HIV diagnosis can help reduce HIV-related mortality, improve health outcomes of those living with HIV and reduce HIV transmission through VL suppression.

904 ANTIRETROVIRAL REGIMEN DURABILITY IS NOT DRIVEN BY VIRAL FAILURE IN AN AFRICAN COHORT

Christina Polya

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Background: Data on durability of first-line regimens in resource-limited settings are limited. We reviewed data from a large ongoing multinational African Cohort study (AFRICOS) to describe reasons and assess time to switching or stopping first-line antiretroviral therapy (ART).

Methods: AFRICOS prospectively enrolls HIV-infected and uninfected adults at 12 President’s Emergency Plan for AIDS Relief (PEPFAR) supported facilities across 5 programs in Kenya (Kisumu and the South Rift Valley), Tanzania, Uganda, and Nigeria. ART regimen history is obtained at entry from available records and updated prospectively every 6 months. Reasons for switching or stopping ART are recorded by study physicians. For these analyses, we included HIV-infected participants who had documented ART start and stop dates, either prior to cohort entry or once enrolled. Time to switching or stopping a regimen was the primary endpoint used to assess durability. We generated Kaplan-Meier curves stratified by variables of interest and used the log-rank test to evaluate for significant differences.

Results: Between January 2013 and June 2018, we enrolled 2820 HIV-infected adults (58% female) with a median age of 36 (IQR 30–44) years. Of these, 2663 (94%) were ART experienced and have initial ART start dates available, including 1154 (43%) that began ART before the study initiation in 2013. The first regimen for the majority (1396; 52%) was efavirenz/lamivudine/tenofovir disoproxil fumarate. The median duration of this regimen was 2.25 (IQR 0.94–3.88) years.

- 1,154 (43%) that began ART before the study initiation in 2013. The first regimen for the majority (1,396; 52%) was efavirenz/lamivudine/tenofovir disoproxil fumarate. The median duration of this regimen was 2.25 (IQR 0.94–3.88) years.
- 42% with males having 31% as compared to females who had 69%. There is an association between duration on ART and viral load suppression. People living on lifelong ART (Antiretroviral therapy) are facing threats to HIV drug resistance (HIVDR) and subsequent treatment failure. World Health Organization 2016 recommended ART initiation for all HIV patients and use of viral load in monitoring treatment response. To understand these recommendations, we conducted a study to evaluate factors associated with ART initiation, viral load, and patient’s demographics.

Results: The sample had 1,636 patients who had been on ART for ≥ 6 years, 66% were females, 60% were adults aged between (20–49) years, 21% were older patients aged (≥50 years), 18% were pediatric and adolescents. Median age was 34 years (IQR: 24–43). Common ART regimen was TDF/3TC/EFV (59%) and AZT/3TC/NVP (28%). Ages between (15–19) years and (10–14) years had poorer resuppression rates 18.6% and 26% respectively. Overall resuppression was achieved by all patients having 31% as compared to females who had 69%. There is an association between duration on ART and viral load suppression, and significance in the duration between (1–2) years (OR 0.70, 95% CI: 0.57 – 0.84), (4–6) years (OR 1.22, 95% CI: 1.05 – 1.43) and > 6 years (OR 1.35, 95% CI: 1.2 – 1.52)

Conclusion: Longevity on ART increases the risk of failing treatment, pediatricians, and adolescents men and are at a higher risk of failing treatment. We need to optimize the use of newer highly efficacious regimens such as dolutegravir, and develop or customize the adherence counselling systems offered to patients who are maturing on ART to improve outcomes.
 SIX YEARS OF INTEGRASE INHIBITOR USE IN A METROPOLITAN CITY  

B. Sharmila Mohanraj1, Qingjiang Hou2, Anne K. Monroe3, Princy Kumar4, Sebelle Kassaye5, for the DC Cohort Executive Committee  
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Background: Integrase strand-transfer inhibitors (INIs) have excellent efficacy, safety, tolerability and ease of dosing and are now part of first-line therapy in the U.S. We investigated trends in INI use in the District of Columbia (DC), an area with 1.9% HIV prevalence, to determine INI treatment effectiveness outside of clinical trials.  

Methods: We conducted a retrospective analysis using data from the DC Cohort, a clinical cohort of HIV-infected persons receiving care at thirteen academic and community-based treatment sites in DC. We used descriptive statistics to determine the incidence of INI resistance and durability of viral suppression (two consecutive viral loads <200 c/mL). Drug resistance was defined using the International Antiviral Society-USA classification system. All analyses were conducted using SAS (v9.4.2).  

Results: Among 6827 participants, 73% were male, 78% Black, and median age was 47 years (IQR:37.1-54.7). INI-based therapy increased from 23% (582/2490) in 2011 to 64% (3783/5898) in 2017, when 52% of total participants on INIs used dolutegravir. From 2011 to 2017 INI resistance was identified in only 1% (38/3783) of participants. Major mutations included Q148H/R (n=11), N155H (n=5), F121Y (n=4), Y143H/R (n=3), and G140S (n=3). Nine individuals had baseline INI resistance mutations. The mean time to suppression was 163 days among non-suppressed treatment-experienced persons starting their first INI regimen and 127 days for treatment-naive persons starting an INI regimen (p=0.003). Viral suppression at 6 months was similar between these groups, 70% among non-suppressed treatment-experienced individuals switching to INI regimen vs 76% among treatment-naive individuals initiating INI-based therapy (p=0.116). Rebound viremia after suppression was most frequent in the first year post INI initiation at 6.6% (158/2403) (Figure 1), and was least frequent among treatment-naive individuals starting INI and 127 days for treatment-naive persons starting an INI regimen.  

Conclusion: The majority of participants in the DC Cohort are now on INI-based therapy. INI resistance remains rare. Long term viral suppression is evident among treatment naive individuals starting INI-therapy, but remains a challenge for those with evidence of viremia on prior treatment regimens. Adherence likely plays a significant role, and increased attention to treatment outcomes and support measures should be in place during the first year of INI-based therapy as the risk for viremia appears to be greatest during this time period.
ANALYSIS

908 PROFILES OF HIV CARE DISRUPTIONS IN ZAMBIA: A LATENT CLASS ANALYSIS

Aaloke Mody1, Kombatende Skombe2, Sheree Schwartz3, Laura K. Beres3, Ingrid Eshun-Wilson1, Sandra Simbeza4, Njekwa Mukamba3, Carolyn Bolton Moore4, Izuzkanji Sikazwe5, Charles B. Holmes6, Nancy Padlan2, Elvin Geng6
1University of California San Francisco, San Francisco, CA, USA, 2Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, 3Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 4Stellenbosch University, Cape Town, South Africa, 5Georgetown University, Washington, DC, USA, 6University of California Berkeley, Berkeley, CA, USA

Background: beyond observed traits (e.g., sex, age), there may also be unobserved (i.e., “latent”) traits—each leading to distinct profiles of barriers to care—that influence retention in care. We used latent class analysis (LCA) of patient-reported reasons for HIV care disruptions in Zambia to identify these patient profiles and examine their associations with engagement in care.

Methods: We traced a probability sample of patients lost to follow-up (LTFU, >90 days late for last visit) as of July 31, 2015 from 64 clinics in Zambia. Among those found alive, we used a semi-structured instrument to identify patient-reported reasons for HIV care disruptions. We performed LCA—incorporating sampling weights—to identify patient subgroups based on the number and types of patient-reported reasons for care disruptions. We characterized patient characteristics for each class and used logistic regression to assess the association between class membership and updated care status (disengaged vs. silent transfer to a new site).

Results: We successfully traced 642 patients LTFU (59.2% female; median age 35y [IQR 30-41]; median enrollment CD4 236 cells/μl [IQR 124-368]). We identified five classes of care disruptions (Table): 1) the “livelihood and mobility” class (29.9% of sample) reported work obligations and mobility/travel as reasons for their care disruptions; 2) the “mobility and family” class (27.5%) were likely to report mobility/travel, family obligations, and transport; 3) the “doubting need for HIV care” class (8.4%) reported care disruptions due to beliefs about their needs for HIV care; 4) the “clinic accessibility” class (25.1%) were likely to report transport-, clinic-, and disclosure-related care challenges; and 5) the “multidimensional barriers” class (9.2%) reported multiple reasons (mean 5.5) across categories. The “mobility and family” class was least likely to be disengaged (19.2% disengaged vs. 80.8% silent transfer), followed by the “livelihood and mobility” (44.1%), “clinic accessibility” (48.8%), and “multidimensional barriers” (57.2%) classes, with the “doubting need for HIV care” class most likely to be disengaged (100%).

Conclusion: There are distinct profiles for HIV care disruptions that are associated with whether a patient disengages or silently transfers their care. Strategies to target these unique patient profiles by concurrently addressing multiple barriers, rather than individual barriers, may be a more effective way to design and implement interventions to improve retention in care.

SURVIVAL OF PEOPLE LIVING WITH AIDS IN BRAZIL: BIAIDS-BRAZIL COHORT

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Background: Brazil was the first middle-income country to offer universal access to AIDS treatment. Monitoring the impact of this policy is relevant for continuous updating of intervention strategies. This study aimed to estimate the survival of people living with AIDS (PLWA) with >13 years of age and to investigate predictors of death with a basic AIDS cause, in Brazil, among 2003-2007, followed up until 2014.

Methods: Retrospective cohort. Data from the Brazilian Integrated Base of AIDS Cohort (BIAIDS-BRASIL Cohort) was obtained from a probabilistic record linkage methodology applied to databases of the Ministry of Health: Information System of Notification Diseases, Control of Laboratory Tests, Logistic Control System of Medicines and Mortality Information System. Kaplan-Meier method, Cox model and estimates of the hazard ratios (HR), with 95% confidence intervals (CI = 95%) were used for survival analysis.

Results: During the 2003-2007 period, 104,806 PLWA were reported, with 27,147 deaths. The probability of surviving 144 months was 33% for those who did not use ART, 75% for those with Pre-HAART, 84% with HAART1 and 89% with HAART2. They were associated with AIDS death independent of other exposures: use of HAART1 (HR=2.1; 95%CI1.7-2.4); use of Pre-HAART (HR=4.8; 95%CI2.5-11.7); without ART (HR=5.3; 95%CI4.0-6.6); feminine gender (HR=0.8; 95%CI0.7-0.9), <8 years of study (HR=1.5; 95%CI1.4-1.6); without study (HR=1.8; 95%CI1.6-2.0); age of 30-49 years (HR=0.9; 95%CI0.9-1.0); >50 years (HR=1.2; 95%CI1.1-1.3), heterosexual (HR=1.2; 95%CI1.1-1.3); injecting drug users (HR=2.1; 95%CI1.9-2.3); black (HR=1.3; 95%CI1.2-1.4);
brown (HR = 1.3; 95% CI 1.0-1.7); indigenous (HR = 1.7; 95% CI 1.1-2.7); TCD4+ in the diagnosis among 350-499 cells/mm³ (HR = 1.2; 95% CI 1.1-1.4); among 200-349 cells/mm³ (HR = 1.3; 95% CI 1.3-1.6); ≤200 cells/mm³ (HR = 2.3; 95% CI 1.2-2.5); and viral load >500 copies (HR = 1.8; 95% CI 1.7-2.0).

Conclusion: Survival was massively increased, from 33% to 89% in 144 months, due to the introduction of more potent therapeutic regimens adopted in the country. HAART, sex, schooling, ethnicity, exposure category, age, TCD4+, and viral load at the time of diagnosis were associated with survival time as an independent prognostic factor.

910 HIGH HIV PREVALENCE AND LOW ART COVERAGE AMONG AGYW WHO SELL SEX: A POOLED ANALYSIS


Background: Adolescent girls and young women (AGYW) and female sex workers (FSW) are both at particularly high risk of acquiring HIV in sub-Saharan Africa. The extent to which AGYW who sell sex engage in HIV care and treatment is not fully understood. We assess age-specific HIV prevalence and antiretroviral therapy (ART) coverage among FSW in West and Southern Africa.

Methods: This pooled analysis includes respondent driven sampling (RDS) data from 2011-2016 in sub-Saharan Africa (West Africa: Burkina Faso (n=699), Cameroon (n=2255), Côte d’Ivoire (n=466), The Gambia (n=251), Senegal (n=758), and Togo (n=684); Southern Africa: Lesotho (n=744), South Africa (n=410), and eSwatini (n=323)). Women were eligible to participate if they had engaged in sex work as their primary source of income in the past year. Interviewer-administered questionnaires used comparable data collection instruments across sites to assess demographics and prior history of HIV testing and ART use. All women received HIV testing and counseling. Generalized linear mixed effect models were used to calculate age-specific HIV prevalence estimates for West and Southern Africa. Differences in self-reported HIV testing and ART coverage were descriptively compared by age for both regions.

Results: A total of 6592 FSW were included in this analysis (median age: 27 years, IQR 22-33). Pooled HIV prevalence estimates increased with age and varied by region (Figure). In West Africa, estimated prevalence steadily increased from 4% (95% CI 2.7 to 27%) (95% CI 17.45). Prevalence estimates for Southern Africa were greater by comparison, ranging from 43% (95% CI 35.35) in very young FSW (≤19 yrs) to 87% (95% CI 80.94) by ages 30-34. Among 1957 FSW living with HIV, overall, 1140 (57%) had received a prior HIV diagnosis; 681 (35%) were on ART. Compared to older FSW living with HIV, young HIV-infected FSW (≤24 yrs) were less likely to know their HIV status (47% (212/447)) vs. 61% (928/1510), p<0.01) and less likely to be on ART (18% (81/447) vs. 40% (600/1510), p<0.01).

Conclusion: HIV prevalence among AGYW in Southern Africa was exceptionally high in this pooled analysis of women who sell sex. Limited knowledge of HIV status and low ART coverage in this age group suggests that even among key populations such as FSW, HIV risk may not be evenly distributed. HIV prevention interventions for AGYW that target those who engage in sex work and those who are vulnerable to early entry into sex work may be most effective in maximizing prevention impact.

911 TIME TO UNDETECTABLE VIRAL LOAD ACHIEVEMENT AFTER ART START AND RISK OF MORTALITY

Vincenzo Spagnuolo1, Laura Galli2, Alessandro Cozzi-Levi3, Giuseppe Lapadula4, Andrea Antinori5, Giancarlo Orofino6, Nicoletta Bobbio7, Maria Cristina Moioli8, Andrea Calcagnò9, Andrea De Luca10, Antonella D’Arminio Monforte11, Antonella Castagna11, for the ICONA Foundation Study Group

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Background: No data on the association between the time to the first undetectable viral load (FUVL) after ART start is predictive of all-cause mortality in a large population of HIV-1-infected patients (pts).

Methods: We included HIV-1-infected treatment-naïve pts, from the ICONA Cohort, who started ART (≥3 drugs) >1998, with ≥1 viral load (VL) and CD4+ values before and after ART start, who achieved undetectable VL (defined by a single HIV-RNA <50 copies/mL) after ART start. Results described as median (IQR) or frequency (%). Cumulative risk of all-cause mortality was summarized using Kaplan-Meier method, with follow-up for these analyses from the date of FUVL achievement until patient’s death, loss to-follow-up or last visit. Factors associated with all-cause mortality were identified using multivariate Cox proportional hazards regression models.

Results: Overall, 10,000 subjects achieved undetectable VL after ART start and were included in the analyses. At ART start, age was 38 (32-46) years, 7805 (78%) males, 1701 (17%) HCV-coinfected, 1028 (10.3%) had a previous AIDS diagnosis, CD4+ 319 (172-464) cells/µL, CD4+/CD8+ ratio was 0.35 (0.20-0.53), <200 cells/mm³ (HR=1.5; 95%CI 1.3-1.6); <200 cells/mm³ (HR=2.3; 95%CI 2.1-2.5); and viral load >500 copies (HR=1.8; 95%CI 1.7-2.0).

Conclusion: High HIV prevalence and low ART coverage among AGYW who sell sex is a serious concern in this region. Better integration of ART coverage must be achieved in key populations who are vulnerable to early entry into sex work to maximize prevention impact.
for other factors (Table) with AHRs ranging from 0.69 to 0.77 depending on the considered model.

Conclusion: In a large cohort of naive HIV-1 infected subjects, the achievement of undetectable viral load within 6 months from ART start was associated with a lower risk of all-cause mortality.

912 CONTRIBUTION OF HIV DISEASE AND CARE STAGES TO HIV TRANSMISSION AMONG BALTIMORE MSM

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Background: HIV incidence remains high among men who have sex with men (MSM) in the United States. We estimated the contributions of MSM at different stages of HIV infection and the HIV care continuum to HIV transmission among MSM in Baltimore, MD, over the past 30 years.

Methods: A deterministic compartmental model of HIV transmission among MSM was parameterised using, and fitted to demographic, epidemiological and care continuum data for MSM in Baltimore, using multiple combinations of plausible parameter values. We estimated the fraction of new direct and secondary HIV infections transmitted by MSM in different disease or care continuum stages, using population attributable fractions (PAFs) estimated over 10-year periods between 1988-1997 and 2008-2017, respectively. The model PAF for diagnosed MSM undiagnosed MSM has declined over time, from 91% (68-98%) over 1988-1997 to 38% (30-49%) over 2008-2017, when undiagnosed MSM represented 87% and 22% of all HIV-positive MSM, respectively. PAFs for diagnosed MSM increased from 15% (5-44%) over 1988-1997 to 82% (67-87%) over 2008-2017. Most new infections attributable to diagnosed PLHIV were transmitted by untreated MSM (PAF for diagnosed untreated MSM: 67% [48-78%] over 2008-2017), who represented 41% of PLHIV (22-48%). Diagnosed MSM (including those treated) transmitted HIV to two-thirds as many individuals as undiagnosed PLHIV per capita over the last ten years (7 vs 11/100py), but around three times more than PLHIV on treatment (2/100py).

Conclusion: Increases in the relative contribution to transmission of diagnosed MSM reflect improvements in HIV testing, but the majority of these transmissions arise from those who remain untreated, showing gaps in treatment provision and retention. Future interventions will need to address the remaining diagnosis and treatment gaps.

913 CHANGING CONTEXTUAL FACTORS POST-HIV DIAGNOSIS PREDICT 5-YR MORTALITY IN SOUTH AFRICA

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1Massachusetts General Hospital, Boston, MA, USA, 2McGill Research Centre, Montreal, QC, Canada

Background: Changes in an individual’s contextual factors following HIV diagnosis may influence long-term outcomes. We evaluated how changes to contextual factors between HIV diagnosis and 9-month follow-up predict 5-year mortality among HIV-infected individuals in Durban, South Africa.

Methods: We used baseline and 9-month survey data from the Sizanani Trial (NCT01188941) in which adults (≥18y) were enrolled prior to HIV testing in 4 outpatient sites between Aug 2010-Jan 2013. We assessed social support, mental health, and competing needs, meaning financial constraints that required deciding between meeting basic needs (food, clothing, or housing) or receiving healthcare. We used the South African National Population Register to ascertain vital status; median follow-up time was 5.8y (IQR 5.2-6.5). We used random survival forests to identify the most important 9-month variables predicting time to subsequent mortality. We incorporated these predictors into a Cox proportional hazards model that included age, sex, and starting ART by 9 months a priori; the full model included changes in social support, mental health, and competing needs between baseline and 9 months.

Results: Among 1,154 HIV-infected participants with valid South African ID numbers, 905 (78%) had baseline and 9-month data available. Mean age was 36 (IQR 25-44) years, 44% were female, and 109 (12%) participants died after 9-month follow up. Time-independent parameters that increased mortality risk included male sex (HR 1.41, 95% CI 1.06-2.08) and not starting ART (HR 1.46, 95% CI 0.97-2.26). Less social support at 9 months compared to baseline significantly increased mortality risk (HR 1.17, 95% CI 1.03-1.33). Going without basic needs or healthcare at both baseline and 9 months more than doubled mortality risk compared to not going without these at either time point (HR 2.45, 95% CI 1.03-5.79). A change from not foregoing basic needs or healthcare to afford the other at baseline to needing to do so at 9-months increased mortality slightly more (HR 2.71, 95% CI 1.47-4.99) when also compared to not foregoing basic needs or healthcare at either time point.

Conclusion: Less social support and changes in competing needs between time of HIV diagnosis and 9-month follow-up significantly increase long-term mortality risk. Reassessing contextual factors during follow-up and targeting interventions to increase social support and affordability of seeking care may reduce long-term mortality for HIV-infected individuals in South Africa.
was 8172 PY and resulted in 156 (8.4%) deaths and 1694 censored patients. The overall mortality rate was 1.9/100 PY. Patients who died were more likely to be male than female (12% versus 7%, p<.01), with WHO stage 3–4 (9%) compared to stage 1–2 (2%), p<.01, and had been of ART for < 5 years (13%) versus those with >= 5 years (2%), p<.01. The main factors associated with mortality were male sex (adjusted hazard ratio [aHR] 2.0; 95% confidence interval [CI] 1.1-3.5, p<.01), WHO stage 3–4 vs 1–2 (aHR 6.9; 95% CI 3.3–13.7, p<.01) and been on ART for < 5 years (aHR 9.1; 95% CI 4.0–20.6, p<.01) (Table 1).

Conclusion: Despite accessibility of ART, HIV related deaths continue to be reported especially among men, adult patients initiating ART with advanced disease, and during early years of treatment. There is a need to improve strategies for HIV case identification and close monitoring of patients during early years of initiating ART. Male-targeted intervention are also needed.

### Table 1: Summary of DEE-related mortality and associated risk factors among HIV-infected adult patients initiated on ART from Oct 2009—Sept 2019 in Kenya

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total n</th>
<th>Deaths (n, %)</th>
<th>IRR (95% CI)</th>
<th>p-value</th>
<th>IRR (95% CI)</th>
<th>p-value</th>
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<td>&lt; 15 yrs</td>
<td>258</td>
<td>2 (0.8)</td>
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<td>&gt; = 15 yrs</td>
<td>1175</td>
<td>55 (4.7)</td>
<td>2.8 (1.9-3.9)</td>
<td>0.0000</td>
<td>2.9 (1.9-3.9)</td>
<td>0.0000</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>873</td>
<td>40 (4.6)</td>
<td>ref</td>
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<tr>
<td>Female</td>
<td>299</td>
<td>15 (5.1)</td>
<td>2.5 (1.3-4.4)</td>
<td>&lt;0.0001</td>
<td>2.5 (1.3-4.4)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Marital status</td>
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<tr>
<td>Single</td>
<td>382</td>
<td>17 (4.5)</td>
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<td>Married</td>
<td>790</td>
<td>24 (3.0)</td>
<td>1.5 (0.9-2.5)</td>
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<td>Employed</td>
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<td>14 (2.2)</td>
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<td>Unemployed</td>
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<td>Disparities/HC</td>
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<td>101 (16.9)</td>
<td>3.0 (2.1-4.3)</td>
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<td>County (National)</td>
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<td>Stage 1 or 2</td>
<td>168</td>
<td>25 (14.8)</td>
<td>ref</td>
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<tr>
<td>Stage 3 or 4</td>
<td>350</td>
<td>30 (8.6)</td>
<td>1.5 (1.2-2.0)</td>
<td>&lt;0.0001</td>
<td>1.5 (1.2-2.0)</td>
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<td>AAS (France)</td>
<td>306</td>
<td>26 (8.5)</td>
<td>1.5 (1.2-2.0)</td>
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<td>NRTI (France)</td>
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<td>DAA (France)</td>
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<td>24 (14.0)</td>
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<tr>
<td>&lt; 2 yrs</td>
<td>500</td>
<td>112 (22.4)</td>
<td>2.9 (2.5-2.5)</td>
<td>&lt;0.0001</td>
<td>2.9 (2.5-2.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;= 2 yrs</td>
<td>942</td>
<td>32 (3.4)</td>
<td>ref</td>
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1. CI excludes data for missing values
2. DEE direct antiviral treatments
3. , DEE and non-DEE treatments
4. CI excludes data for missing values

### 916 LOW RATE OF SEX-SPECIFIC ANALYSES IN CROI PRESENTATIONS IN 2018: ROOM TO IMPROVE

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1University of California San Francisco, San Francisco, CA, USA, 2Harvard T.H. Chan School of Public Health, Boston, MA, USA, 3Social & Scientific Systems, Silver Spring, MD, USA, 4Johns Hopkins University, Baltimore, MD, USA, 5University of California San Diego, La Jolla, CA, USA, 6YR Gaitonde Center for AIDS Research and Education, Chennai, India, 7Emory University, Atlanta, GA, USA, 8Stellenbosch University, Cape Town, South Africa, 9NIH, Bethesda, MD, USA, 10University of Pennsylvania, Philadelphia, PA, USA, 11Kenya Medical Research Institute, Kisumu, Kenya, 12Northwestern University, Chicago, IL, USA, 13University of Nebraska, Omaha, NE, USA, 14Emory University, Atlanta, GA, USA, 15Enhancing Care Initiative, Durban, South Africa, 16University of Arizona, Tucson, AZ, USA

Background: The National Institutes of Health, Food and Drug Administration, and journal editors require examination of sex as a biological variable in the design, analysis and reporting of studies, including clinical trials. As 52% of adults living with HIV worldwide are women, sex-specific analyses can provide insight into HIV prevention, pathogenesis, treatment, cure and HIV-associated conditions. CROI 2018 guidelines recommended reporting of sex-specific analyses. Members of the Women’s Health Inter-Network Scientific Committee (WHISC) of the ACTG and IMPAACT networks reviewed adherence to these guidelines in oral presentations during CROI 2018.

Methods: Two independent reviewers from WHISC reviewed each original oral presentation’s webcast to determine whether the abstract was relevant to both sexes and if it included human participants, animals, or specimens from humans or animals. If those criteria were met, reviewers assessed whether sex demographics were provided and whether sex-delineated outcomes or sex-stratified analyses were presented. If not, the reviewer determined whether an...
**Dealing with Depression and Anxiety**

**Background:**
The global burden for depression and anxiety remains high, and HIV-infected individuals are more vulnerable to experiencing these conditions. Our objective was to determine the association between depression and anxiety on initiation of antiretroviral therapy (ART) and the engagement in HIV care.

**Methods:**
We conducted a prospective clinic-based cohort study of HIV-positive adults at HIV testing from the Umlazi township of KwaZulu-Natal, South Africa. We measured depression using the Patient Health Questionnaire (PHQ-9) and anxiety using the Generalized Anxiety Disorder (GAD-7) scale, both of which have been validated in sub-Saharan Africa, before HIV testing. We used cutoff scores of PHQ ≥ 10 to indicate depression and GAD ≥ 10 to indicate anxiety, as these are recommended cutoff scores for assessing depression and anxiety in clinical settings. We used univariate and multivariate logistic regression and Cox proportional hazards models to analyze the data. We considered sex as a potential confounder and adjusted for other factors such as age, education, and socioeconomic status.

**Results:**
Among 1,878 HIV-positive adults enrolled, the mean (SD) age was 33.1 (9.1) years and 1,110 (59.1%) were female. The prevalence of depression and anxiety was 15.3% and 11.1%, respectively. In adjusted models, HIV-infected adults with depression had a lower odds of initiating ART within 90 days of testing positive (odds ratio [OR]=0.72, p=0.03), and slower ART initiation throughout the one-year study period (hazard ratio [HR]=0.84, p=0.01). Among those who initiated ART, depression was associated with a lower likelihood of missing medication refills (OR=0.66, p=0.04) and missing clinic visits (OR=0.56, p<0.01). Among those who initiated ART, individuals who reported anxiety symptoms had a lower likelihood of missing clinic visits (OR=0.58, p<0.01).

**Conclusion:** Our finding in an urban township of South Africa suggest that depression and anxiety are significant barriers to ART initiation and engagement in HIV care. Integrated care models that offer mental health treatment alongside usual HIV care may improve HIV-related outcomes.

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**Knowledge of HIV Status Decreases Depressive Symptoms Among Female Sex Workers**

**Background:**
The causal effect of knowledge of HIV status on depression is not well understood. It is thus a major worry that knowledge of HIV-positive status may result in depression, which may be a barrier to scaling innovative HIV testing interventions that move testing outside the health system and away from the support of trained counselors (i.e., HIV self-testing).

**Methods:** To estimate the relationship between HIV status and depression, we employ a quasi-experimental approach, individual fixed effects analysis — which controls for all observed and unobserved individual level confounders that do not vary over time. We use longitudinal data from two female sex worker (FSW) cohorts, constructed from randomized controlled trials of HIV self-testing delivery models in urban Ugandan and Zambian transit towns. Participants were provided access to free standard of care HIV testing services and two HIV self-tests (intervention arms only) over the course of four months. Participants completed quantitative surveys at months 0, 1, and 3. At each survey, participants self-reported their knowledge of HIV status. We used the PHQ-9 depression scale (range 0-27 points) to measure the severity of participants’ depressive symptoms (continuous scores) and prevalence of likely depression (scores ≥ 10 indicate clinical depression in this and other setting). To capture time-varying confounders shared by the participants, we controlled for calendar month and survey round.

**Results:**
The majority of the 1,965 enrolled participants (960 Uganda; 965 Zambia) changed their knowledge of HIV status over four months (57% Uganda; 67% Zambia). Knowledge of HIV status significantly decreased the severity of depressive symptom among participants in both Uganda and Zambia and significantly decreased the prevalence of likely depression in Zambia (Figure 1). In Zambia, the prevalence of likely depression (45.7% at enrollment) decreased by 14.3% (95% CI: -23.9% to -4.5%, p=0.002) with knowledge of HIV-negative status and decreased by 14.3% (95% CI: -23.9% to -4.5%, p=0.002) with knowledge of HIV-positive status.

**Conclusion:** Knowledge of HIV status, be it positive or negative, significantly decreased depressive symptoms in two diverse populations of FSWs. This is finding is consistent with literature suggesting that certainty about a health condition is less stressful than uncertainty, even if the results are unwanted. Expansion of HIV testing programs could have mental health benefits for FSWs.
TREATED MENTAL DISORDERS IN PRIMARY AND TERTIARY HIV CARE PROGRAMS IN CAPE TOWN

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Background: The adult 12-month prevalence of common mental disorders in the Western Cape, South Africa is 20% and lifetime prevalence is 40% (South African Stress and Health study 2009). Untreated mental disorders may lead to suboptimal antiretroviral therapy (ART) outcomes. We describe the incidence of treated mental disorders among adults on ART in Cape Town.

Methods: Routinely collected data from two HIV care programs in Cape Town were linked to available province-wide pharmacy dispensing and hospital discharge data using national identifiers. We included adults who initiated ART between 2004 and 2017 at the Tygerberg Academic Hospital, a tertiary care facility and the Gugulethu Community Health Center, a primary care facility. We used the Kaplan-Meier method to estimate the cumulative incidence of pharmacological treatments with psychiatric medication and hospital admissions for mental disorders (i.e. admissions for a mental, behavioral or substance use disorder [ICD10 F00–F99] or admission to a psychiatric ward) after ART initiation.

Results: We included 4,051 patients from Tygerberg and 11,312 patients from Gugulethu. Out of a total of 15,363 patients, 939 (6.1%) received pharmacological treatments: 645 (4.3%) received antipsychotics, 568 (3.7%) antidepressants, and 297 (1.9%) anxiolytics. 197 patients (1.3%) had been admitted to a hospital for a mental disorder: 48 patients (0.3%) for a schizophrenic disorder (ICD10 F20–F29), 44 (0.3%) for a mood disorder (F30–F39), 32 (0.2%) for other/unspecified mental disorders, and 84 patients (0.5%) had been admitted to psychiatric wards without a documented ICD10 diagnosis. Cumulative incidence of pharmacological mental health treatment (solid lines) at 10 years after ART initiation was 28.6% (95%-CI 26.4–31) at Tygerberg and 6.9% (95%-CI 6.2–7.6) at Gugulethu (Figure). Cumulative incidence of hospital admissions for mental disorders (dashed lines) at 10 years was 5.4% (95%-CI 4.3–6.8) at Tygerberg and 1.7% (95%-CI 1.4–2.1) at Gugulethu (Figure).

Conclusion: While it is expected that not all mental health conditions would be diagnosed and treated, an appreciable burden of mental health disorders could be ascertained in these cohorts of patients on ART. The higher incidence of ascertained mental health disorders in the hospital settings likely reflects a combination of differences in underlying incidence, diagnosis and ascertainment of diagnoses.

DATING VIOLENCE AND HIV-ASSOCIATED OUTCOMES AMONG ADOLESCENT SEXUAL-MINORITY MALES

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Background: Adolescent sexual-minority males (ASMM) in the United States are disproportionally affected by HIV and dating violence (DV) compared to their heterosexual peers. While previous research has typically focused solely on one-sided DV, recent studies suggest bidirectional violence in relationships is associated with increased HIV risk and may affect healthcare service use. However, this association has not been examined among ASMM. We used data from CDC’s National HIV Behavioral Surveillance to examine dating violence experiences of ASMM and estimate associations between DV profiles and behaviors known to increase HIV risk in 3 cities participating in the NHBS-Young Men who have Sex with Men pilot.

Methods: ASMM, defined as males aged 13-18 years who reported ever having sex with another male, gay/bisexual identity, or same-sex attraction, were asked about several past 12 month HIV-associated outcomes: condomless anal sex, ≥4 sexual partners, exchanged sex for money or drugs, sexually transmitted infection (STI) diagnosis, non-injection drug use, and HIV testing. DV experience in the past 12 months was divided into three profiles: DV perpetration only (DVP), DV victimization only (DVV), and DV perpetration and victimization (mutual DV). Using log-linked Poisson regression, we calculated separate adjusted prevalence ratios (aPR) for associations between DV profiles and HIV-associated outcomes. Models were adjusted for city and race/ethnicity.

Results: Of 5,488 ASMM, 6% reported DVP, 8% DVV, and 8% reported mutual DV. The majority of ASMM reporting any type of DV visited a healthcare provider in the last year (89%). Compared to those reporting no DV, ASMM reporting mutual DV were more likely to report condomless anal sex (aPR=2.47, 95% CI: 1.38–4.42), ASMM reporting DVP or mutual DV were more likely to report a STI diagnosis (aPR=2.71, CI: 1.09–6.68; aPR=2.71, CI: 1.30–5.62, respectively) drug use (aPR=2.33, CI: 1.12–4.85, aPR=2.45, CI: 1.26–4.94, respectively), and HIV testing (aPR=3.81, CI: 1.58–9.21, aPR=4.23, CI: 1.94–9.26, respectively).

Conclusion: Our findings suggest that DV is prevalent among ASMM. These results highlight that exposure to DV as a victim and perpetrator are associated with increased HIV-related behaviors. The majority of ASMM experiencing DV were engaged in healthcare suggesting an opportunity for provider-initiated screening for violence and additional integration of services to reduce HIV risk among this population.
921 MULTIPLE PREDICTORS OF SUICIDALITY AMONG HIV+ SUBSTANCE USERS IN 11 US CITIES

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Background: People living with HIV/AIDS have an elevated risk for suicide. Although HIV+ substance users are at even greater risk, few studies have been conducted to inform comprehensive management of suicide risk in this population.

Methods: Project Hope (CTN0049) was a 3-arm randomized controlled trial that tested six months of patient navigation (with and without financial incentives) compared to treatment as usual in HIV+ substance-using hospitalized patients. Project Hope recruited 801 patients from 11 hospitals in the U.S. from 2012-2014. Predictors of two time-varying outcomes were examined over 12 months: 1) any suicidal thoughts (past week); and 2) a composite measure of suicidality measuring the frequency of suicidal thoughts, considering methods for suicide, and making plans for suicide in the past week. Medical, structural, and psychosocial predictors of these outcomes at baseline, six, and 12 months were measured using mixed linear and logistic regression models.

Results: The sample was predominantly Black (78%), middle-aged (Mean = 44.6; SD = 10.0), and male (67%) with a median CD4+ count of 109 cells/mm3. Approximately 18% of participants reported any suicidal thoughts at baseline. The figure summarizes the percentage of participants reporting any suicidal thoughts, methods, or plans over the 12-month follow-up. More severe substance (Adjusted Odds Ratio [AOR] = 1.29; 95% CI = 1.07 – 1.55) and alcohol (AOR = 1.26; 95% CI = 1.02 – 1.55) use disorder symptoms were independently associated with greater odds of reporting any suicidal thoughts over 12 months. Hispanic/Latino ethnicity, a CD4+ T-cell count < 200 cells/mm3, injection drug use (IDU) during the past year, and more severe alcohol and tobacco use disorder symptoms significantly predicted higher suicidality composite scores over 12 months. In contrast, stable housing and greater social support were associated with significantly lower suicidality composite scores over 12 months. There were no intent-to-treat effects of patient navigation (with or without financial incentives) on any suicidal thoughts or suicidality.

Conclusion: Greater severity of alcohol, tobacco, and other substance use disorders as well as recent IDU are key risk factors for suicidality among HIV+ substance users. Findings also underscore the need for comprehensive approaches to address the medical, structural, and psychosocial factors that may modify suicide risk in this population.

922 HIV-1/2 DIFFERENTIATION IN THE US HIV TESTING ALGORITHM: HIGH BURDEN, LOW YIELD

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Background: Since 2014, the national algorithm for laboratory-based HIV testing has recommended a supplemental HIV-1/2 differentiation test as the second test for confirmatory HIV diagnosis to resolve issues of HIV-2 antibody cross-reactivity with HIV-1 specific tests and to identify potential HIV-2 infections. HIV-1/2 differentiation testing requires laboratories to acquire specialized equipment or to send out specimens to commercial reference labs for additional testing, which may increase cost and delay confirmation of infection. We therefore sought to assess the burden and yield of HIV-2 testing in the United States under the current algorithm, particularly regarding the HIV-1/2 differentiation test.

Methods: We used results reported to the U.S. National HIV Surveillance System during 2012-2016. HIV-2 mono-infection was defined as confirmed HIV-2 infection (e.g., positive HIV-2 RNA or DNA) in the absence of HIV-1 infection. Dual infection was defined as confirmed infection with HIV-1 (e.g., positive HIV-1 RNA or DNA) and HIV-2. Infections were defined as not confirmed for HIV-2 if an HIV-2 antibody result was positive but there was no confirmatory lab test reported.

Results: Among 202,536 HIV diagnoses reported during 2012-2016, the annual number of persons tested with an HIV-1/2 differentiation assay increased from 5,783 (23.5%) in 2012 to 32,126 (80.6%) in 2016. The annual number of confirmed HIV-2 mono-infections ranged from two to five. Four total dual infections were identified. Possible HIV-2 infection could not be confirmed for 115 (0.06%) persons.

Conclusion: During 2012-2016, use of HIV-1/2 differentiation tests increased substantially, which is consistent with the implementation of the new guidelines for the U.S. HIV testing algorithm. Despite increased testing, the number of confirmed and possible (i.e., undetermined) HIV-2 diagnoses remained extremely low. In light of the substantial burden yet low yield of HIV-1/2 serological differentiation in the national testing algorithm, it’s prioritization as the second step in confirmation of HIV infection merits reconsideration.
HIV SEROLOGICALLY INDETERRMINATE INDIVIDUALS: FUTURE HIV STATUS AND RISK FACTORS

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Background: Indeterminate HIV test results, where two EIA results contradict each other, are common, but little is known about longitudinal patterns in HIV testing results among those with indeterminate results or their sociodemographic and behavioral correlates. We assessed future HIV serological outcomes for people with indeterminate results and associated factors in Rakai, Uganda

Methods: 44,926 adults aged 15–49 years (total of 136,414 person-visits) from 1994 to 2011 in the Rakai Community Cohort Study were assessed. Modified Poisson regression models with generalized estimating equations were used to assess prevalence ratios (PRs) of subsequent HIV serological outcomes for participants with 2 or more visits (n=27,119) and factors associated with HIV serologically indeterminate results. Loreograms were used to assess the within person correlation of indeterminate results over multiple study visits

Results: The overall prevalence of HIV serologically indeterminate results was 4.6%. Participants with an indeterminate HIV test result were more likely to have an indeterminate result at subsequent visits compared to those with negative results (PR 1.19, 95% CI 1.11,1.27). Subjects with an indeterminate result were twice as likely to have a subsequent HIV positive result compared to those with a negative result (PR 2.28, 95% CI 1.96, 2.65). The within-person correlation of indeterminate results was autoregressive with individuals being more likely to test indeterminate closer in time to a prior indeterminate result. In regression analyses, indeterminate results were less likely to occur in women than in men (adjPR 0.77, 95% CI 0.71,0.83), in unmarried participants than in married participants (AdjPR 0.92, 95% CI 0.85,1.00), and in individuals with an education relative to those with no education (primary education: adjPR 0.85, 95% CI 0.78,1.00; secondary education: adjPR 0.79, 95% CI 0.68,0.91; post-secondary education: adjPR 0.73, 95% CI 0.57,0.93). Occupation, number of sex partners, religion and malaria status, were not associated with indeterminate results.

Conclusion: Individuals with HIV indeterminate serological results were more likely to have future indeterminate and positive HIV results compared to those with negative results. Gender, marital status and education were independently associated with indeterminate serostatus. Individuals with indeterminate results should be targeted for follow-up testing as they are more likely to eventually test positive.

ROUTINE TESTING OF NONPATIENTS INCREASES HIV DIAGNOSIS IN WESTERN KENYA

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Background: An estimated 150,000 (36%) persons living with HIV (PLHIV) in Homa Bay, Siaya, and Kisumu counties in western Kenya do not know their HIV status. In 2016, health facilities in these 3 counties implemented universal access to provider-initiated HIV testing and counseling services for both patients and non-patients accompanying patients to the outpatient department (OPD). We assessed HIV testing outcomes among patient and non-patient clients at several health facilities.

Methods: We retrospectively analyzed routinely collected program data from 7 high-volume (>1,000 monthly OPD visits) health facilities in western Kenya. Data from patient and non-patient clients aged 15 years or older who received HIV testing services in OPDs (March–December 2017) were included. We conducted a descriptive analysis of client characteristics and HIV testing outcomes. STATA v14.2 was used to calculate frequencies and proportions and to test for differences in characteristics and outcomes.

Results: During the 9-month period, of the 119,950 clients screened for HIV testing, 66% (79,021) were patients, and 34% (40,929) were non-patients. Overall, 73% (57,873) of patients and 90% (36,892) of non-patients were eligible for testing; testing uptake was >95% in both groups. Among 92,153 clients tested, the median age was 29 years, 57% (52,215) were women, and 40% (36,728) were non-patients. Although more non-patients were men (45% vs. 42%; p-value=<0.001), a greater proportion of patients were younger than 19 years (16% vs. 9%; p-value=<0.001) or older than 49 years (20% vs. 6%; p-value=<0.001). In total, 1.3% (1,185) of clients were HIV positive. Percent yield was higher among non-patients than among patients (1.5% vs. 1.2%; p-value=<0.001), overall and across age categories (Figure 1). Non-patients accounted for 45% (539) of all PLHIV identified, including 57% (117/205) of HIV-positive women aged 15–24 years, 46% (24/52) of HIV-positive men aged 15–24 years, 45% of HIV-positive men (169/377) and 44% of HIV-positive women (188/427) aged 25–49 years.

Conclusion: Nearly half of all HIV-positive individuals identified in the OPD were non-patients. Our findings suggest that in the setting of a generalized HIV epidemic, routine provider-initiated HIV testing and counseling of non-patients is a key strategy for timely diagnosis of PLHIV.

A NEW PREDICTION MODEL FOR CHLAMYDIA AND GONORRHEA SCREENING IN WOMEN WITH HIV

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Background: CDC recommends universal, annual chlamydia (CT) and gonorrhea (GC) screening in sexually active adults with HIV, irrespective of age and gender. The yield of annual CT/GC screening in older women who are engaged in HIV care is low. We applied new epidemiologic techniques using machine learning to develop a more precise prediction model to guide cost-effective STI screening in HIV clinic.

Methods: We calculated annual CT/GC testing and positivity rates among US women in HIV care during 2007-2016 as part of the 8 site, CFAR Clinical Network of Integrated Clinical Systems (CNICS) cohort. Data was collected from the electronic medical record and validated surveys for risk behaviors were conducted every six months using patient reported outcomes (PRO). Traditional prediction models using multivariable logistic regression were compared to new prediction techniques for classification using machine learning, random forest algorithms and gradient boosted regression trees, which calculates the importance of each variable in predicting the CT/GC infection outcome and avoids model overfitting.

Results: We analyzed data from 5,084 women contributing 158,745 HIV visits from 2007 to 2016. During the most recent year in care, median age was 47 years (IQR 39–55), 62% were Black, 70% had CD4 count >350 and 74% had HIV viral load <500 copies/mL. In terms of risk during the most recent year in care, 61% were sexually active, 13% had alcohol abuse, and 12% had active drug use.
Annual CT/GC positivity rates were stable across calendar years with estimates ranging from 1.9% to 3.4% (p=0.36). Prevalence was inversely associated with age: 2016 CT/GC positivity was 16%/3.9% in ages 18-24 compared to 1.1%/0.7% in age 50+ in every predictive model, despite including a variety of potential STI predictors (including race, region, recent STI, CD4/VL, sex partner characteristics, and substance use), age was the most important variable in predicting CT/GC positivity. In the full machine learning model with good performance (area under the curve [AUC] = 0.85), women age <35 years were more likely to have CT/GC and older age (55+) was protective against CTI (see Fig).

Conclusion: In a nationally representative sample of US women living with HIV, younger age (<35 years) was the most important predictor of CT/GC infection in a complex machine-learning model. Age-based STI screening among women engaged in HIV care should be reasonable to adopt and simple to implement, although a precise age threshold is yet to be defined.

926 SELF-TESTS FOR AT-HOME PARTNER TESTING ARE ACCEPTABLE & UTILIZED AMONG PREGNANT WOMEN

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Background: Increasing male partner and couples HIV testing among pregnant women in HIV high-burden settings remains a challenge. Secondary distribution of HIV self-tests within routine antenatal care (ANC) could provide an opportunity to close the gap on partner and couples testing.

Methods: In an ongoing cluster RCT (NCT03070600), we offered self-tests for at-home partner HIV self-testing (HIVST) to HIV-uninfected adult women seeking routine ANC services at 10 facilities in Siaya and Homa Bay, Kenya as part of the PrEP Implementation for Mothers in ANC (PrIMA) Study. Women were provided with instructions on how to use self-tests and received at least 2 oral-fluid-based rapid HIV tests (OraQuick Rapid HIV-1/2 Antibody Test, OraSure Technologies). Data on HIVST outcomes were ascertained in-person at one-month follow-up visits.

Results: Overall, 1299 pregnant HIV-uninfected women with male partners were offered self-tests for at-home partner HIVST. Median age was 23 years (IQR 20-28) and median gestational age was 24 weeks (IQR 20-28). Most women (75%) were in monogamous marriages; 11% were in polygamous marriages; 14% were unmarried. Overall, 43% reported having a partner of unknown HIV status; 52% had an HIV-infected partner and 5% HIV-infected. Among all women, 68% accepted self-tests. Self-test acceptance was 73%, 69%, and 20% among women whose partners’ HIV status was unknown, HIV-uninfected, and HIV-infected, respectively. Among women with partners of unknown HIV status, the most frequently (48%) reported reason for declining self-tests was needing to consult their partner; 10% reported fear of intimate partner violence (IPV). HIVST outcomes were available for 391 (73%) women with partners of unknown HIV status. Among these women, 56% offered self-tests to their male partner; 20% had not seen their male partner since accepting self-tests and 13% feared their partner’s reaction and/or IPV. Among women who offered self-tests to their partner, 92% reported their partner used the self-test and 96% used a self-test with their partner; 6% (2%) male partners with previously unknown HIV status tested positive using self-tests.

Conclusion: Within routine ANC, acceptance of at-home male partner HIVST was high and frequently led to couples’ HIV, enhancing mutual knowledge of HIV status. IPV was a barrier to acceptance and offering of self-tests. Given low male attendance at clinics, distributed HIVST is an attractive strategy to improve male partner HIV testing.

927 MALE PARTNER LINKAGE TO CLINIC STI-HIV SERVICES AFTER COUPLE EDUCATION & HIV TESTING

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Background: Home-based HIV testing and education has potential for increasing HIV testing and access to health information and services among men. However, the extent to which men follow-up to clinic based STI and HIV services is yet to be defined. We aim to understand how a home-based antenatal couple education and HIV testing intervention influences male partner follow-up to clinic-based HIV and STI services including STI treatment, HIV care and treatment, and medical male circumcision.

Methods: We conducted a randomized controlled trial of 601 unaccompanied pregnant women attending a first antenatal visit in Kenya from September 2013 to June 2014. Women and their male partners received either the intervention or standard clinic-based couple HIV and STI testing. Intervention men were invited to complete a home-based couple education and HIV syphilis testing during pregnancy or an invitation letter for standard clinic-based couple HIV testing. Education included identification of STI symptoms and the importance of clinic treatment, in addition HIV treatment for PMTCT and circumcision for HIV-negative men. Male self-reported outcomes were compared between arms at 6 months postpartum.

Results: Among 525 women who completed the study to 6 months postpartum with their infants, we reached 487 men (93%), resulting in 247 and 240 men in the intervention and control arm, respectively. Men of the intervention arm were more likely to respond to an HIVST consultation for symptoms (RR=1.59; 95%CI=1.33-1.89). Syphilis testing at the intervention identified 4 couples requiring treatment and all 4 of these men reported later seeking treatment. Sixty-one men were HIV-infected at study exit, among whom 17 (42%) of 40 intervention men and 5 (24%) of 21 control men were newly diagnosed during the period of the study. Four of 17 men and 3 of 5 men with newly diagnosed HIV in the intervention and control arms, respectively, reported linking to HIV care services (RR=0.69; CI=0.50-0.96). Few eligible men sought medical circumcision for HIV prevention (4 of 72 intervention and 2 of 88 control).

Conclusion: One-time home-based couple education encouraged male partners to seek clinic STI treatment, however, this was not the case for men with newly diagnosed HIV infection who would likely benefit from additional follow-up to link to care and treatment. Newly diagnosed men identified in home-based testing should be targeted to follow-up linkage to HIV care, which could result in equivalent or better access than clinic-based services alone.

928 OUTCOME AND COST OF 3 METHODS FOR INCREASING MALE PARTNER TESTING IN SOUTH AFRICA

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Background: Despite high uptake of HIV testing among pregnant women, male partner testing within antenatal clinics (ANC) remains low. This study
aimed to increase the proportion of men tested within ANC through promotion of facility and home-based HIV testing and distribution of HIV self-test kits.

**Methods:** This study was conducted at a large health center in the Bojanala District of South Africa from January 2017 – October 2017. All pregnant women, whose partner was HIV-negative or of unknown status, were offered three options for partner testing: (1) a partner invitation letter for facility testing; (2) home testing; or (3) up to 2 Ora-Quick self-test kits to take to their male partners. Instructions included with the self-test kit asked men to send a free “call me back” text to a counsellor after completing the test. Counsellors returned men’s calls, collected their results, and provided post-test counseling over the phone. Men could receive up to two R25 (~US$2) airtime vouchers: one for receiving post-test counseling and one for returning the self-test kit via text or physically to the facility. Cost information was collected for all three testing options and is presented in 2017 US dollars.

**Results:** We enrolled 1,166 women (mean age: 28 years, 72% single, 37% primigravida). HIV prevalence was 21% (12% newly diagnosed, 9% documented known positive). Figure 1 illustrates the uptake of facility, home, and HIV self-testing during the study. Records indicated that 223 men tested at the facility (6% concordant positive, 3% sero-discordant), while 28 men tested in the home (7% concordant positive). HIV self-test kits were distributed to 668 men. Of the 313 (47%) test kits returned either physically or via text, no discrepancies were noted between men’s interpretation of the test result and the result obtained by the counselor. The cost per partner tested was $77 for facility, $125 for home, and $83 for self-testing, while the cost per partner testing positive was $403, $1,483, and $2,742 respectively.

**Conclusion:** HIV self-testing was extremely popular among pregnant women as a method for partner testing, but even with incentives, only 60% of men received post-test counseling. The costs of HIV self-testing were similar to facility testing. Further operational research will be needed to ensure linkage to confirmatory testing and HIV treatment in the event of a positive HIV self-test, which will further reduce the cost per positive diagnosis associated with HIV self-testing.

### 929 INDEX CASE FINDING A STRATEGY FOR CLOSING THE GAP FOR HIV DIAGNOSIS IN TANZANIA

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**Background:** Tanzania adopted the 90-90-90 strategy as part of the National HIV Strategic Plan to end HIV by 2030. To achieve the first 90, the identification of PLHIV through HIV testing is key to the strategy’s success, and the whole cascade. In Tanzania, only 52% of PLHIV ages 15 to 64 years know their HIV status of which 55.9% are females and 45.3% are HIV positive males. To increase HIV case identification, the National AIDS Control Programme introduce new strategies including index case testing and partner notification services whereas a trained HTS provider ask people diagnosed with HIV about their sexual partners, drug injecting partners and biological children under 15 years from HIV positive mothers and offered them with HIV testing. These services are provided in both facility and community setting. The index client is the center and partners and contacts are either by the index or HIV testing providers

**Methods:** In 2017 reviewed its HIV strategic plans for 2018 to 2022, one among the new strategies the Ministry of health adopted is intensification of Index testing Services and Partner Notification services as one of the National strategy for Identification of the PLHIV. To prepare for facility and community index case testing, National guidelines, training package and HTS and Care treatment Monitoring tools were reviewed aiming to integrate index testing into existing health systems. Providers training and monitoring of services was important. Monthly data review meeting and identification of patient files which did not attempt to elicit index and took action. The Home Based Care teams facilitated contacts to come for testing. For convenience purposes, holidays and weekend are used for HIV testing services.

**Results:** From July 2017 to June 2018 total 12,455,037 people were tested among them 332,524 were HIV positive (2.7%). Through index tested 933,073 tested and Index positive 44,4796 (48%). Across the months, HIV positive yield increased with age and across the quarters, suggesting sexual partners testing. At the same time yield increase in lower age bands suggesting increased fidelity of index testing. Two third of the positive partners are from community index testing modality. The positive yield of sexual and needle sharing partners ranges from 10%-13%, while for children ranges from 1%-3%. These are the true index contacts that imply fidelity of the index testing.

**Conclusion:** Index case testing is a promising strategy for identification of New HIV case in Tanzania.

### 930 HIGH ACCEPTABILITY AND HIV YIELD AMONG PARTNERS OF KEY POPULATIONS IN CENTRAL AMERICA

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**Background:** Since December 2017, key population clinics, known as VICITS, have implemented assisted partner notification and partner testing in Guatemala, Honduras, and Nicaragua. We describe results of the first study utilizing four partner notification strategies to increase the uptake of HIV testing among partners of HIV positive key populations in these countries.

**Methods:** Individuals diagnosed with HIV between December 2017 and July 2018 at 9 participating VICITS clinics were included in the analysis. HIV diagnosis was performed on-site following national HIV testing guidelines. Newly diagnosed HIV individuals were offered partner notification/testing services and the rapid HIV reency assay (Sedia Biosciences) to determine reency of infection. Three assisted partner notification (dual, contract, provider) and one passive strategy (coupon) were offered to newly diagnosed cases. Non-identifiable demographic and behavioral data of index cases and their partners who returned to the clinic for HIV testing were captured using a smartphone based application on site and uploaded into a server daily. All analyses were conducted using STATA 13.0

**Results:** Of 241 index cases reported during the project period, 109 (45.2%) were from Nicaragua, 106 (44.0%) from Guatemala, and 26 (10.8%) from Honduras. Of these, 149 (61.8%) accepted partner notification and testing services, with higher acceptance seen in Nicaragua (105, 70.6%) followed by Honduras (86, 57.7%) and Guatemala (80, 53.8%) (p<0.01). Eighty (33.2%) index cases tested recent for HIV infection with 47 (58.8%) from Guatemala. A total of 206 sex partners were reported by index cases with 45 (21.8%) already linked to HIV testing services and 61 (29.6%) in care. Provider-assisted notification had the highest number of partners referred (39.3%) followed by contract (24.3%); however the highest proportion of partners returning to the clinic for HIV testing services was by contract (48.0%) followed by dual notification (46.9%). Of 63 partners tested for HIV, 44 (69.8%) tested positive and 8 (23.5%) tested recent for HIV. The highest HIV yield among partners was reported in Nicaragua (87.9%, p<0.01).

**Conclusion:** Partner testing at VICITS clinics was accepted and yielded high HIV positivity among partners in these three countries. Additional strategies are needed to increase notification and linkage of partners to HIV testing services among key populations.
HIV SELF-TEST UPTAKE, YIELD, AND LINKAGE EXPERIENCES AMONG KEY POPULATIONS IN LESOTHO
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Right to Care, Johannesburg, South Africa

Background: Lesotho has one of the world’s highest HIV prevalence of 25.6% with an annual incidence of 1.47%. While Lesotho seems to be on track in achieving the UNAIDS 90-90-90 targets, results from the recent 2017 LePHIA survey revealed that the 1st 90 was lagging behind at 77.2%, despite the increase and rapid scale-up of HTS in the country. Strategies to improve HIV testing uptake and yield are needed. We describe the HIVST uptake, yield and linkage to care among Men who have sex with men (MSM), Female Sex workers (FSW), and Partners of ART, ANC and PNC clients.

Methods: The 6-months HIVST project was undertaken in 19 facilities in 3 districts of Maseru, Mafeteng and Mohale’s Hoek targeting key populations, MSM and FSW and their partners, adolescents, partners of ART, ANC and PNC clients, men, migrants and patients who decline conventional HTS. Trained peer educators and HTS counsellors distributed the HIVST kits to eligible clients. The kits were coded and tracked. Clients were encouraged to drop the used kits in a drop-box. Reactive kits were tracked and their users encouraged to come for confirmation and linkage to care.

Results: A total of 5394 HIVST kits were distributed over the project period between March 14, 2018 and September 14, 2018. 2244 kits were returned (42% return rate), 2164 returned with results, 80 returned unused, 98/2164 kits were reactive giving a 5% HIV reactivity rate. Females (67) had higher reactivity when compared to males (31). High reactivity was observed among ages 20-39 with frequency was greater among non-recent testers. MSM, especially those who accessed HIVST in the second year only. The increase in non-recent testers was reactive among key populations, MSM and FSW and their partners, adolescents, partners of ART, ANC and PNC clients, men, migrants and patients who decline conventional HTS. Trained peer educators and HTS counsellors distributed the HIVST kits to eligible clients. The kits were coded and tracked. Clients were encouraged to drop the used kits in a drop-box. Reactive kits were tracked and their users encouraged to come for confirmation and linkage to care.

Conclusion: HIVST is feasible and generally acceptable in the target population. It should be scaled up as one of the strategies to improve HIV testing uptake and yield and linkage to care. A total of 5394 HIVST kits were distributed over the project period between March 14, 2018 and September 14, 2018. 2244 kits were returned (42% return rate), 2164 returned with results, 80 returned unused, 98/2164 kits were reactive giving a 5% HIV reactivity rate. Females (67) had higher reactivity when compared to males (31). High reactivity was observed among ages 20-39 with frequency was greater among non-recent testers. MSM, especially those who accessed HIVST in the second year only. The increase in non-recent testers was reactive among key populations, MSM and FSW and their partners, adolescents, partners of ART, ANC and PNC clients, men, migrants and patients who decline conventional HTS. Trained peer educators and HTS counsellors distributed the HIVST kits to eligible clients. The kits were coded and tracked. Clients were encouraged to drop the used kits in a drop-box. Reactive kits were tracked and their users encouraged to come for confirmation and linkage to care.
934 EFFECTIVENESS OF DISTRIBUTING HIV SELF-TEST KITS THROUGH MSM PEER NETWORKS IN UGANDA

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Background: Men who have sex with men (MSM) continue to be disproportionately impacted globally by the HIV epidemic and are also highly stigmatized in Uganda. Peer-driven HIV testing strategies can be effective in identifying undiagnosed infections. We examined peer HIV oral fluid self-test kits (HIVST) network distribution effectiveness in identifying undiagnosed HIV infection among MSM in The AIDS Support Organization (TASO).

Methods: From June to August 2018, 15 MSM peers from TASO were identified and trained in HIVST and basic HIV counseling and asked to distribute 10 HIVST each through one wave to MSM who have never tested in the previous six months and link participants who test positive to care. We compared MSM peer HIVST distribution strategy to TASO MSM community and hotspot testing approaches in identifying undiagnosed HIV infection using Fisher exact test

Results: Peers distributed HIVST to 150 MSM participants, 143/150 (95%) completed HIVST (72 Entebbe-urban) and 71 Masaka-semi-urban. A total of 8 participants were newly diagnosed with HIV infection; 8/72 (8.3%) from Entebbe and 2/71 (2.8%) Masaka. This is higher than 4/147 (2.7%) observed in the TASO program Jan-March 2018 (P=0.02). All participants newly diagnosed with HIV infection, disclosed their test results to their peers, were confirmed HIV positive, and initiated on ART. Compared to TASO MSM testing programs, 77% of the MSM reached through the peer HIVST distribution had never tested or tested in the last 12 months.

Conclusion: Our pilot findings suggest that distributing HIVST through MSM peer-network is effective and a promising strategy to increase uptake of HIV testing and reduce undiagnosed infections among MSM in Uganda

935 PREFERENCES FOR HIV SELF-TESTING AMONG SUBPOPULATIONS OF AUSTRALIAN GAY AND BISEXUAL MEN

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Background: In many high-income countries there are divergences in the HIV epidemic, with decreasing rates in locally born men who have sex with men but increasing or higher rates in recent migrants, ethnic populations and younger gay and bisexual men (GBM). Access to prevention services remains a challenge for these subpopulations, so innovative and discrete options for HIV testing are needed. We assessed the preferences among subpopulations of Australian GBM for HIV self-testing (HIVST) relative to other testing methods, and for how to access HIVST.

Methods: We conducted a discrete choice experiment (DCE) among HIV-negative GBM age ≥18 years in January 2018 through Grindr advertisements. Men were randomized to one of two DCEs which included a series of 16 choices, each with two alternatives for HIV testing: DCE1 for HIVST kit attributes (price, accuracy, test type, collection method and who collects the specimen) and DCE2 for HIVST access attributes (price, location, packaging and usage instructions). Latent class conditional logit regression explored variability in preferences among infrequent testers (tested ≥2 years ago or never tested), recent migrants (arriving in Australia <5 years), students, age and multiple partners in the last 6 months (i.e. more than one regular or casual partner). Random parameters logit model explored the most influential attributes on an individual's choice (Figure 1).

Results: Overall, 727 men participated in DCE1 and 275 men participated in DCE2. DCE1 contained four classes of men: 'recent migrants' (prefer fast results and cheaper tests, class size 23%); 'Australian-born men with multiple partners who were frequent testers' (prefer tests with shorter window periods and finger-prick HIVST, class size 33%), and 'students' (prefer fast results and oral HIVST, class size 28%). There were no significant differences in where to access HIVST according to age, number of partners in the last 6 months, recent migrant or student. There were three classes of men: 'price matters' (prefer purchasing kits online or off-the-shelf from pharmacies, class size 48%), 'infrequent testers' (prefer purchasing kits online and vending machines, class size 35%) and 'frequent testers' (disliked purchasing online and prefer purchasing off-the-shelf from pharmacies or staff from medical clinics, class size 7%).

Conclusion: Quantifying preference heterogeneity in HIV testing among subpopulations of GBM may be useful for tailoring public health messages and informing HIVST distribution methods.

936 WILLINGNESS TO USE HIV SELF-TESTING AMONG MSM FROM BRAZIL, MEXICO, AND PERU

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Background: HIV self-testing (HIVST), an important tool within the combined HIV prevention package, is commercially available in Latin America since 2015. This study aims to describe factors associated with willingness to use HIVST among men who have sex with men (MSM) from Brazil, Mexico and Peru.

Methods: MSM were reached via advertisements on Facebook and GSN apps for sexual encounters (Grindr and Hornet) from March-May 2018. Participants were cisgender men, ≥18 years old and HIV negative. Willingness to use HIVST was defined as selecting the highest option on a five-point Likert scale. Factors associated with HIVST willingness were assessed using a logistic multivariable model.

Results: A total of 43,687 MSM started the questionnaire; 8,790(20%) were ineligible and 18,916(43%) completed and were included in this analysis. Median age was 28 years (IQR: 24-34). Most were from Brazil (59%), followed by Mexico (30%) and Peru (11%). The majority reported low (39%) or middle (43%) monthly income, and 32% ≥ secondary education. Recruitment was primarily (85%) via GSN apps; 46% of MSM reported daily use of these apps. Although 53% scored ≥10 points on the HIV Incidence Risk for MSM scale indicating high risk, 65% had low perceived risk of getting HIV in the next year. A total of 3,715(20%) had never tested for HIV, mostly due to fear of a positive result (28%), low self-perceived risk (21%) and shame (24%). HIVST awareness and willingness were reported by 6,578(35%) and 7,609(40%), respectively.
In the multivariable model willingness to use HIVST was associated with:
being from Brazil compared to Peru (AOR1.74[95%CI1.55-1.94]); being 18-24 (AOR1.19[95%CI1.08-1.31]) or 25-35 years of age (AOR1.26[95%CI1.17-1.37]) compared to ≥35; secondary education (AOR1.33[95%CI1.24-1.44]) compared to ≤secondary education; middle income (AOR1.42[95%CI1.32-1.52]) and higher income (AOR2.10[95%CI1.90-2.31]) compared to low; daily use of GSN apps (AOR1.11[95%CI1.32-1.52]); willingness to use PrEP (AOR1.44[95%CI1.35-1.54]); and recent sex under the influence of drugs (AOR1.08[95%CI1.01-1.16]). Testing-related variables (lifetime HIV testing, HIVST awareness and HIVST barriers) were also associated with HIVST in the same model (Table).

Conclusion: Willingness to use HIVST was low among MSM from Brazil, Mexico and Peru. Efforts to increase HIVST knowledge and resolve perceived barriers are warranted. HIVST delivery platforms could be incorporated to PrEP implementation programs in these countries.

<table>
<thead>
<tr>
<th>Barriers to HIVST</th>
<th>OR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.89</td>
<td>0.027</td>
</tr>
<tr>
<td>Income</td>
<td>0.83</td>
<td>0.028</td>
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</table>

**Table 1. Factors associated with willingness to use HIVST in Brazil, Mexico and Peru.**

- **IMPACT OF EARLY ART INITIATION ON PERFORMANCE OF CROSS-SECTIONAL INCIDENCE ASSAYS**

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**Background:** Anti-retroviral treatment (ART) can impact results obtained with assays used for cross-sectional HIV incidence estimation, causing inaccurate HIV incidence estimates. We evaluated the relationship between the timing of ART initiation and the performance of two HIV incidence assays (the Sedia LAg-Avidity assay and the Johns Hopkins modified BioRad-Avidity assay).

**Methods:** We analyzed 302 samples from 55 individuals from, Thailand, Kenya, and Uganda (RV 217, Early Capture HIV Cohort Study). The average number of samples per participant was 5.5 (range 4-7); samples were collected 0.15 to 4.20 years after infection. Participants were assigned to one of three groups: never received ART (N=34); started ART 1-3 years after infection (N=12); started ART <1 year after infection (N=9). Samples were tested using the two assays. LAg-Avidity results from this cohort were compared to results from 17 participants in the Johns Hopkins HIV Cohort who started ART ~10 years after infection. All subjects on ART were virally suppressed.

**Results:** The rate of change for LAg-Avidity values in the first year after infection was 2.77 normalized optical density units (OD-n)/year for those who never started ART, and 2.65 OD-n/year for those who started ART 1-3 years after infection. Most participants (7/9) who started ART ≤1 year after infection, did not exhibit the usual increase in LAg-Avidity values early in infection. The mean decrease in LAg-Avidity values after ART initiation was 0.94 OD-n/year for those who started ART 1-3 years after infection, compared to 0.32 OD-n/year for those who started ART ≥10 years after infection (p=0.003). There was no statistically significant difference in BioRad-Avidity values among those who did and did not receive ART (p=0.069).

**Conclusion:** Individuals who started ART 1-3 years after infection had a significantly faster decline in LAg-Avidity values than those who started ART ≥10 years after infection. BioRad-Avidity values were not impacted by ART and use of this assay may provide more accurate incidence estimates in populations where ART use is unknown or inconsistent. Individuals who started ART <1 year after infection, (especially those that started ART ≥3 months after infection) had persistently low LAg-Avidity values; this could lead to overestimation of HIV incidence estimates.
Methods:

We present preliminary results of the first point-of-care recency test in key populations in Guatemala and Central America. The use of a point-of-care rapid recency test can enable healthcare workers to detect, monitor, and respond to recent HIV infection, enabling interventions to target those with highest risk. Rapid recency tests can also be used to evaluate the performance of point-of-care HIV tests, which are increasingly used in resource-limited settings.

Background:

Determining the recency of HIV infections can help meet the goals set by the United Nations’ 2030 Agenda for Sustainable Development to end the AIDS epidemic by 2030. Accurate recency testing can help identify high-risk populations and guide targeted interventions to prevent new infections. However, current recency assays are not widely available, and their performance in resource-limited settings has not been well-established.

Results:

Our results show a high proportion of recent infections among men who have sex with men (MSM) and transgender women (TGW). This data can help improve prevention interventions targeting these populations.

Conclusion:

The use of rapid recency tests in key populations can improve the detection and monitoring of recent HIV infections, enabling targeted interventions to reduce new infections and improve public health outcomes.

References:


Joseph B. Sempa, Gary Murphy, Jake Hall, Sheila M. Keating, Dylan Hampton, Shelley Facente, Kara Marson, Christopher D. Pilcher, Neil Parkin, Michael P. Busch, Alex Welte, Eduard Grebe, for the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA)

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Background: The HIV-1 Limiting Antigen Avidity EIA (LAg assay) used for detecting recent HIV infection is mainly from two manufacturers: Maxim Biomedical and Sedia Biosciences. We assessed and compared the performance, for incidence estimation, of the Maxim and Sedia LAg assays.

Methods: We ran both assays on a panel of 2,500 well-characterized HIV-1-infected specimens, most with estimable duration of HIV infection. We analysed concordance of assay results, assessed reproducibility using repeat testing, and estimated the critical performance characteristics of a test for recent infection — mean duration of recent infection (MDRI) and false-negative rate (FNR) — for a range of normalized optical density (ODn) recency discrimination thresholds, in combination with viral load thresholds. We further specified three surveillance scenarios defined by incidence, prevalence, treatment coverage, and subtype and infection-time distributions based on A) South African B) Kenyan, and C) concentrated MSM epidemics. Overall performance was measured as precision of incidence estimates.

Results: ODn measurements produced by the two assays on the same specimens were highly correlated (R² = 0.91). The Maxim assay produced systematically lower ODn values (mean ODn of 0.643 vs 0.749), largely as a result of higher calibrator readings. Correlation was greater for non-normalized OD readings (R² = 0.94) and the slope was closer to 1 (1.054 for OD vs 0.899 for ODn). Reproducibility of repeat testing (25 replicates of 3 blinded control specimens) was slightly greater for the Maxim assay (CV 8.9% to 14.8% vs 13.2% to 15.0%). At the ‘standard’ recency discrimination threshold of ODn ≤ 1.5, in combination with a viral load threshold (>1000), the Maxim assay had a longer MDRI of 201 days (95% CI: 180, 223) vs 171 days (152, 191) for Sedia, and a higher FRR.
in treatment-naive subjects (1.7% vs 1.1%). Under surveillance scenario A, the minimal relative standard errors achieved, in combination with viral load, were 22.8% (at ODn≤1.25 & VL>1000) for Maxim, and 23.4% (at ODn≤3.00 & VL>1000) for Sedia.

**Conclusion:** Maxim LAg ODn values can be approximately inferred from Sedia values with a conversion factor of 1.172, arising from differences in the reactivity of calibrators supplied in the assay kits. Performance for surveillance purposes was indistinguishable, although different thresholds were nominally optimal, and, crucially, different values of MDRI and FRR must be used in survey planning and incidence estimation.

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**943 ANTIBODY PROFILING IDENTIFIES NOVEL BIOMARKERS FOR DURATION OF HIV INFECTION**

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**Background:** Improved methods for cross-sectional HIV incidence estimation are needed for surveillance of the epidemic and for evaluating the impact of HIV prevention interventions. We used a massively-multiplexed system, VirScan, to identify novel biomarkers for estimating the duration of HIV infection. This system uses phage display immunoprecipitation sequencing to quantify antibody (Ab) binding to >3,300 peptides spanning the HIV genome.

**Methods:** We analyzed 403 samples from 57 African women with known duration of infection (14 days to 8.7 years), Ab binding to each peptide in the VirScan library was quantified, and peptides with the strongest association of Ab binding with duration of HIV infection were identified. We used generalized estimating equations to analyze the association of Ab binding with duration of HIV infection, accounting for repeat sampling from the same individuals. An
Results: We identified 309 peptides that had a significant association between Ab binding and duration of infection (p<0.05 after adjusting for multiple comparisons); 266 peptides had increasing Ab binding over time and 43 peptides had decreasing Ab binding over time. Four peptides were selected for further analysis (two with increased binding: in gp120 and gp41; two with decreased binding: in gag and pol). The binding scores for these four peptides were combined in a simple, unweighted, linear model to estimate the duration of infection. This estimate was highly correlated with the observed (true) duration of infection (p < 3 x 10^-6 in the independent sample set). The predictive value of the 4- peptide «serosignature» did not appear to be impacted by low viral load, low CD4 cell count, or HIV subtype. We also demonstrated that peptide engineering could be used to improve the association of Ab binding and duration of HIV infection.

Conclusion: Deep profiling of the antibody response to HIV infection identified novel peptide biomarkers for the duration of HIV infection. Peptide identified using this approach could be incorporated into simpler, high-throughput assays for cross-sectional HIV incidence estimation and other applications.

944 INCIDENCE OF HIV IN A NATIONAL COHORT RECEIVING PREEXPOSURE PROPHYLAXIS

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Background: Once daily tenofovir disoproxil fumarate/emtricitabine (TDF/ FTC) was FDA approved for pre-exposure prophylaxis (PrEP) for HIV prevention in July 2012. Veterans Health Administration (VHA) is the largest single provider of HIV care nationally thus offers a unique opportunity to examine PrEP in a large cohort. We aimed to determine the incidence of HIV infection in patients initiating PrEP and to describe relationships between HIV cases and patterns of PrEP use.

Methods: We conducted a retrospective cohort study among patients initiating PrEP in VHA between July 2012 and April 2016 using national VHA data and a previously described algorithm. We identified cases of HIV infection after PrEP initiation based on lab data (i.e. HIV serology and viral load results). We defined the date of PrEP initiation by date of first TDF/FTC fill. Adherence measure was calculated by determining the number of days with TDF/FTC in possession between the first day of the first TDF/FTC fill and the first day of the last fill in the year and dividing this by the number of days in this interval. We defined days without pills as numbers of days without TDF/FTC in possession prior to send date of first positive HIV test. To calculate HIV incidence, we considered the total patient time from first fill to the date of the last pill of the last fill available. We used chart review to determine patient-reported PrEP use around time of diagnosis.

Results: We identified 825 unique patients initiating PrEP with a median observed PrEP duration of 8 months and a cohort total of 736.6 years. Our cohort was composed of 57% men, 67% white patients, and with a mean age of 41 years. Two HIV infections occurred during active PrEP use for an incidence of 0.3 cases per 100 person years (Poisson exact 95% CI = (0.03, 0.98)). Both patients were infected with viruses containing the M184V mutation and had perfect adherence based on fill data. Four additional cases were observed in this cohort, diagnosed periods without PrEP. Among these 4, days without pills ranged from 4 to 162 days.

Conclusion: HIV infection was rare in this nationwide cohort of PrEP users. Most HIV infections occurred off PrEP, emphasizing the need for interventions to improve PrEP persistence in persons with ongoing risk.

945 HIV-1 INCIDENCE AND RISK FACTORS FOR ACQUISITION AMONG KENYAN MSM WITH ACCESS TO PrEP

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Background: There are no data on reduction of HIV-1 incidence following programmatic pre-exposure prophylaxis (PrEP) uptake by men who have sex with men (MSM) in sub-Saharan Africa. We assessed HIV-1 incidence and predictors of HIV-1 acquisition in at-risk MSM with access to PrEP in coastal Kenya.

Methods: Since June 2017, at-risk MSM followed at monthly visits in an HIV-1 vaccine feasibility cohort study were offered PrEP with adherence and risk reduction counselling, monthly HIV-1 testing and X-pert RNA Qual testing if acute HIV-1 risk criteria were met. Participants who acquired HIV-1 and had documented seroconversion were offered immediate ART. MSM were categorized as taking PrEP if they received a PrEP refill at their previous visit and wanted to continue PrEP during their current visit. Those not receiving a PrEP refill in their previous visit or discontinuing, re-starting or starting PrEP during their current visit were categorized as not on PrEP. Participants who reported missing 6 or less days of PrEP since their last monthly refill were categorized as ≥80% adherent. We used population-averaged multivariable Poisson regression with robust variance estimation to identify predictors of HIV-1 acquisition, analyzing PrEP use defined as above, as well as based on ≥80% reported adherence.

Results: Of 178 MSM who were offered PrEP, 142 (79.8%) started, of whom 31 (17.4%) stopped during follow-up. 89.4% of PrEP users reported ≥80% adherence. During a median follow-up of 14.3 (interquartile range: 8.9–14.6) months, 7 MSM acquired HIV-1, for an incidence rate of 4.1 (95% confidence interval [CI] 2.0–6.7) per 100 person-years. Of the 7 MSM who acquired HIV-1, 4 were not taking PrEP and 3 were, including 2 who reported ≥80% adherence. In multivariable analysis, group sex (adjusted incidence rate ratio [aIRR] 9.9, 95% CI 1.4–68.2) and a recent gonorrhea infection (aIRR 11.2, 95% CI 1.1–116.7) were independent predictors of HIV-1 acquisition, after adjustment for age, sexual orientation, and alcohol use. The aIRR for any PrEP use was 0.3 (95% CI 1.0–2.2). When ≥80% adherence was tested in the same model, the aIRR was 0.2 (95% CI 0.0–1.9).

Conclusion: HIV-1 incidence among at-risk MSM with access to programmatic PrEP was high, and did not differ by PrEP use or reported adherence. A substantial proportion of MSM stopped taking PrEP despite frequent risk reduction counselling. Further research on PrEP adherence and tenofovir drug levels in this cohort is necessary.

946 DOSE-DEPENDENT DECLINE IN BONE MINERAL DENSITY BY LONG-TERM TFV EXPOSURE IN iPrEx-OLE

Matthew A. Spinelli1, David Glidden2, Peter L. Anderson1, Valdilea Veloso1, Vanessa McMahan1, Susan P. Buchbinder1, Robert M. Grant1, Monica Gandhi1, for the iPrEx OLE Study Team
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Background: Oral tenofovir (TFV)-containing PrEP is associated with modest declines in bone mineral density (BMD). TFV-DP in dried blood spots (DBS) is a long-term marker of TFV exposure well-suited for evaluating the relationship between exposure and toxicities. Characterization of BMD change by estimated weekly pill-taking can assist clinicians in counseling patients, and potentially support use of intermittent PrEP for those at high risk of toxicity. We evaluate the association of dosing frequency and BMD decline for the first time in a large PrEP demonstration project.

Methods: Men who have sex with men and transwomen in the optional dual-energy X-ray absorptiometry (DXA) substudy of iPrEx OLE underwent DXA scans and DBS collection at baseline and every 24 weeks. TFV-DP levels were measured in DBS; average weekly dosing adherence was estimated from validated cut-offs. The mean % change in BMD was estimated in each strata of average weekly adherence using a linear mixed effects model.

Results: DXA/DBS data were available for 254 individuals over a median of 24 weeks in iPrEx OLE from 6/11-12/13. Overall, the median age was 31 years and 9% identified as transwomen; 15% were Black, 38% Latina. At baseline, 9% had Z-scores <−2 at either spine or hip and 3% developed low Z-scores after starting PrEP. There was a dose-dependent % decline in spine BMD by strata of increasing average weekly adherence (p<0.001 trend); the p-value for trend using the hip BMD outcome was 0.07. When including age, race/ethnicity, gender, body mass index, smoking, stimulant use, and alcohol use in an adjusted model, only DBS levels predicted spine BMD decline (p<0.001). All who developed low Z scores had detectable TFV, and most (57%) had high adherence (≥700 fmol/punch). The average mean decline in spine BMD was −1.15% (95% CI: −1.65, −0.64) for estimated daily adherence vs. −0.53% (95% CI: −1.06; 0.00) for ≥700 fmol/punch. The average Z-score for spine BMD was −0.77 (95% CI: −0.92, −0.62) for estimated daily adherence vs. −0.30 (95% CI: −1.0; 0.41) for ≥700 fmol/punch.
LOW URINE TFV BY A NOVEL IMMUNOASSAY IS ASSOCIATED WITH HIV SEROCONVERSION ON PrEP

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Background: Pharmacologic adherence measures can be used to interpret and support PrEP adherence. Current methods to analyze tenofovir (TFV) levels use liquid chromatography-tandem mass spectrometry (LC-MS/MS), which limits clinical use given cost and run time. We developed a novel antibody-based assay (in development for point-of-care (POC) testing) to quantify TFV in urine. We then tested the association of urine TFV with HIV acquisition in iPrEx OLE, a PrEP demonstration trial that enrolled men and transwomen.

Methods: Spearman's correlations between urine TFV levels via the immunoassay and hair TFV/emtricitabine(FTC) and dried blood spot (DBS) TFV-DP/FTC-TP levels via LC-MS/MS in iPrEx OLE were calculated. We calculated the sensitivity/specificity of an undetectable urine TFV for very low DBS TFV-DP levels (estimated <2 doses/week). We then compared levels of urine TFV by the immunoassay at visits where seroconversion was diagnosed, prior to HIV seroconversion, and in those who remained HIV-negative using Kruskal-Wallis' test. We evaluated the association of an undetectable urine TFV with HIV seroconversion using generalized estimating equations.

Results: Among 125 participants, the median age was 33, 14% were Black, 44% Latino. Urine TFV levels correlated with hair TFV (P=0.4, p<0.001), hair FTC (P=0.5, p<0.001), DBS TFV-DP (P=0.5, p<0.001) and DBS FTC-TP (P=0.7, p<0.001). When comparing an undetectable urine TFV to very low adherence by DBS (estimated <2 tablets/week) it was 70% sensitive, but 94% specific (100% sensitive/81% specific compared to undetectable DBS levels). The median urinary TFV level by the immunoassay was 15,000 ng/ml (IQR: 1,000-45,000) in those who remained HIV-negative; 5,500 (IQR: 1,000-23,000) in 11 individuals who eventually seroconverted (median 36 wks prior) and undetectable(<1000 ng/ml) in all 9 individuals at the time of seroconversion (p<0.001) (Figure). Undetectable urine TFV via the immunoassay was strongly associated with HIV seroconversion (OR 2.8; 95%CI: 1.5-5.4, p=0.002).

Conclusion: Urine TFV levels measured by a novel antibody-based assay were associated with protection from HIV acquisition among participants in a PrEP demonstration project. Urine TFV levels were correlated with other pharmacologic measures (hair/DBS), with high specificity in detecting sub-optimal dosing. Since immunoassays allow for POC testing, this novel assay could detect low PrEP adherence detected in real-time, allowing immediate intervention to optimize PrEP outcomes.

NO EVIDENCE OF SEXUAL RISK COMPENSATION AMONG HIV SERODISCORDANT COUPLES ON PrEP

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1University of Washington, Seattle, WA, USA, 2Kenya Medical Research Institute, Nairobi, Kenya, 3Kenyatta University, Nairobi, Kenya, 4Makerere University, Kampala, Uganda

Background: Recent studies suggest evidence of increased HIV risk-related sexual behaviors, such as condomless sex, following initiation of pre-exposure prophylaxis (PrEP) among men who have sex with men and female sex workers. We explored the effect of PrEP initiation on condomless sex among HIV serodiscordant heterosexual couples in Kenya and Uganda.

Methods: We used longitudinal data from HIV-uninfected participants enrolled in the Partners Demonstration Project, an open-label study of PrEP delivered to HIV-uninfected members of HIV serodiscordant heterosexual couples in Kenya and Uganda from 2012-2016. Participants were encouraged to use PrEP until their HIV-infected partner had used ART for ≥6 months (expected to be commensurate with viral suppression). At each quarterly visit, participants self-reported the frequency of sex and condom use with their study partner in the past month. We used linear regression models with individual-level fixed effects to measure the effect of PrEP initiation and time since PrEP initiation on reports of any condomless sex, controlling for the frequency of sex and self-reported pregnancy desires. We restricted our analysis to participants who reported any sex with their study partner in the past month during follow up time prior to the HIV-infected partner using ART for ≥6 months.

Results: Of the 1013 HIV-uninfected individuals enrolled in the study, 974 (96%) initiated PrEP and reported sex with their study partner in the past month. In the month following PrEP initiation, reporting any condomless sex decreased from 65% to 32%, a decline of 33% (95% CI -37% to -30%, p<0.001). The prevalence of condomless sex between study partners on PrEP then remained relatively constant over the next 20 months (median: 33%, IQR 30%-35%), Figure 1. The overall effect of time since PrEP initiation on condomless sex between study couples was a decline of 33% (95% CI -35% to -20%, p<0.001).

Conclusion: We found no evidence of sexual risk compensation following PrEP initiation in a cohort of Kenyan and Uganda HIV heterosexual serodiscordant couples followed for two years. Despite declines in condomless sex shortly after PrEP initiation, roughly a third of the HIV serodiscordant heterosexual couples in the study continued to engage in condomless sex, emphasizing the importance of continued PrEP use to sustain HIV protection.
Y-CHROMOSOME DETECTION & CONDOMLESS SEX IN SEX WORKERS IN THE SENEGAL PrEP PROJECT

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1University of Washington, Seattle, WA, USA, 2Institut De Recherche En Santé De Surveillance Épidémiologique Et De Formation, Dakar, Senegal, 3Westat, Inc, Rockville, MD, USA, 4Bill and Melinda Gates Foundation, Seattle, WA, USA

Background: Oral Truvada (FTC/TDF)–based PrEP has the potential to reduce HIV acquisition in female sex workers (FSW). Condom use is still recommended with PrEP due to concerns about adherence, HIV and STI acquisition. If FSW think they are protected from HIV from PrEP there may be incentives to reduce condom use: costs, client preference and ability to charge more for condomless sex. Self-reported condom use measures have significant limitations and biases. Detection of male Y-chromosomes (Y-c) in FSW genital swabs is a potential biomarker for condomless sex.

Methods: During the Senegal PrEP Demonstration Project, vaginal swabs were collected from women at baseline (pre-initiation of PrEP) and quarterly from PrEP initiation for 1 year. Vaginal swabs were frozen and tested in bulk at UW-Seattle. A random sample of 165 swabs were chosen for Y-c testing throughout the study period. The Quantifiler® Duo DNA Quantification Kit was used for Y-c detection. We analyzed self-reported condom use, STI (N. gonorrhoeae and C. trachomatis by NAAT (GC,CT)) and Y-c detection.

Results: 165 vaginal swab samples from 132 FSW were tested for Y-c. 164 samples gave valid results. 35/164 (21.3%) samples from 32 (24.2%) FSW contained detectable Y-c. Baseline: 7/42 (16.7%); M1-3: 11/39 (28.2%); M6: 6/21 (28.6%); M9: 4/25 (16.0%); M12: 2/37 (18.9%). Overall, there was no significant difference between baseline and PrEP use for detection of Y-c (P>0.05, Fisher Exact Test). In 32 FSW with serial Y-c sampling, 59.4% were always negative; 9.4% were always positive; 3.1% were initially negative and then positive; and 28.1% were initially positive and then negative. Eight FSW who were screened for Y-c presence had a positive NAAT for GC and/or CT at on least one visit, however only one FSW had concurrent tests positive for both Y-c and GC and CT. All FSW with available data (N=27), whom had detection of Y-c in vaginal swabs, also self-reported consistent condom use in the preceding 7 days with all clients. “Main partner” condomless sex did not account for the majority of Y-c detection.

Conclusion: A significant number (24.2%) of FSW had presence of Y-c on genital swabs suggesting lack of or inconsistent condom use. Y-c detection was consistent throughout the year—long study period, suggesting lack of risk compensation due to Truvada use. STI were infrequent. Condomless sex, as detected by Y-c in vaginal swabs, appears common in FSW who self-reported consistent condom use, casting doubt on this proxy for measuring their use.

Risk Compensation Following PrEP Discontinuation Among HIV-Serodiscordant Couples

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Background: Time-limited PrEP use by HIV-negative members of HIV serodiscordant couples until the HIV-positive partner achieves and sustains viral suppression with antiretroviral treatment (ART) is a highly effective HIV prevention strategy. Whether transitioning from self-controlled PrEP protection by the uninfected partner to relying on effective ART use by the HIV-positive partner results in a reduction in condomless sex has not been assessed.

Methods: Data are from the Partners Demonstration Project, a prospective open-label PrEP demonstration study in Kenya and Uganda. HIV-negative partners in serodiscordant couples were provided with PrEP and encouraged to discontinue PrEP when their HIV-positive partner used ART for >6 months (unless there were additional partners, ART adherence concerns, or immediate fertility desires). We included all couples with an HIV-negative partner that discontinued PrEP due to the HIV-positive partner being on ART for ≥6 months. Self-reported numbers of sex acts and condomless sex acts in the past month were collected quarterly. We used segmented regression with zero-inflated negative binomial models to compare the levels and rates of change of sexual behaviors before and after the HIV-negative partner discontinued PrEP. Multivariable models adjusted for demographics, baseline sexual behavior, pregnancy and couple relationship status.

Results: We included 562 couples who were followed for 622 person-years while the HIV-negative partner was on PrEP and for 506 person-years after PrEP discontinuation. HIV-negative partners had a median age of 30 years and were female in 33% of couples. In multivariable analyses, there was a 40% decrease in condomless sex acts reported after PrEP discontinuation (rate ratio [RR]=0.60, 95% CI: 0.41–0.87) where the HIV-negative partner was female. There was no change among couples where the HIV-negative partner was male (RR=1.03, 95% CI: 0.84–1.28), ≤30 years of age (RR=1.06, 95% CI 0.83–1.38), or >30 years of age (RR=0.77, 95% CI: 0.58–1.02). We found no difference in the rate of change in sexual risk behaviors after PrEP discontinuation regardless of HIV-negative partner gender or age.

Conclusion: Discontinuation of PrEP by HIV-negative partners due to sustained ART use by their HIV-positive partners did not result in an increase in sexual frequency or condomless sex. However, couples with female HIV-negative partners engaged in fewer condomless sex acts immediately after PrEP discontinuation.
Results: Among the 4,815 men (median age 29.2 years, Interquartile range [IQR]: 19.9, 42.8), overall MMC prevalence was 27.1% (95% Confidence Interval [95% CI]: 25.3-29.0%) peaking in the age group 15-19 years 38.7% (95% CI: 35.1-42.3%) and lowest in the age group 65+ years 7.9% (95% CI: 4.8-11.1%), p<0.0001. In the multivariate analysis, the odds of self-reporting MMC were significantly lower among men aged 25+ (aOR=0.69, 95% CI: 0.57-0.85) versus 15-24 yrs men; HIV positive men (aOR=0.55, 95% CI: 0.44-0.69), married men (aOR=0.72, 95% CI: 0.58-0.89) versus never married men; men with no education (aOR=0.52, 95% CI: 0.34-0.83) versus those with primary schooling. Compared to men in the middle wealth quintile, men in the highest quintile were more likely to self-report MMC (aOR=1.47, 95% CI: 1.09-1.97). Among males 18-49 years, MMC prevalence increased from 17% (95% CI: 16.2-18.4) in SHIMS1 to 28% (95% CI: 26.0-30.4) in SHIMS2.

Conclusion: Although a modest increase in MMC prevalence has been observed since 2011, the national and international targets will likely not be met. Innovative MMC approaches are needed to increase MMC prevalence, particularly among unmarried, low educated, and older men.

952 SHIKAMANA INTERVENTION SIGNIFICANTLY REDUCES HIV INCIDENCE AMONG FSW IN TANZANIA

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1American University, Washington, DC, USA, 2Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania, United Republic of, 3Tahoe Hopkins University, Baltimore, MD, USA, 4University of California San Francisco, San Francisco, CA, USA

Background: Female sex workers (FSW) are at dramatically heightened risk for HIV compared to women overall, with 13.5 greater odds of being HIV-infected globally. In Tanzania, modeling has shown FSW and their clients represent 23% of incident HIV infections. A prior systematic review and meta-analysis found that community-driven combination prevention models have been found to reduce the risk for HIV infection by 32% among FSW in Latin America and South Asia, but no proven models exist for FSW in sub-Saharan Africa.

Methods: We conducted a two-community randomized controlled trial of a community-driven combination HIV prevention model among 496 FSW (203 HIV- and 293 HIV+) enrolled in a longitudinal cohort in Iringa, Tanzania. The multi-level intervention model was developed based on extensive formative research and anchored on FSW needs and priorities. The intervention included: community drop-in-center and mobilization activities, peer education and navigation services, mobile HIV testing, clinical care provider and police coordination, Project Shikamana, a community-driven combination HIV prevention intervention developed by FSW in Iringa, Tanzania, was effective in significantly reducing HIV incidence. It is one of the first rigorously evaluated implementation models proven effective in reducing the heightened HIV risk among FSW in Africa.

Results: Among the 496 FSW participating in the intervention and control arms. A positive trend (RR 1.05), but non-significant difference across arms, was found in viral suppression among FSW in the intervention (40% to 50.6%) vs. control (35.9% to 47.4%) community.

Conclusion: Project Shikamana, a community-driven combination HIV prevention intervention developed by FSW in Iringa, Tanzania, was effective in significantly reducing HIV incidence. It is one of the first rigorously evaluated implementation models proven effective in reducing the heightened HIV risk among FSW in Africa.

953 INTERDISCIPLINARY INTERVENTION FOR HOSPITALIZED PWID MAY INCREASE MAT USE

Ellen F. Eaton, Andrew Westfall, Eddie A. Mathews, Cayce Paddock, Peter Lane, Michael Saag, Michael J. Mugavero, Karen Cropsey, Rachael A. Lee

University of Alabama at Birmingham, Birmingham, AL, USA

Background: Medication assisted therapy (MAT) can prevent HIV in persons who inject drugs (PWID). For PWID, acute bacterial infections are one of the few conditions for which they seek medical care. The UAB Hospital Intravenous Antibiotics and Addiction Team (IVAT) uses a 9-item risk assessment to classify one’s risk for continued IV drug use (i.e., low, moderate, or high) and inform discharge planning. We hypothesized that IVAT may improve MAT prescriptions on discharge, especially for “high” risk patients.

Methods: We compared outcomes of hospitalized PWID in the period before and after the IVAT. In the pre-IVAT period (January 2015-February 2016), we analyzed admissions in which IV antibiotics were received for ≥ 14 days by patients with a history of IVDU. In the post-IVAT period (October 2016-February 2018), all patients referred for IVAT consultation were included. MAT use on discharge included methadone, buprenorphine and naltrexone prescriptions. Specific substances used were defined by self-report and/or urine drug screen. Because the intervention included a risk assessment, we used logistic regression to determine if “high” risk participants were more likely to receive MAT on discharge in the post-IVAT era.

Results: A total of 37 and 98 patients met criteria in the pre and post-IVAT periods, respectively. 84% of pre-IVAT were opioid users compared to 80% post-IVAT. Most common bacterial infections in the pre and post-IVAT periods were endocarditis (57 and 34%, respectively) and vertebral osteomyelitis/abscess (13 and 17%). In the pre- and post-IVAT periods, Hepatitis C was present in 68 and 25%, respectively. Percentages of pre- and post-IVAT endocarditis, Hepatitis C were present in 68 and 25%, respectively, and HIV was present in 3 and 5%, respectively. Percentages of patients with an ID consult (97% vs 94%) and Addiction Medicine (78% vs 84%) consult remained unchanged. Although MAT prescriptions increased, the percentage of patients with an ID consult (97% vs 94%) and Addiction Medicine (78% vs 84%) consult remained unchanged. Although MAT prescriptions increased, the percentage receiving MAT did not (32% pre and post IVAT). There was an increase for those deemed “high” risk for continued IVDU (55%). In univariate logistic regression models of those receiving IVAT, neither risk category, age, race, gender, length of stay, or insurance status was associated with MAT prescription.

Conclusion: An interdisciplinary hospital-based intervention may increase the number of MAT prescriptions for PWID, a critical step in the opioid cascade of care and an effective tool in HIV prevention. There is no evidence to suggest
that MAT was preferentially prescribed to any group based on sociodemographic traits or results of 9-item risk assessment.

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<td>29 (32)</td>
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<tr>
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<td>18 (37)</td>
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<tr>
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<td>Median (Q1, Q3)</td>
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<td>25 (14.44)</td>
<td>17 (8.37)</td>
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**954 LINKAGE TO CARE IN THE PARTNER SERVICES PRE-EXPOSURE PROPHYLAXIS (PS-PrEP) STUDY**

Daniel S. Teixeira da Silva,1 Alida Bouris,2 Olivia Blocker,2 Billy Davis,3 James Harris,4 Ramona Bhatia,2 John A. Schneider1

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**Background:** Partner services is a public health intervention that contacts people who were exposed to sexually transmitted infection, including HIV. Black men who have sex with men (BMSM) have low uptake of pre-exposure prophylaxis. The Partner Services Pre-Exposure Prophylaxis (PS-PrEP) study tested the feasibility of integrating a tailored, in-person and mobile intervention into partner services to increase linkage to PrEP care for BMSM.

**Methods:** This single-blind randomized control trial recruited HIV seronegative, PrEP-naive BMSM aged 18-40 years old from partner services, network-based testing or health department STI testing sites. Inclusion criteria were being PrEP eligible, owning a cell phone, and living in metropolitan Chicago. The intervention consisted of an in-person session that used best linkage to care practices in tandem with cognitive-behavioral therapy and motivational interviewing techniques to develop a tailored Linkage Roadmap. This session was followed by 4 booster sessions for 12 weeks, with an optional in-person session for men reporting major barriers to PrEP care. The control group received a low threshold intervention through a phone-based PrEP linkage service that provided PrEP information and offered to schedule an initial PrEP visit. Men completed surveys and linkage to care was defined as having a PrEP care clinic visit within 3 months of enrollment. The difference between groups was determined by chi-squared test, p-value of 0.10, and effect size was determined using Cohen’s h.

**Results:** The study population (n=143) had a mean age of 26 years (SD=4.5), most identified as gay (62%), were employed full- or part-time (65%) and had a high school education or more (91%). Overall, 85% of the intervention group (n=75) completed the booster sessions and none had an optional in-person session. Analyses comparing intervention to control showed that a greater proportion of the intervention group were linked to PrEP care compared to the control group (n=68) (23% vs 12%; p = 0.08; Cohen’s h = 0.36).

**Conclusion:** This study demonstrated the feasibility of integrating a tailored PrEP linkage intervention into partner and network testing services. PS-PrEP increased linkage to PrEP care, and borderline statistical significance is likely due to a small study sample. Future studies that scale-up the PS-PrEP intervention with adequate power may be more likely to evaluate PS-PrEP’s efficacy, and further improve linkage to PrEP care among BMSM at increased risk for HIV infection.

**Table 1: Study population and linkage to PrEP care**

<table>
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<th></th>
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<th>Intervention</th>
<th>P value</th>
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<tbody>
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<td>Total</td>
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<td>75 (L00)</td>
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<td>25 (5)</td>
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<tr>
<td>Employment</td>
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<tr>
<td>Education</td>
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<td>0.56*</td>
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<tr>
<td>Health insurance coverage</td>
<td>62 (68)</td>
<td>56 (77)</td>
<td>0.14*</td>
</tr>
<tr>
<td>Linked to PrEP care</td>
<td>7 (10)</td>
<td>17 (23)</td>
<td>0.06*</td>
</tr>
</tbody>
</table>

N (%) except where noted otherwise

PrEP = HIV Pre-Exposure Prophylaxis

a) T-test
b) Fisher’s exact test
c) Chi-squared test
d) At least 1 PrEP care visit within 3 months of enrollment

* Full-time student, homemaker, unable to work due to illness, retired

**955 PILOT TEST OF A PrEP TELEmedicine SYSTEM FOR YOUNG BLACK MSM IN THE RURAL US SOUTH**

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**Background:** HIV disproportionately impacts young and Black men who have sex with men (MSM), yet PrEP uptake is low among these groups. MSM living in rural areas face additional barriers to care, with an estimated 108,000 PrEP-eligible MSM living more than a one-hour roundtrip drive from their nearest PrEP provider. We sought to develop a culturally appropriate, smartphone-based PrEP telemedicine system to increase uptake by decreasing barriers to care.

**Methods:** We developed and piloted ePrEP, a smartphone telemedicine system with video consultations, lab testing using home specimen collection, and when possible home prescription delivery. The goal was to develop a low-touch system that removes barriers to PrEP care. Eligible participants were Black MSM, aged 18-24, and lived in small towns or rural areas in Georgia and Mississippi. We piloted using ePrEP to initiate patients into PrEP care, who were then linked to care to the nearest PrEP provider. Outcomes were feasibility (PrEP prescription filled) and acceptability (‘acceptable’ or ‘very acceptable’ on a 5-point Likert scale, and willingness to reuse).

**Results:** Of 50 screened-eligible participants contacted, 64% (n=32) completed a baseline survey, returned the self-collected specimen kit, and were enrolled in the study. 9% (3/32) tested positive for HIV. 86% (25/29) with a negative test for HIV had a telemedicine visit and were prescribed PrEP. A confirmed prescription fill was determined for 72% (21/29). A call referring participants to care after PrEP initiation through the study was only moderately successful, with 43% (9/21) linked to care, but 33% (7/21) lost to follow-up and 24% (5/21) refusing linkage to care. For those refusing linkage, the most commonly stated reason was the distance to in-person care. Among 15 participants completing a follow-up survey, the system was rated as acceptable by: video (93%), mailing specimens (93%), urine collection (93%), rectal swab collection (73%), and
956 RAPID PrEP UPTAKE IN A PUBLICLY FUNDED POPULATION-BASED PROGRAM IN BRITISH COLUMBIA
K. Junine Toy1, Jason Trigg1, Wendy Zhang1, Paul Sereda1, Viviane D. Lima1, Katherine Lepik1, Mark Hull1, Raquel M. Espinoza1, Silvia Guillemi1, David Hall1, David M. Moore1, Rolando Barrios1, Julio S. Montaner1
1British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, 2Vancouver Coastal Health, Vancouver, BC, Canada

Background: In January 2018, a 100% publicly funded population-based HIV Pre-Exposure Prophylaxis (PrEP) program was launched in British Columbia (BC), Canada. Persons meeting BC PrEP eligibility criteria qualified for daily emtricitabine-tenofovir DF PrEP at no cost. Here we describe client and prescriber characteristics in the first 6 months of this province-wide program.

Methods: Clients enrolled from 1-Jan-2018 through 30-Jun-2018 were characterized by clinical and demographic characteristics. Prescribers were summarized by practice setting and HIV management experience. Comparisons between prescriber settings for PrEP enrolment, prescriber experience, and days from baseline HIV test to PrEP dispensing used Chi-Squared test for categorical variables and Wilcoxon rank sum test for continuous variables. Reported reasons for PrEP discontinuation and adverse drug reactions (ADR) were summarized.

Results: In the first 6 months, 1955 clients were approved for PrEP (see Table). Clients were 98.7% male, 0.9% transfemale, and <0.5% female, transmale, or other gender identity. Median (Q1-Q3) age was 35 (29-46) years. The majority (85%) of clients resided in the Greater Vancouver area. Most (73%) enrolees were PrEP-naive, the remainder transferred from client-paid or private insurance coverage. There were 351 enrolling PrEP prescribers, of whom 46% had no previous HIV care and treatment experience. 67% of PrEP clients were seen at a Sexual Health or HIV Specialty clinic. The 21 prescribers at specialty clinics had median 32 (5-70) PrEP clients each vs. 1 (1-2) clients for the other 330 prescribers (p<0.001). Time from baseline HIV test to first PrEP dispensing was median 10 (7-13) days for specialty clinic clients vs. 10 (7-14) days for clients seen in general medical settings (p=0.028). PrEP discontinuation was reported for 25 clients (1.3%). Reasons for stopping included: 16 clients no longer at risk, 4 PrEP not tolerated, 1 drug interaction, 4 unspecified. Although BC guidelines recommend daily PrEP, intermittent use was noted for 17 clients. Overall, there were 7 reports of possible PrEP ADRs: 2 dermatologic; 2 gastrointestinal; 2 renal; 1 transient neutropenia.

Conclusion: Rapid uptake of PrEP was seen in the first 6 months of the publicly funded program in BC, with almost 2000 clients enrolled by over 350 prescribers. Early participation was largely represented by the at-risk MSM population in urban areas. To date, there have been few reports of PrEP discontinuation or adverse reactions.

957 RISK FACTORS ASSOCIATED WITH NONPRESCRIPTION USE OF HIV PREEXPOSURE PROPHYLAXIS
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1Robert Koch Institute, Berlin, Germany, 2Praxis Jessen + Kollegen, Berlin, Germany

Background: HIV pre-exposure prophylaxis (PrEP) and the required tests (e.g. for HIV, STIs) before and during PrEP use are currently not covered by health insurances in Germany. Generic PrEP can be purchased with private prescriptions through pharmacies since October 2017. Before, non-prescription PrEP use with drugs obtained through informal sources was common. The objective of this study is to estimate the extent of continued informal PrEP use in a sample of German PrEP users and to identify possible risk factors associated with non-prescription PrEP use.

Methods: From 24 July to 3rd September 2018 we recruited PrEP users on geolocation dating apps for MSM, community-based HIV testing sites, and a community website in Germany for an anonymous online survey. Prescription PrEP use was defined as use of PrEP drugs obtained through German pharmacies and clinical trials; other sources were classified as non-prescription drug use. Risk factors associated with non-prescription PrEP use were assessed with logistic regression models adjusting for age, country of origin, and annual gross income.

Results: We recruited 2,005 current PrEP users into our study, 78.7% of which completed the survey. The median age of the participants was 38 years (IQR: 31–45). 95.4% of the participants obtained medical tests before starting PrEP and 86.9% receive medical tests during PrEP use. 80.4% of the participants obtained PrEP through prescriptions, whereas 19.6% used non-prescription sources (Table 1). PrEP users with non-prescription use were at higher risk of not obtaining medical tests before starting PrEP (OR = 8.1, 95% CI 4.5, 14.5) or during PrEP use (OR = 5.8, 95% CI 4.1, 8.3). We found that among daily PrEP users, non-prescription users were more likely to take PrEP fewer than 26 days per month on average than prescription PrEP users (OR = 3.7, 95% CI 1.5, 8.7).

Conclusion: Non-prescription PrEP users were less likely to use PrEP according to current guidelines. This could increase the risk for undetected HIV and STI infections in this group. Our findings highlight the need for patients to access PrEP through healthcare systems in order to allow safe use.
958 PREFERENCES FOR PREP DELIVERY AMONG FSW IN MALAWI USING A DISCRETE CHOICE EXPERIMENT

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1The Ohio State University, Columbus, OH, USA, 2University of North Carolina Project–Malawi, Lilongwe, Malawi, 3Harvard University, Boston, MA, USA, 4University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Female sex workers (FSW) in Malawi have one of the highest HIV prevalence estimates worldwide. Daily oral PrEP is an effective HIV prevention method, yet implementation strategies for optimizing PrEP delivery among FSW are lacking in Malawi and other sub-Saharan African settings. Discrete-choice experiment (DCE) is a quantitative technique for eliciting preferences by assessing how individuals value selected attributes of a program, product or service by asking them to state their choice over different hypothetical alternatives.

This study used DCE to elicit preferences for PrEP delivery strategies among FSW in Lilongwe, Malawi.

Methods: After formative work involving focus group discussions, a literature review, and cognitive interviews, a DCE survey was developed with five PrEP attributes: dispensing location, clinic wait time, provider gender, frequency of pick-up, and provision of additional services. In June–August 2017, 150 FSW in Lilongwe were enrolled using venue-based sampling. Interviewer-assisted DCEs were administered along with a brief sociodemographic and behavioral survey. DCE data were analyzed within STATA using mixed logit regression to evaluate preferences for each PrEP delivery attribute. Mean level utilities and relative importance between least preferred and most preferred within attributes were also calculated across all respondents.

Results: Dispensing location was the most important factor (β or relative utility=0.54; 95%CI: 0.50, 0.58) for PrEP delivery, followed by the provision of additional services (β=0.36; 95%CI: 0.31, 0.41). Clinic wait time was the least important factor (β=0.22; 95%CI: 0.16, 0.26). Respondents preferred to receive PrEP at family planning clinics or at non-governmental organization (NGO) supported drop-in centers compared to STI clinics, ART clinics, or NGO supported mobile clinics. Male was the preferred provider gender. Respondents preferred picking up PrEP every 2 months to monthly or every 3 months. The preferred additional service was cervical cancer screening, followed by contraceptive provision, while pregnancy testing and partner risk reduction counseling were preferred less.

Conclusion: This was the first study to examine PrEP delivery preferences in Malawi using DCE—a powerful elicitation tool which can be applied within other FSW and key populations at risk for HIV. Dispensing location and the provision of additional services should be prioritized when designing and rolling out FSW tailored PrEP delivery strategies in Malawi.

Table 1: Sources of PrEP in Germany

<table>
<thead>
<tr>
<th>Source</th>
<th>Participants [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription use</td>
<td>80.4%</td>
</tr>
<tr>
<td>Ordering online</td>
<td>9.9%</td>
</tr>
<tr>
<td>Buying drugs in another country</td>
<td>3.2%</td>
</tr>
<tr>
<td>Through friends</td>
<td>2.8%</td>
</tr>
<tr>
<td>Using medication from post-exposure prophylaxis as PrEP</td>
<td>1.0%</td>
</tr>
<tr>
<td>Buying from dealers</td>
<td>0.8%</td>
</tr>
<tr>
<td>Sex Parties</td>
<td>0.8%</td>
</tr>
<tr>
<td>Other sources</td>
<td>1.0%</td>
</tr>
</tbody>
</table>
960 CHANGES IN KIDNEY FUNCTION AMONG MSM INITIATING ON-DEMAND TDF/FTC FOR HIV PrEP

Geoffrey Liegeois1, Guillemette Antonis2, Gilles Pialoux1, Laurent Cotte3, Cécile L. Tremblay4, Catherine Capitant5, Eric Cua6, François Raffi, Eric Senneville6, Pierre Charbonneau1, Soizic Le Mestre8, Veronique Dore8, Laurence Meyer2, Jean-Michel Molina1, for the ANRS-IPERGAY Study Group

1 Hôpital Saint-Louis, Paris, France, 2 INSERM, Villejuif, France, 3 Tenon Hospital, Paris, France, 4 CHU de Lyon, Lyon, France, 5 Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada, 6 CHU de Nice, Nice, France, 7 CHU de Nantes, Nantes, France, 8 France Recherche Nord & Sud Sida-HIV Hépatites, Paris, France

Background: Pre-exposure prophylaxis (PrEP) with TDF/FTC is recommended for HIV prevention. Daily PrEP with TDF/FTC is associated with a small but statistically significant decrease in estimated glomerular filtration rate (eGFR) similar to HIV-infected patients on TDF. We wished to assess whether on demand TDF/FTC-based PrEP could minimize the risk of eGFR reduction among MSM.

Methods: We used data from the randomized double-blind placebo-controlled ANRS-IPERGAY trial conducted among HIV-uninfected MSM with creatinine clearance >60mL/min. eGFR was assessed using CKD-EPI equation at enrolment, months 1, 2 and every 2 months thereafter. We evaluated the mean decline slope of eGFR change from baseline and the occurrence of eGFR <70mL/min/1.73m² in the placebo and on-demand TDF/FTC groups. We also determined risk factors for eGFR <70mL/min/1.73m² in all patients initiating TDF/FTC included in the blind or the open-label extension phases of the study.

Results: During the blind phase, 201 participants were randomized to placebo and 199 to on demand TDF-FTC. Participants on TDF/FTC took a median number of 15 pills/month (IQR 11 to 21). The mean eGFR at baseline was 106mL/min/1.73m². During a median follow up of 9.3 months, the mean decline slope of eGFR was -0.13 and -0.07 mL/min/1.73m² per month in the TDF/FTC and placebo group, respectively (P=0.27). The cumulative proportion of patients with an eGFR <70 mL/min/1.73 m² at 12 months was higher on TDF-FTC 8% [95%CI 4-13%] than placebo: 3% [CI 0-6%], P=0.04. Compared to placebo, the risk of eGFR <70mL/min/1.73m² did not increase significantly in patients who took <15 pills/month: HR 1.75 [CI 0.65-4.7%] as compared to those using ≥15 pills/month: HR 2.54 [CI 1.07-6.04%]. Including both phases, 389 participants initiated on demand TDF/FTC with a median follow up of 19.1 months. Small but significant decline in eGFR occurred over time (mean slope: -0.09mL/min/1.73m² per month, P<0.01). Only 2 participants had persistent eGFR <60mL/min/1.73m² and 3 discontinued TDF/FTC for kidney function decline. The cumulative proportion of eGFR <70mL/min/1.73m² from baseline was 14% [9-18%] at 24 months. Factors associated with eGFR <70mL/min/1.73m² were high pill use (HR 1.9 [CI 1.03-3.49%], P=0.04), age > 40 years (P<0.01) and low eGFR at baseline (P<0.01).

Conclusion: On demand PrEP with TDF/FTC is associated with limited and non-clinically relevant eGFR decline, especially in young participants, those with low pill use and high baseline eGFR.

961 POINT-OF-CARE CREATININE TESTING WITHIN A PROGRAMMATIC PrEP DELIVERY SETTING

Jillian Pintye1, Felix Abuna2, John Kinuthia3, Harrison Lagat4, Kenneth K. Mugwanya5, Julia Dettinger1, Emily R. Begno1, Marlina Serede1, Joseph Sila1, Jared Baren1, Grace John-Stewart1, for the PrEP Implementation for Young Women and Adolescents (PrYWA) Program

1 University of Washington, Seattle, WA, USA, 2 University of Washington in Kenya, Nairobi, Kenya, 3 Kenyatta National Hospital, Nairobi, Kenya

Background: Creatinine (Cr) testing is recommended as part of PrEP delivery to identify pre-existing renal disease prior to PrEP initiation. Whether Cr testing is essential to assure safe use of PrEP is not yet known. We evaluated implementation of point-of-care (POC) Cr testing within a large-scale PrEP program in Western Kenya.

Methods: From June 2017 to August 2018, HIV-uninfected women seeking routine antenatal (ANC), postnatal (PNC), and family planning (FP) services were screened per national PrEP guidelines at 16 facilities in Kisumu, Kenya. Kenyan national PrEP guidelines currently recommend, but do not require, assessment of Cr clearance (CrCl) prior to PrEP initiation and annually thereafter when Cr testing is available. Prior to PrEP initiation, nurses measured height and weight, conducted Cr serum testing using validated Xpress StatSensor® POC machines (Nova Biomedical Cooperation, Waltham, MA, USA), and calculated CrCl by Cockcroft-Gault equation using a mobile application. If a single estimated CrCl measurement was below the normal range (<50mL/min according to Kenyan guidelines), the test was repeated before excluding that client from PrEP services. In a subset, we evaluated the cost and time required per test of the POC test compared to standard laboratory methods when a laboratory was present.

Results: In total, 4070 women were evaluated for PrEP eligibility and received POC Cr testing: 41% from ANC, 50% PNC, and 10% FP. The median age was 24 years (IQR 21-28) and 200 (5%) women were <18 years. The median CrCl was 113 mL/min (IQR 97-132) for ANC clients, 111 mL/min (IQR 93-130) for PNC, and 99 mL/min (IQR 82-120) for FP. Overall, 8/4000 (0.2%) women had estimated CrCl <50mL/min: 1 (0.06%) from ANC, 5 (0.2%) PNC, and 2 (0.5%) FP. POC Cr testing added a median of 3 minutes to PrEP eligibility assessments and cost USD 4.5 per test; in contrast, laboratory-based results took 3 hours and cost USD 5 per test.

Conclusion: It was feasible to implement POC Cr testing during PrEP delivery within MCH and FP settings and low CrCl was very rare among screened women. Given the rarity of medical ineligibility and safety of short-term PrEP, our data support the recommendation of not mandating Cr testing at PrEP initiation. PrEP programs could consider conducting Cr testing at one to three months post-initiation to reduce Cr testing-related time, costs and inconvenience.

962 IMMEDIATE PrEP INITIATION AT NEW YORK CITY SEXUAL HEALTH CLINICS

Tarek Mikati, Kelly Jamison, Demetre C. Daskalakis

New York City Department of Health and Mental Hygiene, Long Island City, NY, USA

Background: New York City (NYC) Sexual Health Clinics (SHC) patients are at increased risk of HIV acquisition. Immediate PrEP initiation (iPrEP) can increase PrEP uptake at walk-in settings where patient visits may be sporadic. At NYC SHC, tenofovir/emtricitabine is offered after a negative rapid HIV test but before results of other lab testing recommended for PrEP initiation are available. PrEP initiation is delayed (dPrEP) if patients report symptoms consistent with acute HIV (AH), history of kidney disease (KD) and/or history of active hepatitis B virus infection (HBV). We determined the prevalence of PrEP-related medical contraindications among candidates evaluated for iPrEP at NYC SHC.

Methods: Using medical record data, we examined demographics and PrEP-related laboratory testing outcomes among patients evaluated for PrEP initiation. Patients were included in the analysis if they were cis-gender men or women, age>18 years, and had no prior HBV serology and serum creatinine testing at NYC SHC. Patients were considered to have PrEP medical contraindications if they had a positive HIV viral load test (absolute contraindication), glomerular filtration rate < 60 ml/min (absolute), and/or a positive Hepatitis B surface antigen (relative).

Results: From January 2017- June 2018, 1437 patients were evaluated for iPrEP; 1387 (97%) qualified and 50 (3%) were delayed. Median age was 28 years (IQR 25-33) and the majority (95%, 1361/1437) were men who have sex with men. Of all 1437 patients, 33% were non-Hispanic (NH) white, 30% Hispanic, and 23% NH Black. One third were foreign born (32%; 456/1437). Inconsistent condom use for vaginal/anal sex in the prior three months was reported by 76% (1059/1437) of patients. The prevalence of any PrEP contraindication was more common among dPrEP than iPrEP patients (14% vs 0.7%; P<0.001) (see table). Patients ≥ 40 years were more likely to have any PrEP contraindication (3.0% vs 0.7%, p<0.01) (see table). Patients had significantly fewer laboratory tests performed within 10 days of iPrEP initiation among PrEP patients with subsequently identified absolute contraindications (N=4). Among dPrEP patients without any contraindication, only 35% (15/43) initiated PrEP within
60 days. Per protocol, no dPrEP patients with contraindications (N=7) initiated PrEP.

**Conclusion:** Immediate PrEP initiation is a promising model for walk-in settings; PrEP was rarely discontinued (0.2%) among PrEP patients due to absolute contraindications. There was a substantial loss to follow up among patients who delayed PrEP due to contraindications concerns.

<table>
<thead>
<tr>
<th>Contraindication Type</th>
<th>PrEP (n=1387)</th>
<th>dPrEP (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HIV (+ HIV viral load)</td>
<td>2 (0.1)</td>
<td>1 (2.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Chronic kidney disease (GFR &lt; 60 mL/min)</td>
<td>2 (0.1)</td>
<td>4 (8.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Active HIV infection (+ HIV SAg)</td>
<td>6 (0.4)</td>
<td>2 (4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any of the above</td>
<td>19 (1.3)</td>
<td>7 (14.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table:** Prevalence of Medical Contraindications to PrEP among PrEP Initiation Candidates: Immediate vs. Delayed; January 2017-June 2018; New York City Sexual Health Clinics.

963 **PrEP Persistence and Discontinuations in a Cohort of Young Black MSM in Atlanta, GA**

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1Emory University, Atlanta, GA, USA, 2State University of New York at Albany, Rensselaer, NY, USA, 3Kaiser Permanente, Atlanta, GA, USA, 4Orlando Immunology Center, Orlando, FL, USA

**Background:** HIV incidence is high among young black MSM (YBMSM) in the US, and effective implementation of pre-exposure prophylaxis (PrEP) has great potential to reduce new infections. Scale up of PrEP is ongoing in this key population; yet, we continue to observe high HIV incidence (interim estimate 6%/year) in our cohort of YBMSM with access to PrEP services. A better understanding of patterns of PrEP persistence and discontinuation among YBMSM is needed.

**Methods:** The EleMENt study is an observational cohort examining relationships between substance use and HIV risk behavior among HIV-negative YBMSM (n=299) aged 18-29 in Atlanta, GA. All participants were offered optional PrEP at each study visit over the 24-month follow-up. Clinical visits, labs, transportation, and navigation services for manufacturer assistance plans (MAP) to obtain no/low cost TDF/FTC were provided by the study. For initiators, we recorded time on and off PrEP based on frequent study surveys, prescription records, dates of MAP approvals, counseling notes, and other participant contacts. PrEP discontinuation events were defined as ≥2 week lapse in PrEP use. Time to first PrEP discontinuation was assessed with the Kaplan-Meier method, with a Cox proportional hazard model used to identify factors associated with discontinuation.

**Results:** After 483 person-years of follow up, 42% (125/299) of YBMSM initiated PrEP through the EleMENt program. Overall, PrEP initiators were "on PrEP" for 69% of possible person-time after initiation. 63% (79/125) discontinued PrEP at least once during study follow-up, and 68% of discontinuers (54/79) subsequently restarted PrEP. 22% (27/125) discontinued two or more times. The median time to first PrEP discontinuation was 219 days (95% CI 181-280). In a multivariable model, marijuana use (adjusted hazard ratio [aHR] 2.07, 95% CI 1.24-3.47), age <22 years (aHR 3.63, 95% CI 1.95-6.74) and having fewer than 3 sex partners (aHR 2.16, 95% CI 1.30-3.58) were associated with PrEP discontinuation.

**Conclusion:** Persistent PrEP coverage in this cohort of YBMSM was suboptimal and discontinuations, including multiple discontinuations, were common despite additional support services available through the study. Interventions to support PrEP persistence, especially for younger and substance using YBMSM, will be necessary to achieve full effectiveness of PrEP. For the future, regimens that do not require adherence to a daily medication could help facilitate PrEP persistence in this key population.

964 **Low Uptake of Preexposure Prophylaxis Among Kenyan Adolescent Girls at Risk of HIV**

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1Kenya Medical Research Institute, Nairobi, Kenya, 2University of Washington, Seattle, WA, USA

**Background:** A fifth (21%) of new adult HIV infection in Kenya occurs among adolescent girls and young women (AGYW) aged 15-24 years. Asymptomatic screening of young women for sexually transmitted infections (STIs) is not the standard of care in Kenya. It has been proven that infection with most STIs make it easy to acquire HIV and even easier to transmit it. We examined whether availability of STI screening results would impact HIV Pre-exposure prophylaxis (PrEP) acceptability and uptake in this population.

**Methods:** We recruited a prospective cohort of adolescent girls aged 16-20 years in Kenya. To be eligible, the girls were either sexually naive or had reported one lifetime sexual partner. The girls were followed up every 3 months with regular STI testing, consisting of nucleic acid testing (NAAT) of vaginal swabs for Neisseria gonorrhoea, Chlamydia trachomatis, and Trichomonas vaginalis, and vaginal gram stains for bacterial vaginosis (BV). ELISA assay for HIV and HSV-2 was also done. Starting in January 2018, girls were screened with an HIV risk assessment tool, including real-time STI testing and offered PrEP based on their score. We used descriptive analysis to characterize this cohort.

**Results:** We enrolled 400 girls, with a median age of 18.6 years (IQR 16-21); the cohort started prior to PrEP rollout in Kenya that was initiated in May 2017. After PrEP rollout, we identified 168 girls (42%) eligible for PrEP: 26 (15%) had a current STI, 133 (79%) reported inconsistent or no condom use with sex, 56 (33%) reported sex partner of unknown HIV status, and 6 reported (4%) other reasons. Median years of education for the eligible girls was 11 years. Ninety seven (57.3%) of these girls reported living in rural settlements. Only 9 (5.4%) of the girls who were offered PrEP accepted it. The PrEP acceptance rate appeared higher in those with current STI (15%), or 4 of 26 accepted PrEP than in those eligible for other reasons (4%), or 5 of 142 accepted PrEP. Girls who declined PrEP reported that they preferred condom use as a mode of HIV prevention.

**Conclusion:** In a cohort of young women with access to targeted PrEP services after testing positive for an STI, PrEP acceptance was low. Specific evidence of their own high HIV risk, coupled with low barrier access to PrEP, did not translate into PrEP uptake among these girls. Specific and targeted research of PrEP uptake reluctance in young women is needed. HIV risk awareness and knowledge is not enough to result in high PrEP uptake in this cohort.
High Curable STI Prevalence and Incidence Among Young African Women in HPTN 082

Sinead Delany-Morette1, Nyaradzo Mgodi1, Linda-Gail Bekker1, Jared Baeten2, Subash Pathak1, Deborah J. Donnell1, Denee Lennon2, Scott M. Rose1, Keolopile Mkgamathe1, Sheetal Kassim1, Shorai Mukaka1, Heather Noble1, Adeola Adeeye1, Connie L. Celum1

1Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 2University of Zimbabwe, Harare, Zimbabwe, 3Desmond Tutu HIV Foundation, Cape Town, South Africa, 4University of Washington, Seattle, WA, USA, 5Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 6Johns Hopkins University School of Medicine, Baltimore, MD, USA, 7FHI 360, Durham, NC, USA, 8University of the Witwatersrand, Johannesburg, South Africa, 9National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

Background: African women face overlapping HIV and STI risks. PrEP programs among men who have sex with men have seen high STI incidence, but few data from African women taking PrEP are available. Syndromic STI case management is the standard of care in Africa but is reliant on symptom recognition and has significant limitations in women.

Methods: HPTN 082 was conducted in Cape Town, Johannesburg (South Africa) and Harare (Zimbabwe) to evaluate the effect of drug level feedback on PrEP adherence. Sexually active HIV-negative women ages 16-25 were enrolled and enrollment vaginal swabs were tested for gonorrhea (GC) and chlamydia (CT) by nucleic acid amplification, and trichomonas (TV) by rapid test. Syphilis was assessed by serology. All women with positive test results received treatment. Repeat testing was conducted at 6 and 12 months.

Results: Of the 412 women who initiated PrEP at enrollment, the median age was 21 years and 84% reported a primary sex partner. Women reported a median of 4 vaginal sex acts (IQR 2.8) in the prior month and 35% reported that they never or rarely used condoms with vaginal sex. 22% reported anal sex in the past month and 27% never or rarely used condoms with anal sex; anal sex was more common among women with a partner ≥5 years older. At enrollment 296 of women had CT, 8% GC, 7% TV and 2% reactive syphilis serology. STI incidence was 29.5 per 100 person-years (p-yrs) for CT (95% CI 24.3, 35.4), 12.2 per 100 p-yrs for GC (95% CI 9.1, 16.2), and 6.9 per 100 p-yrs for TV (95% CI 4.6, 10.1). The majority of incident STIs were new infections: 74% of 113 CT infections, 40 of 47 GC infections, and 21 of 27 TV infections were diagnosed in women who did not have these infections diagnosed at enrollment.

Conclusion: The prevalence and incidence of treatable STIs were high among young women in a PrEP demonstration project in South Africa and Zimbabwe. Most incident STIs were new diagnoses, and unlikely to be reinfections or treatment failures. These data underscore the limitations of syndromic case management to control STIs in at-risk women, and the need for more sensitive diagnostic approaches. Innovative strategies that reduce STI acquisition and complications and their potential impact on future fertility need evaluation within the context of PrEP services.

High Prevalence and Antibiotic Resistance of M. genitalium Infections in MSM on PrEP

Beatrice Berco1, Isabelle Charreau1, Clotilde Rousseau1, Constance Delaegerve1, Christian Chidiac1, Gilles Pialoux1, Catherine Capitant1, Nadege Bourgeois-Nicolaos1, Francois Raffi1, Sabine Pereyre1, Eric Senneville1, Laurence Meyer1, Cecile Bebear1, Jean-Michel Molina1, for the ANRS Ipergay Study Group.

1Hôpital Saint-Louis, Paris, France, 2INSERM, Villejuif, France, 3Hôpitaux Civils de Lyon, Lyon, France, 4AP–HP Paris, France, 5CHU de Nantes, Nantes, France, 6CHU de Bordeaux, Bordeaux, France, 7Centre Hospitalier de Tourcoing, Tourcoing, France

Background: Mycoplasma genitalium (MG) is an emerging pathogen among MSM with raising rates of antibiotic resistance. We assessed the prevalence and incidence of MG infection in MSM enrolled in the open-label phase of the ANRS IPEGAY trial with on demand TDF/FTC for HIV prevention and the impact of doxycycline postexposure prophylaxis.

Methods: During the open-label phase of the ANRS IPEGAY trial, participants could also be enrolled in a prospective randomized (1:1) open-label sub-study of postexposure prophylaxis (PEP) with doxycycline. All subjects were tested at baseline and at 6 months by real-time PCR assays for MG detection in urine samples, oro-pharyngeal and anal swabs. Resistance to azithromycin (AZM) and to fluoroquinolones (FQ) were investigated by the detection of mutations in 235 RNA (ResistancePlusSM MG test, SpeeDx) and in parC determining region, respectively.

Results: From July 2015 to January 2016, 210/232 (90.5%) participants randomized in the PEP study were tested. MG prevalence at baseline was 10.5% all sites combined (95% CI: 6.6-15.9), and was 6.3%, 4.3% and 0.3% for urine, anal and throat sites, respectively. Ten participants acquired MG genitalia infection at the 6-month visit, 6 participants in the PEP arm (6.7%) and 4 in the no PEP arm (4.9%, p=0.75). These infections were detected in urine (n=5), anus (n=5) or throat (n=1, combined with anus). The overall rate of MG resistance (prevalent and incident cases) to AZM and FQ was 69.6% and 14.8%, respectively, with no difference between arms (p=1.00 for AZM, p=0.27 for FQ). The MG isolates were resistant by the presence of the substitutions A2058G/T or A2059G in the 23S rRNA and by FQ by the mutations S83I/R, D87Y and A88I in the QRDR of the topoisomerase ParC.

Conclusion: The prevalence of MG infection among MSM on PrEP with on demand TDF/FTC was high and its incidence was not decreased by doxycycline prophylaxis with a similar high rate of AZM- and FQ-resistance, raising challenging issues for the treatment of this STI.

967 Association of PrEP Use and Past and Current STIs Among MSM in Washington, DC, 2017

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Background: While daily, oral pre-exposure prophylaxis (PrEP) reduces HIV transmission risk, there is a growing concern of its potential association with elevated sexually transmitted infections (STIs). It is unclear whether increased STI diagnoses are a result of initial followed by regular STI testing among PrEP users or from an actual increase in risk while on PrEP. We examined the association between PrEP use and past year and current bacterial STIs among men who have sex with men (MSM) in the DC metro area.

Methods: We used data from the 2017 National HIV Behavioral Surveillance conducted in Washington, DC. MSM recruited via venue-based sampling completed a behavioral survey and HIV test and provided pharyngeal and rectal swab specimens. HIV-negative MSM who were PrEP eligible were included in the analysis (e.g., reporting condomless anal sex). Participants reported on past year PrEP use and physician diagnosis of either Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (GC) in the past year. Current CT (CT and/or GC) was assessed via lab testing of pharyngeal and rectal specimens. Multivariable logistic regression was used to assess the associations between past year PrEP use and past year and current bacterial STIs among men who have sex with men (MSM) in the DC metro area.

Results: Of 275 eligible participants, 41% used PrEP in the past year. PrEP users were more likely to be white and have ≥20 partners in the past year. Overall, 25% self-reported a STI diagnosis in the past year, and 13% were currently STI-positive via lab diagnosis. After adjusting for other confounding factors, past year PrEP users were three times as likely to self-report a STI diagnosis in the past year (aPOR=3.0, 95% CI:1.43, 5.42) compared to non-PrEP users. However, in adjusted analyses, those using PrEP in the past year were not more likely to be currently infected with an oral or rectal STI compared to those not on PrEP (aPOR=1.70, 95% CI:0.69, 4.3).

Conclusion: PrEP use was strongly associated with past year STIs but not with being currently infected, suggesting that being on PrEP may play a role in earlier, active clinical STI screening, diagnosis and treatment. PrEP users regularly interface with the medical system, leading to more opportunities for screening, diagnosis, and treatment, which may have resulted in the lower prevalence of active STIs diagnosed at the time of the survey. Future studies should examine the association of PrEP use with STI diagnosis in conjunction with treatment and use of health services.
968 DETECTED EXTRAN GENITAL STI AMONG US MSM BY PrEP STATUS
Johanna Chapin-Bardales1, Michelle L. Johnson Jones1, Robert D. Kirkcaldy2, Kyle T. Bernstein1, Chirsti Phillips1, John R. Papp1, Henry F. Raymond1, Jenieeive Opolu, Sarah L. Braunecker1, Emma C. Spencer1, Salma Khuwaja1, Cyprian Weinert1, for the NIH Study Group

Background: MSM aged ≥18 years were recruited via venue-based sampling to participate in the 2017 National HIV Behavioral Surveillance. In five cities (San Francisco, Washington, DC, New York City, Miami, Houston), participants completed a questionnaire and were offered HIV testing as well as pharyngeal and rectal testing to detect gonorrhea and chlamydia. The prevalence of extragenital STI was high for both MSM on PrEP and those not on PrEP. The positivity of extragenital gonorrhea and chlamydia among MSM who did and did not report PrEP use in the past year. We also examined PrEP use and STI testing in the past year and condomless anal sex with a male partner at last sex.

Results: In the five cities, 533 of 1922 (29%) self-reported non-HIV-positive MSM reported using PrEP vs. not using PrEP in the United States.

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972 CHANGES IN HIV PrEP AWARENESS AND USE AMONG MEN WHO HAVE SEX WITH MEN, 2014 VS 2017

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Background: The US Food and Drug Administration (FDA) approved the first drug for daily HIV pre-exposure prophylaxis (PrEP) use in 2012. Subsequent to FDA approval, efforts have been made to raise awareness and use of HIV PrEP among men who have sex with men (MSM) and those who are at increased risk for acquiring HIV infection. We evaluated changes in PrEP awareness and use among MSM in the US overall and by race during 2014 and 2017 using National HIV Behavioral Surveillance (NHSBSS) data from 20 U.S. cities.

Methods: Men were recruited at events frequented by MSM in each city using venue-based sampling. We used log-linked poisson regression models with generalized estimating equations clustered on event to estimate the

prevalence ratios (PR) and 95% confidence intervals (CI) for PrEP awareness and use, adjusted for income and health insurance. Analyses were limited to HIV-negative men who reported substantial risk for HIV infection consistent with PrEP indications (had either a male sex partner who was not known to be HIV negative or >1 male sex partner in the past 12 months and had either a sexually transmitted infection or condomless anal sex with a male partner also in the 12-month period).

Results: Among 22,117 male respondents in 2014 and 2017, the mean age was 30; 46% were White, 22% Latinx, 15% Asian, 13% Black, 4% other; 86% were men, 14% TW/NB. Over the past 6 months, the mean number of anal/vaginal sex partners was 7, and 74% reported condomless sex; 25% reported an STI in the past year. Overall, 96% had heard of PrEP, 47% had initiated PrEP, 33% were currently on PrEP, and 32% reported high adherence. Among 244 pts never on PrEP, most (81%) expressed interest in taking it, but only 61% knew where to get PrEP, and few (36%) had talked with a provider about PrEP. In multivariable analyses, higher education, having a primary provider, and drug use were associated with PrEP initiation; younger age, other race, and TW/NB were associated with lower persistence; sex of partner was associated with initiation and persistence (Table). Among 63 PrEP discontinuers, median duration of use was 7 months; the most common reasons for stopping PrEP included not feeling at risk for HIV (46%), insurance/access issues (36%), side effects/concerns (13%), and travel (10%). Among never/prior PrEP users, a substantial proportion would consider starting/restating PrEP if offered on-demand PrEP (84%/73%), long-acting injectable PrEP (56%/68%), or a percoital rectal formulation (douche/suppository) (32%/46%).

Conclusion: While PrEP initiations are relatively high in the SFBA, disparities in persistence exist, particularly in youth and TW/NB. Efforts to address cost/access barriers are critical to reversing disparities. Novel PrEP regimens and formulations could increase PrEP uptake and persistence.
**974 INFLUENCE OF PrEP4LOVE CAMPAIGN ON PrEP UPTAKE AMONG YMSM IN CHICAGO**

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Northwestern University, Chicago, IL, USA

**Background:** While there have been significant increases in awareness of pre-exposure prophylaxis (PrEP) in recent years, uptake remains relatively low in populations most impacted by HIV — particularly young men who have sex with men (YMSM). This may partially be attributed to the lack of conversations between eligible individuals and their providers about PrEP and sexual health in general. Many major cities have launched campaigns aiming to address this gap by using sex-positive messaging to empower individuals to be proactive in seeking out a PrEP prescription. In 2016, the citywide PrEP4Love campaign launched in Chicago. The campaign depicted racially diverse couples with catchy phrases (“Spread Tingle”) in a variety of settings, including bus stops, fliers, and bar coasters. The campaign linked interested parties to additional information about starting PrEP, including a list of providers in Illinois.

**Methods:** RADAR is a longitudinal cohort study of YMSM to investigate multilevel factors associated with HIV infection in Chicago. At baseline, participants reported being assigned male at birth, aged 16–29 years, and either identified as LGBT or reported sex with another man. Between June 2017 and April 2018, additional questions were added to the core survey regarding awareness of the PrEP4Love campaign.

**Results:** 75.9% of the 700 people responding to PrEP4Love questions had seen the ads at least one location. Most saw them online (57.8%), at pride events (95.4%), through friends (35.0%), or at a healthcare provider’s office (32.0%). Participants who saw PrEP4Love ads were significantly more likely to have used PrEP in the prior 6 months (OR = 1.87; 95% CI: 1.15, 3.07). Further, those who saw PrEP4Love ads were nearly three times as likely to have spoken with a healthcare provider than those unaware of the campaign (OR = 2.77; 95% CI: 1.23, 5.39).

**Conclusion:** A multimedia PrEP campaign in Chicago was effective at reaching populations at greatest risk for HIV — YMSM. Seeing ads for PrEP4Love was associated with provider conversations as well as PrEP initiation, two major outcomes for the campaign. Although the impact of citywide campaigns can rarely be evaluated, we saw evidence for the success of PrEP4Love. To encourage PrEP uptake among at-risk populations, other jurisdictions need eye-catching, rare campaigns similar to Chicago.

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**975 ASSOCIATION OF HIGHER RISK AND PrEP AWARENESS AMONG MSM IN BRAZIL, MEXICO, AND PERU**


1University of California Los Angeles, Los Angeles, CA, USA, 2Universidad Peruana Cayetano Heredia, Lima, Peru, 3Instituto Nacional de Infectologia Evandro Chagas (INI/Fiocruz), Rio de Janeiro, Brazil, 4Clínica Especializada Condesa, Mexico City, Mexico, 5Instituto Nacional de Salud Pública, Mexico City, Mexico, 6Ramón de la Fuente Muñiz National Institute of Psychiatry, Mexico City, Mexico

**Background:** PrEP has been publicly available in Brazil since early 2018 and through demonstration projects in Mexico and Peru since mid-2018. We assessed the association between higher risk of HIV infection, indicative of PrEP eligibility, and PrEP awareness among men who have sex with men (MSM) from these countries.

**Methods:** MSM were recruited to complete an online survey via advertisements on Facebook, Grindr and Hornet from March–May 2018. Eligible individuals were cisgender MSM, ≥18 years old, HIV negative or of unknown status, lived in these countries and provided informed consent. Higher risk was defined using a CDC score indicating increased risk of HIV infection and the suggested cutpoint of 10. We used Poisson regression models to calculate adjusted prevalence ratios (aPR) testing the association between higher risk and PrEP awareness; sociodemographics and other risk variables were considered potential confounders. Analyses were conducted in STATA 14.

**Results:** After exclusion criteria were applied, 19,457 MSM were available for analysis of the 43,687 who began the questionnaire. Median age was 28 (IQR: 24–34), most respondents were Brazilian (58%), had post-secondary education (60%) and reported low to middle income (83%). PrEP awareness was 65%, 4% of respondents had ever used PrEP, and 53% were classified as higher risk. However, only 10% of respondents perceived their HIV risk as high. Among individuals classified as higher risk, 66.8% were aware of PrEP vs. 62.3% of lower risk respondents. The association between higher risk and awareness remained significant (aPR 1.03; 95% CI 1.00, 1.05) after adjustment. Additionally being 25+ years old (vs. 18–24 years), Brazilian, post-secondary education, high income and Gay Social Network (GSN) App use were associated with PrEP awareness. While being Peruvian, having less than secondary education and low income were negatively associated with PrEP awareness (all p-values<0.05).

**Conclusion:** Higher risk of HIV infection was associated with increased PrEP awareness. However, this association was weak indicating that MSM at higher risk, who would benefit from PrEP, are often not aware of this prevention strategy. As PrEP is introduced, awareness should increase, as seen in Brazil where PrEP has been available longer. Interventions to increase PrEP awareness are paramount, especially among MSM at higher risk, to increase PrEP uptake and prevent HIV infections. Gay Social Network apps and social media could play an important role to achieve this goal.
Table 1: Factors Associated with PrEP Awareness among MSM in Brazil, Peru, and Mexico in 2018

<table>
<thead>
<tr>
<th>Country</th>
<th>% aware of PrEP</th>
<th>% aware of PrEP</th>
<th>% aware of PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>66.0</td>
<td>7.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Peru</td>
<td>64.0</td>
<td>6.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Mexico</td>
<td>64.0</td>
<td>6.0</td>
<td>2.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education</th>
<th>% aware of PrEP</th>
<th>% aware of PrEP</th>
<th>% aware of PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-secondary</td>
<td>68.0</td>
<td>7.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Completed Secondary</td>
<td>54.7</td>
<td>5.0</td>
<td>2.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Income</th>
<th>% aware of PrEP</th>
<th>% aware of PrEP</th>
<th>% aware of PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>79.1</td>
<td>6.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Middle (ref)</td>
<td>67.9</td>
<td>5.0</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Overall, concern regarding informational barriers was higher than behavioral or belief barriers. Respondents with lower informational barriers were: Brazilian (-1.1), aware of PrEP (-0.6), and at higher risk of contracting HIV (-0.4); while Peruvians (+0.2) and those without secondary education (+0.8) had higher informational barriers. Respondents with lower behavioral barriers were: Brazilian (-1.7), aware of PrEP (-0.6), and at higher risk of contracting HIV (-0.4); and those without secondary education (+0.8) had higher informational barriers. Respondents with lower belief barriers were: Brazilian (-1.7), aware of PrEP (-0.6), and at higher risk of contracting HIV (-0.4); and those without secondary education (+0.8) had higher informational barriers. All regression model coefficients had p-values < 0.05.

Conclusion: Informational barriers were the highest of the 3 domains; simultaneously, those most informed (e.g., Brazilians and PrEP aware) had consistently lower barrier scores across all 3 domains. These findings indicate that PrEP barriers are likely amenable to interventions promoting PrEP awareness and education. Such interventions will be needed to reduce PrEP-related barriers, increase its uptake, and reduce HIV incidence in these countries.
**WOMEN’S PrEP KNOWLEDGE, ATTITUDES, PREFERENCES AND EXPERIENCE IN CHICAGO**

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**Background:** Black women in Chicago are disproportionately affected by HIV, but few are on PrEP. We report the results of a mixed methods study of knowledge, attitudes, experience, and preferences for PrEP among cis-gender women in Chicago.

**Methods:** We administered a survey to 370 HIV(-) women visiting either a public Sexually Transmitted Infection clinic or an Emergency department and conducted focus groups with 16 PrEP-naive women and in-depth interviews with 7 PrEP-using women. Survey data were analyzed using descriptive statistics and multivariate logistic regression as well as thematic analysis for qualitative data.

**Results:** Majority of women identified as black (83%) and had a regular source of healthcare (71%). In the last 6 months, 83% had vaginal or anal sex and 93% inconsistent condom. Women had low rates of perceived HIV risk (90% low/no). Only 30% (112) had heard of PrEP before the survey. The only factor associated hearing about PrEP was knowing someone on PrEP (OR 15.6 95%CI (3.0-80.3)). One third (29% (105)) considered starting PrEP in the next 6 months, with protecting health (77%) and reducing HIV worry (58%) most common reasons. Most (81%) had concerns about taking PrEP with side effects (68%) and incomplete protection (25%) most common;72% would need some form of support. Most preferred source for information and PrEP was their primary healthcare (71%). In the last 6 months, 83% had vaginal or anal sex and 93% inconsistent condom. Among the 51 women reporting an HIV+ partner, 96% thought their partner was on ART and 71% were suppressed. Black women were less likely to know if their partner was HIV+ compared to White and Latina women (p=0.032). Black and Latina women vs. White women (p=0.006), and SW and UP vs. SD (p=0.001) more frequently suspected partner infidelity.

**Conclusion:** Women enrolled in this PrEP demonstration project were predominantly in serodiscordant relationships but many had partners of uncertain risk and almost one in six were engaged in sex work. We found differences between individuals in the three HIV risk groups by race/ethnicity, employment, HIV knowledge and risk behaviors, PrEP motivations and main partner dynamics. Interventions to increase PrEP uptake among women may need to be customized based on the varying partnership types found among women at risk for HIV.

<table>
<thead>
<tr>
<th>Serodiscordant (n=64)</th>
<th>Sex Work (n=21)</th>
<th>Unknown Partner (n=51)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>35 (10)</td>
<td>43 (11)</td>
<td>40 (12)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>Non-Hispanic White 14 (22%)</td>
<td>7 (31%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Latino 13 (26%) 1 (3%)</td>
<td>14 (5%)</td>
<td>12 (23%)</td>
<td></td>
</tr>
<tr>
<td>Other 21 (33%) 3 (14%)</td>
<td>4 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>g High School 29 (45%)</td>
<td>10 (48%)</td>
<td>22 (43%)</td>
</tr>
<tr>
<td>&lt; Some College 35 (55%)</td>
<td>11 (52%)</td>
<td>29 (57%)</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td>&lt; 2000 per month 31 (48%)</td>
<td>13 (76%)</td>
<td>20 (79%)</td>
</tr>
<tr>
<td>≥ 2000 per month 18 (27%)</td>
<td>4 (23%)</td>
<td>23 (40%)</td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td>Full/Part-time/Retired 34 (56%)</td>
<td>4 (23%)</td>
<td>50 (98%)</td>
</tr>
<tr>
<td>Unemployed/Unable to work 27 (44%)</td>
<td>14 (78%)</td>
<td>19 (38%)</td>
<td></td>
</tr>
<tr>
<td>Sex Partners last 3mo**</td>
<td>1, 1-2</td>
<td>10, 4-17 1, 2-3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Main Partner</td>
<td>51 (80%)</td>
<td>10 (48%)</td>
<td>42 (82%)</td>
</tr>
</tbody>
</table>

*Mean, SD = standard deviation; **median, IQR = interquartile range

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**HIV RISK AND CHARACTERISTICS OF WOMEN SEEKING PrEP IN A US DEMONSTRATION PROJECT**

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**Background:** Little information is known about the risk profiles of women who initiate pre-exposure prophylaxis (PrEP) for HIV prevention in the US. We analyzed baseline risk factors of women in a PrEP demonstration project using TDF/FTC to assess correlates of PrEP uptake.

**Methods:** Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGIS) is a PrEP clinical trial in Southern California of 136 HIV-negative cisgender women ≥18 years old at risk for HIV who completed enrollment. At baseline, women were surveyed for sociodemographics and risk behaviors with testing for STIs. Women in three primary HIV risk groups according to main partner type (1) serodiscordant partnerships (SD), (2) sex workers (SW), and (3) risk attributable to known and unknown partner behavior (UP) were compared using Fisher’s exact or Kruskal-Wallis tests to determine differences by risk group.

**Results:** Sixty-four women (47%) were grouped in the SD risk group, 21 (15%) in SW and 51 (38%) in UP. Despite SW reporting significantly more sex partners than SD or UP, overall baseline STI rate was low at 8% with no difference by risk group. SW were more likely to report problem drinking and drug use (p<0.002) and history of intimate partner violence in the last year (p<0.001) compared to SD and UP. HIV literacy was higher among SW vs. the other risk groups (p=0.023). Nearly all SW (95%) and most UP women (83%) wanted to take PrEP to protect themselves from HIV vs. only 33% of SD (p<0.001). There were no differences between groups in depression score or HIV risk perception. Of 103 women reporting a main partner, 80% were aware of partner’s HIV status. Among the 51 women reporting an HIV+ partner, 96% thought their partner was on ART and 71% were suppressed. Black women were less likely to know if their partner was HIV+ compared to White and Latina women (p=0.032).

**Conclusion:** Understanding pregnant women’s risk perception and risk score among pregnant Kenyan women

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1University of Washington, Seattle, WA, USA, 2Kenyatta National Hospital, Nairobi, Kenya

**Background:** Understanding pregnant women’s risk perception and whether this correlates with their actual HIV risk is important to guide PrEP implementation in high HIV prevalence regions.
Methods: The PrEP Implementation for Mothers in Antenatal Care (PrIMA) study (NCT03070600) is a cluster-RCT in western Kenya that assesses strategies for delivering PrEP to pregnant women. At enrollment, HIV risk perception was assessed using two risk perception scales (Napper and Vargas). Intimate partner violence (IPV) was assessed using the Hurt, Insulted, Threatened with Harm and Screamed screening tool. HIV risk was assessed using a validated empiric risk score for predicting HIV acquisition designed for pregnant women which includes behavioral and partner characteristics: scores >6 indicate high-risk for HIV. Women self-reported their partner’s HIV status. Women’s perceived HIV risk was compared between women with a high (≥6) and low (<6) empiric risk scores.

Results: Of the 2,280 women enrolled, median age was 24 years (IQR 20-29), median gestational age was 25 weeks (IQR 20-30), and 84% were married. Overall, 33% reported having partners of unknown HIV status and 40% had empiric HIV risk scores >6; 7% believed they had a ‘great chance’ of acquiring HIV in the next year. Compared to women with lower risk scores, women with scores >6 were more likely to believe they had a ‘great chance’ of acquiring HIV in the next year (15% vs 2%). Mean perceived HIV risk was 21 (SD, 4.5) and 1.8 (SD, 1.9) using the Napper and Vargas scales, respectively, signifying moderate perceived risk. Women with high-risk scores (≥6) reported greater perceived risk in both scales compared to women with lower risk scores (Napper, Mean [M]: 23.2 vs 19.5 and Vargas, M: 2.69 vs 1.19). Women who experienced IPV had greater perceived risk in both scales compared to women with low-risk scores (Napper, M: 24 vs 21) and (Vargas, M: 2.7 vs 1.7). Compared to women with HIV-uninfected partners, women with partners of unknown or known positive status had higher perceived risk (positive partners, Napper, M: 26 vs 19; Vargas, M: 3.8 vs 1.2) and (unknown partner status, Napper, M: 23 vs 19; Vargas, 2.6 vs 1.2). All P values <0.001.

Conclusion: Women with high empiric HIV risk scores were more likely to report a higher perceived risk of acquiring HIV. This suggests that women may accurately assess their own risk for HIV and providers may be able to universally counsel women on PrEP rather than conducting a risk assessment to target PrEP.

981 LOW PEP AWARENESS AND WILLINGNESS AMONG TRANSGENDER WOMEN IN SOUTH AFRICA

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Background: Transgender women (TW) face elevated vulnerability to HIV. Recent studies indicate a pooled prevalence of 25% across 8 sub-Saharan African countries, with no data available for South Africa. In 2016, the South African National Department of Health implemented PrEP for high-risk populations at select sites. However, transgender people were only targeted as a subset of sex workers. Data are needed to guide strategies on how best to implement PrEP among TW in South Africa. This study aimed to identify predictors of PrEP knowledge, willingness, and uptake among South African TW to inform development of effective interventions.

Methods: Between May-September 2018, 210 TW were recruited in Cape Town, East London, and Johannesburg through community outreach. Each TW completed an interviewer-administered survey. Data were collected on psychosocial factors, HIV risk behaviors, self-reported HIV status, and PrEP awareness, willingness, and uptake. Bivariate and multivariable logistic regression modeling tested associations between risk behaviors and perception, violence, and PrEP awareness and willingness. Multivariable models included random effects for city.

Results: Only 50% (105/210) of TW had heard of PrEP. Of those, 87% (91/105) knew where to get PrEP, and 19% (20/105) had ever taken it. The 67 (32%) TW who reported living with HIV had 2.6 times the odds (95% CI: 1.4-4.9; p=0.002) of PrEP awareness compared to HIV-negative TW. Among HIV-negative TW not on PrEP, 51% (54/106) were willing to take it. In multivariable modeling, violence victimization and history of substance abuse were significantly associated with PrEP awareness, while history of sexually transmitted infections and violence victimization were significantly associated with PrEP willingness. In these models, history of sex work was not associated with PrEP awareness, and HIV risk perception was not significantly associated with willingness to take PrEP.

983 ARE ROUTINE RENAL AND LIVER LABS TESTING AMONG PEP PATIENTS ON TDF/FTC/DTV NECESSARY?

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Background: HIV post exposure prophylaxis (PEP) guidelines recommend routine glomerular filtration rate (GFR), aspartate aminotransferase (AST), and...
alanine transaminase (ALT) testing at PEP initiation and follow up visits. Once daily tenofovir (TDF)/emtricitabine (FTC)/dolutegravir (DTV) is the first line PEP regimen in CDC guidelines and New York City (NYC) Sexual Health Clinics (SHC) due to its high safety profile. We assessed the prevalence of abnormal AST/ALT/GFR at baseline (BL) and follow up (FU) testing among patients without self-reported kidney or liver disease who were provided 28 days of PEP at NYC SHC.

**Methods:** We extracted medical record data from PEP initiation visits during 9/2016-12/2017 with TDF/FTC/DTV regimen, a baseline metabolic panel, and no HIV medication dispensed in the prior three months at NYC SHC. GFR/AST/ALT results were examined at BL and at the first FU testing 14-42 days. Normal renal function (RF) was defined as GFR ≥ 70 ml/min and normal liver function (LF) was defined as ALT and AST less < 50 U/L. Abnormal LF/RF tests were classified into grades based on the GFR and higher AST/ALT values (table). Chart review was done for visits ≥ grade 2 to determine whether PEP regimen was changed or discontinued.

**Results:** Overall 1115 PEP initial visits were identified of 1051 unique patients. Median age was 29 years (IQR 25-35); 92% were male. At baseline, 3% of visits had an abnormal RF (33/1115) and 9% had an abnormal LF (95/1115). The majority of BL abnormal labs were grade 1 (RF: 31/32; LF: 77/95). Among 575 BL visits with FU labs, 9% had abnormal RF (50/575) and 11% had an abnormal LF (64/575). The majority of FU abnormal labs were grade 1 (RF: 49/50; LF: 51/64) (table). Visits with and without FU labs were similar with regards to age, gender, race, and baseline RF. Visits with abnormal BL LF were more likely to have FU labs (OR 1.795%CI 1.1-2.6). Only twice was a PEP regimen changed based on BL grade 2 RF or LF abnormality and no PEP regimens were changed based on FU lab abnormalities.

**Conclusion:** Baseline renal and liver testing among PEP visits on TDF/FTC/DTV without known history of kidney and liver disease was normal in > 90% and rarely changed in results in changes to PEP regimens (0.2%). Follow up renal and liver testing did not result in any regimen change. As the safety profile of PEP regimens improves, routine renal and liver testing and monitoring for healthy patient population may not be necessary.

### Table: Results of Renal and Liver Function Testing at Baseline PEP Initiation Visits and First Follow Up Visit within 14-42 Days, New York City Sexual Health Clinics, September 2016-December 2017. (N=575)

<table>
<thead>
<tr>
<th>Baseline Laboratory Results</th>
<th>Normal</th>
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<th>Grade 2</th>
<th>Grade 3</th>
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<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
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<tr>
<td>Normal RF (≥90 ml/min)</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Liver Function</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
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<tr>
<td>Normal LF (≥30 ml/min)</td>
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<td>Grade 3 LF (≥100 ml/min)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
</tbody>
</table>

**RF= renal function; LF= liver function; FU= follow up**

985 E/C/TAF SINGLE TABLET REGIMEN FOR HIV POSTEXPOSURE PROPHYLAXIS

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Background: HIV Postexposure prophylaxis (PEP) compliance rates are often low. Newer antiretroviral combinations, such as the recently approved elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide coformulation (E/C/TAF), may improve PEP adherence.

**Methods:** Prospective, open-label, single-arm trial conducted in 15 French centers (NCT02998320). Individuals with recent HIV exposure who met criteria for PEP initiation received once-daily E/C/TAF for 28 days. Follow-up visits...
were protected from HIV infection at a low incidence rate of 0.14/100 person-years in a diverse geographical population of MSM, individuals taking ≥4 tablets/week had an IRR (95% CI) of 1.53 (1.18−2.00). Younger participants were less likely to remain protective dosage of FTC/TDF PrEP, as compared to those aged 30−39 years (OR 3.41 (2.37−4.90), 1.59 (0.76−3.33), and 0.14 (0.04−0.43) per 100 person-years for those that have persistent low PrEP adherence.

**Conclusions**: In this multi-national pooled analysis of FTC/TDF PrEP use in a diverse geographical population of MSM, individuals taking ≥4 tablets/week were protected from HIV infection at a low incidence rate of 0.14/100 person-years. Age over 40 years was significantly associated with increased adherence.

**Methods**: This study followed an existing PrEP demonstration project, the TAPIR randomized controlled multi-center trial of text messaging versus standard care for adherence to daily TDF/FTC PrEP in MSM, conducted in Southern California between 2014-2016 (NCT01761643). At the last TAPIR trial visit, study provided PrEP was discontinued and participants were provided with information about where to obtain PrEP in the community. During week 48 of the TAPIR trial and during prospective observational post-trial visits at months 6 and 12, adherence was estimated by dried blood spot (DBS) intracellular tenofovir diphosphate (TFV-DP) levels. Adequate adherence was defined as TFV-DP concentration of >719 fmol/punch reflecting four or more tablets per week. Binary logistic regression analysis was performed to assess predictors of completing post-trial visits and PrEP adherence among those who completed ≥ 1 visit.

**Results**: Of 395 TAPIR participants who were provided with free PrEP during TAPIR for a median of 585 days (range 3-757 days), 113 (29%) completed one or more post-trial visits. Multivariate predictors of completing post-trial visits included adequate adherence at the week 48 TAPIR visit, total days of TAPIR participation, and less problematic substance use (Table). Among 113 participants who completed ≥ 1 post-trial visit, 67 (59%) had adequate adherence at their last post-trial visit. Adequate adherence at the week 48 TAPIR trial visit was the only significant predictor of adequate adherence post trial (Table). Participants with adequate adherence at the week 48 TAPIR visit had also significantly higher DBS TFV-DP levels at last post-trial follow up (median 993 fmol/punch, IQR 0-1397 vs. median 636 fmol/punch, IQR 0-758; p<0.03).

**Conclusion**: PrEP users followed for up to 3 years had high rates of adequate adherence suggesting that PrEP can be used effectively by individuals for years. Longer term adequate adherence was best predicted by having adequate adherence at week 48 of the PrEP trial. Additional measures are needed for those that have persistent low PrEP adherence.
Pre-Exposure Prophylaxis (PrEP) is highly efficacious at preventing HIV but is dependent upon optimal adherence, including sustained use during high risk periods. PrEP uptake is escalating among young men who have sex with men (YMSM) and transgender women (TW), but evidence suggests that up to one-third of YMSM/TW PrEP users discontinued use in a 6-month period, which eliminates its protective benefit. The current analyses examined longitudinal predictors of PrEP discontinuation.

Methods: Data came from RADAR (N=1100+), an ongoing longitudinal cohort of YMSM/TW (aged 16-29) in Chicago. Using data from 7 visits at 6-month intervals (collected 2015-2018), mixed effects longitudinal regression models examine change in sexual behaviors and psychosocial factors as predictors of PrEP discontinuation (i.e., use at prior visit, no use at current visit). Predictors included change from the prior to current visit in condomless anal sex (CAS), number of sex partners, relationship status, substance use, and depression, as well as current insurance status. Models adjusted for demographic characteristics.

Results: PrEP use among HIV-negative YMSM/TW increased from 8.4% (visit 1) to 28% (visit 7). PrEP discontinuation similarly increased from 12.6% (visit 2) to 20% (visit 7). In a multivariate model, YMSM/TW who had increases in CAS across visits were less likely to discontinue PrEP (Odds Ratio (OR)=0.93, 95% Confidence Interval (CI): 0.89-0.98), while those who entered a serious relationship were more likely to discontinue (OR=1.85, 95% CI: 1.08-3.19). Number of sex partners, substance use and depression were not associated with discontinuation. We observed no race or gender identity differences in PrEP discontinuation. In a separate model, we examined the association between current insurance status and discontinuation, adjusting for demographics. YMSM/TW who had insurance were significantly less likely to discontinue PrEP (OR=0.54, 95% CI: 0.32-0.92).

Conclusion: That YMSM/TW who increase CAS are less likely to discontinue PrEP is encouraging. Among those entering relationships, it remains unclear how and when YMSM/TW discontinue PrEP and whether or not transmission risk remains after discontinuation. Insurance status is a key structural determinant of the ability to sustain PrEP use and reduce transmission risk. These findings point to encouraging trends and opportunities for structural and behavioral intervention.

Stopping HIV Pre-exposure Prophylaxis: Reasons and Implications

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Background: Use of HIV pre-exposure prophylaxis (PrEP) is increasing, but some users discontinue PrEP. We investigated former PrEP users in Germany and compared them to current PrEP users in order to elucidate reasons for stopping and implications for HIV prevention.

Methods: From 24th July to 3rd September 2018 we recruited current and former PrEP users on geolocation dating apps for MSM, community-based HIV testing sites, and a community website in Germany for an anonymous online survey. Risk factors were assessed with logistic regression models adjusting for age, country of origin, and annual gross income.

Results: We recruited 212 former PrEP users and 2,005 participants currently taking PrEP. 78.7% completed the survey. Most participants identified as male (99.1%, trans*: 0.4%, intersexual: 0.3%, non-binary: 0.2%) and indicated Germany as their country of origin (74.8%) with no significant differences between current and former PrEP users. The median age of former PrEP users (33 years, IQR: 27-41) was lower than of current PrEP users (38 years, IQR: 31-45). The reasons for discontinuing PrEP are shown in Table 1 (multiple responses allowed). Former PrEP users were much more likely to have used PrEP intermittently or on demand (OR = 2.8, 95% CI 2.0, 4.0). In addition, former PrEP users were more likely to be unhappy with their current sex life (OR = 4.1, 95% CI 2.6, 6.6). Most former PrEP users indicated that they always (35.8%) or often (27.9%) use condoms since stopping PrEP, whereas 35.8% indicated using condoms during half or less of their sexual acts. Compared to current PrEP users, former users were more likely to always or often use condoms (OR = 7.9, 95% CI 5.4, 11.6).

Conclusion: The analysis identifies important reasons for discontinuing PrEP, some of which could be overcome if PrEP were covered by health insurances. More than a third of former PrEP users reports inconsistent condom use...
991 FACTORS ASSOCIATED WITH REFUSING OR STOPPING PrEP AMONG AT-RISK MSM IN KENYA

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1KEMRI Wellcome Trust Rsr Prog, Kilifi, Kenya, 2Simon Fraser University, Burnaby, BC, Canada, 3University of Washington, Seattle, WA, USA

Background: There are limited data on reasons for refusing or stopping programmatic pre-exposure prophylaxis (PrEP) among men who have sex with men (MSM) in Kenya, a country rolling out PrEP since May 2017. We assessed factors associated with refusing or stopping PrEP in this population, using a mixed methods approach.

Methods: Since June 2017, at-risk MSM followed at monthly visits in an HIV-1 vaccine feasibility cohort study in the coastal Kenya were offered PrEP with adherence and risk reduction counselling, monthly rapid HIV-1 antibody testing and X-pert RNA Qual testing if acute HIV-1 risk criteria were met. We assessed factors associated with refusing or stopping PrEP at the last available visit for those who refused PrEP and the date of PrEP discontinuation for those who stopped using generalized linear modeling with log-link Poisson regression and robust error variance. Variables associated with refusing or stopping PrEP at P<0.2 in the bivariable analysis were included in the multivariable model.

We also conducted 2 focus groups discussion (FGDs) and 12 in-depth interviews among purposively sampled MSM who were eligible but did not start (N=6) or discontinued PrEP (N=6). Interviews and FGDs were recorded, transcribed and analyzed using a grounded theory framework.

Results: Of 178 MSM offered PrEP, 36 (20.2%) did not start and 142 (79.8%) started, of whom 31 (17.4%) stopped after a median of 4.3 (interquartile range: 1.7–8.9) months. In multivariable analysis, paying for sex (adjusted prevalence ratio [aPR] 1.6, 95% CI 1.0–2.5) was an independent predictor of refusing or stopping PrEP, after adjustment for religion and self-reported unprotected sex, anal sex position, and receipt of payment for sex. In qualitative analysis, participants who had refused or had stopped PrEP showed limited knowledge and misconceptions about PrEP, and often had low perception of HIV risk. Pill burden, side effects, stigma, and storage challenges were cited as reasons for stopping. There was a strong preference for long-acting oral or injectable PrEP as alternatives to daily oral PrEP.

Conclusion: Over one third of at-risk MSM followed up in the cohort study refused or stopped taking PrEP. MSM reporting paying for sex may have low perceived HIV-1 risk. Ongoing community engagement and education are needed to correct misconceptions, raise awareness, and decrease stigma in order to improve uptake and continuous use of PrEP among Kenyan MSM.

992 HIGH PrEP USE IN AFRICAN MEN AND WOMEN CONTINUING PrEP IN PUBLIC-HEALTH HIV CLINICS

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1Kenya Medical Research Institute, Nairobi, Kenya, 2University of Washington, Seattle, WA, USA, 3Ministry of Health, Nairobi, Kenya, 4Massachusetts General Hospital, Boston, MA, USA, 5University of Colorado, Aurora, CO, USA, 6University of Washington, Seattle, WA, USA

Background: Adherence is central to the protective effectiveness of pre-exposure prophylaxis (PrEP) against HIV infection. Limited data are available on adherence in persons initiating and continuing PrEP in real world PrEP programs in Africa.

Methods: The Partners Scale-Up Project is an ongoing cluster-randomized programmatic evaluation of national scale-up of PrEP delivery, primarily for HIV serodiscordant couples, integrated in 24 public health HIV care clinics in Kenya. Dried blood spots (DBS) were collected from individuals taking PrEP from randomly-selected clinics on a random subset of days each month. Intracellular tenofovir-diphosphate (TFV-DP) concentrations were quantified in DBS using validated liquid chromatography-tandem mass spectrometry.

Results: Between February 2017 and October 2018, 3761 initiated PrEP, median age was 31 years [IQR: 26-39], 3208 (85%) reported an HIV-positive partner, and 3487 (93%) reported recent condom use. A total of 2009 (53%) were women of whom 230 (11%) used PrEP while pregnant (130 were pregnant at PrEP initiation and 100 became pregnant while on PrEP). Among those who became pregnant while on PrEP, 47 (47%) reported intending to conceive, while 18 (18%) had not planned to get pregnant at baseline. Of all initiating PrEP, 2444 (65%) continued PrEP (≥ 1 refill in 3 months). Continuation was independently more likely for those >30 years (68% vs 61% for ≤30 years, p<0.01), those with an HIV+ partner (68% vs 45%, p<0.01), and for women (66% vs 63% for men; p=0.04) but did not differ by pregnancy status (68% pregnant vs. 66% not pregnant; p=0.63). A total of 71 DBS were tested a median duration of PrEP use of 1 month (range 1 to 4). Evidence of PrEP use was high with TFV-DP detectable in 68 (96%) of DBS samples; the median TFV-DP concentration was 515 fmol/µl (IQR: 348 to 693) comparable to the estimate for ≥4 doses per week from a directly observed dosing study in the US. DBS TFV-DP concentrations were similar (p=0.05) by sex, age, and desire to conceive.

Conclusion: In a Kenyan PrEP program setting, PrEP uptake was high and was taken by men and women, including pregnant women. TFV-DP was detected in 96% of blood samples of persons continuing PrEP and levels suggested...
relatively consistent adherence; thresholds specific to African populations are needed. These data are encouraging that programmatic level adherence support may be sufficient to achieve PrEP uptake in motivated clients.

993 PERSISTENCE WITH PrEP USE IN AFRICAN ADOLESCENTS AND YOUNG WOMEN INITIATING PrEP

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1University of Washington, Seattle, WA, USA, 2Kenyatta National Hospital, Nairobi, Kenya, 3University of Washington in Kenya, Nairobi, Kenya

Background: Young women in HIV high burden settings are a priority population for PrEP. Limited data are available on PrEP continuation in this population in real world settings.

Methods: Data are from the PrEP Implementation for Young Women and Adolescents (PryLA) project, an implementation program of PrEP integrated in maternal child health (MCH) and family planning (FP) clinics. Between November 2017 and June 2018, women 15–45 years seeking antenatal (ANC), postnatal (PNC) and FP services in 16 health facilities in Kisumu, Kenya were universally screened and offered PrEP according to national guidelines. We assessed for PrEP use and continuation and used robust Poisson regression methods to identify correlates of continuation at 3 and 6 months adjusted for age, marital status, partner HIV status, PrEP delivery point, and facility clustering. Medication possession ratio, assumed to represent PrEP use, was computed as the ratio of the number of tablets dispensed divided by the number of days between initiation and return date, with ratios >1 imputed to 1.

Results: Of 2304 women initiated on PrEP (912 in ANC, 1114 in PNC, and 278 in FP), median age was 24 years (IQR 21–29), 58% had partner of unknown HIV status, and 96% reported recent history of condomless sex. Continuation at 1, 3, and 6 months was 38%, 21%, and 10% overall: 34%, 18%, and 8% for ANC; 39%, 24%, and 10% for PNC; and 41%, 25%, and 15% for FP. Of those continuing PrEP at Month 1 (n=866), median medication possession ratio was 1 (IQR: 0.86–1). Overall, continuation at 3 months was independently higher for women with HIV positive partners (positive 52%, unknown 19%, negative 18%; p<0.01) and in older women (≥20 years 23%, 20–24 years 18%, 25–34 years 22%, and ≥35 years 37%; p<0.01). Only partner HIV status was independently associated with 6 month continuation (positive 30%, unknown 8%, negative 8%; p<0.01). Frequently reported reasons for discontinuing PrEP use were low perceived risk for HIV (23%), side effects (19%), pill burden (17%), and partner known to be HIV negative (17%).

Conclusion: Integration of universal screening and counseling for PrEP in routine MCH and FP clinics in Kenya was feasible. There was high drop-off in PrEP continuation, but subset of women persisted with PrEP use through at least 6 months. Greater efforts to support PrEP normalization and persistence for African women are needed.

994 HIGH ADHERENCE AMONG YOUNG WOMEN IN CAPE TOWN IN THE FIRST 3 MONTHS AFTER PrEP START

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Background: In placebo-controlled PrEP trials, African adolescent girls and young women (AGYW) had low adherence; only 25–30% had any detectable tenofovir in blood samples. PrEP use may be higher when efficacy is known, as demonstrated among men who have sex with men (MSM) in open label studies. The 3P demonstration project was designed to evaluate PrEP demand creation, uptake, and adherence among AGYW in South Africa.

Methods: We enrolled 200 sexually active, HIV negative, PrEP-naive AGYW ages 16–25 in Cape Town, South Africa from March 2017–2018, with visits at 0.1, 2, and 3 months. PrEP adherence was assessed by intracellular tenofovir diphosphate (TFV-DP) concentrations in dried blood spots, a measure of cumulative use in the prior month. All women received adherence counseling, including feedback about their drug levels at months 2 and 3. TFV-DP ≥700 fmol/punch was chosen as the threshold for high adherence, based on directly observed dosing (correlates with ≥4 doses/week and associated with high efficacy in MSM). Half of women were randomized to receive a 200 Rand ($)13 incentive at 2 and 3 months if their TFV-DP was ≥700 at the prior visit.

Results: Women enrolled in 3P were young (median age 19) and at high risk for HIV; 30% had an STI (chlamydia, gonorrhea or trichomoniasis), 19% reported IPV, 13% weekly alcohol use and 71% who had a primary partner reported suspecting he had other partners. Retention was 89% at month 3. All but one sample had detectable TFV-DP, and median TFV-DP at months 1, 2, and 3 were 622, 707, and 694 fmol/punch, respectively. Half of AGYW had high (TFV-DP ≥700 fmol/punch) and ~80% had medium (TFV-DP 350–699 fmol/punch) or greater adherence at months 2 and 3 (Figure). In univariate analyses, significant baseline correlates of TFV-DP ≥700 fmol/punch at month 3 included having an HIV positive partner or a partner of unknown serostatus (OR 2.0, 95% CI 1.1, 3.8), reporting no sex in the month before enrollment (OR 2.3, 95% CI 1.1, 4.9) and disclosure about their PrEP use (OR 3.5, 95% CI 1.0, 15.9).

Conclusion: PrEP adherence was higher in this demonstration project than previous placebo-controlled trials among African AGYW. Intracellular TFV-DP levels indicate that by 2 months half of AGYW were taking the majority of doses in the prior month. Having a partner of unknown or positive serostatus and disclosure about their PrEP use were associated with higher adherence; disclosure about PrEP should be supported among AGYW.

995 ADHERENCE 3 MONTHS AFTER PrEP INITIATION AMONG YOUNG AFRICAN WOMEN IN HPTN 082

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Background: Pre-exposure prophylaxis (PrEP) is highly effective when used consistently. Young women in sub-Saharan Africa are at high risk of HIV and could benefit from PrEP. We evaluated PrEP adherence in young women in the context of known efficacy and open label use.

Methods: HPTN 082 was conducted in Cape Town, Johannesburg (South Africa) and Harare (Zimbabwe) to evaluate the effect of drug level feedback on adherence. Sexually active HIV-negative women ages 16–25 were enrolled using the VOICE risk score. PrEP readiness was scored using 4 categories: standard support (SS), standard support and feedback (S&S), standard support plus drug level feedback (SS&D), and standard support plus drug level feedback with cluster randomization (SS&D+). Women receiving PrEP were randomized to standard adherence support (counseling, 2-way SMS, and adherence clubs) or standard support plus drug level feedback at 2 and 3 months. Follow-up was 1, 2, 3, 6, 9 and 12 months. Adherence at 3 months was assessed by tenofovir-diphosphate (TFV-DP) in dried blood spots. High adherence is defined as TFV-DP >700 fmol/punch (>4 doses/week), which was associated with high protection in men, and medium adherence as 350–700 fmol/punch.
fmol/punch (2-3 doses/week). Baseline predictors of 3 month TFV-DP levels were assessed.

Results: Of 427 who started PrEP, median age was 21 and median VOICE risk score was 7 (≥5 associated with >6% HIV incidence in prior cohorts). Most (84%) reported a primary sex partner (74% HIV+, 21% unknown status, and 1% HIV-). 33% thought their partner had other partners and 47% did not know. 22% reported anal sex in the past month, 23% transactional sex in the past 3 months, 50% intimate partner violence in the past year, and 49% depression symptoms. Among the 381 with a 3 month visit, 69% had attended 1 adherence club (median 2). Median TFV-DP at month 3 was 485 fmol/punch (IQR 166.775). 25% 700, 23% 350-699, 36% detectable<349 and 16% undetectable. Significant predictors (p-value<0.05) of TFV-DP levels at 3 months in multivariate analysis were uncertainty if their partner had other partners (145 fmol/punch lower vs. those who reported their partner did not have other partners) and a higher score on the HIV prevention readiness scale (5 fmol/punch higher for each unit on 100 point scale).

Conclusion: Three months after starting PrEP, TFV-DP levels indicated that most young African women were taking PrEP in the prior month and 25% had high adherence, substantially higher than in the placebo-controlled trials which showed 25-30% had detectable tenofovir in plasma. Additional adherence support may be useful for young African women who are uncertain about their partner’s behavior and are less sure about using PrEP.

996 SHORT-TERM RETENTION ON PREEXPOSURE PROPHYLAXIS IN DEMOCRATIC REPUBLIC OF THE CONGO

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Background: In the Democratic Republic of the Congo (DRC), HIV is concentrated in key populations (KP), primarily among female sex workers (SW) and men who have sex with men (MSM), with prevalence estimates of 7% and 18% respectively, compared to 1.2% in the general population. Pre-exposure prophylaxis (PrEP) to prevent HIV acquisition can impact the epidemic if made accessible to KP at trusted delivery points. In the absence of national PrEP guidelines, DRC’s National AIDS Control Program, US Centers for Disease Control and Prevention, and ICAP at Columbia University collaborated to implement PrEP services for a limited number of clients at 7 HIV facilities providing regular services to KP in DRC. We examined PrEP initiation and retention at these facilities.

Methods: ICAP developed a PrEP training package to capacitate staff to deliver and monitor PrEP services at 4 facilities in Kinshasa and 3 in Lubumbashi. Active follow-up of PrEP patients included text message, phone, and face-to-face appointment reminders by both facility staff and peer outreach workers. PrEP initiation and follow-up visits were recorded by facility staff using ICAP-developed tools; data were summarized into aggregate reports by project staff. Retention on PrEP at 1 and 3 months was defined as a documented clinic visit within 14 days before or after the scheduled 1 month appointment date, and within 30 days before or after the 3 month appointment date. This analysis included data for patients initiating PrEP between February 20th to May 20th, 2018.

Results: During the enrollment period, 356 patients initiated PrEP, 57% (202) in Kinshasa and 43% (154) in Lubumbashi. PrEP patients were 80% (285) SW, 19% (68) MSM, and 1% (3) transgender (TG). Overall retention at 1 month following initiation was 78% (277), including 74% (212) among SW, 94% (64) among MSM, and 33% (1) among TG. Overall 3-month retention was 93% (331); including 92% (262) among SW, 99% (67) among MSM, and 67% (2) among TG.

Conclusion: Comprehensive training and clinic monitoring resulted in the successful introduction of PrEP in DRC. Although 22% of patients did not attend their 1 month appointment, increased outreach efforts led to improved 3 month retention for all clients. Focused efforts are needed to ensure high retention in PrEP services among these populations. Project findings will support the scale-up of PrEP in other impacted populations and facilities in DRC.

997 PREEXPOSURE PROPHYLAXIS: ACCEPTABILITY AND RETENTION IN SOUTH WESTERN UGANDA

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1ICAP at Columbia University, New York, NY, USA; 2CDC, Atlanta, GA, USA, 3CDC, Kinshasa, Congo, The Democratic Republic of the Congo

Background: Pre-Exposure prophylaxis (PrEP) has been recommended for key and priority populations most-at-risk of HIV. In 2017, one of the first large-scale attempts to scale up PrEP using tenofovir and lamivudine at population-level in Uganda, was initiated by the Rakai Health Sciences Program in HIV hyper-endemic trading centers and fishing communities on Lake Victoria with CDC-Uganda under PEPFAR support. We report on acceptability and retention of clients on the program at 9 months of follow-up.

Methods: Program data from implementing clinics were used for the evaluation. Acceptability of PrEP was defined as having been initiated on PrEP after satisfying the eligibility criteria of being at high HIV risk. Retention on PrEP was measured at months 1, 3, 6, and 9 following PrEP enrolment. Multivariable modified Poisson regression was used to estimate prevalence ratios and 95% confidence intervals for the association between covariates, acceptability and retention on PrEP.

Results: A total of 2637 individuals were screened for PrEP of whom 2439 (93%) were eligible; 2285 (94%) of the eligible clients enrolled on PrEP. Enrolled clients included sex workers (54.0%), fisher folk (20.3%), truck drivers (11.2%), Adolescent girls and young women (4.9%), HIV-negative individuals in discordant relationships (7.9%) and others (1.7%). Acceptance of PrEP did not differ significantly by age, gender and risk categories, except for lower acceptance among fisher folk (PR=0.87, 95% CI=0.84-0.91) compared to individuals in discordant couples as well as a slightly higher uptake among those divorced/separated compared to married individuals (PR=1.03, 95% CI=1.0-1.06). Retention, as measured by returning to the clinic for refills, was 47.6% at month 1, 31.3% at month 3, 16.3% % at month 6 and 4.8% at month 9. Retention was lowest among adolescent girls and young women who did not identify as sex workers (PR=0.38, 95% CI=0.23-0.64) and among fisher folk (PR=0.32, 95% CI=0.24-0.42) compared to individuals in discordant relationships. Retention was highest among individuals aged 25-34 (PR=1.21, 95% CI=1.04-1.42) and 35+ (PR=1.38, 95% CI=1.15-1.65) compared to ages 15-24. Retention did not differ by sex and marital status.

Conclusion: Acceptability of PrEP was high in this population; however, clients, especially younger women and fisher folk who are highly mobile, rapidly dropped out of the program. Research on reasons for discontinuation and interventions to optimize retention on PrEP are critical to program success.

998 IMPACT OF A CONTRACEPTIVE RING ON VAGINAL BACTERIA ASSOCIATED WITH HIV ACQUISITION

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Background: Specific vaginal bacteria have been associated with increased risk for HIV acquisition in sub-Saharan African women, including several linked to bacterial vaginosis (BV). Limited data support a favorable effect of a contraceptive vaginal ring (CVR) containing estradiol and progesterone (NuvaRing) on vaginal bacteria. Pregnancy is an independent risk for HIV acquisition and transmission; thus, contraception may comprise biomedical prevention for women with or at risk for HIV, and hormonal modulation of key vaginal bacteria, which are also impacted by menses, might also be advantageous. We randomized women treated for BV in Thika, Kenya to continuous (menstrual suppression) vs. cyclic (regular menses) use of NuvaRing, and assessed effects on key vaginal bacteria associated with HIV acquisition.

Methods: Women aged 18–40 years were enrolled and treated for BV with oral metronidazole. One month later, they were randomized and seen monthly for 7 months, when vaginal swabs were collected. Concentrations of bacterial taxa previously shown to be associated with increased HIV risk, and one associated with protection (L. crispatus), were measured using quantitative PCR. We used linear mixed models stratified by randomization arm and HIV status at
enrollment to compare mean differences in log_{10} bacterial DNA concentrations at the visit prior to CVR initiation relative to 2-3 months post-initiation as an early marker of CVR impact.

**Results:** Between April 2016 to November 2017, 151 women (median age 27 y) were enrolled and 122 (81.9%) initiated CVR use, and 98 had qPCR data available (22 of whom were HIV-infected) at a total of 277 visits (98 pre-CVR and 179 post-CVR insertion). Women in the continuous use CVR group had significantly reduced concentrations of all high-risk bacteria measured at 2-3 months post-insertion (Table). Similarly significant results were seen in women with HIV, with the exception of no change in P. bivia.

**Conclusion:** Continuous CVR use with menstrual suppression over 2-3 months reduced quantities of bacteria previously associated with increased HIV acquisition risk in women. Vaginal rings are a promising strategy that should be evaluated for delivery of multipurpose prevention in Kenyan women.

### Table: Baseline characteristics of women initiating contraception by contraceptive type

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DMMA (n=50)</th>
<th>NHC (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.8 (4.6)</td>
<td>27.9 (4.9)</td>
</tr>
<tr>
<td>Marital status</td>
<td>Single</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td></td>
<td>Married</td>
<td>48 (95.0)</td>
</tr>
<tr>
<td>Plasma HIV RNA level ≥400 copies/ml</td>
<td>22 (44.0)</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Resumed sexual intercourse since last delivery</td>
<td>23 (46.0)</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Currently using condoms</td>
<td>1 (4.0)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Took antibiotics in past month</td>
<td>4.6 (0.9)</td>
<td>4.6 (3.9)</td>
</tr>
<tr>
<td>Sh一番Diversity Index (SDI)</td>
<td>1.2 (0.9)</td>
<td>1.2 (0.9)</td>
</tr>
<tr>
<td>Vaginal pH</td>
<td>5.5 (0.8)</td>
<td>6.4 (0.9)</td>
</tr>
</tbody>
</table>

#### 1000 CHANGES IN VAGINAL MICROBIOTA AMONG HIV-INFECTED AFRICAN WOMEN INITIATING DMPA

**Background:** Depot-medroxyprogesterone acetate (DMPA) has been linked to HIV acquisition, and limited evidence also exists linking DMPA with higher risk of HIV transmission. The biological mechanism underlying these associations is not well understood. DMPA use has been documented to reduce bacterial vaginosis (BV), but there are few molecular studies assessing how DMPA alters vaginal microbiota. We hypothesized that a possible mechanism by which DMPA could increase HIV transmission would be to increase vaginal bacterial diversity.

**Methods:** We conducted a cohort study of postpartum, breastfeeding women in Kenya initiating DMPA or non-hormonal contraception (NHC). Women were followed longitudinally. Vaginal Gram stains were assessed to calculate Nugent score. Vaginal swabs were analyzed with broad-range 16S rRNA gene PCR and sequencing to assess bacterial diversity using Shannon Diversity Index (SDI). Adjusted linear mixed-effects regression was used to estimate mean changes in Nugent score, SDI, and vaginal pH over time in women using DMPA compared to those using NHC.

**Results:** We enrolled 66 HIV-infected women, 50 initiating DMPA and 16 choosing NHC. At baseline, a greater proportion of DMPA users were married and had resumed sexual activity. Mean Nugent score, mean SDI, and mean vaginal pH were similar at baseline (Table). Over 3 months, Nugent score did not significantly change in DMPA users (Δ=-0.71; p=0.51), and this change was not significantly different from the change seen in NHC users (diff.=0.44; p=0.46). Mean SDI also did not change over time in DMPA users (Δ=-0.32; p=0.23), and again, this change was not significantly different from the change in NHC users (diff.=0.46; p=0.29). Lastly, vaginal pH decreased significantly over time in DMPA users (Δ=-0.64; p=0.01), however the change was not significantly different from the change in NHC users (diff.=-0.05; p=0.94).

**Conclusion:** In a cohort of African women, 3 months of DMPA use was not associated with acute, significant changes to vaginal bacterial diversity. Further, DMPA users did not have significantly different Nugent scores or greater vaginal bacterial diversity compared to NHC users. This finding suggests that change in vaginal bacterial diversity is not a main driver of increased risk of HIV transmission among DMPA users. Additional analyses of taxon-specific data will help determine if DMPA causes changes to specific vaginal microbiota which could explain this association.
Background: Reproductive aging may affect the vaginal microbiome, mucosal immune environment and genital tract health in HIV-infected (HIV+) women.

Methods: A cross-sectional study of 102 HIV+ (51 premenopausal, 51 postmenopausal) and 39 HIV-uninfected (HIV-) (20 premenopausal, 19 postmenopausal) women was conducted in Bronx and Brooklyn, NY. Cervicovaginal lavage (CVL) was collected in 10 ml sterile water for quantification of innate antimicrobial activity against E. coli, HSV-2 and HIV and soluble immune mediators by Lumexin and ELISA. Vaginal swabs were obtained for microbiome studies utilizing qPCR and 16S rRNA sequencing.

Results: HIV+ postmenopausal participants had significantly lower median E. coli inhibition, lower median gene copies of L. crispatus and L. iners, and lower mean log10 concentrations of human beta defensins (HBD-2, HBD-3) and secretory leukocyte protease inhibitor (SLPI) compared to HIV+ premenopausal women. In relation to premenopausal, HIV+ postmenopausal participants showed significantly higher proportions of Gardnerella and Atopobium vaginae and lower proportions of Lactobacillus sp. In contrast, HSV-2 inhibitory activity was higher in HIV+ postmenopausal women and correlated with the proinflammatory molecules interleukin (IL) 6, IL-8, human neutrophil peptide (HNP) 1-3, lactoferrin and fibronectin. The HIV inhibitory activity was variable, but higher in participants with suppressed plasma viral load, and inversely correlated with G. vaginalis and BVAB2. A significant proportion of HIV+ participants on antiretroviral therapy exhibited HIV enhancing activity. Similar trends were observed in HIV- postmenopausal compared to premenopausal participants.

Conclusion: HIV+ postmenopausal compared to premenopausal women have less CVL E. coli inhibitory activity, reflecting a lower proportion of lactobacilli species and a greater proportion of Gardnerella and A. vaginae, and more HSV-2 inhibitory activity, reflecting increased mucosal inflammation. The effect of menopause on mucosal immunity was greater in HIV+ than in HIV- participants, suggesting a synergistic impact. It is possible that promotion of a lactobacillus dominant vaginal microbiome and reduced mucosal inflammation in HIV+ postmenopausal women may improve vaginal health and reduce risk for shedding of HIV and potential for HIV transmission.

### 1003 PREVALENCE AND DETERMINANTS OF STI IN HIV+ AND HIV-PREGNANT SOUTH AFRICAN WOMEN

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Background: Sexually transmitted infections (STIs) increase HIV acquisition and transmission risk during pregnancy. Syndromic management is standard in many settings, but there are few data on the occurrence of STIs in HIV-infected and uninfected pregnant women.

Methods: We conducted a cross-sectional study of pregnant women attending a public sector antenatal clinic (ANC) in Cape Town, South Africa. Separate from routine care, after first antenatal care (ANC) visit women ≥18 years were interviewed and self-collected vulvovaginal swabs that we tested for Chlamydia trachomatis (CT), Neisseria gonorrhoea (NG) and Trichomonas vaginalis (TV) using Xpert® assays (Cepheid, Sunnyvale, USA). We used multivariate logistic regression to identify factors associated with having a STI by HIV serostatus.

Results: In 241 women (median age 29 years [IQR=24-34], median gestation 19 weeks [IQR=14-24]) 44% were HIV-infected of whom 33% started ART at their first ANC visit. 47% of women were married/cohabiting. Almost all women reported vaginal sex during pregnancy (93%), 1% reported > 1 partner in the past 12 months and 3% reported anal sex during pregnancy. Prevalence of any STI was 32%; 38% in HIV-infected women vs 28% in HIV-uninfected women (p = 0.078); the prevalence of individual co-infections was consistent by HIV status (Figure). STI-related symptoms in women diagnosed were reported infrequently (4% vaginal bleeding; 13% abnormal discharge; 6% dyspareunia). Of women with STI detected, 1% were diagnosed syndromically during routine ANC; this proportion did not vary by HIV status. In a multivariable model controlling for gestational age and relationship status, HIV+ status (adjusted odds ratio [aOR]=1.86; 95% CI=1.03-3.13), younger age (aOR=0.55/year; 95% CI=0.90-0.99) and suspecting partner of having other partners (aOR=1.68; 95% CI=1.00-3.10) were independently associated with STI detection. STI symptom(s) in pregnancy were not predictive of STI diagnosis (age-adjusted OR=0.58; 95% CI=0.28-1.21; p=0.15) and this did not vary by HIV status. In HIV-infected women, younger age was associated with increased odds of STI diagnosis (aOR=0.89/year; 95% CI=0.82-0.96).

Conclusion: We document a very high prevalence of treatable STIs in pregnancy in both HIV-infected and -uninfected women in this setting. Symptoms were not predictive of infection; novel approaches to improve STI diagnosis and management in pregnancy are urgently required.
INCREASED EFFECTIVENESS WITH MODERN COMMUNICATION TECHNOLOGY

Amelia S. Oliveira, Julia Bilinska, Harsh Mohammadi, Jay Jarman, John Were, Anatole Menon-Johansson, Lisa Hamzah


Background: Prevalence of sexually transmitted infections (STIs) in STI contacts are high. Partner notification (PN) aims to inform and treat partners and reduce onward transmission. UK standards recommend 0.6 partners tested per index case. However, PN is time and labor intensive. Online platforms may reduce costs, expand coverage and increase effectiveness.

Methods: A retrospective analysis of PN initiated via SXT in the UK between 01/12/17-31/07/18 was performed using anonymized data on index case demographics, STIs and PN. Number of contacts screened per index case were compared to national data for chlamydia (CT), gonorrhea (GC) and syphilis (STS). Factors associated with testing at least one partner were examined using multivariable logistic regression. Analyses were performed using STATA 12.

Results: 6414 index cases initiated PN via SXT across 13 sexual health providers, median age 25 (IQR 21-32) years, 66% white ethnicity, 58% male and 26% men who have sex with men (MSM), with 6779 STIs; the majority CT (65%), GC (21%) and STS (5%). The number of verified tested partners per diagnosis via SXT vs. national data were higher for CT, GC and STS (Table 1). Based on known STI prevalence in partners, a predicted 133 GC, 77 CT and 12 STS additional diagnoses were made using SXT during the 7 month period. 23-34% of PN was achieved.

Conclusion: An electronic PN tool demonstrated increased PN compared to national data, exceeded national targets for CT, GC and STS, reduced workload, and was successful in large conurbations. Being MSM, of black ethnicity and a diagnosis of trichomonas vaginalis (TV) were associated with fewer partners tested.

Table 1. Correlates of HSV-2 incident infection in a cohort of Kenyan adolescent girls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women without incident HSV-2</th>
<th>Women with incident HSV-2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>18 (16.21)</td>
<td>18 (18.20)</td>
<td>0.75</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12 (0.14)</td>
<td>12 (8.13)</td>
<td>0.83</td>
</tr>
<tr>
<td>Employed</td>
<td>37% (142/386)</td>
<td>42% (8/19)</td>
<td>0.81</td>
</tr>
<tr>
<td>Age at first intercourse</td>
<td>19 (14.34)</td>
<td>18 (10.21)</td>
<td>0.31</td>
</tr>
<tr>
<td>Household income (USD)</td>
<td>0.60 (13000)</td>
<td>0.60 (13000)</td>
<td>0.86</td>
</tr>
<tr>
<td>Rural residence</td>
<td>62% (235/386)</td>
<td>59% (10/19)</td>
<td>0.47</td>
</tr>
<tr>
<td>Reported no intercourse at baseline</td>
<td>81% (308/386)</td>
<td>74% (18/19)</td>
<td>0.38</td>
</tr>
<tr>
<td>Reported no intercourse follow-up</td>
<td>35% (133/386)</td>
<td>16% (3/19)</td>
<td>0.13</td>
</tr>
<tr>
<td>Nugent score at baseline</td>
<td>0 (0.10)</td>
<td>0 (0.89)</td>
<td>0.028</td>
</tr>
<tr>
<td>Presence of GC or CT at baseline</td>
<td>12% (4/354)</td>
<td>28% (5/18)</td>
<td>0.058</td>
</tr>
<tr>
<td>Gonorrhea at baseline</td>
<td>1% (4/354)</td>
<td>5% (1/18)</td>
<td>0.22</td>
</tr>
<tr>
<td>Chlamydia at baseline</td>
<td>10% (37/354)</td>
<td>22% (4/18)</td>
<td>0.12</td>
</tr>
<tr>
<td>Pregnancy prior to HSV-2</td>
<td>22% (82/386)</td>
<td>32% (6/19)</td>
<td>0.39</td>
</tr>
<tr>
<td>BV (Nugent &gt; 7) at baseline</td>
<td>5% (16/386)</td>
<td>11% (3/18)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

P < 0.05 indicates statistical significance.

**Notes:**
- SXT vs. national data were higher for CT, GC and STS.
- Based on target prevalence, a predicted 133 GC, 77 CT and 12 STS additional diagnoses were made using SXT.
- 23-34% of PN was achieved.
- Factors associated with testing at least one partner were examined using multivariable logistic regression.
- Analyses were performed using STATA 12.
- Compared to testing at least one partner, black vs. white ethnicity (OR 95% CI 0.61-0.90), living outside large conurbations (OR 0.37-0.59) or testing online (OR 0.26-0.35) were associated with fewer partners tested.

Conclusion: An electronic PN tool demonstrated increased PN compared to national data, exceeded national targets for CT, GC and STS, reduced workload, and was successful in large conurbations. Being MSM, of black ethnicity and a having a diagnosis of TV was associated with fewer partners tested, highlighting areas to target for future improvements.
INCIDENCE AND CORRELATES OF UNINTENDED PREGNANCY IN HIV-POSITIVE KENYAN SEX WORKERS

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Background: HIV-positive female sex workers (FSWs) often have high rates of unplanned contraceptive use, but data on the incidence of planned, mistimed, and unwanted pregnancies are sparse. We examined incidence and correlates of pregnancy in HIV-positive Kenyan FSWs.

Methods: Non-negative FSWs enrolled in a cohort study in Mombasa, Kenya were eligible. Participants returned for monthly visits to ascertain sexual risk behavior, and were pregnancy tested quarterly. Pregnancies were considered planned, mistimed, or unwanted according to quarterly fertility desire and pregnancy intention questions. Cox proportional hazards models were used to estimate hazard ratios (HR) for the association between demographic, sexual, clinical, and behavioral characteristics and pregnancy. Correlates associated with pregnancy in univariate analysis at p<0.10 were included in the adjusted model.

Results: A total of 316 FSWs contributed 785.7 person-years of follow-up. Most women had a current/regular partner in the last 3 months (50.8%, 160/315), were not using modern non-barrier contraception (69.3%, 219/316), did not desire a child (69.9%, 221/316), and had CD4 counts >350 cells/mm3 (60.9%, 194/316). There were 46 first incident pregnancies, for a rate of 5.9/100 person-years (p=0.05). The incidence of planned (6.4/100 p-y; n=4), mistimed (7.1/100 p-y; n=12), and unwanted pregnancies (5.9/100 p-y; n=30) were similar (p=0.11), but 90% (n=42) of pregnancies were mistimed or unwanted. In univariate analysis, oral contraceptive pill (OCP) use (vs no contraception or condoms only), condomless sex, vaginal washing, transactional sex in the last year, having a regular partner in the last 3 months, and experiencing intimate partner violence in the last year were significantly associated with a higher pregnancy rate. Being ≥35 years old (vs <25) was associated with a lower pregnancy rate. In multivariable analysis, OCP use (HR 2.9, 95%CI 1.09-7.80), reporting condomless sex (HR 2.19, 95%CI 1.08, 4.46), and having a current/regular partner in the last 3 months (HR 3.64, 95%CI 1.00-13.34) were associated with increased risk of incidence pregnancy.

Conclusion: In this cohort of HIV-positive FSWs, 90% of pregnancies were unintended. As part of comprehensive HIV care for FSWs, identifying women's fertility desire and pregnancy intention could facilitate efforts to increase effective contraceptive use in women not trying to conceive and to implement safer conception strategies for women trying to have a child.

DRIVERS OF UNPLANNED PREGNANCY AND UNMET NEED FOR CONTRACEPTION IN SOUTH AFRICA

Witness Chirola1, Debra Jackson1, Vundli Ramokolo1, Yages Singh1, Trisha Ramraj1, Duduzile Nsibande1, Kondwani Ng'oma1, Sanjana Bhardwa1, Mireille Cheyip1, Mary Mogashoa1, Carl Lombard1, Ameena Goga1

1South African Medical Research Council, Cape Town, South Africa, 2UNICEF, New York, NY, USA, 3South African Medical Research Council, Durban, South Africa, 4UNICEF Rwanda, Kigali, Rwanda, 5CDC, Atlanta, GA, USA

Background: Preventing unplanned pregnancies amongst HIV positive women is a pillar of the WHO prevention of mother to child transmission of HIV (PMTCT) strategy, yet 60% pregnancies in South Africa are unplanned. We sought to identify predictors of unplanned pregnancies and unmet contraceptive among postpartum women in South Africa.

Methods: This analysis involves data from a nationally representative, cross-sectional survey measuring PMTCT effectiveness, in 2012/13. A total of 9277 women with known HIV status were included. All data regarding pregnancy planning and contraceptive use were self-reported during interviews. Unmet need for contraception was defined as unintended pregnancy among women not using any contraceptive method. All analyses were weighted and accounted for the survey design. Multivariable logistic regression models were used to estimate factors associated with unplanned pregnancy and unmet need for contraception.

Results: The mean age of participants was 26.3 years (SD 6.35), with 31.7% (95%CI: 30.6-32.7) self-reported HIV prevalence. More than a third (35.5%) were not using any contraceptive method. All analyses were weighted and accounted for the survey design. Multivariable logistic regression models were used to estimate factors associated with unplanned pregnancy and unmet need for contraception.

Results: The mean age of participants was 26.3 years (SD 6.35), with 31.7% (95%CI: 30.6-32.7) self-reported HIV prevalence. More than a third (35.5%) were not using any contraceptive method. All analyses were weighted and accounted for the survey design. Multivariable logistic regression models were used to estimate factors associated with unplanned pregnancy and unmet need for contraception.

In high burden HIV settings, well-functioning sexual and reproductive health programming prevents unplanned pregnancies and HIV transmission. In Botswana, where HIV incidence approaches 1% per 100 person-years and prevalence among adults age 15-49 is >20%, we sought to quantify pregnancy intention and uptake of contraception among postpartum women living with HIV (WLHIV) and HIV-uninfected (HIV-U) women.

Methods: The Tshilo Dikotla study is prospectively enrolling pregnant WLHIV and HIV-U women ≥18 years old in Gaborone, Botswana, and following mother-infant pairs through 3 years postpartum. WLHIV are on dolutegravir (DTG)- or efavirenz (EFV)-based combination antiretroviral treatment (cART) regimens in pregnancy. Data on future pregnancy intention and contraception use are collected via questionnaire at 6 months postpartum. We compared the proportion of women without plans for pregnancy (ever or within 2 years), proportions of women reporting use of contraception, and adopted contraception methods by HIV status. In women reporting >1 type of contraception, the most efficacious method was used for analysis.

Results: Among 233 women attending the 6-month postpartum visit, 142 (61%) were WLHIV. WLHIV were older (28.5 vs 24.3 years; p<0.001) and had higher gravidity (3 vs 1; p<0.001) compared to HIV-U women. More WLHIV expressed a desire to prevent future pregnancies or defer pregnancy for ≥2 years compared to HIV-U women (87% vs 66%; p<0.001). Among women not planning pregnancy in ≤2 years, only 89 (49%) reported using contraception, with similar uptake by WLHIV and HIV-U women (50% vs 47% respectively; p=0.71). Of the 61 WLHIV using contraception, 57% were on DTG- and 43% on EFV-based cART, with none using hormonal implants. Only 14% of HIV-U women were using implants. (Table 1) Depot medroxyprogesterone acetate was the most commonly used method overall. Uptake of condom use was low as a primary or secondary method, yet a higher proportion of WLHIV reported condom use (39% vs 32%). Only 7 women were using more than one method.

Conclusion: Uptake of contraception at 6-months postpartum was universally poor among women desiring pregnancy prevention, regardless of HIV status. In addition, dual condom use with more efficacious methods was particularly low, a concerning finding in a high burden HIV setting. Understanding individual and programmatic impediments to contraception uptake is needed to better match contraception use to pregnancy desires in Botswana and prevent HIV transmission.
Clinical outcomes were described using frequencies and percentages. These were compared using Chi-square (χ²) tests, Fisher’s exact tests, and McGraw-Hill tests. The prevalence rate of contraceptive practice was calculated for all women and for those with a reported unmet need. Logistic regression was used to estimate the impact of the intervention adjusted to other covariates.

Results: A total of 852 eligible women were surveyed across two sites; 51.6% were married. Modern CPR increased from 33.7% to 41.8% (p=0.003) and unmet FP need decreased from 13.9% to 9.6% (p=0.02). However, unmarried participants showed no significant increase in modern CPR from 36.2% to 41.9% (p=0.235). Long-acting reversible contraception (LARC) use significantly increased from 15.4% to 38.4% (p=0.001) while use of short-acting methods decreased from 86.0% to 63.3% (p<0.001). For specific LARC methods, use of implants increased from 8.8% to 36.2% (p<0.001), while intrauterine contraceptive device use significantly decreased (6.6% to 2.0%, p=0.034). For short-acting methods, condom use decreased (83.1% to 38.3%, p<0.001), while injectable use increased (2.9% to 6.3%, p=0.001). Adjusting for demographic and clinical characteristics, women with unmet FP need were significantly likely to be Catholics (odds ratio (aOR) =1.30, 95% confidence interval (CI): 1.02-1.65) compared to one year HIV treatment.

Conclusion: Integration of FP services into HIV treatment programs in Cameroon resulted in a significant decrease in the unmet need for FP and a significant increase in CPR. Successes of this program, as well as lessons learned during the service integration process, will lay the groundwork for future related programming.
1011 EFFECTIVE TREATMENT OF LYMPHOGRAVULUM PROCTITIS WITH EXTENDED AZITHROMYCIN REGIMEN

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Background: Lymphogranuloma venereum (LGV) is an ulcerative and incapacitating sexually transmitted infection (STI) caused by Chlamydia trachomatis (CT) serovars L1, L2, and L3. In the last 15 years it has become hyperendemic among men who have sex with men (MSM) in Western Europe. Current guidelines suggest treatment with Doxycycline 100 mg twice daily for 21 days (DoxLGV). Azithromycin 1 g orally once weekly for 3 weeks (extended azithromycin regimen (EAzLGV)) may be an alternative treatment, and here we investigate its effectiveness as a treatment for LGV proctitis.

Methods: A prospective study was conducted between 2010 and 2017 at the STD Unit of a tertiary referral hospital in Barcelona (Spain). Males over 18 years of age with clinical proctitis, a recent history of unprotected receptive anal intercourse and microbiological confirmation of the diagnosis of LGV were eligible for inclusion. All patients received a single dose of 1 gr of intramuscular ceftriaxone and were randomly assigned to receive: (i) DoxLGV or (ii) EAzLGV. Following treatment, individuals were assessed weekly for clinical symptoms and microbiologically by real-time multiplex polymerase chain reaction (M-PCR) for CT-LGV. Clinical cure (CC) was defined as disappearance of symptoms for at least 12 weeks; and microbiological cure (MC) as a negative rectal PCR for CT-LGV at week 4-6.

Results: Of 152 individuals with LGV, 136 (89%) met inclusion criteria. All were MSM with a median age of 38 years (interquartile range 33;44), 46% foreigners and 95% HIV+. Median numbers of sexual partners were 3 [1-10] and 10 [4-37], respectively. Average time between onset of the symptoms and diagnosis was 39 days (range: 1-180). Eleven patients with inclusion criteria were excluded because of violation of assigned therapy. From the 136 individuals with proctitis, there were 125 patients left for final analysis, 82 received EAzLGV and 43 received DoxLGV. There were no treatment-related adverse events or losses to follow up. CC was achieved in 81 of 82 (99%) vs 41 of 43 (95%) (p= 0.27) and MC in 97% vs 100% (p=1.00) in the EAzLGV and DoxLGV groups, respectively.

Conclusion: Our findings show that an extended azithromycin regimen was as effective as standard doxycycline regimen and may be considered as an alternative treatment for LGV proctitis in an HIV-infected population of MSM.

1012 ADHERENCE OF HEALTH CARE PROVIDERS TO CDC LUMBAR-PUNCTURE CRITERIA AMONG SYPHILIS/HIV

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Background: Syphilis is a prevalent infection with increased morbidity and more frequent central nervous system invasion in HIV-infected persons. The CDC suggests laboratory criteria to guide cerebrospinal fluid (CSF) examination among asymptomatic HIV-infected patients. However, information about the degree of adherence to such criteria is scarce. In this study, we describe the proportion of adherence of Health Care Providers to CDC lumbar puncture (LP) criteria in syphilis and HIV coinfected patients and report the frequency of neurosyphilis in these patients.

Methods: Retrospective cohort study carried out in all HIV-infected patients under outpatient follow-up in an academic center at São Paulo, Brazil, between 2000 and 2016. We identified all incident syphilis cases, defined as a first positive treponemal test or a ≥4-fold increase in consecutive VDRL titers. We considered lumbar puncture performed < 6 months after incident syphilis. We report the proportion of patients meeting CDC criteria for LP undergoing cerebrospinal fluid testing, and the frequency of confirmed (positive VDRL) or probable (abnormal leukocyte counts: >5 cells/ml among patients with T CD4+ counts <200 and suppressed viral loads; >20 cells/ml otherwise) neurosyphilis.

Results: The initial sample comprised 3448 persons living with HIV. Incident syphilis was detected in 669 patients. Of those, 459 met CDC criteria for CSF collection, and 147 (32%, 95% CI 28-37) were referred to LP. Confirmed or probable neurosyphilis was observed in 18 cases (12%, 95% CI 7-19). Of 312 patients not referred to LP despite CDC criteria, 10 (3%, 95% CI 2-6) collected CSF within 6 to 12 months and 3 (30%, 95% CI 7-65) had abnormal results compatible with neurosyphilis. Of those with abnormal results, 13 (72%) had a positive VDRL in the cerebrospinal fluid.

Conclusion: Adherence to CDC LP criteria for syphilis and HIV coinfected patients was low, despite follow-up in an academic center. In this subset of patients, the frequency of neurosyphilis was 12% for LP performed in the first 6 months and 30% among those submitted to LP within 6 to 12 months.

1013 HEARING LOSS IN UNSELECTED INDIVIDUALS WITH SYPHILIS

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Background: Little is known about the incidence and pathophysiology of otosyphilis.

Methods: Unselected individuals enrolled in a study of cerebrospinal fluid (CSF) abnormalities in syphilis underwent screening audiometry, standardized medical history, lumbar puncture and venipuncture. Serum rapid plasma reagin titers (RPR) and detection of T. pallidum (Tp) in blood by PCR and CSF by RT-PCR were determined in a research laboratory. CSF white blood cell count, CSF Venereal Disease Research Laboratory (VDRL) reactivity, CD4 + T cells and plasma HIV RNA were determined in a clinical laboratory. Relationships between hearing loss (HL, unilateral or bilateral), defined as low-mid (500, 1000, 2000 Hz average) or high frequency (4000, 6000, 8000 Hz average) pure tone averages ≥26 dB, or either (any loss), and other variables were determined by logistic regression. For multivariate models, all variables significant at P<0.10 were included. Those with P-values >0.05 in multivariate models were sequentially removed.

Results: 362 individuals without pre-existing HL were evaluated: 99% men, mean age 41 (SD 11), 82% HIV+ (70% on antiretrovirals [ARVs]), median serum RPR titer 1:64 (IQR, 1:16-1:128), 51% treated for uncomplicated syphilis before study visit. 186 (51%) had any HL, 83 (23%) low-mid and 168 (46%) high frequency HL. In univariate analysis, odds of any HL were higher in HIV+, those with reactive CSF-VDRL, CSF pleocytosis, detection of Tp in blood or CSF,
injection drug use (IDU), older age and higher RPR titers (Table). In multivariate analysis, odds of any HL remained higher in those with CSF pleocytosis, Tp detection in blood, IDU and older age (Table). In multivariate analysis, odds of low-mid frequency HL were higher in those withTp detection in CSF, IDU and older age, and odds of high frequency HL were higher in those with CSF pleocytosis, Tp detection in blood, and older age (Table). Syphilis stage, current ARV use, CD4+ T-cells and plasma HIV RNA were not associated with any category of hearing loss.

Conclusion: HL is common in individuals with syphilis and increases with age. While low-mid frequency HL is more likely in those with Tp detection in CSF, high frequency HL is more likely with CSF inflammation. Low-mid and high frequency HL due to otosyphilis may be due to different pathological mechanisms, and, as such, may respond differently to treatment.

Results: 186 individuals with syphilis underwent self-administered cognitive testing. Serum RPR was ≥1:64 in 81% (151/186), and ≥1:128 in 65% (121/186). Median CSF WBC count (IQR) was 3 (0, 13). 21% had a reactive CSF-VDRL alone, or reactive CSF-VDRL or CSF WBCs> 10/ul. Results were determined by chi square or Fisher exact test.

Methods: Few studies have examined both cognitive function and cerebrospinal fluid (CSF) abnormalities in individuals with syphilis. Methods: 186 individuals with syphilis underwent self-administered cognitive assessment with theCogstate battery, and 132 (71%) underwent lumbar puncture. Cognitive function was categorized as unimpaired; mild, moderate or severely impaired; or unimpaired/mild or moderate/severe based on normative Cogstate data. Serum rapid plasma reagin (RPR) test titer, detection of T. pallidum in CSF by reverse transcriptase PCR and presence of recreational drugs in urine were determined in a research laboratory, and CSF white blood cell (WBC) enumeration and CSF Veneral Disease Research Laboratory (VDRL) reactivity were determined in a clinical laboratory. Neurosyphilis was defined as a reactive CSF-VDRL alone, or reactive CSF-VDRL or CSF WBC>10/ul. Results are described as medians (interquartile range [IQR]) or percents, and differences determined by chi square or Fisher exact test.

Results: Participants were primarily men (98%), age 35 (28-46) with at least a high school education (91%); 62% were HIV infected with 90% on antiretrovirals. 82% had early syphilis, with RPR 1:64 (1:32-1:256). Urine toxicology was positive for stimulants in 19%, cannabinoids in 21% and both in 9%. Overall, 124 participants were cognitively impaired: 72 (39%) mild, 33 (18%) moderate, 19 (10%) severe. Among those with any cognitive impairment, the proportion of individuals with serum RPR titer ≥1:32 increased with increasing level of impairment (52/72 (72%) mild, 26/33 (79%) moderate, 19/19 (100%) severe, P=0.02). Individuals with asymptomatic syphilis (early latent or late latent) were more likely than those with primary or secondary disease to have moderate/severe impairment (33/97 (34%) vs. 19/89 (21%), P=0.05). There was no relationship between cognitive impairment and HIV status, a positive toxology screen, either definition of neurosyphilis, or detection of T. pallidum in CSF.

Conclusion: Cognitive impairment was common in this cohort of individuals with syphilis, was not associated with HIV status or neurosyphilis, but was more common in those with high serum RPR titers, and those with latent syphilis. These results suggest that cognitive impairment in individuals with syphilis may be related to bacterial burden and may be seen in those without symptoms or signs of syphilis.
assessments of the real-world impact of Treat All on antiretroviral treatment (ART) uptake across different contexts.

**Methods:** We used longitudinal data for 814,603 patients enrolling in HIV care during 2004-2018 in six sub-Saharan African countries participating in the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium (Burundi, Kenya, Malawi, Rwanda, Uganda, and Zambia). Using a quasi-experimental regression discontinuity design, we assessed the change in the proportion of individuals initiating treatment within 30 days of enrollment in HIV care (rapid ART initiation) after country-level adoption of Treat All policies. A modified multivariable Poisson model was used to identify factors associated with failure to initiate ART rapidly among persons enrolling in HIV care under Treat All.

**Results:** In all countries, national adoption of Treat All was associated with large increases in rapid ART initiation. The greatest increase in rapid ART initiation immediately after Treat All policy adoption was observed in Rwanda, from 44.4% to 78.9% of patients (34.5 percentage points (pp); 95% CI: 27.2-41.7 pp), Kenya (25.7pp, 95% CI: 21.8 to 29.5pp), and Burundi (17.7pp, 95% CI: 6.5 to 28.9pp), while the rate of rapid ART initiation accelerated sharply following Treat All policy adoption in Malawi, Uganda, and Zambia. Under Treat All, younger patients (16-24 years) and men were at increased risk of not rapidly initiating ART (compared to older patients and women, respectively). However, rapid ART initiation following enrollment increased for all groups as more time elapsed since Treat All adoption.

**Conclusion:** Adoption of Treat All policies had a strong effect on increasing rates of rapid ART initiation and increases followed different trajectories across the six countries. Adoption and implementation of Treat All policies should be accelerated, with particular care to identify and address possible inequities in access to treatment by subgroups at higher risk of not rapidly initiating treatment following diagnosis and care enrollment.

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**1018 SAME-DAY ART INITIATION IN THE SLATE TRIAL IN KENYA: PRELIMINARY RESULTS**

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**Background:** WHO’s and Kenya’s HIV treatment guidelines recommend rapid initiation of ART (<7 or ≤14 days of HIV diagnosis, respectively) and encourage same-day initiation. Identifying efficient procedures for determining same-day eligibility and readiness is a priority. The Simplified Algorithm for Treatment Eligibility (SLATE) trial is testing a clinical algorithm in Kenya and South Africa that allows clinicians to determine eligibility for immediate ARV dispensing at the patient’s first visit. We report early results from Kenya.

**Methods:** SLATE is an individually randomized, pragmatic trial at 3 public hospital-based outpatient clinics in western Kenya. Ambulatory patients presenting for an HIV test or HIV care, but not yet on ART, were enrolled sequentially, consented, and randomized to intervention or standard care. Intervention arm patients were administered the SLATE algorithm, comprised of a symptom self-report, medical history questionnaire, brief physical examination, and readiness assessment, to identify patients eligible for immediate ART initiation (“screened in”) or requiring further care, tests, or counseling before starting treatment (“screened out”). Patients who screened in were dispensed ARVs immediately; those who screened out were referred back to the clinic for further routine care. Follow up was by record review. We report ART initiation within 0 (same-day), 7, 14, and 28 days of study enrollment.

**Results:** From 12 July 2017 to 23 April 2018, we enrolled 477 adult, HIV+, non-pregnant patients. More patients initiated ART in the intervention arm than in the standard arm at 0 (70% vs 54%), ≤7 (86% vs 73%), ≤14 (90% vs 85%) and ≤28 days (94% vs 89%) (Table). In the intervention arm, 109 patients (45.4%
of 240) screened out: 51 (47%) due to TB symptoms alone, 42 (39%) due to TB symptoms and ≥ 1 other reasons, and 16 for reasons other than TB. Among the 109 screened out and referred back to the clinic for further care, 36/109 initiated the same day and 64/109 initiated within 90 days; 9/109 patients did not start within 90 days.

**Conclusion:** Use of the SLATE algorithm increased uptake of ART within 7 days - the WHO’s definition of “rapid” initiation - by 12.8%. Medical officers were able to implement it in routine care settings without additional equipment or clinical supervision. Current TB symptoms accounted for 3/4 of patients screened out. Early results suggest that a simple algorithm for treatment initiation procedures is feasible and can increase same-day and rapid ART uptake.

## 1019B WITHDRAWN / INTENTIONALLY UNASSIGNED

### 1020 IMPLEMENTING UTT IN AFRICAN CORRECTIONAL FACILITIES: A PROSPECTIVE COHORT STUDY

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**Background:** Despite widespread HIV treatment and care scale up, corrections inmates continue to be left behind in the global HIV response. To provide inmates with the known benefits of universal test and treat (UTT) and to describe clinical outcomes for UTT delivery in southern African correctional facilities, we conducted an implementation research study enrolling a prospective cohort of HIV-positive inmates from Zambia and South Africa.

**Methods:** We offered immediate ART to inmates ≥18 years with newly diagnosed HIV or previously diagnosed HIV not yet on ART (regardless of CD4 or WHO stage) who were expected to be incarcerated ≥30 days at a high-volume correctional facilities in Lusaka, Zambia and Johannesburg and Cape Town, South Africa. To enable UTT delivery at each site, we strengthened public, on-site HIV care programming by supporting: HIV testing and anti-retroviral therapy (ART); viral load (VL) monitoring; and corrections officer, health worker, and peer educator training on UTT. We collected clinical and socio-demographic data at study baseline and follow-up visits. We calculated summary statistics for variables of interest, and conducted an exploratory risk factor analysis for unsuppressed VL using logistic regression modelling.

**Results:** From June 2016–March 2018, 1,562 HIV-positive inmates were identified across the study sites, of whom 1,022 (65%) met study eligibility criteria and 977 (96%) enrolled. Participants were mostly young men (n=824, 84%), with median age 32 years (IQR: 28–38) and 29% (n=287) having prior incarceration history. Of those enrolled, 835 (84%) started ART, and did so within 1 day (IQR: 0–7) of HIV diagnosis. Of 141 who did not start ART, most (n=113, 80%) were transferred or released prior to baseline evaluation. Among 384 (44%) participants with a documented 6-month post-ART VL, 74%, 89% and 91% achieved virologic suppression using thresholds of ≤50 copies/c/mL, <400 c/mL, and ≤1,000 c/mL, respectively. Factors associated with VL ≥50 c/mL are reported in the table.

<table>
<thead>
<tr>
<th>Table: Sample characteristics and primary outcomes, by arm</th>
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<tbody>
<tr>
<td><strong>5-year baseline VL</strong></td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>24% (22/93)</td>
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<tr>
<td>28% (14/50)</td>
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<tr>
<td>35% (30/86)</td>
</tr>
<tr>
<td>40% (21/53)</td>
</tr>
<tr>
<td>45% (30/67)</td>
</tr>
<tr>
<td><strong>Duration of incarceration</strong></td>
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<tr>
<td>6 months</td>
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<td>12 months</td>
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<td><strong>Age:</strong></td>
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<td>18-29 years</td>
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<td>30-49 years</td>
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<td>≥50 years</td>
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</tbody>
</table>

**Conclusion:** In the first prospective study of its kind from southern Africa, we demonstrate that it is feasible to implement UTT in correctional settings in Zambia and South Africa, and that such an intervention can achieve high early ART uptake and excellent viral suppression for HIV-positive inmates during incarceration. However, frequent facility transfer and release threatens to undermine UTT by limiting access to timely ART and fragmenting care for inmates living with HIV.

## 1021 IMPROVEMENT IN TIME TO ART INITIATION REGARDLESS OF TB STATUS IN LATIN AMERICA

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**Background:** In 2006, the World Health Organization recommended antiretroviral therapy (ART) for persons with CD4 count <200 cells/mm3 (<350 if co-infected with tuberculosis [TB]) or Stage 4 HIV disease. Subsequent guidelines recommended earlier ART initiation (2009: CD4 <350 cells/mm3 or Stage 3/4 disease [including TB]; 2013: CD4 <500 cells/mm3; 2015: universal ART). The recommended timing of ART initiation relative to TB medications also changed during this period. We characterized temporal trends in the time to ART initiation and compared trends between HIV+ persons with and without TB.

**Methods:** The study included data from HIV clinical sites in Brazil, Chile, Haiti, Honduras, Mexico, and Peru participating in CASAnet. We included all persons ≥18 years old who were ART-naive at first clinic visit from 2006 to 2015. We estimated median time to ART initiation as a function of baseline TB status (within 30 days before or after enrollment), CD4 count, and year of enrollment from a multivariable Cox regression model that included these variables, two-way interactions between these variables, sex, education, and age, and stratified by site. Continuous variables were fit with natural splines to relax linearity assumptions.

**Results:** Of 19,197 patients, 1306 (7%) were diagnosed with TB at enrollment. Patients with TB were more likely to be male, older, less educated, with lower CD4 counts, and living in Haiti or Peru. A total of 17,183 (93%) initiated ART during a median of 3.6 years of follow-up: 96% of those with TB compared to 93% without TB (p<0.001). The median time to ART initiation was 42 days for those without TB, and 43 days for those with TB (p=0.94). The Figure shows the estimated median adjusted time from enrollment to ART initiation as a function of TB status, calendar year, and CD4 count at enrollment. The association between CD4 count and time to ART initiation changed dramatically over time (p<0.0001). The association between TB status and time to ART initiation varied extensively based on CD4 count (p<0.0001) and to a lesser extent the date of enrollment (p=0.06). For a person enrolling with TB and a CD4 count of 500
1022  UPTAKE OF ANTIRETROVIRAL THERAPY IN THE “TREAT ALL” ERA IN RIO DE JANEIRO, BRAZIL

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Background: Randomized controlled trials have proven the efficacy of early antiretroviral therapy (ART) for reducing HIV morbidity, mortality, and transmission. As a result, guidelines recommending treatment for all, regardless of CD4 count, are being scaled up worldwide. The Brazilian Ministry of Health has recommended treatment for all since 2013 and offers free antiretrovirals (ARVs) for all HIV-infected patients. We evaluated uptake of “treat all” guidelines in Rio de Janeiro, Brazil, from 2014–2017.

Methods: HIV has been a notifiable disease in Brazil since 2014. We included all patients diagnosed with HIV and reported to the Rio de Janeiro Health Secretariat from 2014–2017, with follow-up through 2017. HIV notifications and comorbidities were obtained from the national notifiable diseases information system; ARV prescriptions from the Rio de Janeiro pharmacy information system; and death notifications from the Rio de Janeiro mortality registry. We joined databases using a novel probabilistic linkage strategy. We assessed HIV notifications, prevalence of opportunistic infections (OIs), and median time to ART initiation over time. We used Nelson-Aalen cumulative hazard estimates to construct risk curves comparing 3-month ART initiation by diagnosis year and estimated the hazard of ART initiation by diagnosis year using Cox proportional hazards regression.

Results: From 2014–2016, 6,454 persons were diagnosed with HIV and notified to the Rio de Janeiro Health Secretariat. Of these, 2,009 (31%) were female and median age was 34 years (IQR 26–43). 1,725 (27%) had a documented OI, including 417 (6%) with pulmonary tuberculosis. Of 2,628 (41%) patients reported to have initiated ART, 2,028 (77%) did so within 3 months of HIV diagnosis; median time to ART initiation was 42 days (IQR 15–94) and decreased from 51 days (IQR 21–131) in 2014 to 46 days (IQR 20–92) in 2015 and 31 days (IQR 8–68) in 2016. Patients diagnosed in 2015 had an increased hazard of 3-month ART initiation compared to those diagnosed in 2014 (AHR 1.13, 95% CI 1.18–1.46). There was a non-significant increased hazard of 3-month ART initiation for those diagnosed in 2016 compared to 2014 (AHR 1.06, 95% CI 0.95–1.19).

Conclusion: The rate of ART initiation in Rio de Janeiro was low, despite the availability of free ARVs and guidelines recommending treatment for all. “Treat all” guidelines should continue to be scaled-up to achieve 90-90-90 targets and reduce HIV morbidity and mortality.

1023  NARROWING THE GAP IN CD4 COUNT AT ENTRY INTO CARE AND AT ART INITIATION, 2005–2016

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1 Johns Hopkins University, Baltimore, MD, USA; 2 McGill University Health Centre, Glen site, Montreal, QC, Canada; 3 Vanderbilt University, Nashville, TN, USA; 4 Albert Einstein College of Medicine, Bronx, NY, USA; 5 VA Connecticut Healthcare System, West Haven, CT, USA; 6 Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA; 7 University of Washington, Seattle, WA, USA; 8 University of California San Diego, San Diego, CA, USA; 9 Kaiser Permanente, Oakland, CA, USA; 10 Universidad Central del Caribe, Bayamon, Puerto Rico

Background: In March 2012, the US Department of Health and Human Services updated HIV treatment guidelines to recommend antiretroviral therapy (ART) for everyone infected with HIV, regardless of CD4 count, to reduce morbidity and mortality among those infected and prevent transmission to others. Our objective was to describe observed trends in CD4 count, at entry into care and at ART initiation, among patients enrolled in US-based clinical cohorts of the NA-ACCORD between 2005 and 2016.

Methods: The study sample comprised treatment-naïve adults (aged ≥18 years) without a clinical AIDS diagnosis who presented for HIV care with a viral load >500 copies/mL (-180/+14 days) and a recorded CD4 count (-90/+30 days). A subset of the study sample initiated ART (defined as being prescribed a combination ART regimen) with a recorded CD4 count (-90/+30 days). For patients with >1 CD4 count collected during the 120-day window, we used the measurement obtained closest to the visit date of interest. We generated plots of median CD4 counts at entry into care and at ART initiation, by calendar year. We also calculated median number of days from entry into care to ART initiation, by calendar year.

Results: We identified 28862 patients who entered care; of those patients, 23521 initiated ART. Median CD4 count at entry into care was 302 (IQR 115–481) cells/μL in 2005, 346 (IQR 182–507) cells/μL in 2012, and 370 (IQR 211–565) cells/μL in 2016. Median CD4 count at ART initiation was 157 (IQR: 51–287) cells/μL in 2005, 200 (IQR 122–511) cells/μL in 2012, and 222 (IQR: 137–580) cells/μL in 2016. Median number of days from entry into care to ART initiation was 70 (IQR: 20–546) in 2005, 29 (IQR: 12–74) in 2012, and 22 (IQR: 5–25) in 2016. Of patients who initiated ART after entering care in 2016, 31% initiated ART on day of presentation and 4% initiated ART ≥60 days later.

Conclusion: Median CD4 counts at entry into care and at ART initiation have been trending towards convergence since 2005 and clinically equivalent since 2012, reflecting the reduction in time from entry into care to ART initiation and adoption of “treat all” in clinical practice in the US. Additionally, the increase in CD4 count at presentation over time indicates progress towards earlier HIV diagnosis and linkage to care, critical for reaching 90-90-90 targets. These trends suggest that CD4 counts at entry into care and at ART initiation
Patient-Reported Reasons for Declining Immediate ART Initiation in Lusaka, Zambia

Jake Pry, Jenala Chipungu, Carolyn Bolton Moore, Jacob Mutale, Helene Smith, Theodora Savory, Michael Hercz
Centre for Infectious Disease Research in Zambia, Lusaka, Zambia

Background: Programs are focusing increased resources to meet the UNAIDS “second 90” treatment target. To help achieve this goal in Zambia, we developed a quality improvement tool to evaluate reasons people living with HIV (PLHIV) do not immediately link to care (LTC) and start ART. We designed the tool to be used in routine care settings to understand reasons for LTC and ART delays, and to improve individualized post-test counseling.

Methods: We created a simple 1-page screening tool with structured items to capture three broad categories for failed LTC and ART delay: social, personal, and structural. We implemented the tool in three facilities, two urban and one rural, in Lusaka District over a three-month period. We administered the tool to all individuals who refused LTC and immediate ART. Individuals were allowed to choose as many reasons as relevant. Failed linkage risk was modeled using mixed effects logistic regression controlling for age, sex and testing point, and allowing random effect for clinic.

Results: A total of 1,292 people with new HIV infection were identified across clinics, of whom 9.6% reported a refusal reason. Each respondent reported a median of three reasons (IQR: 2-3). Of those who refused immediate LTC, 69.6% were female, with median age 30 years (IQR: 23-40 years). Females refusing LTC were younger on average at 28.5 years (IQR: 21-37 years) than their male counterparts at 34.5 years (IQR: 26-44 years). Of the 504 non-mutually exclusive reasons identified, structural, personal, and social reasons for refusal differed significantly across testing points, males and females, and different age bands, new, tailored LTC approaches warrant further study.

Conclusion: The top refusal reason was associated with facility over-crowding, speaking to the importance of differentiated service delivery model scale-up to decompress busy clinics. Given the differences in refusal reasons observed across testing points, males and females, and different age bands, new, tailored LTC approaches warrant further study.

CASCADE TRIAL: 24 MONTH OUTCOMES AFTER SAME-DAY HOME-BASED ART INITIATION

Alain Amstutz1, Isaac Ringera2, Thabo I. Lejone2, Josephine Muhairwe1, Jennifer A. Brown1, Thomas Klimekait1, Tracy R. Glass1, Niklaus D. Labhardt1
1Swiss Tropical and Public Health Institute, Basel, Switzerland, 2SolidarMed, Luzern, Switzerland, 3University of Basel, Basel, Switzerland

Background: The CASCADE trial, conducted in Lesotho, Southern Africa, has shown that offering same-day initiation of antiretroviral therapy (ART) to individuals found HIV positive during home-based testing resulted in significantly higher proportions engaged in care and virally suppressed 12 months after the testing campaign. At completion of the trial all patients not in care were traced and the protocol was amended to allow for a 24 months follow-up of study participants.

Methods: CASCADE was a randomized clinical trial that assigned individuals recruited during a home-based HIV testing campaign to either the offer of same-day ART start (SD) or referral to a nearby clinic for preparatory counseling and ART start after ≥2 pre-ART clinic visits (UC). Consent ART-naive, HIV-infected individuals, ≥18 years, were enrolled. Methods and 12 month results were published previously (Labhardt et al. JAMA. 2018;319(11):1103). At 12 months those not in care were traced by health workers and encouraged to return to care. At 24 months (range 22-28 months), engagement in care, viral suppression (<100 copies/mL) and reasons for disengagement were assessed among all trial participants. Trial registration: NCT02692027

Results: The care cascade and the status of patients at 24 months are displayed in Figure 1. Of 274 individuals randomized (137 SD, 137 UC), 64% (87/137) in the SD and 48% (66/137) in the UC group were active in care 12 months after testing positive (p=0.011), and 50.4% (69/137) vs 34.3% (47/137) had documented viral suppression (p=0.007). At 24 months, 64% (88/137) in the SD versus 59% (81/137) in the UC arm were in care (p=0.38) and 57% (78/137) vs 54% (74/137) had documented viral suppression (p=0.28). Among those active in care at 12 months, 11% (10/87) and 9% (6/66) were no longer in care at 24 months (p=0.63). Among those not in care at 24 months, 31% (15/49) and 38% (21/56) had been found through tracing but refused care. Most cited reasons were disbelieving in diagnosis/ART (N=6), discomfort taking medication (5), rejection of any contact with health system (4) and perceived ill-treatment by health professionals (3).

Conclusion: After tracing of all participants not in care at 12 months, a significant difference was no longer observed between the SD and the UC arm regarding viral suppression and engagement in care at the 24-month follow-up. Both arms remained below the targeted 90% of people living with HIV receiving ART. One third of those not in care refused attending.
ACCESS TO HIV CARE CORRELATES WITH DEPRESSION SEVERITY AND RATES OF VIRAL SUPPRESSION

Ann K. Avery, Mallika Lavakumar, Allison R. Webel, James Alsop, Doug Gunzer, Diana Gurley, Steven Lewis

1MetroHealth Medical Center, Cleveland, OH, USA, 2Case Western Reserve University, Cleveland, OH, USA, 3University of Minnesota, Minneapolis, MN, USA

Background: Depression is among the most common, yet unaddressed, problems identified in people living with HIV (PLWH). Under-diagnosis and under-treatment of depression in PLWH contributes to negative health outcomes. The collaborative care model (CCM) has been shown to improve both depression outcomes and co-morbid medical outcomes in primary care but there is limited data on its use in HIV care settings. The CCM includes routine screening for depression with the PHQ-9, measurement-based care and care management for all patients scoring ≥10. Using an implementation science framework, we rolled out the CCM in our HIV clinic from June 2015 - June 2016.

Methods: All patients with PHQ screening data were included. Patients with any score ≥10 entered the CCM. Data from June 2015 - Dec 2017 were analyzed to identify factors associated with greater severity of depressive symptoms at initial presentation. A multiple linear regression model was used to regress first PHQ-9 score for patients in CCM on a set of demographic, clinical, access-related characteristics to determine correlates of depression at baseline. A generalized estimating equations approach was used to evaluate if subjects in CCM compared to subjects not in CCM had higher HIV viral suppression over the subsequent 12 months after initial presentation.

Results: 1473 patients were screened for depression between 6/29/15 and 12/31/17. 594 reported moderate to severe symptoms at least once (PHQ-9 ≥10). Patients who did not have a viral load documented in the year prior to the initial PHQ-9 score reported more severe depressive symptoms than those who had a viral load collected in the year prior (p=0.004). Additionally, compared to patients with Medicaid, patients who were uninsured had more severe symptoms (p=0.0003), while Medicare recipients reported less severe symptoms (p=0.0393). The GEE approach did not demonstrate differences in achieving viral suppression over time between groups. However, the CCM group were 34% less likely to be virally suppressed at first PHQ-9 compared to patients who never reported depressive symptoms (OR 0.66 CI 0.52, 0.84). Additionally, patients in CCM but did not follow up for re-measurement within 1 year (n=180) were 63% less likely to be virally suppressed at first PHQ-9 compared to patients who never reported depressive symptoms (OR 0.35 CI 0.19, 0.64).

Conclusion: Depressive symptoms were present in 1/3 of patients; interventions to engage PLWH reporting depressive symptoms should be given priority in efforts to improve HIV viral suppression rates.

WITHDRAWN

PROJECT CORECT: PRELIMINARY RESULTS OF DATA TO CARE WITH CT DPH AND HIV CLINICS

Merceditas Villanueva, Janet Miceli, Constance Carroll, Suzanne Speers, Lisa Nichols, Frederick Altice, Heidi Jenkins

Yale University, New Haven, CT, USA, 2Connecticut Department of Public Health, Hartford, CT, USA

Background: A significant portion of PLWH remain incompletely engaged in care resulting in poor individual health outcomes, as well as ongoing HIV transmission. The CDC sponsored Cooperative Re-Engagement Controlled Trial (CoRECT) tests a Data to Care strategy that aims to establish a collaborative
approach between health departments and HIV clinics to identify, re-engage, retain and virally suppress PLWH recently out-of-care.

**Methods:** The CT DPH, Yale University School of Medicine and 23 HIV clinics conducted the study. Using the DPH eHARS surveillance database and individual clinic level data, “recently out of care patients” were further investigated by clinic personnel to assess eligibility for randomization to either clinic standard of care (SOC) vs DPH field workers (DIS) who were trained to locate, assess barriers to care, and facilitate re-linkage to care within 90 days of randomization. Clinic visit status was collected and compared between DIS and SOC. Additional data on linkage status and barriers to care were collected by DIS. We report this data on patients who completed 90 days post randomization.

**Results:** There were 655 patients randomized: DIS (N=333) vs. SOC (N=322), of which 588 were at 90 days post randomization. Demographics showed: Black (39.80%); Hispanic (38.10%); white (20.20%); male (62.41%); age <30 (16.84%); there was no difference between DIS and SOC arms. Comparison of successful attendance at scheduled clinic visits: DIS (42.6%) vs SOC (32.3%) (p<0.001). Clinic outcomes for patients randomized to DIS showed: returned to clinic by DIS (32.83%); unable to locate (22.80%); located but refused to return to clinic (14.89%). Demographic comparison showed that those who were unable to be located by DIS were not statistically different than those successfully returned to clinic. Last viral load recorded was significantly greater for those not returned to care vs those who did return to care (p<0.0001); last CD4 was lower, (p<0.0001). Among those randomized to DIS with successful linkage, the most common identified barriers to care were life issues (92.5%) and mental/physical health issues (38.3%).

**Conclusion:** 1) The DIS intervention was successful in returning recently OOC pts to care 2) Among OOC PLWH linked by DIS, the most common barriers were “life issues” and “mental/physical health issues” 3) Patients whom DIS were unable to locate were more likely to have higher viral loads and lower CD4 counts 4) This intervention can be used to improve the HIV Care Continuum.

**1029 DEVELOPMENT OF AN EMR-BASED ALGORITHM TO IDENTIFY PATIENTS LOST TO HIV CARE**

**Jason Zucker**1, Jacek Slowikowski2, Kenneth Ruperto3, Peter Gordon1

1Columbia University Medical Center, New York, NY, USA, 2New York Presbyterian Hospital, New York, NY, USA

**Background:** Ending the epidemic requires optimizing primary and secondary prevention. After diagnosis, many HIV positive patients drop out of the care cascade but continue to “touch” the hospital in a variety of settings. Identifying individuals out of care in real time allows for care coordination and restarting antiretroviral therapy. We used a novel EMR based algorithm to develop a dashboard that identifies all HIV positive patients who interact with our institution as well as their linkage and viral load status.

**Methods:** We identified all individuals with an International Statistical Classification of Diseases (ICD) code for HIV, positive HIV antibody, HIV RNA viral load, and the date of visit in any of our clinic locations that routinely provide HIV care. We developed an algorithm to highlight patients as a potential new diagnosis, unlinked to care, unsuppressed viral load, and most recent HIV visit in the past 6 months, 9 months, or longer. To evaluate accuracy, we created a reference standard to replicate a clinician’s review of the chart and performed a review on a random 20% (128) of patients identified from 8/1/18 to 9/15/18.

**Results:** The algorithm correctly categorized 95% of HIV positives, 86% of patient’s linkage to care status, and 91% of viral load status. Causes of errors were false positive HIV screening tests, perinatal HIV exposure, and individuals documented as receiving care at an outside hospital. In the validation cohort, 8/18 – 9/15/18, the algorithm identified 639 patients with a diagnosis of HIV, 78% who were linked to care in the past 9 months, and 66% who were virally suppressed. Of the 22% who were not linked to care 47% (66) were not virally suppressed. Over the prior year, 9/15/2017 – 9/15/2018. the algorithm identified 2851 patients with a diagnosis of HIV, 29% of who were categorized as out of care of the past 9 months

**Conclusion:** Population-level HIV care cascade tools can be developed that are accurate and efficient. Our algorithm has a high accuracy for identifying HIV positive individuals and individuals not linked to care. EMR based algorithms have the potential to provide an efficient method for care coordinators, reducing their workload but still allowing them to identify HIV patients requiring services. This algorithm is generalizable and has the potential to be transported to other EMR systems allowing for the development of electronic care cascades and dashboards.

**1030 ARE THEY REALLY LOST? MULTI-CENTER TRACING STUDY IN ART PROGRAMS IN SOUTHERN AFRICA**

**Benedikt Christ**1, Kathrin Zürcher1, Frédérique Chammartin1, Josephine Muhairwe1, Laura Jefferys1, Jannene van Dijk1, Kombatene Skombe1, Monique van Lettow1, Geophnas Chimbotet2, Sam J. Phiri3, Matthias Egger1, Marie Ballif1

1Institute of Social and Preventive Medicine, Bern, Switzerland, 2SolidarMed, Maseru, Lesotho, 3SolidarMed, Pemba, Mozambique, 4SolidarMed, Masvingo, Zimbabwe, 5Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, 6Dignitas International, Zomba, Malawi, 7Newlands Clinic, Harare, Zimbabwe, 8Lighthouse Trust Clinic, Lilongwe, Malawi

**Background:** Low retention on antiretroviral therapy (ART) is a threat to the UNAIDS 90-90-90 targets. We studied outcomes of people living with HIV (PLHIV) on ART but lost to follow-up (LTFU) in Southern Africa.

**Methods:** We traced patients defined as LTFU (>90 days after a missed visit) using a common protocol in 6 ART programs of the International epidemiology Databases to Evaluate AIDS (IeDEA): Malawi (2 sites), Zimbabwe (2 sites), Lesotho and Mozambique. We randomly sampled PLHIV lost at each site, stratifying for age, sex and time on ART. Tracing consisted of text messages (one attempt), phone calls (max. 3 attempts) and/or home visits (max. 3 attempts). We used descriptive statistics and univariate logistic regressions to assess predictors for mortality.

**Results:** We included 1564 patients LTFU: 435 in Lesotho, 381 in Malawi, 408 in Mozambique and 340 in Zimbabwe. Median age at tracing was 35 years (interquartile range [IQR]: 26–46), 57% were female and 81% from rural clinics. Last median CD4 count was 392 cells/µL (IQR: 226–594, available for 741 [47%] PLHIV), median time on ART was 13 months (IQR: 21–47). Checking patients’ files clarified vital status in 272 (17%) cases, without need for tracing. No file was found in 183 (12%) cases. Among 1109 patients traced, 369 (33%) were found after a mean of 1.4 attempts (range 1–5); 11% of patients were traced by phone calls, 71% by home visits and 17% by both. Text messages were only used for <1%.

The remaining 67% were either not found (230; 34%) or their status was obtained from other informants (400; 66%); Fig. 1. Overall, 922 (59%) PLHIV were alive, 207 (13%) had died and in 435 (28%) cases, vital status remained unclear. Among those alive, 225 (24%) had never missed a visit or returned to care at the same clinic, 368 (40%) had transferred to another clinic (218 silently), 233 (25%) stopped taking ART and there are no details available for 97 (11%). Predictors for mortality were age ≤15 odds ratio [OR] 1.9, 95% CI 1.2–3.1) and >50 (OR 3.4, 95% CI 2.2–5.1) compared to 26–50 years, LTFU for >1 year compared to ≤1 year (OR 2.7, 95% CI 1.3–5.7), WHO stages 3&4 compared to stages 1&2 (OR 3.4, 95% CI 2.2–5.1), and last CD4 count ≤200 compared to >200 cells/µL (OR 2.1, 95% CI 1.2–3.8).

**Conclusion:** Most PLHIV defined as LTFU were found alive and in care. Tracing remains necessary in most instances but needs improvement to locate all PLHIV lost. Better ways to inform health systems and novel approaches to follow up PLHIV are needed in the treat-all era.
HEALTH DEPARTMENT RANDOMIZED TRIAL TO RE-ENGAGE OUT-OF-CARE HIV INFECTED PERSONS

Robyn N. Fanfair1, George Khalil2, Nasima Camp3, Kathleen Brady4, Alfred DeMaria5, Mercedes Villanueva6, Lisa Randall7, Heidi Jenkins8, Crystal Lucas9, Frederick Altice10, Anthony Gerard11, Nina Kishore12, Tiffany Williams13, Taraz Samandari14, Paul J. Weidle15

1CDC, Atlanta, GA, USA, 2Philadelphia Department of Public Health, Philadelphia, PA, USA, 3Massachusetts Department of Public Health, Boston, MA, USA, 4Yale University, New Haven, CT, USA, 5Connecticut Department of Public Health, Hartford, CT, USA

Background: Over a quarter of persons living with HIV in the United States do not receive care, and most transmissions of HIV come from persons known to be infected but not in care. We implemented a data-to-care model using health departments and local clinics to identify out-of-care (OOC) HIV-infected individuals with the objective of increasing the number of such persons re-engaged, retained in medical care, and achieving viral load suppression.

Methods: Criteria for inclusion were age ≥18, and in care at a trial clinic during a 12-month eligibility period followed by no evidence of care in ≥6 months (i.e., no visit or labs). OOC was determined by HIV surveillance and clinic data from three jurisdictions: Connecticut (CT), Massachusetts (MA) and Philadelphia (PHI). All patients deemed OOC were randomized to receive standard engagement in care (SOC) services from the trial clinic or an active public health field services intervention. Re-engagement in care was defined as linking to a trial clinic within 90 days of randomization, as determined by HIV surveillance data. Each jurisdiction was analyzed separately as interventions and services varied by health department. Chi-square tests were performed and a p-value <0.05 was considered statistically significant.

Results: Between 8/16/2016 and 7/31/2018, a total of 533 (CT), 591 (MA), and 609 (PHI) OOC HIV-infected persons were enrolled and had ≥90 days since documentation. Among all sites 64%-76% were born male, 38%-66% were non-Hispanic black, 55%-69% were aged ≥40 years, and 44%-62% were diagnosed with HIV ≥10 years. In CT, 222 (41.7%) re-engaged in care ≤90 days [118 (46.3%) in intervention vs 104 (37.4%) in SOC, P=0.038]; in MA, 285 (48.2%) re-engaged in care ≤90 days [153 (51.2%) in intervention vs 132 (44.9%) in SOC, P=0.108]; and in PHI 306 (50.2%) re-engaged in care ≤90 days [181 (58.6%) in intervention vs 125 (41.7%) in SOC, P<0.0001]. The median times to re-engagement in care for intervention vs SOC arms were: 37 and 48 days (p=0.011) in CT, 38 and 42 days (0.329) in MA and 29 and 45 days (p<0.001) in PHI, respectively.

Conclusion: This randomized controlled trial showed that a collaborative data-to-care model and field services intervention increased the proportion of persons re-engaged in care in two jurisdictions and decreased the time to re-engagement in all three. Health department interventions can improve re-engagement in care among HIV-infected persons who are out of care.

Table 1: Demographics and Proportion of out-of-care HIV-infected persons who re-engaged with HIV medical care within 90 days by randomization group—August 2016–July 2018

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>INTERVENTION GROUP</th>
<th>CONTROL GROUP</th>
<th>TOTAL</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEMOGRAPHICS</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (n=297)</td>
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</tr>
<tr>
<td>Male</td>
<td>142 (48.2%)</td>
<td>155 (52.6%)</td>
<td>297 (53.8%)</td>
<td>0.3230</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>96 (37.0%)</td>
<td>73 (30.1%)</td>
<td>169 (32.4%)</td>
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<tr>
<td>Age ≥25 years</td>
<td>171 (68.4%)</td>
<td>151 (60.5%)</td>
<td>322 (60.5%)</td>
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</tr>
<tr>
<td>HIV diagnosis ≥10 years</td>
<td>138 (46.2%)</td>
<td>152 (59.2%)</td>
<td>290 (55.8%)</td>
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<tr>
<td>Massachusetts (n=401)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>203 (50.7%)</td>
<td>203 (50.7%)</td>
<td>406 (50.7%)</td>
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</tr>
<tr>
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<td>121 (44.0%)</td>
<td>241 (44.7%)</td>
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<tr>
<td>Age ≥25 years</td>
<td>153 (64.8%)</td>
<td>153 (64.8%)</td>
<td>306 (64.8%)</td>
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<tr>
<td>HIV diagnosis ≥10 years</td>
<td>125 (52.3%)</td>
<td>125 (52.3%)</td>
<td>250 (50.5%)</td>
<td>0.9310</td>
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<tr>
<td>Philadelphia (n=699)</td>
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</tr>
<tr>
<td>Male</td>
<td>255 (36.6%)</td>
<td>255 (36.6%)</td>
<td>510 (34.5%)</td>
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<tr>
<td>Non-Hispanic black</td>
<td>204 (28.5%)</td>
<td>204 (28.5%)</td>
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<tr>
<td>Age ≥25 years</td>
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<tr>
<td>HIV diagnosis ≥10 years</td>
<td>136 (34.4%)</td>
<td>136 (34.4%)</td>
<td>272 (34.4%)</td>
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<tr>
<td>COUNTY</td>
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<td></td>
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<tr>
<td>Link to care &lt;90 days</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>118 (48.3%)</td>
<td>144 (57.1%)</td>
<td>262 (54.5%)</td>
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</tr>
<tr>
<td>No</td>
<td>173 (51.7%)</td>
<td>114 (42.9%)</td>
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<td>Massachusetts</td>
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<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>113 (51.5%)</td>
<td>133 (44.8%)</td>
<td>246 (45.4%)</td>
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<tr>
<td>No</td>
<td>146 (48.5%)</td>
<td>162 (55.2%)</td>
<td>308 (54.6%)</td>
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<td>Philadelphia</td>
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</tr>
<tr>
<td>Yes</td>
<td>101 (38.8%)</td>
<td>121 (43.7%)</td>
<td>222 (43.7%)</td>
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<tr>
<td>No</td>
<td>185 (61.2%)</td>
<td>152 (56.3%)</td>
<td>337 (56.3%)</td>
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</tr>
</tbody>
</table>

1Chi-Square tests were conducted to assess differences of overall demographic variable by intervention group.
1.00-1.89, p=0.05). Getting care at a hospital was associated with a reduced hazard of return (aHR: 0.55, 95%CI: 0.35-0.86, p=0.01) (Table 1).

**Conclusion:** Despite in-person peer educator tracing and encouragement to return, fewer than half of disengaged patients did so. Interventions which improve facility access and target young people may reduce treatment interruptions. New approaches to facilitate re-engagement and improve HIV program success should be explored.

### Table 1. Predictors of re-engagement in HIV care or treatment among disengaged, traced patients living with HIV in Zambia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.07</td>
<td>0.79</td>
<td>1.44</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-30 years</td>
<td>1.00</td>
<td></td>
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<tr>
<td>31-40 years</td>
<td>0.98</td>
<td>0.69</td>
<td>1.38</td>
</tr>
<tr>
<td>41-50 years</td>
<td>1.33</td>
<td>0.86</td>
<td>2.04</td>
</tr>
<tr>
<td>≥50 years</td>
<td>1.89</td>
<td>1.04</td>
<td>3.46</td>
</tr>
<tr>
<td>Time out of care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from last visit to tracer interruption (per month)</td>
<td>0.99</td>
<td>0.96</td>
<td>1.01</td>
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<td>Something psychosocial needs to change for return</td>
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**1034 PREVALENCE AND CORRELATES OF NONENROLLMENT IN HIV CARE, CHÓKWÈ DISTRICT, MOZAMBIQUE**

Kristen Heitzinger1, Anne F. McIntyre1, Isabelle Casavant1, Noela Chiccue2, Victor Chivurre3, Aleny Couto4, Keydra Oladapo4, Guoqing Zhang5, Kouadio Leonard Ya2, Andre Tehe2, Mireille Kalou1, Karidia Diallo1, Judith Hedje1, Heather Alexander1, Clement Zeh1, G. Laisa Ouedraogo1, Christiane Adjé-Toure1

**Methods:** Data were sourced from a cross-sectional survey conducted annually in Chókwè District during 2014–2017, with participants aged 15–59 identified via a household demographic surveillance system (HDSS). We analyzed data from participants who reported ever having received a positive HIV test. If surveyed in multiple years, data from first survey were analyzed. The 2013 HDSS census estimates were used to weight by age, sex, and urban residence distributions. We calculated the prevalence of and reasons for non-enrollment. Logistic regression was used to calculate adjusted odds ratios (aOR) and 95% confidence intervals (CI) of the association between sociodemographic and behavioral variables and non-enrollment in HIV care, adjusting for intra-household sampling.

**Results:** Of 2,654 participants who reported ever having received a positive HIV test, 127 (5.3%) had not enrolled in HIV care. There was no difference in non-enrollment after district-wide implementation of Test and Start. Most frequently cited reasons for non-enrollment were did not need care due to good health status (33/126; 27.1%) and did not believe they had HIV (7/126; 7.6%). Participants who first tested positive since 2013 and those who received their first positive test <2 years had increased odds of non-enrollment (p=0.02 and p=0.002, respectively). Compared to testing at a district healthcare facility, testing positive at home had increased odds of non-enrollment (aOR: 3.92, 95% CI: 2.39, 6.45). HIV status nondisclosure was associated with non-enrollment (aOR: 6.15, 95% CI: 3.79, 10.00). Among participants who first tested positive ≤1 year, those who did not meet with someone to help them enroll in care had increased odds of non-enrollment (aOR: 4.60, 95% CI: 1.94, 10.93).

**Conclusion:** Obstacles to enrollment reflect the importance of accurate health messaging, strong social support, and prompt clinical linkage to care, regardless where HIV testing occurs. Enhanced patient advocacy and case management,
1035 HIV TREATMENT CASCADE AMONG MEN WHO HAVE SEX WITH MEN IN KIGALI, RWANDA

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1Johns Hopkins Bloom School of Public Health, Baltimore, MD, USA, 2Emory University, Atlanta, GA, USA, 3Rwanda Biomedical Centre, Kigali, Rwanda

Background: Men who have sex with men (MSM) have high HIV acquisition and transmission risk globally and are defined as a key population in the Rwanda national strategic plan. However, there are no published HIV epidemiological data among MSM in Rwanda. In this study, we characterize MSM engagement in HIV treatment cascade in Kigali, Rwanda.

Methods: MSM > 18 years were recruited in a cross-sectional behavioral and biological survey using respondent driven sampling (RDS) between March – July 2018 in Kigali, Rwanda. Data on socio-demographic characteristics, sexual behavior and engagement in HIV services were collected using an interviewer-administered structured questionnaire. HIV infection and viral load were biologically assessed. We used a cascade framework to characterize engagement in HIV care continuum.

Results: Overall, 736 eligible MSM were recruited in the study. The median age was 27 [range:18-40], the HIV prevalence was 10.1% (74/736) (RDS adjusted prevalence: 9.2%; 95% CI: (6.4-12.1)]. Of the participants found to be living with HIV, only 61% (45/74) reported that they knew their HIV status before enrollment. Higher age (> 35 years) was significantly associated with both HIV positive status (p < 0.01) and knowing HIV diagnosis prior to enrollment (p < 0.05). Of MSM who knew their HIV positive status, 98% (44/45) reported to be on ART and 75% (33/44) were virally suppressed. Overall, we estimated that among the total population of MSM living with HIV in Kigali, 61% know their status, 59% are on ART and 59 % are virally suppressed. This represents gaps of 29%, 22% and 14% respectively to reach the 90-90-90 target in the MSM population in Kigali.

Conclusion: Taken together, these data demonstrate high HIV prevalence with suboptimal engagement in HIV treatment services among particularly young MSM in Rwanda. A quarter of those reporting ART were viiremic suggesting the need for improved retention and adherence programing in addition to screening for HIV drug resistance. Given the challenges in addressing the needs of young MSM, interventions leveraging emerging technologies and social media in addressing engagement and retention may be particularly effective in Rwanda.

1036 LONGITUDINAL HIV CARE TRAJECTORIES IN THE CNICS COHORT: A RETROSPECTIVE COHORT STUDY

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Background: Long-term HIV care engagement is required for optimal clinical and prevention outcomes, but longitudinal patterns of HIV care attendance are poorly understood. Identification of distinct longitudinal trajectories of HIV care, along with predictors thereof, could inform the design of tailored interventions for improving HIV care engagement. We used visit data from the eight-site CFAR Network of Integrated Clinical Systems (CNICS) to examine patterns and predictors of HIV care attendance over a ten-year period.

Methods: We conducted a retrospective cohort study of all adults newly entering CNICS between January 1, 2005 and December 31, 2015 (N=18,160), following them longitudinally until death, ten years, or March 22, 2018. Our outcome was HIV primary care visit attendance (yes/no) in each six-month interval after CNICS entry. We used group-based trajectory modeling to: 1) identify a set of longitudinal HIV care patterns followed from the time of CNICS entry, and 2) examine associations between each pattern and race/ethnicity, age at entry, and transmission risk group. We tested models with 2-7 trajectory groups and selected the final model based on the Bayesian Information Criterion.

Results: We identified five distinct HIV care trajectories (Figure): ~32% of patients had consistently high care attendance over time (>75% probability of attendance in each interval); ~23% exhibited a rapid decline within two years to a sustained, low probability (<5%) of attendance; ~16% showed a very slow decline in attendance; ~17% had an intermediate rate of decline; and ~12% showed a slowly fluctuating pattern that started with a decrease but shifted to an increase starting ~three years after entry. Older age at entry was protective against all sub-optimal trajectories (with the “consistently high” pattern as referent); odds ratios per five-year age increase ranged from 0.79 (95% confidence interval: 0.77-0.81) for the “slow fluctuation” group to 0.86 (0.84-0.88) for the “intermediate decline” group. Race/ethnicity and transmission risk group had mixed associations with care patterns.

Conclusion: Most new CNICS entrants exhibited sub-optimal HIV care trajectories, but there was wide variation in the longitudinal pathways followed. By identifying heterogeneous care engagement patterns and predictors thereof, this analytical approach allows improved understanding of HIV care engagement over time for designing tailored interventions and refined models of the HIV care continuum.

1037 CALL FOR LIFE UGANDA TM: AN RCT USING INTERACTIVE VOICE RESPONSE FOR PLHIV ON ART

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Infectious Disease Institute, Kampala, Uganda

Background: The WHO recommends use of mobile phone health technologies (mHealth) to support adherence in HIV. Studies on text messages show promise but with limited rigorous evaluations. The Call for Life UgandaTM (CfLU) study is a randomized controlled trial (RCT) using an interactive voice response (IVR) calls system designed to support PLHIV on ART. The primary study objective was to determine the effect of CfLU on quality of life (QOL) of people living with HIV (PLHIV) in Uganda.

Methods: MOTECH software-based Connect for LifeTM (Janssen, Johnson & Johnson) was adapted for Ugandan setting, with the Infectious Diseases Institute. The participants were randomized 1:1 to receive either CfLU or
PWID to meet care continuum benchmarks, including awareness of status, HIV-positive MSM were nominally (although not significantly) more likely than PWID to report care received in prior 6 months, ART use, and suppressed viral load (HIV RNA <150 c/ml). Although care continuum outcomes increased over the next 4 years in both groups, the increases were markedly larger for MSM than PWID (Figure). For example, the increase in those reporting HIV care in the prior 6 months was 32 percentage points (95% CI: 16, 48) higher in MSM than PWID sites, and the increase in viral suppression was 15 percentage points (95% CI: 0, 31) higher in MSM than PWID sites.

Conclusion: In serial large population surveys across 22 sites in India, we found that HIV-positive MSM had substantially larger improvements in care continuum outcomes 4 years later compared with HIV-positive PWID. This highlights the value of high-quality HIV treatment surveillance data to target resources for key populations effectively.
1040 ENGAGEMENT IN CARE OF HIGH- RISK PATIENTS AT AN URBAN HIV PRIMARY CARE CENTER

Raaka Kumbhakar1, Mila Gonzalez Davila1, Randi Scott1, Noga Shalev1, Susan Olender1

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Background: Socioeconomic and behavioral factors are associated with poor engagement in HIV care (EIC) and lower rates of viral suppression (VLS) among persons with HIV. Our agency participated in a multidisciplinary care coordination intervention designed to address these disparities as part of New York City’s Ryan White Part A HIV Care Coordination Program (CCP). In this study, we describe our experience with CCP in our hospital-based HIV center, which provides comprehensive HIV primary care with co-located mental health services to a predominantly poor, minority, and immigrant population.

Methods: Clients were eligible for CCP enrollment if they were newly diagnosed with HIV or met criteria for poor EIC. All were paired with a dedicated field navigator and received patient-centered care coordination, health promotion, and outreach services. This study includes all CCP participants enrolled between January 2013 and December 2016. Univariate and multivariate regression analyses were used to evaluate the association between patient characteristics and CCP activities on VLS and EIC.

Results: 241 CCP clients were enrolled from 2013-2016. Factors significantly associated with VLS at 12 months include: EIC (p < 0.05), VLS at enrollment (p = 0), respiratory disease (p < 0.01), cardiovascular disease (p < 0.06), and mental illness (p < 0.09). In the multivariate model, EIC (OR 2.37, CI 0.29-8.83, p<0.01) and VLS at enrollment (OR 2.41, CI 0.13-1.04) remained significant. Univariate analyses showed that new diagnosis (p < 0.02), engagement in psychiatric care (p = 0), VLS at 12 months (p < 0.05), malignancy (p < 0.08), serious mental illness (bipolar disorder and/or schizophrenia; p = 0), substance use (p < 0.08), and homelessness (p = 0) were associated with EIC. In a multivariate model, new diagnosis (OR 4.01, CI 1.26-12.71, p<0.01) and mental illness (OR 2.59, CI 1.42-4.7, p<0.01) remained significant.

Conclusion: Despite intensive interventions, rates of VLS at 12 months and EIC among CCP clients remained below 90%. Disproportionately high rates of mental illness and substance abuse are likely playing in a role in this finding. However, mental illness was significantly positively associated with EIC which suggests that co-location of mental health services has had significant impact on key HIV outcomes. This suggests that additional embedded behavioral health resources are needed to address the complex psychosocial needs of people living with HIV.

1041 PRAISE MESSAGES TO INCREASE ART ADHERENCE AND RETENTION IN CARE FOR FSW IN ETHIOPIA

Nicholas Wilson1, Kristen Little1, Aderaw Anteneh1, Woldemariam Girma1, Kelly Bidwell4

1Reed College, Portland, OR, USA, 2Population Services International, Washington, DC, USA, 3PSI/Ethiopia, Addis Ababa, Ethiopia, 4Office of Evaluation Sciences, Washington, DC, USA

Background: Though female sex workers (FSW) in Ethiopia are disproportionally impacted by HIV, they face numerous barriers to accessing and remaining in HIV care services. PSI/Ethiopia provides HIV care services through a network of FSW-friendly drop-in centers (DICs), and tested a “praise message” intervention to improve ART adherence and retention in care among FSW living with HIV.

Methods: FSW newly diagnosed with HIV were randomized to standard of care (SoC) or a “praise message” arm (PM). The PM arm received “praise messages” (short, positive calls from the DIC nurse thanking them for investing in their health) 24 hours and 2 weeks after each completed ART appointment. Praise messages were provided for those in the PM arm through 6 months on ART.

Results: Of 866 participants, 436 (50.3%) were randomized to the PM arm, and 430 (49.7%) were randomized to SoC. Participants were recruited from 25 DICs, with a median age range of 25-29 years old. Age did not vary significantly between the study arms (mean age SoC: 29.43; PM: 29.59, p-value=0.793). Of the 735 respondents with completed follow-up by September 3, 2018, overall one-month retention in care was 76.1% and ART adherence was 74.5%. Preliminary data analysis found that 1 month retention did not differ significantly by study arm (SoC: 76.4%; PM: 77.4%, p>0.05).

Conclusion: The intervention did not improve retention in care or ART adherence among FSW living with HIV in our study, providing only a statistically insignificant 1.0 percentage point increase in retention and 0.8 percentage point increase in ART adherence at 1 month. While the intervention did not have an impact on the primary outcomes of interest, this study demonstrates the feasibility of conducting rigorous randomized evaluations of important health outcomes in the context of routine service delivery. With the continued scale-up of electronic, client-based record management systems, routine data should increasingly be leveraged to facilitate low-cost research under operational conditions.

Table 1: Multivariate models of Demographic and Clinical Characteristics of all CCP patients with respect to viral load suppression at 12 months (1a) and in care (1b)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engagement in Care1</td>
<td>2.57 (1.29 - 0.83)</td>
<td>0.02</td>
</tr>
<tr>
<td>VLS at enrollment2</td>
<td>2.43 (1.05-5.64)</td>
<td>0.04</td>
</tr>
<tr>
<td>Respiratory disease3</td>
<td>0.58 (0.32 -1.04)</td>
<td>0.06</td>
</tr>
<tr>
<td>Serious Mental illness4</td>
<td>1.42 (0.73 - 2.83)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

1 Engagement in care (EIC) is defined as two medical primary care visits, one in the first six months prior to enrollment and one in the second six months post-enrollment, with these visits being 90 days apart.
2 Viral suppression (VLS) at enrollment was defined as the most recent VL at any time prior to enrollment being <500 c/mL.
3 Respiratory disease defined as asthma and/or COPD.
4 Serious mental illness defined as bipolar disorder and/or schizophrenia; all mental illnesses included those and depression.

Results: Of 2,517 adult patients initiated on ART during the study period, 1,622 (64.5%) were female, 1,203 (48%) from dispensaries/health centers (HC), 1,082 (43%) from primary clinics (PC), and 192 (8%) from specialized clinics (SC).

1042 REPEAT NONADHERENCE TO CLINIC APPOINTMENTS AMONG HIV-INFECTED ADULTS ON ART IN KENYA

Jacques Muthus, Tai Ho Chen, Kenneth Masamaro, Peter W. Young, Emily C. Zielinski-Gutierrez

US CDC Nairobi, Nairobi, Kenya

Background: Since the early 2000s, Kenya has scaled-up antiretroviral therapy (ART) for HIV-infected persons. Patient adherence to medication is key to avoid drug resistance, treatment failure, and death among HIV-infected patients. Occurrences of non-adherence to clinic appointments could be an objective proxy for non-adherence to treatment. We investigated factors influencing repeat non-adherence among HIV-infected adults newly initiated on ART.

Methods: We conducted a retrospective, national survey of adult patients, aged 15 years and above, who initiated ART from October 2003-September 2013 in Kenya. Using clinic appointments data, patients were considered non-adherent if they missed a scheduled appointment by >90 days. We used Chi-square statistics to compare patient characteristics by non-adherence status.

Results: Of 2,517 adult patients initiated on ART during the study period, 1,622 (65%) were female, 1,203 (48%) from dispensaries/health centers (HC), 1,082 (43%) from primary clinics (PC), and 192 (8%) from specialized clinics (SC).
(44%) initiated D4T-based regimens. Median age at ART initiation was 35.1 years, (interquartile range [IQR]; 28.8–42.8), and median CD4 count at initiation was 174 cells/μL, (IQR; 78–258). Thirty-three percent of patients (839) were non-adherent at least once. Non-adherent patients were more likely to be from county referral (38%) or national hospitals (30.7%) versus dispensary/HC (27%, p<.001), to have been initiated on TDF (32%) or D4T-based regimens (36%) compared to AZT-based regimen (28%, p=0.008). Factors associated with repeated non-adherence were being; males (Odds Ratio [OR] 1.4; 95% confidence interval [CI] 1.2–1.6, p<0.004), from national facilities, OR 3.7; 95% CI 2.7–4.9, p<.001, from county referral facilities, OR 1.9; 95% CI 1.6–2.1, p<.001, and initiated on D4T-based regimen, OR 1.3; 95% CI 1.1–1.5, p<.001. Once categorized non-adherent, patients were more likely to have repeated instances of non-adherence, (OR 2.7, 95% CI 2.4–3.1, p<.001).

Conclusion: While patient retention is important to ensure adherence to treatment, substantially high rates of repeat non-adherence to clinic appointments continue to be observed. National and county referral hospitals had non-adherence rates, possibly suggesting high patient load affecting the patient-caregiver relationship and reduced quality patient management. Males may need more targeted intervention to improve adherence.

<table>
<thead>
<tr>
<th>Table 1: Factors associated with repeated non-adherence to clinic appointments among HIV infected adults patients on ART, Eastern Cape</th>
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<tbody>
<tr>
<td><strong>Characteristic</strong></td>
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<td><strong>Frequency</strong></td>
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<tr>
<td>D4T-based</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

P<0.05 excluded from multivariate analysis because of missing data.
after alcohol screening (2 or more HIV care visits 60+ days apart); and HIV RNA control (<75 copies/mL) between 3 months prior and 12 months post alcohol screening. Unadjusted and adjusted odds ratios (OR) from logistic regression models (see Table for covariates in adjusted models).

**Results:** The overall sample had mean age 47.1 years and was 91.2% male; 53.3% white, 18.0% Latino, and 15.3% black; and 70.5% men who have sex with men. Sample size varied due to availability of lab data and because linkage analyses were restricted to those new to KPNC care; linkage to care (n=1,549), retention in care (n=8,397), HIV RNA control (n=8,738). In adjusted analyses, current smoking was associated with worse HIV RNA control (OR=0.69 [0.54-0.88], p<0.001), while previous smoking was not associated with HIV RNA control (OR=0.71 [0.58-0.86], p=0.001). Current smoking was associated with worse retention (OR=0.82 [0.70-0.97], p=0.010), while previous smoking was associated with better retention (OR=0.79 [0.69-0.91], p=0.001). There was little evidence that unhealthy drinking at these thresholds was associated with linkage to care, retention in care or HIV RNA control.

**Conclusion:** Both unhealthy drinking and smoking were associated with worse retention in care and HIV RNA control among PWH, but only the effect of smoking on HIV RNA control remained in adjusted analyses. Future analyses will examine effects of higher levels of unhealthy drinking and changes in drinking, as well as unhealthy drinking in combination with smoking. Clinicians should make a particular effort to help PWH quit smoking.

### Table: HIV Outcomes at 24 Months Among Stably Retained Patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>HIV RNA control</td>
<td>0.70 (0.63-0.77)</td>
<td>0.70 (0.63-0.77)</td>
</tr>
<tr>
<td>Retention in care</td>
<td>0.84 (0.71-0.99)</td>
<td>0.84 (0.71-0.99)</td>
</tr>
<tr>
<td>Linkage to care</td>
<td>0.84 (0.71-0.99)</td>
<td>0.84 (0.71-0.99)</td>
</tr>
</tbody>
</table>

*1 Data values (OR) and 95% confidence intervals (CI) from logistic regression models adjusted for smoking, unhealthy drinking, HIV risk, gender, age, depression, and modified Charlson score excluding AIDS.

*2 Linkages defined as 12 visits within 60 days among those with a new HIV diagnosis.

*3 Retention in care defined as 12 visits 60+ days apart among all persons with HIV

*4 HIV RNA CONTROL defined as ≥75 copies/mL among all values

### 1046 MACHINE LEARNING APPLIED TO ELECTRONIC ADHERENCE DATA TO INFORM VIRAL LOAD MONITORING

**Alejandro E. Benitez,1 Maya L. Petersen,2 Nicholas Musinguzi,3 David R. Bangsberg,4 Yap Boum5, Bosco M. Bwana6, Conrad Muzoora2, Peter W. Hunt,7 Jeffrey N. Martin8, Jessica E. Haberer4**

1University of California Berkeley, Berkeley, CA, USA, 2Mbarara University of Science and Technology, Mbarara, Uganda, 3Massachusetts General Hospital, Boston, MA, USA, 4Epicentre, Mbarara, Uganda, 5University of California San Francisco, San Francisco, CA, USA

**Background:** Approaches for tailoring ART monitoring are needed to optimize the impact and cost-effectiveness of differentiated care delivery systems. Real-time electronic adherence monitoring (EAM) could potentially inform ongoing risk assessment for virologic failure, and thus be used to modify viral load testing schedules. We evaluated the potential of EAM data to contribute to an individually differentiated viral load testing strategy by applying machine-learning approaches to real-time EAM data from Uganda.

**Methods:** We evaluated an observational cohort of persons living with HIV who were treated with ART and monitored with EAM (2005-2015). Super Learner, an ensemble machine-learning method, was used to build a risk score for virologic failure (≥1000 copies/mL) based on clinical (CD4 count, pre-ART viral load, ART regimen) and demographic data, together with EAM-based adherence. Using sample-splitting (cross-validation), we evaluated the performance of this risk score to determine: 1) whether EAM improved prediction of failure beyond clinical and demographic data; 2) potential for real-time EAM data to selective defer viral load tests while minimizing delays in failure detection; and, 3) performance compared to WHO-recommended testing schedules.

**Results:** 485 individuals (242 of whom were initiating ART) contributed 2834 outcome viral loads over 930 person-years. Median CD4 at ART initiation was 200 cells/mm3 (IQR 10, 256), 33% (7,553/22,730), and 27% (4571/17,042) had a viral load test at each recommended time-point respectively. VL results were documented at all recommended time-points for 11.5% (2613/22,730) and 4.9% (838/17,042) of patients on ART for 12 and 24 months respectively. We documented 12% (2,456/20,405) individuals with at least one VL≥1000 copies/mL. Of these, 738 (30%) had a repeat VL within 6 months, and 425 (17%) achieved successful management of virologic failure with either re-suppression or appropriate change to second-line therapy (Figure). For the 150 individuals who switched to second-line, the median time to regimen change was 345 days (IQR 135-671) after their first elevated viral load measurement.

**Conclusion:** We found suboptimal VL monitoring, and delayed or absent responses to VF in public-sector ART clinics in rural South Africa. Such delays are likely to increase the likelihood of patient morbidity, and transmission of drug resistant HIV. We did not investigate how much of our finding could be explained by failure to capture VL results in Tier.Net. Future studies should investigate causes of suboptimal VL monitoring and consider what interventions are needed to improve attention to VF in the region.
would have reduced the number of viral load tests by 30%, while still detecting 87% of all virologic failures without additional delay. By comparison, the WHO-recommended testing schedule would have reduced the number of viral load tests by 69%, but resulted in delayed detection of virologic failure a mean of 74 days (SD = 41 days) for >80% of individuals with failure.

**Conclusion:** Our machine learning approach demonstrates potential for combining EAM data with other clinical measures to develop a selective testing rule that may reduce costs incurred by both researchers and patients, while still identifying those at highest risk for virologic failure.

### 1047 PREDICTORS OF ART INITIATION AND VIRAL SUPPRESSION IN A LARGE COHORT IN UKRAINE

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**Background:** Rapid initiation of ART, treatment adherence support, proper management of virologic failure are important strategies for reaching the ambitious 90-90-90 goals in Ukraine and globally. Key national stakeholders and international donors have set ambitious fast track goals to increase the number of patients from 88,270 on 01/01/2018 to 140,000 by the end of 2018. This study was conducted to obtain reliable data on key treatment quality indicators, contributing factors and trends to inform program planning.

**Methods:** Data from medical charts of all patients who received care at HIV facilities in 2010-2016 in 18 out of 27 regions of Ukraine were entered into an electronic medical record system. After verification of data quality, depersonalized datasets linked by unique patient code were extracted at each facility and merged for analysis. This analysis focused on the effect of clinical variables (HIV mode of transmission, clinical stage, CD4, VL, TB, HCV, injecting drug use [IDU]) on time from diagnosis to ART initiation and to viral suppression (<200c/ml). The entire dataset, excluding children younger than 15 at diagnosis, was analyzed using Cox proportional hazard models.

**Results:** The cohort included 37,690 patients with HIV infection, approximately 30% of all patients receiving care in Ukraine in 2016. Average age at diagnosis 46.4 years were females. Median time from diagnosis to ART was 26 months (95%CI: 25.0-26.9) and 14 months (95%CI: 13.7-14.3) from ART to viral suppression. Multiple significant predictors were identified for both outcomes (see Table). Notably, the time to ART initiation was increasing with male gender (aHR=1.1), negative TB status (aHR=0.9), being at early clinical HIV stage (aHR=.95), IDU mode of transmission (aHR=.77). The chance of getting ART was increasing with lower CD4 (aHR=4.1 for CD4<200), reporting no recent IDU (aHR=1.11), having positive TB test (aHR=1.18), homosexual mode of transmission (aHR=1.18). Viral suppression was associated with younger age (aHR=.98), earlier clinical stage (aHR=0.88), having negative TB test (aHR=.86), IDU mode of transmission (aHR=.93). Overall, coverage of key clinical assessments was not universal, and completion was associated with both outcomes.

**Conclusion:** Quality of HIV care in Ukraine, characterized by coverage of key clinical tests, time to ART initiation and viral suppression indicators remains suboptimal. Patients with advanced disease had priority for ART, reflecting the delayed adoption of test-and-start strategy.

### 1048 SOCIAL NETWORKS AND TIE STRENGTH PREDICT OUTCOMES OF HIV- YOUTH IN SEARCH TRIAL

**Background:** HIV+ youth in sub-Saharan Africa are at high risk of virologic failure on ART, peer support within their social networks may improve clinical outcomes. We used comprehensive social network and HIV testing data from the SEARCH test-and-treat trial (NCT01864603) to evaluate whether HIV+ youth with viral suppression had stronger social networks at baseline, and whether the association was greater for those stronger ties network contacts named in >1 domain. We used logistic regression with robust standard errors to adjust for sex, age, study arm, diagnosis, and region.

**Methods:** Among 1,120 HIV+ youth who were ART-naïve at baseline, 857 remained alive and resident in the community 3 years after follow-up. At years 3, 68% (579/857) had engaged in ART care and among 521 with viral loads, 400 (77%) were virally suppressed. Youth named an average of 2.7 contacts (SD 2.7). 275 (32%) named ≥1 HIV+ contact and 81 (9%) had ≥1 virally suppressed contact. 340 (42%) named ≥1 strong tie; 117 (15%) had HIV+ strong ties and 31 (4%) had ≥1 strong tie. 340 (42%) named 2.7 contacts (SD 2.7). Youth with HIV+ strong ties were more likely to have ART initiation (aOR 2.07; 1.27-3.37) and ≥1 virally suppressed strong tie was associated with viral suppression (aOR 2.53; 1.18-5.42).

**Conclusion:** HIV+ peers, particularly those with viral suppression, in the local social networks of ART-naïve HIV+ youth in rural East Africa may support engagement in care and viral suppression. Interventions that increase social connections to HIV-infected youth in care may improve clinical outcomes.

### 1049 ASSOCIATION BETWEEN HIV CLINIC CASELOADS AND VIRAL LOAD SUPPRESSION IN NEW YORK CITY

**Background:** A goal of the New York State Ending the Epidemic (Ete) Initiative is to achieve viral load suppression (VLS <200 copies/μL) in 85% of all HIV-diagnosed persons by 2020. To accomplish this, factors associated with clinics already achieving VLS in ≥85% of their patients must be identified. We hypothesized that, compared to clinics with lower HIV case loads, those with larger HIV case loads are more likely to achieve ≥85% VLS.

**Methods:** Using purposive sampling, the New York City Department of Health and Mental Hygiene administered a survey assessing clinic capacity and practice to 154 HIV clinics in New York City: 110 (75%) responded. Clinics were classified as either ≥85% VLS (n=36) or <85% VLS (n=74). HIV case load was defined as the total number of unique HIV patients receiving care at a clinic in 2016 and was categorized into quartiles. We used multiple logistic regression to examine the association between HIV case load and clinics achieving ≥85% VLS, adjusting for age, sex, race, and ethnicity of clinic patient populations. Thereafter, chi-square/Fisher’s exact/ Mann–Whitney U tests identified clinic practice characteristics unique to case load quartiles associated with ≥85% VLS.
**1050 VIRAL SUPPRESSION AMONG PEOPLE INITIATING HIV CARE: OUTCOMES FROM THE IENGAGE TRIAL**

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**Background:** Optimizing engagement in HIV care represents the greatest opportunity to maximize the individual and population health benefits of sustained viral suppression (VS; <200 c/ml). Among people living with HIV (PLWH) initiating outpatient HIV care, early missed clinic visits and suboptimal retention in care (RIC) result in failure to achieve and sustain VS, impacting personal health outcomes and onward HIV transmission.

**Methods:** The NIH-funded IENGAGE trial (NCT01900236) enrolled PLWH within 14 days of their initial outpatient HIV care visit at 4 CFAR-affiliated academic HIV clinics. Participants were randomized to an intervention or standard of care (SOC) control arm (1:1). The intervention integrated and adapted 2 evidence-based approaches with demonstrated efficacy for RIC and ART adherence: enhanced personal contact/reminders and a 4 session counseling program based on Motivational Interviewing and grounded in a situated information, motivation and behavioral skills (SIMB) framework. Participant baseline and 48-week computer assisted surveys were done using validated instruments. A sample size of 400, with 10% attrition, provided >80% power to detect a 15% difference in 48-week VS, with 60% VS estimated in the SOC arm based upon historical data.

**Results:** Between 12/13 and 06/16, 371 participants enrolled (62% black, 19% women, 24% uninsured, 60% MSM, 25% D4 <200). Baseline psychosocial comorbidities included: 31% depression, 30% anxiety, 35% high-risk alcohol use, 18% active substance use. Roughly half the sample (49%) reported unmet need for supportive services (e.g. housing, employment, food and transportation). Overall, 86% of participants achieved 48-week VS; 86% intervention, 87% SOC; p = 0.87. Median time to VS was 63 days (IQR 42-101) and did not differ between the two study arms (HR=0.94, 95%CI=0.75-1.19).

**Conclusion:** Among new to care IENGAGE participants with substantial co-morbid psychosocial illness and unmet need for supportive services, 86% achieved 48-week VS in a median time of 63 days with no differences between study arms. Similar findings by study arm and the higher than expected VS rate in the SOC group likely reflects a rapidly evolving HIV treatment landscape, which emphasizes the care continuum, rapid ART initiation and the emergence of integrase inhibitors as first-line therapies. Sustaining care engagement and VS among new to care PLWH beyond the first year is imperative to maximize the individual and population health benefits afforded by modern HIV treatment.

**1051 INCREASES IN KNOWLEDGE OF HIV POSITIVE STATUS, ART, AND VIRAL SUPPRESSION IN BCPP**

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**Background:** Botswana approached the UNAIDS 90-90-90 targets at the onset of the Botswana Combination Prevention Project (BCPP). In this context, we examined the feasibility of further increasing HIV testing, ART coverage, and viral suppression through community-based HIV testing campaigns and universal ART.

**Methods:** BCPP is a community-randomized trial evaluating the impact of HIV testing and universal treatment on HIV incidence. The BCPP HIV testing campaigns included community-wide home, mobile and targeted outreach HIV testing. HIV Testing was offered to all individuals who did not have documentation of positive HIV status. All HIV-positive community residents age 16-64 who were citizens were tracked to determine linkage to care, ART initiation, retention in treatment, and viral suppression. Electronic medical records were examined for clinical outcomes. We used household enumeration and community HIV prevalence data from BCPP in combination with 2011 census information to estimate the total number of adult residents living with HIV (PLHIV).

**Results:** A total of 15,093 estimated PLHIV resided in the 15 intervention communities. BCPP identified 13,676 (91% of estimated PLHIV) HIV-positive persons in these communities (Figure 1). Among these, 11,214 (82%) were known HIV-positive while 2,462 (18%) were newly-diagnosed through BCPP, a 22% increase in knowledge of positive status. Among the 11,214 who knew their HIV status, 9,621 (86%) were already on ART. Of those not on ART (newly and previously diagnosed; n = 4055), 3413 (84%) initiated ART, increasing the coverage of ART to 94%. Among those initiating ART, 11,027 (89%) achieved viral suppression at baseline, knowledge of HIV positive status, treatment uptake, and viral suppression on ART. BCPP intervention communities achieved 48-week VS in a median time of 63 days with no differences between study arms (HR=0.94, 95%CI=0.75-1.19).

**Conclusion:** Despite high levels of HIV testing, ART coverage and viral suppression at baseline, knowledge of HIV positive status, treatment uptake, and viral suppression increased substantially with enhanced testing, linkage interventions and universal ART.
SUCCESSFUL VIRAL OUTCOMES AFTER IMPLEMENTING "TREAT ALL" IN SOUTH AFRICAN CLINICS

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Background: There is little data to determine the impact of WHO ‘Treat All’ guidelines on retention in care and viral load (VL) suppression in low and middle income countries.

Methods: We analyzed routinely collected TIER.net and National Health Laboratory Service data from 8 public clinics in rural and urban KwaZulu-Natal, South Africa, where ‘Treat All’ was implemented in September 2016. Non-pregnant patients aged ≥15 years and initiating ART between September 2014-February 2017 were included in this analysis. We assessed the relationship between time period of ART initiation, initiation CD4 count and the outcomes of retention in care and VL suppression using logistic regression.

Results: Of 9526 patients, 57% (95% CI 56-58) were female, median age was 33 years (IQR 28-41) and median CD4 count was 288 cells/mm³ (IQR 151-429). At 12 months post ART initiation, 75% (95% CI 74-76%) were retained in care, 25% transferred care or were lost to follow up, and 0.5% were confirmed dead. In multivariable analysis, age >35 years (adjusted odds ratio [aOR] 1.54, p<0.001), female gender (aOR 1.42, p<0.001), not having TB at initiation (aOR 1.29, p=0.002) and initiation CD4 count >200 cells/mm³ (p<0.001) were associated with retention in care at 12 months. Among the 7132 with VL and initiation CD4 results, 94% (95% CI 93-94) had VL suppression at <1000 copies/mL. Expected release within 30 days of HIV testing was noted as an important reason for not initiating ART among some those, 647 (47.2%) were HIV-positive of whom 438 (67.7%) were on ART (a 2.3 fold increase in inmates on ART). Of those on ART, 85 had a viral load result; 68 (91.8%) having a viral load <1000 c/mL. Of 222 patients on ART who were expected to be incarcerated ≥30 days after ART initiation, 81% (95% CI 78-84) were retained in care at 12 months. Of those known to be on ART and the numerator of those with a viral load <1000 c/mL included those in the census with HIV testing in the prior 12 months or known to be HIV-positive. The proportion on ART was assessed with a denominator of those known HIV-positive from the virtual cross sections for HIV testing, ART initiation, and viral load suppression. The denominator for status was the prison census, the numerator included those in the census with HIV testing in the prior 12 months or known to be HIV-positive. The proportion on ART was assessed with a denominator of those known HIV-positive from the virtual cross-section and those HIV-positive and on ART as the numerator. Viral load suppression included the denominator of those known to be on ART and the numerator of those with a viral load <1000 c/mL.

Results: On the baseline cross-section day there were 1,467 inmates in the facility. Of these, 857 (58.4%) knew their HIV status and were on ART (18.9%). Of those with known HIV, 188 (67.9%) were on ART. Viral loads were not routinely obtained prior to ART initiation. On the endline day, 1,370 inmates were in the facility and 1,263 (92.2%) had been tested or were already known positive. Of those, 647 (47.2%) were HIV-positive of whom 438 (67.7%) were on ART (a 2.3 fold increase in inmates on ART). Of those on ART, 85 had a viral load result; 68 (91.8%) having a viral load <1000 c/mL. Expected release within 30 days of HIV testing was noted as an important reason for not initiating ART among some HIV-positive individuals.

Conclusion: High levels of HIV testing and virologic suppression are feasible within correctional facilities. Although many more inmates were placed on ART, the second 90 goal was not reached possibly due to many inmates leaving the facility within 30 days of HIV testing. Justice involved populations should be included in efforts to achieve 90-90-90 goals and specific correctional facility programs are feasible.
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Background: Although differentiated service delivery (DSD) models offer a range of health systems innovations, their comparative desirability to patient populations, implementability and effectiveness remains unknown. We conducted a discrete choice experiment (DCE) to quantify model features most desired by patients to inform model prioritization during scale-up in Zambia.

Methods: We surveyed a random sample of HIV positive adults on ART at 12 clinics in Zambia and asked patients to choose between two hypothetical facilities which differed across six attributes: location of ART pick-up (clinic vs. community), frequency of ART pick-up (1 vs. 3 monthly), time spent waiting to pick up ART (1, 3 or 6 hrs), time spent waiting for a doctor (1, 2 or 5 hrs), type of adherence counselling (group vs. individual), and ability for a ‘buddy’ to collect ART. Each respondent answered one of two blocks of seven questions. We used mixed logit models to determine the degree of preference (i.e. preference weights - β) for each DSD feature, preference heterogeneity and willingness-to-trade.

Results: Of 486 respondents, 59% were female and 85% resided in urban locations. Patients strongly preferred infrequent clinic visits (3 vs. 1 month visits: β=2.84, p<0.001) (Figure). Milder preferences were observed for reduced waiting time for ART (1 vs. 6 hrs.: β=0.67, p<0.001) and reduced waiting time to see a doctor (1 vs. 3 hrs., β=0.41, p=0.003) and facilities accommodating ‘buddy’ ART collection (β=0.84, p<0.001). In order to obtain 3 instead of 1 monthly refills, patients were willing to wait 6 hrs. for ART (vs. 1), wait 3 hrs. for a doctor (vs. 1), pick-up ART in the community instead of clinic, attend large group counselling, and forego a buddy system (β difference: 0.23; p=0.487).

Conclusion: Patients in Zambia primarily want to attend health facilities infrequently, and this preference outweighs the desire for all other DSD features. Substantial preference heterogeneity was demonstrated by urban and rural participants, suggesting that Zambia should prioritize DSD models that remain facility-based but require infrequent contact, particularly in urban settings, with consideration of community based drug distribution for those more rural.
Of 549 persons diagnosed with HIV and received a PS interview, 69 (13%) did not reach viral suppression within a year. The two groups did not differ by gender, race/ethnicity, transmission category, foreign birth, primary language, drug use, and exchange sex from PS interviews. We compared characteristics of persons who did and did not reach suppression using a t-test for continuous variables and Pearson's chi-squared for categorical variables. We used Poisson regression to calculate relative risks for variables associated with suppression failure and examined time to suppression failure using a t-test for continuous variables and Pearson's chi-squared for categorical variables. We used Kaplan-Meier survival curves.

Results: Of 549 persons diagnosed with HIV and received a PS interview, 69 (13%) did not reach viral suppression within a year. The two groups did not differ by gender, race/ethnicity, transmission category, foreign birth, primary language, drug use, exchange sex, or median VL at the time of first report post-diagnosis. Persons who reported having no plan for HIV care at the time of HIV PS interview (N=72; 13%) were less likely to achieve suppression than those with a plan (RR 1.2; 95% CI: 1.04-1.4), as were persons with unstable housing compared to stable housing (N=81; 15%) (RR 1.2; 95% CI: 1.1-1.4). However, the majority (74%) of persons who reported no plan for care or unstable housing reached suppression; 42% of non-suppressed persons had one of these risk factors. In the overall population, 42% were suppressed at 3 months, 73% at 6 months, 84% at 9 months, and 87% at 12 months.

Conclusion: U=U represents a paradigm shift in HIV prevention but requires persistent HIV viral suppression. Among patients with one year of suppression in our clinic, approximately 10% per year became non-suppressed, and suppression couldn’t be confirmed in another 10% per year due to lack of PVL testing. This has important implications for counseling, viral load monitoring, and assuring retention in care when implementing U=U, particularly for young patients who may be at higher risk for non-suppression.

1057 FACTORS ASSOCIATED WITH LACK OF VIRAL SUPPRESSION IN THE YEAR AFTER HIV DIAGNOSIS

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Background: Identifying factors associated with poor HIV care continuum outcomes in the first year after HIV diagnosis could guide care engagement efforts at time of HIV diagnosis. Our objective was to identify factors available in HIV surveillance and partner services (PS) interviews associated with failure to reach viral suppression within one year among newly diagnosed persons living with HIV (PLWH) in Seattle & King County, WA.

Methods: We analyzed data from a population-based cohort of individuals newly diagnosed with HIV who received a PS interview in King County, 1/1/2013-6/30/2016. The outcome measure was achievement of viral suppression in a year after HIV diagnosis, defined as ≥ 1 viral load (VL) <200 copies/mL reported to surveillance <12 months from diagnosis date. Predictor variables included patient demographics, HIV transmission category, and value of first VL from case and laboratory surveillance; housing status, foreign birth, primary language, drug use and engagement in exchange sex from PS interviews. We compared characteristics of persons who did and did not reach suppression using a t-test for continuous variables and Pearson’s chi-squared for categorical variables. We used Poisson regression to calculate relative risks for variables associated with suppression failure and examined time to suppression failure using a t-test for continuous variables and Pearson’s chi-squared for categorical variables. We used Kaplan-Meier survival curves.

Results: Of 549 persons diagnosed with HIV and received a PS interview, 69 (13%) did not reach viral suppression within a year. The two groups did not differ by gender, race/ethnicity, transmission category, foreign birth, primary language, drug use, exchange sex, or median VL at the time of first report post-diagnosis. Persons who reported having no plan for HIV care at the time of HIV PS interview (N=72; 13%) were less likely to achieve suppression than those with a plan (RR 1.2; 95% CI: 1.04-1.4), as were persons with unstable housing compared to stable housing (N=81; 15%) (RR 1.2; 95% CI: 1.1-1.4). However, the majority (74%) of persons who reported no plan for care or unstable housing reached suppression; 42% of non-suppressed persons had one of these risk factors. In the overall population, 42% were suppressed at 3 months, 73% at 6 months, 84% at 9 months, and 87% at 12 months.

Conclusion: U=U represents a paradigm shift in HIV prevention but requires persistent HIV viral suppression. Among patients with one year of suppression in our clinic, approximately 10% per year became non-suppressed, and suppression couldn’t be confirmed in another 10% per year due to lack of PVL testing. This has important implications for counseling, viral load monitoring, and assuring retention in care when implementing U=U, particularly for young patients who may be at higher risk for non-suppression.

1058 THE IMPACT OF “CHURN” ON CUMULATIVE PLASMA HIV BURDEN WITHIN A POPULATION UNDER CARE

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Background: Background-The continuum of care (i.e. engagement, retention, treatment, viral suppression) is usually reported using cross-sectional data that often underestimates each stage, especially viral suppression rates. Recently, longitudinal approaches have been developed to address cumulative effects of HIV viral burden, however, these measures may further underestimate viral burden if ‘churn’ (the movements in/out of a population) are not taken into consideration. We examined the impact of churn on cumulative HIV viral burden over a 2 year period in a population under care.

Methods: Methods: All HIV+ patients followed at the Southern Alberta clinic in 2016/2017 with ≥1 clinic visit and ≥1 viral loads were included. Patients were grouped into 5 categories i) continuously followed; ii) newly diagnosed entering care; iii) previously diagnosed patients moving into care; iv) patients who formally moved out of care; and v) patients followed then disengaged from care. We determined the number of days patients spend with a suppressed (≤200 copies/mL), unsuppressed (>200), and transmittable (>1500) viral loads.

Results: Results: 1498 (78%) of 1915 patients followed in 2016/2017 had suppressed VL for the entire 2 years; 22% had at least one unsuppressed VL, 19% had at least one transmittable VL. 88% of patients continuously followed had suppressed VL, 12% at least one unsuppressed VL and 10% ever transmittable. 90% of newly diagnosed patients entering the population had unsuppressed VL however most quickly became suppressed after initiating treatment (mean time ~ 62 days). 35% of patients entering from elsewhere presented with a transmittable VL. Of patients formally moving out of the population, 92% were suppressed prior to moving. Patients disengaging from care (n=106) had the highest rate of unsuppressed/transmittable VL of 54% and 49% respectively. Overall, of 1,168,782 total days followed, 92% were spent suppressed, 8.2% unsuppressed (105,011 days), and 6.6% (84,085 days) transmittable. Patients disengaging from care, although accounting for only 5.5% of all patients, accounted for 34% of days spent unsuppressed and 37% transmittable.

Conclusion: Conclusions: Churn adds complexity to reporting HIV viral burden but provides nuance as patients entering or leaving the population contribute disproportionally to overall viral suppression rates. Longitudinal approaches to HIV viral burden provide different perspectives on who may be driving the local HIV epidemic.
**1060 HIGH AWARENESS BUT UNCERTAIN BELIEF IN U=U AMONG PROVIDERS AND COUPLES IN KENYA**

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**Background:** Sustained viral suppression resulting from antiretroviral therapy (ART) eliminates the risk of HIV transmission. Scientific and popular messaging has framed this elimination of risk in concepts such as treatment as prevention (TasP) and Undetectable = Untransmittable (U=U). We explored knowledge and acceptance of information around the elimination of HIV transmission risk with ART among health providers and HIV serodiscordant couples in Kenya.

**Methods:** The Partners Scale-up Project is evaluating PrEP delivery to HIV uninfected individuals in serodiscordant relationships in 24 public HIV clinics in Central and Western Kenya. We conducted semi-structured in-depth interviews with 69 health providers and 35 HIV uninfected people in serodiscordant relationships receiving PrEP services. Transcripts were coded using framework analysis.

**Results:** Health providers reported being aware of reduced risk of HIV transmission as a result of consistent ART use and used words such as ‘very low,’ ‘minimal,’ ‘like zero’ to describe HIV transmission risk after viral suppression: but did not use the words ‘no risk.’ Additionally, providers reportedly found viral load results helpful when counseling clients on the ‘very low risk’ of HIV transmission after viral suppression. Others believed that U=U works, but only in the context of consistent condom use but concerns were expressed that communicating this message to HIV infected persons would lead them to engaging in multiple sexual relationships. Other providers reported avoiding counseling on risk of HIV transmission even after viral suppression for fear in case a seroconversion occurred they would be blamed. Similarly, members of HIV serodiscordant couples reported being informed about U=U by the providers but they did not believe/trust the message. Even after the HIV infected partners reached viral suppression, most HIV uninfected members of couples reported unwillingness to stop PrEP while others reported that they would use condoms if they stopped PrEP.

**Conclusion:** Despite high awareness that ART eliminates HIV transmission risk, there is both a lack of in depth knowledge and conviction among health providers and PrEP users. New strategies to communicate U=U in a reliable and believable way are urgently needed.

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**1061 RESUPPRESSION AFTER POINT-OF-CARE VIRAL LOAD TESTING TO GUIDE ADHERENCE COUNSELING**

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**Background:** Whilst implementation of virologic monitoring remains uneven across Africa, novel molecular platforms now facilitate adoption at point of care (POC). The OPTIMISE study explored POC viral load testing followed by immediate adherence counselling for its impact on rates of virologic resuppression in a programmatic care setting in Ghana. At the center, the second largest in Ghana, routine virologic monitoring is not yet available.

**Methods:** Consecutive patients who were established on ART and accessed outpatient care over a 2-week period in February 2018 (T1) were invited to complete an adherence questionnaire and to self-report adherence via a visual analogue scale (VAS). HIV-1 RNA was quantified with Cepheid Xpert over 90 min. Patients with viremia (>40 copies/ml) received immediate adherence counselling by trained nurses over 15-20 min, and were invited to reattend 8 weeks later (T2), when adherence was re-assessed and viral load testing repeated.

**Results:** At T1, 333 consecutive patients (74% females, median age 48 years, median CD4 count 626 cells/mm3) underwent POC viral load testing. Patients had received ART for a median of 9 years. Most (297/333, 89%) were on NNRTI-based ART (mainly efavirenz); 36/333 (11%) were on PI-based ART, mainly lopinavir/ritonavir. The NNRTIs comprised mainly TDF/3TC (187/333, 56%) and ZDV/3TC (130/333, 39%). Overall, 164/333 (49%) subjects had viremia, with median levels of 423 copies/ml; 71/333 (21%) had levels >1000 copies/ml. By regression analysis, a self-reported history of ≥1 treatment interruption since first starting ART (usually due to unavailability of the dispensary) independently predicted viremia at T1 (adjusted OR 3.1; 95% CI 1.5-6.3; p<0.01). Of the 164 patients with T1 viremia, 150 (91%) attended at T2 and 32/150 (21%) showed resuppression. By multivariable analysis (Table 1), a T1 viral load >1000 copies/ml independently predicted lack of resuppression at T2.

**Conclusion:** In this programmatic HIV setting lacking access to routine virologic monitoring, half of the cohort had detectable viremia while on ART, and only a fifth achieved resuppression following adherence counselling. Patients established on long-term NNRTI-based ART who report a history of treatment interruption could benefit from viral load testing at POC regardless of current self-reported adherence. Those with a viral load >1000 copies/ml should be offered an immediate switch to alternative therapy.

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**1062 COMORBID CONDITIONS, VIRAL TRAJECTORIES, AND COORDINATED CARE IN LOS ANGELES COUNTY**

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**Background:** In March of 2013, the Los Angeles County Division of HIV and STD Programs implemented a clinic-based Medical Care Coordination (MCC) Program for high-risk people living with HIV (PLWH) with comorbidities (e.g., substance use, homelessness, and mental health disorders) to improve viral suppression...
(VS) (<200 c/ml) through case management services. The present study aims to determine the odds of VS prior to and following MCC enrollment, and to compare trajectories by reported stimulant use, homelessness, and depressive symptom severity.

**Methods:** Data were 52,138 observations from 6,269 PLWH from 12 months (m) prior to MCC enrollment to 36 m post-enrollment. Piecewise mixed effects logistic regression estimated trajectories of VS (1) 12 m pre-MCC, (2) 6-6 m post-enrollment, and (3) 6-36 m post-enrollment—cut-points based on locally weighted scatterplot smoothing. We compared VS trajectories by reported stimulant use (methamphetamine, cocaine, and crack), homelessness, and depressive symptoms (PHQ-9 score), adjusting for sociodemographic and HIV-related covariates.

**Results:** At enrollment, 42.8% of the sample had VS. Reported stimulant use (OR=0.62, 95% CI [0.52, 0.74], p<.001) and pronounced depressive symptoms (OR=0.90, 95% CI [0.85, 0.96], p<.001) were associated with lower odds of VS, while homelessness was not. Odds of VS increased by a factor of 11 in the first 6 months in MCC (ΔOR=10.88, 95% CI [9.98, 11.87], p<.001), then did not significantly change 6-36 m post-enrollment (ΔOR=0.98, 95% CI [0.95, 1.00], p=.800). Post-enrollment changes in odds of VS did not differ by reported stimulant use. In the first 6 m in MCC, those reporting homelessness improved in VS than those stably housed (ΔOR=0.42, 95% CI [0.34, 0.51], p<.001). In later months, those reporting homelessness improved more in VS than those stably housed (ΔOR=1.03, 95% CI [1.00, 1.04], p=0.035). Pronounced depressive symptoms were associated with greater improvement in VS 6-36 m post-enrollment (ΔOR=1.03, 95% CI [1.02, 1.04], p=0.001).

**Conclusion:** MCC patients significantly improved and sustained their VS, with the greatest increase occurring within the first 6 m, likely attributed to improved access and adherence to HIV care as well as support services. While there were significant differences in time to VS among patients with comorbidities, these results suggest potential for this patient-centered program to address these disparities.

**Figure 1:** Proportion of patients developing comorbidities any time and during follow-up by ART status. Longitudinal Surveillance of Treatment in Kenya, 2016 (N=3170)

### NONCOMMUNICABLE DISEASES AS REASONS FOR ADMISSION AMONG HIV-INFECTED ADULTS IN ZAMBIA

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**Background:** Although rates of non-communicable diseases (NCDs) among HIV-infected individuals are anticipated to increase in sub-Saharan Africa (SSA), quantitative data characterizing the true burden of NCDs are scarce. We investigated the proportion of hospitalizations attributed to NCDs among adults with and without HIV at a hospital in Zambia.

**Methods:** We extracted age, sex, HIV status, and reason for admission from a randomly-selected group of adults (18 + years) admitted to the internal medicine inpatient wards at University Teaching Hospital (UTH) in Lusaka. We defined HIV infection by self-reported positivity or a rapid test, and considered self-reported negative patients as unknown status. Among HIV-infected individuals, we also captured CD4+ and HIV viral load and defined viral suppression (VS) as <40 copies/ml. Reasons for admission (up to 2 per patient) were coded as infectious diseases (IDs), non-communicable diseases (NCDs), or unknown as well as by medical specialty (neurology, cardiovascular, renal, etc.). Two physicians coded each admission reason independently, with a third
available to resolve disagreement. We displayed differences in the proportion with ID versus NCD admissions by HIV status and by CD4+ and viral load among HIV-infected individuals.

**Results:** From August 2017 to February 2018, we assessed 1,261 inpatients, 140 (11.1%) of whom were excluded for unknown HIV status. Among those included in analysis, median age was 38 years (interquartile range, 30–48), 564 (50.3%) were women, and 748 (66.7%) were HIV-infected. NCDs accounted for 29.2% of admissions overall and 17.8% among HIV-infected individuals. Among 143 patients with laboratory data (who had similar age and sex \(P>0.05\)) to those without data, median CD4+ was 181 cells/mm³ (interquartile range, 52–299), 42.9% had VS, and in those with CD4+ >200 cells/mm³, NCDs were nearly as common as IDs (40.7% versus 51.2%; Figure 1). Among HIV-uninfected individuals, NCDs were slightly more common than IDs (51.6% versus 49.9%). Heart failure (9.5%), anemia (6.3%), stroke (4.3%), and diabetes (3.8%) were most common NCDs.

**Conclusion:** NCDs were a common cause of hospital admission among HIV-infected individuals and others in Zambia. These data inform recommendations to integrate NCD risk factor screening and care for HIV-infected individuals in SSA. Hospital surveillance data can provide useful information to HIV programs regarding emerging causes of non-HIV-related morbidity and mortality.

### 1066 CASCADES TO EVALUATE THE CERVICAL CANCER SCREENING PROGRAM IN A ZIMBABWEAN ART CLINIC

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**Background:** With advances in science and antiretroviral therapy, HIV has become a manageable condition and people living with diagnosed HIV (PLWH) are living longer. In the United States (US), over 450,000 PLWH were aged ≥50 years in 2015, an increase of nearly 40% since 2011. This rapid growth of the aging population of PLWH highlights the need to identify and implement aging-appropriate HIV care and support services. The Ryan White HIV/AIDS Program (RWHAP) supports HIV care, treatment, and support services for more than 50% of PLWH in the US. This analysis examines sociodemographic characteristics, service utilization, and viral suppression (VS) among current RWHAP clients and projects the growth of the aging RWHAP population by 2030.

**Methods:** Client-level data from the RWHAP Services Report were used to calculate distributions among clients aged ≥50 (older) and <50 (younger), by race/ethnicity, gender, transmission risk, poverty level, health care coverage, and housing status, and trends in service utilization from 2010 to 2016. Among older clients, additional analyses examined differences by gender and race/ethnicity. VS was calculated among older clients receiving RWHAP outpatient health services. Five-year age distribution trends were used to project the number of RWHAP clients aged ≥50 by 2030.

**Results:** In 2016, 44% of RWHAP clients were aged ≥50, an increase from 32% in 2010. A higher proportion of older than younger clients were White, lived above the poverty level, had stable housing, and accessed food-related services. Among older clients, women and transgender clients had higher housing instability and poverty compared to men. Variation was seen by race/ethnicity. In 2016, VS among older clients was 90% compared to 81% among younger clients. VS increased across all subpopulations of older clients from 2010 to 2016; however, clients with unstable or temporary housing had lower percentages compared to other key subpopulations. By 2030, a projected 66% of RWHAP clients will be aged ≥50 years.

**Conclusion:** Older PLWH receiving care and treatment through RWHAP have high percentages of VS. However, social and structural factors, such as housing stability, may impact HIV outcomes. In addition, aging PLWH may have unique needs, such as food insecurity, long-term HIV medication effects, behavioral health needs, and age-related comorbidities. As the population of older PLWH continues to grow, so too will the importance of further assessing and planning for the needs of this emerging population.

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Background: As people living with HIV (PLWH) are living longer, premature morbidity and mortality from age-associated comorbidities are more common. Our objective was to compare prevalence trends and age of onset of comorbidities between PLWH and the general population in British Columbia (BC).

Methods: This retrospective cohort study used longitudinal data from the Comparative Outcomes and Service Utilization Trends study, a population-based cohort of PLWH and 10% random representative sample of BC population. Eligible participants were ≥19 years old and followed for ≥1 year between 2000 and 2012. PLWH were antiretroviral therapy (ART) naïve. Age-related comorbidities were identified from hospital and physician billing provincial databases using the International Classification of Disease versions 9/10. Selected comorbidities included cardiovascular, kidney, lung, and liver diseases, non-AIDS-defining cancers, diabetes, osteoarthritis and hypertension. Generalized non-linear models (assuming a beta distribution and a logit link) modeled the prevalence trends, and the Mann-Whitney U test compared the distribution of age of onset of comorbidities between both populations.

Results: The study included 4,223 PLWH and 454,092 HIV-negative individuals (median age 37 vs. 39 years, 80% vs. 50% men, median follow-up 5 vs. 13 years, respectively). Yearly prevalence of diabetes, kidney, lung, and liver diseases were significantly higher among PLWH, while the remaining comorbidities were significantly higher among HIV-negative individuals. The gap in prevalence of kidney and liver diseases between the two populations is considerably wide, while for cardiovascular diseases and diabetes, it is rapidly narrowing. PLWH experienced all comorbidities at a significantly younger age than their counterparts, ranging between 8 years earlier for hypertension and 22 years for kidney diseases. See figure for an example of trends of prevalence and age of onset of two key comorbidities in these populations.

Conclusion: Our results showed that PLWH experience earlier onset of non-HIV related comorbidities that can contribute to accelerated aging. The gaps in the prevalence of comorbidities could be related to HIV related inflammation, life-style issues and toxicities related to older ART. These results further stress the need for early HIV diagnosis and ART initiation with maintenance of long-term virologic suppression, as well as optimized general clinical screening for comorbidities at earlier age among PLWH.
26% [95%CI: 21%, 31%] at 10 years after DM diagnosis and HIV- women (from 25% [95%CI: 19%, 32%] at 1 year to 18% [95%CI: 13%, 24%] at 10 years after DM diagnosis; p=0.2902 for HIV status*time, see Figure).

Conclusion: We noted large and growing gaps in DM care goal achievement in both HIV+ and HIV- women. Opportunities to improve DM care are numerous; aggressive DM management interventions among HIV+ and HIV- women are needed.

1069  TOTAL AND CENTRAL OBESITY PREDICT COGNITIVE DECLINE: MULTICENTER AIDS COHORT STUDY

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Background: Among adults with HIV infection, obesity may contribute to multisystem dysregulation including cognitive impairments. We examined body mass index (BMI) and central obesity (waist circumference, WC) in association with domain-specific cognitive function and 10-year cognitive decline in adult men living with HIV infection (HIV+) compared to at-risk men without HIV infection (HIV-).

Methods: The longitudinal Multicenter AIDS Cohort Study (MACS) of HIV infection among HIV+ men and at-risk controls (HIV-) provides data for these analyses. Inclusion criteria included: >40 years old at first neuropsychological testing; and for HIV+ men, ≥2 antiretroviral agents and HIV-1 RNA <400 copies/mL at >80% of visits. Outcomes included neuropsychological test scores measured every 2 years. Tests included: learning (RAVLT total learning, Rey immediate recall), memory (RAVLT delayed recall, Rey delayed recall), executive function (TMT-Part B, Stroop interference trial), processing speed (SDMT, Stroop color-naming trial), sustained attention and working memory (CALCAP mean simple and complex reaction time), and fine motor function (GPEG-dominant or non-dominant hand). Exposures included baseline BMI and WC. Linear mixed effects models included all available visits from 1996-2015, adjusted for baseline sociodemographic, behavioral, and clinical characteristics, stratified by HIV-serostatus.

Results: Among 972 (316 HIV+ and 656 HIV-) men at baseline, higher BMI (≥25 kg/m2) was cross-sectionally associated with lower motor function in HIV+ and HIV-, and lower attention/working memory in HIV- men. Obese WC (≥102 cm, 40 inches) was associated with lower motor function in HIV+ and HIV- men. Overweight and obesity may be important predictors of mid-life neuropsychological outcomes and later-life cognitive impairments, and should be considered in prevention and intervention planning.

1070  EFFECT OF OBSTRUCTIVE LUNG DISEASE ON MORTALITY AMONG HIV+ PERSONS WHO INJECT DRUGS

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Background: People living with HIV experience increased prevalence of obstructive lung disease (OLD), even after accounting for greater smoking prevalence in this population. Although excessive lung function decline has been shown to lead to increased mortality in HIV-negative individuals, the effect of OLD on mortality among people living with HIV has not been quantified. We investigated whether the effect of incident OLD on mortality differs by HIV status in a cohort of people with a history of injecting drugs.

Methods: The ALIVE study is a longitudinal, observational cohort of HIV-positive and negative people with a history of injecting drugs. This analysis included ALIVE participants who had at least one spirometry measure to assess OLD between 2007 and 2016, excluding those who reported never smoking (5%, n=62) or who had OLD at baseline (17%, n=269). Incident OLD was defined as a first measurement of pre-bronchodilator FEV1/FVC<0.70 during follow-up. The effect of incident OLD on mortality among HIV-positive and negative participants was estimated using an inverse-probability-of-treatment weighted marginal structural model controlling for confounders including baseline age, black race, sex, baseline calendar year, HIV, baseline smoking pack-years, time-varying smoking status, and calendar time.

Results: Among 1,216 participants, 272 (22.4%) experienced incident OLD and 157 (12.9%) deaths were observed over a median of 5 person-years (IQR=2-8) of follow-up. In the main analysis, OLD did not have a statistically significant effect on mortality (HR=1.22, 95% CI: 0.83-1.79). In the model that assessed effect measure modification by HIV, HIV-positive participants exposed to OLD experienced an increased risk of mortality (HR=1.72, 95% CI 1.06-2.81), while there was no effect of OLD on mortality among HIV-negative participants (HR=0.92, 95% CI 0.80-1.02).

Conclusion: Although OLD did not have a statistically significant effect on mortality after properly accounting for baseline as well as time-varying confounders, there was an apparent effect of OLD among HIV-positive people with a history of injection drug use. These results highlight the need for greater screening and management of OLD among HIV-positive individuals. Further research is needed to determine if there are particular clinical characteristics of HIV-infection that mitigate the risk of death after the occurrence of OLD.
SYNDEMICS AND RETENTION IN CARE AMONG WOMEN LIVING WITH HIV IN RIO DE JANEIRO, BRAZIL

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Background: Syndemic psychosocial and reproductive factors impacting women’s engagement in the HIV care cascade remain understudied worldwide. We hypothesized that syndemic conditions would limit retention in care among a cohort of women living with HIV in Rio de Janeiro, Brazil.

Methods: We analyzed baseline syndemic prevalence and correlates of non-retention in the INI-Fiocruz women’s cohort from 2000-2015. A syndemic score was created for a lifetime history of: physical/sexual violence, illicit drug use, adolescent pregnancy (<20 years old), or induced abortion. Stepwise backward logistic regression models identified predictors of non-retention, defined as <2 HIV laboratory results within the first year of cohort enrollment. Two separate models analyzed syndemic contributions to non-retention: Model 1 incorporated individual syndemic variables; Model 2 used the syndemic score.

Results: Of 915 women, 18% met criteria for non-retention. Prevalence of syndemic factors was: physical/sexual violence 38.3%, illicit drug use 17.2%, adolescent pregnancy 53.2%, and induced abortion 27.3%. Nearly half (41.2%) experienced ≥2 syndemic conditions. Illicit drug use was associated with non-retention in unadjusted analysis (cOR 2.05, 95% CI: 1.37-3.05), but none of the other conditions reached statistical significance.

Conclusion: The syndemic of psychosocial and reproductive factors can limit retention in care for women living with HIV. Syphilis infection independently predicted non-retention, and could be explored as a syndemic factor in future studies. Interventions addressing sex-specific syndemics are needed to optimize HIV care in this vulnerable population.

PROSTATE CANCER SCREENING AND INCIDENCE IN AGING VETERANS INFECTED WITH HIV

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Background: Non-AIDS defining cancers are increasingly important contributors to health outcomes for aging persons with HIV (PWH). Although prostate cancer is prevalent in aging men, the impact of HIV infection on prostate cancer risk remains unclear and may be obscured by less screening in PWH. Therefore, we aimed to study longitudinal prostate cancer screening, incidence, and disease characteristics in Veterans Aging Cohort Study (VACS), a national cohort of PWH and uninfected controls.

Methods: Using data from VACS (2000-2015) we identified a cohort of 119,336 (36,333 PWH, 83,003 controls) men ≥45 years of age. We ascertained PSA testing and prostate biopsy using relevant procedure codes, as well as incident prostate cancer diagnoses using linked cancer registry data. We calculated the incidence of PSA testing by HIV status and then fit multivariable Poisson models comparing the rates of PSA testing, prostate biopsy (among PSA tested persons) and prostate cancer incidence (in the whole cohort and restricting to only PSA tested persons) adjusting for age, race and smoking status. Among patients diagnosed with prostate cancer we compared Gleason grade and clinical stage.

Results: Mean age at enrollment was 50 years, and patients were followed for a median of 15 years. A majority received at least one screening PSA test in the study period, including PWH (30,837, 85% ever tested) and controls (36,333 PWH, 83,003 controls) men ≥45 years of age. We ascertained PSA testing and prostate biopsy using relevant procedure codes, as well as incident prostate cancer diagnoses using linked cancer registry data. We calculated the incidence of PSA testing by HIV status and then fit multivariable Poisson models comparing the rates of PSA testing, prostate biopsy (among PSA tested persons) and prostate cancer incidence (in the whole cohort and restricting to only PSA tested persons) adjusting for age, race and smoking status. Among patients diagnosed with prostate cancer we compared Gleason grade and clinical stage.

Conclusions: In longitudinal follow-up, there was a lower incidence of prostate cancer among PWH compared with matched controls but some suggestion
of differences in grade and stage at diagnosis. Further study is warranted to understand the role of HIV status on prostate cancer treatment and outcome.

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<th>Table 1: PSA screening and prostate cancer incidence among PWH and Controls in VACS</th>
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**Abbreviations:** PSA—prostate-specific antigen; VACS—Veterans Aging Cohort Study; PWH—persons with HIV

1073 SOCIOECONOMIC IMPACTS OF UNIVERSAL ANTIRETROVIRAL THERAPY IN THE SEARCH TRIAL

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**Background:** Improvements in community health due to multi-disease health services and universal antiretroviral treatment have the potential to improve various socio-economic indicators, thereby informing cost-benefit calculations for such investments in healthcare.

**Methods:** We conducted longitudinal socio-economic surveys over a 3-year period in households of approximately 100 HIV-infected and 100 HIV-uninfected adults sampled after baseline HIV testing in 30 pair-matched communities in the SEARCH trial (NCT01864603). Control communities received baseline multi-disease testing and antiretroviral therapy by national guidelines while intervention communities received annual testing and antiretroviral therapy irrespective of CD4 count via patient-centered care. Surveys assessed various outcomes including employment, consumption expenditures, asset holdings, survival expectations, and children’s school enrollment. The primary outcome was employment hours in the past week for individuals aged 18-65 years. Regression models with individual fixed effects and time trends were used to determine causal effects of the SEARCH intervention. Effects were examined for subgroups of HIV-positive adults with CD4 cell counts ≥500 and <500 cells/mm3, their HIV-negative household members, and HIV-negative individuals in households without an HIV-positive adult.

**Results:** Longitudinal data were collected for 34,396 individuals from 5,283 households. Adults worked an average of 29.6 hours and the majority of employment occurred on households’ own farms. Total employment hours among all adults did not change significantly due to the SEARCH intervention but among baseline HIV-positive adults, the intervention increased employment by 6.1 hours (p<0.001). Effects were largest among HIV-positive adults with baseline CD4≥500 (increase of 9.9 hours, p<0.01). Children in households with an HIV-positive adult were 5.3 percentage points more likely to complete primary school due to the SEARCH intervention (p<0.001). Outcomes such as assets, non-food expenditures, and survival expectations improved significantly over time, but there were no significant differences between intervention and control communities.

**Conclusion:** Universal antiretroviral therapy provision led to significant economic benefits for HIV-positive adults, particularly those with high CD4 counts. Improvements in socio-economic outcomes and survival expectations were observed in all communities following multi-disease testing at baseline.

1074 CONDOM USE AND PRICES IN TRANSACTIONAL SEX ENCOUNTERS AMONG HIGH-RISK WOMEN IN KENYA

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**Background:** The exchange of money, goods, or services in sexual relationships is a key driving factor for HIV risk in areas where incidence is above elimination rates. We assessed factors that influence condom use and the monetary value of transactional sex encounters among high-risk women in a high prevalence setting in Kenya.

**Methods:** Baseline data were obtained for an ongoing cluster randomized trial of an HIV self-testing intervention among women in 66 community clusters in Siaya County, Kenya (NCT03135067). Clusters included fishing communities along Lake Victoria and market centers with hotspots for female sex workers. Eligibility criteria for women in clusters included: age ≥18 years, HIV-negative status, and self-report of ≥2 sexual partners in the past month. Data were collected on participants’ most recent transactional sex encounters, including sexual partner characteristics, condom use, and the “price” of each encounter as indicated by the total value of money, goods, and services received. Regression analyses with participant fixed effects were used to assess participant and partner factors that predicted condom use and the price of each encounter.

**Results:** Among 2,087 participants, 1,396 (67%) reported sex work as one of their income sources and 1,983 (95%) reported on 4,474 transactional sex encounters. Participants had an average age of 27.1 years (IQR 22-31) and for 62.2% the highest education level completed was primary or below. Condom use was reported in 51% of encounters and was significantly more likely with first-time male partners rather than with repeat partners (65% vs. 49%, p<0.001). The median price per encounter was $9.9 (interquartile range $5-$19.8). Prices were $1.8 higher with partners aged >30 years vs. ≤30 years (p<0.05). Higher prices were also reported partners who were wealthier ($5.4 higher, p<0.01) and rated as being handsome ($1.9 higher, p<0.01). Encounters in which either the participant or partner were intoxicated had significantly lower prices. Unprotected sex was associated with a 15% higher price among women with some secondary or higher education (p=0.05) but there was no significant difference among women with primary education or less.

**Conclusion:** Among high-risk women in Kenya, there is high prevalence of transactional sex and suboptimal condom use. The large monetary value of transactional sex encounters and lower condom use with repeat partners suggests a need for economic and behavioral interventions that facilitate reduced sexual risk-taking.

1075 SABES: A COST-EFFECTIVE TasP INTERVENTION TO IDENTIFY AND TREAT RECENT HIV INFECTIONS

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**Background:** Sabes, a treatment-as-prevention (TasP) intervention in Lima, Peru, was implemented to test the hypothesis that frequent HIV testing and initiation of ART during early (acute and recent [<3 months]) HIV infection will markedly reduce onward HIV transmission among men who have sex with men (MSM) and transgender women (TW). HIV-negative, high-risk individuals were identified, underwent monthly HIV testing, and were rapidly initiated on ART if they became HIV infected.

**Methods:** We evaluated the cost-effectiveness of the Sabes TasP intervention compared to the standard of care using a government health care perspective,

IAS–USA        Topics in Antiviral Medicine
Cost-effectiveness of long-acting ART for adolescents and young adults in Kenya

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Background: Despite the high efficacy of oral antiretroviral therapy (ART), viral suppression among adolescents and young adults (AYA) living with HIV in sub-Saharan Africa (SSA) remains low. Without the need for daily adherence to oral ART, long-acting injectable ART (LA-ART) may simplify adherence and, consequently, decrease transmission, morbidity, and mortality in this priority population. However, LA-ART may cost more than oral ART and its threshold for cost-effectiveness has not been evaluated in SSA.

Methods: We adapted a mathematical model of HIV transmission and progression in Kenya to capture HIV acquisition and viral suppression among AYA (age 10-24). We projected the health and economic impact of LA-ART, assuming 75% of AYA on ART would switch to LA-ART with a two-month duration of viral suppression per injection. We evaluated two scenarios for LA ART adherence: the first similar to current oral adherence rates (75% viral suppression across AYA) and the second, higher adherence assuming 94% of AYA on LA-ART were virally suppressed. We assessed population-level effects of LA-ART over a 10-year time horizon. We calculated the maximum incremental cost of LA-ART compared to oral ART under both scenarios that would be considered cost-effective, using $500/DALY averted as the cost-effectiveness threshold.

Results: Assuming adherence similar to oral ART, we project LA-ART would avert 10,439 HIV infections and 4,159 HIV-related deaths over 10 years compared to standard of care. With higher adherence (94%), LA-ART would prevent 52,971 infections and 18,433 deaths over 10 years. To have an incremental cost-effectiveness ratio (ICER) below the $500/DALY averted threshold, the annual per-person cost of LA-ART administration can be at most $919 and $266 USD higher than oral ART administration ($169 per year) for the similar and higher adherence scenarios, respectively.

Conclusion: Providing LA-ART to AYA could be cost-effective for reducing HIV burden in Kenya if it is low-cost. Increases in drug resistance due to non-adherence to LA-ART would decrease health benefits and should be evaluated in future analyses.
involved nonadherence (skipping doses, taking less medicine, delaying filling a prescription). Because nonadherence can affect health and transmission, we compared the prevalence of cost-saving related nonadherence by sociodemographic groups, and clinical outcomes among those who did and did not report cost-saving related nonadherence. We used prevalence ratios with predicted marginal means to evaluate significant (P<0.01) differences between groups.

Results: In all, 13% of persons reported using any cost-saving strategy and 8% reported any cost-saving related nonadherence; 8% asked a doctor for lower cost medicine, 1% bought drugs from another country, 2% used alternative medicine, 4% skipped doses, 4% took less medicine, and 6% delayed a prescription. Cost-saving related nonadherence was not associated with age, gender, race/ethnicity, poverty, or homelessness. Cost-saving related nonadherence was significantly higher among persons with a disability, private insurance, and unmet need for medications from the Ryan White AIDS Drug Assistance Program (ADAP), and lower among persons with Medicaid (Table). Persons reporting cost-saving related nonadherence were less likely to be virally suppressed and engaged in care, and more likely to have visited an emergency room or been hospitalized more than once.

Conclusion: Persons with diagnosed HIV in the United States used various strategies to reduce prescriptions drug costs. Cost-saving related nonadherence was relatively low, but was associated with poorer clinical outcomes. Increasing access to ADAP and Medicaid coverage may help to decrease nonadherence due to cost concerns among persons with diagnosed HIV.

Table: Cost-saving related nonadherence among persons with diagnosed HIV, who are taking prescription medications by disability, insurance status, and clinical outcomes. (Adapted from Reference 3. Used with permission from the American Journal of Public Health.)

<table>
<thead>
<tr>
<th>Disability</th>
<th>Any Cost-saving</th>
<th>Cost-saving related nonadherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No disability</td>
<td>13%</td>
<td>8%</td>
</tr>
<tr>
<td>Any disability</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Poverty</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Use of recreational drugs</td>
<td>25%</td>
<td>19%</td>
</tr>
<tr>
<td>Use of recreational drugs and travel</td>
<td>33%</td>
<td>23%</td>
</tr>
<tr>
<td>Use of travel</td>
<td>30%</td>
<td>22%</td>
</tr>
<tr>
<td>Use of accommodation</td>
<td>40%</td>
<td>27%</td>
</tr>
<tr>
<td>Use of transportation</td>
<td>35%</td>
<td>23%</td>
</tr>
<tr>
<td>Use of accommodation and travel</td>
<td>42%</td>
<td>30%</td>
</tr>
<tr>
<td>Use of transportation and travel</td>
<td>46%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Table: Cost of accessing primary healthcare as a proportion of income. (Adapted from Reference 4. Used with permission from the American Journal of Public Health.)

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Cost as Proportion of Income (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>5.4%</td>
</tr>
<tr>
<td>Zambia</td>
<td>12.4%</td>
</tr>
</tbody>
</table>

Cost and impact of community-based, assisted HIV self-testing among youth in Zambia

Brooke E. Nichols, Refilee Cile, Charles Chasela, Zumbe Siwale, Alamwii S. Lungu, Lawrence Long, Crispin Moyo, Sydney Rosen, Roma Chilengi, for the EQUIP Health team

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Background: Uptake of traditional facility-based HIV testing services among adolescents and youth is poor in many countries. HIV self-testing (HIVST) offers one strategy for increasing youth uptake. In order to assess scale-up feasibility, we conducted an economic evaluation of a pilot study that provided assisted, community-based HIVST for 16-24 year olds in Zambia.

Methods: 5,353 youth accepted the offer of assisted HIVST. The yield of newly diagnosed positive per person tested was 1.0% (56/5,353) for facility-based SOC in 10 clusters compared to 3.2% (170/5,353) for facility-based SOC in one cluster. Approximately 60% of youths who tested positive had never been tested before.

Results: 5,353 youth accepted the offer of assisted HIVST. The yield of newly diagnosed positive per person tested was 1.0% (56/5,353) for facility-based SOC in 10 clusters compared to 3.2% (170/5,353) for facility-based SOC in one cluster. Approximately 60% of youths who tested positive had never been tested before.
facility-based SOC. The total testing cost per new positive diagnosis was $580 and $80 in the HIVST and SOC arms respectively. The cost per new ART initiate increases to $978 for HIVST due to low facility linkage. An estimated 1,114,000 youth tested through currently available testing modalities in 2018, leading to 31,663 ART initiations for an annual cost of $3.6m. National HIVST rollout would reach an additional 310,000 youth annually, increasing the proportion of youth diagnosed by 6%, at an additional cost of $2.5m. Of these, a maximum of 2,192 additional youth would initiate ART.

**Conclusion:** Community-based HIVST identifies youth who may not otherwise have tested for HIV, but is unlikely to be economically feasible at a national level. Other methods for improving youth HIV testing uptake, such as unassisted HIVST, index HIVST or targeted community-based strategies should be evaluated and compared.

### Table 1. Cost and impact of community HIVST scale-up and facility-based standard of care in Zambia

<table>
<thead>
<tr>
<th>Facility-based standard of care</th>
<th>Community-based assisted HIVST added to facility-based standard of care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model parameters based on pilot project implementation</strong></td>
<td></td>
</tr>
<tr>
<td>Number tested</td>
<td>6,728</td>
</tr>
<tr>
<td>Number tested newly positive</td>
<td>214</td>
</tr>
<tr>
<td>Number Initiated on ART</td>
<td>unknown</td>
</tr>
<tr>
<td>Cost per test provided</td>
<td>$2.54</td>
</tr>
<tr>
<td>Cost per newly identified positive</td>
<td>$60</td>
</tr>
<tr>
<td>Cost per new ART initiate</td>
<td>unknown</td>
</tr>
<tr>
<td>National scale-up estimates:</td>
<td></td>
</tr>
<tr>
<td>Number of tests provided</td>
<td>1,114,000</td>
</tr>
<tr>
<td>Number of expected new ART-initiates</td>
<td>31,563</td>
</tr>
<tr>
<td>Total annual cost</td>
<td>$2,825,569</td>
</tr>
</tbody>
</table>

**1081 COST-EFFECTIVENESS AND NATIONAL IMPACT OF INDEX HIV SELF-TESTING IN MALAWI**

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**Background:** Testing sexual partners of HIV-positive individuals (index testing) remains a high-yield testing strategy. The secondary distribution of HIV self-testing (HIVST) kits for index testing is highly acceptable in Malawi and promises to increase testing coverage. To assess the cost-effectiveness (CE) and feasibility of index HIVST, we modeled the cost per index partner tested positive and cost per newly confirmed positive (defined as a positive test at the health facility) for HIVST and for the current standard of care, partner referral slips (PRS), as well as the cost and impact of HIVST national scale-up.

**Methods:** A decision analytic model was parameterized using data collected as part of a randomized trial comparing uptake of HIVST to PRS among partners of antiretroviral therapy (ART) clients at 3 district hospitals in Malawi. Clients were randomized 1:2 to standard PRS or HIVST (Oraquick HIV Self-Test: demonstration and distribution). Baseline and follow-up surveys with ART clients were conducted. CE was measured as the cost per newly confirmed positive (index partner) and was calculated for HIVST (including cost of HIVST kit ($52), counselling, confirmatory testing) and PRS (cost of referral slip, counselling, and standard facility-based testing) divided by the total number of positives newly aware of their status and facility-confirmed positives. Model outputs were applied to national facility-level data on number of HIV tests from PRS to determine potential national increase in new diagnoses and related costs for index HIVST scale-up.

**Results:** The cost per index patient was $0.85 per PRS and $2.34 per HIVST provided and $3.08 and $3.17 per test completed, respectively. The cost per person newly aware of positive status was $19.27 for PRS and $16.14 for HIVST respectively. The cost per facility-confirmed positive was $84.53 for index HIVST due to low facility linkage. For national scale-up, 146,785 new positives were identified in Malawi in 2017. 126,949 PRS were given to reach 6,023 new index positives, costing an annual $91,404. National scale-up of index HIVST in place of PRS would increase the number of people newly aware of their positive status by 8% per year nationally (17,545) at an annual cost of $401,795.

**Conclusion:** Index HIVST is less expensive per person newly aware of their positive HIV status than PRS but more expensive per facility-confirmed positive.

Interventions to improve facility linkage should be investigated prior to national rollout.

### Table 1. Cost and impact of HIVST for index testing compared to partner referral slips in Malawi

<table>
<thead>
<tr>
<th>Index testing modality</th>
<th>PRS</th>
<th>HIVST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per referral through index client</td>
<td>$0.85</td>
<td>$2.34</td>
</tr>
<tr>
<td>Cost per test completed</td>
<td>$3.08</td>
<td>$3.17</td>
</tr>
<tr>
<td>Cost per person newly aware of positive status</td>
<td>$19.27</td>
<td>$16.14</td>
</tr>
<tr>
<td>Cost per newly confirmed positive</td>
<td>$84.53</td>
<td>$84.53</td>
</tr>
</tbody>
</table>

**1082 THE COST OF PrEP DELIVERY IN KENYAN ANTENATAL, POSTNATAL, AND FAMILY PLANNING CLINICS**

Allen Roberts1, Ruane V. Barnabas2, Felix Abuna3, Harrison Lagat4, John Kinuthia5, Jillian Fintye1, Aaron Bochner5, Jared Baeten5, Grace John-Stewart1, Carol Levine1

1University of Washington, Seattle, WA, USA, 2University of Washington in Kenya, Nairobi, Kenya

**Background:** Integrating PrEP provision through routine ante-/post-natal care (ANC/PNC) and family planning (FP) clinics is a potential strategy for efficient PrEP delivery to women in high HIV burden settings. The cost of delivering PrEP through ANC/PNC and FP clinics is unknown.

**Methods:** We estimated the incremental economic cost of PrEP delivery from the provider perspective within the PrEP Implementation for Young Women and Adolescents (PrIYA) program in western Kenya. We abstracted program data from November 2017 to June 2018 in 16 facilities and estimated annual numbers of PrEP screening and dispensation visits. We identified all within- and above-facility activities supporting PrEP delivery and measured clinical service time using time-and-motion studies. We obtained input costs from program budgets, expenditure records and staff interviews. We also projected costs under Ministry of Health (MOH) implementation assuming MOH salaries and PrEP supervision by county and sub-county health teams. Under this scenario, we explored the impact of task shifting PrEP screening to HIV counsellors, deferring creatinine (Cr) testing from initiation to first follow-up visit, and varying uptake (proportion of counseling encounters that result in PrEP initiation) and continuation (average number of follow-up visits among returning clients) on program costs. We report the cost per client-month of PrEP dispensed in 2017 USD.

**Results:** For an annual program output of 24,005 screenings, 4198 PrEP initiations, and 4427 follow-up visits, the average cost per client-month was $27. Personnel, drugs, and lab tests comprised 43%, 25%, and 14% of program costs, respectively. In the MOH scenario assuming no changes in outputs, the projected cost per client-month of PrEP dispensed reduced to $17, with drugs (41%), personnel (33%), and lab testing (15%) accounting for the majority of costs. Deferring Cr testing and task shifting PrEP counseling reduced projected costs by 5% and 8%, respectively. Halving both PrEP uptake and continuation lowered the cost to $13.

**Conclusion:** The cost of PrEP delivery through ANC/PNC and FP was similar to costs reported for delivery to other key populations ($11-54 per client-month). Streamlining service delivery and increasing volume may reduce unit costs. Empirical cost data on PrEP is essential for program planners to assess the cost-effectiveness and affordability of scaling up PrEP.
1083 COST-EFFECTIVENESS OF PREEXPOSURE PROPHYLAXIS AMONG ADOLESCENT SEXUAL MINORITY MALES

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1CDC, Atlanta, GA, USA, 2University of Toronto, Toronto, ON, Canada, 3Johns Hopkins University, Baltimore, MD, USA, 4University of Washington, Seattle, WA, USA, 5Emory University, Atlanta, GA, USA

Background: The U.S. Food and Drug Administration recently approved pre-exposure prophylaxis (PrEP) for adolescents at high risk of HIV infection, but it remains unknown whether this is a cost-effective intervention for adolescent sexual minority males (ASMM) generally or for certain highest-risk subgroups. Building on a recent network modeling study of PrEP among ASMM, we estimated the cost-effectiveness of PrEP use in black and white ASMM in higher prevalence US settings.

Methods: Based on the estimated number of infections averted and the number of ASMM on PrEP from the previous model and published estimates of PrEP costs, HIV treatment costs, and quality-adjusted life years (QALY) gained per infection averted, we estimated the cost-effectiveness of PrEP use in black and white ASMM over 10 years using a societal perspective and lifetime horizon. Effectiveness was measured as lifetime QALYs gained. Cost estimates included 10-year PrEP costs and lifetime HIV treatment costs saved. Cost-effectiveness was measured as cost per QALY gained. For our base-case analysis, we considered PrEP for 16-18-year-old ASMM, initiating PrEP 6 months after first anal intercourse, 40% coverage, adherence profiles from the ATN113 trial, and estimated baseline prevalence of 12.4% and 1.4% among black and white 18-year-old ASMM respectively. Multiple sensitivity analyses were performed to assess robustness of the results to uncertainty in the input parameter values and assumptions used.

Results: Under base-case assumptions, PrEP use would yield a cost-effectiveness ratio (CER) of $33,064/QALY in black ASMM and $427,788/QALY in white ASMM. In all PrEP scenarios considered (2 eligibility criteria, 5 coverage levels, 2 adherence profiles), the CER ranged from $10,461/QALY-$45,997/QALY in black ASMM, and $372,306/QALY-$603,887/QALY in white ASMM. In 95% of 10,000 simulation trials of the multivariate sensitivity analysis, the CER of the base-case PrEP scenario ranged from cost-saving to $69,404/QALY in black ASMM and ranged from $170,305/QALY-$538,881/QALY in white ASMM. PrEP use was cost-effective (<$100,000/QALY) in black ASMM but not cost-effective in white ASMM in all scenarios considered. This difference was mainly driven by the difference in the underlying prevalence.

Conclusion: PrEP use in higher risk ASMM can be a cost-effective HIV prevention intervention at current PrEP drug costs. Clinicians should consider black ASMM a priority group for PrEP access among adolescents.

1084 EPIDEMIC IMPACT OF SUSTAINED VIREMIA AMONG FEMALE SEX WORKERS IN SOUTHERN AFRICA

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1University of Toronto, Toronto, ON, Canada, 2St. Michael’s Hospital, Toronto, ON, Canada, 3Johns Hopkins University, Baltimore, MD, USA, 4University of the Western Cape, Cape Town, South Africa, 5TB/HIV Care Association, Cape Town, South Africa

Background: Key populations including cisgender female sex workers (FSW) face barriers that undermine broader programmatic efforts to achieve viral load suppression among people living with HIV. We estimated the potential onward transmissions that could stem from a failure to achieve viral load suppression among FSW living with HIV. We estimated the potential onward transmissions from sustained viremia among FSW living with HIV from 2016 onwards.

Results: Simulations reproduced the observed range of HIV prevalence and HIV cascade indicators over time, such that by 2016, overall HIV prevalence across epidemic realizations was 18-32% and FSW HIV prevalence was 43-76%. The model reproduced observed ART coverage: 49-90% among reproductive-age women compared with 20-40% among FSW living with HIV, and between 8-25% of FSW living with HIV were virally suppressed. From 2016 onwards, a failure to achieve viral load suppression among FSW could contribute to 7-12%, 26-34%, and 15-46% of cumulative HIV transmissions in the wider population over the subsequent 1, 10, and 20 years (Figure). After adjusting for current proportion of FSW who are virally suppressed, the tPAF was highest in settings with increasing HIV incidence among FSW, high turn-over in sex work; and larger number of non-paid partnerships among FSW.

Conclusion: Across the broadly generalized epidemics of Southern Africa, a failure to prevent HIV among FSW or to meet the treatment needs of FSW living with HIV could contribute to a large proportion of onward transmissions, and undermine existing efforts of achieving local epidemic control.

1085 ESTIMATING HIV INCIDENCE AMONG YOUNG WOMEN IN HPTN 082 USING BASELINE HIV RISK SCORES

James R. Moore1, Deborah J. Donnell2, Marie-Claude Boily3, Kate M. Mitchell2, Sinead Delany-Moretlwe1, Connor L. Celum2, Dobromir Dimitrov2
1Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 2Imperial College London, London, UK, 3Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, 4University of Washington, Seattle, WA, USA

Background: Pre-exposure prophylaxis (PrEP) is highly efficacious for prevention of HIV acquisition, but adherence to PrEP remains a major barrier. HPTN 082 is testing strategies to support PrEP adherence in young African women. A mathematical modelling approach is used to predict HIV incidence in the absence of PrEP among HPTN 082 participants, using the previously validated VOICE risk score and baseline sexual activity data from HPTN 082. This predicted incidence will provide a counterfactual to estimate PrEP effectiveness in this population.

Methods: The VOICE risk score (5-10, with 10 the highest risk score) is calculated for each woman based on baseline factors including age, marital status, financial stability, STIs, and alcohol usage. Using these data and self-reported sexual behavior not included in the risk score, we developed a Markov chain model of partnership formation, sexual behavior, and HIV transmission and...
used it to predict HIV incidence in the absence of PrEP. The model is calibrated using reported sexual activity, incidence data from the VOICE trial, and epidemiological data from the 2012 South African National HIV survey.

Results: HPTN 082 enrolled 451 African women ages 16-25 with a median VOICE risk score of 7. 15% (68) reported anal sex in the last month, 30% (115) reported multiple partners in the last three months, and 49% (221) had a partner with unknown HIV status. Without PrEP, we predict an HIV incidence of 9.9% (95% CI 8.9-10.9), ranging from 6.3% (5.7-7.8) in women with a risk score of 5 to 21.5% (18.2-24.6) in women with a risk score of 10. Increased incidence at higher risk scores could be due to self-reported differences in sexual behavior. The remaining increase in incidence was attributed by the model to higher partner HIV prevalence. For example, women who did not live with their main partner were more likely to have multiple partners (OR=2.3, 95% CI 1.7-3.4) but also more likely to use a condom (OR=2.2, 95% CI 1.4-3.4). The model inferred a greatly increased HIV prevalence among their partners (OR=6.2, 95% CI 3.1-12.6).

Conclusion: HPTN 082 recruited a cohort of young African women who had multiple risk factors and would benefit from PrEP, given the predicted HIV incidence of 9.9%. These predictions will allow us to evaluate the effectiveness of PrEP stratified by VOICE risk score using an objective measure of adherence (tenofovir levels) from HPTN 082.

VOCAL § 1086 A MATHEMATICAL MODELING ANALYSIS OF COMBINATION HIV PREVENTION IN ANTENATAL CLINICS

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1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2University of Zambia, Lusaka, Zambia

Background: Given high HIV acquisition risk and increased healthcare engagement during pregnancy, antenatal clinic (ANC) settings in sub-Saharan Africa present major opportunities for HIV prevention. Despite demonstrated success in reducing mother-to-child HIV transmission, few ANC-based programs have considered interventions to prevent horizontal HIV transmission and acquisition among pregnant women and their sexual partners. We hypothesized that combination HIV prevention strategies anchored in ANC settings could substantially reduce HIV incidence among ANC patients, their partners, and their infants.

Methods: We constructed a mathematical model describing horizontal and vertical HIV transmission during pregnancy within patient-partner and patient-infant dyads, respectively. We based biological and behavioral inputs on literature estimates and ANC program data from Malawi and Zambia. We modeled three main HIV prevention strategies, alone and in combination, by varying: 1) male partner HIV testing from a base-case value of 15% to a target of 35%; 2) suppressive antiretroviral therapy (ART) for HIV-positive ANC patients and partners from a base-case of 70% to a target of 90%; and 3) adherent pre-exposure prophylaxis (PrEP) use for HIV-uninfected female ANC patients from a base-case of 0% to a target of 20%. Using the model, we estimated the percentage of horizontal and vertical HIV infections that could be averted with these strategies, relative to the current (base-case) scenario.

Results: Increasing male partner testing to 35% coverage was predicted to reduce horizontal and vertical transmissions by 16.7% and 15.1%, respectively (scenario 2, Table); corresponding reductions with 20% female PrEP use were 13.4% and 12.1% (scenario 4). Jointly increasing coverage of both interventions by 20 percentage points was predicted to reduce horizontal and vertical transmissions by one-quarter (scenario 7); this reduction increased to one-third with a combination of these two interventions plus increasing suppressive ART (scenario 8). Across scenarios, a 20-percentage-point increase in suppressive ART for HIV-positive patients and partners had only a modest incremental impact (scenarios 3 vs. 1, 5 vs. 2, 6 vs. 4, 8 vs. 7).

Conclusion: Our modeling suggests that combination HIV prevention in ANC settings – particularly approaches that increase male partner testing and female PrEP use – could substantially reduce HIV incidence among pregnant women, their partners, and their newborns in sub-Saharan Africa.
1088 SIMULATED VACCINE EFFICACY TRIALS TO ESTIMATE HIV INCIDENCE IN KEY POPULATIONS

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1London School of Hygiene & Tropical Medicine, London, UK; 2MRC UVRI and LSHTM Uganda Research Unit, Entebbe, Uganda; 3International AIDS Vaccine Initiative, New York, NY, USA

Background: We aimed to evaluate the potential impact of strategies to prevent HIV infections among high-risk populations. This study used a validated model to simulate the impact of simulated vaccine efficacy trials (SVETs) in key populations in Africa and the USA.

Methods: SVETs were nested in two observational cohorts, in FF (Jul 2012–Apr 2014) and FSW (Aug 2014–Apr 2017). When observational cohort participants presented for quarterly visits (3–18 months) they were consecutively screened for enrolment into SVET. Eligibility was: age 18–49 years, HIV negative; at high risk of HIV infection; no history of severe allergic reaction to any substance. Those not enrolled continued participation in the observational cohort. In addition to procedures (HIV testing & risk assessment) in the observational cohorts, SVET participants were given a licensed Hepatitis B vaccine following a standard schedule of 0, 1 and 6 months, mimicking a schedule of an HIV vaccine efficacy trial. HIV testing was carried out quarterly for one year.

Results: In total, 3989 participants were enrolled into the observational cohorts. Of these 3622 (90.8%) returned at least once and 1525 (42.1%) were enrolled into SVET. HIV incidence in the observational cohorts pre SVET was 4.5/100 person years at risk (PYAR), 95%CI: 3.8–5.5 [FF=4.9 (3.9–6.2); FSW=4.0 (2.9–5.5)]. When a subset of participants was enrolled into SVETs, the HIV incidence at 12 months was lower in SVETs, 3.5/100 PYAR, 95%CI: 2.2–5.6 [FF=3.8 (2.7–7.1); FSW=3.2 (1.5–6.6)] compared to 5.9/100 PYAR, 95%CI: 4.3–8.1 [FF=8.3 (5.6–12.4); FSW=4.1 (2.5–6.7)] in the observational cohorts’ concurrent period, p<0.034. Compared to observational cohorts, SVETs recruited more men, older participants, long-term residents and non-users of illicit drugs, all previously associated with lower HIV risk.

Conclusion: HIV incidence was generally higher in these observational cohorts before and concurrent to SVET than in the SVET participants. This difference was greatest among FF. Researchers designing HIV efficacy trials using observational cohort data need to consider the potential for lower than expected HIV incidence following screening and enrollment.

1089 THE PROJECTED AGE DISTRIBUTION OF WHITE, BLACK, AND HISPANIC MSM ON ART, 2009–2030

Parastu Kasaie1, Elizabeth Humes1, Stephen J. Gange1, Amy C. Justice1, Kelly Gebo2, Cynthia Boyd2, Emily P. Hyle2, Carolyn Williams3, Jinbing Zhang1, Raquel Cruz-Stratton1, Robert S. Hogg4, Mari Kitahata3, Richard D. Moore3, Keri N.

Methods: We estimated the age distribution of HIV-infected MSM on ART in the US using a national surveillance dataset (NA-ACCORD) and human aging and disease progression models. We performed sensitivity analyses to test the robustness of our findings.

Results: From 2009 to 2015, the age distribution of MSM on ART shifted toward older ages, with the most significant increases seen among Hispanic MSM. The largest age group of older MSM on ART was among Black MSM, with a bimodal distribution peaking in the 45–54 and 55+ age groups. The median age of MSM on ART increased from 38.1 years in 2009 to 47.7 years in 2015.

Conclusion: The shift in the age distribution of MSM on ART is likely due to increased testing and treatment among older populations. This trend is expected to continue into 2030, with the majority of older MSM on ART being Black or Hispanic. However, the age distribution of MSM on ART is expected to remain more diverse, with younger MSM on ART also increasing over time.

Background: The age distribution of MSM on ART is an important factor in understanding the effectiveness of HIV prevention and treatment efforts. As the age distribution of MSM on ART continues to shift, it is crucial to develop targeted HIV prevention and treatment strategies for younger and older populations.
relationship durations) and age-specific herd immunity (ASHI) that protects adolescents entering the sexually active population. In sensitivity analyses, we found ASHI was the biggest driver of the success of age-based TasP. Over time, ASHI gives rise to an ever-expanding “AIDS-free generation” that drives HIV to extinction.

**Conclusion:** As testing rates increase in response to UNAIDS 90-90-90 goals, we suggest that efforts to link all young people to care and treatment could be an effective long-term strategy for ending the HIV epidemic. Youth focused treatment will be particularly important in low and middle income countries with demographic ‘youth bulges’ that are increasing the number of young people at risk for infection.

**1090 YOUTH-FOCUSED HIV TREATMENT-AS-PREVENTION YIELDS LARGE BENEFITS: A SIMULATION MODEL**

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**Background:** Despite increasing availability of Antiretroviral therapy (ART), heterosexual HIV-1 epidemics like those in sub-Saharan Africa continue to have high incidence in young people. ART for youth has the potential to protect their partners who also tend to be younger and at high risk. We hypothesized that focusing HIV interventions on youth could enhance the efficiency of treatment as prevention (TasP) campaigns in resource limited settings.

**Methods:** We used an agent-based network model that includes behavioral and clinical data from multiple sources to examine the effect of targeting different risk groups for linkage to HIV-related treatment services in a heterosexual population. The model accounts for age-based risk factors including the tendency for younger women to partner with older men. We used the model to identify strategies that reduce incidence to negligible levels 20-25 years after initiation of a targeted TasP campaign.

**Results:** Under random allocation or CD4-based targeting, our model predicts a TasP campaign would need to suppress viral replication in 70-80% of infected people to halt the epidemic. Under age-based targeting, by contrast, this percentage drops to 40%-60% (for strategies targeting those <30 and <25 years old, respectively) (Figure 1). Age-based targeting also minimized both total and time-discounted AIDS deaths after 25 years. Age-based targeting did not need to be highly exclusive to yield benefits; e.g. in a model in which 50% of infected people were treated, the majority of those people receiving therapy during a campaign targeting those <30 fell outside the target group. Sensitivity analyses varying background incidence yielded qualitatively similar benefits. Age-based TasP is beneficial due to age-related risk factors (e.g. shorter

**1091 WHO IS LEFT IN 10-10-10? IMPORTANCE OF REACHING KEY POPULATIONS WITH THE HIV CASCADE**

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**Background:** Achievement of the UNAIDS 90-90-90 targets for HIV cascade of care (90% of infected are diagnosed, 90% of diagnosed are on treatment, 90% of those on treatment are virally suppressed) by 2020 is predicted to end the AIDS pandemic by 2030. We sought to determine the influence of heterogeneity across the remaining 10-10-10 on the epidemic features after the UNAIDS targets are achieved in a high-prevalence HIV epidemic in Southern Africa.

**Methods:** We built a deterministic mathematical model of heterosexual HIV transmission to simulate a high-prevalence epidemic in a Southern African context (using demographic health survey and female sex worker (FSW) survey data from eSwatini and South Africa). The model includes 6 different populations at risk for HIV, 4 sexual partnership types; and the HIV cascade (undiagnosed, diagnosed, on ART, and virally suppressed), Figure 1 (a-b). The model simulates observed HIV prevalence ratios by risk group, and trends in cascade of care to 2017. We then compared two scenarios where A) 90-90-90 is achieved in all populations, including FSW; B) 90-90-90 is achieved in the overall population, but not among FSW - and
estimated the relative difference in cumulative HIV incidence between 2020 and 2030.

**Results:** By 2017, the modeled HIV prevalence was 17% overall (total population, including FSW), and 43% among FSW. Under Scenario A, HIV incidence declines to 0.59 per 1000 person-years by 2030. Scenario B (90-90-90 reached in the overall population) is actually achieved if the 2017 rates of testing and treatment are maintained, however the cascade among FSW only reaches 81-60-83 by 2020. As a result, incidence only declines to 1.22 per 1000 person-years by 2030, and the model projects a 60% increase in cumulative new infections in the total population between 2020 and 2030 versus Scenario A.

**Conclusion:** Heterogeneity in HIV transmission risks across the 10-10-10 could undermine the projected impact of achieving 90-90-90 across the Southern African region. Efforts to meet and surpass UNAIDS targets among key populations such as FSW and their clients should be prioritized to maximize incidence reductions and achieve pandemic control by 2030.
2008  NASH IN HIV

Giada Sebastiani, McGill University Health Centre Research Institute, Montreal, QC, Canada

Nonalcoholic fatty liver disease has become the most frequent liver disease in the aging HIV-infected population, with a prevalence at 35%. Its severe form, nonalcoholic steatohepatitis (NASH), is found in 65% of HIV mono-infected patients with chronic elevation of transaminases, which is a frequent occurrence in the practice of HIV medicine. A complex multifactorial pathogenesis, including frequent metabolic comorbidities, lifelong use of antiretroviral therapy and HIV itself, is thought to drive this epidemic. Early diagnosis, preventive and therapeutic strategies may help reduce the burden of NASH in people living with HIV.

2009  RETREATMENT OF HCV IN ADVANCED LIVER DISEASE

John D. Scott, University of Washington, Seattle, WA, USA

Dr Scott will discuss the retreatment of HCV in patients with advanced liver disease. Please see the overview for the Interactive Case-Based Workshop on Hepatitis for a full description of the session.
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