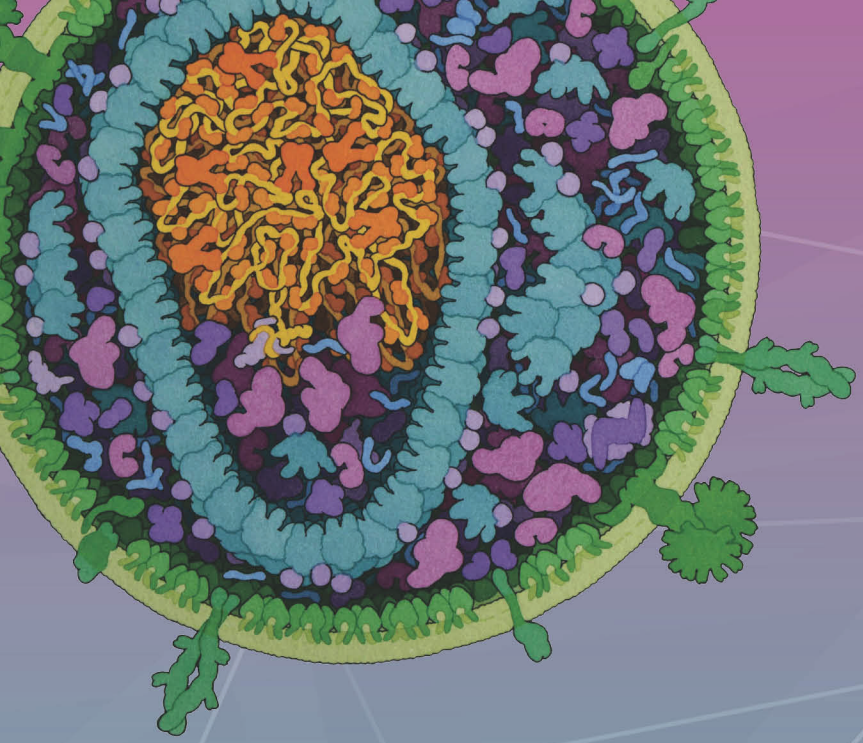

CROI 2024

Conference on Retroviruses and Opportunistic Infections

March 3-6 | Denver, Colorado

ABSTRACT eBOOK

IAS–USA
International Antiviral Society–USA

Version 3 | Updated March 15, 2024

CONTENTS

Version 3 | Last Updated on March 15, 2024
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ISBN #978-0-692-64664-9

ABSTRACT PROCESS

Scientific Categories

Basic Science

- **A.** Virology of HIV, SARS-CoV-2, or Mpox Virus
- **B.** Pathogenesis of HIV, SARS-CoV-2, or Mpox Virus: Human Studies and Animal Models
- **C.** Host Immune Responses, Vaccines, and Immunotherapies: HIV, SARS-CoV-2, or Mpox Virus
- **D.** HIV Reservoirs, Latency, and Curative Strategies Including Therapeutic Vaccines and Gene Therapy
- **E.** Neuropathogenesis and Neurologic Complications of HIV and SARS-CoV-2 Infection and Neurologic Complications of HIV in Adults

Clinical

- **F.** Clinical Pharmacology in Adults
- **G.** Antiviral Therapy: Pre-Clinical Data, Randomized Trials, Efficacy, and Effectiveness Studies in HIV or SARS-CoV-2 or Mpox Virus in Adults
- **H.** Resistance of HIV or SARS-CoV-2 to Small Molecules and Antibodies in Adults
- **I.** Hepatitis Viruses and Liver Complications in Adults
- **J.** HIV-Related Malignancies and Tumor Viruses
- **K.** Cardiovascular Complications of HIV Infection and Antiretroviral Therapy
- **L.** Other Complications of HIV Infection and Antiretroviral Therapy in Adults
- **M.** Clinical Manifestations and Outcomes of SARS-CoV-2, Including Long COVID, and Mpox Infections
- **N.** Tuberculosis and Other Opportunistic Infections, Including the Impact of HIV or SARS-CoV-2 in Adults
- **O.** Maternal and Fetal HIV, SARS-CoV-2, and Mpox Virus
- **P.** Childhood and Adolescent HIV, SARS-CoV-2, or Mpox Virus

Epidemiology/Public Health

- **Q.** Epidemiology of HIV, COVID-19, and Mpox
- **R.** Testing for HIV, COVID-19, and Mpox in Adults: New Tests, Population Studies, and Scale-Up s
- **S.** Prevention of HIV, COVID-19, and Mpox in Adults
- **T.** Contraception, Sexually Transmitted Infections, and Reproductive Health in Adults
- **U.** Implementation and Scale-Up of Prevention and Treatment for HIV, and Impact of COVID-19 and Mpox on HIV-Related Programs

For more information, visit the CROI Abstract Categories webpage. Note, abstracts that were submitted in categories designated with the letters C, S, U, and W were integrated into other categories.

Example citation:

Smith I, Jones RM, Peters S, et al. Randomized controlled trial in HIV infection [CROI Abstract 1261]. Abstracts From CROI 2024 Conference on Retroviruses and Opportunistic Infections. CROI 2024 Abstract eBook. 2024;583.

Note: These abstracts were current at the time they were submitted, which may have been months before the start of CROI. For the most up-to-date data, please view the posters and oral abstract presentations on the conference app.

To search for specific word or term, presenters, or authors on this document, hold the "Ctrl" and press the "F" keys on your keyboard to prompt a word search.

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Abstract Numbering: Presentation summaries for invited sessions begin with abstract 1. Oral abstracts begin at abstract 100. Poster abstracts begin at 300. Abstract numbers 51 to 99 and 213 to 299 were intentionally omitted to accommodate this numbering. Similarly, abstracts that were withdrawn are marked as such next to their preserved number.

Abstract Content

Author names, institutions, titles, and abstracts in the CROI Program Guide, Abstract eBook, Conference App, and other materials are presented largely as provided by the submitting author. THE SUBMITTING AUTHOR IS RESPONSIBLE FOR ENSURING THAT ALL COAUTHORS HAVE REVIEWED AND APPROVED THE ABSTRACT before submission and for providing complete and accurate contact information for all authors, including email addresses. .

Requirements for Abstract Content

Study Design: Presentations from randomized trials and cohorts should follow the ICMJE guidelines, including reporting of study designs (eg, prospective, observational, randomized, double-blind, STROBE, CONSORT, or others), statistical methods, and outcomes by demographic variables. Please also note whether the study is ongoing or completed and whether the results are preliminary or final.

Figures and Tables: Figures, tables, or other illustrations that exceeded the abstract submission guidelines were removed from the submitted abstract and are not included in the Abstract eBook. For examples and for additional information on this review process, visit the Common Reasons for Removal webpage.

New Compounds: For abstracts describing new compounds, the chemical or molecular structure must be shown in the presentation. It need not be part of the abstract or be published in the Abstract eBook.

Sex and Gender: Appropriate information and correct terminology should be used with regard to sex and gender. For human clinical or epidemiologic studies, the presentation should provide sex-stratified results or identify who was included if it only included only a single population. Appropriate terminology such as "cisgender" (people whose gender matches the sex assigned at birth) or "transgender" (people whose gender does not match the sex assigned at birth) should be used. Both sex and gender data should be provided in the presentation. Presentations of preclinical data, including the use of cell lines and animal studies should include the sex of the animals or the sex of the source of the cell lines. If data are not available on sex and gender, this should be identified as a limitation in your presentation.

Person-First Language and Appropriate Terminology: CROI strongly advocates for the use of and strives to incorporate "people-first" language and acceptable terminology in all CROI-related materials and presentations. All abstract authors and presenters should apply the following basic principles of appropriate language and terminology including:

- Describe populations as "people, persons, or individuals with HIV" rather than "HIV-infected people, persons, or individuals."
- Do not characterize people by their disease, infection, or condition; instead, use "people who inject drugs,""individuals with cirrhosis," or other similar constructs.
- Out of respect for their contributions to our scientific advances, do not describe people enrolled in research studies or clinical trials as "subjects" or "patients." Acceptable terms include research study or clinical trial "participants" or "volunteers."
- Do not use the term "sterilizing" when referring to HIV cure; it triggers a negative perception in many people due to historic sterilization campaigns and may discourage participation in research.

Abstract Review Process

For more information, visit the Abstract Guidelines and Submission webpage.

Statistics for Abstracts

General Abstracts Submitted	1682
General Abstracts Accepted	966
Late-Breaking Abstracts Submitted	220
Late-Breaking Abstracts Accepted	101
Total Abstracts Accepted	1067
Ora Abstract Presentations	111
Themes Discussion Presentations	54
Poster Presentations	956

Accepted Abstracts for Emerging Infections or Specific Populations

SARS-CoV-2	193
Mpox	33
Adolescents	137
Men who have sex with men (MSM)	220
People Who Inject Drugs (PWID)	84
Transgender Men or Women	84
Women or girls	259

Please note: Figures, tables, or other graphics have been removed from the following abstracts due to noncompliance with the CROI Abstract Guidelines: 121, 133, 136, 175, 195, 209, 319, 336, 339, 345, 349, 359, 388, 424, 442, 490, 507, 510, 511, 530, 531, 534, 538, 549, 554, 557, 559, 561, 573, 594, 596, 602, 618, 629, 632, 658, 661, 662, 670, 694, 714, 721, 722, 726, 736, 741, 745, 761, 762, 764, 778, 781, 782, 794, 796, 803, 807, 812, 813, 824, 826, 843, 845, 860, 901, 923, 928, 947, 952, 968, 991, 1005, 1009, 1032, 1037, 1046, 1069, 1072, 1077, 1086, 1090, 1095, 1097, 1104, 1119, 1124, 1145, 1146, 1148, 1162, 1169, 1172, 1179, 1186, 1197, 1205, 1212, 1224, 1225, 1240, 1248

INVITED SESSION PRESENTATION SUMMARIES

1 **Overview of the Scott M. Hammer Workshop for New Investigators and Trainees**

Serena S. Spudich[1], Katharine J. Bar [2]
[1] Yale University, New Haven, CT, USA, [2]University of Pennsylvania, Philadelphia, PA, USA

Background: Over the past four decades, remarkable progress has been made in understanding HIV epidemiology, pathogenesis, treatment, and prevention from the combined efforts of community members, clinicians, investigators, and funding agencies worldwide. Yet more work and new approaches are needed to achieve the ambitious goal of ending the epidemic and ensuring optimal quality of life for those living with HIV. To encourage and stimulate the next generation of investigators, the CROI Program Committee organizes an annual Workshop for New Investigators and Trainees comprised of expert and comprehensible talks to introduce key topics in basic, clinical, and public health investigation into HIV and related infections and to highlight relevant work to be presented over the ensuing days at CROI. This year, the program will begin with a presentation by **Mr Adam Castillejo**, an advocate and activist who will provide a community perspective on HIV cure. **Dr Frank Kirchhoff** will provide an overview of the molecular virology of HIV-1 and SARS-CoV-2 and describe key related presentations at CROI. **Dr Elizabeth Connick** will cover the immune responses against HIV and SARS-CoV-2. **Dr Afam A. Okoye** will review advances in preclinical and clinical approaches for HIV remission or eradication. Dr LaRon E. Nelson will address advances in different strategies for preventing HIV transmission. **Dr. Jennifer Jao** will provide an overview of key topics in maternal-child HIV and highlight relevant work presented at CROI. The workshop will end with a presentation by **Dr Jeanne M. Marrazzo**, Director of the National Institute of Allergy and Infectious Diseases at the NIH, who will discuss opportunities in and provide insights on careers in research and discovery, reflecting on her personal career journey to date. By completing the workshop, attendees will have achieved a head start toward maximizing the knowledge gained and research ideas as they navigate CROI 2024.

2 **Cryoelectron Microscopy-Based Polyclonal Epitope Mapping (cryoEMPEM)**

Gabriel Ozorowski
The Scripps Research Institute, La Jolla, CA, USA

Background: Electron microscopy polyclonal epitope mapping (EMPEM) is a powerful technique for rapidly mapping the epitopes of serum antibodies and providing a visual readout of immune responses. EMPEM is performed using blood samples from immunized animal models, human volunteers, or convalescent patients of recent viral infection. Recently, our group has applied high resolution cryoEM methods to the same samples (cryoEMPEM) to visualize the amino acid interactions between antibodies and antigen. This approach can also be used to predict the sequences of the observed antibodies. By integrating NGS data of B cell repertoires with cryoEMPEM data, we are able to rapidly identify and provide unprecedented molecular resolution of epitope specific polyclonal antibody responses. EMPEM studies are complementary to traditional serological approaches, which altogether inform on the types of epitopes targeted, the diversity of epitopes targeted, and the consistency of epitopes targeted between study volunteers. When applied to HIV vaccine research, the molecular details revealed by this approach can confirm whether epitope specific, on-target antibodies are present in the sera and if they contain any structural and genetic features of known broadly neutralizing antibody precursors.

3 **A Spotlight on HIV: Visualizing Post-Entry Events by Correlative Light and Electron Microscopy**

Barbara Müller
University Hospital Heidelberg, Heidelberg, Germany

Background: The post-entry phase of HIV-1 replication - from cytosolic entry of the viral capsid encasing the genomic RNA to the integration of the reverse transcribed viral cDNA into the host cell genome - has long represented an enigmatic part of the viral replication cycle. During this phase, subviral particles need to undergo a complex sequence of transitions in composition and structure, which is challenging to unravel using traditional bulk virological and biochemical approaches. Direct visualization of incoming viral structures in the cytosol by electron microscopy has been hampered by the difficulty to detect and identify rare, small objects with unknown morphology, which are embedded in a vast and complex cytosolic environment of similar electron density. Correlative Light and Electron Microscopy (CLEM) addresses this problem: rare, defined objects of interest are localized within a complex environment via fluorescence-based detection and subsequently analyzed with high spatial resolution using electron microscopic approaches. Today, continuous methodological advancements allow us to analyze the morphology of virus-derived complexes within their intracellular environment in unprecedented detail. Application of this approach to HIV-1 post-entry yielded new insights that, in conjunction with other results, identify the mature capsid as a key organizer of post-entry events. The presentation will introduce the CLEM approach and highlight insights into post-entry events in HIV-1 replication, from the visualization of cytoplasmic reverse transcribing complexes in infected cells approximately 20 years ago to recent high resolution in situ imaging of capsid-like structures in transit through the nuclear pore.

4 **Single-Virus Tracking: Capturing Fast, Three-Dimensional Viral Dynamics in Live Tissue Models**

Kevin Welsher
Duke University, Durham, NC, USA

Background: The epithelium is a nessential first barrier against viral infection. Understanding the interactions that enable pathogens to cross this complex barrier is critical to treating a wide range of diseases, including the recent SARS-CoV-2 pandemic. Single-virus tracking (SVT) is a potentially powerful tool to capture the molecular scale details of viral infection in live cells. SVT typically relies on fluorescence microscopy and can provide different insights from ensemble bulk experiments. However, the reliance on traditional fluorescence microscopy techniques has limited the application of SVT to mono-layer cell cultures with poor temporal resolution upon expansion to three-dimensional tissue models. In this presentation, we will detail current SVT methods and their advantages and limitations. We will then introduce a new active-feedback SVT method for overcoming the current limitations of SVT. This new method, called 3D Tracking and Imaging (3D-TrIm), uses fast, real-time measurement to "lock on" to a single virion and measure its dynamics at kHz or faster sampling rates across large three-dimensional spatial scales in live cells. We will demonstrate how 3D-TrIm captures transient viral contacts with the cell surface with millisecond temporal resolution, and how this new technique can translate SVT from simple monolayer cell culture models to more complex three-dimensional tissue models.

5 **Single-Cell Multi-Omics of HIV Cellular Reservoirs**

Iain C. Clark
University of California Berkeley, Berkeley, CA, USA

Background: HIV persists indefinitely within tissue and blood cell reservoirs, necessitating life-long antiretroviral therapy (ART). Single-cell omics technologies represent a promising approach to understanding cells that harbor provirus, including the unique cell-intrinsic mechanisms that promote cell survival, proliferation, immune evasion, or HIV silencing. However, despite technological advances in single-cell analysis, there are several unique challenges to using these tools in HIV cure research. First, HIV-infected cells are rare in vivo, which necessitates the single-cell sequencing of hundreds of thousands of cells per sample, at great expense. Second, HIV accumulates in heterochromatin and may not express HIV RNA. Methods like scATAC-seq or scRNA-seq therefore only capture HIV+ cells with transcriptionally active

provirus and those in regions of open chromatin. Last, over 95% of HIV provirus in people on long-term ART are defective. Any method that seeks to understand cells with replication-competent virus must first identify the even rarer cell population that contains intact provirus. No technology has yet to address all of these challenges, but in recent years commercial scRNA-seq and scATAC-seq platforms have allowed cure researchers to generate exciting datasets that begin to reveal how HIV persists during effective ART. These datasets, owing to the rarity of HIV+ cells, are large but contain only hundreds of HIV+ cells, presenting additional challenges during bioinformatic analysis and interpretation. Recently, we reported a custom droplet microfluidic technology, FIND-seq, for sorting HIV+ cells. Instead of barcoding every cell in a sample, FIND-seq allows for the isolation of HIV DNA+ cells and is compatible with the intact provirus detection assay (IPDA), which can differentiate many forms of defective provirus. In this talk, I will discuss single-cell analysis technologies, their application in HIV cure research, and the technical advances needed to sequence the replication-competent HIV reservoir.

6 Steatotic Liver Disease in Persons Living With HIV

Jennifer Price
University of California San Francisco, San Francisco, CA, USA

Background: Steatotic liver disease (SLD) is a rising cause of liver-related morbidity and mortality worldwide, including among persons with HIV (PWH). This presentation will review the new nomenclature for SLD, which is predominantly metabolic dysfunction-associated (MASLD) and can overlap with alcohol-related liver injury. We will also review the initial work-up of a patient with SLD and elevated liver enzymes, and we will discuss a stepwise approach to assessing for clinically significant fibrosis using non-invasive tests. Finally, we will review current management of PWH and SLD, including lifestyle modification, adjustment of potentially contributory medications, and pharmacologic interventions.

7 Hepatitis Delta: What to Know, What to Do?

Kathrin van Bremen
University of Bonn, Bonn, Germany

Background: Worldwide, between 12 and 60 million people with chronic hepatitis B (HBV) are estimated to be coinfected with Hepatitis Delta (HDV). HDV infection is caused by a defective RNA virus which is only able to replicate in presence of HBV. Although international guidelines recommend testing of Hepatitis Delta in every person with chronic Hepatitis B-infection, HDV prevalence data and actual numbers are lacking as the testing coverage is poor. There is a wide variation of geographic HDV infection rates with highest prevalence rates in Eastern and central Europe, the Mediterranean basin as well as in West and Central Africa. Hepatitis Delta infection can be prevented through Hepatitis B vaccination, therefore worldwide coverage of Hepatitis B vaccination is indispensable. Shared transmission pathways for HIV, HBV and HDV result in an increased risk for HDV coinfection in persons with HIV (PWH). Recent European data reported HDV prevalence in PWH between 7% and 15%, with the highest rate in people who inject drugs. Interestingly, transmission risks and patterns may be subject to change, as data from Taiwan recently showed an increased HDV incidence in men who have sex with men (MSM). Moreover, increasing migration may also contribute to changes in HDV prevalence. HDV co-infection is known to cause the most aggressive course of liver disease in PWH leading to significantly more liver cirrhosis, hepatocellular carcinoma and eventually an increased rate of liver-related death. Therefore, wide screening coverage is mandatory to detect cases early. With the 2020 European approval of Bulevirtide, a novel entry-inhibitor blocking the HBV-HDV-specific receptor, a new HDV specific drug is now available for treatment of HDV infection as a daily subcutaneous injection. Treatment with Bulevirtide is recommended in persons with HIV/HBV-/HDV-co-infection with compensated liver disease according to EACS guidelines. Recent data have shown a good decline in HDV-RNA and normalization of liver enzymes in PWH which is in the range of HDV treatment responses in HBV/HDV coinfected subjects without HIV. The optimal duration of treatment however, as well as long-term data are still lacking. In conclusion HDV represents a frequently underdiagnosed critical health issue that needs more attention in order to increase HDV diagnosis rate and enable access to new HDV drugs, thereby improving the unfavorable outcome of HDV in HIV/HBV-coinfection.

8 Cirrhosis Management

Mazen Noureddin
Houston Research Institute, Houston, Texas

Background: In our up coming cirrhosis management lecture, we'll cover the diagnosis and management of cirrhosis, with a focus on HIV patients. We'll discuss diagnostic methods, including medical history, physical exams, and advanced tests like liver function and imaging studies. For management, we'll explore lifestyle changes, pharmaceutical options for complications, and the challenges of concurrent HIV and cirrhosis treatment. Our goal is to provide a concise yet comprehensive overview to empower you with the knowledge needed to effectively diagnose and manage cirrhosis, particularly in the context of HIV.

9 Overview of the Case-Based Workshop on Antiretroviral Therapy

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

Background: In this session, Drs. Claudia Cortes and Rajesh Gandhi will present cases to an expert faculty panel from around the world to highlight cutting-edge issues in the care of people with HIV. Topics will include the management of drug-resistant HIV, treating people who are not able to take oral antiretroviral therapy (ART), managing ART during pregnancy, and ART considerations in the setting of HIV/TB coinfection. This fast-paced and exciting interactive session will illustrate current approaches to managing people with HIV and highlight high-priority areas for future research.

10 Exploring Strategies to Measure and Understand Users' Preferences in HIV Prevention and Care

José A. Bauermeister
University of Pennsylvania, Philadelphia, PA, USA

Background: Advances in short- and long-acting pre-exposure prophylaxis (PrEP) and Antiretroviral Therapy (ART) have fueled the need to understand how individuals make trade-offs and competing decisions regarding their preferred PrEP and ART modalities. In this presentation, Dr. Bauermeister provides an overview of the state-of-the-science regarding how HIV researchers have conceptualized and measured users' preferences in HIV prevention and care studies. Dr. Bauermeister will describe key conceptual and methodological approaches to understanding users' preferences and choices, including a discussion on the value and trade-offs between Discrete Choice Experiments (DCEs), Conjoint Analysis (CJAs), and Stated Preference Methods. Using several case studies, Dr. Bauermeister will illustrate how these data may help characterize how users make decisions about HIV prevention and care regimens, inform market segmentation strategies to reach diverse types of potential users, and contribute to the development of more effective, user-centered clinical decision aids for PrEP and ART product selection and counseling. Insights into users' preferences hold significant implications for shaping future HIV prevention and care strategies, ensuring their alignment with user preferences, and ultimately advancing the field towards more tailored and effective interventions.

11 Hybrid Effectiveness Implementation Studies: Unrecognized Challenges and Emerging Directions

Elvin H. Geng
Washington University in St Louis, St Louis, MO, USA

Background: Progress in the HIV response today depends on more than ever of use of rich toolbox of efficacious interventions (e.g., PrEP) with reach, equity, sustainability and quality in the real world. One source reason for existing gaps between identifying efficacious interventions and their use is the is traditional scientific sequence of first efficacy, then effectiveness and finally implementation trials. Hybrid trial designs - studies that seek to study both implementation as well as effectiveness simultaneously - offer important but incompletely realized opportunities to accelerate translational impact. The talk will cover current nomenclature and classification of hybrid trial types (e.g., "Type 1"), highlight current evolution in design and distill key insights that aim to have immediate implications for researchers conducting trials in HIV. In addition, however, I will turn attention to challenges inherent in hybrid designs that seek simultaneous investigation of implementation and clinical outcomes that are to date inadequately addressed. First, current literature in does not fully consider when and how different implementation strategies change observed subsequent clinical effects. I offer principles to help guide determination of relative importance of implementation vs. effectiveness outcomes and the

plausibility of their heterogenous effects across settings or populations. Second, hybrid designs have not fully addressed unanticipated "adverse" effects of implementation. The talk will therefore offer a typology of adverse effects from implementation strategies and ways researchers can capture such effects. Third, literature does not fully explore the role of implementation outcomes act as mediators of the effects of strategies on service delivery or clinical outcomes. I draw from modern epidemiological methods in mediation to highlight opportunities and pitfalls for analysis of hybrid trials, including potential utility of sequential randomization. Looking forward, I suggest that the next generation of hybrid designs can be improved by use of a causal or explanatory theory of how implementation strategies work and that use of causal diagrams can help to surface these mechanistic relationships. Throughout, I illustrate methodological principles with substantive issues importance to HIV field, such as long-acting injectable medications, differentiated service delivery models, HIV self-testing and other areas of contemporary importance.

12 Stopping Clinical Trials Early: When and Why

Sally Hunsberger
National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

Background: Monitoring accumulating data as studies are being performed is important. Data and Safety Monitoring Boards (DSMB) are an independent group of experts, established by the study sponsor, to review accumulating safety and efficacy data. While reviewing interim data, the DSMB may recommend stopping the study for efficacy, futility, harm, or toxicity. A recommendation to stop a study is based on a range of considerations, in this presentation we discuss these considerations. A study is stopped early for efficacy when there is strong evidence that an experimental arm of a study is statistically superior to a comparator arm. In this case, it is important to stop a study so participants and the community can receive the best care as early as possible. Deterrents to stopping a study early include: less data to examine secondary endpoints and subgroups, less safety data/long-term safety data, inconsistent results at end of study due to missing data at the interim analysis. A recommendation to stop a study early for futility can be based on effect size or logistics. Futility can be determined statistically when there is very low probability that there will be a significant result at the end of the study, based on current data and hypothesized future data. Logistical futility could occur if: enrollment is too slow to answer the scientific question while the question is relevant, there is a high dropout rate making the data difficult to interpret, or a lower-than-expected event rate leads to an underpowered study. Statistical errors are of concern when evaluating interim data for efficacy or futility and appropriate statistical procedures are needed. When monitoring for efficacy, it is important to not inflate the α level (the probability of incorrectly concluding the arms of a study are different). When monitoring for futility, it is important to not inflate the β level (the probability of incorrectly concluding the arms are not different). Statistical methods have been designed to appropriately control these errors when evaluating interim data. Stopping a study early is a difficult decision that must take many considerations into account. When recommending stopping a study, a DSMB must carefully balance benefits to study participants against the collective benefits that would be gained by accumulating additional study.

13 Modern Vaccinology: A Legacy of HIV Research

Barney S. Graham
Morehouse School of Medicine, Atlanta, GA, USA

Background: Structure-based vaccine antigen design has been a critical determinant of respiratory syncytial virus and SARS-CoV-2 vaccine success stories. Nucleic acid vaccines and vector-based vaccine delivery have been successfully developed for Ebola and COVID-19. The ability to identify B cell lineages with the capacity for broad neutralization and then target those B cells with novel antigens is being applied to new influenza vaccines. Nanoparticle display is being used for improved influenza, COVID-19, and RSV vaccine designs. Heterologous prime-boost vaccines are now approved for prevention of Ebola. Pseudotyped virus neutralization assays are routinely used to analyze immune responses to high virulence pathogens. Advances in flow cytometry and single cell sequencing have made rapid human monoclonal antibody discovery and repertoire analysis feasible. All of these concepts have common roots in efforts to make an HIV vaccine. Despite 40 years of effort and technological advances we still don't have an HIV vaccine. There are many reasons for this including: 1) rapid establishment of a reservoir of latently-infected cells and infection of immunoprivileged tissues, 2) multiple ways to evade innate immunity, 3) antigenic diversity of infecting strains, 4) genetic variability and rapid T cell immune escape in infected persons, 5) Env conformational evasion of neutralizing antibodies, 6) Env glycan shield against neutralizing antibodies, 7) immunodominance of antigenic sites on Env with low vulnerability to neutralization, 8) paucity of Env targets on virions, 9) mucosal sites of infection, 10) infection of cells critical for induction of immunity, 11) infection of both lymphoid and antigen-presenting Fc-bearing cells, and 12) potential for infection by virus-infected cells as well as cell-free virions. Solving any of these difficult immunological problems creates a potential solution for other infectious and non-infectious diseases. In that respect, despite a small probability of success, working toward successful HIV vaccines has been and will continue to be one of the most productive scientific activities of our time.

14 Reflections on Ending Pediatric HIV: Back to Basics, Confront the Unexpected, Challenge Assumptions

Dorothy Mbori-Ngacha
Formerly with United Nations Children's Fund, New York

Background: Over the past two decades remarkable progress has been made in our efforts to reduce vertical transmission of HIV, thanks to support for and investment in ending AIDS among children. Programmes for preventing the transmission of HIV during pregnancy, birth and breastfeeding have had significant impact and averted an estimated 3.4 million infections in children (aged 0–14 years) since 2000. Nevertheless, with 130 000 [90 000–210 000] new infections occurring among children globally in 2022, we are still off-track towards achieving our global target of eliminating vertical transmission as a public health threat by 2025. Each day in 2022, approximately 740 children became infected with HIV and approximately 274 children died from AIDS related causes, mostly because of inadequate access to HIV prevention, care, and treatment services. In this lecture I will highlight the programmatic developments – taking scientific innovations to scale in policies and programmes - that have underpinned efforts towards the elimination of mother-to-child transmission of HIV over the past decade. The presentation will draw lessons from our past successes and failures in our PMTCT programs and discuss potential approaches to use in addressing the remaining gaps. Key questions that the presentation will reflect on include: Who are we missing in our response? What do we need to do differently to achieve and sustain universal coverage of PMTCT programs? How can we accelerate progress to achieve our 2025 targets? Finally, potential areas for on-going research will be highlighted.

15 Unveiling the Power of Uganda's LGBTIQ Advocacy in Shaping HIV Response and Health Care Access

Frank Mugisha
Sexual Minorities Uganda (SMUG), Kampala, Uganda

Background: Embark on an exploration of Uganda's ongoing battle against state-sponsored homophobia and transphobia, this presentation sheds light on the vital role of LGBTIQ advocacy in shaping the country's HIV response and healthcare access. In the face of eroding rule of law and political repression, discriminatory laws criminalizing consensual same-sex conduct have created an environment of fear and vulnerability. This has resulted in severe consequences, including family banishment, unemployment, and pervasive discrimination, further exacerbated by limited access to targeted healthcare for LGBTIQ Ugandans. Despite commendable achievements, such as thwarting the Sexual Offences Bill 2019 through tireless advocacy, the recent enactment of the Anti-Homosexuality Act 2023 presents a formidable challenge to healthcare access and health-seeking behavior. This presentation delves into the harsh realities confronted by the sexual and gender-diverse community, navigating a landscape deeply entrenched in religious propaganda and community-driven initiatives for change. Join us on this journey as we explore the intricate interplay of policy, legislation, and the lived experiences of the LGBTIQ community, all while striving for progress in healthcare access amidst the alarming prevalence of HIV and STIs in Uganda.

16 What's New in HIV Vaccines: Vaccine-Induced Immune Responses

M. Juliana McElrath
Fred Hutchinson Cancer Center, Seattle, WA, USA

Background: Development of an effective HIV vaccine remains an elusive goal. Yet the search has accelerated, driven by the imperative end HIV and new directions based on promising leads in preclinical and phase 1 clinical trials.

Recent breakthroughs in understanding how broadly neutralizing antibodies interact with their target epitopes on the HIV envelope spike have led to new HIV envelope immunogen designs that may over time provide a path to eliciting these types of antibodies. Also, novel vaccine designs for inducing highly functional CD8+ T cells with antiviral activities. By leveraging new vaccine technologies and delivery systems, and tailored trial designs, we aim to speed up the pace of progress.

17 Shall We Reach Human Papillomavirus Elimination in the Face of Inequity?

Nelly R. Mugo
Kenya Medical Research Institute, Nairobi, Kenya

Background: In the 1950s discovery and implementation of the 'Papsmear' was a game changer and saved millions of women from cervical cancer deaths. Seven decades later, 342,000 women die annually from cervical cancer, the most common human papilloma virus (HPV) infection associated cancer. The scientific world has made great strides in discovery and there is unequivocal scientific evidence of highly effective interventions to prevent, diagnose, and treat human papilloma virus associated diseases. The discovery of a highly effective prophylactic HPV vaccines, sensitive screening and effective treatment interventions led to the 2018 World Health Organization (WHO) call for Global elimination of cervical cancer, a disease almost entirely caused by high risk (hr) HPV infection. An effective vaccine has reduced HPV related morbidities across gender. Countries that have effectively implemented HPV vaccine and screening for pre-cancer lesions have met the threshold for elimination. Global variance in disease burden reflects inequity in access to health care services and challenges in implementation, and countries with high disease burden have low coverage to interventions. HPV self sampling, evidence and adoptation of single dose HPV vaccine are part of innovative strategies to increase uptake of effective interventions. The science world continuous to seek innovative interventions to close the gap to access to effective interventions, with efforts toward therapeutic HPV vaccine, medical therapy for pre-cancer lesions and implementation science. Is Global elimination for HPV infection feasible and does the world have what it takes to make it a Global reality?

18 Neutralizing Antibody Protection: Where Do We Go From Here?

Yunda Huang
Fred Hutchinson Cancer Center, Seattle, WA, USA

Background: The Antibody Mediated Prevention (AMP) trials did not demonstrate HIV prevention efficacy (PE) of the CD4-binding-site-targetting broadly neutralizing antibody (bnAb), VRC01 (10mg/kg or 30mg/kg IV vs. placebo). However, 75% PE was observed against viruses sensitive to VRC01 with an IC_{80} 200 at the estimated time of exposure to a given exposing virus was associated with high PE, validating in humans consistent patterns observed in non-human primate (NHP) challenge studies of different single bnAbs. This knowledge can be applied to predict PE of combinations of long-acting LS-modified bnAbs targeting non-overlapping HIV epitopes. As with combination anti-retroviral-therapy for HIV treatment, combination bnAbs may overcome neutralization resistance and provide more potent coverage for HIV prevention.

19 Germline Targeting Strategies to Get On the Road Again

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Background: It is generally believed that an HIV-1 vaccine should induce broadly neutralizing antibodies (bNAbs), but no vaccine candidate so far has been able to do so effectively. A critical step in the generation of HIV-1 bNAbs is the activation of specific naïve B cells expressing germline antibody precursors that have the potential to evolve into bNAbs. However, envelope glycoprotein (Env) vaccine candidates are generally unable to do so unless specifically modified. Initial germline-targeting vaccine design approaches have focused on VRC01-class B cells named after the first known bNAb of this class. VRC01-class B cells are attractive targets for germline targeting the following reasons: 1) the AMP trial showed that when present at high titer, VRC01 can protect humans from HIV-1 acquisition; 2) VRC01-class bNAbs have been isolated from multiple HIV-1 infected individuals indicating that the human immune system can reproducibly generate such bNAbs; 3) they target the conserved CD4 binding site on HIV-1 Env, limiting the opportunities for viral escape and 4) they have a very specific and distinct genetic signature (a heavy chain derived from VH1-2 combined with a light chain with an unusually short 5 amino acid CDRL3). Three VRC01-class germline-targeting 'priming' vaccine candidates have moved into phase 1 clinical trials (NCT03547245, NCT05471076, NCT04224701). The emerging data from these trials, showing the effective priming of VRC01-class B cells in humans, provide proof of concept that the germline-targeting approach holds much promise. The challenges ahead include the further maturation of these VRC01-class B cells by 'shaping' and 'polishing' immunogens to generate bNAbs. Second, the strategy must be applied to other epitopes as an effective vaccine will likely require the induction of bNAbs against multiple epitopes. New developments in mRNA technology, adjuvant technology, and AI-based immunogen design will accelerate developing germline-targeting vaccination approaches that yield bNAbs.

20 Novel Immunization Strategies to Move on Down the Road

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Background: Progress is being made in the development of HIV Env immunogens with the potential to activate and expand B cell precursors capable of maturing to produce broadly neutralizing antibodies (bnAbs) that could protect against HIV infection. However, such precursors are generally very rare in the human B cell repertoire and must make challenging sets of mutations in their antigen receptors (via somatic hypermutation in germinal centers, GCs) in order to produce bnAbs. In addition, once expanded and matured, these B cells must be driven to differentiate into long-lived plasma cells that can produce high levels of protective circulating antibodies and provide long-lasting protection. These immunological challenges to the development of an HIV vaccine are being tackled by a variety of approaches to formulate engineering vaccine immunogens in a manner that can optimally stimulate the B cell response, amplify GC responses, and promote high titers of output antibody production. This talk will summarize recent advances in the design of nanoparticle immunogens, vaccine dosing schedules that augment the GC response, potent new adjuvants in development, and the use of new vaccine technologies such as mRNA to promote the humoral immune response.

21 Epidemiology of Perinatally Acquired HIV Among Adolescents and Young Adults

Mutsawashe Bwakura-Dangarembizi
University of Zimbabwe, Harare, Zimbabwe

Background: Adolescents (10–19 years) and youth (15–24 years) living with perinatally acquired HIV represent increasing proportions of people living with HIV. Improved access to antiretroviral therapy globally has resulted in children who acquire HIV around the time of birth or through breastfeeding surviving into adolescence. While many are thriving, a significant proportion face several challenges that can affect their long-term outcomes. In particular, poorly controlled HIV disease resulting from suboptimal early regimens and nonadherence, together with the toxicities of some ARV drugs, can predispose them to long-term sequelae including HIV-associated complications and other comorbidities. This talk will be focusing on the state of the epidemic, the global epidemiology and trends of perinatally acquired HIV among adolescents over the years in the different geographical locations. acquired HIV experience poorer HIV-related outcomes compared to younger children and adults with HIV, dying more often and experiencing greater challenges in terms of treatment adherence and staying in care.

22 Historic Evolution of HIV and Mental Well-Being Among Adults Living With Perinatally Acquired HIV

Ezer Kang
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Background: Adults living with perinatally acquired HIV (PHIV) in the United States (US) have experienced key historic epochs of an epidemic since the 1990s. They navigated four lifespan periods – childhood, adolescence, young adulthood, and adulthood - spanning over three decades of the HIV epidemic. This has indelibly shaped the contours of their development and mental health. Influenced by a "complex interplay of individual, social and structural stresses and vulnerabilities" (World Health Organization, 2022), mental health is not merely the absence of mental disorder – it is a state of mental well-being. This paper explores three dimensions of mental well-being – emotional, psychological, and social (Westerhof & Keyes, 2010) - among Black adults living with PHIV in the US, with a focus on their formation in concert with two historic markers – treatment innovation and illness stigma. Drawing from a qualitative study of 20 Black adults living with PHIV in New York City and a select review of the history of pediatric HIV in the US, three dialectic themes will be presented

and aligned with emotional well-being (Terminal Illness vs. Chronic Condition), psychological well-being (Innocence vs Culpability), and social well-being (Visibility vs. Invisibility). These findings suggest that historic narratives of the HIV epidemic, and its many iterations, have enduring effects on individual narratives of mental well-being among a welcomed generation of adults living with PHIV.

23 Cardiometabolic Risks and Complications: Adolescents and Young Adults With Perinatally Acquired HIV

Sahera Dirajlal-Fargo
Ann and Robert Lurie Children's Hospital, Chicago, IL, USA

Background: Antiretroviral therapy (ART) scale-up has dramatically reduced rates of pediatric HIV mortality and morbidity. Children living with perinatally acquired HIV (PHIV) are living through adolescence and well into adulthood, such that adolescents now represent the largest growing population living with HIV. This presentation aims to discuss the literature describing the prevalence of cardiometabolic complications and the research gaps that remain, as well as opportunities to optimize research and care. There are continued challenges in determining the risk of cardiometabolic co-morbidities in adolescents and young adults with PHIV, and their risk factors differ compared to adults with horizontally acquired HIV. Data suggest evidence for subclinical cardiometabolic complications in PHIV in the setting of newer ART and include: 1) Cardiovascular: evidence of functional cardiac abnormalities, subclinical vascular disease and endothelial dysfunction; 2) Metabolic: evidence of alterations in adipose tissues, dyslipidemia and insulin resistance. In addition, previous exposure to thymidine analogues continue to cause increase risk of metabolic complications in this population. Novel techniques available techniques in imaging and omics may help identify early cardiometabolic abnormalities in this population as well as mechanistic pathways. Further studies are needed to understand the long term risk and management strategies in adolescents with PHIV to prevent complications to avoid diabetes and cardiovascular disease.

24 Why Can't We Do Better at Diagnosing Syphilis?

Ina Park
University of California San Francisco, San Francisco, CA, USA

Background: This session will utilize challenging case studies to review methods for syphilis diagnosis, including direct detection, serology (non-treponemal and treponemal tests), molecular diagnostics and point of care testing.

25 The Burgeoning Epidemic of Congenital Syphilis

Angelica Espinosa Miranda
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Background: Congenital syphilis (CS) is transmitted from an infected mother to her unborn child during pregnancy, leading to severe health complications such as stillbirth, miscarriage, infant death, and maternal and infant morbidity. These adverse outcomes can be prevented through timely screening and treatment during antenatal care. The increasing prevalence of CS is associated with several challenges, requiring a comprehensive approach involving improved healthcare infrastructure, enhanced access to antenatal care, strong testing and screening programs, and extensive education initiatives to mitigate the impact on maternal and child health. Addressing the underdiagnosis of syphilis in pregnancy, especially in regions with limited healthcare access, is essential to avoid missed opportunities for screening and early detection. While reliable and accessible syphilis testing during pregnancy, including treponemal and non-treponemal tests, is essential for early detection, challenges may arise due to limited testing facilities, cultural stigma, and the complexity of implementing comprehensive screening programs. Ensuring that infected pregnant women receive timely and appropriate penicillin treatment is another critical measure to prevent CS, as penicillin is the only effective treatment during pregnancy. However, challenges such as limited healthcare access, potential allergic reactions, and penicillin shortages in some countries must be addressed. The stigma surrounding sexually transmitted infections and societal attitudes can discourage pregnant women from seeking testing, treatment, and follow-up care. Therefore, addressing these sociocultural factors is essential to create an environment where pregnant women feel comfortable accessing healthcare services. Despite specific recommendations from the World Health Organization aligned with sustainable development goals, CS remains a public health concern in many countries, with higher rates in developing countries and emerging cases in developed nations. Educating communities, healthcare providers, and pregnant women about syphilis risks, the importance of antenatal care, and available preventive measures is crucial to increase awareness and enable early intervention in CS cases. Syphilis, despite being an ancient infection, presents ongoing challenges that require strategic approaches to enhance the healthcare network's capacity and improve the quality of care provided to pregnant women.

26 Syphilis: Management Conundrums

Khalil G. Ghanem
The Johns Hopkins University, Baltimore, MD, USA

Background: As the rates of syphilis continue to increase, clinicians are caring for patients with complex clinical presentations, and they are facing challenging management dilemmas. In this session, we will answer the following questions: How do we approach rapid plasma reagin (RPR) titers that fail to decline appropriately following therapy? RPR titers that increase following treatment? What is the optimal management of patients with neurosyphilis, ocular, and otic syphilis? Are additional doses of benzathine penicillin G necessary in patients with these complications? How could DOXY-PEP impact the management of syphilis? Approaches that provide consistency in the care of patients with complex presentations of syphilis are feasible despite a paucity of data.

27 HIV Assembly, Maturation Inhibitors, and Drug Resistance

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Background: HIV-1 particle assembly is driven by the viral Gag polyprotein precursor, which initiates assembly by forming an immature Gag lattice at the inner leaflet of the infected cell plasma membrane. Following completion of immature particle assembly and virus budding, the viral protease (PR) cleaves the Gag precursor at a number of sites to generate the mature Gag proteins matrix (MA), capsid (CA), nucleocapsid (NC), p6, and two small spacer peptides SP1 and SP1. PR-mediated Gag cleavage triggers a morphological transformation of the nascently released virion (known as maturation) during which the newly liberated CA protein assembles to form the viral capsid, into which are packaged the viral RNA genome and the viral enzymes reverse transcriptase (RT) and integrase (IN). Our work and that of others has demonstrated that the finely tuned stability of the immature Gag lattice is essential for particle assembly and subsequent maturation, and proper capsid stability is essential for early post-entry events. The stability of immature and mature Gag lattices is modulated by the cellular polyanion inositol hexakisphosphate (IP6). From a translational perspective, two classes of HIV-1 inhibitors - maturation inhibitors and capsid inhibitors (including the recently FDA-approved drug lenacapavir) - act by tipping the stability/instability balance of the immature Gag lattice and the mature capsid, respectively. Thus, elucidating the determinants of Gag complex stability is crucial for both achieving a basic understanding of HIV-1 replication and also for moving forward drug discovery efforts that target assembly, maturation, or capsid-mediated post-entry events, including nuclear import. In a separate line of investigation, our recent work has shown that the lipid composition of the HIV-1 virion plays a key role in HIV-1 maturation, as disrupting the cellular lipid biosynthesis enzyme neutral sphingomyelinase 2 (nSMase2) blocks Gag processing, particle maturation, and virus replication. In all of the above-described studies, drug resistance selections and forced evolution experiments have provided key mechanistic insights.

28 Accelerating Tuberculosis Elimination: Short-Course Prevention and Treatment

Vidya Mave
Center for Infectious Diseases in India, Johns Hopkins India, Pune, India

Background: Tuberculosis (TB) is among the leading cause of morbidity and mortality from an infectious disease, among patients with and without HIV, worldwide. Despite cost-free 6- months anti-TB therapy (ATT), the cure rates for TB have been suboptimal due to inadequate exposure/ adherence to ATT, causing a higher risk of failure, relapse, or acquired drug resistance, particularly in the setting of HIV. Recent research developments demonstrated that highly potent ATT regimens can allow shortening of TB treatment for both drug-sensitive and drug resistant TB in adult, adolescent and paediatric populations. In addition, shortened TB preventive therapy containing highly potent rifamycins and isoniazid is as good as the traditional 6-9 months of isoniazid prophylaxis among at-risk populations. Furthermore, emerging evidence shows that shortened course TB treatment and prevention regimens

may reduce the impact of drug-drug interactions with antiretrovirals. This plenary talk will summarize the most recent research evidence on the shorter course TB prevention and treatment, several of which have now informed the WHO guidelines. Further, the talk will provide an updated information on the drug-drug interactions between ATT and antiretrovirals as well as briefly discuss the recent rapid expansion of TB therapeutics pipeline.

29 HIV-1 Genome Packaging During Virion Assembly: Selecting the Right RNA

Wei-Shau Hu
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Background: During virus assembly, HIV-1 must identify and selectively package the unspliced viral RNA into nascent virions to transfer genetic information to its progeny. A vast majority of HIV-1 virions contain two copies of full-length unspliced HIV-1 RNA that form a dimer, indicating that the RNA packaging is a regulated and efficient process. The viral polyprotein Gag orchestrates virus assembly and mediates RNA genome packaging. During this process, Gag preferentially binds unpaired guanosines within the highly structured 5' untranslated region (UTR) of HIV-1 RNA. Additionally, the HIV-1 unspliced RNA provides a scaffold that promotes Gag:Gag interactions and virus assembly, thereby ensuring its packaging. However, not all HIV-1 unspliced RNAs are created equal. Recent studies showed that HIV-1 uses neighboring sequences as transcription start sites to generate multiple unspliced RNA species with a few nucleotides difference at the 5' end. However, these 99.9% identical RNAs can differ functionally, and one species of unspliced HIV-1 RNA is preferentially packaged over other nearly identical RNAs. These studies reveal the complex regulation of HIV-1 genome packaging process.

30 Virion Maturation: Folding Into the Right Shape

Mamuka Kvaratskhelia
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Background: HIV-1 capsid is a closed conical structure formed during virion maturation. It houses the viral RNA genome and key viral enzymes reverse transcriptase and integrase needed for conversion of the single stranded viral RNA into double stranded DNA and its subsequent integration into a host cell chromosome. The viral capsid consists of the capsid protein (CA) arranged predominantly into hexameric lattices, as well as into 12 pentamers, which introduce curvatures at the capsid periphery to completely close the conical structure. The capsid assembly is mediated by the cellular polyanion inositol hexakisphosphate (IP6), which binds to central arginine rings in pentamers and hexamers to stabilize these crucial assembly intermediates. Recent structural studies have elucidated a molecular switch that directs CA assembly into pentamers and hexamers. Lenacapavir (LEN, Gilead Sciences) is the first-in-class capsid targeting, long-acting and highly potent antiretroviral. Mechanistic and structural studies have revealed a multimodal mechanism of action of the inhibitor. LEN inhibits both early and late steps of HIV-1 replication with picomolar concentrations. Yet, the underlying mechanism for such a high potency of LEN is unclear. We have developed a LC-MS/MS based methodology to quantitate LEN concentrations in virions and found that sub-stoichiometric inhibitor to CA ratios hyper-stabilize HIV-1 capsid and block infection. The inhibitor remains stably bound to HIV-1 capsid for >24 h. Furthermore, we have investigated an additional antiviral activity of LEN during virion maturation. Our biochemical assays uncovered that LEN binding to CA monomers specifically interfered with the formation of pentamers, whereas the inhibitor promoted the assembly of hyper-stable hexametric lattices. The ability of LEN to offset the delicate balance between pentamers and hexamers resulted in formation of defective or atypical assemblies of CA both in vitro and in virions. These findings provide a new insight into molecular mechanisms of action of LEN.

31 Intact HIV Capsids facilitate innate immune evasion and enter the nucleus via karyopherin mimicry

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University College London, London, UK

Background: HIV has a core built of around 250 capsid protein hexamers and exactly 12 pentamers. This cone shaped core contains the viral single stranded RNA genome which is converted into a double stranded DNA genome by encapsidated reverse transcription, catalysed by viral reverse transcriptase. Early data suggested that viral capsids come apart or "uncoat" before viral DNA synthesis, but we now understand that the infectious cores are the ones that remain intact until after nuclear entry. Genetic studies have associated conserved capsid features with recruitment of a series of specific host cofactor proteins in the cytoplasm, in nuclear pores and in the nucleus and pioneering microscopy techniques have clearly illustrated intact capsids in the nucleus and associated them with successful infection. We have shown that the single pandemic HIV-1(M) lineage capsid has unique features that promote evasion from innate immune sensors. We hypothesise that this is explained by a more sophisticated regulation of the timing and location of capsid uncoating and genome release by the cofactors. This more effectively hides viral DNA and therefore permits more effective innate immune evasion. We hypothesise that this in turn promotes human-to-human transmission because innate immune activation is expected to reduce viral replication at the site of exposure and therefore establishment of infection. In collaboration with David Jacques and Till Boecking of the University of New South Wales we have also discovered that, despite their huge size, intact capsids can traverse nuclear pores through mimicking karyopherin nuclear transport proteins. Capsids do this by recruiting the FG motifs found in the nuclear pore diffusion barrier to a conserved binding pocket found in each capsid monomer. Thus, HIV capsids are molecular machines that have evolved to protect the process of viral genome synthesis from innate immune detection and to transport the genome across the cytoplasm, through nuclear pores, and to chromatin where they uncoat, and release genome, in exactly the right location and at exactly the right time for successful, undetected integration into host chromatin.

32 Novel Markers of Hepatitis B: Clinical Utility For New Treatment Strategies

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Institut National de la Santé et de la Recherche Médicale; Université Claude Bernard Lyon 1, Lyon, France

Background: In the context of novel treatment strategies aimed at HBV cure by eliminating or silencing the cccDNA reservoir, its non-invasive evaluation with blood viral biomarkers is critical to monitor intrahepatic viral clearance and guide treatment cessation. One of the caveats of these biomarkers is their ability to accurately distinguish biomarkers expressed from cccDNA versus those expressed from integrated viral sequences. HBsAg can be expressed from viral sequences integrated in the host genome which undermines its value in predicting cccDNA levels and transcriptional activity, particularly in HBeAg(—) patients and in patients under NUC therapy. Circulating HBV RNA (cirB-RNA) concentration is a promising novel biomarker for antiviral treatment monitoring. Quantification of cirB-RNA, measured with research laboratory developed assays, have good predictive power for both on-treatment serological response and off-treatment durability. New generation investigational assays allowed the quantification of cccDNA derived viral RNAs in serum but not from integrated sequences. CirB-RNA detection correlates with cccDNA transcriptional activity in NUC treated or untreated patients. HBV core-related antigen (HBcrAg), a composite biomarker of core/pre-core derived proteins, is thought to be mainly expressed from cccDNA derived RNA template and was also shown to have a good predictive value for antiviral treatment response. cirB-RNA and HBcrAg are usually correlated. The combination of undetectable cirB-RNA and HBcrAg at the end of treatment is more predictive for sustained suppression of replication off-treatment compared with either biomarker alone. Other biomarkers are in development to assess the cccDNA reservoir, e.g. the quantification of phosphorylated and non-phosphorylated HBc in the blood circulation. These investigational biomarkers are now used for the evaluation of target engagement and antiviral efficacy to assist the development of new antivirals (Capsid Assembly Modulators, SiRNA, antisense oligonucleotides, etc.) and immunomodulatory agents (check point inhibitors, TLR agonists, therapeutic vaccines, etc.). Altogether, these non-invasive viral markers show promise for a deep phenotyping of patients and show potential for patient stratification and novel treatment evaluation.

33 Advances in HBV Immunotherapy: The Beginning of the End?

Adam Gehring
University Health Network, Toronto, Canada

Background: Encouraging data demonstrates that new combination therapies are beginning to achieve HBsAg loss in a significant proportion of chronic hepatitis B (CHB) patients. In some patients, HBsAg loss is durable, achieving functional cure, while others relapse, with HBsAg becoming detectable again during follow up. What determines cure vs. relapse remains unclear but, in the absence of a sterilizing cure, the immune system is believed by many to

be a critical component to long-term, off-treatment HBV control. Therefore, immunological adjuvants such as IFN-α, therapeutic vaccines, checkpoint inhibitors, and innate immunomodulators are being/will be combined with novel direct acting antivirals (DAAs) to try and increase the durability of cure. Whether immunomodulation will be a requirement for durable cure, or endogenous immunity will be sufficient, is likely to be patient/cohort specific. This presentation will look at immune correlates of viral control, clinical trials where immunomodulation enhances functional cure rates, and immunological questions that need to be addressed in DAA therapies.

34 How New WHO Guidance Can Transform Hepatitis B in Sub-Saharan Africa

Olufunmilayo Lesi
World Health Organization, Geneva, Switzerland

Background: The presentation will provide the latest epidemiology of HBV in sub-Saharan Africa (including Hepatitis delta) and highlight the unique consideration and status of elimination (and comparison to other regions); recent evidence related to reducing new infection (HB PMTCT); strategies for transforming the HBV public health response; and highlights from the updated 2024 WHO guidelines for hepatitis B treatment and care.

35 Introduction to DoxyPEP: Understanding the Issues

Chase Cannon
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Background: New strategies are needed to address persistently increasing rates of bacterial sexually transmitted infections (STI). Recent trials demonstrate that doxycycline post-exposure prophylaxis (doxy-PEP) significantly reduces the risk of chlamydia, syphilis, and gonorrhea in cisgender men and transgender women who have sex with men. One study found doxy-PEP did not reduce risk for STI in cisgender women, potentially due to low adherence to the intervention in the trial. Despite its potential benefits for STI risk reduction in some populations, several potential implications of doxy-PEP in the near and longer term merit consideration. This presentation will review current evidence to frame the knowns and unknowns about doxy-PEP, highlight the range of doxy-PEP guidance and position statements, discuss the basis for concerns about antimicrobial resistance, and introduce future considerations for implementation to maximize benefit and minimize harms related to doxy-PEP use.

36 DoxyPEP: Should We Worry About Antimicrobial Resistance?

Beatrice Bercot
St Louis Hospital, APHP, University Paris City, Paris, France

Background: Increased rates of bacterial sexually transmitted infections (STIs) are reported among men who have sex with men (MSM), particularly among those using HIV pre-exposure prophylaxis (PrEP). Interventions to reduce the incidence of STIs are needed. In the field of STI prevention using doxycycline on-demand post-exposure prophylaxis (PEPdoxy), we are witnessing significant advances. Three large-scale randomized clinical trials (ANRS Ipergay, ANRS Doxyvac trial, DoxyPEP) have demonstrated a reduction of more than two-thirds in the incidence of bacterial STIs among MSM, notably for Chlamydiae trachomatis (CT) and Treponema pallidum (TP) infections, thanks to PEPdoxy. However, efficacy against Neisseria gonorrhoeae (GC) varies according to tetracycline resistance rates within populations, with Europe showing higher resistance rates than the US. This approach raises two major concerns: (i) the potential emergence of antimicrobial resistance, mainly to tetracycline, in pathogens responsible for STIs, as already observed for GC, which could worsen, or a new acquisition of resistance for CT and TP which has never been described, and (ii) the impact of doxy-PEP on the composition of the various microbiota and the pathogens present in these flora, in particular for Escherichia coli and Staphylococcus aureus. This presentation will give an overview of the available data on the impact of doxy-PEP strategies on the microbiota and the molecular mechanism conferring resistance. These studies on the microbiome and antimicrobial resistance surveillance for bacterial STIs should be continued over time to fully assess the impact of this strategy.

37 Implementation of DoxyPEP: Challenges and Opportunities

Stephanie E. Cohen
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Background: Doxycycline post-exposure prophylaxis (doxy-PEP) is highly effective in reducing bacterial STIs among men who have sex with men (MSM) and transgender women (TGW). Optimizing the public health impact of this highly effective STI prevention tool while minimizing potential risks will require a multi-pronged, equity-centered implementation strategy. The US Centers for Disease Control and Prevention draft doxy-PEP guidelines give a grade 1A recommendation for doxy-PEP for MSM and TGW with a history of an STI in the past year. Other national, state and local health jurisdictions have released guidance with broader or more limited eligibility for the use of doxy-PEP. Key implementation considerations include: Who should be offered doxy-PEP and in what settings? What counseling should be provided to individuals receiving doxy-PEP? How can doxy-PEP uptake, adherence and persistence be maximized across age and racial/ethnic groups? What training and tools do providers need to integrate doxy-PEP into their practice? What is the risk of antimicrobial resistance in STI and non-STI pathogens with longer-term use of doxy-PEP, and how should this be monitored? How can the effect of doxy-PEP on STI incidence be monitored and how success can be measured? What are the findings to date in terms of the uptake and impact of doxy-PEP in early adopter cities? In this symposium, we will review these key questions, highlight areas of controversy across existing doxy-PEP guidelines, and discuss the available evidence on doxy-PEP implementation outside of the clinical trial setting.

38 Overview of the Global Displacement Crisis

Mesfin T. Tessema
International Rescue Committee, New York, New York

Background: Globally, over 110 million people have been forcibly displaced from their homes due to various factors such as conflict, violence, persecution, and human rights abuses. Displaced people, especially women and children face a heightened risk of sexual violence, exploitation, and trafficking exposing them to increased health risks including exposure to HIV infection. Many face discrimination and stigma. Addressing HIV in these contexts is not only a protection and human rights issue but also a public health priority.

39 The End of Oral? How Long-Acting Formulations Are Changing the Management of Infectious Diseases

Charles W. Flexner
The Johns Hopkins University, Baltimore, MD, USA

Background: Despite having near-perfect single tablet regimens, adherence to daily oral HIV treatment and prevention is unacceptably low in many settings. Long-acting and extended-release drugs and formulations hold promise for solving this problem and improving outcomes, facilitating the achievement of WHO targets for controlling this epidemic. The first LA/ER formulations for HIV treatment and prevention are now approved and available but are underutilized in LMICs, mainly because of access issues. There is a need for products with less frequent dosing, greater patient convenience, and reduced risk of virologic failure, as well as regimens that also suppress hepatitis B virus infection. Novel products must be accessible in resource-limited settings and for vulnerable populations that include children, adolescents, and pregnant women. Long-acting drug delivery also has the potential to transform the treatment and prevention of other infections including tuberculosis, malaria, and viral hepatitis. This presentation will review recent advances in formulation science that are going to help make available better replacements for daily oral drugs for HIV and many other infectious diseases.

40 Diagnostics 4.0: The Future of Diagnostics for HIV and Related Infections

Nitika P. Pai
McGill University, Montreal, Canada

Background: Overview Since the late 1980s, novel HIV screening and diagnostic technologies have led the way in the field of HIV/STBBIs and changed the landscape of diagnostics in Infectious Diseases. Global interest and awareness of timely testing have translated to an enhanced momentum for developing and growing novel testing technologies and related strategies. Multiplexed (nucleic acid amplification) based next-generation sequencing for HIV/STBBI, "omics," and CRISP-R-based technologies are here to stay. Together with connected digital solutions (Apps, machine learning, platforms, wearables), diagnostic technologies have the potential to impact health care through expanded access and precision diagnostics. Home-based testing for HIV, HCV, syphilis, and CT, GC, and HPV self-sampling strategies offer tremendous potential to enhance service delivery in diverse settings, from clinics to communities to homes. In parallel, digital and machine learning technologies are growing exponentially, offering tremendous opportunities for integration and efficiency with data-driven decisions. We will discuss these technologies' role in catalyzing digital health transformation as it

unfolds with many solutions. This talk will attempt to provide an overview of exciting technological developments and solutions in HIV/STBBI screening and diagnosis. Solutions that promise efficient surveillance/tracking, education/empowerment, rapid access to testing and treatment, or an offer of personalized care lead to clinical/public health impact. We will also offer a vision of near-term scientific advancement in diagnostics. Learning objectives and outcomes After this session, participants will be able to 1) Identify the state-of-the-art screening and diagnostic technologies for HIV/STBBIs 2) Identify the evidence on promising digital and machine learning technologies that will impact health service delivery. 3) Potential for digital health transformation with impact on operational and patient-centered outcomes. 4) Envision the future of diagnostics and tech-enabled digital transformation in HIV/STBBI.

41 From Mechanisms to Therapeutics: Eliminating HIV-infected Cells by the CARD8 Inflammasome

Liang Shan
Washington University in St Louis, St Louis, MO, USA

Background: A successful curative strategy for HIV should aim at selective elimination of HIV-infected cells. The 'shock-and-kill' approach involves inducing viral gene expression to trigger immune clearance of infected cells. One of the main obstacles is the presence of immune escape variants in HIV reservoirs. Therefore, broadly reactive T cell and antibody responses are required to overcome viral diversity. Another challenge lies in effectively triggering cell death. Immune effector cells including CD8+ T cells and NK cells induce apoptosis in target cells. However, quiescent CD4+ T cells, which are a major reservoir for the virus, are less susceptible to T cell and NK cell attacks compared to cycling T cells. Moreover, cells harboring latent HIV may undergo positive selection to become more resistant to apoptosis. To this end, our goal is to identify new immune pathways that specifically target highly conserved viral components and effectively induce cell death in HIV reservoirs. We reported that caspase recruitment domain–containing protein 8 (CARD8) is an innate immune sensor that can be activated through proteolytic cleavage of its N-terminal fragment. In HIV–infected cells, CARD8 cannot detect the virus because the viral protease remains inactive as a subunit of unprocessed Gag–Pol polyprotein. Some HIV–specific non-nucleoside reverse transcriptase inhibitors (NNRTIs) can trigger intracellular viral protease activation. Treating HIV–infected macrophages and CD4+ T cells with NNRTIs leads to CARD8-mediated caspase 1 activation and pyroptotic cell death. Targeting CARD8 for HIV reservoir elimination offers two significant advantages. Firstly, the viral protease activity against CARD8 is well conserved across major HIV subtypes. Secondly, CARD8 exhibits high functionality in quiescent CD4+ T cells and can trigger cell death independently of apoptosis. Further research should be conducted to explore and discover more potent activators of CARD8 that specifically target HIV-infected cells. This will help in enhancing the effectiveness of CARD8-based therapies for eliminating the HIV reservoir.

42 Mechanisms to Therapeutics: TACK Molecules Kill HIV-Infected Cells Through Inflammasome Activation

Tracy L. Diamond
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Background: The viral reservoir, consisting of both HIV-1–expressing and latently infected cells, necessitates life-long antiretroviral therapy (ART) to suppress HIV-1 replication in people living with HIV (PLWH). Current ART blocks viral replication and prevents spread to healthy cells. In doing this it maintains, but does not reduce, the HIV infected cell reservoir. A common approach to address the reservoir is known as "shock and kill", which seeks to reactivate latent HIV-1 such that cells can be targeted and eliminated through viral cytolysis or host cellular immunity. This approach has yielded some clinical success in inducing viral reactivation but has had little to no impact on reducing the reservoir. Cytotoxic agents that are selective for HIV-infected cells could enhance or complement such a strategy. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are common components of ART that have been designed to enzymatically block the viral reverse transcriptase (RT), however studies have demonstrated that some NNRTIs also have a secondary mechanism of action resulting in HIV-specific cell kill. Through this targeted activator of cell kill (TACK) mechanism NNRTIs enhance HIV-1 Gag-Pol dimerization causing premature HIV-1 intracellular protease maturation which induces HIV-1 cytotoxicity through CARD8 inflammasome activation. Although current marketed NNRTIs have potent RT inhibitory activity, they contain weak to no secondary TACK activity and therefore are not expected to be relevant inducers of HIV-cell kill at clinical exposures. Here, we optimized this secondary activity to identify TACK compounds with potencies compatible with clinically achievable concentrations. Pre-clinical proof of concept for cell kill was demonstrated in ex vivo studies with cells from PLWH as well as in an HIV-infected humanized mouse model. These novel NNRTI-TACK molecules have a potential application in HIV cure via reduction in the viral reservoir.

43 From Transcriptomics to Therapeutics: A Host Restriction Factor That Targets HIV Expression

Rasmi Thomas
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Background: Advances in unbiased next-generation sequencing methods for characterizing all RNA transcripts in a sample have revolutionized scientific research in the past decade, leading to discoveries related to how variation in people impacts responses to disease outcomes, vaccination and therapeutics. Transcriptomics assays expression from every gene in an organism's genome to reveal the global pattern of transcription. Measuring gene expression in different tissues, conditions, or at different times can reveal details of an organism's biology that result in differential disease outcomes. Transcriptomics was first developed as bulk RNA sequencing (RNA-seq), which yields an aggregate of all gene expression in many cells. Recent single cell RNA-seq (scRNA-seq) techniques provide transcriptomics data for individual cells, which delineate changes in each cell relative to another. This talk describes how we used scRNA-seq to measure not only the host transcripts, but also HIV RNA (vRNA) expression in people living with HIV during acute HIV-1 infection (AHI). This method allowed us to identify host factors restricting HIV-1 transcripts in vivo without any additional laboratory manipulation. A subset of CD4+ T cells with a memory phenotype had the most vRNA+ cells, recapitulating previous data using other methods. Frequency of these cells correlated with important clinical parameters like plasma viremia and cell-associated HIV DNA levels, suggesting that the identified vRNA+ cells were biologically meaningful. When analyzing viral transcripts as a continuous phenotype across individual cells, we identified several host genes for which higher expression levels associated with lower vRNA. PTMA showed the strongest association with lower vRNA expression. This observation was validated in additional participants from different world populations and HIV subtypes. PTMA expression at timepoints after initiation of treatment showed an inverse correlation with frequency of vRNA+ cell measured during AHI, suggesting that changes in PTMA even in the absence of viremia can affect viral transcript levels. In vitro overexpression experiments provided direct evidence that expression of the prothymosin α protein encoded by PTMA inhibited HIV-1 transcription and expression. These results identify prothymosin α as a host factor that restricts HIV-1 infection in vivo, which has implications for viral transmission and cure strategies.

44 From Structure to Therapeutics: CD4 Mimetics "Open" Env and Sensitize HIV-1-Infected Cells to ADCC

Andrés Finzi
Centre de Recherche du CHUM, Université de Montréal, Montreal, Quebec, Canada

Background: Combination antiretroviral therapy (cART) controls human immunodeficiency virus (HIV-1) replication and extends the longevity of persons living with HIV-1 (PLWH). Even with optimal cART, latent HIV-1 proviruses persist in long-lived reservoirs, from which virus rebounds within days to weeks of treatment interruption. Therefore, new approaches aimed at eliminating HIV-1 reservoirs are needed. Persistently infected cells can potentially be eliminated by harnessing host immune responses. One promising strategy relies on the ability of immune effector cells to kill infected cells expressing the HIV-1 envelope glycoprotein (Env). Non-neutralizing antibodies (Abs) targeting highly conserved CD4-induced (CD4i) Env epitopes have the potential to eliminate infected cells by antibody-dependent cellular cytotoxicity (ADCC). Unfortunately, as a countermeasure, the HIV-1 Vpu and Nef proteins downregulate CD4, preventing the exposure of ADCC-vulnerable CD4i Env epitopes. Small CD4-mimetic compounds (CD4mcs) can "open-up" Env, exposing vulnerable CD4i Env epitopes and sensitizing HIV-1-infected cells to ADCC. A cocktail of two families of CD4i Abs (anti-cluster A and anti-coreceptor binding site Abs) together with a CD4mc was shown to significantly decrease the size of the reservoir and delay viral rebound after cART interruption in humanized mice. A summary of the development of new families of CD4mc with improved potency, new cocktails of CD4i Abs with higher ADCC activity, their

impact on the viral reservoir in humanized mice and ongoing studies in non-human primates will be presented. These new developments have the potential to accelerate the application of this powerful approach to PLWH.

45 Sex-Differences in Atherosclerotic CVD Risks and Mechanisms: Insights from REPRIEVE

Markella Zanni
Harvard University, Cambridge, MA, USA

Background: The presentation highlights risks for atherosclerotic cardiovascular disease, particularly myocardial infarction, among ART-treated people with HIV, with attention to sex-differences in such risks. Sex-differences in the pathophysiologic mechanisms contributing to risks for myocardial infarction among people with HIV are also explored. Finally, data supporting sex-specific risk mechanisms among women with HIV are presented.

46 Immunomodulation and Cardiovascular Disease: Lessons Learned From HIV

Priscilla Y. Hsue
University of California San Francisco, San Francisco, CA, USA

Background: For this invited talk, the role of inflammation and cardiovascular disease will be reviewed both in the context of the general population and persons living with HIV. In particular, the impact of statin therapy on inflammation as part of the JUPITER (non-HIV) and REPRIEVE (HIV) trials will be compared. Among persons with HIV, proof-of-concept studies have provided insight by probing different targets in the inflammatory cascade. In the general population, anti-inflammatory interventions such as colchicine and canakinumab have significantly reduced clinical events. Differences in immmune-based therapeutics among persons with HIV and the general population will be discussed. Finally, future therapeutic strategies for immunomodulation which may be more relevant in the context of HIV disease pathogenesis will be considered.

47 Implications for Implementing CVD Risk Prevention Strategies for Low- and Middle-Income Countries

Mpiko Ntsekhe
University of Cape Town, Cape Town, South Africa

Background: The implications of the results of Reprieve trial for Low and Middle Income Countries (LMICs), where the global burden of HIV, and the number of PWH who would be eligible to receive a statin based on the trial entry criteria are highest, are not clear. At face value it would seem that the potential to derive significant benefit from CVD morbidity and mortality reduction in PWH, should make the decision to adopt a pharma based primary CVD prevention public health strategy straightforward. On the other hand there are a number of challenges to implementing such a strategy in LMICS for policy makers, clinicians and health finance authorities, particularly in sub-Saharan Africa where the largest number of PWH live and resources are lowest. Whereas ASCVD is now the major cause of morbidity and mortality in PWH in many HICS, the same is not be true in most LMICS. Despite modeling estimates which suggest both a high incident ASCVD rate and large fraction of ASCVD attributable to HIV, observational (real world) data and clinical practice paint a different picture. AIDS related opportunistic infections still dominate the list of major causes of overall morbidity and mortality and amongst the non-HIV related causes of morbidity and mortality, CVD contributes a small proportion. Finally, amongst those with CVD, non-ischemic causes predominate. This may explain the relatively low LMICS MACE rate in the trial and significantly limits the justification for allocation of scarce resources to this important cause over others. Second, there are significant challenges to the use of conventional ASCVD risk scoring tools such as the Pooled Cohort Estimate (PCE) used in the trial to both HIV and non-HIV populations in LMICs. For example whereas the anticipated MACE rate based in part on study baseline PCE scores in the REPRIEVE trial was 12/1000, the observed MACE in the placebo arm was less than 3.5/1000 in participating LMICs and less than 2 in SSA. Such a low event rate would almost double the number of participants needed to treat to benefit from a statin, and by extension add significant costs to already constrained healthcare budgets. Given these and related challenges, a focus on healthy lifestyle and optimization of traditional risk factors, is likely to remain the primary prevention strategy of choice in PWH living in LMICs for the near term future.

48 Why Is Cabotegravir Rollout So Slow?

Rupa Patel
Washington University in St Louis, St Louis, MO, USA

Background: Long-acting injectable cabotegravir as pre-exposure prophylaxis for HIV prevention (LAI CAB PrEP) has been FDA approved in the U.S. since December 2021. Approvals are in place or pending in many countries and regions globally, and it is being evaluated for programmatic implementation in a variety of contexts. Since FDA approval in the U.S., LAI CAB PrEP implementation and scale-up has been relatively slow across the nation. In this presentation, we will highlight the challenges and opportunities in LAI CAB PrEP program initiation and describe select strategies that have supported successful programs.

49 The Ring Comes Full Circle: Navigating the Complex Landscape of Biomedical Prevention Post-Phase III

Leila E. Mansoor
Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa

Background: The biomedical prevention landscape enters a pivotal phase as dapivirine (DPV) vaginal ring progresses beyond Phase III clinical trials. This presentation explores: the role of open-label extension (OLE) studies in refining Phase III results, insights from recent PEPFAR-based data in Zimbabwe on real-world ring use, and the intricate balance required in shaping future target product profiles within a complex regulatory landscape. Topical HIV prevention methods offer not only localized defense but also systemic protection. DPV ring Phase III trials revealed a 30% efficacy point estimate, rising to a promising 50% in women over 21. While pivotal for safety data, OLE studies complement and refine Phase III outcomes. Incorporating real-world scenarios, diverse populations, and long-term observations, these studies provide essential insights for optimizing DPV ring deployment. DPV ring OLE studies found increased counterfactual efficacy estimates. Increased adherence and retention relative to the randomized controlled trials were also noted. WHO's endorsement propels DPV ring implementation in 11 countries, targeting empowerment for young women, who often face heightened vulnerability due to age-related power dynamics, influencing the cycle of transmission. Favorable views expressed by women in Zimbabwe, underscore the tangible impact of DPV ring implementation. Examining usage patterns, adherence challenges, and demographic factors bridges the gap between clinical trials and practical implementation in resource-limited settings. Additionally, local manufacturing in South Africa aims to reduce ring costs significantly. Navigating a complex regulatory environment, DPV ring demands careful consideration for future target product profiles. Despite Phase III outcomes, studies in adolescents (MTN-034/REACH), pregnant women (MTN-042/DELIVER), and breastfeeding women (MTN-043/B-Protected) affirm safety and acceptability. Emerging 90-day variants and multi-purpose prevention technologies (MPT) underscore the pivotal balance for widespread acceptance and global success. "The Ring Comes Full Circle" represents a crucial juncture in biomedical prevention. Through open-label studies, real-world insights, including vulnerable populations, and a nuanced regulatory approach, we pave the way for effective, user-friendly, and globally applicable interventions. Beyond Phase III perils, DPV ring, with evolving iterations, contributes to our global arsenal against HIV.

50 Challenging the Dogma of Event-Driven PrEP

Jenell Stewart
Hennepin Healthcare and University of Minnesota, Minneapolis, MN, USA

Background: HIV is preventable with the use of daily oral PrEP or long-acting injectable PrEP for all populations regardless of sex or gender. Additionally, event-driven PrEP is an option for cisgender men who desire intermittent use of medications. The IPERGAY Trial provided an important answer, intermittent dosing of PrEP is an effective method to prevent HIV, and as the only randomized controlled trial of event-driven PrEP, we are left with a persistently unanswered question, does event-driven PrEP only work for cisgender men? Real-world data and observational studies in Paris, San Francisco, Bangkok, Johannesburg, Amsterdam, and Harlem suggest that event-driven PrEP is desired, effective, and cost-effective. Cisgender women in Southern and Eastern Africa have reported a preference for an HIV prevention method that did not require taking daily pills, which made event-driven dosing more user-friendly and acceptable. However, efficacy data on event-driven PrEP among cisgender women are lacking. Pharmacokinetic studies on drug levels in plasma, rectum, and genital samples from cisgender women, cisgender men, and transgender

women suggest that drug levels are higher in the rectum than the vagina and lower in the presence of estrogen, and yet despite these differences across sex and gender, daily oral Tenofovir Disoproxil Fumarate-Emtricitabine is highly effective at preventing incident HIV in all populations. Are these differences in drug concentrations a valid justification limiting event-driven PrEP use to cisgender men who have sex with men? In many settings, cisgender women who are not interested in or have barriers to daily dosing, even in settings of infrequent sexual exposures, have been dissuaded from using oral PrEP due to concerns about the need for perfect adherence for vaginal protection. Seven doses of oral PrEP a week offers excellent protection against HIV and recent retrospective data demonstrated that four single strength doses a week had similarly high protection among cisgender women suggesting that dosing frequency needs may not differ by sex assigned at birth.

ORAL ABSTRACTS

100 Safety Profile and Immunogenicity of a Phase I Clinical Trial Using Germline-Targeting Trimer GT1.1

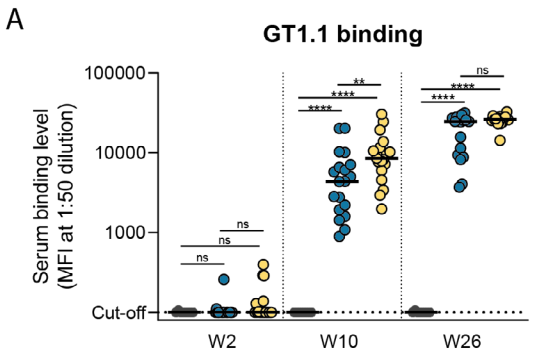
Karlijn van der Straten[1], Tom Caniels[1], Emma Reiss[1], Annelou L. van der Veen[1], Katrina Millard[2], David C. Montefiori[3], Georgia D. Tomaras[3], Dagna Laufer[4], Vincent Philiponis[4], Michelle J. Klouwens[1], Marit van Gils[1], Rogier W. Sanders[1], David Diemert[5], Godelieve J. de Bree[1], Marina Caskey[2]
[1]Academic Medical Center, Amsterdam, Netherlands, [2]The Rockefeller University, New York, NY, USA, [3]Duke University, Durham, NC, USA, [4]International AIDS Vaccine Initiative, New York, NY, USA, [5]George Washington University, Washington, DC, USA

Background: An effective HIV-vaccine should induce broadly neutralizing antibodies (bNAbs) targeting the viral envelope glycoprotein, which is challenged by the low frequencies of bNab precursor B cells. Pre-clinical studies have shown the ability of the BG505 SOSIP.GT1.1 gp140 (GT1.1) vaccine to prime bNAb precursor B cells, including those targeting the CD4-binding site. Here, we report the first safety and immunogenicity data from a first in-human clinical trial using GT1.1.

Methods: This phase I, double-blinded, placebo-controlled, dose-escalating vaccination trial was conducted at two US sites and one in the Netherlands. Participants received intramuscular injections of either 30µg (low-dose) or 300µg (high-dose) of the GT1.1 vaccine with AS01B adjuvant system, or saline placebo at 0, 8, and 24 weeks. Reactogenicities were reported during the 15 days post-vaccinations, Serious AEs for the entire study period. Serum antibody binding and neutralization responses were quantified using BAMA and TZM-bl pseudovirus neutralization assays, respectively.

Results: We enrolled 47 adults without HIV (low-dose: n=20, high-dose: n=19, placebo: n=8), with an average age of 30 years and an similar sex distribution between groups. Ninety-four percent of participants reported at least one solicited Adverse Event (AE). Most AEs were graded mild (59.2%) or moderate (37.7%). There were no significant differences in number of AEs between the vaccine administrations (Chi-Squared test, p=0.17), or dose groups (p=0.13). No vaccine-related Serious AEs were reported. All vaccinated participants developed detectable GT1.1-binding serum antibodies at weeks 10 and 26, with the high-dose recipients showing a higher response rate after the first vaccination (10.5% low- vs. 31.5% high-dose) and significantly higher responses at week 10 (p=0.008) (Fig. 1A). GT1.1 neutralizing antibodies (NAb) were more prevalent in the high- compared to the low-dose recipients after the second (68% vs. 28%, respectively) and third vaccination (100% vs. 89%, respectively) (Fig.1B). Serum NAb activity was at least in part directed against the CD4-binding site

Conclusion: The adjuvanted GT1.1 vaccine has an acceptable safety and reactogenicity profile and induced a potent vaccine-specific serum antibody response. Here, a higher GT1.1 dose induced a more rapid and robust serum antibody binding response without compromising safety. Thus, germline-targeting trimer GT1.1 may represent a promising vaccine candidate for priming bNAb responses in humans.



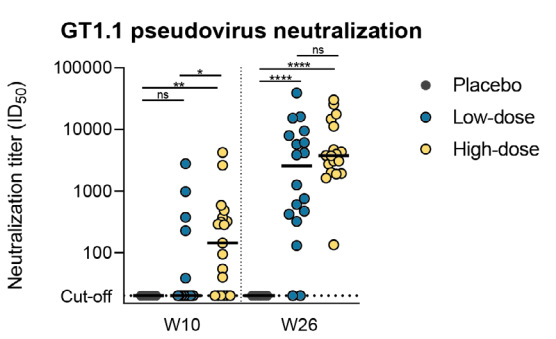


Figure 1. Serum antibody responses against BG505 SOSIP.GT1.1 gp140 following GT1.1 vaccination. Serum IgG binding (A) and neutralization responses (B). MFI: Median Fluorescent Intensity, ID_{50}: 50% inhibitory dilution. Serum responses were compared using a Mann-Whitney U test. P>0.05: ns, p<0.05:* p<0.01:**, p<0.0001: ****

101 Vaccine Combining Slow-Delivery and Follicle-Targeting Improve Humoral and Germinal Center Responses

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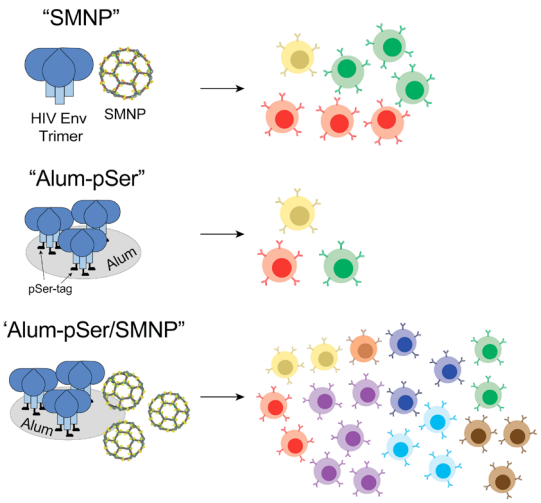
Background: Vaccines generate humoral immunity by activating antigen-specific helper T cells and B cells, which cooperate in germinal centers (GCs) to generate high-affinity antibodies. To provide antibody-based protection, an HIV vaccine will likely need to induce broadly neutralizing antibodies (bnAb). To date, identified bnAbs exhibit unusual features like extensive and improbable mutations and lengthy CDR3s; their precursor clones are often rare and have low affinity for HIV En v trimers. Emerging strategies to prime these rare precursors involve achieving prolonged antigen exposure, formulating multivalent and particulate immunogens, or employing potent adjuvants; these strategies have been shown to amplify GCs in preclinical studies, but combining these effects in a single shot is challenging.

Methods: Toward this goal, we engineered aluminum hydroxide (alum), the most common clinical adjuvant, into a slow-delivery vehicle by tagging HIV Env trimer immunogens with short phosphoserine (pSer) linkers to promote alum-binding-individual alum particles are decorated with antigens and mimic virus-like particles. We term this multivalent antigen and alum complex "alum-pSer." In parallel, we developed a potent saponin-based adjuvant, SMNP, to modulate the inflammation. In this study, we examined the impact of alum-pSer, SMNP, or combining these two adjuvants (Abstract Figure) on humoral response and GC B cells in mice using flow cytometry, ELISA, scRNAseq, and microscopy.

Results: The alum-pSer approach bolstered immunogen bioavailability. The SMNP adjuvant enhanced lymph drainage and immunogen transport to follicles. Notably, the combination exhibited remarkable synergy in amplifying humoral responses compared to SMNP or alum-pSer alone, eliciting 3.3-fold and 56-fold more antigen-specific GC B cells on day 14 and 1.8-fold and 12-fold greater serum IgG titers on day 28, respectively. The combination adjuvant augmented GC B cell clonal expansion and diversity and revealed an enrichment of S-phase, indicative of stronger positive selection by T cells. Moreover, we found that only the combination approach led to pronounced accumulation of intact HIV Env trimer on follicular dendritic cells.

Conclusion: These findings indicate this simple combination adjuvant approach achieves both sustained antigen availability and altered antigen localization, productively steering the GC response in a way conducive to priming rare B cell clones against protective HIV epitopes and broadly applicable to other pathogens.



102 Multi-Specificity Is a Common Trait of HIV-1 Broad Neutralizing Capacity

Peter Rusert[1], Chloé Pasin[2], Merle Schanz[1], Borys Pedenko[3], Daniel Schmidt[1], Irene A. Abela[2], Nikolas Friedrich[1], Cyrille Niklaus[1], Michèle Sickmann[1], Jaqueline Weber[1], Gregory Effantin[3], Winfried Weissenhorn[3], Huldrych F. Günthard[2], Roger Kouyos[2], Alexandra Trkola[1]

[1]University of Zurich, Zurich, Switzerland, [2]University Hospital Zurich, Zurich, Switzerland, [3]Université Grenoble Alpes, Grenoble, France

Background: Multi-specific responses have been described in rare people who evolved broadly neutralizing antibody (bnAb) activity in HIV-1 infection but their relevance remains unclear. Here we screened the Swiss HIV Cohort Study for multi-specificity by examining the XbnAb cohort comprising bnAb inducers (N=304) identified in the Swiss 4.5k Screen (Rusert Nat Med 2016).

Methods: Plasma neutralization fingerprints of bnAb inducers were evaluated against a 41-virus multiclade panel and compared to reference fingerprints of known bnAbs using an established Spearman based correlation method and a novel delineation strategy, termed virus panel classification, we developed to record multi-specificity. BCR were cloned from 16 cases by 10xGenomics and bnAbs of interest epitope mapped (mutational scanning, competition binding, mutant neutralization, cryo-EM).

Results: Classical bnAb plasma delineation of the XbnAb cohort assigned a single bnAb activity in 90% of plasmas. As the prediction records a dominant activity, secondary multi-specific activity cannot be excluded also in successfully assigned plasmas. This hidden extent of multi-specificity can be substantial as shown by elite neutralizer S51434, a Subtype B infected, slow progressor with predicted silent face activity based on the Spearman correlation method, from which we identified five distinct bnAb types as CD4bs, MPER, a fusion peptide/interface, PGT145-like and a novel V3-glycan bnAb type, with moderate to high breadth (44 - 80%). Virus panel prediction, we developed a novel delineation strategy for multi-specific responses, correctly classified S51434 as multi-specific. Across the XbnAb cohort the virus panel strategy identified a high proportion of bnAb inducers with one dominant bnAb activity (203/304) alongside a substantial number of individuals with multi-specificity (101/304), comprising mostly 2 to 3 predicted bnAb specificities. Extending the comparison of cloned bnAbs and specificity calling by the virus panel method to in total 16 bnAb inducers, substantiates the wide occurrence of multi-specificity.

Conclusion: Employing a new bnAb specificity prediction tool, the virus-panel fingerprinting method, we demonstrate that multi-specific bnAb activities are common in HIV-1 infection and can lead to elite neutralization. Our findings call for a paradigm shift in the evaluation of bnAb responses, where multi-specificity must be considered as likely as single-specificity and should become the ultimate goal of vaccine-induced responses.

103 CD4 Binding Site Glycan-Deficient SHIVs Elicit Broadly Neutralizing Antibodies in Rhesus Macaques

Daniel J. Morris[1], Hui Li[1], Jinery Lora[1], Kirsten Sowers[1], Christian Martella[1], Yingying Li[1], Barton F. Haynes[2], Tongqing Zhou[3], Peter D. Kwong[3], George M. Shaw[1]

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Background: Previous work has demonstrated that modifying soluble HIV-1 envelope (Env) trimers to remove glycans around the CD4 binding site (CD4bs) can immunofocus potent neutralizing antibody (NAb) responses to this epitope. However, such immunogens generally did not elicit broadly neutralizing antibodies (bNAbs). Understanding how to better boost these responses can inform vaccine design. Infection of rhesus macaques with replicating simian-human immunodeficiency viruses (SHIVs) bearing WT glycan-intact Envs rarely elicits bNAbs targeting the CD4bs. Here, we designed novel SHIVs lacking glycans surrounding the CD4bs (197, 363, and 462) to test the hypothesis that infection with these evolving SHIVs could immunofocus, boost, and affinity-mature CD4bs-targeted NAb and bNAb responses.

Methods: We disrupted glycosylation sequons at the above residues in three SHIVs bearing primary transmitted/founder Envs (CH505, BG505 and CH1012) and used these to intravenously infect a pilot cohort of 14 rhesus macaques (RMs). RMs were monitored to evaluate viral kinetics, Env sequence evolution, and NAb and bNAb development.

Results: 9 of 14 RMs exhibited ideal viral kinetics for further analysis. All 9 RMs developed potent autologous neutralizing responses targeting the protein surface beneath the engineered glycan hole. 4 of 9 RMs developed responses capable of neutralizing heterologous glycan-deficient viral strains. Longitudinal sequencing of plasma viral RNA revealed rapid, sequential restoration of the deleted glycans as well as CD4bs bNAb escape mutations arose temporally with rising neutralizing titers. Two RMs developed antibody responses capable of neutralizing WT heterologous viruses. Based on these results, we downselected from these constructs SHIV.CH505.CD4bs.GH to infect an additional 8 RMs. We observed CD4bs-targeted neutralization breadth in an additional 6 RMs. Epitope mapping of these broad responses showed that 7 of 8 RMs targeted the CD4bs.

Conclusion: These results show that SHIV Env trimers with targeted glycan deletions can immunofocus B cell responses to the CD4bs. Viral evolution in response to these glycan hole targeted NAbs can boost and affinity mature these responses, in some cases leading to bNAbs that target WT heterologous viruses with intact glycan shields. Ongoing studies will isolate and characterize mAbs responsible for this breadth and analyze Env-Ab coevolution to identify key Envs that can be selected as priming and boosting immunogens.

104 MHC-E Presentation Mediates SIV-Specific NK Cell Responses in SIV-Infected Rhesus Macaques

Philippe Rascle, Rhianna Jones, Griffin Woolley, Kyle Kroll, Karen Terry, Esther Lee, Stephanie Jost, Keith Reeves

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Background: Natural killer (NK) cells provide rapid and robust responses against viral infections. Multiple studies have shown that NK cells are also capable of antigen-specific recall to eliminate infected cells. In nonhuman primates (NHP), antigen-specific memory-like NK cell can be designed by MHC-E dependent response. During SIV infection, the stabilized MHC-E molecule may induce a potent pathway to restrict the virus via antigen-specific memory NK responses.

Methods: To study antigen-specific NK cells in NHP, we developed a novel in vitro method to clonally expand single rhesus macaque (RM) NK cells (rhNKCL) from SIV naive or chronically infected RM. We identified SIV- derived peptides by in silico analysis and confirmed their MHC-E binding using a peptide stabilization assay on K562 cells stably expressing MHC-E (HLA-E and Mamu-E) and primary RM cells. We characterized the effector functions of NK and rhNKCL cells via intracellular staining and cytotoxicity assays in combination with K562 cell lines or autologous BLCL loaded with SIV-derived peptides.

Results: Ten SIV-derived peptides showed MHC-E stabilization on K562 MHC-E+ (HLA-E and Mamu-E) cells and RM primary cells. Enriched NK cells exhibited an increase in IFNgamma, TNFalpha, and Ki67 during SIV acute infection against SIV-derived peptides, and a decrease in these responses in chronic infection. Interestingly, NK cells from RM with chronic SIV infection showed higher cytotoxic responses compared to NK cells from SIV-naïve RM against K562 Mamu-E+ cells loaded with SIV-derived peptides. To further investigate

the existence of antigen-specific NK cells, we established a novel procedure for single-cell clonal expansion of NHP NK cells, which maintain a conserved NHP NK cell phenotype of CD3- NKG2A/C+ CD16+ CD56+ following expansion. Autologous peptide-loaded BLCL elicited a broad-spectrum of rhNKCL cytotoxic responses, with higher response for SIV ENV-derived peptide.
Conclusion: In summary, these findings elucidate antigen-specific NK responses during SIVmac infection dependent on MHC-E-mediated SIV-derived peptide presentation. Also, we introduced a ground-breaking method for the clonal expansion of single NK cells in RM. This study may provide valuable insights into antigen-specific NK cells, including the establishment of epigenetic, metabolic, transcriptional, and phenotypic profiles. Such insights could be leveraged to enhance antiviral NK cell activity in future vaccine strategies and cell therapies.

105 [18F]F-AraG PET Imaging Reveals Unique Tissue T-Cell Activation Patterns Across HIV Infection States

Basic Science:

Timothy J. Henrich[1], Robert Flavell[1], Michael J. Peluso[1], Kofi Asare[1], Maya Aslam[1], Emily Fehrman[1], Meghann C. Williams[1], Viva Tai[1], Rebecca Hoh[1], Youngho Seo[1], Jelena Levi[2], Steven G. Deeks[1], Henry VanBrocklin[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]CellSight Technologies, San Francisco, CA, USA

Background: Non-invasive tools that can test the hypothesis that abnormal T cell activation in various tissues differs across HIV-1 disease states are needed. We used [18F]F-AraG, a small-molecule PET tracer highly specific for activated T cells (CD8>CD4), to compare whole-body T cell activation states in people with HIV (PWH) on and off ART, and experiencing post-intervention control (PIC), compared to uninfected control participants.
Methods: [18F]F-AraG (~5mCi) was administer i.v. to13 PWH (12 male, one transgender female; 8 on ART, 2 viremic, 3 PIC following combination immunotherapy) and 6 uninfected volunteers [3 male, 3 female]) followed by whole-body PET-MR imaging. Maximum and mean standardized uptake values (SUVmax/mean) were calculated for regions of interest (ROI) and compared across cohorts using non-parametric tests adjusted for multiple comparisons.
Results: We observed significantly higher [18F]F-AraG SUVmean and SUVmax in many tissues (nasal turbinates, axial bone marrow, distal spinal cord/cauda equina, lung parenchyma, pulmonary artery, and rectal wall) in PWH comparted to uninfected controls (all $P<0.05$; Fig 1). Elevated T cell activation was evident even among those on ART (VL<40 c/mL) in these ROI with the exception of lung tissue. Interestingly, tracer uptake was significantly lower in inguinal lymph nodes from all PWH, PWH on ART, and PTC, compared to uninfected controls (all $P<0.02$). PWH experiencing PIC had significantly higher SUVmean/max in pulmonary artery, axial marrow and rectal wall (SUVmean) compared to uninfected controls, but not in lungs or nasal turbinates. There were no significant differences in tracer uptake in male versus female control participants in any ROI and analyses of all PWH excluding female controls yielded similar results.
Conclusion: This study is the first to show persistent T cell activation in bone marrow, pulmonary artery, and nasal and gut tissue across a range of HIV-1 disease states using non-invasive PET-MR imaging. Interestingly, T cell activation in lung parenchyma appears to be driven by viremic PWH, and all PWH had lower T cell activation in inguinal lymph nodes compared to uninfected controls, regardless of disease phenotype. We previously observed high uptake of a HIV gp120-specific bnAb PET tracer in inguinal lymph nodes from viremic and ART-suppressed PWH suggesting that combinations of non-invasive imaging tools may play an important role in determining the interplay between host immune responses and viral persistence.

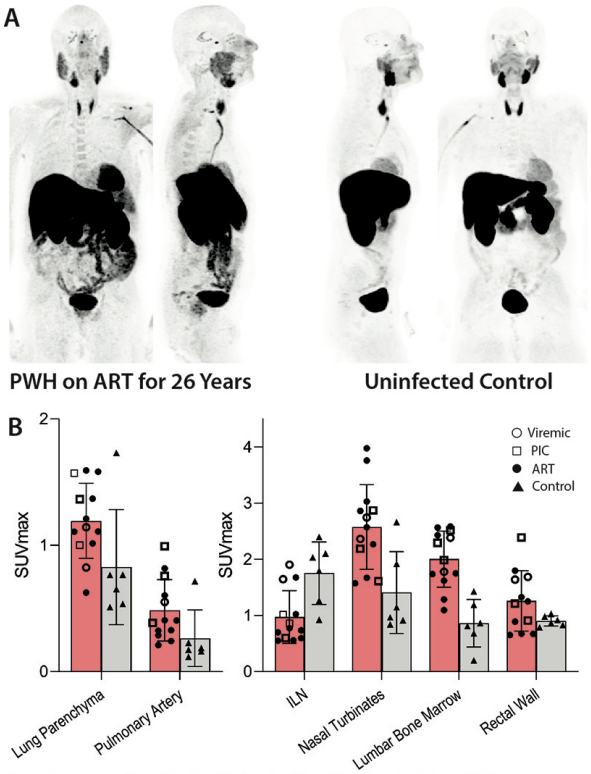

Fig 1. Increased [18F]F-AraG Uptake (T cell activation) in a PWH on ART compared with an uninfected control participant (**A**). [18F]F-AraG SUVmax values across cohorts for representative tissue regions of interest (**B**; mean and standard deviation shown).

106 Biomarker Signatures in Phase Ib Study With PD-1 Inhibitor, Budigalimab, in PLWH Undergoing ATI

Preethi Krishnan[1], Ana Gabriela Pires Dos Santos[1], Harsh Sharthiya[1], Rakesh L. Tripathi[1], Thomas J. Reisch[1], Tanaya Vaidya[1], Fei Zhou[1], Moti Ramgopal[2], Meri Oliva[1], Aparna Vasanthakumar[1], Daniel E. Cohen[1], Jean-Pierre Routy[3], Patrick K. Dorr[1]
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Background: HIV infection is a major global health problem with ART-free viral control remaining an unmet need. PD-1 blockade offers a promising approach to help address this. We conducted a phase 1b randomized double-blind study (NCT04223804) with an investigational PD-1 inhibitor, budigalimab, in people living with HIV-1 (PLWH) and included planned analytical treatment interruption (ATI) enabling exploratory efficacy and biomarker analyses. Budigalimab was well tolerated, and ART-free viral suppression was observed in a subset of participants. Preliminary exploratory biomarker analyses characterizing the impact of treatment and ATI are presented.
Methods: Safety, pharmacokinetics and pharmacodynamics were examined across multiple intravenous doses of budigalimab (2–10 mg; n=31) and placebo (n=10). Exploratory analyses examined off-ART viral load kinetics, PD-1 receptor saturation, T cell activation and proliferation, plasma cytokines and chemokines, and genome-wide transcriptomic abundances.
Results: High peripheral PD-1 receptor saturation was observed for a period of approximately 10 weeks with 10mg Q2Wx4 doses of budigalimab. Six of 9 participants who completed the 10mg Q2Wx4 doses administered during ATI had delayed viral rebound and/or off-ART viral control (HIV-1 RNA <1000 copies/mL), with 2 participants maintaining viral control off ART at <200 copies/mL for over 29 weeks. None of the participants receiving placebo demonstrated this viral load kinetic profile. Increased CD8+ T cell activation was observed and correlated with viral load during ATI. Participants with high viral load during ATI displayed differential transcriptomic trajectories as compared to the profile in participants with low viral load (HIV-1 RNA <1000 copies/mL). Budigalimab treatment was associated with more frequent increases in plasma CXCL9 and CXCL10 during ATI as compared to placebo, though there was no association of these markers with treatment response. A trend in budigalimab-mediated

expansion of peripheral CXCR5+CD8+ T cells, T follicular helper- like cells and CCR6+CD4+ T cells was observed in the participants with low viral load, potentially contributing to HIV-specific T cell responses.
Conclusion: Low dose budigalimab was well-tolerated in Phase 1b studies in PLWH. The exploratory efficacy and biomarker responses highlighted encouraging characteristics of budigalimab in facilitating immune- mediated viral control, warranting further evaluation in Phase 2 studies.

107 Live Single-Cycle SARS-CoV-2 Vaccine Elicits High Protection and Sterilizing Immunity

Fabian Otte[1], David Hauser[1], Martin J. Lett[2], Jacob Schoen[3], Enja T. Kipfer[1], Donata Hoffmann[3], Nico J. Halwe[3], Angele Breithaupt[3], Lorenz Ulrich[3], Tobias Britzke[3], Lorena Urda[1], Christian Mittelholzer[1], Martin Beer[3], Thomas Klimkait[1]
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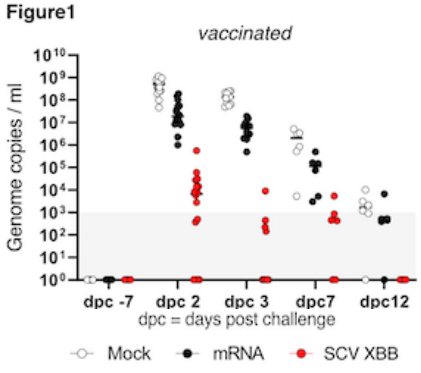
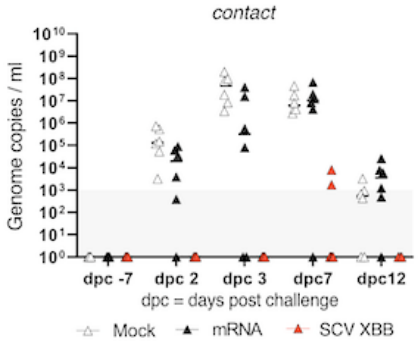
Background: The SARS-CoV-2 pandemic called attention to an urgent need for fast and versatile vaccine development platforms to combat infectious RNA viruses. However, there is a continuous need for new, innovative tools to study viruses with large RNA genomes that have a pathogenic potential for human disease.
Methods: We developed the novel vaccine concept of 'single-cycle infection viruses' (SCV) and completed the proof-of-concept for SARS-CoV-2 in the Syrian hamster model. 'CLEVER' (Cloning-free and Exchangeable system for Virus Engineering and Rescue), a DNA-based strategy for rapidly generating RNA viruses directly from PCR products, enabled the specific deletion of individual viral genes in a single step. We generated and profiled replication-deficient SARS-CoV-2 variants, for which the missing function could efficiently be complemented in trans. Animals were intranasally prime/boost vaccinated, challenged with wild-type SARS-CoV-2, and assessed for protection against viral infection, transmission, and pathogenesis. Moreover, primary human T cells were utilized to assess the potency in eliciting a specific T-cell response by our SCV candidate.
Results: Several SCV candidates were produced and tested for functionality, stability, and safety (single-cycle properties) in vitro. After intranasal vaccination, animals tolerated the vaccine very well and experienced no weight loss, even when high doses were applied, validating excellent in vivo safety. All animals were fully protected against an autologous challenge with a high dose of infectious SARS-CoV-2 virus. With the specific deletion of three immune-modulatory viral genes sterilizing immunity was achieved, preventing any viral spread to unvaccinated contact animals. Superior immune function was further shown by specific memory T cell responses in primary PBMCs from SARS-CoV-2 pre-exposed individuals. The SC vaccine effectively prevented viral infection with reduced inflammatory cytokine levels and pathology in the lung. In a direct comparison with the most recent bivalent mRNA vaccine superior immunity was confirmed for omicron-adapted SCV: full protection of vaccinated animals, no sign of viral replication and pathology in the contact animals, achieving again sterilizing immunity (Fig. 1).
Conclusion: SCVs can induce broad protection and even sterilizing immunity against viruses, as demonstrated for SARS-CoV-2. We will use the concept to build a vaccine platform targeting other RNA viruses of concern, like Dengue or Chikungunya.

Figure1





108 Mini-Lecture on Neuropathogenesis of HIV

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Background: The central nervous system (CNS) presents a unique challenge for HIV cure strategies given the diverse infected cells that persist on antiretroviral therapy (ART) – including infected microglia, astrocytes and circulating T-cells, as well as the presence of the blood brain barrier (BBB), and the adverse acute and chronic consequences of localised inflammation. Numerous studies have now clearly demonstrated the persistence of intact and transcriptionally active cells in the CNS and that the frequency of infected cells and or free virus in the cerebrospinal fluid is associated with adverse neurological outcomes in people with HIV on ART. Using in vitro infection models, latency reversing agents (LRAs) have been shown to have greater potency in astrocytes compared to monocyte derived macrophages. Several clinical trials of LRAs that can cross the BBB, have demonstrated no adverse effects on the CNS in vivo, although the combination of disulfiram with vorinostat had significant neurotoxicity. Newer HIV-specific LRAs using Tat mRNA in a lipid nanoparticles will need to be evaluated in animal models to determine if the theoretical risk of neurotoxicity will be a barrier to further development. With the high interest in immunotherapy and gene therapy currently for an HIV cure, more data is needed to fully understand whether the specific intervention can cross the BBB, whether the intervention is effective in the CNS and whether there are CNS-specific adverse events of concern. Finally, in small prospective studies, antiretroviral therapy interruption has been shown to have limited adverse outcomes on the CNS, but some participants are at higher risk for an adverse outcome and these issue should be considered in the inclusion criteria of future HIV cure clinical trials. Our understanding of the impact of cure interventions on the CNS is critically important but currently limited and needs to be prioritised.

109 Assessing the Contribution of Glial Activation to Cognitive Control and Declarative Memory in PWH

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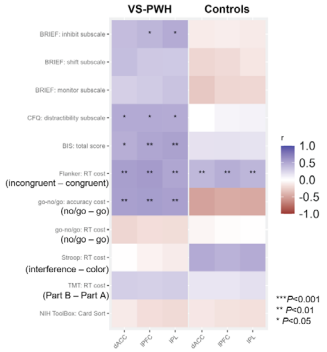
Background: Virally suppressed people with HIV (VS-PWH) demonstrate impaired cognitive control (CC; executive function) and declarative memory (learning and memory), subdomains of the NIMH Research Domain Criteria framework. Building on evidence supporting a microglial contribution to central nervous system complications in VS-PWH, we used [11C]DPA-713 with positron emission tomography (DPA-PET) to track the translocator protein (TSPO) on activated microglia in the brains of VS-PWH. We hypothesized that VS-PWH (vs. controls) would show higher TSPO in brain regions that subserve CC (lateral prefrontal cortex [lPFC], dorsal anterior cingulate [dACC], inferior parietal lobe [lPL]) and declarative memory (PFC, hippocampus) and that higher TSPO in these regions of interest (ROI) would relate to poorer CC and declarative memory self-report and behavioral measures.
Methods: Twenty-five VS-PWH and 18 demographically-similar control participants completed one 90-min DPA-PET scan with arterial blood sampling, structural brain magnetic resonance imaging, as well as CC (see Figure) and declarative memory measures (Buschke Selective Reminding test, Pattern Separation and Completion, Cognitive Failures Questionnaire-forgetfulness subscale). Regional [11C]DPA-713 total distribution volume (VT) values were

estimated using Logan graphical analysis with metabolite-corrected arterial input function. Regional VT values were compared between serostatus groups (adjusting for TSPO rs6971 genotype) using a linear mixed model with repeated measures. Partial correlations were conducted between ROIs and CC/declarative memory assessments controlling for TSPO genotype.

Results: Higher [11C]DPA-713 VT values in CC and DM ROIs were found in VS-PWH vs. controls (P<0.05), with similar magnitude of group difference across the ROIs. In VS-PWH, but not controls, higher [11C]DPA- 713 VT in CC regions associated with greater subjective complaints of impulsivity and distractibility (see Figure). Higher VT in CC regions also related to objective measures of CC (Flanker; go-no/go) in each group. For declarative memory, reported forgetfulness but not declarative memory performance associated with higher [11C]DPA-713 VT in PFC in VS-PWH.

Conclusion: Higher [11C]DPA-713 VT in CC regions associated with subjective impulsivity and distractibility and lower performance on CC measures. Localized microglial activation in the lPFC, dACC, and IPL may contribute to lower CC in VS-PWH. In contrast, associations with declarative memory were not evident.

Figure. Associations between [^{11}C]DPA-713 V_T binding in cognitive (CC) regions (dorsal anterior cingulate [dACC], lateral prefrontal cortex [lPFC], inferior parietal lobe [IPL]) and CC measures (Barratt Impulsiveness Scale-BIS, Behavior Rating Inventory of Executive Function-BRIEF, Cognitive Failures Questionnaire-CFQ, Flanker, go/no-go, Trail Making Test-TMT, Stroop, Card Sort) in VS-PWH and controls. RT=reaction time.



110 Associations Between Depressive Symptom Severity and Incident Stroke Among People With HIV

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Background: Among people with HIV (PWH), depression is a common psychiatric condition and an independent stroke risk factor. To clarify potential pathways in this association, we examined different levels and patterns of depressive symptom severity and incident stroke in PWH.

Methods: We studied adult PWH in clinical care at 5 US sites in the CFAR Network of Integrated Clinical Systems (CNICS) cohort with ≥1 assessment for self-reported depressive symptoms (PHQ-9) through 2022. Neurologists centrally adjudicated all strokes. Participants were followed from the closest encounter on/after the first PHQ-9 measure until stroke, death, loss to follow-up, or study end. A PHQ-9 score ≥10 was a positive screen for depression. We used adjusted Cox models to evaluate (1) associations between time-varying depressive symptom severity and incident stroke, (2) moderation of this relationship by age and sex, and (3) different patterns of depressive symptom severity. Patterns were based on whether the baseline and next PHQ-9 measure (median time between measures 224 days, IQR 140-461) had a positive screen for depression: (1) none/mild: negative screens for both, (2) new onset: negative then positive screen, (3) remitted: positive then negative screen, (4) persistent: positive screens for both.

Results: Among 13817 PWH, at baseline, mean follow up was 7.6 years [SD 3.5], mean age was 45 years [SD 11], 19% were female, 58% reported non-white race/ethnicity, 78% had HIV RNA <200 copies/mL, and 23% screened positive for depression. A total of 173 had an incident stroke during follow up. Time-varying depressive symptom severity (per 5-pt PHQ-9 score) was associated with higher stroke risk (aHR 1.16, P=0.01) with greater impact in PWH <50y than ≥50y (Interaction P=0.02) but no significant difference by sex. Adjusting for baseline antidepressant use did not change the main estimate (aHR 1.16, P=0.02). New onset depressive symptoms were associated with the highest stroke risk among different patterns of depressive symptoms: none/mild (referent), new onset (aHR 1.93, P=0.009), remitted (aHR 1.31, P=0.3), persistent (aHR 1.31, P=0.1).

Conclusion: Higher severity depressive symptoms were associated with higher stroke risk with greater impact in younger PWH. Stroke risk was considerably elevated with new onset depression. Findings suggest depression may be a modifiable stroke risk factor and potential benefits of early screening and interventions for depression, especially for younger PWH and those with new onset depression.

Table. Cox proportional hazards models[a] of depressive symptom severity and incident strokes.

Parameterization, Stratum, or Category		Outcome N	Hazard Ratio	95% Confidence Interval	P	Interaction P
Parameterization 1: Time-varying depressive symptom severity (per 5 points PHQ-9 score) (N=13817)		173	1.16	1.03, 1.30	0.01	-
Adjusting for baseline antidepressant use		173	1.16	1.03, 1.31	0.02	-
Moderation by Age	Stratum: <50y	75	1.29	1.10, 1.51	0.002	0.02
	Stratum: ≥50y	98	1.01	0.84, 1.21	0.9	
Moderation by Sex	Stratum: Male	128	1.18	1.03, 1.35	0.02	0.7
	Stratum: Female	45	1.14	0.91, 1.43	0.2	
Parameterization 2: Patterns of depressive symptom severity (N=10915)						
New onset pattern (relative to none/mild pattern as referent)		20	1.93	1.18, 3.16	0.009	-

[a]Models adjusted for age, sex, race/ethnicity, CNICS entry year, and baseline treated hypertension, diabetes, statin use, eGFR, and tobacco use unless otherwise mentioned. Separate models were completed for interaction or stratification for each moderation covariate.

111 Carotid Inflammation on FDG-PET Is Associated With Lower Cognitive Function in Treated HIV Infection

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Background: Studies investigating the relationship between cardiovascular disease (CVD) and cognition in people with HIV (PWH) have largely focused on CVD risk factors and cerebral small vessel disease. We examined the relationship between subclinical carotid arterial inflammation on 18F-fluorodeoxyglucose (FDG)- PET and cognitive function in PWH.

Methods: ART-treated PWH at moderate to high CVD risk underwent PET/CT of the neck and chest, from which we calculated FDG uptake in the carotid arteries and ascending aorta. Participants completed a battery of neuropsychological tests (Hopkins Verbal Learning Test-Revised, Digit Symbol, Grooved Pegboard, Trail Making Test Parts A & B, Stroop, Letter Fluency) and stress measures within 2 weeks of the PET scan. Z scores were created by comparing raw scores to age, sex, ethnicity, and education-matched norms and then averaged into a global cognitive summary score. In addition to individual CVD risk factors, we devised a CVD risk score reflecting the total number of CVD risk factors (history of heart disease or stroke, hypertension, diabetes, dyslipidemia, or current smoking) per participant. We used partial correlations to examine the relationship between arterial inflammation and global cognition adjusted for age, race, and education.

Results: Forty-seven PWH (mean age 60, 98% men) with undetectable viral load were included. Carotid inflammation was negatively correlated with global cognition (r=-0.32, p=0.037), even after adjusting for CVD risk (r=-0.34, p=0.029). In contrast, aorta inflammation was not associated with global cognition (r=-0.05, p=0.75). Current smoking was the only individual CVD risk factor that correlated significantly with global cognition (r=-0.35, p=0.018). The correlation between carotid inflammation and global cognition was slightly attenuated after adjusting for current smoking (r=-0.30, p=0.055). Of stress measures that correlated significantly with global cognition (post-traumatic stress, r=-0.47, p=<0.001; early childhood stress, r=-0.43, p=0.003), the negative correlation between carotid inflammation and global cognition remained significant after accounting for post-traumatic (r=-0.33, p=0.033) but not early childhood stress (r=-0.25, p=0.10).

Conclusion: Carotid but not aorta inflammation was negatively correlated with global cognition independent of CVD risk. Future studies should focus on identifying upstream factors that may be targeted to reduce carotid inflammation and potentially preserve cognitive health in PWH.

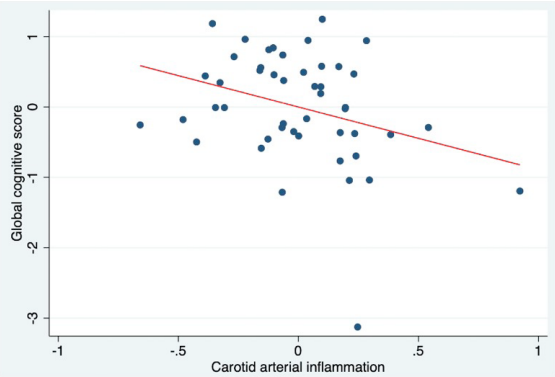

Figure. The relationship between carotid arterial inflammation and global cognition in people with treated HIV. The partial regression plot shows a significant association between carotid inflammation and cognition adjusted for age, race, and years of education (p=0.037).

112 Low Levels of HIV-1 in CSF During ART Are Associated With Neurocognitive Impairment and Inflammation

Laura P. Kincer[1], Sarah B. Joseph[1], Jessica R. Keys[1], Natalie M. Bowman[1], Chris Evans[1], Alyssa Vecchio[1], Serena Spudich[2], Magnus Gisslén[3], Prema Menezes[1], Frank Maldarelli[4], Robert Gorelick[4], Joseph J. Eron[1], Richard W. Price[5], Ronald Swanstrom[1]

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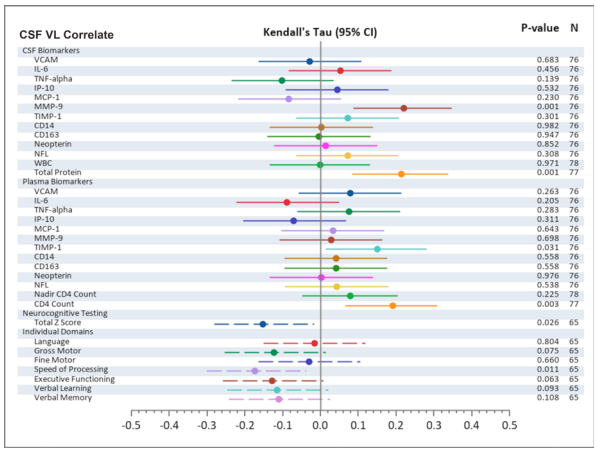
Background: Antiretroviral therapy (ART) typically reduces HIV-1 RNA to below the limit of detection of standard vial load (VL) assays and facilitates immune reconstitution, but neurocognitive impairment (NCI) persists in many people on ART. Previous studies have suggested that higher HIV-1 cell-associated DNA and cell-free RNA levels in cerebrospinal fluid (CSF) are positively associated with neurocognitive impairment (NCI), but the mechanisms driving this association are unknown.

Methods: In a cross-sectional cohort of participants (N=78) who were on ART for at least a year and lacked overt neurologic symptoms, we examined whether the amount of HIV-1 RNA in cerebrospinal fluid (CSF) during ART is associated with elevated inflammation and/or NCI. We measured neurocognition by an 11-test battery and also measured plasma and CSF VLs (by both standard [Abbott Real Time assay, limit of detection (LOD) 40 cps/ml] and single copy assays [SCA, HHMCgag assay, LOD 0.25 cps/ml]), cell counts, and 12 inflammatory biomarkers.

Results: ART regimens were NNRTI- (34%), PI- (33%), and InSTI-based (29%). Median blood CD4+ T cell counts, nadir blood CD4+ T cell counts, and CSF WBC counts were 506 cells/µl, 127 cells/µl, and 1 cell/µl, respectively. The cohort was divided into three groups with increasing HIV-1 RNA levels in CSF (median, IQR cp HIV-1 RNA/ml): (1) undetectable by all assays, (2) detectable by SCA only (0.33, 0.27-1.2 by SCA), (3) detectable by standard assay (40, 40-40 by standard assay). Using Kendall's tau rank correlation (Figure 1), we observed that levels of HIV-1 RNA in CSF were positively correlated with CSF MMP9 (p=0.001), CSF protein (p=0.001), plasma TIMP1 (p=0.031) and blood CD4+ T cell count (p=0.003) and negatively correlated with total neurocognition z score (p=0.026) and speed of processing z score (p=0.011).

Conclusion: We observed that during ART small increases in HIV-1 RNA that do not reach the level of treatment failure or CSF escape are associated with increased immune activation (CSF MMP9, plasma TIMP1), blood-brain barrier disruption (CSF protein) and neurocognitive impairment (total z and speed of processing z). This contributes to the growing evidence that persistent exposure to HIV-1 in the CNS during ART is associated with NCI and suggests that inflammation may play an important role in this process.



113 HIV Transcription Persists in the Brain of People With HIV and Viral Suppression

Janna Jamal Eddine[1], Thomas A. Angelovich[1], Jingling Zhou[1], Sarah J. Byrnes[1], Carolin Tumpach[2], Nadia Saraya[2], Emily Chalmers[1], Stephanie Marinis[1], Paul R. Gorry[2], Jacob D. Estes[3], Bruce J. Brew[4], Sharon R. Lewin[2], Sushama Telwatte[2], Michael Roche[2], Melissa J. Churchill[1]

[1]RMIT University, Melbourne, Australia, [2]Peter Doherty Institute, Melbourne, Australia, [3]Oregon Health and Sciences University, Portland, OR, USA, [4]St Vincent's Hospital, Sydney, Australia

Background: HIV persistence in the brain is a barrier to cure, and potentially contributes to HIV-associated neurocognitive disorders (HAND) that affect ~30% of people with HIV (PWH) despite viral suppression with antiretroviral therapy (ART). Persistent HIV transcription and blocks to transcription have been identified in latently infected CD4+ T cells from blood and lymphoid tissues. However, whether HIV transcription persists in the brain despite viral suppression with ART and is subject to the same blocks to transcription seen in other tissues and blood cells, is unclear.

Methods: HIV transcriptional profiling of autopsy frontal cortex brain tissue from virally suppressed (n=12; undetectable plasma viral load [pVL]: <50 c/mL; 335 CD4+ T cells/mm³) and non-virally suppressed PWH (n=13; pVL: 61,223 c/mL; 8 CD4+ T cells/mm³) was performed using nanowell digital PCR based assays. Associations between levels of HIV transcripts, clinical parameters, and levels of the intact and defective HIV reservoir in frontal cortex tissue as measured by IPDA were assessed by correlative analysis.

Results: Frontal cortex tissue from PWH had HIV TAR (n=25/25) and Long-LTR (n=23/25) transcripts, indicative of transcriptional initiation and early elongation, respectively. Completion of HIV transcription (PolyA) and multiple splicing (Tat/Rev) was evident in frontal cortex tissue from 7/13 non-virally suppressed PWH and from 4/12 virally suppressed PWH. HIV p24 protein was also detected in all PWH with PolyA and Tat/Rev transcripts (11/11), demonstrating production of viral proteins in these individuals. Proximal and distal blocks to transcription were present in both groups. However, the block to proximal elongation (TAR→Long-LTR) was more extensive in virally suppressed PWH than in non-virally suppressed individuals (P<0.05; ratio: 2.7-fold greater block). Levels of all HIV transcripts correlated with levels of total and intact HIV proviruses (P<0.05 for all), demonstrating that the level of HIV transcription is associated with HIV reservoir size in the brain.

Conclusion: These findings demonstrate that the brain is a transcriptionally active HIV reservoir in virally suppressed PWH which may contribute to ongoing neuroinflammation and HAND.

114 Infected T-Cell Clones Are Shared Across CSF and Blood Compartments in PWH

Meng Wang[1], Jennifer Yoon[1], Hailey Reisert[1], Bibhuprasad Das[1], Jennifer Chiarella[1], John W. Mellors[2], Alina P. Pang[1], Joshua C. Cyktor[2], Margaret Fikrig[1], Elias K. Halvas[2], Yuval Kluger[1], Serena Spudich[1], Michael J. Corley[3], Shelli Farhadian[1]

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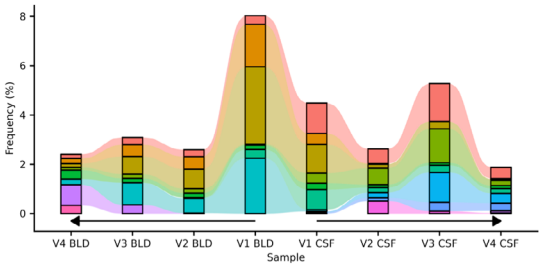
Background: The central nervous system (CNS) is a site of persistently infected cells during HIV infection. However, the dynamics of CNS infection and T cell trafficking in PWH are incompletely understood. Here, we utilized single-cell

T cell receptor (TCR) and transcriptome profiling of paired CSF and blood from PWH to gain insights into the dynamics of rare HIV-1 RNA-producing T cells in both compartments, and under the pressure of ART.

Methods: We enrolled eight PWH; seven were on suppressive ART and one had chronic HIV profiled before and 3, 7, and 9 months after ART. We also enrolled six HIV-uninfected controls, demographically matched to PWH. We profiled single cell TCR and RNA from paired CSF and blood using 5' V(D)J 10x Genomics scRNA-seq and scTCR-seq. To identify whether there were detectable transcriptionally active HIV-1 RNA producing cells in CSF and blood, we aligned the single cell transcriptome sequencing reads against consensus and autologous HIV-1 genomes.

Results: In total, we examined the single-cell transcriptomes of 129,544 CSF cells and 262,818 PBMCs from PWH and controls. We detected transcriptionally active HIV-1 RNA producing cells in 8/11 (72.7 %) CSF samples and 6/11 (54.5 %) blood samples, with a higher frequency of infected single CD4+ T cells in CSF than in blood. Among infected CD4+ T cells, a majority (83.6 %) were identified as CD4+ central memory T cells. Differential expression analyses revealed infected CSF T cells displayed a unique transcriptional profile compared to uninfected CSF T cells. We utilized scTCR data to identify 36 T cell clones containing infected cells. Most (78%) of these T cell clones were tissue specific (found in blood or CSF but not both), but some (22%) clones containing infected cells were found in both CSF and blood. Most infected cells belonged to singletons (unique TCR clones), but 28% belonged to TCR clones with evidence of clonal expansion. Longitudinally following one PWH before and at three time points after initiating ART, we found infected T cell clones that persisted after ART initiation, in both CSF and blood, including a T cell clone that expanded in the CSF several months after ART initiation.

Conclusion: By tracking T cell clones across times and tissue, we find that T cell clones persist in the CNS over time. Infected, identical, and expanded T cell clones are found across tissue compartments. Our findings suggest that maintenance and expansion of infected T cell clones contributes to the CNS reservoir in PWH on ART.



Longitudinal changes in TCR repertoire before and after ART. Frequency of the largest twelve TCR clones in blood and CSF of one PWH, before ART (V1) and after ART (V2-V4). Note that time points were shown in reverse order for blood samples.

115 Single Dose Administration of MK-8527, a Novel nRTTI, in Adults With HIV-1

Russ P. Carstens[1], Yash Kapoor[1], Ryan Vargo[1], Arinjita Bhattacharyya[1], Graigory Garrett[1], Jean- Francois Denef[2], Kemira Naidoo[1], Liliana Preotescu[3], Richard Kaplan[4], Mohammed Rassool[5], Johannes Lombaard[6], Randolph P. Matthews[1], S. Aubrey [0]. Stoch[1], Marian Iwamoto[1], Gillian Gillespie[1]

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Background: MK-8527 is a novel oral nucleoside reverse transcriptase translocation inhibitor (NRTTI) under clinical development as an antiretroviral for HIV-1 infection. Based on previous preclinical and phase 1 clinical studies, the pharmacokinetic properties of MK-8527 support extended once-weekly or longer dosing. Two phase 1 single dose monotherapy studies were conducted to evaluate the antiretroviral activity of MK-8527 in treatment-naive participants with HIV-1.

Methods: Eligible participants were treatment-naive adults 18–60 years of age with HIV-1. In two phase 1 studies (NCT03615183 and NCT05494736), participants received a single oral dose of MK-8527 (0.5, 1, 3, or 10 mg). Reduction in viral load (measured as $\log_{10}$ plasma HIV-1 RNA copies/mL), safety, tolerability, and intracellular pharmacokinetics of MK-8527-triphosphate (TP, the active form of MK-8527) in peripheral blood mononuclear cells were assessed. Data were analyzed and presented per dosing panel; data for the 1-mg dose group were pooled from both studies. Incidence of adverse events were descriptively summarized.

Results: A total of 31 participants have been enrolled and completed dosing. Following single doses of 0.5 to 10 mg, the mean decrease in HIV-1 RNA at Day 7 following dose administration was ≥1.0 $\log_{10}$ copies/mL (Table). The inhibitory quotient (defined as the ratio of geometric mean of MK-8527-TP C168 and IC_{50}) exceeded 3 at all doses assessed. MK-8527 at all dose levels was generally well tolerated, with a limited number of mild to moderate adverse events determined by investigators to be unrelated to the study treatment; there were no serious adverse events, events of clinical interest, or deaths.

Conclusion: In treatment-naive persons with HIV-1, single doses of MK-8527 as low as 0.5 mg achieved ≥1 $\log_{10}$ decreases in HIV-1 RNA at Day 7 following dose administration.

Table. Change in plasma HIV-1 RNA at 168 hours following a single oral dose of MK-8527.

[a]Data for 1 mg group were pooled from two phase 1 studies.

Outcome	10 mg N = 6	3 mg N = 6	1 mg N = 13[a]	0.5 mg N = 6
Change in plasma HIV-1 RNA, mean, (range), log10 copies/mL	−1.39 (−1.67 to −0.87)	−1.66 (−2.02 to −1.23)	−1.21 (−2.10 to 0.03)	−1.39 (−1.54 to −1.24)

116 Antiviral Activity, Safety, and Pharmacokinetics of GS-1720: A Novel Weekly Oral InSTI

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Background: Significant medical need exists for antiretroviral agents that can be administered less frequently. GS-1720 is an orally bioavailable integrase strand transfer inhibitor (INSTI) with potent antiviral activity and physiochemical properties well-suited for a long-acting formulation. We are investigating the antiviral activity, safety, and pharmacokinetics (PK) of GS-1720.

Methods: An open-label, multi-cohort Phase 1b study is being conducted in participants with HIV who are treatment-naïve or viremic and off antiretroviral therapy for at least 12 weeks. Based on safety and PK data from a Phase 1a study in healthy volunteers, participants are being administered GS-1720 on Day 1 and 2 and followed for a total of 10 days. The primary endpoint is plasma HIV-1 RNA ($\log_{10}$ copies/mL) change from baseline to Day 11. Secondary endpoints include plasma HIV-1 RNA change at Day 8 in addition to PK parameters and safety assessments. Genotypic and phenotypic sensitivity testing to drugs from the INSTI class is also being conducted from samples collected during screening and Day 11 visits.

Results: Preliminary PK from the Phase 1a study showed a median half-life of 9.4 days with a single GS-1720 dose of 450 mg. In the first Phase 1b cohort (n=7; 6 males, 1 female and mean age 35) dosed daily on Day 1 and Day 2 with 450 mg, GS-1720 demonstrated an HIV-1 RNA mean $\log_{10}$ copies/mL reduction at Day 11 of 2.44 (95% confidence interval [CI] 2.04, 2.83) and at Day 8 of 2.04 (95% CI 1.72, 2.36). No participants experienced any serious adverse events (AEs), Grade 3 or higher treatment-emergent AEs, or AEs related to study drug. No treatment-emergent INSTI resistance was observed.

Conclusion: GS-1720 demonstrated potent antiviral activity and PK supportive of once weekly oral dosing while being well-tolerated. The observed >2 $\log_{10}$ copies/mL decline in HIV-1 RNA and half-life >1 week in this cohort demonstrates the potential of GS-1720 as part of an oral weekly INSTI-based regimen.

117 VH3810109 (N6LS) in Adults With HIV-1 Who Are ART-Naive: Phase IIa BANNER Efficacy Data

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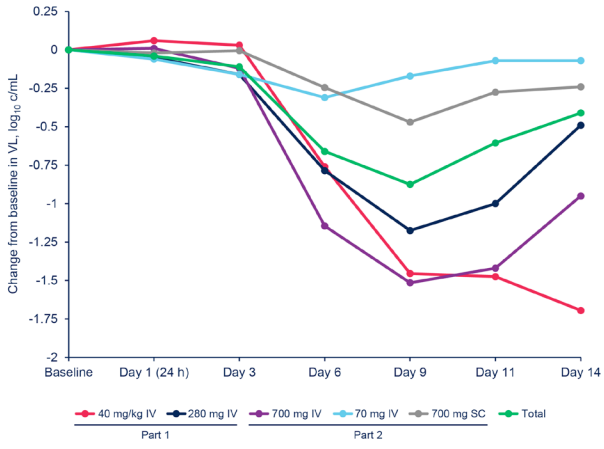
Background: The broadly neutralizing antibody (bNAb) VH3810109 (N6LS), a CD4-binding site antibody with broad and potent neutralizing activity in vitro, demonstrated robust antiviral effect (median viral load [VL] decline of 1.72 log_{10} c/mL and maximum viral nadir from baseline [BL] of −2.60 log_{10} c/mL) when given at 40 mg/kg intravenously (IV) in people with HIV-1 in part 1 of the proof-of-concept BANNER study and a good safety profile in parts 1 and 2. We report efficacy data for N6LS administered IV or subcutaneously (SC) in parts 1 and 2 of BANNER.

Methods: BANNER is a randomized, open-label, 2-part, multicenter study assessing safety, pharmacokinetics, and antiviral activity of N6LS in treatment-naive adults with VL ≥5000 c/mL. N6LS was evaluated during monotherapy after a single IV infusion or SC injection, followed by 48 weeks of standard-of-care antiretroviral therapy. Monotherapy duration was determined by virologic non-response (VL <0.5 log_{10} by Day 11) or rebound (VL ≥1.0 log_{10} over nadir or <0.5 log_{10} from BL).

Results: Of 62 participants, 8 received 40 mg/kg IV and 6 received 280 mg IV in part 1; 16 received 700 mg IV, 16 received 70 mg IV, and 16 received 700 mg SC in part 2. Most participants were male (94%), White (61%), and Hispanic (82%). Median (range) age was 29 (18-61) years. At BL, median VL ranged from 4.1 to 4.5 log_{10} c/mL across dose groups. Median (range) maximum VL decline ranged from −0.43 (−1.29 to −0.12; 70 mg IV group) log_{10} c/mL to −1.72 (−2.60 to −0.60; 40 mg/kg IV group) log_{10} c/mL and was reached in a median of 9 days (Figure). Among responders, median (range) time to rebound ranged from 13 (10-22; 70 mg IV group) days to 35 (12-78; 40 mg/kg IV group) days. Across dose groups, there was a weak-to-moderate correlation between BL viral sensitivity and maximum VL decline. N6LS was well tolerated when given IV or SC, with few drug-related adverse events (AEs) and no serious AEs.

Conclusion: Robust antiviral activity was observed after IV and SC administration of N6LS; response was correlated with N6LS exposure. Response with SC vs IV dosing was lower and likely due to differences in BL susceptibility, serum antibody levels, and slower time to reach C_{max}. Overall, N6LS led to dose-dependent declines in VL consistent with antiviral activity reported for other bNAbs. Results support the ongoing development of N6LS into phase IIb.

Figure. Median log_{10} change from baseline in VL by visit during the first 14 days of the monotherapy phase in parts 1 and 2 of BANNER (safety population).



118 A First-in-Human Study of the Trispecific HIV-1 Broadly Neutralizing Antibody, SAR441236

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Background: The trispecific broadly neutralizing antibody (bNAb) SAR441236 combines the HIV-1 specificities of VRC01 (CD4 binding site), PGDM1400 (V1/V2 glycan binding), and 10E8v4 (membrane proximal external region) into one molecule with amino acid modifications (LS) in the Fc-region for half-life extension. SAR441236 provided complete protection against macaque SHIV challenge but has not been tested in people with HIV (PWH).

Methods: ACTG A5377 was a phase I study evaluating the safety, pharmacokinetics (PK), and antiviral activity of SAR441236, a trispecific HIV-1 bNAb. Escalating intravenous (IV) or subcutaneous (SC) single doses of SAR441236 (from 0.3 – 10 mg/kg) or 4 doses at 30 mg/kg IV (every 12 weeks with 72 weeks of follow up) were assessed in ART-treated PWH with plasma viral RNA <50 copies/mL. Dose cohorts were randomized 2:1 to SAR441236 or placebo. Single open-label IV doses of 1 mg/kg or 30 mg/kg were assessed in viremic participants (ART-naïve or no ART in the preceding 3 months). Primary outcomes were study treatment-related Grade ≥3 adverse events, AUC**0-12**wk of SAR441236, and the day 7 change in plasma HIV-1 RNA levels in viremic participants.

Results: A total of 52 participants were enrolled and 51 received study treatment. Median age was 53 years. 10% were female, 37% were Black, and 12% were Hispanic. No events met the primary safety outcome (95% CI 0-0.09). Population PK analysis demonstrated an overall clearance (CL) of 137 ± 86 mL/d, a volume of distribution (Vds) of 6.3 ± 2.4 L, population SC bioavailability of 35 ± 7%, and a half-life ($t_{1/2}\beta$) of 38 ± 10 days. SAR441236 CL was 38% higher in viremic cohorts. For the 30 mg/kg single dose in aviremic participants, the AUC0-12wk was 22,292 ± 889 µg*d/mL (mean ± SD). Monte Carlo simulations predicted 30 mg/kg IV every 12 weeks to result in a median steady-state trough of 74 µg/mL (90% PI 25-185 µg/mL). Only 7 of 24 planned viremic participants were enrolled. The mean change to day 7 plasma HIV-1 RNA levels in the 1 mg/kg cohort (n = 5) was -0.10 log_{10} copies/mL and -0.38 log_{10} copies/mL in the 30 mg/kg cohort (n = 2).

Conclusion: SAR441236 administration was safe and well tolerated. The PK of SAR441236 was similar to traditional HIV-1 IgG antibodies with half-life extension modifications, such as VRC07-523LS. The favorable PK and convenience of administering a single biologic with three binding specificities support the evaluation of novel trispecific or multispecific bnAbs for HIV-1 treatment or prevention.

119 Safety and Efficacy of VRC07-523LS Plus Long-Acting Cabotegravir in the Phase II ACTG A5357 Trial

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Background: Background: Broadly neutralizing antibodies (bNAbs) hold promise for antiretroviral therapy (ART). ACTG A5357 is a phase II, single-arm clinical trial, investigating the combination of VRC07-523LS, a bNAb targeting the HIV-1 CD4-binding site, and long-acting cabotegravir (LA CAB) for maintenance ART

Methods: Participants are adults with HIV, virally suppressed for >2 years, a current CD4 count ≥350 cells/mm³, and susceptibility to VRC07-523LS (IC_{50} 0.25 µg/mL and a Maximum Percent Inhibition (MPI) >98% on the Monogram PhenoSense mAb Assay using screening PBMCs). In Step 1, participants received 4 or 5 weeks of oral CAB and two NRTIs. Those still suppressed entered Step 2

and received intravenous VRC07- 523LS (40 mg/kg) Q8 weeks plus intramuscular LA CAB (600mg load followed by 400mg Q4 weeks). At the end of 48 weeks on Step 2 or premature treatment discontinuation, participants returned to a standard of care regimen for 48 weeks in Step 3. The primary outcomes were: 1) grade 3 adverse event (AE) or treatment discontinuation related to VRC07-523LS and LA CAB; and 2) virologic failure (VF) defined as confirmed viral load (VL) ≥200 c/mL at or prior to week 44 of Step 2. Efficacy analyses were as-treated; participants with VL<200 c/mL at the treatment discontinuation were censored.

Results: Analysis included complete Step 1/2 follow-up for 74 participants: 26% cis-female, 51% White (non- Hispanic), median age 54. At baseline, 96% had VL <50 c/mL, median CD4 count 720 cells/mm^3. Median IC_{50} was 0.076 µg/mL, median MPI 99.9%. Seventy-one (96%) participants initiated Step 2 treatment; 61 (86%) completed Step 2 treatment and 10 (14%) prematurely discontinued the regimen (5 VFs, 1 death, and 4 participant/physician request). Twelve (16.9%) participants met the primary safety endpoint: 11 (15%) had grade ≥3 AEs (mostly chills, myalgia, fatigue) and one discontinued therapy due to a grade 1 infusion-related reaction. The only death was unrelated to study treatment. The five VFs (Table) include two of the three participants with VL 51-200 c/mL at week 4. The cumulative probability of VF at or prior to week 44 of Step 2 treatment was 7.3% (95% CI 3.2-16.0%). The integrase R263K mutation was seen in a participant at VF. Pharmacokinetics and anti-idiotype antibodies results are expected in late 2023

Conclusion: The parenteral maintenance ART regimen of VRC07-523LS plus LA CAB was safe. Most participants maintained viral suppression. Observed potential vulnerabilities should inform future bNAb based ART strategies.

Table: Characteristics of the five participants with virologic failure on VRC07-523LS plus LA CAB (Step 2)

Participant	HIV-1 RNA (copies/mL) Step 1 Wk 4 / 5	HIV-1 RNA (copies/mL) Step 2 Initial Rebound / VF Confirmation	INSTI HIV Genotype at VF	VRC07-523LS Susceptibility [A] IC50 (ug/mL) Screening / VF	VRC07-523LS Susceptibility [A] MPI (%) Screening / VF	Other Observations [B]
31311489	<50 / NA	267 (Wk32) / 251	Failed to amplify	0.102/ NR	99.825 / NR	Received Mpox vaccine 9 days before Week 32
80680715	<50 / NA	829 (Wk20) / 546	None	0.038 / NR	100 / NR	
53632785	113 / <50	401 (Wk28) / 282	None	0.056 / 0.022	99.928 / 99.913	Received COVID vaccine booster 21 days before Week 28
45708818	<50 / NA	220 (Wk12) / 841	None	0.077 / 0.052	100 / 100	Received Mpox vaccine 14 days before Week 12
40864428	138 / <50	887 (Wk6) / 5780	R263K	0.249 / 0.209	99.877 / 99.837	bNAb IC_{50} at screening was close to the study cut-off

A. IC50 and MPI determination using VF plasma was NR *except* for 40864428 that showed IC50 of 0.610 ug/mL and MPI of 99.377
B. 38 participants received 83 vaccinations before 70 unique study visits
VF = Virologic Failure
MPI = Maximum Percent Inhibition
NA = Not applicable
NR = Non-reportable

120 Lenacapavir Plus bNAbs for People With HIV and Sensitivity to Either Teropavimab or Zinlirvimab

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Background: Lenacapavir (LEN) is a first-in-class, long-acting HIV-1 capsid inhibitor approved for treatment of HIV-1 infection in adults with multidrug resistance. Teropavimab (TAB) & zinlirvimab (ZAB) are long-acting broadly neutralizing antibodies (bNAbs), targeting the CD4-binding site & V3 loop of gp120, respectively. In a phase 1b study (NCT04811040), LEN+TAB+ZAB maintained virologic suppression (VS) for 6 months in 18/20 participants with HIV with high-level sensitivity to both bNAbs. We evaluated safety & efficacy of LEN+TAB+ZAB for maintenance of VS in a cohort of participants who met viral sensitivity criteria to either TAB or ZAB.

Methods: Virologically suppressed adults with HIV on antiretroviral therapy (ART; HIV-1 RNA <50 copies/mL for ≥18 months), with high-level sensitivity to TAB or ZAB but not both by HIV proviral DNA phenotype (PhenoSense monoclonal antibody assay IC_{90} ≤2µg/mL), a CD4 nadir of ≥350 cells/µL, & CD4 ≥500 cells/µL at baseline were randomized 1:1 to one of two active treatment groups: LEN (927 mg subcutaneously after oral loading) + TAB (30 mg/kg intravenously [IV]) + ZAB (Group 1, 10 mg/kg IV; Group 2, 30 mg/kg IV). The primary endpoint was incidence of treatment-emergent serious adverse events at Week 26; secondary endpoints included virologic outcomes (VS or ≥50 copies/mL) at Week 26 by FDA Snapshot analysis.

Results: Eleven participants were randomized & treated (Group 1, n=5; Group 2, n=6). Age range was 28–63 years; 3/11 were female; 4/11 were Black; & median CD4 count was 916 cells/µL. There was 1 serious adverse event of soft tissue infection not related to study treatment. No adverse events led to study drug. Safety outcomes were similar between groups. One participant restarted baseline ART due to a protocol violation (chronic hepatitis B infection) & was excluded from the efficacy analysis. At Week 26, 8/10 participants maintained VS (Group 1, 2/4; Group 2, 6/6). Of the two participants in Group 1 who had virologic rebound, one had sensitivity to TAB & was diagnosed with acute COVID-19 at the time of rebound, & one had sensitivity to ZAB & rebounded at Week 26; both had HIV RNA <100 copies/mL.

Conclusion: The long-acting combination of LEN+TAB+ZAB was well tolerated, with a favorable safety profile. All participants in the higher ZAB dose group maintained VS for 6 months, which suggests that more inclusive sensitivity criteria may be appropriate for treatment studies of LEN+TAB+ZAB when higher bNAb levels are maintained.

121 Therapeutic Efficacy of a Triple Combination of HIV-1 Broadly Neutralizing Antibodies

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Background: Human immunodeficiency virus type 1 (HIV-1) specific broadly neutralizing monoclonal antibodies (bNAbs) have to date shown limited therapeutic efficacy when administered as monotherapy or as a cocktail of two antibodies. A combination of three bNAbs provides improved neutralization coverage of global viruses. Here we show that a triple bNAb cocktail targeting three distinct epitopes on HIV-1 Env results in long- term virologic control in persons living with HIV-1 (PLWH) following discontinuation of antiretroviral therapy (ART).

Methods: We first evaluated the pharmacokinetics of the bNAbs PGT121, PGDM1400, and VRC07-523LS, which target the V3 glycan supersite, V2 apex, and CD4 binding site, respectively. We then assessed the therapeutic efficacy of up to six monthly infusions of this triple bNAb cocktail in 12 PLWH who discontinued ART after the first antibody infusion (NCT03721510). Participants were not screened for bNAb sensitivity at baseline.

Results: 83% of participants (10 of 12) maintained virologic suppression for the duration of the antibody dosing period for at least 28 weeks. Moreover, 42% of participants (5 of 12) demonstrated virologic suppression for the duration of follow-up for at least 38-44 weeks, despite the decline of serum bNAb concentrations to low or undetectable levels. Early viral rebound in 2 individuals correlated with baseline resistance to PGT121 and PGDM1400, whereas late viral rebound in 5 participants in the context of declining bNAb levels was characterized by both sensitive and resistant rebound virus.

Conclusion: Our data demonstrate the potential of a triple HIV-1 bNAb cocktail to provide long-term virologic control in the majority of PLWH in the absence of ART. Long-acting versions of these three bNAbs are currently being developed for HIV-1 prevention and therapy.

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122 Randomized Trial of Cabotegravir and Rilpivirine Long-Acting in Africa (CARES): Week 48 Results

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Background: Long-acting injectable therapy (LA) is a recommended option for individualized treatment of human immunodeficiency virus type 1

(HIV-1) infection in resource-rich settings. Additional evidence is required to determine the role of LA for treatment programs in Africa, where demographic factors, viral subtypes, prior treatment exposure, prevalence of pre-existing antiviral drug resistance and standardized approach to treatment delivery and monitoring differ.

Methods: This ongoing phase 3b randomized, multicentre, open-label trial evaluates efficacy, safety, and tolerability of switching from oral antiretroviral therapy (ART) to LA. HIV-1 positive adults, stable on first-line ART (TDF +3TC/FTC+EFV/NVP/DTG) with VL <50 copies/ml at screening were enrolled at 8 African sites. Main exclusion criteria were past virologic failure, pregnancy and HBV infection. Participants were randomized (1:1) to continue oral ART (OT group) or switch to cabotegravir (CAB) and rilpivirine (RPV) intramuscular injections every 8 weeks (LA group). VL was monitored every 24 weeks. Primary outcome was the proportion of participants with VL <50 copies/ml at week 48, by FDA snapshot algorithm (non-inferiority margin 10%). Confirmed virologic failure (CVF, secondary outcome) was defined as 2 consecutive VL ≥200 copies/ml. Resistance testing was done retrospectively on archived DNA at baseline in all participants, and at CVF.

Results: 512 participants were enrolled (median age 42y; 58% female; 92% on DTG-based ART; 74% with prior NNRTI exposure; 14% baseline archived RPV resistance mutations; 57% viral subtype A1; 21% baseline BMI ≥30kg/m²). Four withdrew by week 48 (2 LA, 2 OT group). At 48 weeks, 248/255 (97.3%) in LA and 252/257 (98.1%) in OT group had VL<50 copies/mL (difference -0.8%; 95%CI -3.4 to 1.8%); demonstrating non-inferiority (Table). One participant in LA group met the definition of CVF. Adverse events of grade ≥3 severity occurred in 24 (9%) in LA and 10 (4%) in OT group; only one adverse event in LA led to treatment discontinuation (injection-site abscess).Treatment satisfaction increased after switching to long-acting therapy.

Conclusion: At 48 weeks, CAB and RPV LA showed non-inferior efficacy to standard oral ART when used in the public health approach with sparse VL monitoring and where pre-existing RPV resistance, subtype A1 virus and obesity are common. CVF and acquired resistance was rare. LA was effective and safe and may be considered for use in treatment programs in sub-Saharan Africa.

Outcome	LA group (n=255)	OT group (n=257)	Difference (95% CI)
HIV-1 RNA level (primary outcome, ITT, adjusted) – no (%)			
< 50 copies/ml	248 (97.3)	252 (98.1)	-0.8 (-3.4 to 1.8)
≥ 50 copies/ml	5 (2.0)	3 (1.2)	0.8 (-1.8 to 3.4)
No virological data	2 (0.8)	2 (0.8)	-
Main secondary outcome			
Confirmed virological failure (≥ 200 copies/ml, ITT) – no (%) *	1 (0.4)	0	0.4 (-0.3 to 1.2)

Table: main virological outcomes by randomised group

* Mutations to rilpivirine (V108I, E138K and V179L) and cabotegravir (E92E/V, N155H and L74M) at failure. One additional LA participant had VL≥ 200 copies/ml at week 48 that could not be confirmed (participant died before repeat); mutations to rilpivirine and cabotegravir were present.

123 Phase I Safety, Tolerability and Pharmacokinetics of Tenofovir Alafenamide Implants in African Women

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Background: Long-acting antiretroviral formulations offer an innovative solution to support adherence in African women seeking HIV pre-exposure prophylaxis. Micro-tabletted tenofovir alafenamide (TAF), a potent antiretroviral drug with established systemic safety, was formulated in a silicone elastomer sub-dermal implant and tested for safety, tolerability, and pharmacokinetics (PK).

Methods: Healthy, adult South African women at low HIV risk enrolled in the CAPRISA 018 Phase I trial. To assess initial safety, six women received a single TAF (110mg) implant with an estimated 0.25mg/day in vivo release rate for 4 weeks (Group 1). Thereafter, 30 women randomized 1:1 to either one or two TAF implants, assigned blinded in a 4:1 active (n=24) to placebo (n=6) ratio, for 48 weeks (Group 2). Implant safety (systemic and implant site reactions [ISRs]: frequency, severity grading, time to resolution), tolerability (scheduled vs early removals), and PK evaluations (TAF plasma concentrations, and active metabolite tenofovir diphosphate [TFV- DP] in peripheral blood mononuclear cells (PBMCs) with a target protection threshold set at 36 fmol/10^6 cells) were assessed throughout implant placement and 4 weeks post-removal.

Results: Study participant median age was 26 years and 13% had a history of contraceptive implant use. Common ISRs (Figure1) were mostly mild (Grade 1) with scarring, hyperpigmentation, and induration, continuing for the duration of the study. In Group 2, Grade 3 ISRs, reported in two participants, resolved on implant removal. Early implant removal prior to 48 weeks occurred in 11 (37%) (10 active arm) in a median [IQR] of 19 [10-27] weeks post-insertion, mostly due to ISRs. Plasma TAF was detectable in 77% of samples from Group 2 participants in the active arm, with 100% and 50% detection 0.5 and 6 hours post insertion while median [IQR] TFV-DP concentrations were 3.9 [1.7-13.3] and 14.8 [6.0-29.1] fmol/million cells in women with 1 and 2 active implants respectively, with 15% of samples reaching or exceeding the target concentration

Conclusion: In this first-in-human TAF implant trial, we found an expected safety profile, predominantly as insertion site reactions, but sub-optimal tolerability. Implant drug release rates did not reach targeted PBMC TFV-DP concentrations in most participants. Inserting additional implants or increasing release rates would need to be counter-balanced with the potential for increased side effects and reduced tolerability. Additional PK analyses are underway.

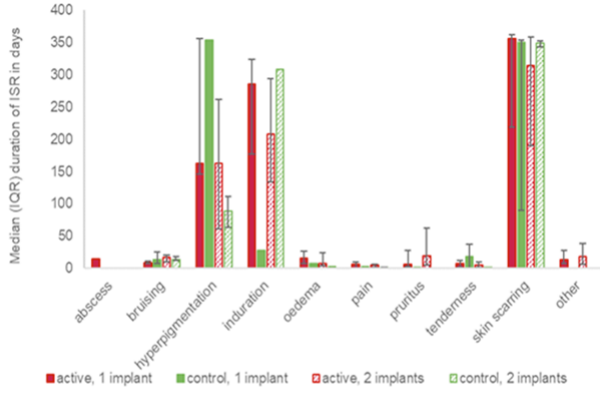

Figure 1: Duration of insertion related ISRs (Group 2)

124 Final Results of ANRS 174 D OXYVAC: A Randomized Trial to Prevent STI in MSM on PrEP

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Background: Interim results of the ANRS Doxyvac trial (NCT04597424) have shown significant reductions in the incidence of chlamydia, syphilis and gonorrhea with doxycycline PEP and a significant reduction in the incidence of a first episode of gonorrhea with the 4CMenB vaccine, but not of cumulated gonorrhea episodes.

Methods: MSM on PrEP with a history of STI, were randomized in an open-label factorial design trial to receive doxycycline PEP (200 mg within 72h of condomless sex) or no PEP (2:1); and 2 shots of the 4CMenB vaccine or no vaccine (1:1). Participants were tested centrally at baseline, every 3 months and when symptomatic for N. gonorrhoeae (GC) and C. trachomatis (CT) by PCR in throat, anus and urine with serologic tests for syphilis. The co-primary endpoints were: the incidence of first episode of CT or syphilis from baseline for Doxy PEP and the incidence of a first episode of GC from 3 months for the vaccine intervention, using an intent-to-treat analysis. We used Cox proportional hazard models to compare incidence between Doxy PEP and no PEP adjusted for vaccine intervention and vice versa. Following external evidence, a single interim analysis occurred in September 2022 at the request of the DSMB who recommended to stop the trial for efficacy. All participants were then invited to come back for a final visit which occurred up to February 28, 2023. Final results are presented.

Results: Between January 19, 2021, and September 19, 2022, 556 MSM were randomized and 545 were analyzed. Median age: 40 years (IQR 34-48), median

of 10 sexual partners in past 3 months. Median follow-up: 14 months. There was no interaction between the two prevention strategies for the primary endpoints. The incidence of a first episode of CT or syphilis was 8.8 per and 53.2 per 100 PY in the Doxy PEP and no PEP arms, respectively (aHR: 0.17; 95%CI: 0.12-0.26). The incidence of a first episode of GC was 45.5 and 68.4 per 100 PY in the Doxy PEP and no PEP arms, respectively (aHR: 0.67; 95%CI: 0.52-0.87). The incidence of a first episode of GC was 58.3 and 77.1 per 100 PY in the 4CMenB vaccine and no vaccine arms, respectively (aHR: 0.78; 95%CI: 0.60-1.01) and the incidence of cumulative episodes was 52.6 and 62.4 per 100 PY, respectively (aIRR: 0.84 (0.67-1.07). One drug-related SAE was reported (Erythema).
Conclusion: Among MSM on PrEP, doxy PEP significantly reduced the incidence of CT and syphilis and to a lesser extent of GC. 4CMenB vaccine no longer showed a significant impact on the incidence of GC.

125 Sustained Reduction of Bacterial STIs During the DoxyPEP Study Open-Label Extension

Annie Luetkemeyer[1], Deborah Donnell[2], Stephanie E. Cohen[3], Julia C. Dombrowski[4], Cole Grabow[4], Clare E. Brown[4], Chase A. Cannon[4], Eric Vittinghoff[1], Hyman M. Scott[3], Edwin Charlebois[1], Susan P. Buchbinder[3], Diane V. Havlir[1], Olusegun Soge[4], Connie L. Celum[1], for the DoxyPEP Study Team
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Background: After early demonstration of 65% efficacy in reducing bacterial STIs in the DoxyPEP Study, participants (ppts) in the standard of care (SOC) arm were offered doxy-PEP. We subsequently examined uptake, adherence, sexual activity, and incident bacterial STIs, as awareness of STI prevention efficacy may impact patterns of doxy-PEP use and sexual behavior.
Methods: DoxyPEP is an open-label trial conducted in Seattle and San Francisco among men who have sex with men (MSM) and transwomen (TW) living with HIV (PWH) or on PrEP who had a bacterial STI in the past year, randomized 2:1 to doxy-PEP or SOC. After the efficacy threshold was reached in a planned interim analysis, SOC ppts were offered doxy-PEP and both arms were followed in an open label extension (OLE) for up to 12 months total. OLE quarters were defined as those with doxy-PEP for a full quarter after 5/2022 results were disclosed. Self-reported sexual behavior and quarters with ≥1 STI endpoint are compared descriptively during OLE doxy-PEP use vs. SOC as-randomized (SOC-AR) without doxy-PEP.
Results: Of the 637 ppts enrolled, 279 contributed to OLE follow-up: 193 from the doxy-PEP arm (D-OLE) and 86 of 87 ppts from the SOC arm (SOC-OLE). Of those in the OLE: 96% MSM, 4% TW, 78% were on PrEP, 22% PWH, 62% White, 4% Black, 13% Asian, 22% other; 27% Hispanic. ≥1 STI endpoints were observed in 13.4% of D-OLE and 18.2% of SOC-OLE quarters, compared to 12.1% during doxy-PEP as-randomized (D- AR) and 31.2% during SOC-AR (Table). Reductions in each STI (gonorrhea, chlamydia and syphilis) were observed in both D-OLE and SOC-OLE groups compared to the SOC-AR. Doxy-PEP use after condomless sex was 78% in D-OLE and 79% in SOC-OLE ppts, compared to 83% of D-AR ppts. Median self-reported doxy doses taken per quarter were 19 (IQR 7-32) in D-OLE and 16 (5-30) in SOC-OLE, compared to 14 (IQR 4-30) during D-AR. During OLE, SOC-OLE ppts reported higher median sex partners per quarter: 15 (IQR 5-30) compared to 8 (IQR 4-15) during SOC-AR and D-OLE ppts reported a median of 12 (IQR 5-25) partners per quarter vs.10 (IQR 4-25) during D-AR.
Conclusion: In the OLE period after doxy-PEP efficacy was known, almost all SOC ppts accepted doxy-PEP and both OLE groups reported high doxy-PEP coverage (>78%) of condomless sex in the context of a higher number of sexual partners during OLE. Doxy-PEP was associated with sustained decreased rates of incident STI's in both groups during the OLE compared to no doxy-PEP use among ppts initially randomized to the SOC arm.

Table: STI endpoints, sex partners, and doxycycline PEP use among DoxyPEP study participants in the 'as-randomized' (2:1 to doxy-PEP and standard of care, SOC) period and 'open label extension' (OLE, after efficacy results were released May 2022)

	As-randomized (AR)		Open Label Extension (OLE)	
	Doxy-PEP n quarters = 1078	Standard of care (SOC) n quarters = 462	Doxy OLE (doxy-PEP → doxy-PEP) n quarters = 397	SOC OLE (SOC → doxy-PEP) n quarters = 165
Quarters with > 1 STI endpoint (%, 95% CI)	12.1% (10.1%–14.0%) n = 130	31.7% (26.9%–35.4%) n = 144	13.4% (10.0%–16.7%) n = 53	18.2% (12.3%–24.1%) n = 30
Quarters with gonorrhea (%, 95% CI)	9.4% (7.6%–11.1%) n = 101	19.3% (15.7%–22.9%) n = 89	10.3% (7.3%–13.3%) n = 41	12.7% (7.6%–17.8%) n = 21
Quarters with chlamydia (%, 95% CI)	2.6% (1.6%–3.5%) n = 28	12.8% (9.7%–15.8%) n = 59	1.8% (0.5%–3.1%) n = 7	4.2% (1.2%–7.3%) n = 7
Quarters with syphilis (%, 95% CI)	0.6% (0.2%–1.1%) n = 7	3.2% (1.6%–4.9%) n=15	1.3% (0.2%–2.4%) n = 5	1.2% (-0.5%–2.9%) n = 2
Sex partners per quarter (median, IQR)	10 (4–25)	8 (4–15)	12 (5–25)	15 (5–30)
Doxy doses per quarter (median, IQR)	14 (4–30)	N/A	19 (7–32)	16 (5–30)
% of condomless sex acts covered by doxy-PEP per quarter	83.1%	N/A	78.0%	79.0%

126 Doxycycline PEP: High Uptake and Significant Decline in STIs After Clinical Implementation

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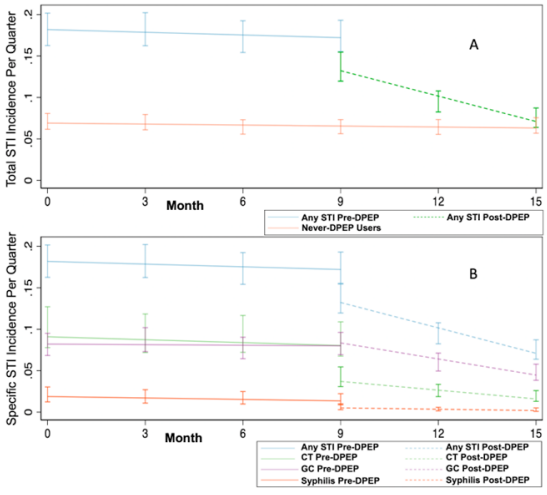
Background: Doxycycline as bacterial sexually transmitted (STI) post-exposure prophylaxis (DPEP) has shown high prevention efficacy in clinical trials. We evaluated the uptake and impact of DPEP on Chlamydia (CT), Gonorrhea (GC), and Syphilis incidence among PrEP users in a sexual health clinic in San Francisco.
Methods: DPEP was offered to all active PrEP clients at their clinical visits starting on 11/30/22. We included PrEP clients with at least one STI test who received DPEP for at least 30 days (DPEP users), or never initiated DPEP (non-DPEP users). The "pre-DPEP" period was defined as 6/1/22-11/30/22; and the "post-DPEP" period started after DPEP initiation for DPEP users. STI testing included GC and CT (urine, rectal, and pharyngeal), and syphilis. Adjusted STI incidence rate ratios (IRR) per quarter for the pre- and post-DPEP periods were evaluated, and a controlled interrupted time series (CITS) analysis with mixed-effects Poisson regression used to evaluate intervention effects.
Results: Of the 3,081 active PrEP clients, 1,209 (39%) received DPEP during the study period. Those who received DPEP were racially/ethnically diverse with 33% White, 26% Latinx, 16% Asian, and 4% Black; and the majority were cisgender men (90%), gay (91%), and 30-49 years (62%). The demographics of non-DPEP users were similar to DPEP users. Among DPEP users, any STI incidence declined from 18.1% in the first quarter of the study period to 7.5% in the last quarter. Among non-DPEP users, any STI incidence was stable between the first and last quarter: 7.0% and 6.5%, respectively. In the pre- post-DPEP analysis, DPEP was associated with decreased STI incidence for any STI [IRR: 0.42, 95% Confidence Interval (95% CI): 0.24-0.74; p=0.003], CT (IRR: 0.33, 95% CI: 0.23-0.46; p<0.001), and syphilis (IRR: 0.22, 95% CI: 0.07-0.54; p=0.001); but not GC (IRR: 0.89, 95% CI: 0.69-1.15; p=0.383). In the CITS analysis DPEP was associated with a significant decline in the slope for any STI incidence among PrEP clients (IRR: 0.67, 95% CI: 0.46-0.96; p=0.03) (Figure 1). This decline was also significant for CT (p=0.021) and GC (p=0.003), but not syphilis (p=0.360).
Conclusion: DPEP uptake was high reflecting strong demand when offered as part of routine PrEP care. Overall STI incidence declined rapidly after implementation demonstrating high impact of this intervention in a real-world setting. Continued evaluation of uptake, adherence, and impact on bacterial STIs will be essential as DPEP implementation expands.



127 Doxy-PEP Associated With Declines in Chlamydia and Syphilis in MSM and Trans Women in San Francisco

Madeline Sankaran[1], David V. Glidden[2], Robert P. Kohn[1], Courtney Liebi[2], Thiago S. Torres[3], Susan P. Buchbinder[1], Annie Luetkemeyer[2], Monica Gandhi[2], Diane Havlir[2], Janet Q. Nguyen[2], Hyman Scott[4], Jorge Roman[4], Oliver Bacon[1], Trang Q. Nguyen[1], Stephanie E. Cohen[1]

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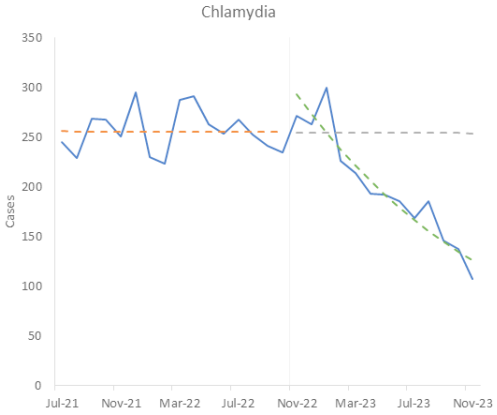
Background: In October 2022, the San Francisco (SF) Department of Public Health disseminated guidelines through community and public health networks recommending doxycycline post-exposure prophylaxis (doxy- PEP) for men who have sex with men (MSM) and transgender women (TGW) with a history of sexually transmitted infections (STIs) or multiple sex partners. Doxy-PEP's effect on population-level incidence of STIs is unknown.

Methods: To monitor doxy-PEP uptake at sentinel sites, we tracked the quarterly number of new patients initiating doxy-PEP from three high-volume SF sexual health clinics. To assess the ecological association between doxy-PEP program implementation and citywide STI incidence, we conducted interrupted time series analyses on monthly reported SF cases of chlamydia (CT), gonorrhea (GC), and early syphilis (ES), among MSM/TGW before (7/1/21–10/31/22) and after (11/1/22–11/30/23) release of doxy-PEP guidance, and used autoregressive integrated moving average (ARIMA) models to forecast expected post-period monthly case counts in the absence of doxy-PEP. Observed case counts were based on citywide surveillance data. Analyses were repeated for monthly CT case counts among cis women for comparison.

Results: From 11/1/22 to 9/30/23, 3,288 MSM/TGW initiated doxy-PEP at the three sentinel clinics. Citywide, the number of monthly reported CT (-6.7%/month, p<0.0001) and ES (-3.12%/month, p<0.0001) cases among MSM/TGW decreased significantly after the release of doxy-PEP guidelines compared to model forecasts (Figure). By the end of the 13-month post-period, CT and ES cases decreased 51% (95% CI: 39%-60%) and 50% (95% CI: 38%-59%), respectively, compared to expected counts in November 2023. No significant change in GC cases was seen (p=0.087). Among cis women, the number of monthly reported CT cases in the post-period increased significantly (2.43%/month, p<0.01).

Conclusion: Release of SF doxy-PEP guidelines and early implementation at high volume clinics were associated with a substantial sustained decrease in reported SF cases of CT and ES, but not GC, among MSM/TGW over a 13-month period. Other factors, including changes in screening and sexual practices (e.g., in response to mpox), may have contributed to observed trends. Future analyses are planned with extended post- period data to determine whether observed trends continue to align with citywide doxy-PEP uptake and to assess for demographic disparities in doxy-PEP uptake and STI incidence.



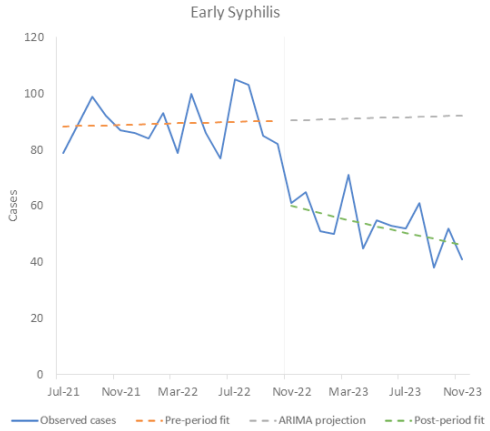


Figure. Observed and modelled chlamydia and early syphilis cases among MSM and TGW in San Francisco pre and post doxy-PEP implementation

128 Site-Based HIV Testing Assay Performance for Cabotegravir and TDF-FTC PrEP Failure in HPTN 083

Raphael J. Landovitz[1], Emily Voldal[2], Brett Hanscom[2], Susan H. Eshleman[3], Estelle Piwowar- Manning[3], Philip Sullivan[3], Marybeth McCauley[4], Lydia Soto-Torres[5], James F. Rooney[6], Alex R. Rinehart[7], Myron S. Cohen[8], Mina Hosseinipour[8], Sinead Delany-Moretlwe[9], Beatriz Grinsztejn[10], for the HPTN 083

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Background: HPTN 083 demonstrated superiority for long-acting injectable cabotegravir (CAB) compared to daily oral TDF-FTC for HIV pre-exposure prophylaxis (PrEP) in cisgender men and transgender women who have sex with men (MSM, TGW). The study was conducted at 43 sites in North and South America, Asia and Africa. During the blinded and first unblinded year study periods, site-based HIV testing algorithms included a US FDA cleared rapid test (RT) with results prior to product administration, and a laboratory-based antigen/antibody assay (Ag/Ab) that was not resulted until after product administration. We present the PPV of these tests in people receiving CAB or TDF/FTC PrEP.

Methods: All sites performed RTs and Ag/Ab tests at all study visits and required a non-detected HIV RNA within 14d of study entry; some sites performed two rapid tests prior to product administration based on local practice. HIV status was determined by an external, blinded adjudication committee based on site HIV testing and retrospective HIV testing at a central laboratory. Positive predictive value (PPV, 95% confidence intervals [CI]) for initial site-based reactive testing was assessed for permutations of site test results.

Results: Of 4566 enrolled participants, 70 were excluded (results could not be adjudicated, reactive test results at enrollment, or no HIV testing data after enrollment), 48 had a false reactive test, 130 had a true reactive test, and 4322 had no reactive tests. The analysis included data from 113,316 visits, including 177 initial reactive visits with a reactive RT or Ag/Ab test. PPVs for one or two RTs (regardless of Ag/Ab result), one RT plus one Ag/Ab test, and one Ag/Ab test (regardless of RT result) are in the Table.

Conclusion: The PPV of one reactive RT plus one reactive Ag/Ab was 100% for both CAB and TDF-FTC; The PPVs of two reactive RTs for TDF-FTC PrEP and CAB PrEP were 95% and 83% respectively. The PPVs of one reactive Ag/Ab with a negative RT performed were low for both groups and were lower for CAB. In the absence of more sensitive testing, a reactive RT plus a reactive Ag/Ab test, or two reactive RTs had sufficient PPV to warrant initiation of ART. In settings where RNA testing is unavailable or infeasible, algorithms using RTs and Ag/Ab tests had high PPV in the context of MSM/TGW PrEP. Lower PPVs of all tests in CAB cases are attributable to lower HIV incidence in CAB arm participants.

Table: PPV for initial reactive visits with adjudicated HIV status (177 total, 129 confirmed HIV-positive) by treatment arm from HPTN 083

	HIV-positive/ total reactive (CAB)	HIV-positive/ total reactive (TDF/FTC)	PPV (95% CI) (CAB)	PPV (95% CI) (TDF/FTC)	Difference in PPV (95% CI) (CAB vs. TDF/FTC)
RT (all types)	38/45	86/94	84% (71%,94%)	91% (84%,96%)	-7% (-21%, +7%)
Ag/Ab test (all types)	42/64	85/99	66% (53%, 77%)	86% (77%, 92%)	-20% (-35%, -5%)
Any reactive RT + any reactive Ag/Ab	27/27	65/65	100% (87%,100%)	100% (94%,100%)	0% (-14%, +6%)
Any reactive RT + non-reactive Ag/Ab	0/5	0/7	Insufficient sample size	Insufficient sample size	Insufficient sample size
Two reactive RTs	10/12	20/21	83% (52%, 98%)	95% (76%, 100%)	-12% (-42%, +11%)
Non-reactive RT (1 or 2) + reactive Ag/Ab	14/36	20/34	39% (23%, 57%)	59% (41%, 75%)	-20% (-46%, +6%)
Any reactive RT or Ag/Ab	43/70	86/107	61% (49%, 73%)	80% (72%, 87%)	-19% (-34%, -4%)

129 Safety and Pharmacokinetics of MK-8527, a Novel nRTTI, in Adults Without HIV

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Background: MK-8527 is an oral nucleoside reverse transcriptase translocation inhibitor (NRTTI) in clinical development. Two phase 1 trials evaluated ascending single doses (trial A) and ascending multiple doses (trial B) of MK-8527 in adults (aged 18–55 years) without HIV.

Methods: In trial A, male participants received single oral doses of MK-8527 (0.5–200 mg; fasted) or placebo; 25 mg was also assessed after a high-fat meal. In trial B, male and female participants received 3 once-weekly (QW) oral doses of MK-8527 (up to 40 mg) or placebo. In both trials, participants were randomized (3:1) to receive MK-8527 or placebo. Safety and pharmacokinetics of MK-8527 (plasma) and MK-8527-triphosphate (TP; measured in peripheral blood mononuclear cells [PBMCs]), the active form of MK-8527, were assessed.

Results: In both trials, MK-8527 was generally well tolerated. In trial A, adverse events (AEs) were reported in 27 of 34 participants (79.4%); 5 (14.7%) were considered drug-related AEs. In trial B, AEs were reported in 29 of 32 participants (90.6%); 11 (34.4%) were considered drug-related AEs. In both trials, all drug-related AEs were mild or moderate, and there were no serious AEs, events of clinical interest, or deaths. After single doses, plasma exposure of MK-8527 increased in an approximately dose-proportional manner, and intracellular exposure of MK-8527-TP (PBMCs) was slightly less than dose proportional over 5–200 mg. Administration of MK-8527 with a meal resulted in a 41% decrease in plasma MK-8527 C_{max}, with no effect on plasma MK-8527 AUC0-168, and a 22% increase in intracellular MK-8527-TP C_{max} and 58% increase in MK-8527-TP AUC0- 168. After multiple QW doses, accumulation of plasma MK-8527 was minimal (range of C_{max} and AUC0-168 ratios [Day 15/Day 1] was 0.9–1.4) and accumulation of intracellular MK-8527-TP was moderate (range of C_{max} and $AUC_{0\text{-}168}$ ratios was 1.1–1.6; C168 was 1.2–2.4). Across QW doses, the range of MK-8257-TP median T_{max} was 10–24 hours, and apparent half-life was 216–291 hours. After administration of MK-8527, the true geometric mean C168 of intracellular MK-8527-TP was above the previously identified pharmacokinetic threshold for antiviral activity against HIV-1 (≥0.2 pmol/10^6 PBMCs).

Conclusion: Single (0.5–200 mg) and multiple (QW) doses (up to 40 mg) of MK-8527 administered to adults without HIV were generally well tolerated. The safety and pharmacokinetic profiles of MK-8527 support continued clinical investigation.

130 Phase I Study of Cabotegravir Long-Acting Injectable Formulations Supports ≥4-Monthly Dose Interval

Kelong Han[1], Ronald D'Amico[2], Jörg Sievers[3], Darin Brimhall[4], Brian Spears[5], Dale Taylor[6], David Dorey[7], Paul Benn[3], Lisa Morgan[1], Randa Hareedy[8], Gilda Bontempo[9], Max Lataillade[9], William Spreen[2]

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Background: Long-acting cabotegravir (CAB) administered intramuscularly (IM) every 2 months (Q2M) is approved for HIV-1 prevention; CAB and rilpivirine administered IM monthly or Q2M is approved for HIV-1 treatment. To support less frequent dosing, we evaluated safety and pharmacokinetics (PK) of the approved CAB 200 mg/mL (CAB200) formulation administered subcutaneously (SC) with recombinant human hyaluronidase PH20 (rHuPH20) and a new CAB 400 mg/mL (CAB400) formulation administered SC or IM without rHuPH20.

Methods: This is an ongoing, open-label, single-dose, dose-escalation, phase I study (NCT05418868) in healthy adults with 2 sentinel participants (pts) per cohort. In part A, rHuPH20 (10,000 IU) and CAB200 (A1, 800 mg; A2, 1600 mg; A3, 3200 mg; 4 to 16 mL) were sequentially co-administered SC (abdominal). In part C, CAB400 (800 mg, 2 mL) was administered SC (abdominal; C1) or IM (gluteus medius; C2). To evaluate potential CAB400 dosing regimens, CAB PK profiles were simulated using an established CAB200 IM population PK model modified based on observed PK data in part C.

Results: To date, 38 pts total received CAB (Table); 61% were male sex at birth, and 61% were non-White. Median age, weight, and BMI were 37.5 years, 74.7 kg, and 26.7 kg/m^2, respectively. In part A, maximum observed plasma concentration (C^{max}) and area under the plasma concentration–time curve from 0 to infinity (AUC0-∞) increased with dose proportionally and were higher than CAB200 IM, indicating potentially increased bioavailability, while $t_{1/2}$ was similar to CAB200 IM. C_{max} in C1 was lower than in C2; both were **lower** than CAB200 IM. CAB $t_{1/2}$ in C1 was longer than in C2; both were longer than CAB200 IM, even though some pts have not reached terminal phase due to long $t_{1/2}$. PK simulations predict a CAB400 SC/IM dose interval of ≥4 months achieves similar exposure to the approved CAB200 IM. Injection site reactions (ISRs) occurred in all pts dosed SC in part A (22/22) with a dose-related trend for increased ISR grades. A sentinel pt in cohort A3 experienced a drug-related serious adverse event of injection site erythema with necrosis. ISRs in C1 (8/8 pts) and C2 (3/8 pts) were grade 1 or 2.

Conclusion: Safety and PK results from part A indicate low potential to achieve less frequent dosing with CAB200 and rHuPH20. The new CAB400 formulation (SC and IM) exhibits favorable safety and PK commensurate with dose intervals of ≥4 months and is in ongoing clinical development.

Table. Pharmacokinetics and Safety: CAB200 + rHuPH20 (A1-A3) and CAB400 (C1-C2)

Parameter	CAB 200 mg/mL + rHuPH20 10,000 IU A1: 800 mg (4 mL) SC (N=10)	CAB 200 mg/mL + rHuPH20 10,000 IU A2: 1600 mg (8 mL) SC (N=10)	CAB 200 mg/mL + rHuPH20 10,000 IU A3: 3200 mg (16 mL) SC (N=2)	CAB 400 mg/mL C1: 800 mg (2 mL) SC (N=8)	CAB 400 mg/mL C2: 800 mg (2 mL) IM (N=8)
Geometric mean $AUC_{0-\infty}$ (%CVb), µg·h/mL	6059.6 (27.8)	11,284.5 (29.9)	27,198.1 (5.9)	4641.7 (2.2)[a]	5345.4 (27.4)[b]
Geometric mean Cmax (%CVb), µg/mL	4.7 (47.4)	7.7 (46.2)	16.2 (10.1)	0.7 (35.5)	1.8 (53.5)
Geometric mean $t_{1/2}$ (%CVb), days	51.5 (51.5)	38.4 (48.0)	45.5 (37.3)	135.3 (2.5)[a]	59.3 (106.1)[b]
Grade 1 ISRs, n (%)	0	1 (10)	0	6 (75)	2 (25)
Grade 2 ISRs, n (%)	10 (100)	6 (60)	0	2 (25)	1 (13)
Grade ≥3 ISRs, n (%)	0	3 (30)	2 (100)[c]	0	0

[a]Calculated for n=2; remaining 6 have not reached terminal phase due to long $t_{1/2}$. [b]Calculated for n=6; remaining 2 have not reached terminal phase due to long $t_{1/2}$. [c]1 drug-related serious adverse event of injection site erythema with necrosis.

131 Cabotegravir Maintains Protective Efficacy in the Setting of Bacterial STIs: HPTN 083

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Background: Bacterial sexually transmitted infections (STIs) have been shown to facilitate HIV transmission and acquisition. Long-acting cabotegravir (CAB-LA) demonstrated superiority vs daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for HIV prevention in two large randomized controlled trials, but an assessment of efficacy in the setting of STIs has not been performed.

Methods: From the blinded period of HPTN 083, we calculated incident STI events per 100 person-years (PY), including repeat events, from enrollment to last STI testing prior to May 15, 2020. We used Cox proportional hazards modeling with STI status as a time-varying covariate to look for potential interactions between STI status and the relative efficacy of CAB-LA vs. TDF/FTC. Serologic testing for syphilis and nucleic acid amplification testing for rectal and urethral gonorrhea and chlamydia were conducted every six months or when participants reported STI symptoms or exposures. Date of first HIV diagnosis

was determined by an independent adjudication committee. Since the precise dates of STI infection and completion of STI treatment were unknown, each time interval between STI tests was classified as STI-positive or STI-negative. Intervals before and after each positive STI test were considered STI-positive, and all others were considered STI-negative. Sensitivity analyses were conducted with different methods of STI-status extrapolation. For Cox-Models, we included those without follow-up.

Results: Among 3859 participants (ppts) included in the analysis, the overall STI incidence rate was 50.7 infections/100PY. STIs were diagnosed in 1562 (40.5%) ppts, with multiple STIs reported for 691 (17.9%), and 79% of STI diagnoses occurring in 25% of ppts. There was no difference in STI incidence by PrEP arm. In a m- ITT analysis (Table), HIV incidence was lower with CAB-LA vs TDF/FTC regardless of presence or absence of STIs (hazard ratios of 0.37 and 0.31, respectively, with no significant interaction between STIs and the HR for HIV incidence (p = 0.75). Sensitivity analyses yielded similar results.

Conclusion: In a large PrEP trial with high STI incidence among participants, CAB-LA maintained robust protective efficacy relative to TDF/FTC in the setting of bacterial STIs. It is not a foregone conclusion that all HIV pre-exposure prophylaxis agents will maintain protective efficacy in the presence of bacterial STIs, and robustness to STIs should be interrogated for each agent. Future analyses should include HSV-2.

Table. Cox Proportional Hazards Models by STI Status, n=4558*

STI Status	Model	Base Case Model	Sensitivity Analysis #1	Sensitivity Analysis #2
STI Present	Incidence Rate –CAB (95%CI)	0.70 (0.25, 1.48)	0.5 (0.23, 1.03)	0.50 (0.11, 1.59)
	Incidence Rate –TDF/FTC (95%CI)	1.8 (1.04, 2.86)	1.5 (0.96, 2.24)	2.3 (1.28, 3.93)
	Hazard Ratio (95%CI)	0.37 (0.15, 0.95)	0.34 (0.15, 0.76)	0.23 (0.07, 0.80)
STI Absent	Incidence Rate –CAB (95%CI)	0.30 (0.12, 0.62)	0.30 (0.10, 0.70)	0.40 (0.18, 0.69)
	Incidence Rate –TDF/FTC (95%CI)	1.0 (0.62, 1.49)	0.90 (0.53, 1.55)	1.0 (0.62, 1.43)
	Hazard Ratio (95%CI)	0.31 (0.13, 0.71)	0.316 (0.11, 0.87)	0.39 (0.19, 0.81)
	p-value for interaction term	**0.75**	**0.90**	**0.48**

Sensitivity analysis #1 dichotomized participants as having an incident STI (ever) or never; Sensitivity analysis #2 carried STI status backwards to the last STI negative test (assuming rapid STI treatment to interrupt the transmission cycle). CI=confidence interval.
*Modified Intent-to-Treat population includes those with baseline STI testing but without follow-up testing.

132 COVID Incidence and Severity in Persons With Reinfection vs Post-Vaccination Breakthrough Infection

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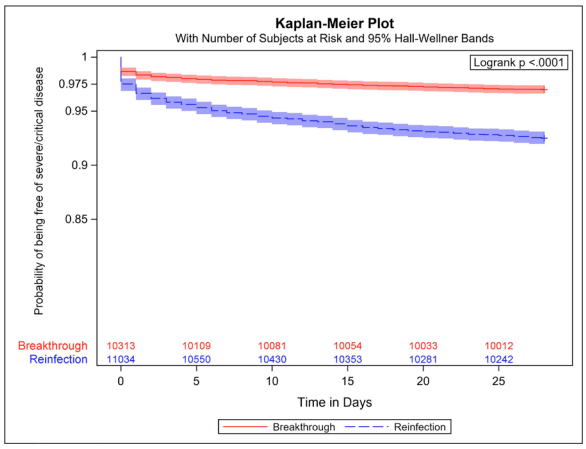
Background: COVID-19 vaccine effectiveness wanes over time. Natural infection also provides a high level of protection from reinfection and from severe, critical, or fatal disease. While both natural and vaccine induced immunity are highly protective, reinfections after natural infection and breakthrough infections after vaccination have been reported. Our aim was to determine the incidence rate and rate of severe/critical COVID-19 disease among those with breakthrough infection after full vaccination compared with reinfection among unvaccinated persons

Methods: The study was conducted using the US Department of Veterans Affairs (VA) COVID-19 databases. Individuals with a first confirmed infection >14 days after 2 doses of Pfizer or Moderna vaccine were matched 1:1 to individuals with a second confirmed infection in unvaccinated individuals >14 days after the first infection. Severe/critical disease, defined as admission to an intensive care unit, mechanical ventilation, or death within 28 days of the index test positive date, was compared among the two groups.

Results: We identified 55,251 matched pairs. Median age was 56 years, 88% were male, 75% were White, median Charlson Comorbidity Index was 1, 31% were symptomatic at baseline. The incidence rate of breakthrough infection among vaccinated individuals was 0.29/1,000 person-years (PY; 95% CI 0.28,0.3) of follow up. Rate of reinfection among unvaccinated was 0.38/1,000 PY (95% CI 0.37,0.39). (P<0.001) The probability of remaining free of severe/critical disease was higher among vaccinated individuals with breakthrough infection compared with individuals with reinfection. (Figure)

Conclusion: Incidence and severity of breakthrough infection and the risk of severe/critical disease after such infection is lower among vaccinated individuals compared with incidence and severity of reinfection among unvaccinated individuals.



133 MRNA Vaccine Versus Hybrid Immunity Against COVID-19 Among People

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Background: CoVPN 3008 (Ubuntu), the largest multicenter phase 3/4 trial of mRNA vaccines in sub-Saharan Africa, was designed to assess the safety of mRNA-1273, the effectiveness of hybrid versus vaccine immunity, and SARS-CoV-2 viral persistence among people with HIV (PWH).

Methods: We enrolled adults aged ≥18 years living with HIV or another comorbidity associated with severe Covid-19. Previously vaccinated individuals were excluded. Participants were assigned vaccinations at enrollment only or enrollment and month 1 based on whether their baseline point-of-care SARS-CoV-2 serostatus was positive (hybrid immunity) or negative (vaccine immunity). For the first 6 months of follow-up, the association between hybrid versus vaccine immunity with Covid-19 and severe Covid-19 was assessed using calendar-time-scale Cox regression models and counterfactual cumulative incidence methods.

Results: Between December 2021 and September 2022, 14237 participants were enrolled, of which 11681 PWH (median age 39 years, 77% female) were included in the Full Analysis Subset (FAS). Among PLWH, the median CD4 count was 635 cells/mm^3 (IQR 423-866), 769 (6.6%) had a CD4 count <200 cells/mm^3, 2157 (18.5%) had a detectable viral load (≥50 copies/ml), and 14.5% were not on ART. Retention was high (>95%) through the month 6 visit. The vaccinations were well tolerated. Among PWH, the 6-month cumulative incidence (Fig1A) in the vaccine immunity and hybrid immunity groups, respectively, was 7.77% (95% confidence interval [CI] 6.21 to 9.23) and 3.90% (95% CI 3.30 to 4.49) for SARS-CoV-2 infection, 3.40% (95% CI 2.30 to 4.49) and 2.02% (95% CI 1.61 to 2.44) for Covid-19, and 0.32% (95% CI 0.59 to 0.63) and 0.048% (95% CI 0 to 0.1) for severe Covid-19. The covariate-adjusted hazard rate was 42% lower in the hybrid immunity group for Covid-19 (hazard ratio [HR] 0.58; 95% CI 0.44 to 0.77; p=<.001), and 73% lower (HR 0.27; 95% CI 0.07 to 1.04; p=0.056) in the hybrid immunity group for severe Covid-19 (Fig1B). Twenty-two individuals had persistent SARS-CoV-2 infection ≥50 days, which was more often among those with prior TB infection, HIV viremia, or low CD4 count.

Conclusion: Individuals with hybrid immunity, even if living with HIV, were more effectively protected from Covid-19 and severe Covid-19 compared to those with vaccine immunity. Our results also highlight the importance of better understanding the role of persistent infections in transmission and in the emergence of new variants of concern through mutation evolution.
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134 SARS-CoV-2 Viral Clearance and Evolution Varies by Extent of Immunodeficiency

Yijia Li[1], Manish C. Choudhary[2], James Regan[2], Julie Boucau[3], Anusha Nathan[3], Tessa Speidel[4], May Y. Liew[5], Gregory E. Edelstein[2], Michael S. Seaman[4], Gaurav D. Gaiha[5], Mark J. Siedner[5], Amy K. Barczak[5], Jacob E. Lemieux[5], Jonathan Z. Li[2], for the POSITIVES Study Team

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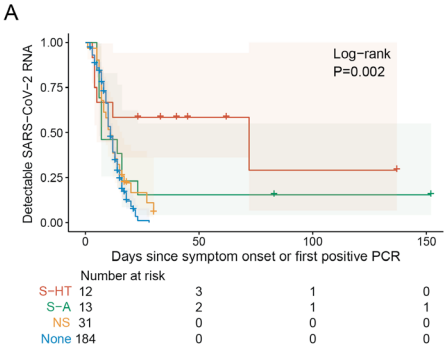
Background: Despite vaccination and antiviral therapies, immunocompromised individuals are at risk for prolonged SARS-CoV-2 infection, but the immune defects that predispose to persistent COVID-19 remain incompletely understood.

Methods: Participants enrolled in the POSt-VaccInaTIon Viral CharactEristics Study (POSITIVES), a prospective cohort study enrolling participants with confirmed SARS-CoV-2 infection. Participants were categorized based on the extent of immunocompromise into severe hematologic malignancy/transplant group (S- HT), severe autoimmune/B-cell deficient (S-A), non-severe immunodeficiency (NS), and non- immunocompromised (None). Longitudinal nasal SARS-CoV-2 levels were measured with a quantitative PCR assay and viable virus levels were evaluated by viral culture. Neutralizing antibody, binding antibody to nucleocapsid, and T cell profiling (enzyme-linked immunosorbent spot [ELISpot] and Spike-specific proliferation assay) were performed in a subset of participants with available blood samples.

Results: The median time to nasal viral RNA and culture clearance in the severe hematologic malignancy/transplant group (S-HT) were 72 and 40 days, respectively, which were significantly longer than clearance rates in the severe autoimmune/B-cell deficient (S-A), non-severe, and non-immunocompromised groups (P=0.002 Figure 1A and P<0.001 Figure 1B). Individuals with B-cell deficiency (S-A group) had an intermediate risk of persistent infection. Participants who were severely immunocompromised (S-HT and S-A) had greater SARS-CoV-2 evolution and a higher risk of developing antiviral treatment resistance. Both S-HT and S-A participants had severely diminished SARS-CoV-2-specific humoral responses. In contrast, S-A group had the highest level of SARS-CoV-2-specific CD4+ and CD8+ T cell proliferation response among all groups, while S-HT demonstrated neither antibody maturation nor increased T cell proliferation response to Spike peptide pools. NS and non-immunocompromised participants showed both increasing neutralizing antibody levels (until a plateau ~25-30 days post symptom onset) and SARS-CoV-2-specific T cell responses.

Conclusion: Our study demonstrated a hierarchy of immunocompromised conditions that increase the risk of delayed viral clearance and SARS-CoV-2 evolution, with the highest risk in those with severe hematologic malignancy/transplant. The findings may be explained by the suppression of both SARS-CoV-2-specific B and T cell responses.



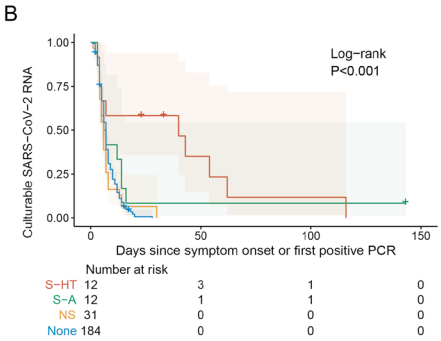


Figure 1. Kinetics of SARS-CoV-2 viral RNA and culturable virus among different immunocompromised groups. A, Kaplan-Meier estimates of upper respiratory viral clearance (viral load below lower level of quantification). B, Kaplan-Meier estimates of upper respiratory culturable virus clearance.

135 Analysis of Emergent SARS-CoV-2 Antiviral Resistance and Its Association With Virologic Rebound

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Background: Nirmatrelvir-ritonavir (N-R) and remdesivir (RDV) are SARS-CoV-2 antivirals that reduce the risk of hospitalization and progression to severe COVID-19. N-R and RDV resistance have been described previously, but the frequency and risk factors for emergent drug resistance remains unclear.

Methods: We enrolled non-hospitalized participants with acute SARS-CoV-2 infection into the POSITIVES study, a prospective observational cohort, where we collected anterior nasal swabs thrice weekly during the first two weeks after diagnosis. From these samples, we performed deep sequencing of nsp5 among N-R treated (n=53) and untreated (n=42) participants and nsp12 among RDV treated (n=14) participants. We compared the incidence of emergent N-R resistance between N-R treated and untreated participants and evaluated its association with post-treatment virologic rebound, while also characterizing emergent RDV resistance.

Results: Compared with untreated individuals, those treated with antivirals were older, more immunosuppressed, and had received more COVID-19 vaccinations, reflecting guidelines for N-R and RDV use. Emergent N-R mutations expected to at least confer moderate resistance (≥2.5-fold reduced susceptibility to N-R in vitro) were detected more often in those who received N-R than those who did not (5/53 [9%] vs 0/42 [0%], p=0.06). However, these mutations (E166V, H172Y, Q189K, P252L) were detected at low frequencies, with all but one mutation present in <25% of the viral population. Additionally, for those with detectable viral loads at follow-up timepoints after cessation of treatment, all (4/4) of the emergent resistance mutations subsequently reverted to wild type. Viral rebound occurred in 28% (15/53) of participants receiving N-R, but there was no difference in resistance emergence in those who experienced virologic rebound compared to those who did not (2/15 [13%] vs 3/38 [8%], p=0.6). Emergent RDV resistance mutations were detected in two immunosuppressed participants (14%). However, similar to the N-R mutations, all four mutations (V166L, N198S, V792I, M794I) were low-frequency and reverted to wild type at successive timepoints.

Conclusion: Mutations that confer resistance emerge with N-R and RDV treatment, but they are transient, present at minor frequencies, and are not associated with virologic rebound. These data suggest that the risk of widespread dissemination of significant drug resistance to N-R and RDV remains low.

136 Molnupiravir Does Not Increase 3CLpro Resistance Mutations When Co-Administered With Nirmatrelvir/r

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Background: Current treatments for SARS-CoV-2 rely on direct-acting antivirals including the 3CLpro inhibitor nirmatrelvir/r (NMV/r) and the mutagenic nucleoside analog molnupiravir (MOV). There have been concerns regarding the use of MOV including the generation of new viral variants. In a previous study, we compared the antiviral effect of MOV or NMV/r alone, or the co-administration of both in a SARS-CoV-2 macaque model. We showed an additive effect of the two antivirals on several markers of disease. In this follow-up study, we investigated the mutation profiles of SARS-CoV-2 in samples collected in the previous study.

Methods: Twenty macaques received the oral treatment of MOV, NMV/r, combination therapy or vehicle control (5 in each group) starting 12 hours after exposure to SARS-CoV-2, and they were followed for 4 days before necropsy. Viral RNA was extracted from lung tissue samples at necropsy. Primer ID sequencing approach was used to sequence nsp5 (3CLpro), a portion nsp12 (RdRp) and the S gene receptor binding domain (S-RBD). Substitutions with a FDR-adjusted p value of less than 0.05 were considered as true mutations. This work was partially funded by the Intramural Research Program, NIAID.

Results: In the MOV group, the overall substitution rate was approx. 0.05%, significantly higher than other groups. The mutation profile was driven by the increase of C-to-U and G-to-A mutations. The overall substitution rates were significantly increased in the MOV+NMV/r group compared with NMV/r or vehicle groups, but lower than MOV group (Fig 1A). We further studied the impact of MOV on the potential development of resistance mutations on 3CLpro against NMV. We did not observe any mutation hotspots in this region beyond those mediated by MOV. Mutations identified in the MOV group were largely distinct in frequency from those in the combination group. We assessed the amino acid codon changes at four positions (L50F, E166A, E166V, and L167F) that have been reported to contribute to NMV resistance. We did observe an increase in the abundance of L50F in the MOV group but it was not further enriched in the combination group (Fig 1B).

Conclusion: Our results suggest that co-administration of NMV/r lowered the magnitude of the mutagenetic effect of MOV against SARS-CoV-2, likely due to the additive effect of the combination therapy on reduced rounds of viral replication. There is no evidence that combination therapy potentiated selection for NMV resistance mutations during 4 days of treatment.

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137 Mini-Lecture: Progress in Understanding the Mechanisms of Long COVID

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Background: Millions of people across the globe have experienced new or persistent symptoms for 3 or more months following COVID-19, a syndrome termed long COVID. The US Census estimates that over 15% of US adults have ever had long COVID. Investigations are underway to understand the biologic mechanisms of long COVID and develop effective therapeutics. This mini-lecture will highlight the progress made in the past year on understanding the pathogenesis of long COVID.

138 Multimodal Assessment of Antigen Persistence in the Post-Acute Phase of SARS-CoV-2 Infection

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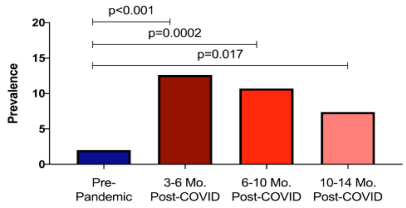
Background: Although RNA viruses like SARS-CoV-2 are considered transient, viral components can persist beyond the acute phase due to various virologic and immunologic factors. Recent studies have suggested that SARS-CoV-2 antigens may persist following COVID-19 but were limited by a lack of comparison to true negative control samples.

Methods: We assessed viral persistence in two ways: (1) Single molecule array (Simoa) assays for SARS-CoV-2 spike, S1, and nucleocapsid antigen in plasma from 171 individuals in the post-acute phase of SARS-CoV-2 infection and 250 pre-pandemic control samples, and (2) RNAscope assessing SARS-CoV-2 spike RNA in situ in rectal tissue obtained via flexible sigmoidoscopy in 5 individuals between 90 and 676 days post-COVID (without reinfection), with H&E and immunohistochemical visualization of CD3 and CD68 to localize viral RNA signals within tissue regions and immune cell types.

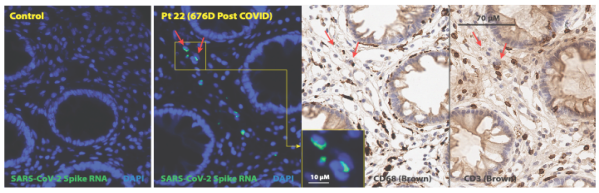
Results: In plasma, compared to the proportion of antigen positivity in pre-pandemic controls (2.0%), detection of any SARS-CoV-2 antigen was more frequent across all post-acute COVID-19 time periods (3-6 months: 12.6%, p<0.001; 6-10 months, 10.7%, p=0.0002; 10-14 months, 7.5%, p=0.017; (a)). These differences were driven by spike for up to 14 months and nucleocapsid in the first 6 months after infection. Hospitalization for acute COVID-19 was associated with detectable antigen in the post-acute phase (OR 2.27, p=0.054) and strongly associated with detectable N antigen (OR 11.82, p=0.001). In gut, RNAscope revealed readily detectable SARS-CoV-2 RNA in multiple cells from all rectal tissue regions surveyed from 4/5 individuals (b), except for one who had rare RNA+ cells detected in 1/3 regions. Nearly all RNA+ cells were detected in the lamina propria, without an epithelial signal. A small percentage of RNA+ cells expressed CD68, a monocyte marker, but many RNA+ cells did not express CD68 and none expressed CD3. In 3/4 samples with readily detected RNA, the signal was associated with macrophage-dense areas.

Conclusion: Our findings provide strong evidence that SARS-CoV-2 antigens can persist beyond the period of acute illness. The observation that 7-13% of plasma samples for over a year following initial SARS-CoV-2 infection contain detectable viral antigens, which are potentially immunogenic, has significant implications given the sheer number of people infected with SARS-CoV-2 to date. Work to determine if persistent antigen contributes to post-acute sequelae such as Long COVID is needed.

a) Prevalence of SARS-CoV-2 antigen (Spike, N, or S1) detection in true negative versus post-COVID samples.



b) Representative slide showing SARS-CoV-2 Spike RNA detected in gut lamina propria in association with CD68+ cells 2 years post-COVID using RNAscope and immunohistochemistry.



139 HIV-1 Transcription Start Sites Usage and Its Impact on Unspliced RNA Functions In Vivo

Saiful Islam[1], Zetao Cheng[1], Olga Nikolaitchik[1], Robert Gorelick[2], Vinay K. Pathak[1], Frank Maldarelli[1], Wei-Shau Hu[1]
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Background: HIV-1 unspliced RNA plays two crucial roles in viral replication: it is packaged into particles to serve as viral genome, and it is translated to generate Gag/Gag-Pol polyproteins required for virus assembly and replication. Studies using cell culture systems demonstrated that HIV-1 transcription can initiate at three conserved consecutive guanosines located at the junction of U3 and R regions, producing RNAs containing three, two, or one guanosine at the 5' end, referred to as 3G, 2G, and 1G RNA, respectively. Furthermore, 1G RNA selectively packaged over 3G RNA into viral particles to serve as virion genome, suggesting these almost identical HIV-1 RNA species differ functionally. To investigate whether HIV-1 uses multiple transcription start sites and preferentially packages a specific RNA species in vivo, we examined HIV-1 unspliced RNA in paired PBMC and plasma samples collected from infected individuals.

Methods: To study HIV-1 transcription start site usage, we established a next-generation sequencing (NGS)- based 5' rapid amplification of cDNA end (5' RACE) method. The accuracy and reproducibility of this assay were verified using in vitro-transcribed RNAs as templates and by determining the 5' context of HIV-1 unspliced RNA in multiple biological replicates of infected cells and virions. Using samples with characterized HIV-1 transcripts, we further determined the copy number of HIV-1 unspliced RNA required to obtain accurate measurement.
Results: To study HIV-1 transcription start site usage in vivo, we used NGS-based 5' RACE to analyze RNA samples isolated from PBMCs of infected individuals. In most samples, there are several HIV-1 unspliced RNA species with varied 5' ends, indicating that multiple transcription start sites are used. Furthermore, 3G RNA is often the most abundant RNA species in PBMC samples. We have also examined the HIV-1 RNA species in corresponding plasma samples. Intriguingly, the distribution of HIV-1 unspliced RNA species in the plasma is distinct from that of the PBMCs: 1G RNA is the most abundant RNA species in the patient plasma samples, consistent with preferential packaging of 1G RNAs into virions.
Conclusion: Our preliminary results indicate that in vivo, HIV-1 uses heterogeneous transcription start sites to generate multiple unspliced RNA species. Furthermore, these 99.9% identical HIV-1 unspliced RNA species differ functionally. The 1G RNA is preferentially selected as virion genome to transfer genetic information to the progeny.

140 Investigation of the Functional Role of DDX42 in HIV-1 Viral RNA Splicing

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Background: Understanding the mechanism of HIV-1 viral RNA splicing could lead to the discovery of therapeutic potential drugs that target HIV-1 viral splicing pathways. HIV-1 splicing is regulated by cis-acting regulatory sequences and trans-acting splicing factors. We aim to identify host splicing factors that play roles in HIV-1 splicing through high-throughput assays.
Methods: We generated a stable HEK-293T cell line harboring an HIV-1 splicing reporter which contains GFP in Gag position and RFP in Nef position in the viral genome. This reporter indicates the expression of unspliced viral RNAs and completely spliced viral RNAs through the expression of GFP and RFP respectively. We introduced genome-wide CRISPR knockout sgRNA library into the splicing reporter cell line and sorted cells with significantly higher or lower GFP/RFP expression through fluorescence-activated cell sorting. We analyzed enriched sgRNA guides in each sorted cell populations to identify genes whose disruption might affect HIV-1 viral RNA splicing.
Results: We identified an RNA helicase DDX42, whose disruption caused an increase in completely spliced viral RNA species and a decrease in incompletely spliced viral RNA species. HIV-1 viral RNA splicing assays based on next generation sequencing show that the usage of specific HIV-1 viral RNA splice acceptors is affected in DDX42 knockout cells. For example, the usage of viral splicing acceptor A3 is increased significantly upon DDX42 knockout, which is also reflected in the increase of Tat protein expression in DDX42 knockout cell clones in western blot analysis. RNAseq analysis also reveals a role for DDX42 in the regulation of alternative splicing for a subset of host genes.
Conclusion: DDX42 plays a role in the regulation of HIV-1 viral RNA splicing through up- and down- regulation of the usage of specific viral RNA splicing acceptors.

141 Structural Basis of Translation Inhibition by MERS-CoV Nsp1 Reveals a Conserved Mechanism for β-CoVs

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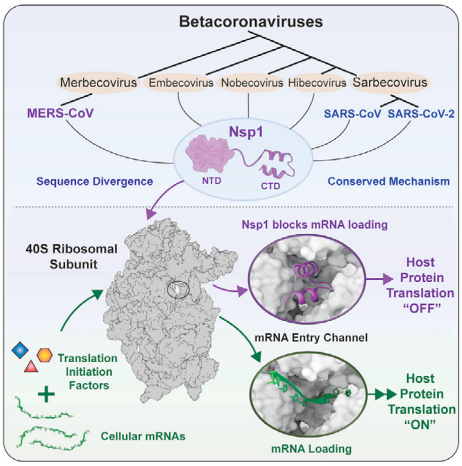
Background: Since 2002, three deadly human betacoronaviruses (β-CoVs) have emerged: SARS-CoV, MERS, and SARS-CoV-2, however our therapeutic arsenal remains inadequate to restrict current and novel β-CoVs. All β-CoVs encode non-structural protein 1 (Nsp1), an essential pathogenicity factor that potently inhibits host gene expression. Three distinct mechanisms are proposed for Nsp1: two cytosolic involving the ribosome and one nuclear stopping mRNA export. Also, across β-CoVs Nsp1 has very low amino acid conservation. Previous literature suggests MERS Nsp1 function is restricted to the nucleus and does not bind 40S ribosome, contrasting SARS-CoV-2 Nsp1. However, due to conserved structure prediction, we hypothesized that Nsp1 function is highly conserved across β-CoVs.
Methods: Nsp1's effects on translation were evaluated in-vitro. HeLa cytoplasmic extracts were incubated with an exogenous luciferase reporter mRNA and recombinant Nsp1. Nsp1-40S ribosome binding was evaluated via fluorescence polarization. Fluorescein was conjugated to Nsp1 and incubated against a range of 40S ribosomes. A high-resolution structure of MERS Nsp1 binding the 40S ribosome was obtained by single particle cryo-EM of in vitro assembled complexes.
Results: Contrary to previous reports, MERS Nsp1 robustly inhibits the translation of luciferase mRNA in- vitro. Compared to MERS Nsp1, SARS-CoV-2 Nsp1 inhibits translation at the ribosomal level more efficiently. However, fluorescence polarization showed that MERS and SARS-CoV-2 Nsp1 bind the 40S ribosome with very similar Kd's, 40nM and 27nM respectively. We resolved a 2.6-Å structure of MERS Nsp1 binding the 40S ribosome. The CTD of MERS Nsp1 adopts a helix-turn-helix motif binding in the mRNA entry channel of the 40S subunit interacting with the 18S rRNA and ribosomal proteins uS3 and uS5. Mutating this binding interface completely ablates Nsp1 function in vitro.
Conclusion: We show divergent Nsp1 proteins exhibit a remarkably conserved mechanism by targeting the 40S ribosome to restrict host gene expression. Since SARS-CoV-2 and MERS Nsp1 have similar Kd's for the 40S ribosome, we speculate the increased potency of SARS-CoV-2 Nsp1 is due to effects beyond initial binding to the 40S ribosomal subunit. Diversified therapeutics targeting multiple stages of the viral life cycle will be critical for containing β-CoV outbreaks. We present that Nsp1 of β-CoVs is an essential pathogenicity factor and an attractive target for therapeutic intervention which can broadly restrict β-CoVs.



142 "Traitor"-Virus-Guided Discovery of Novel Antiviral Factors

Caterina Prelli Bozzo[1], Alexandre Laliberté[1], Aurora De Luna[1], Chiara Pastorio[1], Meta Volcic[1], Alexander Graf[2], Stefan Krebs[2], Helmut Blum[2], Konstantin M. Sparrer[1], Frank Kirchhoff[1]
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Background: Cellular innate defense mechanisms govern the outcome of pathogen exposure. Studies on HIV-1 identified a variety of restriction factors (RFs) that may inhibit different viral pathogens at various steps of their replication cycle. They also revealed, however, that RFs playing roles in HIV-1 transmission and/or are targeted by the viral accessory Vif, Vpr, Vpu and Nef protein remain to be discovered. Thus, improved screens are urgently needed for a better understanding of host-pathogen interplay and antiviral defense mechanisms.
Methods: To develop effective, sensitive and versatile screens for novel RFs, we combined the CRISPR/Cas9 technology with the adaptive capacity of replication-competent HIV-1. In brief, we generated libraries of infectious molecular clones (IMCs) of HIV-1 equipped with single guide RNAs (sgRNAs) that target >500 potential restriction factors. Passaging of the library in Cas9 expressing CD4+ T cell lines allows enrichment of HIV-1 variants expressing sgRNAs associated with increased replication fitness. Enrichment of the sgRNAs thus identifies anti-viral genes.
Results: Passage of NL4-3 and CH077 based HIV-1 gRNA constructs in CEM-M7 and SupT1 cells stably expressing Cas9 revealed that sgRNAs against GRN, CIITA,

EHMT2, CEACAM3, CC2D1B, RHOA and HMOX1 provide significant advantages for viral replication fitness. Knock-out studies confirmed that GRN, CEACAM3 and CIITA inhibit HIV-1 in primary CD4+ T cells. Several factors were identified with high reproducibility in our virus-driven screen but not in common overexpression or knock-down assays. Finally, lack of the nef gene increased selection of sgRNAs targeting SERINC5 and identified IFI16 as putative Nef target. Subsequent analysis confirmed that Nef attenuates the inhibitory effects of IFI16.

Conclusion: We established an innovative, robust and highly versatile virus-driven approach that allows the identification of antiviral factors by turning HIV-1 into "traitors" revealing their cellular opponents.

143 Immunoregulatory Pathways Predict Mortality More Strongly in People With Versus Without HIV

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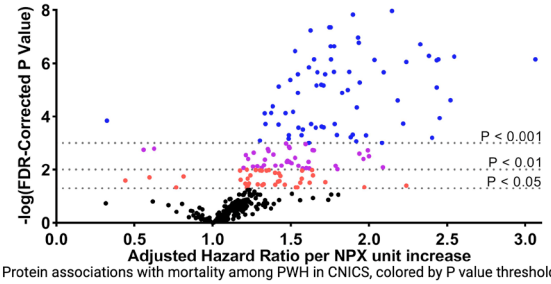
Background: While people with HIV (PWH) on suppressive antiretroviral therapy (ART) have higher levels of inflammation and are at greater risk for morbidity and mortality than the general population, the immunologic pathways most strongly linked to this excess HIV-associated risk remain incompletely characterized.

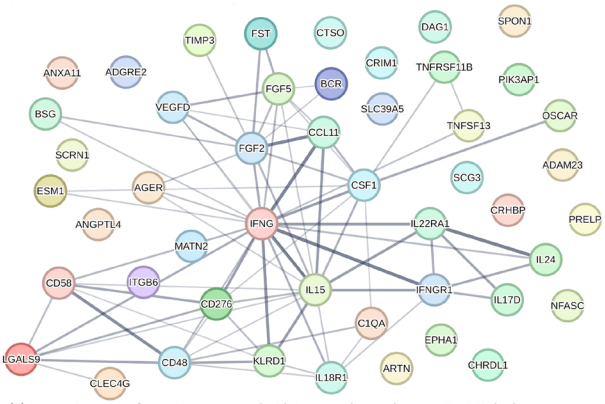
Methods: The first available plasma sample after 1/1/2010 was selected from a random sample of all PWH from 8 CNICS sites with ≥6 months of ART-mediated viral suppression. Plasma was assessed for 363 detectable inflammatory proteins (Olink Inflammation I Explore Panel). The relationship between each protein and all- cause mortality was assessed via Cox proportional hazards modeling, adjusted for VACS index (1.0) and CNICS site, controlling for the false discovery rate (FDR) via the Benjamini-Hochberg method. To identify pathways more relevant in PWH than in the general population, adjusted hazard ratios (aHR) were compared to published UK Biobank (UKB) data, which reported the association between the same Olink panel and all-cause mortality in 47,600 participants from the general population via FDR-corrected multivariate Cox modeling.

Results: Among 922 PWH in CNICS, median age was 47 and 18% were women. Median current and nadir CD4 counts were 579 cells/mm^3 and 245 cells/mm^3, respectively. Over a median follow-up time of 9 years, 103 deaths occurred. After adjustment and FDR correction, 147 (40%) proteins were associated with an increased (N=140) or decreased (N=7) hazard of death in CNICS (all FDR-corrected P<0.05, Figure A). Compared to the same proteins assessed in UKB, higher levels of 48 proteins were uniquely associated with increased mortality in CNICS (N=21) or had an aHR at least 50% higher among PWH than in the UKB general population (N=27) (Figure B). While some of these HIV-associated mortality predictors were pro-inflammatory (IFNg, IFNgR1, IL- 18R1, and IL-15), the largest cluster comprised immunoregulatory proteins linked to suppressing T, NK, and myeloid cell activation (CD276, CD58, CD48, ITGB6, CLEC4G, and KLRD1) or pro-fibrotic and endothelial cell regulatory processes.

Conclusion: While numerous pro-inflammatory proteins are associated with mortality in both PWH and the general population, immunoregulatory rather than pro-inflammatory proteins were preferentially associated with mortality risk in PWH. Whether the immunoregulatory response to inflammation is an important causal mediator of increased morbidity and mortality in treated PWH should be explored.



(A) Protein associations with mortality among PWH in CNICS, colored by P value threshold.



(B) Interaction map of proteins associated with increased mortality or aHR ≥50% higher among PWH in CNICS vs. the UKB general population (bar thickness indicates interaction strength).

144 HIV-1 Soluble gp120 Is Associated With Immune Dysfunction in Individuals on Antiretroviral Therapy

Mehdi Benlarbi[1], Jonathan Richard[2], Carl Chartrand-Lefebvre[1], Marc Messier-Peet[2], Andrew Clark[3], Walther Mothes[4], Daniel E. Kaufmann[2], Frank Maldarelli[5], Nicolas Chomont[2], Cécile Tremblay[2], Ralf Duerr[6], Marzena Pazgier[7], Madeleine Durand[2], Andrés Finzi[2], for the Canadian HIV and Aging Cohort Study

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Background: Chronic inflammation persists in some people living with HIV (PLWH), even during ART, and is associated with premature aging. The gp120 subunit of HIV-1 Env can shed from viral and cellular membranes, persists in plasma and tissues, and has been suggested to exert immunomodulatory properties. We evaluated whether plasmatic soluble gp120 (sgp120) and a family of gp120-specific anti-cluster A antibodies (Abs), previously linked to CD4 depletion in vitro, could contribute to chronic inflammation, immune dysfunction, and sub-clinical cardiovascular disease in participants of the Canadian HIV and Aging cohort (CHACS) with undetectable viremia.

Methods: We developed a novel assay to specifically detect plasmatic sgp120. We performed a cross-sectional assessment of sgp120 and anti-cluster A Abs in individuals from CHACS. We evaluated their associations with immune parameters (CD4 counts, CD4:CD8 ratios) and IL-6. In a subgroup participating in a cardiovascular imaging sub-study, we also studied the association between sgp120, anti-cluster A Abs, and sub-clinical cardiovascular disease, measured by computed tomography coronary angiography. Measures of association were obtained using linear regression models, adjusted for the following clinically-defined potential confounders: age, sex, smoking, low/high-density lipoproteins, diabetes, hypertension, nadir CD4, and duration of antiretroviral therapy.

Results: We included 386 participants for measurements of sgp120 and anti-cluster A Abs, 157 of whom also had measurements of IL-6, and 145 of whom took part in the cardiovascular imaging sub-study. The mean age of participants was 55.8, 90% were males, and 82% were Caucasian. The median duration of HIV infection was 18.3 years. sgp120 was detected in 107/386 (28%). Anti-cluster A Abs were inversely associated with CD4 cell counts (adjusted beta -15.29 95%CI -26.74 to -3.84, p=0.009) and CD4:CD8 ratio (adjusted beta -0.055 95%CI -0.080 to -0.030, p=0.004). The strength of these associations was increased in the subset with high sgp120. sgp120 was associated with increased

levels of IL-6 (p=0.0015). In participants with detectable atherosclerotic plaque, levels of sgp120, anti-cluster A Abs, and their combination were associated with increased volume of atherosclerotic plaques (p=0.01, 0.018, and 0.006, respectively).
Conclusion: sgp120 could act as a pan toxin, causing immune dysfunction and sustained inflammation in a subset of PLWH, contributing to the development of premature comorbidities.

145 Rapid Emergence and Adaptive Evolution of SARS-CoV-2 Variants in Advanced HIV Infection

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Background: Prolonged SARS-CoV-2 RNA shedding and intra-host evolution in people with HIV (PWH) suggested that SARS-CoV-2 variants, including variants of concern (VOCs), may preferentially arise in PWH. Nonetheless, the evolutionary processes remain incompletely understood due to consensus-based genetic characterization of intra-host virus from short-read whole genome sequencing. Alternatively, high-throughput single-genome amplification and sequencing (HT-SGS), which enables detection of unique linked groupings of mutations (i.e. haplotypes) at the level of single genomes, is more suitable for estimates of intra-host population diversity and allows a better understanding of evolutionary relationship among viruses.
Methods: We sequenced SARS-CoV-2 spike genes in nasal swabs of longitudinal sample sets from 25 people without HIV (PWOH) and 22 PWH, who were subgrouped on the basis of CD4 T cell counts (CD4 counts). We developed HT-SGS, which used Pacific Biosciences single molecule, real-time technology (SMRT) coupled with unique molecular identifiers (UMIs) of virus genome sequences, to generate up to ~ 1000 single-copy sequences per sample with high accuracy.
Results: Intra-host spike gene diversity was significantly higher in PWH with CD4 counts <200 cells/μL than in the other subgroups. These individuals had a median of 3.5 secondary Pango lineages/person, while PWOH had showed no secondary lineages. Through longitudinal analysis, remarkable features of SARS-CoV-2 dynamics were observed in PWH with CD4 counts <200 cells/μL, including 1) high early diversity, beginning shortly after COVID-19 symptom onset, 2) rapid changes in frequency of the most abundant haplotypes, and 3) large changes in population haplotype composition over time. Intra-host polymorphisms in PWH with CD4 counts <200 cells/μL included greater numbers of synonymous (reflecting more virus replicative cycles) and nonsynonymous mutations (often overlapping with defining mutations of VOCs) than other subgroups, indicating a high mutational burden. In addition, we found that patterns of gene evolution in PWH with CD4 counts <200 cells/μL resulted from adaptation of the virus to the host by selective forces (positive selection).
Conclusion: These reveal unique virus genetic aspects of SARS-CoV-2 infections in people with advanced HIV infection that markedly increase the risk for generation of new variants. Our results suggest that HIV treatment with antiretroviral therapy can help limit intra-host SARS-CoV-2 persistence and evolution.

146 Temperature-Dependent SARS-CoV-2 Spike-ACE2 Interaction Is Associated With Viral Transmission

Mehdi Benlarbi[1], Shilei Ding[2], Étienne Bélanger[1], Alexandra Tauzin[1], Halima Medjahed[2], Raphaël Poujol[3], Omar El-Ferri[4], Yuxia Bo[4], Julie Hussin[3], Judith Fafard[5], Marzena Pazgier[6], Inès Levade[5], Cameron Abrams[7], Marceline Côté[4], Andrés Finzi[1]
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Background: The persistent evolution of SARS-CoV-2 gave rise to a wide range of variants harboring new mutations in their Spike glycoprotein. We previously demonstrated that temperature modulates the interaction between SARS-CoV-2 Spike and its host receptor ACE2, with low temperature increasing ACE2 binding affinity and viral entry. Here we characterized the latest Omicron subvariants and evaluated whether this property is associated with viral transmission.
Methods: We first tested the capacity of plasma from 18 individuals who received a fifth dose of bivalent (BA.1 or BA.4/5) mRNA vaccine to recognize and neutralize Spikes from 13 recent Omicron subvariants. We also tested the susceptibility of Spikes to cold inactivation and measured their processing. We also measured how temperature affects the interaction between Spike and ACE2 by using biolayer interferometry, flow cytometry and virus capture assay. The associations between these parameters and the viral growth rate of each Omicron subvariants in the population between October 2022 and August 2023 was determined.
Results: Compared to the early D614G strain, most Omicron subvariants Spike glycoproteins possess improved ACE2 binding, enhanced immune escape and are more susceptible to cold inactivation. Their Spikes bound ACE2 in a temperature-dependent manner, enhancing Spike binding and protomer cooperativity to ACE2. We also found that Omicron subvariants Spike processing is associated with their susceptibility to cold inactivation ($r = -0.6124$, $p=0.0199$) and with ACE2 interaction at low temperatures at the surface of pseudoviral particles ($r = -0.6271$, $p=0.0164$). Intriguingly, we found that Spike-ACE2 binding at low temperatures is significantly associated with growth rates of Omicron subvariants in the human population ($r = 0.9842$, $p<0.0001$).
Conclusion: Our findings indicate that Omicron subvariants acquired mutations enhancing resistance to neutralization by plasma, improving Spike processing, and increasing affinity for ACE2 at both low and high temperatures. Importantly, we found that Spike-ACE2 interaction at the surface of viral particles at low temperatures is strongly associated with Omicron subvariants growth rates. Our study underscores the necessity for ongoing surveillance of emerging subvariants and underscores the importance of measuring Spike-ACE2 interaction at low temperatures, since this parameter is highly associated with viral transmission.

147 IFNα2 Autoantibodies Post-SARS-CoV-2 Wave 1 in India Are Associated With Lower Omicron Symptomology

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[1]King's College London, London, UK, [2]St John's Research Institute, Bangalore, India

Background: Neutralizing autoantibodies against type I IFNs have been associated with life-threatening SARS-CoV-2 infection in the first wave of the pandemic. As part of a wider immunophenotyping study aimed at comparing susceptibility and immunopathogenesis of COVID-19 between the UK and India, we examined the levels of anti-IFNα2 neutralization in sera collected.
Methods: We used sera from these cohorts to measure anti-Spike (S) and anti-Nucleocapsid (N) responses, screen for IFNα2 autoantibodies that neutralized both activation of JAK-STAT signalling in a HEK-Blue IFN alpha/beta reporter cell line, and to attenuate the antiviral state in IFNα2-treated U87-MG cells when challenged with VSV-G pseudotyped HIV-1 vectors. As controls we used autoimmune polyendocrine syndrome type 1 (APS-1) patients with a deleterious variant of AIRE, a mediator of immune tolerance leading to excessive production of type I interferon autoantibodies that ameliorate autoinflammation.
Results: Most pre-pandemic individuals in both the UK and India had no detectable neutralising IFNα2 autoantibodies. In line with previous studies, a small number of UK patients (2) hospitalized during wave 1 of the pandemic had detectable IFNα2 neutralizing activity. By contrast, the majority of Anti-S/Anti-N+ healthy donors in India had low-level neutralizing activity compared the UK cohort. Intriguingly, amongst those hospitalized during the Omicron BA.2 wave in Bangalore, circulating anti-IFNα2 activity was significantly reduced in severe vs moderate disease. This correlated with a global increase in inflammatory phenotype in circulating leukocyte subsets in these. Notably, autoantibody levels did not correlate with age and gender across the various groups. In India, the sex distribution is closely balanced, while the UK cohorts are predominately male.
Conclusion: In the first wave of the pandemic, while high levels of autoantibodies against IFNs were associated with severe disease in previously non-exposed individuals, our results suggest the interplay between such antibodies and SARS-CoV-2 pathogenesis may be more complex in different populations. We do not understand what biological and environmental factors underlie the presence of low-level autoantibodies to IFNα2 in healthy SARS-

CoV2 Ag+ individuals post first wave in India, but their reduction in severe Omicron cases suggests that their presence in conjunction with pre-existing SARS-CoV-2 immunity may ameliorate disease severity in those that become reinfected.

148 Treatment of Prehypertension in People Living With HIV: A Randomized Controlled Trial

Lily D. Yan[1], Vanessa Rouzier[2], Rodney Sufra[2], Colette Guiteau[2], Mirline Jean[2], Fabyola Preval[2], Joseph inddy[2], Pierre Obed Fleurijean[2], Alexandra Apollon[2], Nour Mourra[1], Myung Hee Lee[2], Suzanne Oparil[3], Marie Deschamps[2], Jean W. Pape[2], Margaret McNairy[1]

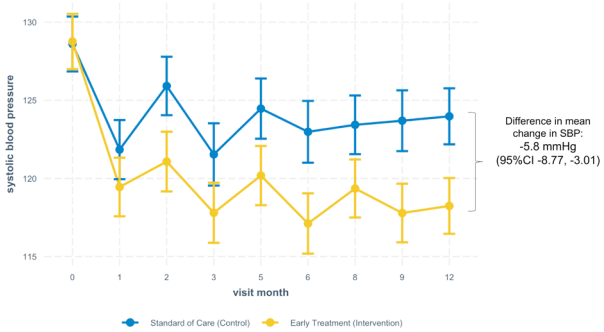
[1]Weill Cornell Medicine, New York, NY, USA, [2]GHESKIO, Port-au-Prince, Haiti, [3]University of Alabama at Birmingham, Birmingham, AL, USA

Background: Elevated systolic blood pressure (SBP) >120 mmHg is associated with increased cardiovascular disease (CVD) risk and mortality among people living with HIV (PLWH). The dual burden of HIV and CVD is highest in low-middle income countries (LMIC), yet the World Health Organization recommends PLWH initiate medication at SBP/DBP ≥140/90 mmHg, despite lower thresholds for diabetes and renal disease. We conducted a randomized controlled trial to evaluate acceptability and mean change in SBP among PLWH with prehypertension who initiate first-line antihypertensive treatment in a LMIC.

Methods: A total of 250 PLWH were enrolled from GHESKIO's HIV Clinic, between March 2021 to April 2023 in Port-au-Prince, Haiti. Participants were 18-65 years old, on stable antiretroviral therapy ≥6 months, had prehypertension (SBP 120-139 mmHg or DBP 80-89 mmHg), not on antihypertensive treatment, and randomized to intervention (initiation of amlodipine 5mg) or control (no medication unless reached SBP/DBP ≥140/90) in a 1:1 ratio. Participants were followed for 12 months with standardized clinic and community visits measuring CVD health behaviors, BPs, physical exam, imaging, and laboratory data. The primary outcome was difference in mean change in SBP between study arms, from enrollment to 12 months. Secondary outcomes were difference in mean change in DBP, acceptability, incident hypertension, and adverse events. We analyzed the primary outcome using a linear mixed-effects model accounting for repeated measures and correlations within subjects.

Results: The baseline characteristics of the two groups were similar. Mean SBP/DBP change over 12 months was -10.6/-8.9 mmHg in intervention and -4.6/-3.2 mmHg in control. The difference in mean change in BP between intervention vs control was SBP -5.8 mmHg (95%CI -8.77, -3.01), DBP -5.5 mmHg (95%CI -7.92, -3.16). For incident hypertension, the hazard ratio of intervention vs control was 0.43 (95%CI 0.26, 0.70). The most common adverse events (26 total) were dizziness (13) and edema (5), and no serious adverse events were drug related. Participants and study staff reported high acceptability of amlodipine initiation.

Conclusion: Treatment of prehypertension in PLWH compared to standard of care reduced BP and incident hypertension, with few adverse events. There is an urgent need for CVD prevention among PLWH with elevated BP, who have alarmingly high risk of CVD events and mortality. (ClinicalTrials.gov number, NCT04692467).



149 A Nurse-Led Strategy Improves Blood Pressure and Cholesterol in People With HIV: The EXTRA-CVD Trial

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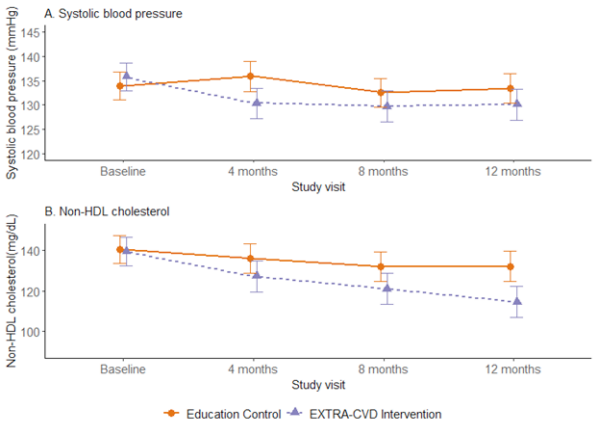
Background: Despite higher atherosclerotic cardiovascular disease (ASCVD) risk, people with HIV (PWH) experience unique barriers to ASCVD prevention care. Using a human-centered design approach, we developed EXTRA-CVD-a nurse-led multicomponent strategy of care coordination, home blood pressure monitoring, evidence-based treatment algorithms, and electronic health records tools to improve blood pressure and cholesterol management in 3 HIV clinics in the United States.

Methods: We conducted a randomized controlled trial among 298 PWH with suppressed HIV-1 viral load on antiretroviral therapy with comorbid hypertension and high cholesterol. Participants were stratified by site and randomized 1:1 to the EXTRA-CVD strategy or general health education control. Change in systolic blood pressure (SBP) was the primary outcome assessed at baseline, 4, 8, and 12 months. Change in non-HDL cholesterol was secondary. Primary intention-to-treat analyses were conducted using linear mixed models, with pre-specified moderation analyses by natal sex, baseline ASCVD risk, and site.

Results: Mean (SD) age was 58(9.6) years; 21% were female and 66% were non-white race. Baseline mean (SD) SBP was 135(19) mmHg and non-HDL cholesterol was 140(45) mg/dL. Half were currently prescribed 2 or more antihypertensive drugs and two-thirds were on a statin at baseline. At 12 months, participants assigned to EXTRA-CVD had 4.2mmHg (95% CI 0.3-8.2; p=0.04) lower SBP and 16.9mg/dL (95% CI 8.6-25.2; p<0.001) lower non-HDL compared to controls (Figure). Non-HDL change was driven more by a 29.5mg/dL reduction in triglycerides (95% CI 5.3-53.7; p=0.02), rather than LDL [9.6 mg/dL (95% CI -6.3-25.5; p=0.24)]. EXTRA-CVD participants had higher odds of reaching treatment goal for SBP [<130/80 mmHg; OR 2.9(95% CI 1.0-8.3; p=0.05)] and for non-HDL [<100mg/dL for high-risk and <130mg/dL for others; OR 7.3(2.3-23.3; p<0.001)]. There was some evidence that the SBP effect was greater in females compared to males (11.8 mmHg greater at 4-months, 9.6 mmHg at 8-months, and 5.9 mmHg at 12-months; overall joint test p=0.06), but other intervention effects were similar by sex (all p>0.3). Intervention effects were not moderated by baseline ASCVD risk or site (all p>0.2).

Conclusion: A nurse-led multi-component strategy lowered blood pressure and cholesterol over 12 months in diverse PWH with these comorbid ASCVD risk factors. These results should inform future implementation of multifaceted ASCVD prevention programs for PWH in the United States.

Figure: Model-estimated systolic blood pressure and non-HDL cholesterol and associated 95% confidence intervals showing the effects of a nurse-led multi-component strategy (EXTRA-CVD) over 12 months compared to general health education control.



150 Community Health Worker-Facilitated Telehealth for Severe Hypertension Care in Kenya and Uganda

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Background: Expanding the HIV care model to include HIV status-neutral hypertension treatment can improve cardiovascular disease outcomes; however, individuals with severe hypertension face additional barriers to care, including need for frequent clinic visits to titrate medications. We conducted a pilot study to test whether a clinician-driven, community health worker (CHW) facilitated telehealth intervention would improve hypertension control among adults with severe hypertension in rural Uganda and Kenya.
Methods: We conducted a randomized controlled trial of hypertension treatment delivered via telehealth by a clinician (adherence assessment, counseling, decision-making) and facilitated by a CHW in the participant's home, compared to clinic-based hypertension care (NCT04810650). We recruited adults ≥40 years with BP ≥160/100 mmHg at household screening by CHWs, with no restrictions by HIV status. After initial evaluation at the clinic, participants were randomized to telehealth or clinic-based hypertension follow-up. All participants were treated using standard country guideline-based antihypertensive drugs. The primary outcome was hypertension control at 24 weeks (BP <140/90); secondary outcomes included severe hypertension (BP ≥160/100) and retention in care (not late by ≥30 days at 24 weeks). We used TMLE to compare outcomes by arm, overall and among key subgroups.
Results: We screened 2,965 adults ≥40 years, identifying 266 (9%) with severe hypertension and enrolling 200 (102 control, 98 intervention). Participants were 70% women, median age 62 (IQR 51-72); 14% were HIV- positive. Mean number of hypertension drugs prescribed at last visit was 1.6 in intervention and 1.7 in control. Week 24 hypertension control was 77% in intervention and 52% in control (RR 1.48, 95%CI 1.20-1.83); effect on hypertension control was greater among women (81% vs 53%; RR 1.53, 95%CI 1.21-1.94). Prevalence of severe hypertension at 24 weeks was 7% in intervention and 25% in control (RR 0.30, 95%CI 0.14-0.64), with similar effects among people with HIV (8% vs 21%, RR 0.39, 95%CI 0.04-3.82). Retention in care at 24 weeks was 91% in intervention and 61% in control (RR 1.49, 95%CI 1.26-1.76).
Conclusion: Clinician-driven, CHW-facilitated telehealth for hypertension management improved hypertension control and reduced severe hypertension compared to clinic-based care. Telehealth focused on individuals with severe hypertension is a high-yield approach to improve outcomes among those with highest risk for CVD.

151 Pitavastatin Reduces Non-Calcified Plaque via Pro-Collagen PCOLCE Independently of LDL in REPRIEVE

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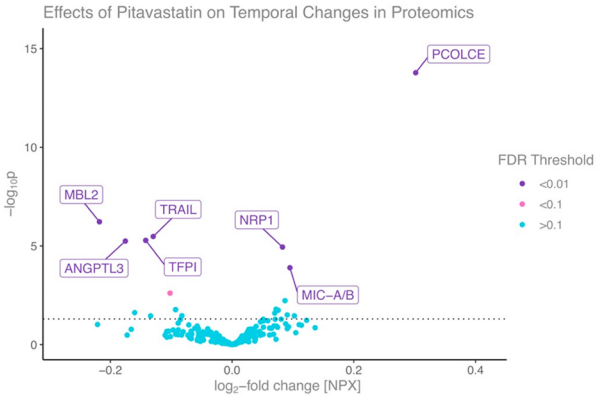
Background: Pitavastatin reduced major adverse cardiac events (MACE) and non-calcified coronary artery plaque volume (NCPvol) among people with HIV (PWH) in REPRIEVE. However, the biological pathways responsible are not well understood. We utilized a targeted discovery proteomics approach to evaluate the biological pathways mediating statin effects on NCPvol in REPRIEVE.
Methods: Changes in 255 plasma protein levels (Olink, see Figure 1) were analyzed among REPRIEVE mechanistic substudy participants continuing their assigned treatment over a 2-year follow-up period. Changes in protein levels were related to changes in NCPvol in mediation analysis among participants with evidence of plaque on baseline coronary CT angiography using linear regression analysis.
Results: Among the 542 individuals (age: 51 years, 18% female) included in the assessment of protein changes, 275 received placebo and 267 pitavastatin. After correcting for false discovery rates, pitavastatin use was significantly associated with increased expression of 3 proteins (PCOLCE, NRP-1, MIC-A/B) and decreased expression of 4 proteins (TFPI, TRAIL, ANGPTL3, MBL2, Figure 1). Among the 196 participants (107 pitavastatin, 89 placebo) with plaque at entry, while pitavastatin associated changes in LDL were observed, they did not correlate with NCPvol (ρ=0.08, p=0.20). However, among the proteins changing with pitavastatin, the increase in PCOLCE was significantly related to the reduction in NCPvol (ρ=-0.27, p<0.001). Mediation analysis including PCOLCE and LDL indicated that pitavastatin resulted in a 26% [CI: 16; 38%, p<0.001] increase in PCOLCE and a 30% [CI: 23; 37%, p<0.001] decrease in LDL. While each fold increase in PCOLCE was associated with a 25% decrease in NCPvol [CI: 13; 35%, p<0.001], LDL changes had no relationship (2%, CI: -12; 18%, p=0.82). Overall, 93% of the 8.8% reduction in NCPvol was mediated through the effects of pitavastatin on PCOLCE. Other proteins were either borderline or nonsignificant in the mediation analysis.
Conclusion: The effects of pitavastatin to reduce NCPvol in REPRIEVE were significantly mediated by changes in PCOLCE, the rate-limiting enzyme in collagen deposition. Surprisingly, LDL change was not related to changes in NCPvol. Further studies will investigate if higher levels of PCOLCE mediates the beneficial effects of pitavastatin on MACE. Statin effects on collagen formation to stabilize noncalcified plaque may be an important unrecognized mechanism to reduce coronary artery disease in PWH.



Pitavastatin significantly increased expression of PCOLCE, NRP-1, and MIC-A/B and decreased levels of TFPI, TRAIL, ANGPTL3, and MBL2 beyond FDR threshold <0.01. Analyses used Cardiovascular III, Immuno-oncology, and Cardiometabolic Olink panels. Dashed line=nominal p-value 0.05.

152 Pitavastatin Has No Effect on Long-Term, Objective Physical Function in REPRIEVE

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Background: Declines in physical function occur with age, and are common among people with HIV (PWH). Due in part to the anti-inflammatory effect, statins may alleviate declines in physical function though most studies assessing the effect of statins on physical function in the general population have been observational and randomized controlled data have been limited to one year of follow-up. We hypothesized that physical function would decline among PWH, but with the known anti-inflammatory effects of statins, PWH randomized to pitavastatin would have slower declines compared to placebo.
Methods: REPRIEVE is a double-blind randomized trial evaluating pitavastatin for primary prevention of major adverse cardiovascular events in PWH; the PREPARE substudy assessed physical function in a subset of participants annually for up to 5 years. Chair rise rate based on time to complete 10 chair rises (primary outcome), 4-meter gait speed, grip strength, and a combined modified short physical performance test were analyzed using linear mixed models.
Results: Of 602 PWH, 52% were randomized to pitavastatin and 48% to placebo. Median age was 51 years; 18% were natal female; 2% transgender; 40% Black, and 18% Hispanic; median BMI was 27.2 (Q1, Q3 24.3, 30.1) kg/m^2. 45% of participants enrolled at REPRIEVE entry; 55% enrolled within 24 months

after REPRIEVE treatment initiation. Median PREPARE follow-up was 4.7 (4.3, 5.0) years; 81% completed follow-up. Physical function was similar between the two treatment groups at PREPARE entry. There was no evidence of decline in chair rise rate in either treatment group (Figure), and no significant difference in the pitavastatin group compared to placebo (difference -0.10 [95% CI: -0.30, 0.10] rises/min/year; p=0.31). Small declines were observed in other physical function tests in both treatment groups, with no apparent differences between groups (Figure). The findings were consistent in subgroup analyses by age, sex, race, ART duration, CD4 cell count, baseline physical function, and presence of muscle symptoms (not shown).

Conclusion: We observed minimal declines in physical function over 5 years of follow-up among middle-aged PWH, with no differences among PWH randomized to pitavastatin compared to placebo. Our findings do not support the use of statins to maintain physical function in this population, but do expand upon the overall REPRIEVE trial findings to support the long-term safety of statin therapy on physical function in PWH.

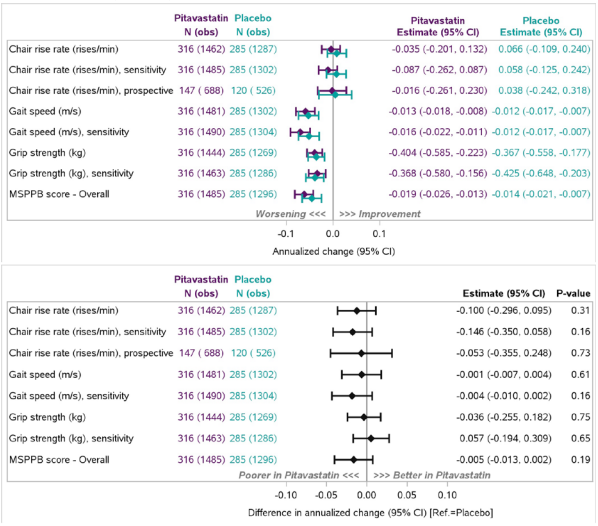

FIGURE: Annualized change in physical function within treatment groups (top) and treatment group difference (bottom). In sensitivity analyses, evaluations not attempted for non-administrative reasons were considered worst outcomes. 'Prospective' is among participants with physical function evaluations before initiating REPRIEVE study treatment. For visual purposes, data are plotted in standardized scale.

153 Lung Function, HIV and Mortality: Analyses From the AIDS Linked to the Intravenous Experience Cohort

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Background: Chronic lung disease is an increasingly important comorbidity for persons aging with HIV. Persons with HIV(PWH) can experience accelerated decline in lung function, including spirometry measures(FEV1). The current implications of this lung function decline on all cause and HIV-related mortality warrants further investigation. Additionally, the normalized FEV1Q has recently been developed to improve interpretation of lung function without biases related to sex or race but has not yet been studied in cohorts of PWH. We leveraged the AIDS Linked to the Intravenous Experience(ALIVE) cohort in Baltimore, MD, consisting of PWH and matched HIV-uninfected participants, to study the implications of impaired lung function in a high-risk HIV cohort.

Methods: We analyzed 2009-2019 ALIVE participant data. Lung function(FEV1 and FEV1Q) and clinical data(HIV RNA, comorbidity data) were collected at semi-annual visits. Mortality was derived from the national death index and clinical records, assessing all-cause and mortality due to HIV and chronic disease. Associations between time-updated lung function and mortality were analyzed in cox-proportional hazard models, adjusted for demographics, smoking(pack-years and status), injection drug use(IDU), HIV status, and comorbidity index. Models were also stratified by HIV status with adjustment for viremic control(<400copies/ml).

Results: 1534 participants(474 PWH) contributed 10515 lung function measures over 10 years. Mean age at entry was 50, with 34% reporting active IDU and 84% current smokers. Among PWH, 53% had detectable HIV RNA. Mortality was high with 410(26%) deaths during the study period; 35% among PWH. In adjusted models, accounting for comorbidities and risk factors, a 1SD increase in FEV1 (HR 0.70; P<0.01) and FEV1Q (HR 0.73; P<0.01) was associated with lower all-cause mortality. Higher lung function was protective for HIV-related mortality (FEV1, HR 0.52, P<0.01; FEV1Q, HR 0.57, P<0.01). Among PWH, after adjusting for viremic control, lung function remained associated with all cause(HR 0.62; P<0.01) and HIV-related mortality(HR 0.54; P<0.01).

Conclusion: We demonstrate that in a high-risk HIV cohort, after accounting for behavioral risk factors and comorbidities, lung function remains highly associated with all cause and HIV related mortality. These results are consistent when using the normalized FEV1Q, which may be less susceptible to bias. The results highlight the importance of lung disease and interventions to preserve lung health in PWH.

Table. Association of Lung Function Measures with All-Cause and Cause-Specific Mortality.* Hazard ratios represent the change in hazard related to a 1 standard deviation increase in each lung function measure

Mortality Cause	All-Cause Mortality		HIV - Infection Related Mortality		Chronic Disease Related Mortality		Injection Drug Use / Trauma Mortality	
	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value
Lung Function Measure								
FEV_1	0.70 (0.60,0.81)	**<0.001**	0.52 (0.38, 0.73)	**<0.001**	0.73 (0.58, 0.91)	**0.006**	0.81 (0.64, 1.03)	0.081
FEV_1Q	0.73 (0.64, 0.83)	**<0.001**	0.57 (0.43, 0.77)	**<0.001**	0.77 (0.63, 0.94)	**0.010**	0.82 (0.66, 1.02)	0.080

*Adjusted for age, sex, race, current injection drug use, smoking (pack-years and smoking status), HIV serostatus and RNA levels, comorbidity index (cardiac disease / myocardial infarction, renal disease, liver disease and hepatitis C virus, obesity, diabetes, stroke).

154 Prostate Cancer Characteristics and Outcomes for Veterans With HIV in the Antiretroviral Era

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Background: Prostate cancer is the leading cancer diagnosis among Veterans with HIV and will soon be the leading cancer among all US persons with HIV (PWH). Despite the substantial prostate cancer burden for PWH, there are little data on prostate cancer clinical characteristics and outcomes. Therefore, we studied prostate cancer characteristics at diagnosis and survival by HIV status in the Veterans Aging Cohort Study (VACS)-HIV, a national cohort of Veterans with HIV and demographically similar Veterans without HIV.

Methods: We used data from VACS-HIV (2001-2018) to identify a cohort of male PWH prior to prostate cancer diagnosis (n=791), as well as male comparators without HIV (PWoH n=2,778). We compared patient demographics, prostate specific antigen (PSA) testing and prostate cancer clinical characteristics by HIV status. We then compared prostate cancer risk groupings (D'Amico) and prostate cancer-specific and overall survival by HIV status, stratified by risk group using age-adjusted Cox regression models.

Results: VACS-HIV patients with prostate cancer had a median age of 62 years, which did not differ by HIV status. Race/ethnicity proportions were also similar, with non-Hispanic Blacks being the most common group diagnosed with prostate cancer. PWH with prostate cancer frequently had detectable HIV viremia at prostate cancer diagnosis (>60%). HIV infection was associated with higher PSA (median 6.8 vs. 6.3 ng/mL; p=0.005) but no difference in Gleason grade. There was less frequent PSA testing among PWH prior to prostate cancer diagnosis (1.25 fewer tests than PWoH, age adjusted; p<0.001). PWH were more likely to be diagnosed with D'Amico intermediate/high risk localized prostate cancer (68% vs. 63%; p= 0.02) and advanced prostate cancer (either nodal involvement or metastatic disease) than PWoH (4.0% vs. 2.7%; p=0.04). Both relationships persisted after adjustment for age. HIV was significantly associated with worse age-adjusted all-cause mortality for intermediate-, high-risk localized and advanced cancers. PWH did not have higher prostate-cancer specific mortality in any cancer risk group compared to PWoH.

Conclusion: PWH were diagnosed with higher risk prostate cancers more frequently in VACS-HIV than those without HIV possibly reflecting lower rates of PSA testing in this group. Higher non-cancer mortality seen in those with HIV infection may impact the relative risks and benefits of prostate cancer management strategies- including observation-for appropriate patient groups.

Table. All cause and prostate cancer-specific death by D'Amico prostate cancer risk group and HIV status.

All-cause death, n (%)	PWH (N=759)	PWoH (N=2,703)	p*
Low risk	46 (19.1)	153 (15.5)	0.11
Intermediate	76 (21.2)	192 (15.8)	<0.001
High Risk	41 (25.6)	123 (24.6)	0.013
Prostate cancer death, n (%)			
Low risk	1 (0.42)	5 (0.51)	0.92
Intermediate	5 (1.4)	26 (2.2)	0.80
High Risk	11 (7.0)	37 (7.5)	0.41

*p-values presented are from age-adjusted Cox proportional hazards models.
Abbreviations: PWH- persons with HIV, PWoH – persons without HIV

155 InSTI Switch During Menopause Is Associated With Accelerated Body Composition Change

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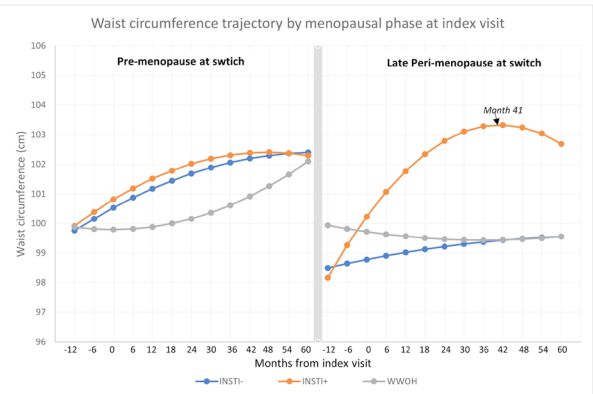
Background: Integrase strand transfer inhibitors (INSTIs) have been associated with greater weight gain in women with HIV (WWH) than men with HIV. The transition to menopause is also associated with body composition changes. Whether INSTI initiation during the menopausal transition affects waist circumference (WC) and BMI trajectories is unknown.
Methods: From 2006-2019, 1159 non-pregnant virally-suppressed WWH [(424 who switched to an INSTI (INSTI+); 735 who did not switch (INSTI–) during a similar time window] and 904 women without HIV (WWOH) from the Women's Interagency HIV Study were included. The visit at which WWH reported switching to an INSTI was defined as the index visit. Mixed effect models including quadratic terms were used to evaluate change in WC and BMI by menopausal phase defined using anti-Müllerian hormone, a biomarker of ovarian reserve, at the index. Models were adjusted for demographics, baseline WC or BMI, behavioral factors, comorbidities, and HIV-related factors.
Results: Overall, 66% identified as Black and 28% were premenopausal, 10% early peri-, 28% late peri-, and 34% postmenopausal at the index. INSTI+ were older than INSTI- and WWOH (median 52 vs 49 vs 47 years) with median BMI 30 vs 29 vs 31.5kg/m^2, respectively. 64% of INSTI+ and 79% of INSTI- were on tenofovir DF prior to the index visit. Figure shows the WC trajectory for INSTI+, INSTI-, and WWOH who were premenopausal and late perimenopausal at index visit. In premenopausal women, INSTI+ and INSTI- was associated with a 0.06cm per 6 month (mo) (95%CI:-0.27,0.38) and 0.08cm per 6mo (95%CI:-0.11,0.28) faster linear increase in WC respectively, compared to WWOH; INSTI+ had a 0.05cm per 6mo (95%CI:-0.31,0.40) faster increase than INSTI-. In late perimenopausal women, when compared to WWOH, INSTI+ was associated with significantly faster increases in WC which peaked at 41mo and then declined, while INSTI- had smaller increases in WC (0.14cm per 6mo;95%CI:-0.55,0.33); INSTI+ had a 0.39cm per 6mo (95%CI:0.15,0.63) faster linear increase in WC than INSTI-. In postmenopausal women, INSTI+ was associated with faster WC increases up to 39mo then declines compared to INSTI-. BMI trajectories were similar for late peri- and postmenopausal women.
Conclusion: Switching to an INSTI-based regimen during late peri- and postmenopause is associated with early accelerated increases in WC and BMI when compared to women who did not switch. Our findings suggest that menopausal status should be considered when switching to an INSTI.



** Based on linear mixed effect model adjusted for baseline WC, age, race, site, smoking, drinking, menopausal phase, Center for Epidemiologic Studies Depression Scale, chronic kidney disease, and hypertension.*

156 Simultaneous Initiation in ART-Naive PWH of DTG-Based ART & 3HP Maintains Efficacious DTG Levels

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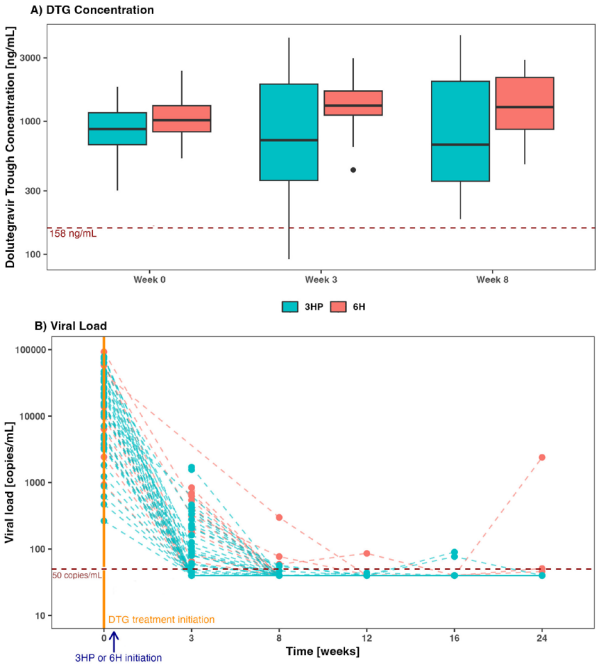
Background: People with HIV (PWH) living in areas of high TB endemicity have high potential to benefit from short-course tuberculosis (TB) preventive therapy (TPT) with weekly isoniazid and rifapentine for 3 months (3HP). 3HP given to virally suppressed PWH on dolutegravir (DTG)-based regimens has been found to be safe and to maintain virologic suppression with adequate DTG levels. No data yet supports simultaneous 3HP with DTG-based ART initiation among ART-naïve people.
Methods: A phase 1/2 comparative trial of simultaneous initiation of 3HP or 6 months isoniazid (6H) with DTG-based ART was performed among antiretroviral (ART)-naïve adults with HIV in South Africa. Participants were sequentially enrolled and assigned to 6H (N=25) and 3HP (N=50). PK sampling for DTG trough was performed at: day 1 (prior to first HP dose), day 17 (3 days after 3rd HP dose), and day 52 (3 days after 8th HP dose) in both groups. Primary endpoints were safety and DTG pharmacokinetics during 3HP/DTG coadministration. Safety and the secondary endpoint of HIV viral load at TPT completion were previously reported.
Results: By week 8, viral suppression (VL < 50 copies/mL) was achieved in 100% of participants in both groups. At week 12, viral suppression (VL < 50 copies/mL) was present in 44/50 (88%) and 23/25 (92%) participants in the 3HP and 6H groups, respectively. Nonlinear mixed-effects modeling showed that there was a 72% induction effect of rifapentine on DTG clearance, from 0.95 L/hr to 1.64 L/hr. DTG trough concentration was above the PA-IC$_{90}$ (64 ng/mL) in all participants at all timepoints, and >158 ng/mL (the lower 5th percentile confidence bound of concentrations achieved with fully suppressive 10 mg daily dosing in the SPRING-1 trial) in all but 2 individuals at week 3 and in all individuals at week 8. The 2 individuals w DTG concentrations below 158 ng/mL at week 3 both suppressed by week 8.
Conclusion: Simultaneous initiation of 3HP for LTBI treatment and DTG-based ART resulted in rapid viral suppression among ART-naïve PWH. Despite a 72% induction of DTG clearance in the 3HP group, DTG concentrations enabled viral suppression < 50 copies/mL in all individuals in both groups at 8 weeks. This information is critical to informing global guidelines around LTBI treatment in ART-naïve individuals.



157 Early Bactericidal Activity of the Alpibectir-Ethionamide (AlpE) Combination Against Tuberculosis

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Background: Dose-dependent tolerability reduces the utility of ethionamide for tuberculosis (TB) treatment at standard doses (750 to 1000 mg). Alpibectir (formerly BVL-GSK098) stimulates an alternative pathway of bacterial ethionamide bioactivation leading to retained activity at lower exposures in vivo. We report results on the first cohort evaluating the early bactericidal activity (EBA), safety and tolerability of the alpibectir-ethionamide (AlpE) combination (NCT05473195).

Methods: Adults with newly diagnosed, rifampicin- and isoniazid-susceptible pulmonary TB were randomised 5:1 to receive 7 days of AlpE 9 mg/250 mg or isoniazid 300 mg as microbiological control. EBA was assessed by the change in time to culture positivity (TTP-EBA0–7) using a mixed-effects model. Serum concentrations of ethionamide and its active sulfoxide metabolite were explored as covaries in a pharmacokinetic/pharmacodynamic (PK/PD) model. Treatment-emergent adverse events (TEAEs) were assessed daily.

Results: 15 participants were randomised to AlpE and 3 to isoniazid. Most participants were male (78%) with a mean age and weight of 33.6 years and 52.9 kg, respectively. One participant withdrew for reasons unrelated to treatment. Median TTP-EBA0–7 (2.5th–97.5th percentiles) was 45.28 (28.78 – 78.12) and 48.41 (42.02 – 54.89) hours for AlpE and isoniazid, respectively. Isoniazid activity was in range of previous results. The median maximum serum concentrations (C) of ethionamide (1230 ng/mL) and ethionamide-sulfoxide (2050 ng/mL), were reached approximately 1 hour after AlpE administration. The mean half-life for ethionamide and ethionamide-sulfoxide was 1.47 hours. Median area under concentration-time curve (AUC) of ethionamide and ethionamide-sulfoxide was 3662 and 5119 h*ng/mL, respectively. Higher ethionamide-sulfoxide exposure significantly increased EBA where each 100 h*ng/mL unit of increase resulted in a 3.68% increase in time to positivity (TTP) slope. 19 (73%) of the 26 mild (76.9%) and moderate (23.1%) TEAEs occurred in AlpE arm, among them self-limiting nausea, flatulence, and diarrhoea in 5 participants.

Conclusion: AlpE was well tolerated, safe and showed bactericidal activity similar to isoniazid in participants with tuberculosis. AlpE can be added to the growing list of novel antituberculosis agents for drug-susceptible and drug-resistant TB. The study is ongoing with escalating doses of alpibectir and ethionamide to optimize the combination.

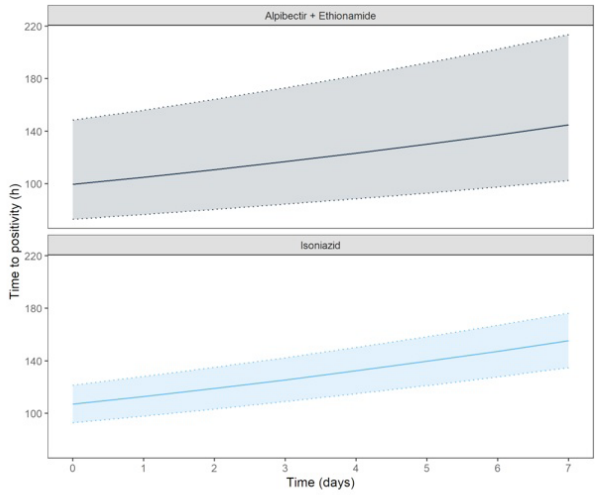

Figure 1. Prediction of individual time to positivity (TTP) over time based on Bayes estimates of the final model Lines show predicted median with shaded area corresponding to the 95% prediction interval for that median.

158 NAFLD and Advanced Fibrosis Are Common in Adults With HIV and Associated With Unique Histology

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Background: Non-alcoholic fatty liver disease (NAFLD) may be more common among people with HIV (PWH), but unique risk factors for NAFLD in PWH (NAFLD-PWH) are poorly understood. We examined the prevalence of and risk factors for NAFLD and advanced fibrosis (AF) in a cohort of PWH without other known causes of liver disease, as well as histological features of NAFLD in persons with and without HIV.

Methods: In an ongoing prospective study, PWH ≥18 years of age on suppressive antiretroviral therapy (ART) were screened for NAFLD (controlled attenuation parameter ≥263 dB/m) and AF (liver stiffness measurement ≥11 kPa) using vibration controlled transient elastography. For histology, 107 biopsies each from NAFLD-PWH (cases) and NAFLD in people without HIV (controls) were matched on age/sex/race/ethnicity/BMI/ALT. Biopsies were centrally read using the NASH CRN scoring system. Logistic regression evaluated associations with NAFLD and AF.

Results: PWH (n=654) had mean age 53 years, 73% male sex at birth, 51% were non-Hispanic Black and 20% Hispanic. NAFLD and AF prevalence were 53% and 6%, respectively. Older age, male sex, greater BMI or waist circumference and higher ALT and triglyceride concentrations associated with greater NAFLD odds, and non- Hispanic Black race with lower odds. Greater BMI or waist circumference, higher AST and alkaline phosphatase concentrations and lower platelet counts associated with greater odds of AF, and non-Hispanic Black race with lower odds (all $p<0.05$). NAFLD-PWH had less steatosis (63% grade 1/2 vs. 47%, $p=0.01$), less inflammation (70% grade 1/2 vs. 60%, $p=0.03$) and less hepatocyte ballooning (none: 61% vs. 45%, many 15% vs 27%, $p=0.03$) and portal inflammation (8% >mild vs. 21%) than controls. As a result, NAS was lower in NAFLD- PWH (3.2 ± 1.6 vs 4.0 ± 1.6, $p<0.001$), with a trend towards less steatohepatitis (61% vs. 71%, $p=0.09$). Regression analyses observed less steatosis, portal inflammation and ballooning but more fibrosis in NAFLD-PWH (all $p<0.05$).

Conclusion: In summary, in our cohort of PWH undergoing systematic screening, NAFLD prevalence was high, with traditional metabolic risk factors but not HIV-/ART-specific characteristics dominating risk for NAFLD and AF. Traditional histologic drivers of fibrosis were less pronounced in NAFLD-PWH and yet fibrosis stage was higher vs. matched controls without HIV, suggesting HIV-specific factors beyond hepatic necroinflammation may contribute to fibrosis in NAFLD-PWH.

159 Semaglutide Reduces Metabolic-Associated Steatotic Liver Disease in People With HIV: The SLIM LIVER

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Background: Metabolic-Associated Steatotic Liver Disease (MASLD) is common among people with HIV (PWH) and likely synergistic with HIV-1 to accelerate hepatic injury and organ dysfunction. The glucagon-like peptide-1 receptor agonist semaglutide is associated with cardiometabolic improvements in the general population through its effects on weight reduction and systemic inflammation. We designed a phase IIb, single-arm, pilot study of the effects of semaglutide on magnetic resonance imaging-proton density fat fraction (MRI-PDFF)-quantified intrahepatic triglyceride (IHTG) content in PWH and MASLD.

Methods: ACTG A5371 enrolled PWH ≥18 years of age on suppressive antiretroviral therapy (ART) with central adiposity, insulin resistance or pre-diabetes and SLD (defined as ≥5% IHTG on MRI-PDFF). All participants received semaglutide for 24 weeks (titrated to 1mg sc weekly by week 4). IHTG content was measured by a central, blinded reader. Mean changes and 95% confidence intervals (CI) were estimated using linear regression. Spearman correlations assessed associations between outcome measures.

Results: Participants (n=49) had median age 52 years, BMI 35 kg/m^2, 39% Hispanic ethnicity and 33% Black/African American race; 43% were cis or trans women and 82% were on integrase strand transfer inhibitor- based ART. Semaglutide was well-tolerated, with only 2 possibly-related Grade 3 (1 nausea, 1 serotonin syndrome) and no Grade 4 adverse events. Mean baseline (standard deviation) IHTG was 12.7% (6.1%). Mean (95% CI) absolute and relative declines in IHTG were -4.2% (-5.4, -3.1) and -31.3% (-39.0, -23.6), respectively (both p<0.001); 29% of participants had complete resolution of MASLD (absolute IHTG <5%); and 58% had a ≥30% relative reduction in IHTG. Trends toward greater improvements in IHTG were seen in women, Hispanics, non-Hispanic whites and with increasing age. Significant improvements in weight, waist circumference, fasting glucose and triglyceride concentrations were also observed (Table). Improvements in IHTG correlated with weight loss on semaglutide (r=0.54, p<0.0001).

Conclusion: Low-dose (1mg weekly) semaglutide is a safe and effective pharmacologic therapy for MASLD in PWH and shows evidence of broader cardiometabolic benefit. Further analyses will assess specific immunologic and inflammatory pathway changes with semaglutide therapy in PWH, including those that may be unique to this population.

	24-week Change (effect size [95% confidence interval])	P value
Absolute IHTG (%)	-4.2 (-5.4, -3.1)	<0.001
Relative IHTG (%)	-31.3 (-39.0, -23.6)	<0.001
Absolute weight (kg)	-7.8 (-9.5, -6.1)	<0.001
Relative weight (%)	-8.1 (-9.8, -6.4)	<0.001
Waist circumference (cm)	-6.7 (-8.5, -4.8)	<0.001
Fasting glucose (mg/dL)	-9.9 (-14.7, -5.1)	<0.001
Fasting triglycerides (mg/dL)	-26.8 (-46.0, -7.5)	0.007

160 Trends in HIV and HCV Prevention Efforts and Incidence Among People Who Inject Drugs in Baltimore

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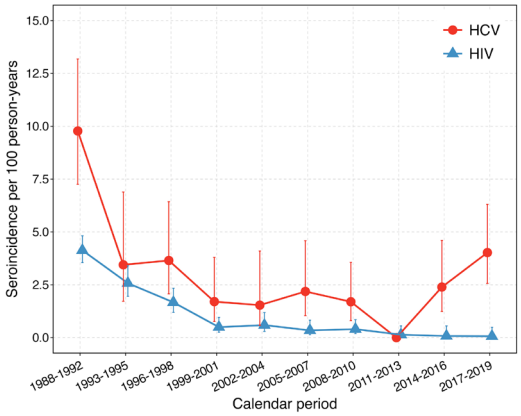
Background: Advances in HIV and hepatitis C virus (HCV) prevention and treatment have led to plans to end the HIV epidemic and achieve HCV elimination by 2030. Data on long-term trends in the uptake of combination HIV/HCV prevention services and their impact on HIV/HCV incidence among people who inject drugs (PWID) are limited.

Methods: The AIDS Linked to the IntraVenous Experience (ALIVE) study is a community-based cohort of PWID aged ≥18 years in Baltimore, Maryland with 5 enrollment periods: 1988-89, 1994-95, 1998, 2005-08, and 2015-18. We assessed trends in HIV and HCV seroincidence, prevalence of injection practices, self-reported use of prevention and treatment services, HIV viremia (>400 c/mL) and HCV viremia (>500 IU/mL) using Poisson and logistic regression with generalized estimating equations. Data were censored at 12/31/2019 (prior to the COVID-19 pandemic).

Results: Overall, 5,506 participants attended 68,107 semi-annual visits. At enrollment, median age was 37 years; 26% were female. Of 2,657 initially HIV-seronegative participants, 282 seroconversions occurred over 18,452 person-years (py). Of 593 initially HCV-seronegative participants, 115 seroconversions occurred over 3,576 py. HIV incidence declined from 4.1/100py in 1988-1992-a period without combination prevention services-to 0.5/100py in 1999-2001 (IRR=0.12 [95%CI=0.06-0.23]) and continued to decline to 0.1/100py in 2017-2019 (IRR=0.02 [0.00-0.13]) (Figure). Although HCV seroincidence similarly declined from 9.8/100py in 1988-1992 to 1.7/100py in 1999-2001 (IRR=0.18 [0.08-0.39]), it generally remained high thereafter (e.g., 4.0/100 py in 2017-2019). Early declines in HIV and HCV incidence were associated with declines in injection drug use (89% in 1988; 51% in 2001; 36% in 2019) and increases in prescribed methadone use (10% in 1988; 22% in 2001; 44% in 2019) and syringe services program use (36% in 1998; 44% in 2001; to 51% in 2019). Later declines in HIV incidence were also associated with increases in ART use (55% in 2006; 96% in 2019) and declines in HIV viremia (63% in 2007; 36% in 2019). However, HCV seroincidence remained high during periods in which HCV treatment uptake increased (2% in 2014; 56% in 2019) and HCV viremia declined (84% in 2006; 36% in 2019).

Conclusion: In a cohort of PWID, HIV and HCV seroincidence decreased over time corresponding with increased prevention efforts and behavioral changes; however, HCV seroincidence remained high. Intensified efforts are needed to achieve HCV elimination among PWID.

Figure. Temporal trends in HIV and hepatitis C virus (HCV) seroincidence among a community-based cohort of people who inject drugs in Baltimore.



161 Preclinical Pharmacokinetic Assessment of a Hepatitis C Virus Long-Acting Injectable Formulation

Usman Arshad[1], Henry Pertinez[1], Joanne Sharp[1], Joanne Herriott[1], Edyta Kijak[1], Eduardo Gallardo-Toledo[1], Andrew B. Dwyer[1], Catherine Unsworth[1], Alison C. Savage[1], James J. Hobson[1], Lee Tatham[1], David Thomas[2], Paul Curley[1], Steve Rannard[1], Andrew Owen[1]
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Background: Eight weeks of daily, oral glecaprevir (G) and pibrentasvir (P) cures 98% of people with chronic Hepatitis C Virus (HCV) infection. However, major challenges, including medication adherence and loss of patients to follow-up, impede delivery of this combination. As such, 58 million people remain infected worldwide. A long-acting injectable (LAI) providing 8 weeks of pharmacokinetic exposure from a single administration would overcome many of these challenges by providing a one-shot cure. Moreover, G and P possess key physicochemical and pharmacokinetic properties shared by other LAI paradigms.

Methods: G and P were co-formulated as a fixed dose combination LAI (250 mg/mL G, 250 mg/mL P). Dosing volumes of 0.075, 0.15 and 0.3 mL (representing active doses of 18.75, 37.5 and 75 mg) were administered to male Sprague Dawley rats (n = 4, 250-300 g) via intramuscular injections to the thighs. Plasma samples were collected from the tail vein over 13 weeks and livers were harvested at the end of the study. G/P concentrations were quantified in plasma and liver using validated LC-MS/MS.

Results: Rat plasma concentration-time profiles for G and P demonstrated a dose-proportional increase in exposure (Fig. 1) with dose-linear increases in AUC for both G and P (AUC0-tlast, 106, 220 and 390 µg·h/ml [G] and 157, 346 and 513 µg·h/ml [P] at 18.75, 37.5 and 75 mg doses, respectively). A less-than-dose-proportional increase in C_{max} was observed (1203, 3033 and 4334ng/ml [G] and 428, 799 and 907ng/ml [P] at 18.75, 37.5 and 75 mg doses, respectively). Doses of 37.5 and 75 mg maintained plasma exposures above the reported median human Ctrough for the oral product. For the 18.75 mg dose, G and P concentrations remained above the human Ctrough for 5 and 11 weeks, respectively. Liver:plasma concentration ratios were comparable to those previously reported after oral administration to rats for both drugs. No behavioural issues were encountered, animals gained weight throughout and no overt injection site issues were visible upon inspection.

Conclusion: Preclinical data for a novel G/P LAI demonstrate sustained therapeutic concentrations in rats over a period of 13 weeks, exceeding the 8-week human target duration. Parenteral administration did not adversely affect hepatic penetration in comparison to the oral route. Further work is

required to optimise drug ratios and confirm safety through GLP toxicology assessments to support first-in-human evaluation.

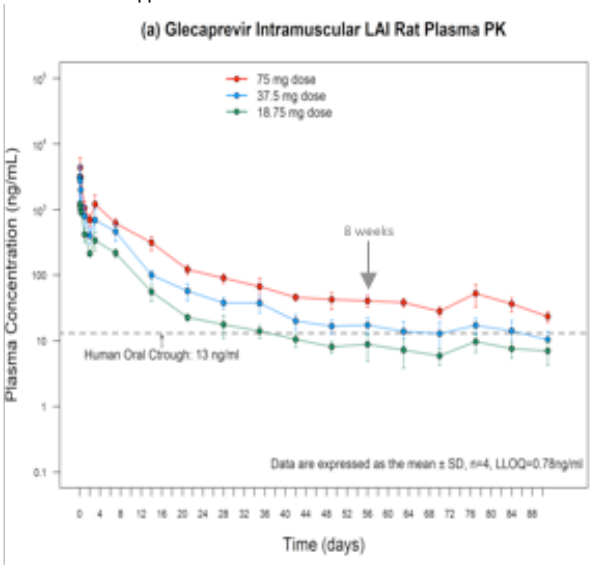

Figure 1. Plasma concentration profiles for (a) Glecaprevir and (b) Pibrentasvir in Rats.

162 Intrahepatic HDV Activity Is Fueled by Integrated HBV DNA-Derived HBs Independently From cccDNA Size

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Background: HDV exploits HBV surface proteins (HBs) for its morphogenesis and de novo entry into hepatocytes. Here, we investigate HBV and HDV replicative activity and their still undefined interplay in liver biopsies from patients (pts) with chronic co-infection.

Methods: Liver tissue was analysed from 25 pts (71% NUC-treated; 96% HBeAg[-]). Intrahepatic levels of covalently closed circular DNA (cccDNA), pregenomic HBV-RNA (pgRNA) and HDV-RNA were quantified by droplet digital PCR (ddPCR), also used to quantify total-, cccDNA derived- and integrated HBV-DNA derived- HBs transcripts as in Grudda, 2022.

Results: Pts were characterized by high serum levels of HDV-RNA and HBs (median [IQR]: 6.3[3.8-7.7] logIU/mL and 14,460[5,207-21,118] IU/mL) and low HBV viremia (detectable in 48% of pts, median[IQR]: 50[34-214] IU/ml). Median (IQR) ALT was 72 (52-102) U/L. Intrahepatic HDV-RNA was median (IQR) 787(1-2913) copies (cps)/1000cells and positively correlated with serum HDV-RNA (Rho=0.63, P=0.05). Regarding HBV intrahepatic reservoir, median (IQR) cccDNA was 3 (0.1-24) cps/1000cells and pgRNA was 8 (1-147) cps/1000cells. Nevertheless, we observed an abundant production of total HBs transcripts (median[IQR] total HBs RNAs: 6,028[409-19,137] cps/1000 cells), positively correlated with serum HBs (Rho=0.54; P=0.04). By analyzing the source of HBs transcripts, we found that >90% of them derived from integrated HBV-DNA, with a poor contribution of cccDNA transcriptional activity, supporting that HDV persistence is mainly sustained by integrated HBV DNA-derived HBs in HBeAg[-] HDV chronic infection. Finally, no difference in intrahepatic HDV-RNA levels was observed according to HBV reservoir size (median[IQR]: 787[1-5,495] and 880[1-3,338] cps/1000cells in pts with cccDNA5 cps/1000cells, p=0.9), while HBV markers were significantly lower in pts with a more restricted HBV reservoir (median [IQR]: 1[1-10] vs 147[9-406] cps/1000cells for pgRNA and 0.3[0.2-1] vs 73[7-243] cps/1000cells for cccDNA-derived HBs transcripts in cccDNA5 cps/1000cells, p<0.01 for both). Overall data suggest the existence of independent HBV and HDV replicative pathways.

Conclusion: HDV replication pathway acts independently from the size of intrahepatic HBV reservoir and is fueled by an abundant production of HBs transcripts, mainly derived from integrated HBV-DNA. These issues are crucial for defining mechanisms underlying HDV persistence, that could hamper the success of therapeutic strategies.

163 A 4-Month Regimen of Quabodepistat, Delamanid, and Bedaquiline for Pulmonary TB: Interim Results

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Background: There remains an urgent need for short-duration, potent, and safe anti-tuberculosis (TB) agents effective against drug-susceptible and drug-resistant strains of Mycobacterium tuberculosis. Quabodepistat (QBS; formerly OPC-167832) is a novel anti-TB agent that targets decaprenylphosphoryl-β-D-ribose 2′-oxidase (DprE1). In a prior study, QBS in combination with delamanid (DLM) and bedaquiline (BDQ) for 14 days was well tolerated and exhibited similar early bactericidal activity to the standard of care regimen, RHEZ (rifampicin, isoniazid, ethambutol, and pyrazinamide) in patients with drug-susceptible pulmonary TB (DS-TB).

Methods: This interim analysis of the phase 2b/c, randomized trial (NCT05221502) evaluates the safety, efficacy, and pharmacokinetics of QBS in combination with DLM and BDQ for 4 months in participants with DS-TB compared to 6-month RHEZ treatment. Participants were randomized (1:2:2:1; stratified by chest x-ray bilateral cavitation and HIV status) to once-daily QBS 10 mg, 30 mg, or 90 mg in combination with DLM and BDQ, or RHEZ. The follow-up period (to 52 weeks post-randomization) is ongoing. The primary endpoint was proportion of participants achieving sputum culture conversion (SCC) by the end of the treatment period. Here, we report interim results after 117/122 (96%) randomized participants completed study treatment.

Results: At enrollment, most participants were male (65%), of Black African race (68%) with a median age of 31 years (range 18–65), a median BMI of 19 kg/m^2, with bilateral cavitation (19%), and HIV-negative (100%) status. In the modified intention-to-treat population (n=121), SCC at end of treatment was achieved by 96% (96/100) in the pooled QBS arms and 91% (19/21) in the RHEZ arm (Table 1). Similar SCC rates were observed in the per-protocol analysis (n=108). The percentages of participants experiencing at least one Division of AIDS ≥Grade 3 adverse event (AE) were 15%, 12%, 11%, and 5% in the QBS 10-mg, 30-mg, 90-mg, and RHEZ arms, respectively. There was one treatment discontinuation due to death (QBS 30-mg arm) from severe/worsening TB. No serious AEs were attributed to trial medications. No clinically significant QTc prolongation events, QTc prolongation ≥500 ms, or liver enzyme (ALT/AST) elevations ≥5 times the upper limit of normal were reported.

Conclusion: In this interim analysis, high rates of SCC were achieved with the QBS-based three-drug treatment regimen. The regimen was generally well tolerated and warrants further investigation.

Table. Sputum culture conversion (SCC) by arm and by bilateral cavitation status

		QBS 10 mg + DLM/BDQ	QBS 30 mg + DLM/BDQ	QBS 90 mg + DLM/BDQ	Pooled QBS arms	RHEZ
mITT Analysis Set	**Overall**, n/N (%) [95% CI]**	20/20 (100.0) [83.2, 100.0]	39/42 (92.9) [80.5, 98.5]	37/38 (97.4) [86.2, 99.9]	96/100 (96.0) (90.1, 98.9]	19/21 (90.5) [69.6, 98.8]
	With Bilateral Cavitation*, n/N (%) [95% CI]**	2/2, (100.0)	6/6 (100.0) [54.1, 100.0]	5/5 (100.0)	13/13 (100.0) [75.3, 100.0]	3/4 (75.0)
	Without Bilateral Cavitation*, n/N (%) [95% CI]**	18/18 (100.0) [81.5, 100.0]	33/36 (91.7) [77.5, 98.2]	32/33 (97.0) [84.2, 99.9]	83/87 (95.4) [88.6, 98.7]	16/17 (94.1) [71.3, 99.9]
PP Analysis Set	**Overall**, n/N (%) [95% CI]**	20/20 (100.0) [83.2, 100.0]	38/40 (95.0) [83.1, 99.4]	36/37 (97.3) [85.8, 99.9]	94/97 (96.9) [91.2, 99.4]	19/21 (90.5) [69.6, 98.8]
	With Bilateral Cavitation*, n/N (%) [95% CI]**	2/2 (100.0)	6/6 (100.0) [54.1, 100.0]	5/5 (100.0)	13/13 (100.0) [75.3, 100.0]	3/4 (75.0)
	Without Bilateral Cavitation*, n/N (%) [95% CI]**	18/18 (100.0) [81.5, 100.0]	32/34 (94.1) [80.3, 99.3]	31/32 (96.9) [83.8, 99.9]	81/84, (96.4) [89.9, 99.3]	16/17 (94.1) [71.3, 99.9]

*Randomization was stratified by human immunodeficiency virus status and presence of bilateral cavitation at screening.
**95% Confidence intervals are not presented for sample sized <5.
CI, confidence interval; mITT, modified-intention-to-treat; PP, per-protocol.

164 Provisional Results From a 3-month Clofazimine/Rifapentine-Containing Regimen for Drug-Sensitive TB

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Background: Clo-Fast (ACTG A5362; NCT04311502) is a randomized, controlled, open-label phase IIc clinical trial evaluating the safety and efficacy of a 3-month rifapentine (P1200mg)/clofazimine (CFZ)- containing regimen versus 6-month standard of care (SOC) for drug-susceptible (DS) TB that stopped enrollment early due to lack of clinical efficacy. We present results from data through Sept 25, 2023, when the last participant completed study treatment.

Methods: Adults enrolled at six sites in Malawi, Zimbabwe, South Africa, India, and Haiti. Randomization, stratified on HIV status and advanced disease on chest X-ray, was to: Arm 1 (13-week experimental regimen): 3PHZEC; Arm 2 (26-week SOC): 2RHZE/4RH; or Arm C (PK subgroup without CFZ load, then SOC): 1PHZEC/1RHZE/4RH. The primary outcomes were (efficacy) time to stable liquid culture conversion through week 12 and (safety) proportion experiencing an AE ≥ grade 3 through week 65 in Arms 1 and 2. The proportion with an unfavorable clinical/bacteriologic outcome in Arms 1 and 2 by week 65 was a key secondary outcome.

Results: Between June 2021 and April 2023, when the trial was stopped for inefficacy per DSMB recommendation, we enrolled 58 of 110 planned participants to Arm 1, 31 of 55 planned participants to Arm 2, and 15 of 20 planned participants to Arm C. Most participants were male (79%), 29% were living with HIV (median baseline CD4+ 265 cell/mm^3, IQR 185-379 cell/mm^3), 71% had radiographically advanced TB disease, and 25% were 3+ smear-positive at entry. Median (IQR) follow-up on study was was 50.2 weeks (39.7, 57.6 weeks). By week 12, 89% (n=48) in Arm 1 and 90% (n=28) of participants in Arm 2 achieved stable culture conversion (adjusted HR 1.17, 90% CI, 0.79 to 1.73, adjusted for baseline HIV status and presence of advanced disease). The cumulative proportion of participants experiencing an AE ≥ grade 3 was higher in Arm 1 (46%) than Arm 2 (16%; difference 30%, 90% CI 14-45%), driven by change in creatinine clearance in Arm 1. The cumulative probability of an unfavorable outcome in Arm 1 was 49% (95% CI 34-67%) versus 34% (95% CI 19-58%) among Arm 2 participants (difference -15%; 95% CI -41% to 11%). The table describes the clinical/bacteriologic unfavorable outcome events.

Conclusion: A 13-week regimen containing CFZ and rifapentine was not efficacious for treatment of DS-TB. The SOC arm also had a high rate of unfavorable events, despite high week 12 culture conversion.

Table. A5362 Provisional Unfavorable Composite TB Outcomes as of September 25, 2023

	Experimental Arm 1 (n=54;* *planned 110*)	Standard of Care Arm 2 (n=31; *planned 55*)
Participants with protocol-defined *M. tuberculosis*-related unfavorable outcome †	22 (41%)	9 (29%)
-- Two or more positive cultures at or after week 13 (Arm 1) or week 17 (Arm 2)	11 (20%)	4 (13%)
-- Treatment extension due to clinically inadequate response that was not microbiologically confirmed	11 (20%)	4 (13%)
-- TB-related death	1 (2%)	0 (0%)
-- Positive culture at last visit	3 (6%)	2 (6%)

* 58 enrolled, 4 late exclusions
† Categories are not mutually exclusive

165 Association of State-Level PrEP Coverage and State-Level HIV Diagnoses, US, 2012-2021

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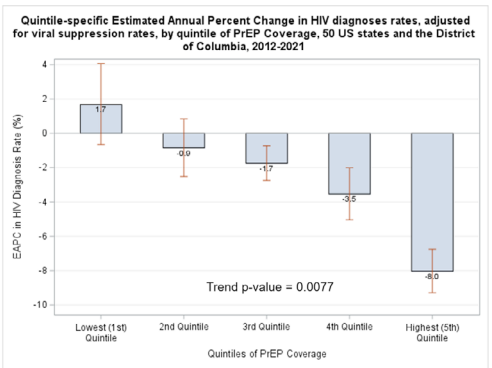
Background: Pre-exposure prophylaxis (PrEP) is highly effective to reduce risk of HIV infection; the population-level impact of PrEP is predicted to depend on PrEP coverage (e.g., PrEP prescriptions among those with indications), adherence to prescribed PrEP, the extent to which PrEP is used by those at greatest risk for HIV infection, and the extent of viral suppression among community risk contacts.

Methods: We used publicly available data on PrEP prescriptions and calculated PrEP coverage per 100 persons with indications in each state during each year. We calculated quintiles of mean PrEP coverage (e.g., proportion of PrEP users among people with an indication for PrEP) during 2012-2021 for 50 US states and the District of Columbia. For each quintile, we calculated the estimated annual percent change (EAPC) in HIV diagnosis rates from 2012-2021 with 95% confidence intervals using temporal trends models and calculated a p value for trend across state-specific quintiles of coverage. Because higher PrEP coverage in a state might be confounded by higher levels of viral suppression, we adjusted EAPC estimates for prior year state-level viral suppression.

Results: The estimated state-specific EAPC in HIV diagnosis rates between 2012-2021 ranged from -11.9% (95% CI: -13.0%, -10.8% in Washington, DC) to +10.5% (95% CI: +5.1%, +16.2% in West Virginia). Mean PrEP coverage among states and the District of Columbia between 2012-2021 ranged from 3.8% (West Virginia) to 22.2% (New York). From 2012-2021, the quintile-specific change in HIV diagnosis rates ranged from a 1.7% increase (95% CI: -0.7% to +4.1%) in the lowest quintile of PrEP coverage to an 8.0% decrease (95% CI: -9.3% to -6.8%) in the highest quintile of PrEP coverage, after controlling for yearly changes in viral suppression rates (Figure; p value for trend across quintiles: 0.0077).

Conclusion: In an ecologic analysis, increasing PrEP coverage was associated with decreasing new HIV diagnoses from 2012-2021 among US states, even controlling for differences in state-viral suppression. Our data suggest that PrEP coverage is a meaningful measure to assess the progress of PrEP programs. However, our analysis also documented stark differences in the trajectories of PrEP program among US states: there was an 8- fold difference between the extent to which PrEP needs were met between the lowest and highest performing states. PrEP coverage data is useful to monitor progress in state PrEP programs.



166 HIV Incidence in Users of HIV Preexposure Prophylaxis in Australia: A Whole-of- Population Analysis

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Background: Use of HIV pre-exposure prophylaxis (PrEP) at scale has been associated with reduced community HIV transmission: diagnoses of recently acquired HIV (under one year) among gay and bisexual men in Australia fell from 223 in 2018 to 107 in 2022. We examined HIV incidence and risk factors in all people receiving PrEP in Australia's national health system.
Methods: Linked de-identified records for all government subsidised PrEP and antiretroviral therapy (ART) from April 2018 to June 2023 allowed us to identify HIV acquisition in PrEP users who initiated ART. ART initiation was used as a proxy for HIV acquisition given high rates of HIV testing among PrEP users (at least 6- monthly) and high treatment uptake (over 95% after six weeks) in Australia. The date of HIV acquisition was the midpoint between 30 days before ART initiation and either six months prior or the most recent PrEP prescription. We calculated days covered by PrEP and HIV incidence in people using PrEP and its predictors using Poisson regression over the study period of April 2018 to December 2022.
Results: Of 62,563 people receiving PrEP (97.8% men, median age 33), 190 acquired HIV during the study period with an overall incidence rate of 1.09/1000 person years (95%CI 0.94-1.25). HIV incidence was 2.65/1000PY among those dispensed PrEP once only (20.0% of PrEP users, 31.6% of HIV cases), compared with 1.02/1000PY among those with <60% of days covered (52.4% of PrEP users, 54.2% of HIV cases) and 0.53/1000PY among those with ≥60% of days covered (28% of PrEP users, 14% of HIV cases). Using the group dispensed PrEP only once as a comparator, those with ≥60% days covered had an 80.2% reduction in incidence (p<.001) and those with <60% days covered a 61.5% reduction (p=.009). Incidence was also higher in specific subgroups: those with a record of hepatitis C treatment (10.05/1000PY, 0.6% of PrEP users, 6.3% of HIV cases) and 18-29 year-olds (1.32/1000PY, 35.1% of PrEP users, 40.0% of HIV cases). PrEP usage, younger age and hepatitis C treatment were independent predictors of HIV incidence.
Conclusion: HIV acquisition in people previously engaged in PrEP accounted for 57.9% of diagnosed newly acquired HIV among gay and bisexual men in Australia in 2022, highlighting the need for interventions focused on this population to achieve elimination. In particular, support is needed for those who don't return for repeat dispensing and less frequent PrEP users. Programs should also be tailored for specific socio-demographic characteristics.

People dispensed Australian government HIV pre-exposure prophylaxis (PrEP) between April 2018 and December 2022, those with HIV acquisition during this period and incidence analysis using Poisson regression.

	PrEP users n (%)	HIV acquisition n (%)	Incidence Rate per 1000 PY (95% CI)	Adjusted incident rate ratio (95% CI)	p
Age: 18-29	21,957 (35.1%)	76 (40.0%)	1.32 (1.05-1.65)	1.48 (1.03-2.12)	.035
30-39	20,647 (33.0%)	64 (33.7%)	1.10 (0.86-1.40)	1.38 (0.95-2.00)	.09
40+	19,959 (31.9%)	50 (26.3%)	0.84 (0.64-1.11)	ref	
Hepatitis C Treatment	256 (0.57%)	12 (6.3%)	10.05 (5.71-17.7)	9.08 (4.95-16.64)	<.001
PDC >=60%	17,222 (27.6%)	27 (14.2%)	0.53 (0.36-0.77)	ref	
PDC < 60%	32,704 (52.4%)	103 (54.2%)	1.02 (0.84-1.24)	1.76 (1.15-2.70)	.009
One PrEP supply	12,447 (20.0%)	60 (31.6%)	2.65 (2.06-3.41)	4.35 (2.71-6.97)	<.001

Note: PDC = proportion of days covered by PrEP in those with more than one PrEP supply

167 High PrEP Uptake and Adherence Measured Objectively Among Young African Women in the INSIGHT Cohort

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Background: Adolescent girls and young women (AGYW) account for 1 in 5 new HIV infections in sub– Saharan Africa and can greatly benefit from PrEP. While studies among AGYW show high oral PrEP uptake, early discontinuation is common. Objective adherence measures may enhance counselling and promote adherence, but are often costly, require specialized tests and require long turnaround times for spectrometry- based metrics. We evaluated a novel point-of-care urine tenofovir (TFV) assay, using antibody-based technology, to measure adherence and its alignment with self-reported adherence and HIV seroconversion among AGYW.
Methods: From August 2022-July 2023, we enrolled an open label PrEP cohort of sexually active AGYW aged 16-30 years and interested in PrEP from 20 sites (15 in South Africa and 1 site each in Eswatini, Kenya, Malawi, Uganda, and Zambia). Participants attended study visits 1, 3 and 6 months after enrollment and were offered PrEP and adherence counselling at each visit. PrEP use was assessed via self-report and a qualitative lateral flow urine TFV assay, for which a predetermined threshold of >1500 ng/ml indicates TFV use in the past 4 days. Acceptability of urine TFV testing was assessed at Month 6 via questionnaire.
Results: The INSIGHT cohort enrolled 3087 AGYW. At enrolment, 95.6% of participants-initiated PrEP. At months 1, 3, and 6, 95.7%, 94.4%, and 88.8% received PrEP refills and 77.5%, 79.6%, and 64.1% of those with urine tests had TFV detected in the urine assay respectively. The 3 main reasons for PrEP discontinuation were side effects, low risk perception, and peer influence. Self-reported good, very good, or excellent adherence was well aligned with positive results from the urine TFV test (OR=8.5, 95% CI 7.4-9.8). HIV incidence was 1.38/100 person-years (95% CI 0.97-2.08). At Month 6, 58.3% of women reported that a positive urine TFV result motivated them to take PrEP, 23.6% reported that the counsellor helped them identify ways to remember PrEP, and 21% reported that a negative urine test result was not surprising.
Conclusion: Oral PrEP uptake was >95% among a multisite cohort African AGYW with almost 90% refilling PrEP at Month 6 and the majority (64-80%) had evidence of recent use, based on a novel urine TFV assay, which is higher PrEP adherence than in prior studies. Oral PrEP can be an effective PrEP option for African AGYW. Real time drug feedback using the urine TFV assay is acceptable and warrants further study to support PrEP adherence.

168 Safety of Dapivirine Vaginal Ring and Oral PrEP for HIV Prevention in the Second Trimester

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Background: Pregnant people are at 3X higher risk of HIV per coital act than nonpregnant people. MTN- 042/DELIVER was a phase 3b study of Dapivirine Vaginal Ring (DVR) and oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) to assess safety, adherence, and acceptability when used during pregnancy (NCT03965923). The results of the first two cohorts of women enrolled during the 3rd trimester have been reported. The results from the 3rd cohort of women initiating product during the 2nd trimester of pregnancy are reported here.
Methods: Healthy, HIV uninfected, 18–40-year-old pregnant people from South Africa, Uganda, Zimbabwe and Malawi were enrolled and randomised 4:1 to monthly DVR or daily TDF/FTC between 12 0/7 and 29 6/7 weeks gestation. Product use continued until delivery or 41 6/7 weeks' gestation. Pregnancy outcomes, complications and congenital anomalies reported at the time of delivery were summarized using descriptive statistics. Local background rates from a separate systematic chart review (> 10,000 deliveries) at the participating health centres (MTN-042B) provided a comparator.
Results: 251 participants were enrolled with 202 randomized to DVR and 49 to TDF/FTC. The cohort had a mean age of 25.4 years and gestational age of 23.3 weeks. Of 248 available pregnancy outcomes, there were two stillbirths and one miscarriage. Most deliveries were at term (96%), 4% were preterm and pregnancy complications were uncommon (Table 1). Preterm premature rupture of membranes occurred in three (1%) cases in the DVR arm. Eleven (4%) of the 245 infant participants had congenital anomalies none of which was related to study product with umbilical hernias most frequent (7/11). No HIV infections occurred in these 251 women.
Conclusion: Adverse pregnancy outcomes related to DVR and TDF/FTC use were uncommon in the second trimester of pregnancy, with rates similar to the communities where the study was conducted. These data, combined with the data from cohorts 1 and 2 and the safety data from women who used the DVR

at the time of conception, support using DVR and TDF/FTC as HIV prevention options for pregnant people at risk of HIV.

MTN-042 Cohort 3 Pregnancy Complications

Pregnancy Complication	Cohort 3		MTN-042B[2]
	DVR (n=200)[1] n (%)	TDF/FTC (n=48)[1] n (%)	
Any hypertensive disorder of pregnancy	19 (9%)	7 (14%)	10.5% (10.0,11.3)
Gestational hypertension	15 (7%)	6 (12%)	4.4% (4.0,4.8)
Pre-eclampsia without severe features	3 (1%)	0 (0%)	2.2% (1.9,2.5)
Pre-eclampsia with severe features	1 (0.5%)	1 (2%)	2.1% (1.9,2.4)
Eclampsia	0 (0%)	0 (0%)	0.6% (0.5,0.8)
Peripartum/Antepartum hemorrhage	5 (3%)	0 (0%)	-
Postpartum hemorrhage	3 (1%)	1 (2%)	3.2% (2.9,3.6)

[1] N reflects obtainable pregnancy outcomes
[2]Balkus JE, Neradilek M, Fairlie L, et al. Assessing pregnancy and neonatal outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results from a systematic chart review.

169 Phone Calls for PrEP Persistence in Kenyan Women in Postabortal Care: A Cluster Randomized Trial

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Background: In Kenya, women of reproductive age face dual epidemics of HIV and unintended pregnancy yet persistence with HIV PrEP is low when initiated in reproductive health settings.
Methods: PrEP delivery was launched in 15 postabortion care (PAC) clinics in Kenya and data were abstracted on women seeking care for 6 months post PAC. Six months after all clinics began to deliver PrEP, we initiated a cluster randomized trial (CRT) and clinics were randomized to conduct either a phone call program (4 calls during the first month, 2 calls in month 2, and 1/month thereafter) or standard of care (SOC) to support PrEP retention and adherence. Data on PrEP refills were abstracted from medical charts. Additionally, women were offered participation in research procedures through which women were tested for tenofovir (TFV) detection using a point-of-care urine assay.
Results: From April 2021 to March 2023, 8362 women sought PAC from participating clinics: median age 24 years (IQR 22-27), 53% married/cohabiting. Of the 15 facilities included, 40% were public and 40% were high volume. The PrEP cascade highlights that 55% received PrEP information, 73% of those had HIV testing, and 36% of those received counseling and initiated PrEP. After the CRT launch, 4112 women sought PAC and 655 (15.9%) initiated PrEP. Overall, 11.8%, 4.9%, and 1.8% of 655 received a PrEP refill at 1, 3, and 6 months after initiation. At month 1, 14/247 (5.7%) women in facilities randomized to SOC and 63/408 (15.4%) of women in the phone call program received a PrEP refill (RR=2.7, 95% CI 0.90–8.2). At month 1, TFV was detected in 4.9% of the SOC arm and 11.8% of the phone call arm (RR = 2.4, 95% CI 0.73–8.0), assuming those who did not return were undetectable.
Conclusion: In the PrEP cascade, we observed large gaps in the provision of PrEP information and PrEP counseling that contributed to low PrEP uptake. Among women who initiated PrEP, persistence and adherence was very low even in the context of research visits. However, follow up via phone calls resulted in substantially more frequent PrEP refills, a finding that warrants further investigation.

170 Adherence Benchmarks for TFV-DP in DBS and PBMCs for African Women Using FTC/TDF PrEP

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Background: Intracellular tenofovir-diphosphate (TFV-DP) concentration benchmarks in dried blood spots (DBS) from oral emtricitabine-tenofovir disoproxil fumarate (F/TDF) pre-exposure prophylaxis (PrEP) have informed adherence-concentration-efficacy relationships for men who have sex with men, derived from observed dosing studies in US populations. Similar thresholds for African cisgender women have not been defined.
Methods: Between April 2022 and June 2023, we conducted a prospective, randomized, pharmacokinetic study of TFV-DP in DBS and peripheral blood mononuclear cells (PBMCs) among 54 non-pregnant Kenyan women without HIV taking 2, 4, or 7 oral F/TDF PrEP doses per week and 18 pregnant women without HIV taking 7 doses per week (clinicaltrials.gov: NCT05057858). Dosing was directly observed until 8 weeks to achieve 90% steady-state in DBS. TFV-DP was quantified in DBS and PBMCs using validated LC-MS/MS assays at University of Colorado. TFV-DP concentrations were compared between groups using Wilcoxon test.
Results: Median (IQR) age was 23 (20–25) years for nonpregnant and 23 (20–27) years for pregnant participants; baseline gestation age was 16 (14-20) weeks. TFV-DP was dose proportional in DBS and PBMCs. Observed median (IQR) week 8 TFV-DP concentrations in DBS in non-pregnant women were 359 (266–464), 749 (504–923), and 1389 (1151–1551) fmol/punch for 2, 4, and 7 doses/week, respectively (Table 1). During pregnancy, observed median (IQR) week 8 TFV-DP in DBS from daily dosing was 792 fmol/punch (759–946), similar to concentrations arising from 4 doses/week in non-pregnant women, but 55% lower than corresponding concentrations from daily dosing in non-pregnant women ($p<0.001$). Importantly, pregnant women achieved similar median (IQR) steady-state TFV-DP concentrations in PBMCs versus those observed in non-pregnant women on daily dosing [50 (35–58) versus 49 (36–63) fmol/10^6, $p=0.71$]. TFV-DP concentrations in PBMCs for both pregnant and non-pregnant women were lower than levels (>80 fmol/10^6) previously observed in US populations.
Conclusion: In this adherence benchmark study among African women, TFV-DP in DBS was more than one-half lower in pregnant versus non-pregnant women, but PBMC concentrations were similar. Concentrations were lower than levels observed in US cohorts. These benchmarks will help to define women-specific concentration- efficacy relationships and accurate interpretation of HIV prevention trials in African women.

Table 1: Observed TFV-DP concentration in DBS and PBMC, by study arm

	Non-pregnant 2 Doses/week	Non-pregnant 4 Doses/week	Non-pregnant 7 Doses/week	Pregnant 7 Doses/week
A: TFV-DP concentration in DBS (fmol/punch) at week 8				
Range	47–605	187–1578	496–2979	138–1112
Mean ± SD	368 ± 151	765 ± 376	1375 ± 523	804 ± 235
Median (IQR)	359 (266–464)	749 (504–923)	1389 (1151–1551)	792 (759–946)
% Difference; p-value (Wilcoxon exact)	118%; <0.001	60%; <0.001	—ref—	55%; <0.001
B: TFV-DP concentration in PBMCs (fmol/10^6) at week 4				
Range	2–48	10–43	21–121	11–71
Mean±SD	13 ± 11	28 ± 10	52 ± 24	47 ± 17
Median (IQR)	9 (7–19)	28 (21–34)	49 (36–63)	50 (35–58)
% Difference; p-value (Wilcoxon exact)	138%; <0.001	54%; <0.001	—ref—	2%; 0.71

171 HIV Incidence in the INSIGHT Cohort of African Women: Recency Testing and Prospective Follow-Up

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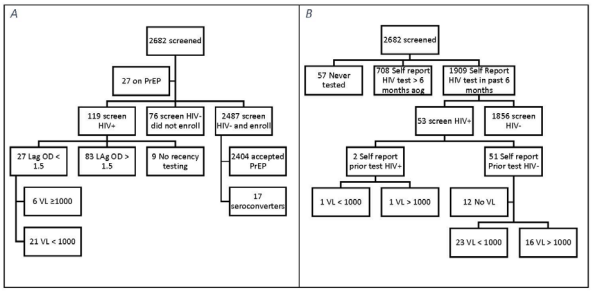
Background: For efficacy trials of novel agents with an active control, cross-sectional recency testing could estimate HIV incidence in the population screened. There is limited experience with use of recency testing to estimate HIV incidence for this purpose.
Methods: From Aug-Dec 2022, women ages 16-30 were enrolled into the prospective INSIGHT cohort from South Africa (15 sites), eSwatini, Kenya, Malawi, Uganda, and Zambia. Women who screened HIV+ had samples collected for LAg avidity and HIV RNA testing, those with LAg avidity ≤1.5 and viral load (VL)≥1000 copies/ml were classified as recent infections. Women who were HIV-negative were offered enrollment into an open-label PrEP cohort

for 6 months. At screening, all were asked about their HIV testing history and prior results. Reporting includes only South Africa and Eswatini, where recency testing is complete. Incidence estimates used ABIE v3.

Results: In South Africa and Eswatini, 2682 women were screened (87% of the INSIGHT cohort) and 119 (4.4%) tested HIV-positive, among whom 6 were classified as recent infections (27 had LAg avidity ODn≤1.5 and 21 had VL<1000 copies/ml, Figure A), for an estimated HIV incidence rate (IR) of 0.71 (95% CI 0.14-1.28). Among the 2487 in the HIV-negative cohort followed for 6 months, 97% accepted TDF/FTC PrEP, and there were 17 incident infections, IR=1.23/100 p-y (95% CI 0.77-1.97). 1909 (71%) of this cohort self-reported an HIV test within the past 6 months, including 51 HIV-positive at screening who self-reported a prior HIV negative test (Figure B). Among these 51 possible new infections, 39 had VL obtained; 23/39 (59%) had VL<1000 copies/ml, suggesting ART had been initiated. If the remaining 16/1909 were infections occurring in the prior 6 months, this would be consistent with an IR of at least 1.7/100 p-y, although self-reported test timing and results were unverified.

Conclusion: In this first reported use of recency testing during screening of women in Africa, estimated incidence using recency was lower than our observed incidence in prospective follow-up with high PrEP uptake and recent placebo incidence rates of 3-4% in HIV prevention trials. Cross-sectionally assessed HIV incidence may have been underestimated due to 1) selection bias if HIV testing is frequent and women with HIV are reluctant to screen, and 2) viral suppression from undisclosed early ART. Understanding sources of bias is critical for refining the recency approach and obtaining accurate contemporary HIV incidence estimates.

Figure 1:A. Recency testing at Screening and HIV seroconversion during follow-up B. Self-reported recent testing and VL



172 Randomized Trial of SEARCH Dynamic Choice HIV Prevention Including Injectable Cabotegravir (CAB-LA)

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Background: We hypothesized that an oral PrEP, PEP and CAB-LA biomedical prevention package with structured choice between products and opportunities to switch would increase biomedical prevention coverage compared to standard-of-care (SoC) among men and women at risk for HIV in rural Uganda and Kenya.

Methods: Participants were recruited from three randomized studies of the SEARCH dynamic choice HIV prevention (DCP) intervention vs SoC in antenatal clinics, outpatient departments and the community. Eligible participants were > 15 years and reported risk of acquiring HIV. Participants in the SoC arm had access to oral PrEP (TDF/XTC) and PEP (TLD) at local Ministry of Health (MoH) clinics. The SEARCH DCP model included person-centered, structured choice between oral PrEP, PEP (MoH-supplied) or CAB-LA (study-supplied at MoH clinics) and the ability to switch between or stop products over time based on patient product preference and risk. Primary outcome was biomedical covered time over 48 weeks (proportion of follow-up covered by PrEP/PEP/CAB-LA), assessed via study logs and self-report; secondary outcomes included coverage during periods of retrospectively self-assessed HIV risk and incident HIV infections.

Results: We enrolled 984 participants (487 DCP; 497 SoC). 73% were women, 30% aged 15-24. Mean biomedical covered time was higher in DCP (69.7%) vs. SoC (13.3%), a difference of 56.4% (95% CI 50.8- 62.1%; p<0.001). Biomedical covered time with DCP vs SoC was 65.6% and 52.8% higher for men and women, respectively. Intervention effect on coverage during periods at risk of HIV was larger; mean at-risk covered time was 76.5% in the DCP arm vs. 16.2% in SoC (difference 60.2%; 95%CI: 53.8-66.6%; p<0.001). In the DCP arm, 56%, 53%, 2% ever used CAB-LA, PrEP or PEP, respectively. 43% of persons who used CAB-LA were not using prior oral PrEP or PEP, showing benefit of adding the CAB- LA option. 28% and 0.4% of participants used at least 2 different products in the DCP and SoC arms, respectively. There were 7 participants who acquired HIV infection and one perinatal transmission in the SoC arm (incidence rate: 1.8%) and 0 in the DCP arm (p=0.01).

Conclusion: In the first randomized study of a person-centered model offering structured choice between CAB-LA, oral PREP and PEP with option to change over time, enrolling both women and men at risk of HIV, the SEARCH DCP intervention increased biomedical covered time by >5 fold to 69.7% and reduced HIV incidence to 0% compared to 1.8% in standard-of-care.

173 Selection of Epigenetically Privileged HIV-1 Proviruses During Treatment With Panobinostat and IFNα

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Background: CD4 T cells with latent HIV-1 infection persist despite treatment with currently available antiretroviral agents and represent the main barrier to HIV-1 cure. Pharmacological disruption of viral latency may increase the immunological vulnerability of HIV-1 infected cells, but the efficacy of latency-reversing agents for reducing HIV-1 persistence remains to be proven

Methods: We conducted a randomized controlled human clinical trial in which panobinostat (PBT), a potent histone deacetylase inhibitor (HDACi), was evaluated in combination with pegylated IFNα2a (PEG-IFNα2a). ART-treated participants were randomized to receive PBT alone (n=4), the combination of PBT and PEG- IFNα2a (n=9) or PEG-IFNα2a alone (n=4). We quantified CD4 T cell-associated HIV-1 RNA by RT-ddPCR and proviral HIV-1 DNA using the intact proviral DNA assay (IPDA). Cellular immune responses were analyzed by flow cytometry and CD4 T cell gene expression profiling was conducted by RNA-Seq. The integration sites were collected using ISLA or LM-PCR and we conducted a genome-wide assessment of H3K27ac histone marks using CUT&RUN sequencing.

Results: The combined treatment with PBT and PEG-IFNα2a increased CD4 T cell-associated HIV-1 RNA (fold increase 1.83, p=0.0029). In parallel, the study medication induced activation of cDC2, pDCs, and cytotoxic NK cells and enhanced the expression of IFN-stimulated genes. The combined treatment also resulted in a trend for reduced frequencies of intact proviruses, determined by IPDA (p=0.0547). To evaluate effects of the study medication on the proviral landscape, we collected 2,695 integration sites; these studies showed that the combined treatment induced a structural transformation of the HIV-1 reservoir cell pool, characterized by an accumulation of HIV-1 proviruses integrated in ZNF genes (p=0.032), in chromatin regions with reduced H3K27ac marks, and, to a lesser extent, in centromeric/satellite DNA regions.

Conclusion: Treatment with PBT and PEG-IFNα2a can induce notable changes in the proviral reservoir landscape, with preferential elimination of proviruses in proximity to H3K27ac marks, the molecular target site for PBT. Together, these results provide proof-of-principle that the viral reservoir is vulnerable to "shock and kill" interventions.

174 Role of Cytoskeleton and Adhesion in a Rare Subset of HIV-Infected Cells That Resist CTL

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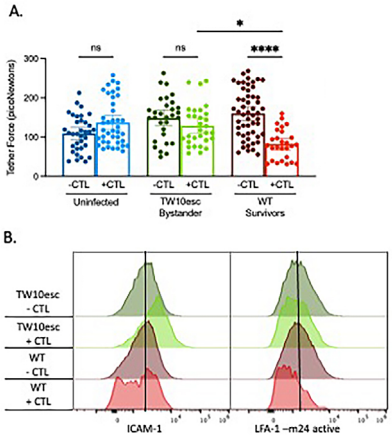
Background: Although latency is a key mechanism of HIV persistence, the reservoir continues to be shaped by cytotoxic T lymphocytes (CTL) pressure under antiretroviral therapy (ART). Growing evidence suggests that this selects for reservoir-harboring cells with CTL-resistant properties, including over-expression of BCL-2, PVR and the granzyme B inhibitor SERPINB9. Here, we lay a foundation for identifying novel mechanisms by comprehensively profiling

HIV-infected CD4+ T-cells that resist CTL in vitro. We uncover and investigate mechanisms that limit immunological synapse formation – including unique biophysical profiles – as novel modalities of CTL resistance.

Methods: Central memory CD4+ T cells (Tcm) from each of 4 HIV-neg donors were divided and infected with either 'WT'JRCSF or 'TW10esc'JRCSF with an escape mutation in the Gag-TW10 CTL epitope. These were labeled with CTFR (WT) or CFSE (TW10esc), mixed and cultured with or without TW10-specific CTL clones. Viable HIV-Env+ cells were sorted by flow cytometry into WT 'Survivors' (CTFR) and TW10esc 'Bystanders' (CFSE) and profiled by RNA-sequencing. Stiffness of Bystander and Survivor cells were measured by optical tweezer, and expression of integrins were quantified by flow cytometry.

Results: In the absence of CTL, WT- and TW10esc-infected Tcm had very similar transcriptional profiles. In striking contrast, the rare (~10%) WT-infected 'Survivors' of CTL coculture were divergent from TW10esc- infected 'Bystanders' (2,234 DEGs, padj<0.05). Gene ontology highlighted downregulation of genes involved in cytoskeletal regulation in Survivors (NES: -1.59, padj<0.003) and we confirmed by optical tweezers measurements that Survivor cells had a lower stiffness (n=27 mean +/-SEM tether force 82pN [+/-89-74pN]) than Bystanders (n=30 129pN [+/-138-119pN]). As the cytoskeleton plays a pivotal role in modulating integrin activation, cell adhesion genes were also down in survivors (NES: -1.68, padj<0.007). We confirmed using flow cytometry reduced surface expression of ICAM-1 and activation of LFA-1 on Survivors, suggesting impaired adhesion to CTL.

Conclusion: Killing by CTL requires the formation of immunological synapses which occurs less efficiently with softer target cells. In cancer, lower stiffness and reduced integrin expression are mechanisms of escape. Small molecule and engineered CAR-T therapeutic approaches to target less adherent cells are under development for cancer and should be tested for their abilities to enhance elimination of HIV reservoirs.



A. Forces (pN) required to break membrane tethers pulled from CD4+ T cells uninfected or infected with WT or TW10esc using optical tweezers. B. Surface expression of ICAM-1 and active form of LFA-1 on CD4+ T cells infected with WT or TW10esc before and after CTL pressure.

175 Sex-Specific Innate Immune Selection in Vertical HIV Transmission and cART-Free Aviraemia in Males

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Background: Following case reports of paediatric post-treatment control, it has been proposed that very early cART without additional interventions might achieve remission in a subset of children. To investigate this possibility, from 2015-2023 we conducted a longitudinal study of >300 mother-child pairs in KwaZulu-Natal, South Africa monitored from birth after in utero HIV transmission.

Methods: All infants received ART at birth; 92% of infants received transplacental maternal cART pre-birth. cART adherence was assessed via history, pill-counting, pharmacy records and plasma cART concentrations determined by liquid chromatography-tandem mass spectrometry. Chimeric Gag-Protease-NL4-3 viruses were generated following viral RNA isolation and nested RT-PCR amplification of mother and child gag-pro from baseline plasma. Viral type I interferon (IFN-I) sensitivity and replicative capacity were determined using the reporter cell lines U87-snLuc/EGFP and CEM-GXR, respectively.

Results: Despite very early cART initiation, sustained suppression of viraemia to 3 yrs was observed in only 32% of children. Aviraemia was usually cART-dependent. Unexpectedly, 5 'atypical' males were identified in whom aviraemia persisted despite complete cART discontinuation for 3m-19m in 4 cases; and 17 m intermittent cART in one case. By contrast, 60% of the cohort was female (p=0.01). Higher in utero transmission rates to female fetuses were only observed in the setting of recent maternal infection (p=0.0005). This was associated with transmission to females of IFN-I resistant (p<0.0001), low replication capacity ('fitness') virus (p<0.0001). HIV transmitted to male fetuses was typically IFN-I sensitive/high 'fitness'. Viruses transmitted to females by mothers who seroconverted in pregnancy were more IFN-I resistant than those not transmitted (p=0.019). Viruses transmitted to males were more IFN-I sensitive than those not transmitted (p=0.02). In sex-discordant twins where only one twin became infected, the female was infected in >90% of cases (p=0.002); the viruses not transmitted to the male twin were more IFN-I resistant than those transmitted to male singletons (p=0.001). Viruses transmitted to the 'atypical' males maintaining cART-free aviraemia had lower 'fitness' (p<0.0001) versus those transmitted to 'typical' males.

Conclusion: These data indicate that early life innate immune sex differences selectively influence vertical HIV transmission and modulate post-treatment control in children living with HIV (figure).

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176 Sex-Based Differences in HIV-1 Reservoir Profile in Individuals With Long-Term ART Suppression

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Background: Women account for over half of people living with HIV (PLH) but they are largely underrepresented in HIV-1 cure studies. Biological sex impacts host immune responses which may lead to sex- specific selection and evolution of HIV reservoir cells. However, sex-specific differences in HIV reservoir landscapes, including proviral reservoir size, composition, and integration site profile among long-term ART-treated (LT-ART) individuals remain unclear.

Methods: We included a total of 64 participants (34 males and 30 females, all cisgender), who remained on continuous suppressive ART for a median of 20 (range: 15 – 25) consecutive years with no more than 2 recorded plasma viremia blips (< 100 copies/mL). HIV-1 proviruses and chromosomal integration sites were analyzed using FLIP-seq and MIP-seq, as described in our previous work.

Results: There were no significant differences in the demographic characteristics between female and male participants in the study. In total, n=4012 HIV genomes were detected in the LT-ART cohort (n=1490 in females and n=2522 in males). Frequencies of total and defective HIV-1 genomes were not different between males and females; however, we found a small trend toward higher frequencies of intact proviruses in females (0.69 vs 0.53 median intact DNA per million PBMC, p = 0.15). Moreover, relative proportions of intact proviruses among total proviruses were higher in females (6.51% vs 3.65%, p < 0.0001). This difference appeared to be at least partially attributable to a higher frequency of clonally-expanded intact proviruses in females compared to males (3.37 vs 0.34 median clonal intact DNA per million PBMC, p = 0.0029). Intriguingly, within a total of 246 integration sites (145 intact, 101 defective) identified, we observed higher proportions of intact proviruses integrated in heterochromatin locations (including centromeric/satellite DNA, ZNF genes) and non-genic DNA in females than males (88% vs 58%, p < 0.0001).

Conclusion: Taken together, our results suggest a sex-based difference in host immune-driven proviral landscape evolution during long-term suppressive ART. Immune mechanisms responsible for viral reservoir cell selection are unclear

at present but may include sex-specific immune responses. The HIV reservoir in women is associated with features of deeper latency; therefore, women may be primed to achieve a state of HIV control, and the inclusion of women in cure studies should be a priority.

177 AAV-Expressed HIV IgG Biologics Enable Durable ART-Free Viral Control in Infant Macaques

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Background: There were 1.5 million children living with HIV (CLWH) in 2022, only half of whom had access to antiretroviral therapy (ART). Even when ART is available, lifelong daily adherence can be challenging for CLWH, emphasizing the need for alternative strategies to durably suppress HIV replication. Here we evaluated whether a combination of early ART initiation and adeno-associated virus (AAV)-vectored delivery of HIV IgG biologics could maintain ART-free virus control in simian-HIV (SHIV)-infected infant rhesus macaques (RMs).
Methods: Ten 4-week-old infant RMs (7 males; 3 females) were orally infected with SHIV-SF162P3 and placed on ART 7 days later, at which time the animals also received intramuscular injections of AAV9 vectors encoding IgG2 versions of the V3 glycan bNAb 10-1074 and the immunoadhesin eCD4-Ig. Three control RMs (2 males; 1 female) were similarly infected and placed on ART but did not receive AAV vectors. After 30 weeks, ART was interrupted and the kinetics of virus rebound compared between the two groups.
Results: Peak SHIV plasma viral loads pre-ART ranged from 1.8E+6 to 1.9E+7 vRNA copies/ml. All 10 AAV- treated RMs developed persistent levels of eCD4-Ig in plasma; expression of 10-1074 was more variable due to fluctuating anti-10-1074 antibodies. Following ART interruption (ATI), control RMs became viremic within 2 weeks, whereas 7/10 AAV-treated RMs remained aviremic for over 6 months ($P = 0.0005$). Low plasma amounts of 10-1074 (<6.0 µg/ml) were associated with virus rebound or "blips" in viremia in 3/10 AAV-treated RMs, even when concentrations of eCD4-Ig exceeded 10 µg/ml. One year after ATI, two aviremic experimental RMs were treated with a neonatal Fc receptor (FcRn)-blocking antibody to probe the mechanism of virus suppression. FcRn blockade markedly reduced plasma levels of total IgG, including eCD4-Ig and 10-1074, resulting in breakthrough viremia 2 weeks later, thus demonstrating the direct role of AAV-expressed HIV IgG biologics in ART-free viral control.
Conclusion: A one-time dose of AAV vectors given to 5-week-old infant RMs starting ART early after SHIV infection was safe and resulted in levels of eCD4-Ig and 10-1074 that prevented virus rebound and maintained virus control for up to 1 year post ATI. Maintenance of virus control required continuous expression of both eCD4-Ig and 10-1074 in plasma at >6.0 µg/ml. In sum, AAV-vectored delivery of HIV biologics holds promise for achieving sustained virologic remission in CLWH in a practical and scalable manner.

178 Broadly Neutralizing Antibody-Secreting T Cells and CAR-Ts Potently Suppress In Vivo HIV Infection

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Background: We hypothesized that combining anti-HIV CAR-T cells and with T cells engineered to secrete broadly neutralizing antibodies (bNAbs) could provide an approach to achieve ART-free HIV remission. As a proof-of-concept, we engineered a lentiviral vector (LV) encoding 3BNC117 bNAb (3BNC) to transduce T cells. We further evaluated the in vivo synergistic effects of 3BNC-expressed T (3BNC-T) cells and anti-HIV CAR-T cells against HIV infection in a humanized mouse model.
Methods: CD3 T cells were purified from HIV-seronegative donors and transduced with 3BNC LV and evaluated for in vitro and in vivo 3BNC production in NSG mice. In vivo synergistic antiviral function was tested by intrasplenically co-injecting autologous HIV-infected PBMCs with 3BNC-T cells or CAR-T cells or both into NSG mice for 3 weeks. Mouse serum and tissue HIV levels were measured to determine viral suppression.
Results: Using the same MOI, the level of 3BNC LV transduction in CD4 T cells was 2.8 times as high as that in CD8 T cells. When normalizing to a single cell, the level of 3BNC secretion by CD4 T cells was 4.6 times as high as that by CD8 T cells. For in vivo evaluation, 30 million T cells (59.4% were 3BNC+) were intrasplenically injected into NSG mice and when the mice were sacrificed at 8 weeks, 46.6% of spleen human T cells were 3BNC+. Weekly measurement of plasma 3BNC concentration remained above 1,500 ng/ml for the full 8 weeks before sacrifice. In HIV-infected NSG mice, spleen CD4 T cells were preserved in the combinational 3BNC-T and CAR-T cell treated (25.2%), and CAR-T cell only treated (23.1%) animals, but not in 3BNC-T cell only treated (9.9%) or control (11.8%) animals. Plasma 3BNC was detected in 3BNC-T cell only (471.5 ng/ml) and combinational therapy (1504.8 ng/ml) treated animals. Plasma HIV RNA was most suppressed in combinational therapy treated mice (91.7%), and CAR-T cell only treated mice (65.9%), comparing to control mice. Consistently, spleen HIV DNA was most suppressed in combinational therapy treated mice (78.8%), and CAR-T cell only treated mice (55.4%), compared to control mice.
Conclusion: We successfully engineered T cells that secrete bNAb in vitro and exhibited sustained in vivo bNAb production. BNAb-secreting T cells synergized with CAR-T cells to potently suppress in vivo HIV infection. This combinational therapy incorporating cellular and humoral anti-HIV approach provides a new strategy to generate more potent immunotherapeutics to contribute to a functional cure of HIV infection.

179 Autologous Neutralizing Antibodies Contribute to Virus Control in a Subset of PWH Treated With bNAbs

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Background: BnAbs are being tested in clinical trials of treatment and cure in people with HIV (PWH) who have existing autologous neutralizing antibody (anAb) responses. To determine the relative selective pressure of bnAbs and anAbs in the BEAT2 study of 3BNC117, 10-1074, and IFNa2b, we performed a sieve analysis comparing the potency of administered bnAbs and host anAbs against reservoir and rebound Envs.
Methods: In 8 participants of BEAT2 (NCT03588715), we sequenced provirus from PBMCs collected at study enrollment via FLIPseq or MIPseq (n= 314) to identify intact HIV-1 genomes in single and clonally-expanded populations. In 12 participants, plasma rebound envs (n=233) were sequenced by SGS at first detectable rebound viremia. Reservoir and rebound Envs were cloned and tested for neutralization sensitivity via TZM.bl assay to bnAbs and longitudinal plasma IgG (collected at a median of 8 time points over 12-24 study months). Statistical comparisons were by Wilcoxon matched-pairs test.
Results: In all 8 participants, rebound envs aligned within reservoir phylogenies, but were not identical to any sampled reservoir viruses. Comparing rebound Envs (1 per participant) and reservoir Envs (2-6 per participant), rebound Envs were significantly more resistant to 10-1074 (IC_{50} 6.44 µg/ml vs. 0.71 µg/ml; p=0.02), and trended towards greater resistance to 3BNC117 (ns). When tested against baseline plasma IgG (prior to bnAb dosing), rebound Envs were generally more resistant than reservoir Envs, with markedly greater resistance (30- fold difference in IC_{50}) in the 2 participants with most delayed rebound (>12 weeks post-bnAb dosing). Potency of plasma IgG against both rebound and reservoir Envs rose significantly during bnAb dosing (mean >3-fold change in IC_{50} for both; p=0.001). Post-ART restart, after bnAbs had waned and anAbs had responded to recent rebound viremia, plasma IgG potency increased vs. rebound Envs (mean 2.5-fold change in IC_{50}; p=0.001), but not reservoir Envs (ns).
Conclusion: In the BEAT2 study of 2 bnAbs and IFNa2b, the greater potency of the administered bnAbs against reservoir vs. rebound Envs indicates bnAb selective pressure. In 2 participants with delayed rebound, baseline anAbs also exerted selective pressure. After rebound and ART restart, anAbs evolved to selectively target rebound Envs. Together, results suggest that anAbs contributed to virus suppression in a subset (25%) of studied bnAb trial participants. Approaches to boost anAbs may increase this proportion.

180 A T Cell-Targeting mRNA SIV Vaccine Extends Time to Rebound and Enhances Post-ART Viral Control

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Background: Natural CD8+ T cell responses are ineffective at intercepting rebounding reservoirs after antiretroviral therapy (ART) release until after systemic viral replication and spread. Here, we evaluated whether a nucleoside unmodified mRNA vaccine (RNActive®) expressing full length SIV Gag and formulated in lipid nanoparticles (LNP) can be used to enhance Gag-specific CD8+ T cells in SIVmac239-infected rhesus macaques (RM) on ART. We hypothesized that vaccination during ART followed by a boost just prior to ART interruption (ATI) will enhance the immune intercept of reactivating SIV infections and facilitate post-ART viral control.

Methods: 16 RMs were infected with 5000IU of SIVmac239M and started on ART 9 days post-infection. Following viral suppression, RM were divided into 2 balanced groups that received 5 intramuscular injections at 100µg each of the SIV-Gag (n=8) or control mRNA/LNP vectors (n=8) at 59-, 62-, 65-, 79- and 106-weeks post- infection (wpi). SIV-specific T cell responses were assessed by intracellular cytokine stimulation assay. Two weeks after the last immunization, at 108wpi, ART was stopped to assess the impact of vaccine-induced immune responses on post-ART viral replication using RT-PCR.

Results: SIV-Gag mRNA/LNP increased Gag-specific CD8+ T cells in multiple tissues, particularly the bronchoalveolar lavage (BAL), which saw responses peak to 25% (mean ± 4.4% SEM) of CD8+ T cells. Indeed, overall frequencies of Gag-specific CD8+ T cells in BAL were higher in SIV-Gag mRNA/LNP vaccinated RM relative to controls after 47 weeks (AUC, p=0.0002). A boost SIV-Gag mRNA/LNP at 16 days prior to ATI significantly increased frequencies of Gag-specific CD8+ T cells in blood (p=0.0002), BAL (p=0.0002), lymph node (p=0.0003), bone marrow (p=0.0002), spleen (p=0.0002), rectum (p=0.02) and liver (0.0002) relative to controls. Upon ART cessation, time to viral rebound was delayed in RM that received the SIV-Gag mRNA/LNP (median 20 vs. 11.5 days, p=0.0005) (Figure 1A). Additionally, SIV-Gag mRNA/LNP RM had lower post-ART peak viremia (p=0.002) and lower viral burden up to 5 weeks after rebound (AUC, p=0.002) (Figure 1B).

Conclusion: Collectively, these data suggest that a T cell-targeted vaccination strategy that systemically increases the frequencies of SIV-specific CD8+ T cells immediately prior to ATI can restrict early viral spread and facilitate enhanced post-ART viral control.

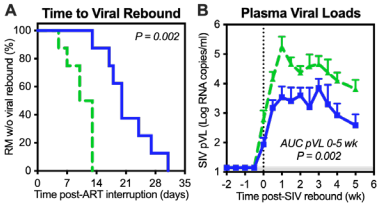

Figure 1: After SIVmac239M infection and ART suppression, RM were divided into 2 groups and given 5 intramuscular injections of SIV-Gag mRNA/LNP (n=8) or control mRNA/LNP (n=8) at 100µg each. (A) Kaplan-Meier curve of SIV rebound. (B) Mean (+SEM) post-rebound viral loads in SIV-Gag mRNA/LNP RM (blue) and control RM (green).

181 IL-15/IL-15RA Cytokine Therapy Enhances Control of Viral Rebound in SIV-Infected Macaques

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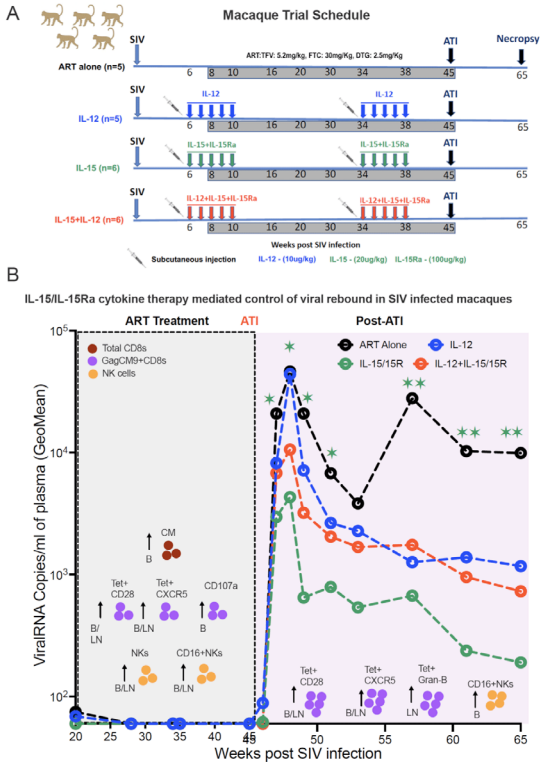
Background: Immunotherapeutic cytokines can enhance immune responses against chronic infections. Cytokines such as IL-15 and IL-12 expand CD8 T and NK cells and increase their cytotoxicity. Importantly IL- 15 can enhance follicular homing of CD8 T cells, and IL-15 + IL-12 enhances follicular homing of NK cells during chronic SIV infection. Here we tested the therapeutic effects of IL-15 and IL-12 when administered alone or in combination during chronic SIV infection in rhesus macaques (RMs).

Methods: Twenty-two RMs infected with SIVmac251 were initiated on antiretroviral therapy (ART) at 8 weeks post-SIV infection for 9-months. Three groups of animals received cytokine treatments - IL-15/IL-15Ra (n=6), IL-12 (n=5), IL-15/IL-15Ra+IL-12 (n=6) - in two phases (5 doses once a week). The first phase was administered at 6 weeks post SIV (2 weeks prior to ART) and the second phase was during ART at 12 weeks pre- ATI. ART alone (n=5) group served as the control. Animals were monitored longitudinally for immunological and virological parameters.

Results: IL-15/IL-15Ra and IL-15/IL-15Ra+IL-12 therapies induced significant expansion of functional SIV- specific CD8 T cells with proliferative capacity (Ki-67) and follicular homing (CXCR5); and CD16+ NK cells in blood and LN. Importantly, IL-15/IL-15Ra therapy resulted in the significant expansion of degranulating CD107a+CD8 T cells pre-ATI (P=0.03). In addition, the blood transcriptomic profile confirmed the induction of cytolytic molecules (granzyme-B, perforin), Jak/Stat signaling pathway in IL-15/IL-15a group, while genes associated with cell cycle arrest, DNA damage (MDM2, DDIT4) were significantly reduced. Post-ATI, virus rebounded in all animals but IL-15/IL-15Ra treated animals showed nearly 3-log lower viremia compared to ART only animals (p=0.004) with 83% of animals below 500 copies/ml at 20 weeks post ATI. This level of viral control was not observed in IL-12 or dual cytokine treated group. SIV-specific CXCR5+ CD8 T cells in blood (p=0.04) and LN (p=0.02) and SIV-specific CD28+ cells in blood (p=0.002 and LN (p=0.03), were associated with control of viremia post ATI.

Conclusion: The IL-15/IL-15Ra therapy at the initiation of ART and during ART markedly enhance the magnitude and function of SIV-specific CXCR5+CD8 T cells and CD16+ NK cells and contribute to profound control of viremia post ATI. These studies define IL-15/IL-15Ra as a potentially effective immune therapy for HIV cure strategy.



182 High Rates of Viral Suppression in Pregnancy Drop Postpartum in South African Women on TLD

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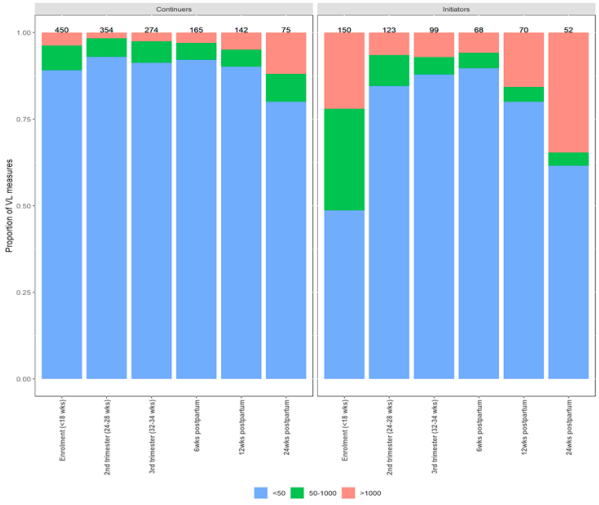
Background: The global transition to 1st-line antiretroviral treatment (ART) with tenofovir+lamivudine+dolutegravir (TLD) has shown high rates of viral suppression (VS) in adults and children but little is known about pregnant and postpartum women.

Methods: Pregnant women with HIV (PWH) already on TLD (Continuers, PWHc) or starting TLD <14 days prior to enrollment (Initiators, PWHi), were enrolled in ORCHID, an observational study of metabolic health, in Cape Town, South Africa, Sept 2021-Sept 2023. PWH were enrolled <18 weeks (wks) gestational age (GA); ART was managed by routine clinical services; viral load (VL) samples were collected at enrollment, trimester2 (T2, 24-28 wks), T3 (32-34 wks) and Q6-12wks postpartum (PP). Analyses described VS (<50 cps/mL), the incidence of major (>1000 cps/mL) and minor (50-1000 cps/mL) viremic episodes (VE) and associated factors among PWH using Poisson models.
Results: Among 600 PWH, 450PWHc/150PWHi, median (IQR) age was 30.0 yrs (16-47), GA was 13 wks (10- 16), and duration on TLD was 218 days (15-554) at enrollment [366 (149-716) and 1(0-7) for PWHc and PWHi respectively]. Median VL at enrollment was 19 cps/mL (range 19-980,148): 475 (79%) PWH had VL<50 cps/mL (89%PWHc, 49%PWHi), 76 (13%) had 50-1000 cps/mL (PWHc7.1%, PWHi29%) and 49 (8.2%) had >1000 cps/mL (PWHc3.8%, PWHi21%) [fig1]. Overall, 3142 woman-months of observation were accrued: 567 (95%) PWH had ≥1 VL <50 cps/mL; of these women 45 (8%) had ≥1 minor VE (8%C vs 7%I, p=0.8) and 39 (7%) had ≥1 major VE (4%C vs 15%I, p=<0.001). The proportion of VL measures with VS increased from enrollment (79%), was high at T2 (91%), T3 (90%), and 6wks PP (91%) but decreased thereafter. By 24wks PP, 21% of 127 VL measures were >1000cps/mL, (12%C vs 35%I, p=0.007). In multivariable analyses the incidence of VE >1000 cps/mL after VS was independently associated with decreased age [incidence rate ratio (IRR) 16- 22yrs vs 34+yrs, 3.26; 95% confidence interval (CI) 1.1-10.5) and elevated VL (>1000 cps/mL) at enrollment (IRR 4.65, 95%CI: 2.0-10.5).
Conclusion: This is among the first reports of VL in pregnant and postpartum women on TLD. We found high rates of VS in pregnant women, but postpartum viremia remains a pressing concern, particularly for younger women and those initiating ART during pregnancy.

Figure 1: Distribution of viral load test results during pregnancy and postpartum among women entering pregnancy on TLD (continuers) and initiating TLD (initiators)



183 Hypertension in a Randomized Trial of DTG vs EFV-Based ART in Pregnant and Postpartum Women

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Background: Dolutegravir (DTG) and tenofovir alafenamide(TAF) have been associated with incident hypertension (HTN), but limited data exist in pregnant and postpartum women. We performed a post-hoc analysis of blood pressure (BP) data collected in IMPAACT 2010 to characterize by-arm incidence of elevated BP and hypertensive disorders during pregnancy and postpartum.
Methods: Women with HIV were randomized at 14-28 weeks gestational age (GA) to start DTG+emtricitabine(F)/ TAF, DTG+F/tenofovir disoproxil fumarate(TDF), or efavirenz (EFV)/F/TDF. Incident gestational HTN was defined by ≥2 BPs ≥140/90 (mild) or ≥160/110 (severe) at ≥20 weeks GA with resolution by 12 weeks postpartum. We also characterized incident HTN from antepartum to 50 weeks postpartum defined by ≥2 values in the following categories (and not meeting the definition of gestational HTN): elevated BP 130-139/80-89, mild HTN 140-159/90-99, moderate HTN 160-179/100-109, or severe HTN ≥180/110 mmHg, with the most severe reading defining the category. The Cox proportional hazard model was used for by-arm comparisons of incident HTN, defined as either elevated BP or gestational or non-gestational HTN, with and without adjustment for time-varying weight.
Results: 626 participants were included: 211 in DTG+F/TAF, 208 in DTG+F/TDF, and 207 in EFV/F/TDF (11 were excluded for HTN at entry). Baseline medians were: age 26.4 yrs, GA 21.9 wks, HIV RNA 938 cp/mL, CD4 cell count 472 cells/uL, BMI 24.6 kg/m^2. Incident elevated BP or HTN (mild+) was high overall (55%) and more common with DTG+F/TAF (59%) and DTG+F/TDF (56%) relative to EFV/F/TDF (51%). Moderate and severe HTN occurred in 1.6% of women (Table). 12 women had pre-eclampsia and 1 had eclampsia, with no apparent pattern by arm. While the estimated difference between DTG arms was small, there was a trend toward an increased hazard of incident elevated BP or gestational or non-gestational HTN for DTG+F/TAF vs EFV/F/TDF (HR 1.26, 95%CI 0.98, 1.64) and DTG+F/TDF vs EFV/F/TDF (HR 1.18, 95%CI 0.9,1.53); results adjusted for time-varying weight were similar.
Conclusion: Our data are consistent with findings that DTG-based ART may be associated with incident HTN, largely represented by numerically more women with BP ≥130-139/80-89mmHg in this cohort of young, pregnant and postpartum women. Our findings should be confirmed with additional studies. Pending further data, efforts should focus on early identification and management of hypertensive disorders in pregnant and postpartum women on DTG.

Elevated blood pressure and HTN by-arm*

	DTG+F/TAF (N=211)	DTG+F/TDF (N=208)	EFV/F/TDF (N=207)	Total (N=626)
Any elevated blood pressure (≥130-139 and/or ≥80-89 mmHg) or mild or worse HTN (≥140 and/or ≥90 mmHg)	125 (59%)	117 (56%)	105 (51%)	347 (55%)
Elevated blood pressure, non-gestational (≥130-139 and/or ≥80-89 mmHg)	98 (46%)	92 (44%)	84 (41%)	274 (44%)
Mild, moderate, or severe HTN, non-gestational (≥140 and/or ≥90 mmHg)**	18 (9%)	15 (7%)	13 (6%)	46 (7%)
Mild gestational HTN (≥140-159 and/or 90-110 mmHg)	4 (2%)	3 (1%)	3 (1%)	10 (2%)
Severe gestational HTN (≥160 and/or ≥ 110mmHg)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Gestational HTN with elevated blood pressure or HTN (mild or worse) persisting beyond 12 weeks postpartum	4 (2%)	7 (3%)	5 (2%)	16 (3%)
No elevated blood pressure or hypertensive disorders (<130/80 mmHg)	86 (41%)	91(44%)	102 (49%)	279 (45%)

*Excludes prevalent hypertension at entry based on antihypertensive use or a diagnosis of hypertension (n=11); Systematic collection of new antihypertensives was not performed, but if recorded was counted as incident HTN, regardless of blood pressure.
**40 mild, 6 moderate, and 0 severe non-gestational hypertension.

184 ART-Free HIV-1 Remission in Very Early Treated Children: Results From IMPAACT P1115

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Background: Very early initiation of antiretroviral therapy (ART) may limit the establishment of HIV-1 reservoirs in neonates, potentially enabling ART-free remission. We describe 6 children who received very early NVP- and PI-based ART and underwent analytical treatment interruption (ATI) in IMPAACT P1115 to assess for remission.
Methods: Fifty-four infants with in utero HIV-1 (confirmed by 2 positive nucleic acid tests) initiated ART within 48 hours of birth and received the study regimen (NVP+2NRTIs with LPV/r added ≥42 weeks postmenstrual age) for up to 294 weeks. Eligibility criteria for ATI included sustained virologic suppression with no plasma HIV-1 RNA detected from 48 weeks onwards and no HIV-1 DNA detected in ≥850,000 PBMCs (droplet digital PCR), normal CD4, and negative HIV-1 serostatus (4th generation ELISA). Children meeting all criteria interrupted ART with frequent clinical, virologic, and immunologic monitoring; remission was defined as no confirmed plasma HIV-1 RNA above the limit of detection (LOD) of the assay for ≥48 weeks off ART. ART was resumed upon viral

rebound (HIV-1 RNA confirmed ≥LOD). Plasma ARV drug levels were assessed retrospectively to confirm absence of ARV during ATI.

Results: Six children underwent ATI at median age 5.5 years. Three of 6 achieved study-defined remission, one through 80 weeks of ATI, when viral rebound (299,538 cp/mL) occurred. The other two who achieved remission remain on ATI (>48 and >60 weeks). A fourth child remains on ATI (>44 weeks). Two children had viral rebound 3 and 8 weeks after ATI (Table). Earliest available HIV-1 RNA and DNA values ranged from 96 to >5 million cp/mL and from not detected to 130 cp/106 PBMCs. The child with 80 weeks of remission had no ARVs detected in plasma during ATI (tests pending for others). Two of 3 children with rebound (at 8 and 80 weeks) experienced acute retroviral syndrome (ARS); no other clinical or immunologic events of concern were identified during or following ATI. The children with rebound at 3 weeks (67,606 cp/mL) and 8 weeks (1801 cp/mL) had HIV-1 RNA <LOD 8 weeks and 20 weeks after resuming ART. The child with rebound at 80 weeks had HIV-1 RNA 724 cp/mL 2 weeks after resuming ART.

Conclusion: ART-free remission for ≥48 weeks was achieved with very early treatment of in utero HIV-1. Very early treatment with durable virologic suppression may enable sustained remission in children; however, the occurrence of ARS warrants careful clinical oversight during ATI.

Table: Key Characteristics of IMPAACT P1115 Participants Who Received Very Early ART and Underwent Analytical Treatment Interruption (ATI)

Participant	Sex at Birth	Age at ART Initiation Age at ATI	Earliest HIV-1 RNA Earliest HIV-1 DNA	Earliest Age with No HIV-1 RNA Detected Earliest Age with No HIV-1 DNA Detected	Time off ART* with No HIV-1 RNA Detected	Highest DAIDS Grade Sign or Symptom of Acute Retroviral Syndrome	Time to HIV-1 RNA <LOD Duration of Follow-Up after Resuming ART
A	Female	1 day 5.6 years	>5 million copies/mL 69.8 copies/10^6 PBMCs	10 weeks 12 weeks	**80 weeks**	Grade 1	not yet determined** 2 weeks
B	Female	2 days 5.5 years	96 copies/mL 3.6 copies/10^6 PBMCs	9 weeks 12 weeks	**>60 weeks**	not applicable	Still on ATI
C	Male	1 day 5.3 years	1969 copies/mL no DNA detected	11 weeks 1 week	**>48 weeks**	not applicable	Still on ATI
D	Female	2 days 5.7 years	87 copies/mL no DNA detected	3 weeks 2 days	>44 weeks	not applicable	Still on ATI
E	Male	1 day 5.4 years	118 copies/mL 3.7 copies/10^6 PBMCs	9 weeks 25 weeks	8 weeks	not applicable	20 weeks 46 weeks
F	Female	1 day 5.5 years	15,017 copies/mL 130.4 copies/10^6 PBMCs	17 weeks 49 weeks	3 weeks	Grade 2	8 weeks 36 weeks

*Study visit week counted from initiation of ATI, duration of remission bolded. **Most recent value (2 weeks after resumption of ART) was >LOD.

185 GIVE MOVE: Randomized Trial on Genotype-Informed Management of Viremia in Children and Adolescents

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Background: Children and adolescents with HIV experience high rates of treatment failure. Genotypic resistance testing (GRT) to inform onward antiretroviral therapy (ART) is often inaccessible, and its effect on clinical outcomes in the context of viremia is unknown.

Methods: The Genotype-Informed Versus Empiric Management Of VirEmia (GIVE MOVE) open-label randomized clinical trial enrolled children and adolescents <19 years who were receiving ART and had a recent (<16 weeks before enrolment) viral load (VL) ≥400 copies/mL. Participants were randomised 1:1 to receive either GRT with expert recommendation (GRT arm) or repeat VL testing and empiric decision-making (usual care arm) to inform onward treatment. The composite primary endpoint was the occurrence of i) death, ii) hospitalisation, iii) a new World Health Organization (WHO) clinical stage 4 event, or iv) no documented viral resuppression (<50 copies/mL) at 36 weeks. Secondary endpoints included separate analyses of the primary endpoint components and 36-week VL ≥50 copies/mL among those with a 36-week VL result. Adjusted odds ratios and adjusted risk differences were estimated in the modified intention-to-treat (mITT) population. The trial was conducted at ten sites in Lesotho and Tanzania. Trial registration: ClinicalTrials.gov (NCT04233242).

Results: Between March 2020 and July 2022, 286 participants were enrolled of whom 284 were included in the mITT analyses (144 GRT arm; 140 usual care arm). Of these, 158 (55.6%) were female (versus male); 116 (40.8%) were aged 0-11 years (versus 12-18 years); and 13 (4.6%), 101 (35.6%), and 170 (59.9%) were taking non-nucleoside reverse transcriptase inhibitor-, protease inhibitor-, and integrase inhibitor-based ART, respectively, at enrolment. The composite primary endpoint was reached by 67 (46.5%) in the GRT arm and 73 (52.1%) in the usual care arm (adjusted odds ratio [95% confidence interval]: 0.79 [0.49-1.27]; adjusted risk difference: -0.06 [-0.17-0.06]) (Table). No differences were observed for secondary endpoints (Table). No deaths were recorded; one WHO clinical stage 4 event requiring hospitalisation occurred in the usual care arm (Table).

Conclusion: In this randomized trial conducted in Tanzania and Lesotho, GRT-informed management did not improve viral resuppression rates or clinical treatment outcomes in children and adolescents with viremia while taking ART.

Table: GIVE MOVE primary and secondary endpoints. aOR: adjusted odds ratio; aRD: adjusted risk difference; ART: antiretroviral therapy; CI: confidence interval; GRT: genotypic resistance testing; WHO: World Health Organization.

Endpoint	Usual care arm	GRT arm	aOR (95% CI)	aRD (95% CI)
Primary endpoint	73/140 (52.1%)	67/144 (46.5%)	0.79 (0.49-1.27)	-0.06 (-0.17-0.06)
Secondary endpoints				
All-cause mortality	0/140 (0%)	0/144 (0%)		
Hospital admission of ≥24 hours [1]	1/140 (1%)	0/144 (0%)		
New WHO stage 4 event [1]	1/140 (1%)	0/144 (0%)		
No documented viral resuppression to <50 copies/mL at 36 weeks	73/140 (52.1%)	67/144 (46.5%)	0.79 (0.49-1.27)	-0.06 (-0.17-0.06)
Viral load ≥50 copies/mL among those with a viral load result at 36 weeks (n=271)	66/133 (49.6%)	61/138 (44.2%)	0.82 (0.51-1.34)	-0.05 (-0.16-0.07)

[1] Possibly, probably, or definitely related to HIV and/or ART.

186 ODYSSEY 192-Week Follow-Up Evidences Superior Efficacy of DTG for Children on First/Second-Line ART

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Background: ODYSSEY demonstrated superior 96-week efficacy for dolutegravir(DTG)+2NRTIs versus standard-of-care (SOC, 77% efavirenz first-line, 96% boosted PI second-line) in children starting first-line (ODYSSEY A) or second-line ART (ODYSSEY B). During a further ~3 years' extended follow-up in Africa and Thailand, children on SOC were switching to DTG following national guidelines. Here we present efficacy and safety of DTG compared to SOC over 192 weeks and virological suppression in SOC participants post-switch to DTG.

Methods: The proportion of children with treatment failure (confirmed viral load (VL) ≥400c/mL after week 36, lack of virological response by week-24 with ART switch, death or new/recurrent WHO4/severe WHO3 event) was compared between trial arms by intention-to-treat using Kaplan-Meier. Viral suppression in SOC participants was defined as VL<400c/mL in the most recent sample within 24 weeks pre-DTG switch and 48 weeks post-switch.

Results: 792 children were randomised (392 DTG,400 SOC); median(range) age 11.4(0.1-18) years, and weight 29(3.4-85)kg. 383 children started first-line; 409 second-line. 683 children (349 DTG, 334 SOC) consented to extended follow-up (97% of 707 approached). Overall, median follow-up was 5.5 years (286 weeks; IQR: 234-310). At 192 weeks, only 13% of SOC had switched to DTG, without prior treatment failure. 76(19%) DTG vs. 129(32%) SOC participants experienced treatment failure by 192 weeks (treatment difference [95% CI]:-13.3%[-19.2,-6.5]; p<0.001). Treatment effects were similar on first- and second-line [heterogeneity p=0.22]. Mean change in CD4% from baseline to week 192 was 12% in DTG versus 11% in SOC (difference (DTG-SOC) 1.4[95% CI:-0.2,3.0]; p=0.095). 11 children had died (4 DTG, 7 SOC) and 18 children had experienced a new/recurrent WHO4/severe WHO 3 event (9 DTG, 9 SOC) by week 192. By the end of follow- up, 309 (77% of randomised, 99% of those completing extended follow-up) of SOC arm had switched to DTG; 297(95%) of DTG arm remained on DTG. 248/275(90%) SOC participants switching to DTG were virologically suppressed post-switch (ODYSSEY A 96%, B 86%), including 179/193(93%) of those suppressed pre-switch (A 99%, B 89%) and 29/35(83%) with pre-switch VL≥400c/mL (A 87%, B 80%).

Conclusion: Superior efficacy of DTG-based ART versus SOC was maintained up to 192 weeks in children starting both first- or second-line ART. On average,

for every eight children treated with DTG versus alternative ART, one treatment failure will be prevented.

187 Emerging Dolutegravir Resistance Among Children Being Investigated for Treatment Failure in Malawi

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Background: Malawi switched from protease inhibitor- (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based paediatric first- and second-line antiretroviral therapy (ART) regimens to dolutegravir-based regimens (DBR) in 2020. By 2022, over 98% of children living with HIV (CLHIV) were on DBR, requiring monitoring of dolutegravir (DTG) resistance. We evaluated the prevalence and patterns of drug resistance (DR) to DBR in children in Malawi.

Methods: We conducted a cross-sectional survey in 19 clinics randomly selected from the 25 highest volume ART clinics in Malawi from November 2022 to March 2023. We included CLHIV aged <15 years, on a DBR ≥9 months, returning to the clinic after a previous high viral load (VL) ≥1000 cps/ml and having completed at least 1 session of intensive adherence counselling (IAC) per national guidelines. A plasma sample was obtained for VL re-testing. Samples with VL ≥1000cps/ml were genotyped for DR using HIV-1 Genotyping kit with Integrase (ThermoFisher) and interpreted using Stanford University HIVDR Database Algorithm (version 9.4). We present weighted estimates of DR (level 3-5) with 95% confidence limits accounting for correlation within clinic using SAS.

Results: Of the 297 CLHIV re-tested for VL, 43.1% (128/297) remained unsuppressed. Out of the 128 CLHIV that remained unsuppressed, 97.7% (125/128) were successfully genotyped for DR mutations (DRMs). For those successfully genotyped, median age was 10 years old (IQR 5-13); 58% were male, median time since ART initiation was 5.4 years (IQR 2.5-9.0); median time on DTG was 1.5 years (IQR 1.2-2.3); and 89% were ART- experienced at DTG initiation. The weighted prevalence of high-level DTG resistance among children with virological failure was 15.5% (95% CI: 6.7-24.3). The most common major DTG DRMs were R263K (10), E138K/A (5), S147G (4), and G118R (4). Resistance to any nucleoside reverse transcriptase was 41.1%, (95%CI: 27.6-54.6); to any NNRTI was 65.0%, (95%CI: 53.8-76.2); and any PI was 5.2% (95%:CI: 0.0-12.2).

Conclusion: Among Malawian CLHIV with confirmed virological failure on DBR, DTG DRM prevalence was 15.5%, twice as high as the 8.5% found in a parallel study among Malawian adults. Prevalence of DRM to PI was rare. These collective results raise concern about effective future treatment of CLHIV, as there are no convenient alternative 2nd or 3rd line ART options currently available for this population.

188 Long-Acting Cabotegravir Plus Rilpivirine In Adolescents With HIV: Week 24 IMPAACT 2017(MOCHA) Study

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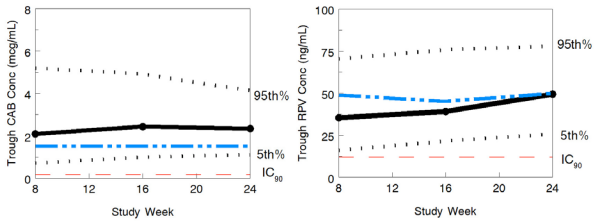
Background: Long-acting (LA), intramuscular (IM) cabotegravir (CAB) + rilpivirine (RPV) constitutes the first LA combination antiretroviral treatment (ART) regimen for people with HIV-1. The goal of the ongoing IMPAACT 2017 study (MOCHA [More Options for Children and Adolescents]; NCT03497676) is to evaluate the safety, tolerability, and pharmacokinetics (PK) of this LA combination in virologically suppressed (HIV-1 RNA < 50 c/mL) adolescents. Here we present PK and safety data through the primary Week 24 timepoint and available safety data beyond Week 24.

Methods: In this Phase I/II, open-label, noncomparative trial, virologically suppressed adolescents (12 to <18 years of age; ≥35 kg) with HIV-1 switched from their pre-study ART to 4 weeks of daily oral CAB + RPV followed by 600 mg CAB LA and 900 mg RPV LA IM (3 mL each) in the contralateral gluteus medius per the every 2-month dosing regimen. The 1st and 2nd injections were 4 weeks apart, with subsequent injections every 8 weeks.

Results: 144 participants were enrolled at 18 sites in 5 countries. Median (min, max) age was 15 years (12, 17), body mass index 19.5 kg/m² (16, 34), weight 48 kg (35, 101), 49% male and 74% Black or African American. Most participants received ≥1 injection (142/144) and completed the Week 24 visit (141/144); mean (standard deviation) study duration was 56 weeks (13). No deaths or adverse events (AEs) leading to study drug discontinuation occurred; no serious AEs attributable to study product occurred. Through Week 24, 16/144 (11%) had a ≥ Grade 3 AE, most common being increases in blood creatine phosphokinase (n=6) and systolic blood pressure (n=3); none of these non-injection site reaction (ISR) AEs were considered study drug related. For all safety data, 49/142 (35%) participants reported an ISR, most (86%) ISRs resolved within 7 days and were Grade 1 (91%). Two of 144 (1%) participants experienced a drug-related ≥ Grade 3 AE (injection site pain and abscess [n=1]; injection site abscess [n=1]). The outcome of the single unintended pregnancy in a study participant was a healthy live birth. There was no virologic failure through Week 24. The median (5%, 95%) Week 24 predose concentrations for CAB [2.34 µg/mL (1.11, 4.15)] and RPV [49.5 ng/mL (25.9, 78.1)] were similar to those in adults (Figure). One participant had low CAB concentration at Week 24 (0.03 µg/mL).

Conclusion: IMPAACT 2017 (MOCHA) data support using CAB-LA plus RPV-LA every 2 months in virologically suppressed adolescents.



IMPAACT 2017 CAB and RPV troughs (Black lines - medians [solid] with 5th%-95th% [dashed]) compared to adults (Blue lines) from LATTE-2 / ATLAS-2M studies and protein adjusted IC_{90}s (Red lines)

189 SEARCH: Youth Intervention Impact on Symptoms of Depression in East African Youth Living With HIV

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Background: Depression is common among youth with HIV and is associated with adverse outcomes. The SEARCH Youth intervention included a life-stage based assessment of psychosocial issues in youth with HIV. We sought to determine if the intervention affected the prevalence of depressive symptoms.

Methods: SEARCH Youth was a cluster-randomized trial of youth aged 15-24 years in 28 clinics of rural Kenya and Uganda that demonstrated increased viral suppression at 2 years. Intervention clinics utilized a life- stage discussion tool at each routine visit, with rapid viral load testing and flexible clinic access. To assess for depression in both arms at study exit, trained clinicians completed the Patient Health Questionnaire-9; scores were categorized as any depressive symptoms (≥1), at least mild depression (≥5) or moderate-severe depression (≥10). Overall and within pre-specified subgroups, we compared outcomes by arm using TMLE accounting for clustering. We evaluated predictors of depression using logistic regression.

Results: Of the 1,811 eligible, 662 intervention and 572 control participants were assessed after a median 3.8 years of follow up. Median age was 21 years, and 80% were female with baseline characteristics balanced by arm. Overall, 53% of the intervention arm compared to 73% in the control had any depressive symptoms, representing a 28% risk reduction [relative risk:0.72 (95% CI: 0.59-0.89)]. There was a trend to risk reduction for at least mild (0.45; 0.13-1.57) or moderate-severe (0.48; 0.10-2.29) depression in the intervention arm. Across subgroups, the intervention conferred risk reduction for any depressive

symptoms with the greatest effects among participants in Kenya (0.54; 0.38-0.79) and those re-engaging in care (0.67;0.55-0.82). Predictors (odds ratio; 95% CI) of at least mild depression included feeling sexual pressure (10.6;3.8-29.4), feeling physically threatened (6.5;3.3-12.5), and recent life events (4.2;2.6-6.7), including sickness (4.1;2.4-7.0) or family death (7.5;4.0-14.1).
Conclusion: The SEARCH Youth intervention reduced the prevalence of depressive symptoms particularly for those re-engaging in care. Recent major life events and the perception of sexual or physical threat were key drivers of depression in this population. We postulate that life-stage based discussions helped providers and patients identify and navigate challenging issues, building resilience against both depression and lapses in adherence and care.

190 Role of Community-Level Factors in Declines in HIV Incidence and Prevalence Among Rakai Adolescents

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Background: HIV acquisition among adolescents (15-19 years) and young adults (20-24 years) is influenced by individual factors, community factors, and public policies and programs. We explored the association of HIV incidence and prevalence with these factors over time among adolescents and young adults (AYA) in Rakai, Uganda.
Methods: We examined trends among AYA (n= 35,938 person rounds) from nine survey rounds (2005-2020) of the Rakai Community Cohort Study (RCCS), a population-based open cohort of individuals living in 30 continuously followed communities in southcentral Uganda. We evaluated the impact of community viremia (CV, a measure of community-level ART use and HIV prevalence) on HIV incidence and prevalence among AYA. Logistic GEE, Poisson GLM and univariate models were run for HIV prevalence, HIV incidence, and predictors of interest, respectively.
Results: HIV incidence and prevalence declined after round 14 (2010-2011) by 66% among AYA men and after round 17 (2015-16) by 60% among AYA women. Between survey round 11 and round 19, the proportions reporting sexually experience declined from 58% to 38% in adolescent men and from 65% to 35% among adolescent women. The prevalence of male medical circumcision (MMC) among AYA men increased from 20% in round 11 to 79% in round 19. At the community-level, we found substantial increases in ART use among PLHIV (15% in round 11 and 86% in round 19) and corresponding declines in CV. In multivariable analyses, a combination of individual and community-level factors were found to predict HIV incidence and prevalence among AYA, notably MMC among young men and CV among young women.
Conclusion: Declines in HIV incidence and prevalence occurred first among AYA men and later among AYA women. These coincided with declines in sexual experience and with public policies to increase access to MMC and ART. Combination HIV prevention with AYA needs to address risk factors at multiple levels. Individual risk behaviors continue to play a role in HIV incident and prevalence infection. Thus, it remains important to have conversations with AYA about their individual behaviors. However, community level factors are playing an important role and therefore these conversations should occur within the context of larger social forces of transmission risk.

191 Investigation of HIV Transmission Associated With Receipt of Vampire Facials: New Mexico, 2018-2023

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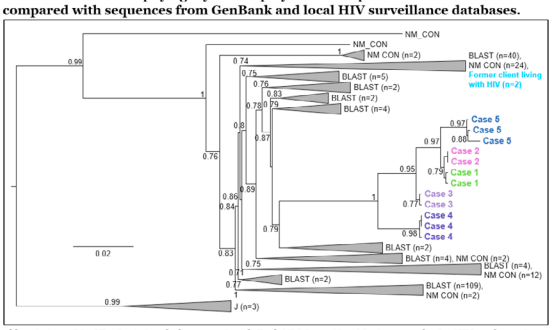
Background: HIV transmitted through cosmetic injection services via contaminated blood has not been previously documented in the United States. In summer 2018, the New Mexico Department of Health (NMDOH) was notified of a diagnosis of HIV infection in a female with no known HIV risk factors who reported exposure to needles from cosmetic platelet-rich plasma micro-needling (vampire facial) received at a spa in spring 2018.
Methods: This report led NMDOH and CDC to investigate possible transmission of HIV through cosmetic injection services. The period of interest for active case finding was from spring 2018, when the initial case received a vampire facial, to fall 2018 when the spa closed, and on-site inspection of the spa was conducted. Names and phone numbers were compiled and cross-referenced from spa client consent forms, handwritten appointment records, and cell phone contacts to form a list of potentially affected clients who were directly contacted to encourage testing for bloodborne pathogens. From 2018-2023, suspected cases were reported to NMDOH from clinical providers throughout the state, and blood specimens were submitted to CDC for nucleotide sequence analysis (NSA) to determine cluster association.
Results: Active case finding identified one client with a previous diagnosis of HIV in 2012, 20 clients who received vampire facials, and 59 clients who received other injection services (e.g., Botox) during spring-fall 2018. Among the 198 former spa clients and their sexual partners tested during 2018-2023, no new HIV, Hepatitis B, or Hepatitis C infections were identified. The on-site inspection revealed several unsafe infection control practices including storage of unlabeled tubes of blood on the kitchen counter. Five suspect cases, four former spa clients plus one sexual partner of a spa client, were reported to NMDOH all of whom had HIV diagnosed during 2018–2023 and no known HIV risk factors. NSA revealed highly similar HIV strains among all cases indicating vampire facials as the likely transmission route of HIV for three cases in this cluster. The other two cases, who had previous HIV infections, were likely attributed to sexual contact. Sequences from the former client living with HIV did not cluster with any sequences from cases.
Conclusion: This investigation underscores the importance of assessing novel sources of HIV transmission among persons with no known HIV risk factors, and adequate infection control practices at spa facilities offering cosmetic injection services.

Maximum likelihood phylogeny of HIV polymerase sequences from cluster cases compared with sequences from GenBank and local HIV surveillance databases.



Abbreviations: BLAST = Basic Local Alignment Search Tool; NM Con = New Mexico controls; J = HIV-1 subtype J reference sequences used as the outgroup.

192 Trends in Black-White Disparities in HIV Diagnosis: 2017-2021, United States

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Background: The largest disparities in HIV diagnoses in the United States are between Black and White persons. Federal initiatives for HIV prevention have evolved over the years, with the 2025 National HIV/AIDS Strategy including a focus on health equity. We examined trends in Black-White HIV diagnosis disparities to evaluate progress towards achieving equity in HIV diagnosis in the United States.
Methods: Data from CDC's National HIV Surveillance System were used to assess temporal trends in absolute and relative disparities in HIV diagnosis between Black and White persons during 2017–2021. Predicted values based on four years (2017–2019 and 2021) of data were used. Data for the year 2020 were excluded due to the impact of COVID-19 on HIV diagnoses. Estimated annual percentage change (EAPC) and 95% confidence intervals (CIs) were calculated to assess trends by selected characteristics.
Results: During 2017 to 2021, absolute disparities in Black-White HIV diagnosis decreased among males from 65.7 per 100,000 population to 57.6 per 100,000 population (absolute: EAPC = -3.2 [CI: -3.6, -2.7]) and from 22.5 per 100,000 population to 17.7 per 100,000 population (absolute: EAPC = -5.8 [CI: -6.5, -5.0]) among females. Relative disparities decreased from 15.1 per 100,000 population to 10.8 per 100,000 population among females (EAPC = -7.2 [CI:

-8.4, -5.9]) and remained the same for males. Among male subpopulations, disparities increased among those with HIV attributable to male-to-male sexual contact (Absolute: EAPC = 1.2 [CI: 0.8, 1.5]; Relative: EAPC = 1.5 [CI: 1.0, 1.9]). Relative disparities increased among males aged 13—24 years (EAPC = 7.4 [CI: 7.0, 7.7] and males in the West (EAPC = 2.0% [CI: 1.1, 2.9]. Among female subpopulations, no increases in disparities were found.
Conclusion: Overall, Black-White HIV diagnosis disparities mostly decreased in the United States, indicating progress toward eliminating disparities; however, increases or no changes were observed for some subpopulations, suggesting little to no progress in improvements for health equity. Efforts to address both absolute and relative disparities must be accelerated to eliminate Black-White disparities in HIV diagnosis.

193 Estimating Lifetime Risk of a Diagnosis of HIV Infection Among MSM: United States, 2017-2021

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Background: Estimates of lifetime risk are used to compare the burden of disease across populations. This method may be a useful tool for clinicians, outreach workers and policy makers when describing the burden of HIV since it can be more easily understood by the general population. We estimated lifetime risk of a HIV diagnosis among MSM by race/ethnicity and age.
Methods: HIV diagnosis, mortality and census population data were used to derive lifetime risk estimates and 95% confidence intervals of HIV diagnosis among MSM by race/ethnicity and age. HIV diagnoses data reported to the National HIV Surveillance System (NHSS) by December 2022 were used. The numbers of HIV diagnoses (NHSS) and non-HIV deaths (National Center for Health Statistics mortality data) during 2017—2021 were used to calculate probabilities of a HIV diagnosis at a given age, conditional on never having received a HIV diagnosis prior to that age using a competing risks method. The lifetime risk estimate is the cumulative probability of HIV diagnosis from birth. Comparisons were made to findings from a 2010—2014 analysis. The analysis was conducted in DevCan 6.7.3.
Results: During 2017—2021, the lifetime risk of a HIV diagnosis among MSM was 1 in 7 overall. Lifetime risk among MSM was 1 in 3 for Black/African American persons, 1 in 5 for Hispanic/Latino persons, 1 in 7 for Native Hawaiian/other Pacific Islander persons, 1 in 11 for American Indian/Alaska Native persons and 1 in 15 for Asian persons and White persons. Lifetime risk improved for all races/ethnicities except for American Indian/Alaska Native, Hispanic/Latino and Native Hawaiian/other Pacific Islander MSM which stayed the same, compared to 2010—2014 (Table). For 10-year age-conditional risk of a HIV diagnosis, the highest 10-year risk experienced overall and for all races/ethnicities was at age 20, with risk decreasing with age. Compared to 2010—2014, improvements occurred for some but not all race/ethnicities. Estimating missed diagnoses in 2020 due to COVID-19, the unadjusted lifetime risk (14.60%) was 2.6% lower than the adjusted risk (14.98%) among MSM.
Conclusion: Overall, lifetime risk of HIV diagnosis improved among MSM, but this decrease was not seen across all races/ethnicities. The Ending the HIV Epidemic in the U.S. initiative is designed to scale up key HIV prevention and treatment strategies and is also working to address disparities. There is need for continued progress in HIV prevention and treatment since disparities persist by race/ethnicity among MSM.

Table. Estimated Lifetime Risk of a Diagnoses of HIV Infection Among MSM by Race/Ethnicity, United States, 2017—2021 vs. 2010—2014

Race/Ethnicity Among MSM	2017—2021 "One in n"	2017—2021 95% CI[b]	2017—2021 No. of HIV diagnoses	2010—2014[a] "One in n"	2010—2014[a] 95% CI[b]	2010—2014[a] No. of HIV diagnoses
American Indian/Alaska Native	11	10-12	581	12	11-13	487
Asian	15	15-16	3,002	14	13-14	2,910
Black/African American	3	3-3	44,608	2	2-2	49,538
Hispanic/Latino[c]	5	5 5	36,362	5	5 5	32,029
Native Hawaiian/other Pacific Islander	7	5-8	223	8	5-9	191
White	15	15-15	29,036	11	11-11	41,378
Total[d]	7	7-7	117,993	6	6-6	131,100

[a]DOI: 10.1016/j.annepidem.2017.02.003
[b]CI=Confidence Interval
[c]Hispanic/Latino persons can be of any race
[d]Includes 4,181 multiracial persons for 2017—2021 and 4,572 multiracial persons for 2010—2014

194 Quantifying HIV-1 Transmission Between People Who Inject Drugs and Other Populations in Kenya

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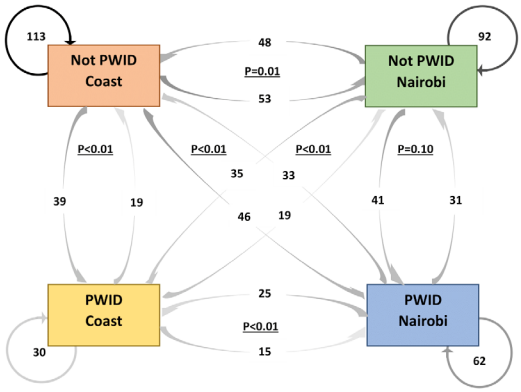
Background: Although recent modeling suggests needle-syringe programs have reduced parenteral HIV transmission among people who inject drugs (PWID) in Kenya, the prevalence in this population remains high (~14-20%, compared to ~4% in the larger population). Reducing transmission or acquisition requires understanding historic and modern transmission trends, but the relationship between the PWID HIV sub- epidemic and the general epidemic in Kenya is not well understood. Incorporating 6-times more HIV sequences from PWID in Kenya than in prior studies, we quantified rates and direction of HIV-1 transmission involving PWID and other populations from the coast and Nairobi regions.
Methods: We aligned 303 new (2018-2021) HIV-1 pol sequences from PWID and their sexual and injecting partners with 2,666 previously published Kenyan sequences. We used genetic similarity cluster analysis (thresholds: patristic distance <0.045, aLRT >0.90) and maximum likelihood ancestral state reconstruction to estimate transmission histories at the population (female sex workers, men who have sex with men, PWID, or not key population) and regional (coast or Nairobi) levels. Transition counts estimate how often an ancestor sequence gave rise to a descendant sequence from a different population and/or region.
Results: In this cohort, 1,081 participants lived with HIV, of whom 274 (25%) were not virally suppressed and 303 (28%) had sequences available. Of new PWID sequences, 55% were in phylogenetic clusters, and the vast majority were interspersed with sequences from other key populations and from those not in key populations. Only 22% of clusters containing PWID sequences included a second PWID sequence. Ancestral state reconstruction (Figure 1) identified substantial transmission between the coast and Nairobi regions and more not-PWID to PWID transmission than PWID to PWID transmission.
Conclusion: Despite recruiting PWID from local injecting networks, we found minimal linked transmission in this population. This suggests low rates of recent parenteral transmission and supports interventions to reduce sexual transmission while maintaining needle-syringe programs. Because the epidemic among PWID and other populations are inter-related, interventions within the larger population, where we also observed the most transmission between regions, may have carry-over benefits for reducing HIV prevalence in PWID and vice versa. However, greater understanding of how PWID and non-PWID populations interact is needed.

Figure 1. Trait transition counts based on ancestral state reconstruction of population (PWID and not PWID) and region (coast and Nairobi), uniformly subsampled on an HIV-1 subtype-A1 phylogeny. P-values test for disproportionate transitions in either direction, resampling tip traits to derive the null distribution.



195 Demographics Are Crucial to Interpret 95-95-95 Targets in African Populations With High ART Coverage

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Background: Characterising the shifting dynamics of HIV unsuppressed populations in Africa is crucial to tailor cost-effective interventions necessary to end AIDS by 2030.

Methods: We analyzed HIV testing and viral load data collected between 2013 and 2019 from four consecutive surveys of the Rakai Community Cohort Study (RCCS), an open population census and HIV surveillance cohort in Uganda, to estimate HIV seroprevalence and population viral load (VL) suppression over time by location, gender, and one-year age bands. Eligible participants were individuals aged 15 to 49 years old, resident in 40 communities under RCCS surveillance, four of which were hyperendemic Lake Victoria fishing communities. Surveys coincided with the implementation of Universal Test and Treat (UTT), starting in 2014 in fishing communities, and in 2017 elsewhere. All estimates were standardized to population level using census data and compared to UNAIDS 95-95-95 targets.

Results: Following UTT, viraemia decreased from 4.9% (4.6 - 5.3) at baseline to 1.9% (1.7 - 2.2) in 2019 in inland communities and from 19.2% (18.0 - 20.4) at baseline to 4.7% (4.0 - 5.5) in 2019 in fishing communities. Crucially, reflecting population pyramids and the age and gender profile of HIV burden, population-level viral load did not concentrate in the age groups furthest from achieving UNAIDS 95-95-95 targets (Figure 1). For example, by 2019, in inland communities, women aged 15-19 and men aged 20-24 were furthest from achieving 95-95-95 targets but contributed only 4.7% (2.9-7.2) and 5.5% (3.8-7.8) to population-level viraemia. In contrast, women aged 25-29 and men aged 30-34, who were close to or had achieved the 95-95-95 targets, each contributed approximately 10% to population-level viraemia in 2019.

Conclusion: While 95-95-95 targets provide a useful benchmark for HIV control, they do not take into consideration the underlying population structures and may direct interventions towards groups which contribute marginally to the unsuppressed population. In this cohort, targeting men aged 25-34 rather than men aged 15-24 would result in larger reductions in the number of unsuppressed individuals, despite larger suppression rates in the former age-group.

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196 High Prevalence of Advanced HIV Disease in Sub-Saharan Africa: An Analysis of 11 Household Surveys

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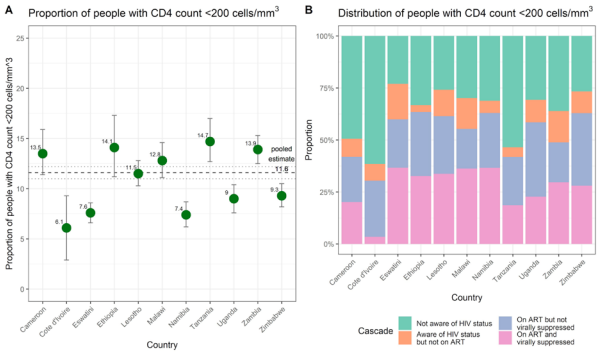
Background: Advanced HIV Disease (AHD) among adults is defined as a CD4 count <200 cells/mm³ or a World Health Organization HIV clinical stage 3 or 4. Estimates of the burden of AHD in sub-Saharan Africa are still scarce.

Methods: We analysed data from eleven Population-based HIV impact assessment (PHIA) household surveys conducted between 2015 and 2020 to determine the proportion of adults living with HIV who have a CD4 count <200 cells/mm³ stratified by demographic factors and the HIV treatment cascade. We then estimated the number of individuals with AHD in sub-Saharan Africa by combining these proportions with the latest HIV estimates from UNAIDS.

Results: A total of 21,826 people living with HIV (PLHIV) were included in this study of which 15,012 (64%) were female and the median age was 38 years (interquartile range 30–46). Pooled across the eleven countries, 11.6% (95% CI 11–12.2%) of PLHIV had a CD4 cell count <200cells/mm³ – ranging from 6.1% in Côte d'Ivoire to 14.7% in Tanzania (Figure A). AHD was more common among males than females (15.6% versus 9.5%) and more common in urban than rural areas (12% versus 11.3%). Overall, 16.1% of people who did not know their HIV status had a CD4 count <200cells/mm³, as did 21.4% of people who knew their status but were not on ART, 35.6% of people who were on ART but not virally suppressed, and 5.1% of people who were virally suppressed. Among all people with a CD4 count <200cells/mm³, 26% (95%CI 23–28%) were virally suppressed (Figure B). Extrapolating these results to sub-Saharan Africa yielded an estimated 2.1 million people living with AHD (1.8– 2.5 million); 1 million females and 1.1 million males.

Conclusion: Despite advances in ART that have transformed HIV into a manageable chronic condition, a significant number of people continue to develop AHD, even as conservatively calculated from household surveys which do not capture data from health facilities. A considerable proportion of people with AHD have a suppressed viral load; this includes people who might have recently initiated ART or have re-engaged in ART care after treatment interruptions. These figures highlight the need for urgent and innovative programmatic improvements in monitoring, prevention and diagnosis of AHD in the context of well-established and maturing ART programmes.



197 Low-Level Viremia Trends Among Persons With HIV: A 5-Country Analysis From 10 PHIA Surveys

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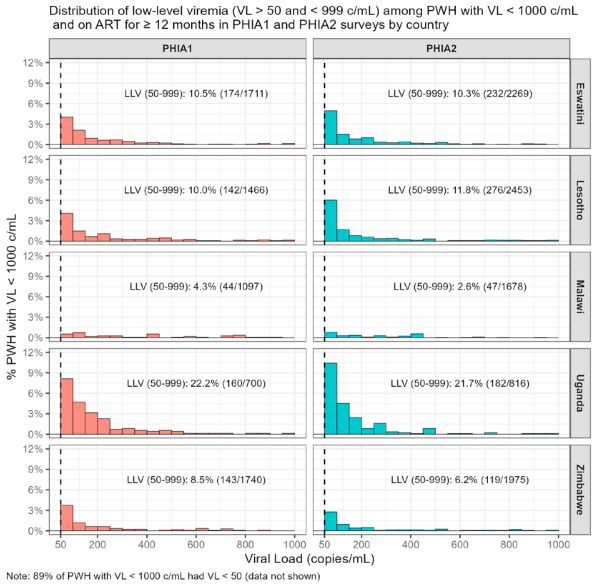
Background: The World Health Organization defines HIV viral load (VL) suppression as <1,000 copies/mL (c/mL). However, low-level HIV viremia (LLV) has been associated with drug resistance mutations and virologic failure. Limited data are available on population-based prevalence of LLV in low and middle-income settings, especially following the expansion of dolutegravir-containing regimens.

Methods: We examined temporal trends in prevalence of LLV, defined as HIV RNA >50 and <999 c/mL, among persons with HIV (PWH) aged 15y+ who reported ≥12 months of ART use, by analyzing data from five African countries (Eswatini, Lesotho, Malawi, Uganda and Zimbabwe) which conducted two sequential, nationally representative population-based HIV impact assessments (PHIA1 [2015-19] and PHIA2 [2020-21]). VL values of 'target not detected', <20, <40 and <50 c/mL were all categorized as '<50 c/mL'. Dolutegravir was qualitatively measured in PHIA 2 blood samples using analytic methods. Weighted prevalence and distribution of LLV by demographic characteristics and use of dolutegravir were assessed.

Results: Among 185,552 individuals enrolled across the 10 surveys, 27,202 were PWHIV. Of these, 17,347 (58%) reported ≥12 months of ART use; of these, 15,978 (91%) had VL <1,000 c/mL. Among those with VL <1,000 c/mL, 14,386 (89.2%) had VL < 50 c/mL and 1,519 (10.8%) had LLV. LLV varied by survey from 2.6% to 22.2% but was largely stable over time in each country. LLV was similar among younger (age <30 y) adults vs older adults (13.1% [95% confidence intervals (CI):10.8, 15.8] vs 10.5% [9.7, 11.3]). Four of five countries had a similar distribution of LLV (Figure). Overall, 70.4% of the 1,519 individuals with LLV had values >50 and < 200 c/mL, with little variation by country or survey year. In the PHIA2 surveys, across all five countries, LLV was similar among those with and without detectable dolutegravir (10.3% [8.8, 12.0] and 10.5% [9.0, 12.3]). LLV was significantly less common, however, among those with vs without dolutegravir in Eswatini (9.2% [7.9, 10.8] vs 18.1% [13.4, 24.0]) and Malawi (1.9% [1.2, 2.9] vs 7.4% [4.6, 11.6])

Conclusion: The population-based prevalence of LLV among PWH who have been on ART ≥12 months, based on two sequential, nationally representative general population surveys in five African countries, was stable and relatively low at approximately 10%. Most of the LLV values were under 200 c/mL, suggesting the risk of drug resistance and ongoing HIV transmission due to LLV are likely to be minimal.



198 A New 2023-2024 Mpox Outbreak in Brazil: Lessons From a Reemerging Neglected Disease

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Background: The 2022 mpox multi-national outbreak highly affected the Americas, with Brazil reaching 10,962 confirmed cases as of December 11th, 2023. After a peak in July-August, 2022, global mpox diagnoses decreased, and Brazil reported no cases between July and August, 2023 despite the absence of the mpox vaccine. We present initial evidence of an emerging and continuous mpox outbreak in Rio de Janeiro, Brazil, starting in September 2023.

Methods: We conducted a prospective cohort of participants (ppts) diagnosed with mpox (detectable MPXV PCR from any site) at a major infectious diseases' referral center in Rio de Janeiro, Brazil. The data were analyzed as 1st outbreak (12th, June 2022 – 31st May, 2023) and 2nd/current outbreak (September 26th, 2023 – January 7th, 2024).

Results: We enrolled 471 ppts during the 1st outbreak, with no further mpox cases until the 2nd outbreak, when we enrolled 83 ppts (1 case of reinfection). Compared to the 1st outbreak, the 2nd/current outbreak presented higher proportions of cisgender men (96% vs 90%, p=0.02) and men who have sex with men (MSM) (94% vs 81%, p=0.01). There was an increased number of sexual partners (median 3 vs 2, p<0.01) and reported anal sex (91% vs 68%, p<0.01). Age, race and clinical characteristics were similar across the outbreaks. In the 2nd outbreak, most ppts took more than 5 days from symptoms onset to first assessment (71% [n=58/82] vs 59.3% [n=259/437], p=0.05), and more ppt with mpox live with HIV (63% vs 51%, p=0.05) (Table). Among PLHIV from the 2nd outbreak (n=52), 5.9% had CD4<100 cells/mm³, 19% HIV-RNA viral load > 1,000 copies/mL, 9.6% concomitant opportunistic infections and 5.8% had suspected immune reconstitution inflammatory syndrome. During the 2nd outbreak, ppts showed a high frequency of concomitant bacterial STI (36%, n=26/72) and HCV past/current infection (11%, n=9/83). The hospitalization rate was 12% (n=10/83) and as of January 7th, 2024, 18 ppts were still under follow-up.

Conclusion: This marks the inaugural report of a recent mpox outbreak in Brazil, following a period without diagnosed cases, once again disproportionately affecting MSM and PHIV individuals. Our findings suggest ongoing unnoticed community mpox transmission in Rio de Janeiro, Brazil, emphasizing the crucial need to enhance surveillance strategies to promptly identify emergent STIs in the context of HIV care and prevention services. Vaccines should be made available in LMIC to prevent new outbreaks.

Table. Sociodemographic, behavioral and clinical characteristics of participants diagnosed with mpox, according to the outbreak, first (June, 2022 – May, 2023) or second/current (September, 2023 – January, 2024)

	First outbreak (June, 2022 – May, 2023), N = 471[1]	Second outbreak (September, 2023 – January, 2024), N = 83[1]	p-value[2]
Median age (IQR)	33.00 (28.00, 40.00)	31.00 (28.00, 38.50)	0.33
Cisgender men	422/471 (90%)	80/83 (96%)	0.02
Men who have sex with men	364/401 (90.8%)	78/80 (97.5%)	0.01
Black or *pardo*	235/390 (60.3%)	57/82 (69.5%)	0.27
Median number of sex partners in the 30 days before symptoms onset (IQR)	2.00 (1.00, 3.00)	3.00 (1.00, 5.00)	<0.01
Reported anal sex in the 30 days before symptoms onset	195/286 (68%)	75/82 (91%)	<0.01
Living with HIV	234/459 (51%)	52/83 (63%)	0.05

[1]n (%); Median (IQR)

[2]Fisher's exact test; Wilcoxon rank sum test; Pearson's Chi-squared test

199 Vaccine Effectiveness Against COVID In-Hospital Mortality by HIV Status Across SARS- CoV-2 Variants

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Background: There is limited data on the impact of COVID-19 vaccines on mortality reduction among people living with HIV (PLHIV) across the different SARS-CoV-2 variant waves. We assessed the impact of COVID- 19 vaccine in reducing in-hospital mortality among PLHIV relative to HIV negative population during the different SARS-CoV-2 variant waves.

Methods: We analyzed individual-level data from the WHO Global Clinic Platform comprising 198,886 hospitalized children (0-18 years) and adults (>18 years) with information on COVID-19 vaccine from 43 countries. We used Cox regression to evaluate association of COVID-19 vaccine with in-hospital mortality across SARS-CoV-2 pre-Delta, Delta and Omicron variant waves.

Results: Among HIV negative populations, vaccinated individuals had a 40% lower risk of death (aHR 0.60, 95%CI 0.56-0.63) during pre-delta, 38% lower risk during delta (aHR 0.62, 95%CI 0.57-0.68) and 41% lower risk (aHR 0.59, 95%CI 0.53-0.65) during the omicron variant wave compared to unvaccinated people. Compared to the HIV negative unvaccinated population, vaccinated PLHIV had a significant higher risk of death during pre-delta and omicron variant wave (aHR 1.76 95%CI 1.18-2.64) and (aHR 1.44, 95%CI 1.08-1.93) respectively. Among unvaccinated populations, PLHIV faced significantly higher mortality risks compared to HIV negative individuals across variant waves: aHR 1.97 (95%CI 1.81-2.16) during pre-delta, aHR 2.46 (95%CI 2.12-2.85) during delta and aHR 2.43 (95%CI 2.10-2.81) during the omicron variant wave. Conversely, vaccinated PLHIV had a 60% lower risk of in-hospital death during the pre-delta (aHR 0.40, 95%CI 0.31-0.51), 50% lower risk during delta (aHR 0.50, 95%CI 0.33-0.75) and 54% lower risk (aHR 0.46, 95%CI 0.36-0.59) during the omicron variant wave compared to unvaccinated PLHIV.

Conclusion: Vaccinated PLHIV had a significant reduced risk of death compared to the unvaccinated PLHIV across the three variant waves. Vaccination reduced the risk of death among HIV negative people compared to the unvaccinated population, and we observed the same pattern among PLHIV but with a lower protective effect when compared to the unvaccinated HIV negative group. Overall, the risk of death remained relatively high among vaccinated and unvaccinated PLHIV across pre-delta, delta and omicron variant waves. These findings highlight the need to implement WHO guidelines recommending booster vaccine for populations most-at-risk of severe COVID-19 outcomes including PLHIV.

200 Together TakeMeHome: Launch of a National HIV Self-Test Distribution Program, March-December 2023

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Background: HIV testing is the first step to accessing both HIV treatment and prevention services. HIV self- testing is a key strategy for overcoming barriers to HIV testing.

Methods: The Together TakeMeHome (TTMH) program is a CDC-sponsored, direct-to-consumer, HIV self- test distribution program. CDC's Let's Stop HIV Together campaign implemented marketing on platforms including social media, dating apps, and search and display advertising. Marketing was primarily to men who have sex with men (MSM), especially Black and Hispanic MSM, Black women, and transgender women. Building Healthy Online Communities developed messages and in-app buttons in partnership with dating apps including Grindr and BLK. Persons ages 17+ in the US and Puerto Rico were eligible to order 1-2 HIV self-tests every 90 days. Ordering wasn't restricted by prior HIV diagnosis or PrEP usage, but persons reporting ARV use were encouraged to give ordered HIV self-tests to others. A short survey was offered post-order with an opt-in for follow-up surveys. Ten- and 60-day follow-up surveys on their HIV self-test experience were conducted.

Results: In March 2023, TTMH launched, with 181,558 orders placed in the first 9 months. Most orders (86%) were for two tests, with 337,812 total tests distributed. Most participants (109,956, 62%) came from the Grindr app. Sixty percent (108,715) of all orders contained enough information to describe participants in terms of the priority populations. Of these 61% were from men reporting male partners in the past 12 months (18% from Black MSM and 33% from Hispanic MSM), 10.7% from gender diverse persons, and 10% from Black women. Most orders (26%) were placed by persons who had never tested for HIV, or who had last tested >12 months ago (27%). Over half of participants, 86,143 (56.5%) opted into follow-up communications and as of December 11, 2023, 5,294 (6.1%) completed the 10-day survey. Among them, 109 (2.1%) reported a positive result with the HIV self-test, 6.5% sought additional STI testing, and 4.5% self-reported starting PrEP after receiving the self- test.

Conclusion: Overall, the TTMH program has very high demand, with many persons from priority populations accessing HIV testing for the first time. Many sought additional clinical services after HIV self-testing. It is important for clinicians to be aware of the demand for HIV self-testing and how it may fit into their patient care, including preparing for discussions about HIV follow-up testing, pre-exposure prophylaxis and treatment.

201 Incidence of Health Facility Switching and HIV Viral Rebound in Uganda: A Population- Based Study

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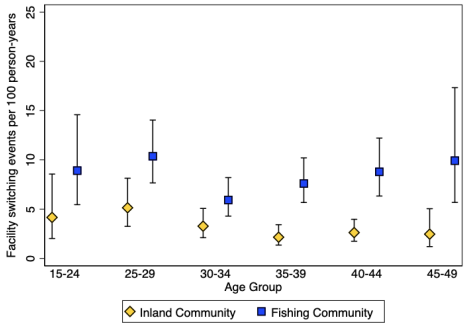
Background: Prior studies have shown that a sizeable fraction of persons on antiretroviral therapy (ART) in Africa, once believed to be care-disengaged, have actually transferred to other healthcare facilities for continued HIV treatment. However, the relationship between facility switching and virologic outcomes, specifically HIV viral rebound, among persons on ART is poorly understood.

Methods: We used population-level data collected between 2015 and 2020 from 40 continuously surveilled communities, including four hyperendemic Lake Victoria fish landing sites, in the Rakai Community Cohort Study. Persons aged 15-49 years with serologically confirmed HIV infection self-reporting current ART use and contributing ≥1 follow-up visits were included in the study. Facility switching and virologic outcomes were assessed between two consecutive study visits (i.e., index and follow-up visits, ~18-month visit-interval). Persons attending different HIV treatment facilities between index and follow-up visits were classified as having switched facilities. The primary outcome was laboratory-confirmed viral rebound, defined as ≥200 HIV RNA copies/mL at follow-up visit among individuals exhibiting viral load suppression (<200 copies/mL) initially. Multivariable Poisson regression with generalized estimating equations and robust standard errors was used to model associations between facility switching and viral rebound, reported as adjusted incidence rate ratios (adjIRR) with 95% confidence intervals (95%CI).

Results: Overall, 2,257 persons self-reporting current ART use (median age: 35 years, 65% women, 92% virally suppressed at index visit) contributed 3,335 visit-pairs and 5,959 person-years (py) to the analysis. Facility switching was common (4.8 switches per 100 py, 95%CI: 4.2-5.5) and highest in persons aged 15-29 years (7.3 switches per 100 py, 95%CI: 5.9-9.1), fishing community residents (7.4 switches per 100 py, 95%CI: 6.3-8.6), and in-migrants (10.4 switches per 100 py, 95%CI: 8.3-13.1). Among initially suppressed persons (n=2,076), the incidence of viral rebound was over twice as high in persons switching facilities relative to those attending the same clinic over the visit-interval (adjIRR 2.27, 95%CI: 1.16-4.45).

Conclusion: Facility switching was common and associated with viral rebound among initially suppressed persons. Investments in more agile, person-centered HIV care models for mobile clients are needed to address system inefficiencies and bottlenecks that can disrupt HIV treatment continuity.



202 Lakeside Combined HIV and Schistosomiasis Services in Malawian Fishermen: A Cluster Randomized Trial

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Background: Undiagnosed HIV and Schistosomiasis are highly prevalent among fishermen in the Great Lakes region of Africa. Combined interventions to address barriers to diagnosis, treatment and prevention for both infections are urgently needed.

Methods: Between March 2022-January 2023, we conducted a cluster-randomized trial with 45 lakeside "boat-team" (clusters) in Lake Malawi. Clusters were randomly allocated (1:1:1) to: 1) enhanced standard of care (SOC), with beach clinics offering HIV testing and referral, and schistosomiasis presumptive treatment (praziquantel) advertised by leafleting; 2) peer-educator (PE), with a peer-nominated boat crew member trained to promote beach clinic services; or 3) peer-distributor-educator (PDE), where PEs distributed oral HIV self-test (HIVST) kits in addition to promoting beach clinic services. The co-primary outcomes (measured at 28 days) were: composite self-reported ART initiation, or booked for voluntary male medical circumcision (VMMC); and 1 S. haematobium egg seen on light microscopy of the filtrate from 10mls urine ("egg-positive"). Secondary outcomes included self-reported HIV testing in the PDE arm, and observed HIV testing in eSOC and PE arms as well as perceived acceptability of HIV pre-exposure prophylaxis (PrEP). Analyses were by intention-to-treat with multiple imputation while accounting for clustering and any baseline imbalance.

Results: Of 6036 fishermen screened, 5207 (86.3%) were eligible: (SOC: 1745 [87.6%]; PE: 1687 [81.9%]; PDE: 1775 [89.5%]). Participant characteristics were balanced across arms. Mean age was 33y (sd: 12.3), 3032 (58.3%) were literate, 5.9% (308) reported taking ART, and 44% were egg-positive for S. haematobium

egg at baseline. 28-day follow-up was high (SOC: 1519 [87.0%]; PE: 1450 [86.0%]; PDE: 1559 [87.8%]). Outcomes are shown in Table 1. ART initiation or VMMC booking was higher in the PE arm (PE vs SOC: aRR:1.16; 95%CI:0.99; 1.37; p = 0.069) whereas the PDE arm was associated with significant reduction in active Schistosomiasis compared to eSOC (aRR:0.80; 95%CI:0.69; 0.94; p = 0.005).

Conclusion: Peer educators marginally increased uptake of ART and VMMC, whereas the addition of HIVST kit distribution, significantly reduced the prevalence of active Schistosomiasis. Combining HIV and Schistosomiasis services using beach clinics is feasible and would improve current policy and practice.

Table 1: Primary and secondary outcome results measured at 28 days

	eSOC arm (clusters=15; N=1745)	PE arm (clusters=15; N=1687)	PDE arm (clusters=15; N=1775)
Primary outcome 1: Fishermen with active schistosomiasis (%)	292 (16.7%)	263 (15.6%)	241 (13.6%)
Adjusted RR* (95% CI); p-value	1	0.92 (0.79; 1.07); p = 0.277	0.80 (0.69; 0.94); p = 0.005
Primary outcome 2: Fishermen starting ART or undergoing VMMC (%); excludes those on ART	230 (13.2%)	281 (16.7%)	215 (12.1%)
Adjusted RR* (95% CI); p-value	1	1.16 (0.99; 1.37); p = 0.069	0.88 (0.74; 1.05); p = 0.149
Secondary outcome: Fishermen tested for HIV (%), excludes those on ART	1406 (85.2%)	1315 (84.4%)	1483 (88.0%)
Adjusted RR* (95% CI); p-value	1	1.00 (0.99; 1.01); p = 0.526	1.01 (1.01; 1.02); p = 0.009
Secondary outcome: Fishermen approving use of pre-exposure prophylaxis (%)	1130 (64.8%)	1329 (78.9%)	1238 (69.8%)
Adjusted RR* (95% CI); p-value	1	1.22 (1.17; 1.27); p < 0.001	1.08 (1.03; 1.13); p < 0.001

MI: multiple imputation; eSOC: enhanced standard of care; PE: peer educators; PDE: peer distributor educator; RR: risk ratio; CI: confidence interval; ART: antiretroviral therapy; VMMC: voluntary male medical circumcision. *Adjusted for clustering, literacy and HIV testing in last 12 months and VMMC status. Intra cluster correlation coefficient (ICC) = 0.08

203 Improving Posthospital Outcomes in People With HIV: A Multicenter Randomized Trial in Tanzania

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Background: In spite of the widespread availability of antiretroviral therapy (ART), people living with HIV (PLWH) still experience poor outcomes with high mortality during and after hospital admissions. Delayed linkage to HIV care after hospital discharge is a major risk factor. We tested a linkage case management intervention ("Daraja" = "Bridge" in Kiswahili) to address barriers to HIV care engagement after hospital discharge.

Methods: We conducted a single-blind, individually randomized trial to evaluate the effectiveness of the Daraja intervention (NCT03858998). PLWH who were either ART-naïve or ART defaulters were recruited from 20 hospitals in northern Tanzania. Participants were randomized before hospital discharge to receive either the Daraja intervention or standard of care. The Daraja intervention consisted of 5 sessions conducted by a social worker over a 3 month period. The primary outcome of all-cause mortality at 12 months was confirmed by death certificates, hospital records, or verbal autopsies. Secondary outcomes related to HIV clinic attendance, ART use, and viral load suppression were extracted from HIV medical records.

Results: We enrolled 500 hospitalized PLWH between March 2019 and February 2022. The mean age was 37 years, 77% were female, 35% had CD4 counts <100 cells/μL, 75% were ART naïve, and characteristics were similar between arms. Intervention uptake was high with 86% of expected sessions successfully completed; 496 participants completed 12 months of follow-up (2 withdrew consent; 2 lost-to-follow-up). Eighty-five (17%) participants died; mortality did not differ by study arm (43 vs. 42 deaths, p=0.96). Half of deaths occurred within 30 days after discharge. By contrast, the Daraja intervention reduced time to HIV clinic attendance and ART initiation (p<0.0001). Intervention participants also achieved higher rates of HIV clinic retention (87% vs. 76%, p=0.005), ART adherence (81% vs. 68%, p=0.002), and HIV viral load suppression (79% vs. 67%, p=0.01) at 12 months.

Conclusion: In hospitalized PLWH, a linkage case management intervention was effective in accelerating the HIV continuum of care but did not reduce mortality. Intervention recipients who survived to 12 months had higher rates of ART adherence and viral load suppression. Our trial highlights the need for earlier diagnosis of HIV infection and for continued improvement of hospital and post-hospital care in the global effort to get to zero AIDS-related deaths.

204 What Are the Outcomes for Established Clients Enrolled in DSD During the First 3 Years on ART?

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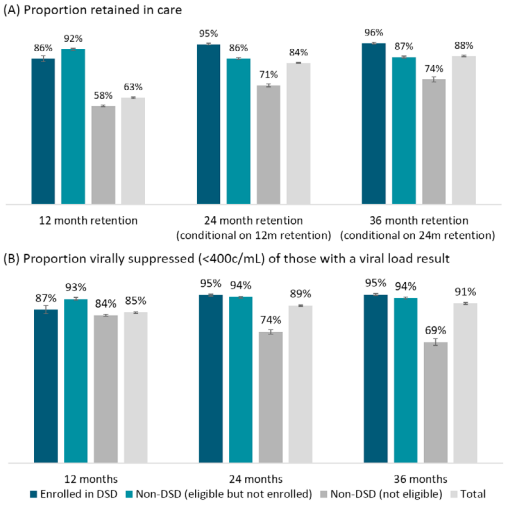
Background: Replacing routine clinic visits with differentiated service delivery (DSD) models for HIV treatment could benefit DSD clients and the health system, but its value depends on maintaining or improving patient outcomes. South Africa's DSD models include facility pick-up points, external pick-up points and adherence clubs, which facilitate easier access to medication. We conducted a prospective record review to compare outcomes of DSD clients to those eligible but not enrolled in DSD in South Africa.

Methods: Among adults initiating ART between 2016-2021 at 18 primary healthcare facilities, we compared retention and viral suppression for DSD clients to those DSD eligible but not enrolled using TIER.Net records. For reference we also included those not DSD eligible. DSD eligibility was defined per guidelines (2016-2019: 2 suppressed viral load (VL) (<400c/mL) and ≥12 months ART; 2020-2021: 1 suppressed VL (<50c/mL) and ≥6 months ART). DSD enrollment was defined as any DSD interaction in the previous 12 months before the 12, 24, or 36 month time point. DSD eligibility and enrollment were reclassified every 12 months. Outcomes were assessed at 12, 24, and 36 months after ART initiation. 12, 24 and 36 month retention was defined as attending a visit 13-24 months, 25-36 months and 37-48 months after ART initiation, respectively. Outcomes after 12 months were conditional on being retained in the previous period.

Results: 59,118 clients (67% female, 17% age 18-24) initiated ART during the study period. Proportion enrolled in DSD was 2% (N=1,431), 23% (N=7,238), 37% (7,845) by 12, 24 and 36 months; eligible but not enrolled was 12% (N=7,339), 48% (N=15,087), 46% (N=9,761) by 12, 24 and 36 months. Retention and viral suppression at 12 months were lower for those in DSD vs eligible. Retention at 24 and 36 months was higher for those in DSD vs eligible (relative risk: 1.10 [95% confidence interval 1.07-1.13]; 1.09 [1.06-1.13]). Viral suppression among those with a VL at 24 and 36 months was similar between those in DSD vs eligible. There were no differences in outcomes by gender or age group.

Conclusion: South African DSD clients had higher retention and similar viral suppression at 24 and 36 months after ART initiation. The observed decrement to outcomes for DSD clients at 12 months requires further examination, particularly as new guidelines allowing DSD enrollment ≥4 months on ART. There was a missed opportunity for DSD enrollment as most of those eligible were not enrolled ≤ 3 years on ART.

Figure. Facility-based retention and viral suppression at 12, 24, and 36 months after ART initiation, by DSD status



205 Opt-Out HIV Testing in Emergency Departments Successfully Addresses Key Gaps in Testing

Lisa Hamzah[1], Kathryn Childs[2], Ian S. Cormack[3], Olubanke Davies[4], Roddy Font[5], Lewis Haddow[6], Elizabeth Hamlyn[2], Kathryn Harrop[7], Rachel Hill-Tout[8], Steven Kegg[9], Iesha Lovatt[7], Larissa Mulka[2], Melanie Rosenvinge[9], Lucy Wood[9], for the South London HIV ED Opt Out Testing Group

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Background: 'Getting to zero' and ending new HIV transmissions by 2030 is a major focus for HIV prevention in the UK. To achieve this, national funding was provided to expand opt-out testing for HIV across all South London emergency departments (ED) from April 2022 for attendances aged over 16-18 years having a blood test for any reason. We describe new HIV diagnoses in South London during the first 12 months of testing and compare HIV prevalence and new diagnoses rates in ED to national published data.

Methods: Demographic data were collated and summarised for all new HIV diagnoses across South London ED. Prevalence data were calculated, including previously known HIV diagnoses, overall and by region and compared to local published prevalence data. The project was registered as service evaluation.

Results: Between April 2022 and March 2023, across 10 acute hospital EDs, there were 446881 eligible attendees and 335263 HIV tests performed. HIV test uptake increased from 61% in April 22 to 80% in March 2023. We identified 128 new HIV diagnoses: 65% male, 72% heterosexual, median age 43.5 years (range 16- 77), 55% black ethnicity, 84% within the lowest multiple deprivation deciles (1-5). 92% were engaged in care within median (IQR) 5 (2-13) days with median (IQR) baseline CD4 271.2 (79-385.3 cells/uL), mean (SD) viral load 5.0 (1.2) log copies/ml. 69% had a CD4<350 and 41% CD4<200 cells/uL. 75% overall, 64% with CD4<350 and 35% with CD4<200, did not report HIV indicator conditions at presentation to ED. 22% were subsequently diagnosed with an AIDS related illness. After median (IQR) 6.8 (3.8-9.9) months follow up, median CD4 was 350 (210-600) and 70% had an undetectable viral load. New diagnosis rates in the ED population exceeded the overall new diagnosis rates in London by almost 6-fold and 4-fold in South-East and South-West London respectively. In South-East London, HIV prevalence in ED was higher than previous reported estimates across London (Table).

Conclusion: ED HIV opt out testing was successful in achieving high rates of new diagnoses, in areas of high deprivation, with excellent linkage to care. Over two-thirds of diagnoses were late (CD4<350) and less than a quarter had indicator conditions at presentation. This intervention is a powerful tool to reach individuals who would not have otherwise been identified, reduce health inequalities and address key gaps in testing for groups such as heterosexual men, who may not attend traditional testing services such as antenatal and sexual health.

	New HIV Diagnoses (per 100,000)	HIV Prevalence (per 1,000)
London (2021 data)* [95% CI]	7.6 [7.1,8.2]	5.4 [5.29,5.41]
South-West London Emergency Departments [95% CI]	29.8 [21.3, 38.3]	5.2 [4.8, 5.5]
South-East London Emergency Departments [95% CI]	44.5 [34.7, 54.3]	8.1 [7.7,8.5]

*Public Health Data https://fingertips.phe.org.uk CI: confidence interval

206 Few Discordant HIV Ag/Ab and RNA Test Results Among Persons in a National Cohort of PrEP Users

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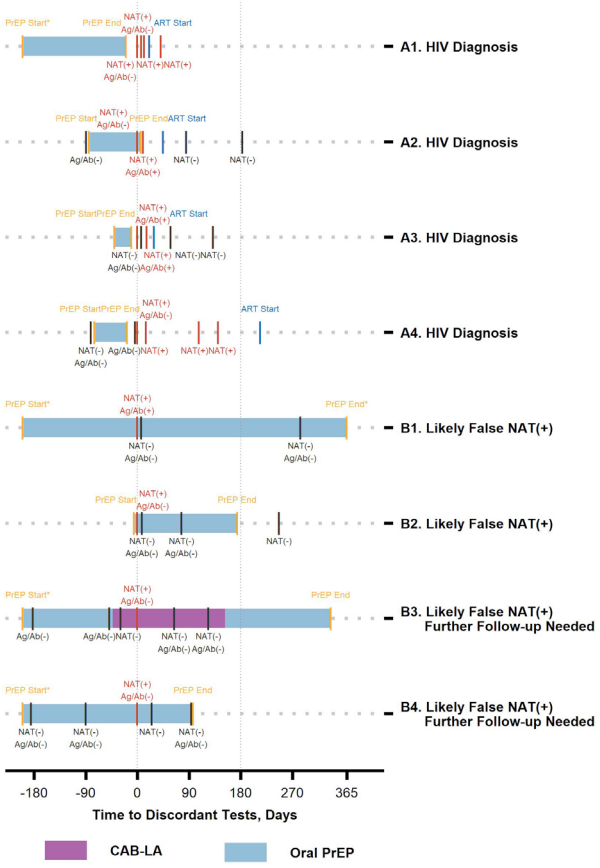
Background: PrEP users can have ambiguous HIV test results for detection of primary infection. The CDC 2021 PrEP guidelines recommend HIV RNA testing for PrEP initiation and monitoring. We evaluated occurrence of discordant HIV test results in oral and long-acting cabotegravir (CAB-LA) PrEP users in a large real-world cohort of PrEP users.

Methods: We analyzed the HealthVerity HIV cohort with linked longitudinal medical claims, antiretroviral prescriptions, and laboratory testing records. Our primary outcomes were discordant HIV Ag/Ab and RNA test results, new HIV diagnoses, and Long-acting Early Viral Inhibition (LEVI) cases among PrEP users. We used a validated algorithm and identified persons prescribed oral or injectable PrEP and extracted all their laboratory records. We defined a "combined test" as both Ag/Ab and RNA testing within 7 days. We analyzed all tests from 30 days before the first PrEP prescription through 30 days after last prescription. Among persons with discordant results, we reviewed all their laboratory tests, diagnosis records, and ARV prescriptions.

Results: Among 30 548 PrEP users, we identified 9090 combined tests in 5391 individuals; 8995 (99.0%) were same-day tests. HIV Ag/Ab and RNA results were concordant for 9070 (99.8%) tests with 18 dual positives (+) in 17 persons, and 9052 dual negatives (-) in 5374 persons. We identified 14 combined tests in 12 persons with Ag/Ab(-) and RNA(+) results, accounting for 0.15% of all combined tests. Review of records found 4 HIV diagnoses; 4 likely false positive RNA tests (with repeated dual (-) tests and follow-up >30 days); and 4 inconclusive results (insufficient follow-up) (Figure). Excluding inconclusive cases, RNA tests had a false positive rate (FPR) of 0.04% and a positive predictive value (PPV) for HIV infection of 84% among PrEP users. No LEVI cases were observed among 439 CAB-LA users. We also found 6 discordant tests in 4 patients with Ag/Ab(+) and RNA(-) results. Of these, one person had a likely false positive Ag/Ab test (FPR of 0.01%, PPV 94.4%), while 3 persons had insufficient follow-up.

Conclusion: Discordant combined test results among PrEP users were rare and a third of discordant tests identified a new HIV diagnosis, accounting for 19% of all diagnosed HIV infections. Combined testing resulted in similar early HIV diagnoses rates and potential false positive NAT rates. The FPR of Ag/Ab testing was low. Further assessment of predictive values and cost-effectiveness of HIV RNA testing of PrEP users is warranted.



207 Missed Opportunities to Prevent Congenital Syphilis in Antenatal PrEP Services in South Africa

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Background: Pregnant women are a key population for HIV prevention through pre-exposure prophylaxis (PrEP) services and women at risk of HIV acquisition are also at risk of syphilitic infection. There is growing concern around congenital syphilis globally, yet there are few insights into the burden of syphilis in pregnant women on PrEP and their infants in Africa.

Methods: We evaluated syphilis positivity and congenital syphilis in a cohort of pregnant women in Cape Town without HIV (>16 years) on oral PrEP in between March 2022 and December 2023. Per local standard of care, women were tested

with a rapid treponemal test on site to guide treatment, followed by laboratory testing (TPHA confirmed with RPR). Maternal and infant data were abstracted from antenatal care (ANC) files, neonatal clinical records and laboratory testing data. We evaluated risk factors of maternal syphilis using logistic regression, adjusted for maternal age.

Results: Of 500 pregnant women attending routine primary care clinics on oral PrEP, 496 (99%) were tested for syphilis at least once in ANC: median age was 25 years, median gestation was 28 weeks. At first ANC visit, 413 women received a rapid Treponemal test (83%); 26 tested positive (6.3%). Of 496 women lab tested, 51 were TPHA+ (10.3%) and 23 RPR+ (overall prevalence of current infection=4.6%, 95% CI=3.1, 6.9). After the first ANC visit, 281 women (59% of 473 who did not have prevalent syphilis) were retested at least once during pregnancy; of these, 8 had incident syphilis detected (incidence, 2.9%; 95% CI=1.5, 5.5). Overall, 31 of 496 pregnant women tested were RPR+ (6.3%, 95% CI=4.3, 8.8). In those RPR+, 16 (52%) were 'adequately treated' with 3 doses of penicillin >30 days before delivery, and 15 of 31 (48%) had 4-fold RPR titer decrease. Two congenital syphilis cases were identified (RPR titer 4x mother's RPR; 6.4% vertical transmission and 0.4% population prevalence) both with maternal diagnosis and treatment <30 days before delivery. Age-adjusted risk factors associated with maternal syphilis included younger age, reporting no sex partners, experiencing recent intimate partner violence and alcohol use (Table).

Conclusion: These novel data demonstrate a remarkably high occurrence of syphilis in pregnancy among women enrolled in antenatal PrEP services, with half of women not fully treated in pregnancy leading to preventable congenital syphilis. There is a clear and urgent need to integrate syphilis prevention and treatment into antenatal PrEP services.

Table 1. Baseline demographics and health characteristics among pregnant women on oral PrEP tested for syphilis during pregnancy in Cape Town, South Africa (March 2022- December 2023)

	Overall (N=500)	RPR negative (N=469, 94%)	RPR+ during pregnancy (N=31, 6.3%)	OR (95% CI)	Age adjusted OR (95% CI)
Maternal age (median, IQR) years	25 (21 - 31)	26 (21 - 31)	24 (22 - 28)	0.96 (0.90, 1.02)	-
16 – 24	224 (45%)	203 (43%)	21 (68%)	**2.75 (1.30, 6.22)**	-
Relationship status					
Married / cohabiting	175 (35%)	166 (35%)	9 (29%)	-	-
Not married / not cohabiting	283 (57%)	268 (57%)	15 (48%)	1.03 (0.45, 2.51)	0.88 (0.36, 2.23)
No partner	42 (8%)	35 (8%)	7 (23%)	**3.69 (1.24, 10.6)**	**3.07 (0.98, 9.22)**
Intimate partner violence (IPV) experienced in past 12m	43 (9%)	37 (8%)	6 (19%)	**2.80 (0.99, 6.87)**	**2.81 (0.99, 6.91)**
Any alcohol use in last 12m	212 (42%)	191 (41%)	21 (68%)	**3.06 (1.44, 6.91)**	**2.89 (1.35, 6.58)**

208 Efficacy and Safety of Weekly Islatravir Plus Lenacapavir in PWH at 24 Weeks: A Phase II Study

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Background: Islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor, and lenacapavir (LEN), a capsid inhibitor, have potent anti-HIV-1 activity and pharmacokinetic profiles permitting once-weekly (QW) oral dosing. We investigated efficacy and safety of ISL+LEN in virologically suppressed people with HIV-1.

Methods: In this Phase 2, randomized, open-label, active-controlled study (NCT05052996), virologically suppressed adults on bictegravir/emtricitabine/tenofovir alafenamide fumarate (B/F/TAF) were randomized to either oral ISL 2 mg + LEN 300 mg QW or to continue daily B/F/TAF. The primary efficacy endpoint was the proportion of participants with HIV-1 RNA ≥ 50 copies/mL (FDA-defined Snapshot algorithm) at Week 24 (W24). Safety parameters, including CD4+ T-cell and absolute lymphocyte counts (ALC) and adverse events (AEs), were also evaluated.

Results: A total of 104 participants were randomized and dosed (52/group); median age (range) was 40 (26–76) years, and 19 (18.3%) were female at birth. One (1.9%) participant in the ISL+LEN group (whose baseline HIV RNA was 251 copies/mL) had HIV-1 RNA > 50 copies/mL at W24, then suppressed on ISL+LEN (64 copies/mL at W24, < 50 copies/mL at W30); no participant in the B/F/TAF group had HIV RNA > 50 copies/mL at W24. Forty-nine (94.2%) and 48 (92.3%) participants maintained viral suppression in the ISL+LEN and B/F/TAF groups at W24, respectively; 2 (3.8%) and 4 (7.7%) participants had no data at W24 due to discontinuation or missing visits. No between-group differences were seen in changes in CD4+ T-cell counts or ALC at W24 (Table). AEs occurred in 39 participants (75.0%) on ISL+LEN and 38 (73.1%) on B/F/TAF. The most common AEs in ISL+LEN participants included diarrhea (n=7; 13.5%), upper respiratory infection (n=6; 11.5%), and arthralgia, pain in extremity, and fatigue (each n=3; 5.8%). No grade 3 or 4 AEs related to study drug were reported. Two participants discontinued ISL+LEN due to AEs unrelated to drug (large intestine perforation/renal colic; hepatitis B).

Conclusion: In this Phase 2 study, the first QW oral ARV regimen of ISL+LEN maintained viral suppression at W24 and was well tolerated. The ISL 2 mg dose showed no clinically significant decreases in CD4+ T-cell counts or ALCs as were seen previously with higher daily, weekly, and monthly doses of ISL.

Parameter	Median (Q1, Q3)	
	ISL+LEN (n=52)	B/F/TAF (n=52)
CD4+ T-cells/μL		
Baseline	711 (623, 862)	765 (688, 890)
W24 (change from baseline)[a]	14 (–102, 133)	–7 (–128, 67)
ALC x10³/μL		
Baseline	1.84 (1.61, 2.25)	1.82 (1.53, 2.19)
W24 (change from baseline)[b]	0.04 (–0.22, 0.20)	0.01 (–0.22, 0.25)

ANOVA: [a]p=0.3477; [b]p=0.6301. ALC: absolute lymphocyte count; B: bictegravir; F: emtricitabine; ISL: islatravir; LEN: lenacapavir; Q: quartile; TAF: tenofovir alafenamide fumarate; W: week.

209 HepB-CpG Vaccine Is Superior to HepB-alum in People With HIV and Prior Vaccine Nonresponse: A5379

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Background: Conventional Hepatitis B surface antigen (HBsAg)-based vaccines achieve seroprotection response (SPR, HBsAb≥10 mIU/mL) in 35-80% of people with HIV (PWH) with 3 doses. HepB-CpG (vaccine with a TLR-9 agonist adjuvant) achieves high SPR in PWH, but limited data exist for non-responders to conventional vaccines.

Methods: ACTG A5379 is an ongoing, open-label study to evaluate immunogenicity of HepB-CpG in PWH. Prior vaccine non-responders were on ART with CD4 ≥100 cells/mm³ and HIV-1 RNA <1000 copies/mL without past or present serologic evidence of HBV or HBV vaccine response. Participants were randomized 1:1:1 to: 2 doses of HepB-CpG intramuscularly (IM) (20 mcg recombinant HBsAg, 3000 mcg CpG 1018® adjuvant) at Wks 0 and 4 (2-CpG); 3 doses of HepB-CpG IM at Wks 0, 4, 24 (3-CpG); or 3 doses of HepB-alum IM (20 mcg recombinant HBsAg) at Wks 0, 4, 24 (3-alum). Primary SPR was defined at Wk12 for 2-CpG and Wk28 for 3-CpG and 3-alum. We assessed noninferiority (NI) of 2-CpG vs 3-alum with a 10% margin and superiority of 3-CpG vs 3-alum. Predefined primary analysis set excluded missed sample collection. Safety was also assessed.

Results: Of the 561 eligible participants enrolled at 41 sites from 10 countries: 64% were male, 42% Black, 35% White, 17% Asian, 22% Hispanic. Median age was 46 years (range 18-70), 56% enrolled in the US, 21% Africa, 17% Asia, 6% S. America. Median CD4 was 638 cells/mm³, 94% had HIV-1 RNA <40 copies/mL, 29% BMI >30, and 13% diabetes. 96% completed all prescribed doses. The analysis included 505 participants (99% of 508 in the primary analysis set). SPR was achieved in 93% of 2-CpG (n=174), 99% of 3-CpG (n=169), and 80% of 3-alum (n=162). SPR difference between 2-CpG and 3-alum was 13% (97.5% CI: 5%, 22%), achieving NI and indicating superiority. SPR of 3-CpG was superior to 3-alum with a difference of 19% (97.5% repeated CI: 11%, 27%). By Wk12, >90% of participants who received HepB-CpG achieved SPR (Figure 1). Three doses of HepB-CpG achieved a higher proportion with titers >1000 mIU/ml compared to two, and to 3 doses of HepB- alum. One or more AEs related to

vaccines were experienced by 33%, 45% and 36% of 2-CpG, 3-CpG and 3- alum participants, respectively, mostly Gr 1 and 2. Vaccination site pain, fatigue, headache, malaise and myalgia were most frequent.

Conclusion: In this study of PWH with prior vaccine non-response, both 2 and 3 doses of HepB-CpG achieved superior SPR compared to 3 doses of HepB-alum. No unexpected safety issues were observed.

210 Efficacy, Safety, and Immunogenicity of H56:IC31 Vaccine for Prevention of Recurrent TB

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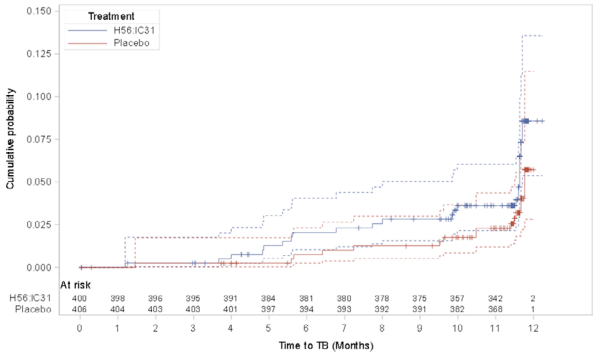
Background: Persons with tuberculosis (TB) who are deemed cured on completion of treatment remain at higher risk of recurrent disease. The TB vaccine candidate H56:IC31 has been shown to be safe and immunogenic in phase 1/2 studies, including in treated TB patients. Whether H56:IC31 can reduce the risk of recurrent TB is unknown.

Methods: In a multicenter, double-blind, randomized, placebo-controlled, event-driven trial in South Africa and Tanzania, we enrolled participants aged 18-60 years, without HIV, who were sputum smear-negative upon completion of treatment for drug-sensitive pulmonary TB. Participants were randomly assigned (1:1) to receive two doses of H56:IC31 or placebo (56 days apart) and followed up for 1 year. The primary endpoint was recurrence of culture-confirmed pulmonary TB. Vaccine efficacy (VE) estimates with 95% confidence interval (95%CI) were derived from Cox proportional hazard models. Secondary endpoints included TB relapse or reinfection as differentiated by whole genome sequencing of paired sputum samples, safety, and immunogenicity.

Results: 831 participants (mean age 34.7 years; 27.6% female; 66.1% black African; 76% from South Africa) were enrolled; 415 received H56:IC31 and 416 placebo. In the primary analysis, recurrent TB was observed in 23 (12 relapse; 8 reinfection; 3 indeterminate) of 400 participants (5.8%) in the H56:IC31 group; and 14 (6 relapse; 7 reinfection; 1 indeterminate) of 406 participants (3.4%) in the placebo group. VE for recurrence was -73.8% (95%CI:-246.9 to 9.8%; P=0.10). VE for relapse was -116.1% (-522.2 to 16.3%; P=0.11) and for reinfection VE was -21.1% (-245.3 to 56.5%; P=0.71). Participants in the H56:IC31 group reported more mild- to-moderate local injection reactions than in the placebo group. No H56:IC31-related serious adverse events were observed. Participants receiving H56:IC31 mounted robust H56-specific CD4+ T cell responses and H56- specific humoral (serum IgG) responses.

Conclusion: This is the first reported trial with a prevention of recurrent TB design. Vaccination with H56:IC31 upon treatment completion for pulmonary tuberculosis did not reduce the risk of recurrent tuberculosis. H56:IC31 was well-tolerated and immunogenic, but may have increased the risk of relapse by endogenous strains.



211 Efficacy, Safety, and PK of BIC/FTC/TAF in Adults With HIV and Tuberculosis on Rifampicin at Week 24

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Background: Integrase strand transfer inhibitors, bictegravir (BIC) and dolutegravir (DTG), are currently recommended for the treatment of HIV. However, the efficacy, safety, and pharmacokinetics (PK) of BIC in people with HIV (PWH) and tuberculosis (TB) taking rifampicin-based therapy has not been evaluated.

Methods: INSIGHT (NCT04734652) is an open-label, non-comparative, phase-2b randomised controlled trial in ART-naïve or non-naïve adults with HIV (CD4+ >50 cells/μL) and TB, taking a rifampicin-based TB regimen (for ≤ 8 weeks). Participants were randomised 2:1 to the BIC arm [bictegravir/emtricitabine (FTC)/tenofovir alafenamide (TAF)] or a standard of care DTG arm [tenofovir, lamivudine, dolutegravir (TLD)], with BIC/FTC/TAF or DTG dosed twice daily, until 2 weeks post-TB treatment and once daily thereafter, until 48 weeks. Participants underwent regular clinical and safety visits, including HIV viral load measurements at baseline and weeks 4, 8, 12, 24, 40 and 48. Semi-intensive PK sampling was performed during TB treatment and post-TB treatment. Non-compartmental PK analyses for BIC were conducted in R using the PKNCA package (version 10.2). We report preliminary endpoint results for the proportion of participants with plasma HIV-1-RNA <50 copies/mL at week 24).

Results: We enrolled 122 participants: 80 in the BIC and 42 in the DTG arm. Overall, 43 (35%) were female, with median (IQR) baseline viral load (copies/mL) and CD4+ (cells/μL) of 75649 (22784-391299) and 172 (108-352) (BIC arm) and 73735 (21242-544830) and 139 (97-237) (DTG arm). Geometric mean (CV%) trough concentrations for twice daily BIC during TB treatment (75 PK-profiles) and once daily BIC after TB treatment (22 PK-profiles) were 0.397 (73.4%) mg/L and 2.29 (45.1%) mg/L. Serious adverse events were common in this population with advanced HIV and TB, but none of the 15 were related to study treatment. Median CD4+ (cells/ μL) at week 24 was 257 (197-485) (BIC arm) and 231 (170-311) (DTG arm). HIV-1-RNA at week 24 was <50 copies/mL in 71/73 (97%) and 36/37 (97%) of participants in the BIC and DTG arms, respectively, in the per-protocol analysis (Figure 1), [71/75 (95%) in BIC arm (two early withdrawals) and 36/38 (95%) in DTG arm (one death) in FDA snapshot analysis]

Conclusion: Data from INSIGHT suggest that twice daily bictegravir/emtricitabine/tenofovir-alafenamide is effective in PWH with TB taking rifampicin-based treatment. Safety, PK, and virologic response data support the use of this regimen in PWH and TB.

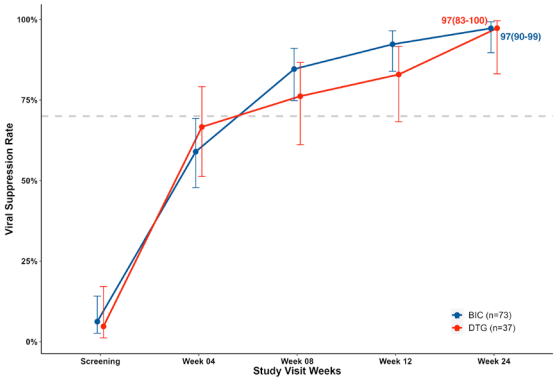

Figure 1: Viral Suppression rate (per protocol analysis) over study visits by Arm with two-sided 95% Confidence Interval

212 Long-Acting Injectable CAB/RPV Is Superior to Oral ART in PWH With Adherence Challenges: ACTG A5359

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Background: Data from randomized clinical trials of long acting injectable treatment with cabotegravir and rilpivirine (LAI) are lacking for persons with HIV (PWH) and a history of adherence challenges.

Methods: ACTG A5359 is a phase III, prospective, randomized, open-label trial comparing LAI vs. oral standard of care (SOC) ART in PWH in the U.S. with a history of suboptimal adherence (persistent HIV-1 RNA >200 c/mL or loss to follow-up). Enrolled participants received conditional cash incentives for viral suppression on SOC of up to 24 weeks (Step 1). Participants achieving HIV-1 RNA ≤200 c/mL in Step 1 were randomized to monthly LAI (with/without oral lead-in) vs. continuation of SOC ART for 52 weeks (Step 2). Primary composite endpoint was the earliest occurrence of virologic failure (VF, confirmed HIV-1 RNA>200 c/mL) or treatment discontinuation. Key secondary efficacy endpoints included VF, treatment-related failure (VF or discontinuation due to adverse events, AEs) and treatment discontinuation. On Feb 12, 2024 a pre-planned interim review by an independent Data and Safety Monitoring Board recommended to stop randomization and offer LAI to all eligible participants. We present the interim results on which the DSMB recommendation was made.

Results: As of 3 Jan 2024, 434 eligible participants were enrolled in Step 1. Median age 40 years, 70% male, 64% Black/African American, 17% Hispanic, 5% transgender, 14% current/prior injection drug use, median CD4+ cells 270/mm^3, and median HIV-1 RNA 3.55 $\log_{10}$ c/mL. 294 eligible participants were randomized in Step 2 (LAI n=146, SOC n=148). Cumulative probability of AEs was similar in both arms. Three participants on LAI had ≥ Grade 3 injection site reactions (ISR) and one discontinued due to ISR. All efficacy endpoints favored the LAI arm (Table). Although the primary endpoint did not meet the predefined stopping criterion for this interim analysis (nominal 98.75% confidence interval excluding zero), key secondary endpoints of VF and treatment related failure met this stringent criterion, demonstrating superiority of the LAI arm vs. SOC. Two confirmed VFs in each arm had new resistance associated mutations (RAMS) including ≥2 new integrase inhibitor RAMs in both LAI participants.

Conclusion: When considering all endpoints together, long-acting CAB/RPV demonstrated superior efficacy compared to daily oral SOC in PWH with adherence challenges.

Table: Kaplan-Meier cumulative probabilities for primary and key secondary endpoints and difference in probabilities between LAI and SOC arms

Endpoint	CAB-LA/RPV-LA (n= 145*)		SOC (n=148)		Difference (nominal 98.75% CI)
	Failure, n	Cumulative Probability	Failure, n	Cumulative Probability	
Primary: Regimen failure (virologic failure+ discontinuation)	28 (5+23)#	24.1%	47 (28+19)	38.5%	-14.4% (-29.8%, 0.8%)
Secondary: Virologic Failure	6#	7.2%	28	25.4%	-18.2% (-31.1%, -5.4%)
Secondary: Treatment-related failure (virologic failure + discontinuation due to AE)	9 (6+3)	9.6%	29 (28+1)	26.2%	-16.6% (-29.9%, -3.3%)
Secondary: Permanent treatment discontinuation	25	20.9%	30	24.9%	-4.1% (-18.0%, 9.8%)

* One participant with ART information pending was excluded from the interim efficacy analyses. # One participant assigned to LAI had treatment discontinuation as the primary endpoint but subsequently experienced VF.

POSTER ABSTRACTS

300 Targeting Tat-Dependent Transcriptional Rewiring to Manipulate HIV Latency

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Background: Integrated HIV-1 proviruses rely on host transcriptional machinery for RNA expression. To enhance transcriptional activity, the virus encodes the transactivating protein Tat, which recruits positive transcription elongation factor b (P-TEFb) to sites of nascent proviral transcription through recognition of the TAR RNA stem loop. P-TEFb phosphorylates the C-terminal tail of RNA polymerase II (RNA Pol II) to enhance processivity and trigger transcriptional elongation. During normal cellular transcription, P-TEFb is recruited to RNA Pol II by the joint action of the PAF1 complex (PAF1C) and the Super Elongation Complex (SEC). Given the apparent functional redundancy between these complexes and Tat, we set out to determine their role in HIV-1 replication and latency.
Methods: HIV-1 spreading infection was monitored following genetic or chemical perturbation of these complexes in primary CD4+ T cells. For genetic perturbation, CRISPR-Cas9 gene editing was used to knock-out each complex member in cells from independent donors. For chemical perturbation, we developed and validated first-in-class small molecule inhibitors of the SEC and PAF1C, which were delivered prior to challenge. These small molecule inhibitors were also tested for their impact on latent proviruses in cell line models of latency and in peripheral blood mononuclear cells (PBMCs) from people living with HIV (PLWH).
Results: Both genetic and chemical perturbation of the SEC and PAF1C significantly increased HIV-1 replication in primary CD4+ T cells, suggesting that these complexes inhibit viral replication. In J-Lat models of latency, neither inhibitor was sufficient for latency reactivation, though they did act synergistically with other latency reversing agents (LRAs). In contrast, both inhibitors significantly increased the expression of HIV-1 gag in PBMCs from PLWH, both individually and with other LRAs. Mechanistic studies suggest that the latency reversing activity of these compounds is Tat-dependent, and that they otherwise promote latency due to an inability to recruit P-TEFb.
Conclusion: These results demonstrate that the SEC and PAF1C inhibit HIV-1 replication and serve as blocks to Tat-dependent transcription in latently infected cells. Small molecule inhibitors of these complexes reactivate latent proviruses in patient PBMCs and act synergistically with other known LRAs. Future directions will explore the Tat-dependency of these compounds and their potential as dual-acting latency reversing and promoting agents..

301 Impact of HIV-1 TAR Sequence Diversity on Its RNA Secondary Structure in HIV-1 DNA Genomes

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Background: HIV-1 TAR is an RNA secondary structure located at the 5' end of the viral transcript. It binds to HIV-1 Tat protein to facilitate viral transcript elongation and plays a role in virologic rebound during therapy cessation. Here, we hypothesize that TAR secondary structures and stability significantly differ across viral subtypes and across intact versus defective HIV-1 DNA genomes.
Methods: Near-full-length HIV-1 DNA genome sequences from 47 study participants from Uganda (n=28, subtype A1, C, D), Canada and the US (n=19, subtype AE, B) were obtained using nested PCR (HXB2 638- 9632) and Illumina sequencing; TAR was inferred from the 3'LTR. Each genome was classified as intact or defective (e.g., containing hypermutations and/or large deletions) using the software HIVSeqinR. To obtain TAR associated with transcription-competent genomes, cell-associated viral mRNA transcripts were sequenced from six matching participants (subtype B n=5, AE n=1) using PacBio IsoSeq. TAR secondary structure and its stability as measured by Gibbs free energy (ΔG) values were inferred using Quikfold; a higher ΔG is associated with decreased TAR stability.
Results: In the HIV-1 DNA genome analysis, among the 47 study donors (1970 TAR sequences), TAR nucleotide diversity associated with intact viral genomes varied up to 13% interhost and 3% intrahost. Subtype D intact genomes had the least stable TAR relative to A1 and B ($p<0.004$). TAR in subtype A1 and AE did not share the same secondary structure as subtype B, C and D (linear versus bent hairpins). Per donor, ΔG of TAR associated with intact genomes did not differ from any defective genome categories except was higher when associated with hypermutated genomes ($p<0.0006$). In the ex vivo viral mRNA transcript analysis, we detected hypermutated genomes that were actively producing viral transcripts which were associated with significantly higher ΔG than non-hypermutated transcripts ($p<0.0001$), whereas TAR associated with non-hypermutated transcripts had similar ΔG values relative to TARs in the intact viral DNA pool from the same donor ($p=0.5$).
Conclusion: Our study reveals HIV-1 TAR genotypes are not identical across viral subtypes or between genome-intact versus defective viruses, and they can be genetically diverse intrahost. Differences in TAR stability may imply differences in the extent of viral transcription activity. Future studies should examine whether TAR stability can predict the quantity of viral transcripts produced.

302 Crosstalk Between Resistance to the HIV-1 Capsid Inhibitor Lenacapavir and Viral Fitness

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Background: Lenacapavir (LEN) is the first capsid inhibitor to be FDA-approved for HIV-1 treatment. Despite high potency and slow-release kinetics, a significant drawback of LEN is its low barrier to viral resistance. A mutation in the HIV-1 capsid, M66I, confers > 80,000-fold resistance to LEN and has been observed in cultured cells and in HIV-1-infected individuals treated with LEN. However, in the absence of LEN, M66I causes a substantial defect in viral fitness (<5% infectivity relative to WT). Given the high mutation rate of HIV-1, it is important to understand how HIV can adapt to circumvent the M66I-induced fitness defect before compensatory mutations are manifested in patients.
Methods: We propagated LEN-resistant HIV-1 mutants (pNL4-3) in T-cell lines (SupT1 and MT4) to select for compensatory mutations. Replicating viruses were sequenced to identify compensatory mutations. Identified mutations were sub-cloned into pNL4-3 to examine their effects on virus infectivity and drug sensitivity.
Results: M66I propagation in T-cells repeatedly led to WT reversion (I66M). We examined the effects of mutating M66 to other amino acids and determined whether these substitutions recapitulate the behavior of M66I, specifically its resistance to LEN and fitness defect. Of the M66 mutants examined, M66L, M66V, and M66F exhibited similar infectivity defects evident in M66I, but only M66V displayed high-level resistance to LEN. Propagation of these M66 mutants led to several second-site mutations. Of note, H12Y, in combination with A105T and other capsid substitutions, resulted in a >10-fold rescue of M66L infectivity.
Conclusion: This study investigates viral escape strategies of M66I, a highly LEN-resistant but fitness- impaired HIV-1 mutant. As a clinically significant variant, this work will reveal important insights into how HIV-1 may maintain LEN resistance while bypassing the fitness defect inherent to M66I.

303 Identification of a New Class of Capsid-Targeting Inhibitors That Specifically Block Nuclear Import

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Background: Nuclear localized viral genomes account for the persistence HIV-1 in patients despite successful antiretroviral therapy. Drugs that target reverse transcription or integration do not prevent HIV from reaching the nucleus and producing viral transcripts and proteins. Inhibiting HIV-1 nuclear import could make a significant contribution by reducing the reservoir.
Methods: A total of 85 compounds and structural analogues were tested following an in silico screen of compounds that recognize the previously described TRN-1 binding pocket on HIV-1 capsid (Fernandez et al. Nat Microbiol 2019). Antiviral activity was assessed in cell lines and primary human lymphocytes, using X4- and R5-tropic molecular clones, clinical isolates from treatment-naive patients, and ART-resistant mutants. Toxicity and pharmacokinetic properties were obtained in primary human lymphocytes and humanized mice. Co- immunoprecipitation, surface plasmon resonance, proximity ligation assays, and methyl-Trosy NMR, were used to quantify binding to CA and TRN-1; quantitative PCR to analyse reverse transcripts, 2-LTR circles and integrated provirus; and confocal imaging to measure capsid nuclear import. The effects on uncoating were tested in vitro and in cells, and a total of 16 capsid variants from divergent lentiviruses or stability mutants were compared. Control drugs were NVP, RAL, 3TC, DRV, DTG, PF-74 and LEN.
Results: Six compounds (hit H27 and 5 out of 45 structural analogues) inhibited HIV-1 in a dose-dependent manner. The IC_{50} was in the low micromolar range and CC50 values were >100µM, indicating a high selectivity index. All 6 compounds inhibited the nuclear import of HIV-1 specifically, without impacting other steps of the viral life cycle such as reverse transcription or particle production. Although H27 reduced the TRN-1-CA association, binding sites were distributed over the entirety of CA. All tested HIV-1 molecular clones, clinical isolates, stability or PF74/LEN-resistant mutants, and resistant mutants to NRTI, NNRTI, PI and INSTI, were sensitive to H27 (25 viruses in total). In contrast, HIV-2, SIVagm and SIVmac were resistant, and infection with the hypostable P38A mutant was even stimulated by H27. Escape mutations to H27 first appeared at day 49 in cell culture and were stability mutants E45L/G46A.
Conclusion: This study identifies a new family of capsid-targeting compounds that specifically inhibit HIV-1 nuclear import by modulating the stability of capsid and its ability to bind to nuclear import factors.

304 Impact of Capsid Polymorphisms on Viral Fitness and the Susceptibility to Lenacapavir

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Background: Lenacapavir (LEN) is a first-in-class, long-acting capsid (CA) inhibitor for the treatment and prevention of HIV-1 infection. While LEN has shown full potency against different HIV-1 subtypes, it remains unclear how viral diversity encountered in the clinic may impact its efficacy. Herein we analyzed HIV-1 CA sequence diversity to identify natural polymorphisms within the LEN binding site and assessed each for their impact on viral fitness and susceptibility to LEN.
Methods: CA binding site residues within a given radius of LEN were identified in Pymol. HIV-1 CA sequences from public (N=9232) and Gilead trial datasets (N=825) were analyzed for naturally occurring binding site polymorphisms across subtypes A1, B, C, D, F1, G, CRF01_AE and CRF02_AG. Site-directed mutants encompassing CA polymorphisms with a > 0.5% prevalence were expressed as single-cycle NL4.3- based reporter viruses. Infectivity and antiviral EC_{50} values for WT and mutant viruses were determined in MT- 4 cells.
Results: Of the 25 CA amino acids identified within a 5Å radius of LEN at its binding site, 10 (40%) were completely invariant among the >10K unique HIV-1 CA sequences analyzed. Half (5/10) of these conserved residues (M66, Q67, K70, N74 and A105) matched those previously associated with LEN resistance when mutated. Among each of the remaining 15 LEN binding site residues, at least 1 variant was identified across the 8 subtypes evaluated, with codons S41, Q50, T54 and N183 being the most variable with 6, 8, 7 and 9 substitutions detected, respectively. Site-directed HIV-1 reporter viruses encompassing all of the observed CA variants (n=48) were produced and evaluated for infectivity and drug susceptibility in MT-4 cells. Approximately half (25/48) of these mutants showed impaired infectivity (<50%, range 0.006 – 47%) relative to the WT, with 6 (I37Y, Q50P, N53K, T54Y, I73F, R173K) being so severely impaired that it prevented LEN resistance profiling. Of the remaining 42 CA variants, 39 (93%) remained fully susceptible to LEN (FC=0.6- 2.4). Three variants (Q50E, L56V and N57H), with prevalence of ~0.5% in a single subtype (C or D) and impaired infectivity (0.6-25% of WT), showed reduced susceptibility to LEN relative to WT (FC=3.1, 72 and 4890, respectively).
Conclusion: With few exceptions, our mutant HIV panel comprising rare naturally occurring LEN binding site variants in CA remained fully susceptible to LEN, suggesting that the existing natural viral diversity should minimally impact LEN efficacy in the clinic.

305 Massive Endocytosis Mechanisms Are Involved in CD169-Mediated Uptake of HIV-1 by Dendritic Cells

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Background: Myeloid cells, such as monocytes, macrophages, and dendritic cells (DCs), are main sentinels of the immune system against invading viruses. However, HIV-1 can take advantage of this to disseminate throughout the body. This process relies on the recognition of gangliosides on the viral envelope by the CD169/Siglec-1 receptor expressed on the cell surface of activated myeloid cells. This interaction triggers the internalization of HIV-1 in a structure named Viral Containing Compartment (VCC), where viral particles remain infectious. Although VCC formation process is largely unknown, previous data suggest that it is independent of clathrin and requires cholesterol in the cell membrane, as well as transient deregulation of cortical actin. Therefore, we hypothesized that HIV-1 exploits the machinery used during Massive Endocytosis (MEND) to enter dendritic cells after binding to CD169.
Methods: Live cell confocal imaging of DCs was conducted to obtain a 3D reconstruction of VCC formation and measure its dimensions and dynamics. Actin and cholesterol staining was performed in fixed and live cells to assess their roles during this process. PI3K inhibitors and protein palmytoilation inhibitors were used to evaluate their effect in the uptake of Viral Like Particles (VLP) by confocal microscopy. Images were processed with ImageJ and data analysis with GraphPad.
Results: HIV-1 VLP uptake dynamics and VCC dimensions do not match with classical endocytic pathways, but VCC size (2.9 ± 0.7 µm diameter and 20 ± 9.9 µm3 volume) indicates massive plasma membrane invagination. Although actin was not observed by phalloidin staining in the early steps of VCC formation, it is essential for VCC maintenance. PI3K and protein palmitoylation inhibition arrested the process before VLP entry, reducing the rate of VCC formation in DCs from 70% to 40% and 20%, respectively. Strikingly, cholesterol coalescence determined VCC formation as the cholesterol probe signal was doubled in the VLP uptake regions, as observed by live cell imaging.
Conclusion: These data suggest that MEND mechanisms participate in the internalization of viral particles and subsequent formation of VCC in DCs. This work provides new insights into the interaction of HIV-1 with myeloid cells revealing new therapeutical targets to hinder virus dissemination. Blocking VCC formation offers potential cross-protection against enveloped viral infections that use CD169 receptor, such as Ebolaviruses and other hemorrhagic fever viruses.

306 Antagonism of Viral Glycoproteins by Guanylate-Binding Protein 5

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Background: Guanylate binding protein (GBP) 5 is an interferon-inducible cellular factor with broad antiviral activity, reducing the infectivity of progeny virions by interfering with processing and incorporation of viral glycoproteins. GBP5 is believed to inhibit the infectivity of HIV-1, highly pathogenic influenza A, and dengue virus by reducing the proteolytic activity of furin. However, the exact mechanism by which GBP5 inhibits processing of viral glycoproteins and whether it only affects furin-dependent glycoproteins remains poorly understood.

Methods: HIV-1 Δenv luciferase reporter viruses were pseudotyped with either HIV-1 envelope glycoprotein (Env), murine leukemia virus (MLV) Env, vesicular stomatitis virus G glycoprotein (VSV G), SARS-CoV spike (S) or SARS-CoV-2 S glycoprotein and the effect of producer-cell GBP5 expression on particle infectivity was determined. The effect of GBP5 expression on viral glycoprotein glycosylation was determined by treating virus- producing cell lysates with N-glycosidase F (PNGase F), which removes N-linked oligosaccharides from glycoproteins.
Results: We found that GBP5 reduces the infectivity of particles bearing each of the viral glycoproteins tested in a concentration-dependent manner. Western blot analysis demonstrated that GBP5 causes a dose-dependent shift in the electrophoretic mobility of the viral glycoproteins. Moreover, GBP5 strongly reduced glycoprotein incorporation into virions while increasing virion-associated levels of the uncleaved glycoprotein precursors. PNGase F treatment abolished the GBP5-mediated shift in the electrophoretic mobility of the glycoproteins, indicating that GBP5 affects N-linked protein glycosylation and glycan modification.
Conclusion: Our data establish that GBP5 impairs viral infectivity by interfering with glycoprotein function. Furthermore, we provide evidence that GBP5 not only inhibits furin cleavage of viral glycoproteins but also affects their glycosylation regardless of whether they undergo furin-dependent processing. Moreover, our data on VSV G indicate that GBP5 targets the glycosylation of proteins other than class I fusion proteins. These results provide novel insights into the broad antagonism of viral glycoprotein function by the cellular host innate immune response. In the ongoing studies, we are testing the ability of GBP5 to restrict the replication of human and murine pathogens in mouse models, thereby providing the first insights into GBP5 antiviral activity *in vivo*.

307 Retinoic Acid Blunts the Aryl Hydrocarbon Receptor/SAMHD1-Dependent HIV-1 Restriction in Macrophages

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Background: As part of the cell-autonomous innate immune system, SAMHD1 restricts HIV-1 replication by limiting the pool of deoxyribonucleoside triphosphate required for efficient reverse transcription. The antiviral activity of SAMHD1 is abrogated by phosphorylation. Among regulators of SAMHD1 activity, ligands of aryl hydrocarbon receptor (AhR) were reported to decrease SAMHD1 phosphorylation via mechanisms involving the transcriptional repression of kinases CDK1/2. Conversely, we demonstrated that retinoic acid (RA) promotes HIV-1 replication in macrophages by inducing SAMHD1 phosphorylation. Considering the role of macrophages in HIV-1 infection in anatomic sites rich in both AhR ligands and RA, such as the intestine, here we investigated how the crosstalk between these two pathways governs SAMHD1 activity and HIV-1 replication in macrophages.
Methods: Monocyte-derived macrophages (MDM) generated in the presence of M-CSF were exposed to all trans RA (ATRA) and/or AhR agonist (FICZ) and exposed to replication-competent or single-round VSV-G- pseudotyped HIV-1. HIV replication was measured by ELISA, FACS, and nested real-time PCR using specific primers for early/late reverse transcripts and integrated HIV-DNA. RNA-Sequencing was performed using the Illumina technology. Validations were performed by Western Blot, RT-PCR or FACS.
Results: While exposure to FICZ inhibited HIV-1 replication in MDM at the level of reverse transcription, integration, and translation, this antiviral effect of was absent in the presence of ATRA, which significantly increased HIV-1 replication via CCR5-dependent entry and post-entry mechanisms. FICZ decreased SAMHD1 phosphorylation in the absence but not in the presence of ATRA, consistent with the robust RA-mediated increase in CDK1 expression. Similarly, the insulin-induced gene 1 (INSIG1), involved in Gag metabolism, was induced by FICZ only in the absence of ATRA. The analysis of differentially expressed genes in ATRA-treated MDM revealed the downregulation of the AhR nuclear translocator (ARNT) and other AhR target genes, and the upregulation of the gene for AhR repressor (AHRR), indicating a blunted AhR signaling pathway
Conclusion: Our results demonstrate opposing roles for AhR and RA pathways in the modulation of the antiviral activity of SAMHD1 and reveal a blunted AhR-mediated antiviral program in MDMs in the presence of RA. These studies identify the need for natural SAMHD1 modulators as novel therapeutic targets for HIV-1.

308 Monitoring the Infection of a New Strain of Simian Betaretrovirus in Southern Muriquis From Brazil

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Background: Neotropical primates are natural hosts of several viruses, but many are poorly studied. One example was the identification through massive sequencing of a new strain of simian betaretrovirus (SRVbar) in an individual (2506) of Southern Muriqui (Brachyteles arachnoides), a critically endangered species, who died of immunodeficiency at the Primatology Center of Rio de Janeiro (CPRJ). The phylogenetic analysis showed that the SRVbar grouped close to the SRV of Asian primates, which also causes clinical signs similar to those presented by Muriqui. Four muriquis from the same enclosure as 2506 were also positive for SRVbar, but were asymptomatic. Objective: The objective of the study was to monitor the infection of SRVbar in specimen 2506 and in asymptomatic contacts.
Methods: Oral swab and blood samples were collected from five muriquis in CPRJ between 2016 and 2020. Nucleic acids were extracted from plasma, peripheral blood mononuclear cells (PBMC) and oral swab and a qPCR was performed for the env to analyze the proviral and viral loads from SRVbar. For serological analysis, a recombinant SRVbar p27Gag protein produced on the Escherichia coli cell platform was synthesized and purified by affinity chromatography to be used as a viral antigen in the Western Blot.
Results: Results: The proviral load in the PBMC was 10x higher than in the oral swab of all animals tested (p=0.0001). Specimen 2506 showed similar proviral DNA loads in PBMC and oral swab 10x higher (log 8.12/10^6 cells and 7.66 copies/10^6 cells, respectively) than compared to asymptomatic animals (log 7.66 copies /10^6 cells and 6.57 copies/10^6 cells, respectively) (p=0.038). All asymptomatic animals had detectable viral loads and the average was 2.34 $\log_{10}$ copies/mL of plasma (1.4 - 3.18, min-max) while 2506 had a viral load greater than 3.96 $\log_{10}$ copies/mL of plasma (p=0.044). There was success in the production of the recombinant SRVbar p27Gag protein and seropositivity for this antigen varied between animals over time, where for two animals (2506 and 3078) there was an inverse relationship with viral load, as already described in Asian primates of the genus Macaca infected with SRV.
Conclusion: For the first time, a study on the course of betaretrovirus infection is being investigated in Neotropical primates, contributing to the knowledge of this new viral strain.

309 WITHDRAWN

310 Species-Specific APOBEC3 Splicing and Variations in Viral Mutagenesis

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Background: APOBEC3 (A3) proteins are known for their antiviral activities, acting as restriction factors to directly mutate viral genomes or block different stages of viral replication. Among the seven A3 enzymes in humans, A3G is the most restrictive enzyme, unique in its ability to cause GG>AG mutations that can generate stop codons. While HIV-1 Vif counteracts A3 enzymes by targeting them for ubiquitination and proteasomal degradation, G>A mutations are still common in clinical isolates, and sublethal levels of A3-induced mutations contribute to viral diversification, drug resistance, and immune evasion in vivo.
Methods: Non-human primate models are often used to study these various aspects of HIV biology even though intrinsic antiviral immunity differences between human and nonhuman primate models at a molecular level are not well characterized. A study by Zhang et al (PMID: 31776266) began to address this gap through the identification of an aberrant mRNA splicing pattern in pig-tailed macaque A3G, which is associated with a reduced level of GG>AG mutations in SIV sequences obtained from these animals. To better understand the source, prevalence, and consequence of this A3G mRNA splicing defect, we analyzed all (>250K) publicly available HIV-1 and SIV sequences as well as >100 short-read RNAseq datasets and a recent long-read RNAseq dataset from different human populations and a wide range of nonhuman primates.
Results: Our investigation revealed that this splicing defect is present in many Old-World monkeys but not in Great Apes and New-World monkeys, and that the mutational signatures of SIV reflect this immune defect. Contrary to the

previous report, we found that A3G mRNA splicing defect is independent of the insertion of an Alu element in the A3G locus. Instead, it is strongly associated with a small intronic variation in only rhesus macaques and other similar nonhuman primates used frequently in HIV studies.
Conclusion: Taken together, our studies have unveiled and characterized a significant difference in A3G-mediated anti-HIV/SIV immunity across human and nonhuman primate models. These findings have significant implications for our understanding of the disparities in viral restriction, drug resistance and immune evasion mechanisms between humans and nonhuman primate models of HIV.

311 High Replication Fitness and Potent Innate Immune Evasion Function of a HIV-1 VB Strain

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Background: A highly virulent subtype B (VB) HIV-1 has been detected in >100 individuals (Wyant et al., 2022). On average, infected patients show 5-fold higher viral loads and 2-fold faster CD4+ cell loss compared to other subtype-B infected individuals. To determine molecular determinants of its virulence, we functionally characterized a clone (VB_6) of this HIV-1 variant.
Methods: HIV-1 VB_6 isolate sequence was found to be most similar to VB consensus and used to synthesize an infectious molecular clone. Following transfection into HEK293T cells to generate infectious virus, particle infectivity, cold stability and ability to infect primary T cells and monocyte-derived macrophages were examined. Replication kinetics of VB_6 in activated T cells were compared to 8 other HIV-1 subtype B strains. Sensitivity to CCR5 and CXCR4 inhibitors was measured in primary T cells by flow cytometry. Resistance to IFI16 and activation of NF-κB reporter were tested by co-transfection of the molecular clone into HEK293T cells. Induction of cell death, modulation of immune receptors and proinflammatory cytokine release by VB_6 were determined by flow cytometry.
Results: VB_6 had average particle infectivity and stability, and like most primary subtype B strains is T-cell tropic and utilized CCR5 entry co-receptor. However, the replication fitness of VB_6 in T cells was superior to all tested (8) primary subtype B CCR5-tropic strains, including 3 transmitted-founder viruses. VB_6 potently downmodulated immune receptors (CD4, CCR5, CXCR4 and tetherin) from the cell surface using Vpu and Nef in a more efficient manner than the NL4-3 reference strain. VB_6 infection of primary T lymphocytes induced increased levels of cell death and proinflammatory cytokines, while suppressing type I and III IFN production. In addition, VB_6 was more active at inducing NF-kB signaling and more resistant to IFI16 than most other tested subtype B strains.
Conclusion: The hyper-virulent HIV-1 VB_6 strain shows high replicative fitness in primary human T lymphocytes and expresses Vpu and Nef proteins that potently downmodulate immune receptors. VB_6 is also adept at downmodulating tetherin and shows reduced sensitivity to inhibition by IFI16. In line with increased replication, VB_6 infected primary T cells produce more proinflammatory cytokines and show reduced viability. A combination of potent immune evasion and high replicative fitness likely contribute to the virulence of VB HIV-1.

312 The HIV-1 Protein ASP Promotes Viral Replication and Is Associated With Faster Disease Progression

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Background: Decades after its discovery, the HIV-1 antisense gene asp remains an enigma. Asp overlaps env and is present exclusively in pandemic group-M HIV-1 strains. Thus, its creation may have improved HIV-1 fitness or spread. We reported that ASP is found on the surface of HIV-1 virions. We studied how ASP expression impacts HIV-1 entry and replication and the underlying mechanisms. We also studied the evolutionary mechanisms that created asp, and its association with disease progression.
Methods: We used fusion and infection assays to assess how ASP expression impacts HIV-1 entry and replication. Identification and molecular validation of ASP interacting partners were performed by mass spectrometry (MS) and co-immunoprecipitation (Co-IP). Functional validation of MS results was carried out by studying ASP nuclear import and its impact on DNA repair, as well as the impact of ASP on mitochondrial function. We used computational methods to identify the evolutionary mechanisms that created the asp gene and its association with HIV-1 disease progression.
Results: We created asp deficient HIV-1 strains by mutating the start codon or by introducing early stops via single nucleotide substitutions that lead to synonymous codons in env. ASP-deficient strains show reduced fusion and replication capacity compared to wildtype. To determine potential mechanisms, we identified ASP binding partners by MS and validated the results by co-IP. We found that the Transportin 1 pathway mediates ASP nuclear import, and that in the nucleus ASP interacts with factors involved in multiple DNA damage repair pathways. Functional studies confirmed that ASP promotes DNA repair. Also, ASP interacts with and increases the expression of mitochondrial factors of the oxidative phosphorylation and ATP biosynthesis pathway. Finally, sequence analyses show that creation of asp occurred via evolution of codon usage in env involving differential use of synonymous codons or conservative amino acid substitutions that eliminated early stops in asp. While presence of asp constrains env genetic diversity, it provides a selective advantage as the presence of asp is significantly more frequent in rapid progressors than long-term nonprogressors.
Conclusion: For the first time our studies link a full-length asp ORF to HIV-1 entry and replication in vitro and disease progression in vivo. We identified possible molecular mechanisms including impact of ASP on DNA repair and mitochondrial function, and the evolutionary mechanisms that created asp.

313 In Vivo Detection of HIV-1 Antisense Transcripts in Donors Before and During ART

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Background: Natural antisense transcripts (NATs) are expressed by viruses, prokaryotes, and eukaryotes and primarily function in regulating sense gene expression through multiple mechanisms. In vivo studies have shown that HIV-1 expresses antisense transcripts (AST) from a Tat-independent negative sense promoter in the 3' LTR. In cell line studies, AST was demonstrated to promote HIV latency through epigenetic modification of histones in the 5' LTR by the Polycomb Repressor Complex 2 (PRC2). Here, we asked whether HIV AST is expressed in infected PBMCs collected from untreated and ART-treated donors.
Methods: PBMCs were obtained from 10 donors in the SCOPE cohort and 2 donors from University of Pittsburgh. Untreated donors were either ART-naïve or undergoing treatment interruption with viral loads ranging from <50–200,000 copies/ml of plasma (n=10). Donors on ART had viremia suppressed (<50 cp/ml) for a median of 5.4-years (n=3). AST levels were measured by cell-associated antisense RNA single-genome sequencing (SGS) of a 1.7kb fragment in the opposite orientation of the env coding region. An endpoint digital PCR approach with tagged-cDNA and donor-specific primers was also used to quantify AST copies in the samples.
Results: We detected HIV AST in 11/12 donors with a median of 14 [IQR 5-34] copies/100 infected PBMCs (Figure-Left Panel). Antisense SGS revealed that about 5% of infected PBMCs collected from donors on ART contained AST at any given time. The genetic diversity of the antisense transcripts was consistent with expression from a diverse population of proviruses. Proviral clonal populations were identified with matched HIV AST from multiple aliquots of single-infected PBMC (Figure-Right Panel). Digital PCR showed similar levels of AST expression in untreated donors with varying levels of plasma viremia. Further, in the donors on ART, we observed no statistical difference between the levels of sense and antisense transcripts.
Conclusion: As in the case of other NATs, HIV antisense transcripts are expressed at low levels in both ART- treated and untreated individuals. The in vivo expression of AST irrespective of treatment status warrants further investigation into its potential role as a long non-coding RNA capable of regulating HIV-1 sense gene expression and inducing HIV latency. Understanding the role of HIV AST in vivo may inform future strategies for controlling HIV replication without ART.

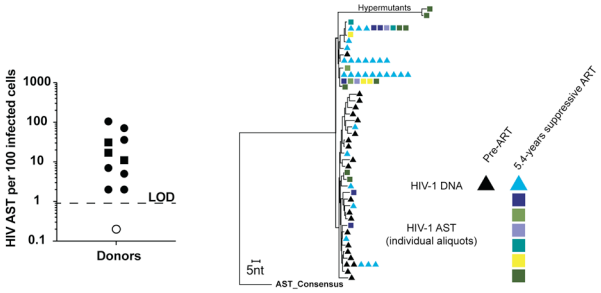

Figure. *Dection of HIV AST.* (**Left**)Digital PCR measurement of HIV AST copies per 100 infected PBMC. Untreated donor (circles), treated donors (squares), not detected (open-shapes). (**Right**)*env* distance tree with PBMC HIV-1 DNA pre-/post-ART (triangles) and reverse-complement of AST (squares).

314 Exacerbation of the RSV Infectivity by SARS-CoV-2 in an In-Vitro Coinfection Cellular Model

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Background: Concurrent infections with two or more pathogens with an analogous tropism, such as Respiratory Syncytial Virus (RSV) and SARS-CoV-2, may antagonize or facilitate each other modulating host disease outcomes. Clinically, a severe phenotype has been reported in children with RSV/SARS-CoV-2 co- infections. However, experimental models to study the cellular, molecular and immunological dynamics of co-infections are extremely limited. Herein, we propose an in-vitro co-infection model to assess RSV/SARS-CoV-2 immune and viral evolution.
Methods: A549-ACE2 expressing cells were single or co-infected with RSV and SARS-CoV-2 (MOI=0.01 each) (Figure 1A). SARS-CoV-2 and RSV replication was assessed at 24, 48 and 72 hours post infection (hpi) by Droplet Digital PCR (ddPCR), immune-fluorescent (IF) and transmission electron microscopy (TEM) analyses. Secretome analyses (17 Multiplex Cytokine ELISA) on cell culture supernatants and anti- viral/immune/autophagy gene expression (RT-qPCR) were evaluated as well. All the experiments were performed in the BSL3 facility.
Results: The RSV/SARS-CoV-2 co-infection was characterized by a significant increase in the replication rate of RSV (co-infection vs single RSV $p<0.001$) (Figure 1B). The co-infection was able to modulate the viral host receptors' expression, as significant increase in ICAM1 expression, one of the RSV host receptors, was observed in the co-infected condition compared to the uninfected control ($p<0.0001$) and to the RSV ($p<0.0001$) and SARS-CoV-2 ($p<0.0001$) single infections. Remarkably, co-infection was accompanied by a significant rise in the expression of pro-inflammatory genes, further confirmed by secretome analysis. Moreover, substantial morphological changes were evident in the co-infected A549-ACE2 cells showing an increase in the number and length of cellular conduits. Finally, following co-infection, cells displayed a significant increase in LC3B gene expression ($p<0.05$), which was further confirmed by IF analysis, suggestive of an alteration of the autophagy pathway.
Conclusion: The RSV/SARS-CoV-2 co-infection model displays a unique and specific viral and molecular fingerprint. These findings give clues of augmented severity upon RSV infection in the context of a concomitant SARS-CoV-2 co-infection. This in-vitro co-infection model may represent an attractive, cost/effective approach to mimic both viral dynamics and host immune responses, providing readily-measurable targets predictive of co- infection progression.

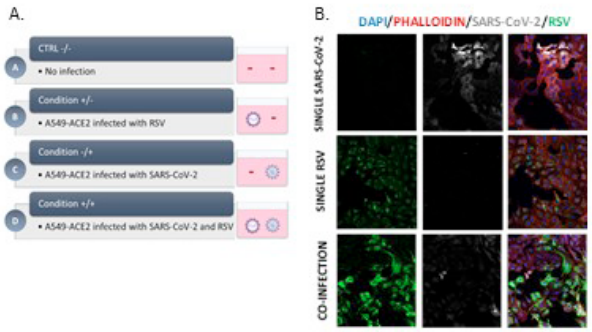

Figure 1. A) Experimental design. B) Viral replication evaluated in IF.

315 A Quiescent NK Cell Phenotype With Gut Homing Potential in HIV-1 Exposed Seronegative Individuals

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Background: HIV-exposed seronegative individuals (HESN) are a unique model to study mechanisms of protection against HIV-1. In previous studies, an increased NK cell activity has been correlated with protection in HESN, suggesting the involvement of the innate immune responses in decreasing the risk of HIV-1 acquisition. Here we compare circulating NK cell phenotype in HESN and HIV-exposed seroconverted (HESC) participants prior to HIV-1 acquisition.
Methods: Specimens from participants in the RV217 Early Capture HIV Cohort (ECHO) were used to investigate NK cell in 25 HESC and 75 HESN participants. For our analysis, preinfection samples were collected for each HESC individual and were matched for collection time and location, age, gender, and risk behavior with 3 HESN. A 26-parameter flow cytometry panel was used to quantify NK cell frequency and phenotype. A pre-infection time point, between 28-365 days prior to first HIV positive test was chosen for the HESCs.
Results: Compared with HESC individuals, NK cells from HESN participants were significantly less activated, as measured by the expression of HLA-DR (%, $p=0.003$ & MFI, $p=0.001$) and had a tendency for lower expression of the proliferation marker Ki67. Moreover, NK cells from HESN showed a higher potential to migrate to the gut measured by the expression of $\alpha4\beta7$ (%, $p=0.010$ & MFI, $p=0.015$) and a lower expression of the inhibitory receptor ILT-2 (%, $p=0.035$ & MFI, $p=0.023$) compared to HESC participants. No differences were observed related to total NK cell frequency, distribution of the CD56hi immature, CD56dim mature, or CD56low NK cell subsets. No associations were found between NK cell phenotype and peak or set point viral load following acquisition in the HESC participants.
Conclusion: Our preliminary data show significant differences in NK cells between HESN and HESC. The increased activation and expression of the inhibitory receptor ILT2, together with a lower expression of gut homing marker $\alpha4\beta7$, suggest that NK cells from HESC participants might have an exhausted and dysfunctional phenotype with lower ability to migrate to the gut mucosa. It is possible that this may be associated with an increased risk of HIV-1 acquisition relative to a more beneficial quiescent NK cell profile as observed in the HESN participants.

316 Mucosal-Homing Invariant NKT Cells Are Elevated in HIV-Exposed Seroconverters Prior to Infection

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Background: Studies in both humans and macaques have identified markers of HIV susceptibility such as the gut-homing integrin $\alpha4\beta7$, whose expression in memory CD4+ T cells increases in the context of HIV infection and is associated with increased susceptibility to acquisition. However, the phenotypic characteristics of unconventional T cells in the context of HIV

infection susceptibility are not fully understood. We therefore sought to characterize unconventional T cell phenotypes in 25 HIV-exposed seroconverted (HESC) individuals prior to seroconversion and compare them to HIV-exposed seronegative (HESN) individuals.

Methods: RV217 is a prospective natural-history study which recruited individuals at high risk for HIV acquisition. PBMC from the RV217 cohort were used to investigate T cell phenotypes in 25 HESC individuals prior to seroconversion. Each HESC study participant was matched for age, gender, and risk behavior with 3 HESN individuals for comparative analysis. A multicolor flow cytometry panel was developed to investigate mucosal associated invariant T (MAIT), invariant natural killer T (iNKT), gamma delta T, and CD4+ T cell phenotypes prior to HIV seroconversion.

Results: Our analysis showed increased frequency of total $\alpha4\beta7$ expressing CD4+ memory T cells in HESC individuals (%$\alpha4\beta7$+, p=0.0755; %$\alpha4\beta7^{high}$, p=0.0030) compared to HESN individuals. Additionally, our study shows increased frequency of $\alpha4\beta7$ expressing iNKT cells in HESC individuals compared to HESN individuals ((%$\alpha4\beta7$+, p=0.0039). To further characterize $\alpha4\beta7$ expressing iNKT cells, we analyzed $\alpha4\beta7$ expression in major iNKT cell subsets: CD4+ iNKT cells, CD8+ iNKT cells and CD4-CD8- (DN) iNKT cells. Our results reveal that $\alpha4\beta7$ expression in HESC individuals is increased in CD4+ iNKT cells (p=0.0342) and not CD8+ iNKT (p=0.5424) or DN iNKT cells (p=0.7334) compared to HESN individuals. No differences were found in MAIT and gamma delta T cells.

Conclusion: Our study supports the existing role of $\alpha4\beta7^{high}$ CD4+ memory T cells in HIV susceptibility and identifies a potential role for gut homing $\alpha4\beta7$+ CD4+ iNKT cells in HIV susceptibility in the context of individuals at high risk for HIV acquisition.

317 Mobility of Transmitted/Founder HIV-1 Variants in Human Cervicovaginal Mucus

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Background: HIV-1 needs to traverse the mucus barrier overlaying the mucosal epithelia for infection of the target cells to occur. A single or a limited number of HIV-1 variant(s), known as Transmitted/founder (T/F) HIV- 1, are typically responsible for successive infections, overcoming the mucosal barriers, including the protective mucus layer. Factors affecting cervicovaginal mucus physical and chemical properties may influence its barrier function. How this influences the mobility of T/F HIV-1 variants in the mucus is yet to be determined. Our study sought to unravel how factors affecting the cervicovaginal mucus properties, such as serum levels of reproductive hormones, cervicovaginal pH, microbiome, immunoglobulin content and cytokines, may influence the mobility of T/F HIV-1 variants in cervicovaginal mucus.

Methods: A cross-sectional evaluation was conducted to assess the mobility of three T/F HIV-1 clades in cervicovaginal mucus from at least 80 adult women, both HIV-1 infected and uninfected, aged between 18 and 45 years in Nairobi, Kenya. Spearmen correlation was used to correlate the mobility data to the cervicovaginal mucus pH, serum estradiol and progesterone levels and age. A t-test and ANOVA were used for comparing viral mobility between different HIV-1 infection statuses, bacterial vaginosis statuses, and viral clades, respectively.

Results: Our results show a significant impediment to the mobility of T/F HIV-1 variants in the cervicovaginal mucus. We observed significant variabilities in the mobility of the different T/F HIV-1 clades in the cervicovaginal mucus. Clade B lab adopted strain (R9 Bal) and T/F HIV-1 variant (CH040) had the lowest mobility compared to clade C (CAP045) and the CRF_AE (92TH023). The mobility of the CRF_AE (92TH023) negatively correlated to the mucus pH and viscosity. Interestingly, we observed significant positive mobility correlations among some viral clades.

Conclusion: Our study results demonstrate that cervicovaginal mucus impedes the mobility of T/F HIV-1 variants, which varies among clades. These results also show that cervicovaginal microenvironment may influence the mucus barrier function. This study is crucial for gaining insights into the biological traits of T/F HIV-1 variants, enabling them to bypass the mucosal immune bottleneck. By understanding these early interaction events, we can facilitate the development of preventive strategies and treatments that enhance mucosal barrier function, thus reducing the transmission of HIV-1.

318 IL7RA rs10491434 Polymorphism Is Related to Spontaneous HIV Infection Control: A Retrospective Study

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Background: Interleukin 7 receptor (IL7R) is vital in the adaptive immune response against HIV. We assessed IL7RA polymorphisms (SNPs) in antiretroviral therapy (ART)-naïve HIV patients for their association with spontaneous HIV infection control.

Methods: We conducted a retrospective cohort study involving 667 ART-naïve patients categorized by HIV progression (ordinal variable): 150 rapid progressors, 334 moderate/typical progressors, 86 long-term nonprogressors elite controllers (LTNPs-EC), and 97 LTNPs-non-EC. We genotyped three IL7RA SNPs using Agena Bioscience's MassARRAY platform. The association between IL7RA SNPs and spontaneous HIV infection control was evaluated using ordinal logistic regression.

Results: Individuals carrying the rs10491434 G allele have a higher likelihood of spontaneous HIV infection control (adjusted odds ratio (aOR)=1.33; p=0.023). Moreover, the IL7RA GCT haplotype, consisting of three specific SNPs (rs6897932, rs987106, and rs10491434), demonstrated an association with the control of untreated HIV infection (aOR=1.34; p=0.050). Remarkably, the rs10491434 SNP and the IL7RA GCT haplotype exhibited similar aOR values, suggesting that rs10491434 may be primarily responsible for the observed effect of the haplotype.

Conclusion: IL7RA rs10491434 G allele is associated with a higher likelihood of spontaneous HIV infection control, indicating its significant role in the pathogenesis of HIV, possibly influencing infection course and viral replication control.

319 Genetic Variants Associated to HIV Control Are Associated With NK Cell Markers and Response to CMV

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Background: Genome-wide association studies (GWAS) have shown that genetic variants in the MHC region are associated with spontaneous HIV-1 control. How these variants affect immune functioning is, however, poorly understood. We used a functional genomics approach in which we integrated GWAS with transcriptomic, plasma proteomic and functional immunological data to understand how genetics contribute to HIV control.

Methods: 1380 people living with HIV of European ancestry were included as part of the 2000HIV study (clinicaltrials.gov NTC03994835). To find genetic variants associated to control, a GWAS was performed in 67 HIV controllers (HIC) and 272 matched non-HIV controllers on ART (non-HIC) using a logistic regression model. To unravel how genetics affects phenotype, we performed quantitative trait locus (QTL) mapping with data from the 2000HIV cohort. A linear regression model was used to associate genetic dosages with: 1) cytokine production upon ex vivo PBMC stimulation with various stimuli (cQTLs), 2) levels of 2367 plasma proteins as measured by Olink technology (pQTLs), 3) bulk RNA expression in PBMCs (eQTLs) measured by RNA- sequencing in 1146, 1222 and 1208 individuals, respectively. All genome-wide significant ($P < 5 \cdot 10\text{-}8$) QTLs were intersected with suggestive GWAS loci.

Results: In agreement with previous GWAS, the strongest association with HIV control was identified in the MHC locus (Fig A), where we found 8 independent suggestive SNPs ($P < 1 \cdot 10\text{-}5$, $r2 < 0.5$). SNP rs2524092-C ($P = 2.44 \cdot 10\text{-}6$, $OR = 3.4$) was associated with higher GZMA and KLRF1 and lower KIR2DL2, KIR2DL3 and MICA/MICB plasma levels (Fig B), lower HLA-C and higher HLA-H and PSORS1C3 gene expression in PBMCs. Additionally, rs2524092-C is in linkage disequilibrium ($r2 = 0.52$) with rs9264388-T ($P = 1.13 \cdot 10\text{-}5$, $OR = 4.33$), which was associated with lower IL-1β and TNF production upon PBMC stimulation with CMV (Fig B).

Conclusion: We showed that genetic variants associated to HIV control are associated to plasma and gene expression levels of NK cell receptors, their ligands MICA/MICB and HLA-C, and effector molecule granzyme A. This suggests that these variants might contribute to HIV control by modulating NK cell function. The association of variants in the MHC locus with immune responses against CMV hints to a shared genetic basis of immune responses against HIV and CMV. Finally, we showed that our QTL mapping studies are valuable resources that can aid understanding how genetics contributes to disease outcome in PLHIV.
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320 Plasma Proteome Signature of Immune Inhibition Is Associated With CMV Coinfection in People With HIV

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Background: Cytomegalovirus (CMV) coinfection is highly prevalent and is associated with persistent inflammation in people with HIV (PWH). A comprehensive analysis of the plasma proteome in PWH with or without CMV has never been performed previously. Identifying proteomic signatures of CMV infection in PWH will improve understanding of CMV-associated comorbidities in PWH and may lead to the development of novel therapeutics.
Methods: The Olink Proteomics proximity extension assay was used to characterize the plasma proteome from age- and CD4 count-matched PWH with (CMV+, N=30, 23.3% female) or without (CMV-, N=19, 10.5% female) CMV coinfection on suppressive antiretroviral therapy (ART). Resulting normalized protein expression (NPX) values were analyzed using a linear mixed effects model to determine protein expression differences between groups; P-values were adjusted using the Benjamini-Hochberg method. Partial least squares-discriminant analysis (PLS-DA) was used to discriminate between CMV groups using the NPX values as input features. To measure the predictive power of the PLS-DA model, we used five-fold cross-validation with 100 repeats to estimate the generalization error in terms of accuracy and area under the receiver operating characteristic (ROC) curve (AUC).
Results: We found that 117 of 368 (31.8%) proteins were differentially expressed (P<0.05) after adjustment for multiple comparisons. Proteins most significantly upregulated in CMV+ participants were associated with inhibition of the immune response (e.g., FCRL6, HLA-DRA, KLRD1, CD70, LY9, SLAMF7) or inflammation (e.g., CXCL9, CXCL10). Several of the most significantly downregulated proteins in CMV+ PWH were associated with apoptosis (e.g., CASP2, TRIM21, TRAF2). Using our PLS-DA model, we were able to predict CMV serostatus with a cross-validated accuracy of 80.8% and AUC of 87.8%.
Conclusion: CMV serostatus substantially influences protein expression with nearly a third of proteins differentially expressed. Our data demonstrate that CMV is a major contributor to the plasma proteome in PWH and suggest that targeting CMV in PWH may be a viable strategy for therapeutic interventions. While the cross- sectional design limits causal inference, the increase in immune inhibitory elements and the reduction of pro- apoptotic molecules in CMV+ PWH suggest that CMV may facilitate the maintenance of the latent HIV reservoir in PWH on suppressive ART.

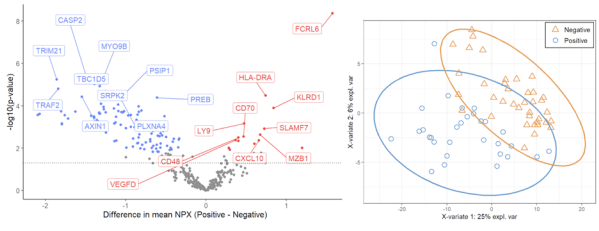

Figure. Left: Differential expression volcano plot showing proteins significantly up-regulated (red), down-regulated (blue), or non-significant (gray) in CMV+ PWH after BH adjustment. Right: PLS-DA model score plot.

321 B-Cells Augment HIV-1 Expression in Secondary Lymphoid Tissues

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Background: HIV-expressing (vRNA+) cells are consistently found in secondary lymphoid tissues (SLT) of people with HIV (PWH) on antiretroviral therapy (ART) and likely drive viral rebound upon ART cessation. Little is known about what affects HIV expression in SLT. We hypothesized that B cells promote HIV expression.
Methods: Disaggregated tonsil cells from persons without HIV were depleted of CD19+ cells by magnetic beads. CD19- cells were spinoculated with X4 or R5-tropic HIV GFP reporter virus, cultured 3 days with dye- labeled CD19+ or CD19- cells and saquinavir, and %GFP+ of unlabeled CD3+CD8- cells and GFP median fluorescence intensity (MFI) determined by flow cytometry. Tonsil cells were also sorted into CD4+ T follicular helper (TFH; CD3+CD8-CXCR5hiPD-1hi), nonTFH (CD3+CD8-CXCR5+/-PD-1+/-), memory B (IgD-CD38-), pre-germinal center B (pre-GCB; IgD+CD38+), GCB (IgD-CD38+), and naïve B (IgD+CD38-). TFH and nonTFH were infected with X4 HIV, incubated with B cell subsets or control CD4+ T cells, and %GFP+ and GFP MFI determined. Sections of inguinal lymph node (LN) from 6 male PWH on ART for 7-29 years and spleen from 6 male PWH on ART for >5 years were analyzed by in situ hybridization for vRNA and immunofluorescent antibody staining for CD20 to determine follicular (F) regions. Frequencies of vRNA+ cells in F and extrafollicular (EF) regions, EF B cells, and EF B cells adjacent to vRNA+ cells were determined by visual inspection and quantitative image analysis. Data reported are medians. Nonparametric statistical tests were used.
Results: CD19 depletion reduced %GFP+ and GFP MFI by 32% and 30% in X4 (n=7; p=0.02 and 0.03) and 37% and 29% in R5-HIV infected cells (n=7; both p=0.02) compared to cultures with CD19+ cells. Memory, pre-GCB, GCB, and to a lesser extent naïve B cells elevated HIV expression in both nonTFH (%GFP+ p<0.05; GFP MFI p<0.05; n=6) and TFH (%GFP+ increased by all B cell subsets except naive, p<0.05; n=6; all B cell subsets augmented GFP MFI, p<0.05; n=6). Frequencies of vRNA+ cells were higher in B cell-rich F than EF regions in LN (0.28 vs 0.17 cells/mm^2; p=0.03) and spleen (0.07 vs 0.05 cells/mm^2; p=ns). In EF areas, vRNA+ cells were adjacent to B cells more often than predicted by chance in all four LN (3.1-fold; range, 3-5.2) and four spleens (1.4-fold, range 1.1-2) evaluated.
Conclusion: B cells upregulate HIV expression in SLT CD4+ T cells and are associated with vRNA+ cells in SLT of PWH on ART. Mechanisms by which B cells augment HIV expression merit investigation.

322 Herpesviruses Reactivation and Associated Systemic Inflammation During Initiating ART, Rakai-Uganda

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Background: We conducted a prospective observational study to evaluate HSV-2, Cytomegalovirus (CMV), and HHV-8 herpesviruses shedding after ART initiation and associated markers of systemic inflammation in women living with HIV (WLWH).
Methods: We recruited 187 WLWH not on ART, aged ≥18 years from three HIV/ART clinics in south-central Uganda. CMV and HSV-2 shedding was quantified by PCR on vaginal secretions and HHV-8`s shedding on oral swabs. McNemar's test was used to evaluate changes in shedding of HSV-2, CMV and HHV-8 pre-ART (study baseline visit) and after ART initiation (weeks 4 and 8). Logistic regression models were used to evaluate associations of markers of systemic inflammation (plasma levels of IL-6, CRP, TNFα or sCD14) with viral- shedding at similar time points. We conducted a stratified analysis by pre-ART CD4 counts (≤200 cells/µl versus >200 cells/µl).
Results: 187 out of 196 (95%) screened women were eligible with a mean age 30.1 years and enrolled at ART initiation. 25.9% of participants had a pre-ART CD4 count less than 200 cells/µl. Follow-up occurred for 91% and 87% of participants at weeks 4 and 8 post-ART initiation, respectively. During the study, 69.1% of participants shed CMV, 44.1% shed HSV-2, and 30.1% shed HHV-8.

Shedding of HSV-2 and HHV-8 pre-ART versus at week-4 or week-8 post-ART was not significantly different while CMV shedding significantly increased from 53% pre-ART to 77% at week-4 visit (p-value=0.016), and 73% at week-8 visit (p-value=0.027) in participants with a pre-ART CD4 count <=200 cells/ul. At week-4 post ART, a 4-fold increase in IL-6 levels was associated with HSV-2 shedding if there was no shedding pre-ART, while a 0.76-fold decrease in IL-6 levels wμas associated with HSV-2 shedding if there was shedding pre-ART. At week 8 post-ART, a 2-fold and 8-fold increase in CRP and TNFα levels respectively were associated with the risk of CMV shedding irrespective of shedding pre-ART. A 4-fold and 1.5-fold increase in IL-6 and sCD14 levels respectively was instead associated with HSV-2 shedding if there was no shedding pre-ART while at least a 0.17-fold decrease in IL-6 and sCD14 levels was associated with HSV-2 shedding if there was shedding at baseline.

Conclusion: ART initiation was associated with increased CMV, but not HSV-2, shedding at weeks 4 and 8 after starting treatment. Mucosal shedding of CMV and HSV-2 was associated with different patterns of changes in systemic inflammatory biomarkers IL-6, CD14, CRP and TNFα.

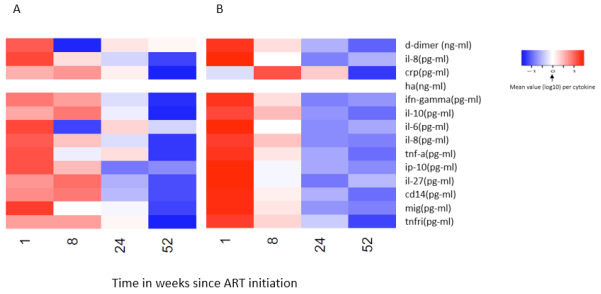

Figure 2: Heatmap of median cytokine value over time for CMV Ever-shedders (panel A) and Never-shedders (panel B) that had a baseline CD4 count of 0-200 cells/ul

323 HIV-1 Coinfection Skews iNKT Cells Toward Anergy and Exhaustion in People With Hepatitis C

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Background: Hepatitis C virus (HCV) infection related liver disease remains a leading cause of morbidity and mortality in people with HIV (PWH). Liver fibrosis progression is more rapid in HIV/HCV coinfection compared to HCV monoinfection. Although direct acting antivirals (DAA) have improved treatment response substantially, access to DAA has declined since 2015, thus liver disease remains a threat to people with HIV/HCV. iNKT cells, a rare innate-like subset of T cells, may play a role in the rapid progression of fibrosis because of their liver tropism and due to the early loss of "pro-healing" CD4+ iNKT cells in early HIV infection. How this impacts long term iNKT subset diversity and functionality, and the role of iNKT in fibrogenesis in people with HIV/HCV is unknown.

Methods: To investigate the phenotypic and functional differences of iNKT cells in people with HIV/HCV coinfection, we consented persons with HIV (N=7), HCV (N=6), HIV/HCV (N=7), and healthy controls (N=6). All patients with HIV were virally suppressed on antiretroviral therapy and all patients with HCV had chronic active infection. We collected PBMCs and used 12-color flow cytometry to evaluate the phenotypes and functionality of iNKT following T-cell receptor (TCR) stimulation. Phenotypes were compared using Leiden clustering and dimension reduction.

Results: iNKT from PWH cells showed impaired expansion to TCR stimulation (~2 fold) compared to iNKT cells from persons with HCV or neither infection (up to 50-fold). The iNKT cells from PWH also showed a higher degree of TCR downregulation and lower CD38 expression following TCR stimulation, consistent with a more anergic state. We observed a higher frequency of CD8+ iNKT cells in PWH, which represents an effector subset. In addition, they were more likely to express CD57, a marker of terminal differentiation.

Conclusion: iNKT cells from PWH and people with HIV/HCV have impaired expansion, higher TCR downregulation in response to stimulation, and are biased towards "effector" and terminally differentiated subsets. These results suggest a picture of proinflammatory but relatively anergic iNKT cells. This altered distribution of iNKT subsets could explain why PLWH are less likely to control acute HCV infection and if this dysfunction persists on entry to the liver, may play a role in liver fibrogenesis.

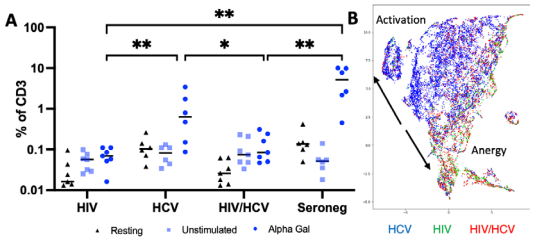

Figure 1. iNKT cells from PWH have impaired expansion to TCR stimulation and are anergic. A. iNKT frequency after overnight rest (Resting), 2 weeks of culture (Unstimulated), or 2-week expansion with Alpha-Gal (Alpha-gal). B. UMAP of iNKT phenotypes from HCV (Blue), HIV (Green), and Coinfection (Red).

324 Low SKAP1 Levels Indicate a Potential New Mechanism in HIV Immunological Non- Responders

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Background: Immunological non-responders (INRs) are people living with HIV (PLHIV) who fail to adequately restore CD4+ T-cell levels during suppressive ART. In contrast, immunological responders (IRs) do achieve CD4+ T-cell levels comparable to healthy individuals. Morbidity and mortality are increased in INRs. However, the pathogenesis of INRs is multifactorial and not fully elucidated yet. In this exploratory proteomics study, we looked for proteins which might be related to INR. SKAP1 is a lymphocyte protein which is important for T-cell migration, activation and proliferation. Previous work has shown that lymphocyte proliferation and IL- 2 production were severely impaired in SKAP1 knock-out mice. The main function of SKAP1 is activating LFA- 1, an integrin binding receptor. Knockdown of one of the LFA-1 heterodimers causes impaired CD4+ T-cell migration to the intestine and lymph nodes. SKAP1 has never been described in the context of HIV.

Methods: The 2000HIV study (clinicaltrials NTC03994835) is a Dutch cross-omics multi-center study enrolling 1895 virally suppressed PLHIV, divided into a discovery and an independent validation cohort. We performed linear regression differential expression analysis on targeted serum proteomics (Olink, 2368 proteins) of INRs compared to IRs. In addition, we analyzed whole blood DNA methylation (NanoDrop spectrophotometer).

Results: The discovery cohort consists of 62 INRs and 1224 IRs, and the validation cohort of 26 INRs and 243 IRs. INRs were older and had more advanced HIV disease before starting cART. Proteomic analysis showed that SKAP1 was significantly downregulated in INRs in both the discovery (logFC = -0.545, FDR<0.0001) and the validation cohort (logFC = -0.628, pval<0.0001) (Figure 1A). SKAP1 was the most significant protein in both cohorts. In addition, we observed hypermethylation at cg26532208, a CpG site in the promotor area of the SKAP1 gene in the discovery cohort (logFC = -0.096, FDR = 0.042) (Figure 1B), as well as in the validation cohort (logFC = -0.093, pval = 0.00078) which suggests decreased transcription. Finally, a significant correlation between CD4+ T-cell count and SKAP1 levels was found in the overall cohort irrespective of immunological responder status.

Conclusion: We found evidence for decreased SKAP1 expression levels in INRs in a large cohort study across two separate -omics layers. Previous work on SKAP1 function and these new data emphasizes its potential role in INR pathogenesis and might open new therapeutic avenues.

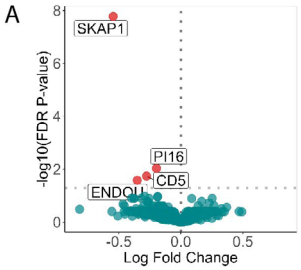
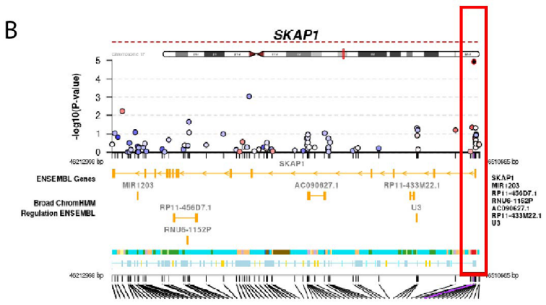


Figure1A: Targeted serum proteomics differential expression analysis in the discovery cohort. SKAP1 is downregulated in INRs.

Figure1B: DNA methylation analysis of the discovery cohort shows hypermethylation in the promotor region of SKAP1 on chromosome 17 in INRs.



325 Disruption of Intestinal Germinal Centers During HIV Infection

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Background: HIV infection causes a profound dysregulation of the humoral immune system. Humoral responses occur mostly in secondary lymphoid tissue and involve the formation of Germinal Center (GC) and T- dependent antibody production results from interaction between cognate T and B cells. While the impact of HIV infection on mucosal T cells is well-reported, less is known regarding the effects of HIV on the humoral immune compartment. We investigated changes induced by HIV infection on humoral immunity, focusing on GC as the sites of T-dependent antibody production in the gut-associated lymphoid tissue (GALT).

Methods: We prospectively enrolled people with HIV (18 with HIV viral load (VL)>1000copes/mL and 46 with HIV VL <50copies/mL on antiretroviral treatment (ART) as well as people without HIV (n=80) and examined intestinal immune cell changes with immunohistochemistry, flow cytometry and single cell RNA sequencing (scRNA seq).

Results: Immunohistochemical staining showed a significant decrease in GC size in participants with detectable VL compared to participants without HIV [median, IQR size 0.008 (0.0006–0.03) vs 0.1 (0.009– 0.15)mm^2 p=0.04], despite similar overall lymphoid follicle size. Additionally, we found a marked reduction of BCL6 expression in germinal centers in participants with detectable VL, even when accounting for the reduced GC size [556 (20–2375) vs 4120 (3363-6400) cells/mm^2 p=0.065]. Using flow cytometry, in both Ileum and colon, a significant depletion of GC B cells was observed in PWH with detectable VL as compared to both participants with undetectable VL and without HIV [0.07 (0.03–0.42) vs 0.4 (0.16-2.53) vs 0.88 (0.17–2.98)% of Live Cells in the ileum, p=0.008 and 0.39 (0.21–0.91) vs 0.75 (0.4–1.3) vs 1.04 (0.4–1.4)% of Live Cells in the colon, p=0.004]. Within the scRNAseq dataset, cells mapping to GC B cells (BCL6, AICDA, CD38) were almost absent in participants with detectable VL at both sites. Differentially expressed gene analysis revealed increased expression of genes related to B cell activation and proliferation (MIF, CD74) in GC B cells from participants with HIV and suppressed VL and in genes related to migration of B cells to the GC (GNAI2, SWAP70) and T cell dependent B cell maturation (BASP1) in GC B cells from participants without HIV.

Conclusion: HIV infection is associated with a profound loss of intestinal GC B cells and may represent a major source of perturbation of humoral immunity at these sites of viral replication.

326 Persons With Residual Viremia on ART Have Higher Frequencies of Myeloid-Derived Suppressor Cells

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Background: Myeloid-derived suppressor cells (MDSC) are a heterogenous population that suppress T, B, and NK cell function through multiple mechanisms and expand with acute and chronic inflammatory conditions. We evaluated whether frequencies of MDSC are associated with measures of HIV persistence and levels of inflammation in persons with HIV (PWH) on long-term ART.

Methods: In the ACTG A5321 cohort of PWH with well-documented suppression of HIV-1 viremia on ART, we measured peripheral blood frequencies of classic (c) MDSC [Lineage(-), CD33+, HLADR-] and monocytic (m) MDSC [Lineage(-), CD33+, HLADR-, CD14+, CD11b+] by flow cytometry. To evaluate anti- or pro- inflammatory profile, we calculated the ratio of %mMDSC (anti-) and %intermediate monocytes (iMono; CD14+CD16+; pro-inflammatory). We then determined associations between MDSC frequencies and mMDSC/iMono (higher ratio – more anti-inflammatory) with measures of HIV persistence, including residual viremia, HIV DNA, cell-associated HIV RNA, and intact proviral DNA, and with soluble measures of inflammation.

Results: The 225 participants had a median age of 49 yrs, CD4 count of 681 cells/mm^3, and ART duration of 7 yrs. The median cMDSC frequency was 0.13% of all live cells while mMDSC was 0.08%. Frequencies of both MDSC populations correlated with each other (r=0.31; p<0.001, Spearman). Lower mMDSC frequencies were associated with longer ART duration (r= -0.20; p<0.001). Participants with residual viremia (HIV RNA≥0.4 cps/mL) had higher %cMDSC than those with HIV RNA <0.4 cps/mL (0.14% vs 0.11%; p=0.016, Wilcoxon; Fig 1). There was also a trend for higher %mMDSC in those with residual viremia (0.09% vs 0.07%; p=0.05). Higher frequencies of mMDSC and cMDSC were associated with lower levels of pro-inflammatory cytokines IP-10 (r= -0.23, p<0.001 & r= -0.18, p=0.008, respectively) and TNF (r= -0.15, p=0.024 & = -0.15, p=0.021, respectively) even after adjusting for pre-ART RNA. The mMDSC/iMono ratio did not correlate with any measure of HIV persistence. Higher ratios were associated with lower IP-10 (r= -0.24, p<0.001) and TNF (r= -0.15, p=0.028) levels even after further adjusting for age, pre-ART CD4 count, and years on ART.

Conclusion: Our finding that higher MDSC frequencies are associated with residual viremia despite long-term ART suggests that MDSC could inhibit virally suppressive HIV-specific immune responses. Reversing MDSC- mediated suppression would possibly enhance immune control of HIV but could also increase chronic inflammation.

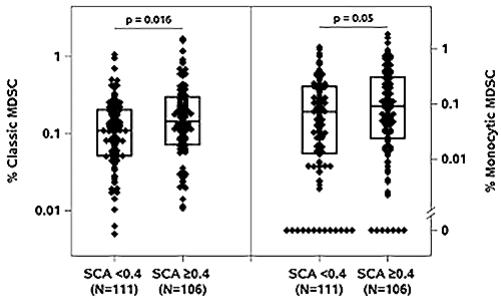

Fig 1: Figure shows the median (IQR) percentage of classic and monocytic MDSC in all live cells among A5321 participants with (single copy assay [SCA]≥0.4) and without (SCA<0.4) residual viremia.

327 Persistent HIV-1 Plasma Viremia in Patients on Therapy Caused by Macrophage-Tropic Lineage

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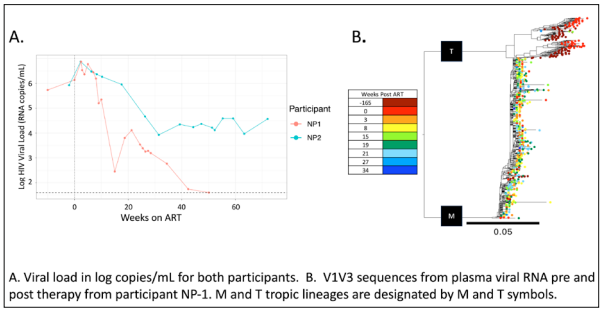
Background: Antiretroviral therapy (ART) usually suppresses plasma HIV-1 RNA to limits of detection within months of initiation. Rarely, persistent low-level

viremia occurs despite good ART adherence due to viral release from a large, clonally-expanded reservoir of HIV-infected CD4 cells. We describe two PWH on ART with persistent, high-level viremia that failed to fully suppress for >10 months, and was associated with persistent macrophage-tropic virus.
Methods: Two PWH (NP1, NP2) initiated ART with high HIV-1 viral load and low CD4 counts. Both were adherent to ART regimen, by observation and drug levels and no evidence of resistance emergence by Sanger and deep sequencing. Plasma samples were collected from both participants, and total PBMCs from one. Viral RNA was sequenced using MiSeq with Primer ID on portions of pol and the env V1/V3 region. Near-full length sequencing was conducted on proviral DNA from PBMCs and viral RNA from the plasma. Full length env were cloned from plasma RNA and proviral DNA for pseudoviral assays to assess infection efficiency at low CD4 density as a predictor of macrophage tropism.
Results: No DRMs were detected in either participant and a diverse plasma RNA population was seen in the V1V3 region. In NP1, a viral lineage representing ~50% of the total sequences rapidly declined, leaving a single, diverse persistent lineage, with no evidence of ongoing replication. In both participants, pseudoviruses generated from HIV envelopes of the persistent viremia were able to infect Low CD4 density cells to a similar degree as other described macrophage tropic viruses. In NP1, the plasma viral lineage that disappeared with ART initiation and that was present in total PBMC DNA did not infect at low CD4 density, consistent with T cell tropic viruses. Sequencing of PBMC DNA in NP1 found 2% of proviruses recovered were of the macrophage tropic lineage. Viral integration site analysis suggested intact proviral DNA from PBMCs was not clonal. Curiously, in this participant all M-tropic viruses were also found to have mutations in Vpr that abolished its open reading frame.
Conclusion: We describe two PWH with persistent high-level plasma viremia derived likely from infected macrophages with a long half-life, with additional studies being explored to confirm this. This has both clinical significance as the treatment regimens are still effective at preventing further infection, and has implications to the persistence of the reservoir in long-lived macrophages.



A. Viral load in log copies/mL for both participants. B. V1V3 sequences from plasma viral RNA pre and post therapy from participant NP-1. M and T tropic lineages are designated by M and T symbols.

328 Variable HIV-1 C Env Characteristics Associated With Predicted bNAb Resistance in Botswana

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Background: Characterizing HIV-1 early founder viruses is essential for informing vaccine design and broadly neutralizing antibody (bnAb) design. We analyzed variable region characteristics (VC) in HIV-1 seroconverters and compared them with predicted bnAb resistance/sensitivity using machine learning techniques.
Methods: We analyzed HIV-1 near-full-length proviral sequences from 140 adults with documented recent HIV-1 seroconversion who were enrolled in a previous population-based household study (BCPP, 2013-2018). We determined the variable loop (V1-V5) length and net charge patterns using the Variable Region Characteristics (VC) tool in the LANL HIV sequence database (hiv.lanl.gov). VC were stratified by bNAb resistance predicted using the bNAb-ReP algorithm (https://github.com/RedaRawi/bNAb-ReP). Wilcoxon ranksum test was used for assessment of variables between predicted bnAb resistance or sensitivity. We also assessed the presence of signature mutations associated with predicted resistance.
Results: A total of 140 consensus sequences were included in this analysis. Median log viral load (VL) of participants was 3.9 (Q1, Q3: 3.2, 4.4), median age 27 years (Q1, Q3: 22,33) and 20.7% were male. Few differences were observed between resistant and sensitive variants when looking at V1-V4 loop lengths, except for VRC26.25 and NIH45-46 where V1 loop was shorter in resistant compared to sensitive strains ($p<0.01$ and $p=0.04$) respectively. The most significant differences in variable regions between resistant and sensitive strains were observed with V5 loop length; where CD4 bnAb 2G12, DH270.5 and FP interface 35022 resistant strains had shorter V5 loop lengths; $p = <0.01$, <0.01 and 0.02 consecutively. V1 charge distributions were significantly different for VRC26.25 ($p=0.01$), PGT121($p<0.01$) and VRC01 ($p=0.01$) resistant strains. In terms of mutations, E164 was observed and associated with resistance to both CH01 and PGT145. We observe the mutation T234N in sequences resistant to 3BNC117 and b12. We did not record mutations N671T, W672L, WG80G and F673L among all 2F5 resistant strains. We did however observe K683R mutation in all strains resistant to 2F5.
Conclusion: Our findings further highlight the need to evaluate VC from sequence data, to determine the optimal vaccine design and best bnAb combinations to use for neutralization of highly variable HIV-1 subtype C.

329 Cannabis Use Enhances Mucosal Immunity and the Microbiome in Individuals With HIV

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Background: Cannabis is widely used by people living with HIV (PLWH) both recreationally and to mitigate HIV- or antiretroviral therapy (ART)-associated nausea, pain, anorexia, or other symptoms. Here, we evaluated immune function and intestinal health among a cohort of ART-treated, cannabis-using, and non-using PLWH. We hypothesized that cannabis using PLWH would have reduced inflammation and immune activation linked with a more immunomodulatory gastrointestinal (GI) microbiome.
Methods: Colon single-cell suspensions from cannabis-using and non-using ART-treated PLWH were analyzed for cellular immune function by multiparameter flow cytometry. Plasma levels of short-chain fatty acids (SCFA) as indicators of colonic function were assessed by GC-MS. GI microbial communities were profiled through colonic mucosa 16s rRNA sequencing. Cannabis use or non-use was verified in all participants by LC-MS.
Results: Although overall frequencies of CD4+ and CD8+ T-cells were unchanged ($p=0.692$ and $p=0.204$, respectively), the frequencies of activated HLA-DR+CD38+ CD4+ and CD8+ T-cells were significantly decreased in the colon of ART-treated cannabis-using as compared to non-using PLWH ($p<0.0001$ for both subsets). Frequencies of colon IgA+ and IgG+ B cells were significantly increased in cannabis users vs. non- users ($p=0.0006$ and $p=0.0259$, respectively). Cannabis users had significantly lower frequencies of colon TNF- α+CD20+B cells as compared to non-users ($p=0.0001$). Plasma concentrations of the SCFAs acetate ($p<0.0001$), propionate ($p=0.0034$), butyrate ($p=0.0001$), and isobutyric acid ($p=0.0043$) but not valeric acid and isovaleric acid were increased in cannabis users vs. non-users. Lastly, ART-treated cannabis using PLWH possessed colonic mucosa microbiomes dominated by Prevotella, followed by Bifidobacterium, Faecalibacterium, Succiniclasticum, and Collinsella. No differences in alpha diversity were observed between ART-treated cannabis-using and non-using PLWH.
Conclusion: ART-treated cannabis using PLWH had significantly lower frequencies of activated CD4+ and CD8+ T-cells and TNF-α+CD20+B cells, suggesting lower inflammation and immune activation as compared to non-cannabis users. Cannabis use has the potential to alleviate HIV-associated inflammation through alterations in microbial community structure and function. Overall, this study provides important insights into the impact of cannabis use on immunity and the microbiome of PLWH.

330 HIV, Not Integrase Inhibitor-Based ART, Modifies Gut Microbiota Composition in MSM

Marta Rosas Cancio-Suárez, Luis Miguel Nieto-Salas, **Claudio Díaz-García,** Jorge Díaz- Álvarez, Alejandro G. García-Ruiz De Morales, Clara Crespillo Andujar, Laura Luna Garcia, Elena Moreno, Laura Martín-Pedraza, Maria Fons, Javier Martínez-Sanz, Raquel Ron, Santiago Moreno, Matilde Sánchez-Conde, Sergio Serrano-Villar
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Background: Understanding gut microbiota variations in HIV is confounded by factors like antiretroviral therapy (ART), immune status, and sexual orientation. We aimed to isolate the impact of integrase inhibitor (INSTI)-based ART on gut microbiota among men who have sex with men (MSM) across varying conditions of HIV status and immune recovery.
Methods: We conducted an observational study with three cohorts: 1) MSM HIV-negative (HIV-) initiating post-exposure prophylaxis (PEP) with raltegravir, tenofovir disoproxil fumarate, and emtricitabine, sampled on days 0 and 28. 2) MSM with advanced HIV (HIV+ <350 CD4+ T-cells), sampled before and 48 weeks after starting INSTI-based ART. 3) MSM with HIV and adequate immune recovery (HIV+ >500 CD4) after an average of 9.5 years on ART. Stool samples were processed for DNA extraction, sequenced for the V3-V4 regions of the 16S rDNA gene using the Illumina platform and analyzed through the QIIME2 workflow. DADA2 was used to infer Amplicon Sequence Variants, which were assigned to taxonomic entities up to the genera level with a Silva-based 16S Naive Bayes classifier. Differential abundance testing to identify specific taxa was executed with ANCOM.
Results: We included 22 MSM HIV-, 23 MSM HIV+ <350 CD4, and 29 MSM HIV+ >500 CD4 participants. Pairwise comparisons were performed to delineate the effects of ART, HIV status, and immune function on microbiota composition. Alpha diversity varied significantly between specific groups (Figure 1A), with highest values in HIV- MSM compared to HIV+ MSM. Weighted UniFrac analysis also demonstrated microbial composition differences between MSM with and without HIV (Figure 1B). Lachnoclostridium genera was more abundant in MSM HIV+ < 350 CD4 ($p = 0.0017$). Alloprevotella was significantly higher in MSM HIV+ <350 CD4 before ART ($p=0.0002$) than in MSM HIV-. ART itself showed no significant impact on microbiota composition across all cohorts.
Conclusion: In this study not confounded by sexual orientation, HIV and immune status significantly affected gut microbiota composition. However, we found no evidence to suggest that INSTI-based ART negatively influences gut microbiota composition.

Figure

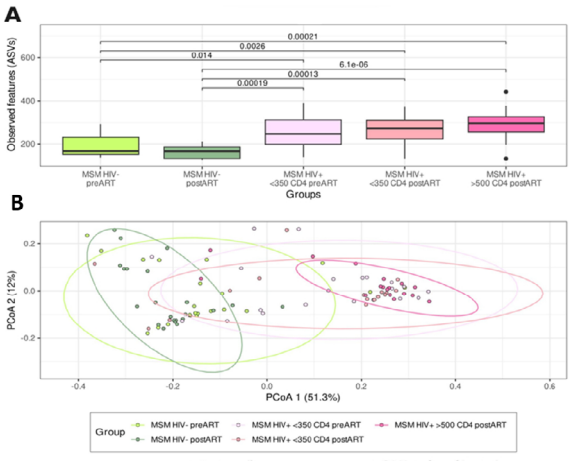

Figure 1. Diversity analysis
A. Alpha diversity analysis. ANOVA analysis differences between grupos ($p<0.001$). Significant Tukey post-hoc test results ($p<0.05$)
B. Beta diversity analysis. PERMANOVA significant differences between most clusters ($p<0.05$).
ART: Antiretroviral therapy, MSM: men who have sex with men

331 Microbe-Drug Interactions Between Antiretrovirals and the Gut Microbiome in HIV Infection

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Background: For people living with HIV (PLWH), antiretroviral therapy (ART) typically controls HIV replication and greatly reduces mortality, however, does not cure HIV and PLWH must maintain ART treatment inevitably. During passage through the GI tract, ARVs encounter the gut microbiome, where they may affect the growth of microbes or potentially be metabolically transformed by bacteria into less active or toxic forms. Here, we investigated the antimicrobial effects of 17 different ARVs and their in vitro ability to alter microbes to better understand how ART may impact the gut microbiome in PLWH. Furthermore, we investigated the ability of gut bacteria to metabolize ARVs to understand if the gut microbiome may play a role in bioavailability of ARVS.
Methods: Bacterial isolates and stool communities were grown from glycerol stock and diluted into fresh media containing the selected ARVs. Growth of bacterial isolates was monitored by measuring the OD600 every 30 minutes for 48 hours. Changes in the bacterial stool communities was determined by 16S V4 rRNA sequencing after 24 hours of incubation with ARVs. ARV drug metabolism by bacterial isolates and whole stool communities was determined by measuring drug concentrations by LC-MS/MS utilizing a novel assay developed in our lab to concurrently measure 17 ARVs.
Results: ARVs, especially the integrase inhibitors dolutegravir and elvitegravir, significantly inhibit the growth of gut bacteria including Bacteroides fragilis and Prevotella stercorea ($p < 0.05$, Welch's t-test). The total bacterial load of in vitro stool cultures measured by the 16S region was significantly different between drug treatments ($p < 0.05$, Kruskal-Wallis). Furthermore, bacterial stool communities from HIV-infected individuals significantly depleted tenofovir disoproxil fumarate ($p = 0.005$, Welch's t-test) and cultures with bacterial isolates including Bacteroides fragilis depleted elvitegravir and cobicistat ($p = 0.0102$ and $p = 0.0108$ respectively, Welch's t-test).
Conclusion: Overall, these results show that specific ARVs can inhibit the growth of strains of gut bacteria and have an impact on a bacterial community's composition in vitro. This has potential implications in how ART affects the gut microbiome of PLWH and associated microbial metabolic products, which is under further study in the lab. Finally, bacterial communities from stool have the metabolic potential to deplete specific ARVs in vitro, which may be important in the interindividual success of ART for PLWH.

332 Gut-Microbiome Changes Over 4 Years in PLWH With Good Immune Status on ART

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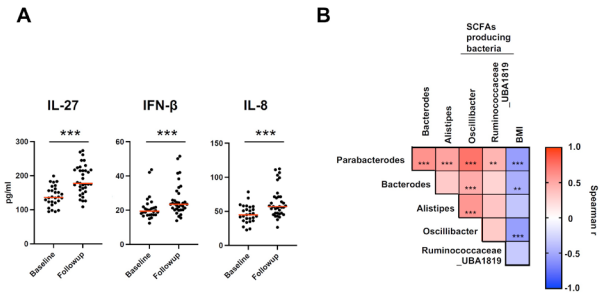
Background: The gut microbiota of PLWH who have achieved good immune recovery through ART is as diverse as that of healthy individuals, but the composition of the bacterial taxa is significantly different, which is indicated to be related to chronic inflammation. We evaluated the correlation between changes in the gut microbiota, clinical information, and inflammation biomarkers in PLWH between baseline and after 4 years of follow-up.
Methods: Stool and blood samples, along with the laboratory parameters, were collected from 46 PLWH at baseline and after 4 years of follow-up. The microbiome was characterized by sequencing of the 16S rRNA V3- V4 regions on the Illumina MiSeq platform, and data were analyzed using QIIME2 software. Functional gene predictions of the bacterial microbiota were inferred from the 16S rRNA using PICRUSt2 pipeline. The concentrations of cytokine and LPS-binding protein (LBP) were quantified using a Bio-Plex System and ELISA, respectively.
Results: There were no significant changes in laboratory parameters between baseline and follow-up except for body mass index (BMI). However, the progression of gut dysbiosis was observed; Lachnospiraceae, involved in short-chain fatty acid (SCFA) production, decreased, while Enterobacteriaceae, potentially pathogenetic bacteria, increased. A decrease in vitamin B1 (thiamine) biosynthesis was predicted from 4-year alternations, suggesting an intestinal environment that is less conducive for SCFA-producing bacteria to proliferate. Higher levels in IL- 27, IFN-β (an LPS/TLR4-inducible cytokine) and IL-8 at follow-up suggested the progression of intestinal permeability while HIV RNA remained low on ART. These cytokines were positively correlated with the bacterial translocation measured by plasma LBP. An increased

BMI was significantly associated with IL-16 and CXCL13, both of which are involved in intestinal inflammation and bacterial migration. A low abundance of Parabacteroides which lead to the disturbances of secondary bile acid metabolism, was associated with a BMI of 25 and over, low α diversity, low abundance of SCFA-producing bacteria, as well as weight gain for 4 years.
Conclusion: HIV-specific dysbiosis progressed despite effective ART. This dysbiosis correlated with weight gain and was characterized by Intestinal permeability that also persisted and was associated with systemic inflammation. This suggests that the intestinal environment in PLWH may potentially affect metabolic imbalance and inflammation.



Panel A) Comparative analysis of inflammatory cytokine levels in PLWH between baseline and follow-up. Panel B) Correlation analysis between gut microbiota (genus) and BMI. * p<0.05, ** p<0.01, *** p<0.001

333 Comparisons of Oral and Gut Bacteria Highlight Role of *Veillonella* in Systemic Inflammation in HIV

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Background: Chronic inflammation contributes to multiple comorbidities in people living with HIV. Translocation of gut bacteria and resultant immune activation may in part drive this inflammation; however, the role of the oral microbiome in this phenomenon is unknown. We investigated the effects of HIV on the oral microbiome and the relative contribution of oral and gut bacteria to systemic inflammation.
Methods: Oral and gut microbiome composition was determined by 16S rRNA gene sequencing of saliva samples and rectal swabs from 98 men who have sex with men (MSM) with HIV and 99 MSM without HIV. Biomarkers were quantified in serum using multiplex Luminex assays. Relative contributions of oral versus gut bacteria to biomarker variation was analyzed using PERMANOVA and significant relationships identified using mixOmics. Anti-bacteria IgG ELISAs were developed to assess oral bacteria translocation and quantified by serum endpoint IgG titers. Relationships between immune biomarkers and endpoint IgG titers were examined using correlation analysis.
Results: The oral microbiome composition in MSM differed by HIV status with increased *Veillonella*, *Capnocytophaga*, and *Megasphaera* seen with HIV. Known inflammatory biomarkers also increased with HIV (fatty acid binding protein 2 (FABP2) p<0.001; sCD27 p=0.006; sCD163 p=0.01; CXCL10 p<0.001; IL-6 p=0.03; TNF-alpha p=0.007). The oral microbiome was an important contributor to inflammatory biomarker variance showing greater influence than the gut for several biomarkers (sCD27, LPS-binding protein (LBP), CRP, CXCL10, TNF-alpha, IL-6) (Figure). Anti-bacteria (*Veillonella parvula, Fusobacterium nucleatum, Porphromonas gingivalis*) endpoint IgG titers did not differ by HIV status. However, there was a significant correlation between both LBP (r_s=0.34, p=0.02) and sCD14 (r_s=0.3, p=0.04) with Veillonella parvula IgG in MSM with HIV. mixOmics analysis also identified key correlations between oral Veillonellla with IL-6 and FABP2. In vitro studies showed heightened inflammatory potential of Veillonella parvula with peripheral immune cells.
Conclusion: The oral microbiome differs in MSM with HIV and is an important contributor to altered inflammatory biomarkers. Correlations between key oral bacteria and inflammatory biomarkers suggest that systemic circulation of oral bacteria, including *Veillonella parvula*, could be another important mechanism driving chronic inflammation in HIV.

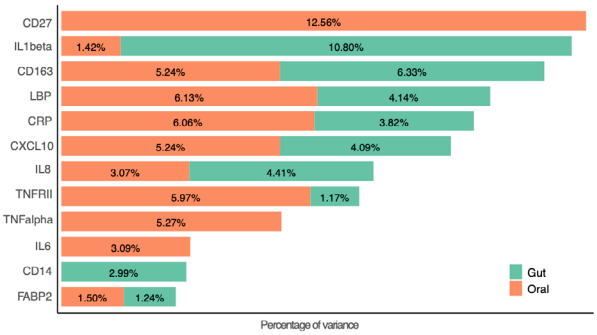

Figure: Relative contribution of oral vs gut bacteria to inflammatory biomarker variance as determined using PERMANOVA. Percentages represent the percent variance explained by each microbiome compartment.

334 CX3CR1+ Vδ1 T-Cells Are Clonally Expanded and Driven by CMV, Microbiota, and HIV- 1 in the Gut on ART

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Background: The Vδ1 subset of γδ T cells resides mainly in tissues, where it participates in innate and adaptive immunosurveillance, notably in the gut, a major site for HIV-1 persistence. Vδ1 cells normally represent a minor part of blood γδ T cells, but they expand during HIV-1 infection, with an inversion of the Vδ1/Vδ2 ratio, the causes of which are not yet clear.
Methods: Duodenal biopsies and blood samples from 15 virologically suppressed people living with HIV-1 (PLWH) and 15 uninfected controls recruited in the ANRS EP61 GALT study were used to assess the frequency, phenotype and function of Vδ1 T cells by FACS. Samples from 5 PLWH and 5 controls were used to sequence the TRDV1 chain repertoire. Single-cell RNAseq was performed on sorted circulating Vδ1 T cells from 6 PLWH and 6 controls. Total and intact HIV-1 DNA and residual HIV-1 RNA were quantified, and 16S-RNA PCR was used to amplify and sequence bacterial DNA in gut and blood samples. All selected subjects were CMV seropositive.
Results: PLWH had increased circulating CX3CR1+ Vδ1 effector cells compared with uninfected controls (median 17.2/µL, [4.5-26.3] vs. 3.3/µL [1.2-7.3] respectively; P=0.03). The phenotype of expanded CX3CR1+ Vδ1 cells globally clustered with terminal differentiation markers (TEMRA: CD27-CD45RA+), and into subpopulations expressing the activating receptor NKG2C and the exhaustion marker TIM-3. CX3CR1+ Vδ1 TEMRA cells were highly cytotoxic, with high levels of granzyme B and perforin, but low production of IFNγ and TNFα. Gut intra-epithelial lymphocytes (IEL) were more cytotoxic (perforin+) and activated (NKG2C+) in PLWH, the latter correlating with the Vδ1/Vδ2 ratio in blood. Repertoire analysis revealed clonal expansions in PLWH blood, compared with matched duodenal IELs and uninfected controls. The expansion, phenotype, and cytotoxicity of blood Vδ1 cells in PLWH were notably associated with the CMV IgG index, the abundance of various bacterial species in the duodenal and blood microbiome, and HIV-1 RNA and DNA in blood and gut (Figure).
Conclusion: Highly cytotoxic CX3CR1+ Vδ1 effector cells are clonally expanded in the blood and associated with Vδ1 IEL activation in the gut of PLWH on ART. They may be triggered by the interplay between residual CMV replication, gut and blood microbiome, and the gut HIV-1 reservoir. CX3CR1+ Vδ1 effector cells may contribute to the control of HIV-1 persistence on ART, but might also be involved in chronic vascular inflammation in PLWH due to their endothelial tropism.

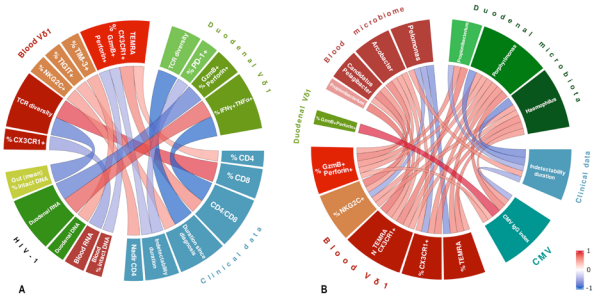

Figure. Associations between circulating and IELs Vδ$_1$ T cells and (A) HIV-1 reservoir, (B) microbiome and CMV in PLWH (N=15). Color scale indicates Spearman's correlation coefficient.

335 Bacteria-Induced Granzyme B Contributes to HIV-1-Mediated Gut CD4 T-Cell Depletion Ex Vivo

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Background: The gastrointestinal (GI) tract is a major site for early, massive, and persistent CD4 T cell depletion following acute HIV-1 infection. The mechanisms driving this profound death of gut CD4 T cells remain poorly understood. Among persons with HIV-1 (PWH), a disrupted epithelial barrier results in the translocation of bacteria from the gut lumen to the underlying lamina propria (LP) and systemic circulation. We reported that ex vivo exposure of LP mononuclear cells (LPMC) to enteric bacteria augmented HIV-1-mediated gut CD4 T cell death, shifting the death mechanism from pyroptosis to apoptosis. Microbial exposure of gut CD4 T cells ex vivo upregulated granzyme B (GZB) – an enzyme that facilitates target cell killing by cytotoxic T/NK cells via apoptosis. GZB+ CD4 T cells were detected at higher frequencies in colon biopsies of PWH compared to uninfected controls, despite lower overall CD4 T cell frequencies.

Methods: To test if GZB plays a critical role in HIV-1-mediated gut CD4 T cell death, LPMC (n=6 donors) were infected with Transmitter/Founder (TF) HIV-1 (CH040) or mock then exposed to bacterial lysate (Escherichia coli) in the presence/absence of a specific GZB inhibitor, Z-AAD-CMK. 4dpi LPMC were collected and GZB expression, infection (HIV-1 p24), apoptosis (AnnexinV, viability dye/AqVi), and number of CD4 T cells were determined by flow cytometry. OX40 and TNFR2 expression were assessed by flow cytometry.

Results: Higher levels of TF HIV-1 infection were observed in GZB+ versus GZB- CD4 T cells (3-fold, p=0.003). GZB+ CD4 T cells showed 1.56-fold higher levels of apoptosis markers (AqVi- AnnexinV+) compared to GZB- cells (p=0.007). TF HIV-1 infection led to substantial CD4 T cell death compared to mock – on average 44% of CD4 T cells depleted in TF HIV-1 infected cultures (p=0.01). Z-AAD-CMK inhibited GZB activity in E. coli-stimulated CD4 T cells by 64%; GZB inhibition rescued CD4 T cells from HIV-1-mediated death (16% vs 44% depletion; p=0.02). HIV-1-infected GZB+ CD4 T cells that survive to 4dpi showed higher expression of anti-apoptotic factors OX40 and TNFR2 compared to GZB- cells (p<0.05).

Conclusion: Our findings suggest that bacteria-mediated GZB induction may be a mechanism contributing to massive CD4 T cell death in the GI tract during acute HIV-1 infection. The induction of anti-apoptotic factors in GZB+ CD4 T cells that survive in vitro HIV-1 infection raise the possibility that surviving GZB+ CD4 T cells in the gut may serve as a significant HIV-1 reservoir.

336 Distinct Intestinal Microbial Signatures Linked to Accelerated Biological Aging in People With HIV

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Background: HIV infection disrupts the intestinal barrier, resulting in persistent inflammation, even with antiretroviral therapy (ART). This inflammation contributes to aging-related comorbidities in people with HIV (PWH). However, it remains unclear whether ART-suppressed HIV affects intestinal biological aging and whether microbial dysbiosis and translocation contribute to aging in PWH on ART.

Methods: Colon and ileal biopsies, blood, and stool were collected from 25 PWH on ART (viral load <50 copies/ml) and 23 age, sex, and ethnicity-matched HIV-negative controls. Accelerated biological aging in colon, ileum, and blood was assessed by regressing biological age estimated by several epigenetic aging clocks (Horvath1, Horvath2, Hannum, PhenoAge, GrimAge, and DunedinPACE) against chronological age. Intestinal integrity was assessed by immunofluorescence staining for tight junction proteins (Z01, occludin). Markers of microbial translocation (e.g., LBP) and inflammation were measured by ELISA/multiplex arrays. Microbiota profiles of stool, ileum, and colon were determined via 16S rRNA sequencing, and metabolic analyses of plasma and stool were conducted using mass spectrometry.

Results: Despite similar chronological age (Fig. 1A), PWH exhibited accelerated biological aging of the ileum, colon, and blood. Colon and ileum from PWH showed reduced tight junction proteins and increased microbial translocation, significantly associated with accelerated biological aging and higher inflammation (P<0.05). Putative pro-inflammatory bacteria like Catenibacterium and Prevotella 2/9 were enriched in PWH, correlating with accelerated aging (FDR<10%). Conversely, short-chain-fatty-acid-producing and anti-inflammatory bacterial genera, like Subdoligranulum and Erysipelotrichaceae UCG-003 were depleted in PWH, correlating with decelerated aging. Correlation networks revealed associations between specific microbial genera in the colon and ileum (not shown) with accelerated aging, enrichment of pro- inflammatory microbial-related metabolites, and depletion of anti-inflammatory metabolites (P<0.05).

Conclusion: Distinct microbial profiles are linked to intestinal and systemic biological aging in PWH on ART. Further research is needed to understand the mechanisms connecting microbial dysbiosis/translocation to intestinal and systemic biological aging in PWH and to develop preventive strategies.
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337 Deep Metabolic Profiling for Tissue-Specific Responses Against SARS-CoV-2 Variants in Hamster Models

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Background: While most people recover from acute COVID-19, a significant percentage experience long-term health issues known as post-acute sequelae of SARS-CoV-2 infection (PASC). The underlying host tissue response during acute infection might contribute to long-term effects in people with PASC. To understand this, we investigated the host-tissue responses of SARS-CoV-2 variants using the hamster model.

Methods: Syrian golden hamsters (SGHs) were infected with the delta and omicron variant, and uninfected SGHs were used as controls. The hamsters were euthanized four days post-infection, plasma and tissue samples from the lung, brain, heart and kidney were collected to analyse SARS-CoV-2 viral load and untargeted metabolomics.

Results: Compared to omicron-infected SGHs, delta-infected SGHs had a higher viral load in lungs (p=0.02), heart (p=0.009), brain (p=0.019), and plasma (p=0007). However, viral load in the kidney of delta- and omicron-infected SGHs did not differ significantly. Principal component analysis (PCA) identified distinct brain metabolite profiles, while showing no disparity in heart metabolites between three groups. Kidney metabolites in infected SGHs differed from naïve ones, and plasma metabolites in omicron-infected and naïve SGHs were distinct from delta-infected SGHs. Detailed investigation of individual metabolites showed the varied effect of delta and omicron variants across multiple tissues. Delta variant infection led to differential regulation of 46, 34, 60, 165, and 37 metabolites, whereas omicron variant infection resulted in 21, 112, 67, 160 and 4 differentially regulated metabolites in lung, brain, heart, kidney and plasma respectively. In the brain and heart, major distinctions were observed in amino acids, with arginine, aspartate, methionine, proline, and tyrosine levels being higher in omicron-infected SGHs compared to those infected with the delta variant suggesting the dysregulation of amino acid biosynthesis/metabolism, nucleotide metabolism and energy metabolism pathways.

Conclusion: Our findings indicate that SARS-CoV-2 mediated tissue insult leads to altered host metabolites during acute infection in a strain specific manner.

Therefore, our data provide a basis for understanding tissue responses during infection and potentially some mechanistic basis on developing PASC once confirmed in human subjects. Further, this information will be valuable for developing/refining mucosal vaccines against emerging SARS-CoV-2 variants.

338 Markers of Microbial Translocation and Inflammatory Cytokines Are Predictive of Severe COVID-19

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Background: The novel SARS-CoV-2 virus caused the global COVID-19 pandemic resulting in approximately 770 million global cases and 7 million deaths to date. Several factors predict severe COVID-19 including comorbidities such as age, cardiovascular disease and diabetes. Furthermore, gastrointestinal symptoms and microbial dysbiosis are commonly observed in COVID-19 and may therefore be indicators of severe disease. In this study, we aimed to understand the differences in markers of microbial translocation and circulating cytokines between healthy individuals and patients with severe COVID-19. We then investigated the accuracy of these biological factors in predicting whether an individual was healthy or had severe COVID-19.

Methods: A cohort of California-based participants were entered into the study, consisting of 62 patients hospitalized with COVID-19 and 115 healthy individuals. Plasma samples were used to measure circulating concentrations of cytokines by Luminex and markers of microbial translocation including LPS-binding protein (LBP), soluble CD14 (sCD14), intestinal fatty acid binding protein (I-FABP), and Zonulin were measured by ELISA.

Results: Hospitalized COVID-19 patients had significantly higher plasma concentrations of markers of microbial translocation including LBP and sCD14 compared to healthy individuals (p=1.4-17, p=9.35-5). Hospitalized patients also had elevated inflammatory plasma cytokine concentrations, most notably IL-6, TNF-α, IFN-γ, and IL-18. Spearman correlation analysis showed that IL-6 was significantly positive correlated with markers of microbial translocation including LBP and sCD14 (p=1.42-25, p=1.455-4). A random forest model showed the best accuracy in predicting healthy versus hospitalized individuals with a true positive percent (TPP) of 94%. LBP and IL-6 were the greatest drivers of prediction. This model was further tested on two other COVID-19 datasets with varying accuracy: 81% TPP and 75% TPP.

Conclusion: Hospitalized individuals were characterized by elevated inflammatory cytokines (especially IL-6) and microbial translocation measured by sCD14 and LBP. The correlation between inflammatory cytokines and markers of microbial translocation suggests a relationship between gut barrier integrity and systemic inflammation in COVID-19, which may better predict whether an individual is healthy or has severe COVID-19, with IL-6 and LBP being the most important variables in the prediction.

339 Pathogenic Monocyte, Th17, and NK Cell Immune Networks in the Lung From Critical COVID-19 Patients

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[1]Universidad Autónoma de Madrid, Madrid, Spain, [2]Hospital Universitario de La Princesa, Madrid, Spain, [3]Vall d'Hebron Research Institute, Barcelona, Spain, [4]Hospital Ramón y Cajal, Madrid, Spain

Background: Pathogenic inflammation in the lung has been connected to non-classical monocytes (NC-Mo), Natural Killer (NK) cells and Th1/Th17 cell immune responses in critical COVID-19 patients. However, the pathogenic inflammatory networks in the pulmonary tissue of these patients, including interactions between specific innate immune cell subsets, the underlying molecular mechanisms involved in their activation and the functional impact on pathogenic Th1/Th17 cells is not completely understood and may lead to new therapeutic targets.

Methods: Frequency, activation and functional maturation of NC-Mo and memory NK cell subsets from n=17 Bronchoalveolar lavage (BAL) and n=16 peripheral blood (PB) samples from critical COVID-19 patients and n=9 healthy controls were assessed at baseline or after in vitro stimulation with SARS-CoV-2 Spike (S1) peptide pools. Histological distribution and activation of Mo and Th1/Th17 was also addressed by immunofluorescence in lung tissue from n=3 deceased critical COVID-19 patients. Induction of SARS-CoV-2 specific Th1 and Th17 cells in response to S1 peptides or S1-primed Mo was analyzed in PB and BAL from critical COVID-19 patients. Correlation network between immune, functional and clinical parameters from BAL samples was also assessed.

Results: SARS-CoV-2 S1 induced Mo differentiation into NC-Mo in BAL and PB samples from critical COVID-19 patients and required NFκB activation. In addition, activation of NC-Mo in response to S1 was associated with higher ability to induce IFNγ+ and IL-17+ CD4+ T cells (p=0.0156) and was dependent on NLRP3 inflammasome. Importantly, NLRP3+Caspase1+ Mo, IFNγ+ and IL-17+ T cells were detected in in highly infiltrated areas from the lung of deceased COVID-19 patients. Consistently, higher levels of the inflammasome target ferritin correlated with increased detection of Th17 cells in these individuals (p=0.037). Additionally, memory NKG2C+ NK cells were enriched in BAL and PB in critical COVID-19 patients and increased expression of TRAIL on this population significantly correlated with higher frequencies of NC-Mo in the lung (p=0.016) and increased levels of systemic inflammation biomarkers such as procalcitonin (p=0.017), C-reactive protein (p=0.0027) and ferritin (p=0.016) in these subjects.

Conclusion: Interconnection between inflammasome activation in Mo, induction of Th1/Th17 and NKG2C+ memory NK cells feed pathogenic immune cell environments during critical COVID-19 and may represent promising therapeutic cellular targets.

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340 Complement-Driven Type-I IFN Response Enhances mTOR Activation and T-Cell Immunity

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Background: Uncontrolled SARS-CoV-2 infection is associated with disorders of the innate immune and delayed adaptive immune systems. Yet, it remains unclear how SARS-CoV-2 causes local and systemic dysregulation. The role of the complement system in SARS-CoV-2 pathogenesis is well established, in particular as a driver of systemic inflammation which is characteristic of severe COVID-19. Although complement is traditionally known as a central arm of innate immunity, it has equally important roles in the regulation of adaptive immunity. However, how mechanistic complement affects dendritic cell (DC) functionality and T cell- priming upon SARS-CoV-2 infection, is still poorly defined.

Methods: Effects of differently opsonized SARS-CoV-2-loaded primary DCs were measured by RT-PCR, ELISA, PathScan and flow cytometry. Co-culture with naïve CD4+ and CD8+ T cells, T-cell activation, cytotoxic T-cells GRZB/PRF production and SARS-CoV-2–specific cytokine-producing T-cells were measured by flow cytometry and ELISpot.

Results: DC were not susceptible to SARS-CoV-2 infection, and exposure to SARS-CoV-2 triggered neither induction nor secretion of type-I IFN and inflammatory cytokines. Notably, complement-opsonized-SARS-CoV- 2 loaded-DCs displayed enhanced maturation and efficient type-I IFN and IL-1β responses, suggesting that complement is crucial for mediating immunity against SARS-CoV-2. Here, we describe that IL-1β secretion occurs following intracellular caspase-1 activation by inflammasome activation, revealing a mechanistic link between complement and IL-1β secretion in human DCs. Strikingly, complement-triggered IL-1β production was mediated by the mammalian target of rapamycin (mTOR). NLRP3 inhibition resulted in impaired priming of IFN-gamma-producing CD4+ and CD8+ T cells, suggesting an essential role of complement in increasing antigen-specific T-cell responses.

Conclusion: The potential for myeloid cells to act as bona fide targets of SARS-CoV-2 infection remains unclear. Here, we show that complement-opsonized SARS-CoV-2 induces type I IFN secretion, upregulates the mTOR pathway and directly activates NLRP3, which leads to IL-1ß secretion. The role of IL-1 β as part of the bridge between innate and adaptive immunity may be clinically translated into therapeutic strategies to empower the formation of T cell immunity. Our data demonstrate distinct immunological functions for DCs and consider the role of complement and mTOR activation in regulating immune system responses in SARS-CoV-2 infection.

341 Prolonged SARS-CoV-2 Viral Burden and Impaired Immunity in SIV/SARS-CoV-2 Coinfected Macaques

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Background: People living with HIV (PLWH) have increased risk of morbidity and mortality from COVID-19. SARS-CoV-2 infection in PLWH poses a risk of prolonged infection and viral shedding, and emergence of variants of concern. Using the SIV macaque model for AIDS, we test the hypothesis that immune dysfunction during HIV infection alters SARS-CoV-2 viral infection and COVID-19 disease.
Methods: Eight female rhesus macaques were intravaginally infected with SIVmac251, then intranasally and intratracheally inoculated with SARS-CoV-2 (WA-1) at 17-34 weeks post-SIV inoculation. Blood, bronchoalveolar lavage, stool, and nasal, oral, and rectal swabs were collected pre-infection through 14 days post-infection (DPI). ELISAs, ELISPOT, qRT-PCR, lung pathology, cytokine multiplex, and virus neutralization assays were performed to measure viral loads, pathogenesis, and immune responses.
Results: We observed no significant changes in SIV clinical symptoms or viremia post-SARS-CoV-2 co- infection, and COVID-19 disease was typically mild. At 14 DPI, SARS-CoV-2 replication persisted in the upper, but not the lower respiratory tract. Notably, SARS-CoV-2 RNA levels in nasal swabs were significantly higher 7- 10 DPI in SIV+/SARS-CoV-2 infected rhesus when compared to published data in SIV-/SARS-CoV-2 rhesus (PMCID: PMC8462335, PMC8829873). Anti-SARS-CoV-2 binding antibodies in sera were significantly lower in the SIV+ macaques when compared to those from historical SIV-/SARS-CoV-2 infected controls. Furthermore, generation of SARS-CoV-2 spike-specific T-cell responses were hindered at 14 DPI.
Conclusion: Here, we provide evidence for the utility of the rhesus macaque in modeling human HIV/SARS- CoV-2 co-infection. Our results suggest that SIV-induced immunosuppression impairs generation of anti-SARS- CoV-2 immunity, that may, in turn, contribute to prolonged SARS-CoV-2 viral shedding, increased transmission windows, altered disease pathogenesis, and lower protection against subsequent SARS-CoV-2 exposures. Studies in progress will determine whether SARS-CoV-2 viral evolution is accelerated in SIV-infected macaques.

342 Viral Shedding and Mucosal Lymphocyte Disruptions in SARS-CoV-2 Infection Exacerbated by Fatty Diet

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Background: Although numerous co-morbidities such as diabetes, obesity, and pulmonary disorders like COPD are known to enhance the risk of severe COVID-19, dietary influences on disease outcome have not been thoroughly studied. Diets high in sugar and fat associate with several co-morbidities and have been shown to enhance disease in a chronic viral infection, SIV, but have not been investigated for an impact on the acute viral infection SARS-CoV-2. In this study we examine the impact of diet on pathology and immune responses to SARS-CoV-2 infection.
Methods: Pigtail macaques (3M, 3F) were fed a commercial monkey chow, then provided a high fat and sugar chow (high fat diet, HFD) for approximately two months preceding SARS-CoV-2 infection (Delta stain). HFD was maintained during infection until euthanasia at day 30-32 of SARS-CoV-2. Three control pigtail macaques (2M, 1F) were infected with the same SARS-CoV-2 strain and dose, and maintained on a commercial monkey chow diet until euthanasia at day 30.
Results: Viral RNA (vRNA) was detected for up to 28 days post-infection in nose swabs of both control and HFD macaques, with mean viral loads highest at day 2 and declining thereafter. Mean viral loads were higher at all time points assessed in animals fed a HFD vs. controls, with area under the curve (AUC) of the HFD animals more than 100 times greater than controls ($6.6x10_{10}$ and $1.6x10^8$, respectively). Subgenomic RNA (sgRNA, indicating viral replication) was greater in HFD animals as well, with AUC $1.1x10_{10}$ vs. 2.7x10 . Shedding of vRNA in stool was greater in animals fed HFD, with higher AUC and detectable vRNA for a longer duration. Rectal biopsies indicated decreased B cell frequency following SARS-CoV-2 infection in both control and HFD animals, however significantly lower B cell frequencies were observed between baseline and approximately two months following HFD administration (p=0.03, Wilcoxon). B cell loss was coupled with significant T cell expansion during HFD administration (p=0.03, Wilcoxon), then frequencies declined modestly following infection.
Conclusion: SARS-CoV-2 infection can induce lymphopenia, and our sampling of gut mucosal tissue indicates B cell depletion with a HFD that is further exacerbated by SARS-CoV-2 infection, as well as greater shedding of vRNA in both GI tract and respiratory tracts of animals fed a HFD. Excess dietary fat and sugar may disrupt gut barrier integrity and immunity, in turn predisposing the tissue to pathology during viral infection.

343 Impact of COVID-19 Progression in Patients With Hypertension

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Background: Coronavirus disease (COVID-19) due to SARS-CoV-2 infection is aggravated by some comorbidities, with arterial hypertension being one of the most common. Hypertensive patients are more vulnerable to developing severe COVID-19 complications through different joint mechanisms. The main objective is to find biomolecules and metabolic pathways through a multiomic approach that may explain the relationship between hypertension and unfavourable COVID-19 disease progression.
Methods: One hundred and three patients with COVID-19 were classified according to disease severity (mild, severe and critical) and divided into hypertensive (n=26) and non-hypertensive (n=77). Serum samples were collected at the time of admission (acute phase) and four to eight weeks later (recovery phase), and multiomics studies of proteins, lipids and metabolites were performed. Statistical analyses were carried out by Metaboanalyst 5.0 and SPSS Statistics 25.0.
Results: Hypertension was present in 25.2% of COVID-19 patients as a previous comorbid disease. Hypertension was significantly related to COVID-19 severity (p=0.008), in fact, 84.6% of the hypertensive patients belonged to the unfavourable COVID-19 group (severe and critical). The profile of biomolecules changed depending on the study phase, with the number of significant molecules in the acute phase (n=43) greater than those in the recovery phase (n=25). In the acute phase, myo-inositol (AUC=0.695), phosphatidylcholine 32:1 (AUC=0.643) and gelsolin (AUC=0.696) were best able to distinguish between hypertensive and non-hypertensive patients and in the recovery phase, gelsolin (AUC=0.674), zinc-alpha-2- glycoprotein (AUC=0.711) and octanoic acid (AUC=0.699) presented the best discriminatory power. Notably, relative abundance (mean±SD) of gelsolin decreased with COVID-19 severity (mild=1.082±0.622, unfavourable=0.763±0.367) (p=0.002) but increased in unfavourable patients with hypertension (0.919±0.388) compared to non-hypertension (0.681±0.332) (p=0.03) in the acute phase.
Conclusion: The results confirmed hypertension as a frequent comorbid disease in patients with unfavourable COVID-19 progression, which significantly increases the severity of the disease. Gelsolin, myo-inositol and lipids were those molecules that could be determinants in COVID-19 progression and could explain the clinical worsening of COVID-19 patients through different pathways such as immune system processes, inflammation, oxidative stress and lipid metabolism.

344 SARS-CoV-2 Evolution, Reinfection, and Sustained Viremia in Cancer Patients

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Background: Several studies with longitudinal follow-up on SARS-CoV-2 infection have been reported. Most of them focus only on cases with suspected reinfection or prolonged infection in immunosuppressed individuals. Herein, we describe 26 different cases of SARS-CoV-2 infections in cancer patients with multiple longitudinal samples analyzed and described the different scenarios of sustained viremia, reinfection and viral evolution.
Methods: Cancer patients followed at Brazilian National Cancer Institute (INCA), Rio de Janeiro, Brazil, with more than one SARS-CoV-2 nasopharyngeal swab RT-PCR-positive test from April to August 2020 were included. Viral

RNA was isolated, cDNA was synthesized and complete genome amplification using ARTIC network V3 multiplex primers was done and sequenced in a MiSeq platform. Reads were assembled and consensus sequences extracted using Geneious R11. Maximum likelihood phylogenetic analysis was performed using PhyMLv.3.0 with representative sequences from different lineages and the ten best matched SARS-CoV-2 genomes for each timepoint consensus. Infection cases were defined according to the phylogenetic reconstruction and comparisons between the SARS-CoV-2 consensus sequences infecting the different timepoints of each patient in the longitudinal analysis.

Results: A total of 55 samples derived from 26 different cancer patients were analyzed. Assembled genomes belong to B.1.1.33 (n=37) and B.1.1.28 (n=7) lineages. The 11 remaining were not classified due to low genome coverage. Most of the patients (n=16) showed the same identical viral sequence in the different timepoints analyzed, and were classified as sustained viremia. For 4 cases, the genomes analyzed were distributed in different clades of the maximum likelihood reconstruction and were considered reinfections. Finally, six cases showed overtime virus evolution, and the timespan of the samples ranged from 7 to 78 days.

Conclusion: In this study, evaluating the SARS-CoV-2 complete genome from 26 cases, we report different longitudinal profiles of SARS-CoV-2 infection in cancer patients.

345 SARS-CoV-2 Mild Infection as Risk Factor for Herpes Human Viruses Reactivation

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Background: Reactivation of Herpes Human Viruses (HHV) has been described mostly in severe SARS-CoV-2 patients (pts) [1]. We aim to study HHV reactivation, HHV-mediated T-cell response and inflammatory milieu during SARS-CoV-2-mild infection.

Methods: We enrolled pts with SARS-COV-2 infection at baseline (T0), days 7 (T7) and 30 (T30) and healthy donors (HD). We evaluated HHV-serology, HHV-DNA-plasma level and the IFN-γ production after whole blood stimulation with SARS-CoV-2-spike peptides, HHV peptides designed to elicit CD4/CD8 response for Varicella Zoster Virus (VZV), Cytomegalovirus (CMV), HHV1/2, Epstein-Barr virus (EBV), and IL-2, IL-6, IL-8, TNF- α, IFN-γ, CXCL-10 plasma levels.

Results: We enrolled 19 HD and 53 COVID pts with WHO median score 2 (IQR 2-4). No differences in terms of age, sex, and SARS-CoV-2 vaccinations in the 2 groups were observed. All HD referred a previous SARS- CoV-2 infection. There were no clinical HHV reactivations. At T0, no difference in lymphocytes count (while CD3 and CD4 T cells differed both with a $p<0.01$), in HHV-seroprevalences, HHV-antibodies level and HHV reactivation were reported between groups. Blood EBV-DNA was more commonly detected at T0-T7-T30, with no difference between groups. A higher CMV-T-cell response compared to that induced by the other HHV was constantly found in both pts ($p<0.0001$) and HD ($p=0.003$). However, the CMV-CD8 response of pts was significantly higher compared to HD at T30 ($p=0.032$), whereas the EBV-induced CD4 and CD8 response was lower compared to HD at T0 and T7 (T0 $p=0.005$; $p=0.003$; T7 $p=0.008$ $p=0.003$). As expected, at T7 the SARS- CoV-2 response of pts was higher compared to HD ($p=0.026$). In pts an increased EBV-CD8 response (T0/T7 $p=0.005$; T0/T30 $p=0.0004$) was reported. Pts showed the highest SARS-CoV-2-specific response at T7 compared to T0 ($p=0.044$). No difference in HD over time was found. Plasma IL-2, IL-6, IFN-γ and CXCL-10 were significantly higher at T0, T7 in pts compared to HD (for all $p<0.007$), while no difference at T30 was observed.

Conclusion: Inflammatory milieu, HHV T-cells response are present during SARS-CoV-2 mild infection, despite not significant plasma HHV detection. In COVID pts we observed a consistently high CMV and a decreased EBV T-cell response, probably reflecting EBV viremia. Indeed, among HHV, the CMV response appears to be the driving force with a higher CD8-mediated proportion. The identification of subclinical HHV- reactivation during SARS-CoV-2 mild infection is worthy of further investigations.

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346 Neutrophil Activation and Their Derived Nets Contribute to Thrombotic Risk in Pulmonary PASC

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Background: Over one-third of all individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience persistent residual symptoms. Previously, we found that COVID convalescents with pulmonary symptoms had elevated low-density granulocyte (LDG) levels and enhanced ability to form neutrophil extracellular traps (NETs) and aggregation with platelets. Although evidence supports that immunothrombosis plays a crucial role in COVID-19 pathogenesis, its involvement in pulmonary post-acute sequelae of SARS-CoV-2 infection (PPASC) is poorly known.

Methods: To analyze markers linked to thrombosis and inflammation in COVID-19 convalescents, plasma samples collected from participants naïve to SARS-CoV-2 (NP; n=11), infected with SARS-CoV-2 with no residual symptoms (NRS; n=10), and with pulmonary symptoms (PPASC; n=12) were used. We assessed ten analytes (coagulation: vWF-a2, Protein C, ADAMTS13, Tissue Factor (TF); inflammation: IFN-gamma (IFN-γ), MMP-9, MPO; complement pathway: Complement component C2, C5, and C9 in the plasma samples by Luminex assay. To identify factors involved in neutrophil activation in COVID-19 convalescents, we further assessed associations between LDG parameters (number, activation, NET formation) and soluble factors.

Results: The median age of participants was 57, 55, and 54.5 years for the NP, NRS, and PPASC groups respectively. Months post-infection did not differ between NRS (5 [IQR;1.5-9.5]) and PPASC (6 [IQR:4-14]). Compared with NP, TF and ADAMTS13 levels were statistically decreased in PPASC, and PPASC individuals tended to have higher MPO and vWF-a2 levels. C2a levels were statistically higher in both PPASC and NRS than in the NP, while C5a and C9 expressions were comparable between groups. Further correlation analysis of LDG parameters with soluble factors in PPASC showed that the percentages of LDGs and NET-forming counts were positively correlated with MMP9, MPO, IFN-γ, and vWF-a2 expression, but negatively correlated with ADAMTS13 expression (Table 1). Interestingly, C9 levels were positively associated with the percentages of NET-forming LDGs, vWF-a2, and C5a in PPASC, but these associations were not shown in NRS.

Conclusion: The associations between LDG parameters and markers for coagulation and neutrophil activation in PPASC suggest that neutrophils and their derived NETs contribute to thrombotic risk in PPASC. Further studies are necessary to understand the role of sC5b-C9 complex in PPASC.

	LDGs %		NET forming Count	
Analyte	rho	p-value	rho	p-value
MMP9	0.699	0.014	0.755	0.006
MPO	0.766	0.004	0.741	0.008
vWF-a2	0.671	0.020	0.650	0.026
ADAMTS13	-0.671	0.020	-0.601	0.043
INF-γ	0.760	0.006	0.725	0.010

Table 1. Spearman's correlation of soluble analytes with LDG parameters in PPASC (n=12)

347 Persistence of SARS-CoV-2 in Platelets and Megakaryocytes in Long COVID

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Background: We have shown that acute COVID-19 pathophysiology is profoundly altered by infection of lung megakaryocytes (MKs) and platelets by SARS-CoV-2 (Zhu et al, 2022). A significant proportion of COVID-19 patients have symptoms persisting for > 3 months after initial infection with SARS-CoV-2, referred to as Long COVID or Post-acute Sequelae of SARS-CoV-2 (PASC) patients. Persistent or re-emerging symptoms are varied, with a predominance of asthenia, neuro-cognitive impairment and cardio-vascular symptoms. The pathophysiology underlying long-onset COVID remains poorly understood.

Methods: Blood was collected from patients with Long COVID with symptoms duration > 3 months (LC) (n=30), previously infected by SARS-CoV-2 but without persistent symptoms (resolved COVID-19 (CR), n=10), or healthy donor (n=20). MK frequency in blood was quantified by flow cytometry. Platelets and blood MKs were analysed for microclots, the presence of Spike protein and

SARS-CoV-2 RNA by in situ hybridization and immunodetection visualized by confocal microscopy. Spike and serotonin were quantified in plasma.
Results: The frequency of CD41+ MKs in peripheral blood mononucleated cells (PBMCs) was significantly higher than healthy donors (0.28±0.05 versus 0.03±0.02) as a sign of MK infection, as we previously shown in acutely infected individuals with SARS-CoV-2 in platelets. Accordingly, in all samples analyzed, circulating MK in Long COVID sheltered both Spike and SARS-CoV-2 ssRNA, but also dsRNA suggestive of viral replication. These infected MKs produced blood platelets that contain also P Spike and SARS-CoV-2 ssRNA. Platelets microclots were detected in all tested Long COVID patients. Spike protein was detected at the pg level in 30 % of analyzed plasma from Long COVID but not CR individuals. The level of serotonin in platelet and of tryptophan hydroxylase-1 (TPH-1), the enzyme that regulates serotonin synthesis decreased significantly ($p<0.0001$) in blood of Long COVID patients compared to CR individuals.
Conclusion: In patients developing Long COVID, SARS-CoV-2 persists and replicates in MKs producing virus-containing platelets. The presence of spike in plasma might be an additional sign of viral persistence that could be used as a Long COVID biomarker. The presence of the virus could lead to abnormal platelet activation and the formation of microclots, which would contribute to the various symptoms and to deregulation of serotonin uptake, contributing to the neurocognitive symptoms observed in long-onset COVID.

348 Low-Level HIV Viremia Affects T-Cell Activation and Senescence in InSTI Era

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Background: 10% of people with HIV (PWH) show low-level viremia (LLV) under antiretroviral therapy (ART). We evaluated the influence of this poor virological response on the immune system in comparison to individuals with suppressed viremia (SV).
Methods: Prospective observational study in 54 subjects matched by clinical and epidemiological characteristics: i) n=27 PWH with persistent LLV (50-200 copies/mL) and ii) n=27 PWH with SV (<50 copies/mL) as controls. 45 soluble biomarkers of systemic inflammation were evaluated by multiplex immunoassays. Activation (CD25, HLADR and CD38) and senescence (CD57, PD1 and TIM-3) levels in peripheral T-cell subsets were characterized by spectral flow cytometry. Differences in plasma biomarkers and cell frequencies were evaluated by generalized linear models, adjusted by age, gender, and ART.
Results: The median age was 53 years and 77.8% were male. 74% of PWH with LLV were on integrase inhibitors compared to 48% in SV group. LLV group showed no significant differences in the maturation of CD4+ T cells, which were more activated (CD38+) and exhausted (PD1+, TIM3+ and PD1+TIM3+) compared to SV, especially the more immature stages of development (Figure 1A). A decrease in PD1+ subpopulations in effector memory (EM) (Th0-1 and TEMRA pE1) and a trend in central memory (CM) were also observed in LLV group, as well as an increase in TIM3+ expression. Significant differences were observed in the most senescent phenotype (PD1+TIM3+) in EM Th0-1 and TEMRA E populations in the LLV group. In addition, LLV group showed a trend towards a lower CD8+ naïve and EM1 T cell count and a higher frequency of CM and TEMRA E cells (HLADR+), as well as a higher up-regulation of TIM3+ in CD8+ compartment (Figure 1B). We also observed a lower frequency of CD8+ EM PD1+ subpopulations (EM1, EM2, EM4, TEMRA pE1 and TEMRA pE2) and an increase of these same subpopulations expressing TIM-3+. Overall, LLV group showed a highly senescent EM response (EM3 PD1+TIM3+ and TEMRA E PD1+TIM3+) compared to controls. No significant differences were found in inflammatory markers between groups.
Conclusion: The persistence of LLV (50-200 copies/mL) leads to a decrease of CD8+ EM1 population and an increase in activation mainly in EM subpopulations that are functionally exhausted. This could partially explain the absence of significant differences in the inflammatory profile between both groups, suggesting an aberrant immune function in LLV individuals unable to control and eliminate infected cells.

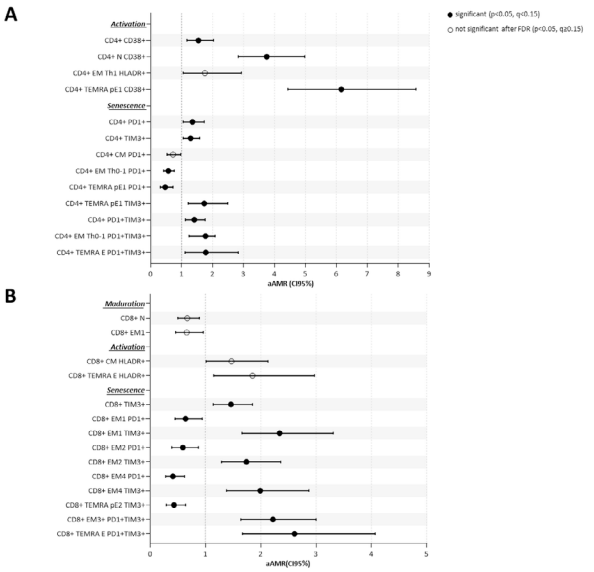

Figure 1. Comparison of A) CD4+ and B) CD8+ profile between LLV and SV groups. Statistics: Only statistically significant populations (p<0.05; q<0.15) or initially significant but not after FDR correction (p<0.05, q≥0.15) are shown. Abbreviations: aAMR, adjusted Arithmetic Median Ratio; N, naïve; CM, central memory; EM, effector memory, TEMRA, terminally differentiated effector.

349 Ultra-Low Level HIV p24 Production as a Driver of Immune Activation in Individuals Treated with ART

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Background: Similar to the persistent presence of HIV, residual immune activation has been observed despite antiretroviral therapy (ART). It was shown that in treated people with HIV, T cells remain activated even when the virus is undetectable. The causes of this chronic inflammation and immune activation in treated HIV are not fully understood.
Methods: Here, we have developed an ultrasensitive p24 single-molecule array to detect p24 in plasma at a 1000-fold lower concentration (fg/ml) compared to previous assays. This advancement allowed us to analyze people with chronic HIV who are undergoing treatment (with undetectable viral load) and compared it to immune correlates measured by a multicolor immune assay.
Results: We first investigated whether plasma p24 is detectable at ultra-low concentrations in a cohort of 172 individuals with chronic and ART-treated HIV infection, who have maintained HIV RNA levels below the detection limit (<50 HIV RNA copies/ml) for >4 years. Ultra-low level HIV p24 [range 4.5 fg/ml – 330 fg/ml] was detectable in 48 out of 172 individuals (28%). There was no significant correlation between age, gender, ART regimen and the average duration of therapy was identical between groups with or without detectable HIV p24 (p24+: 8.4 years [4.3 – 17]; p24-: 8.4 years [4 – 30]; $p>0.05$). Next, we hypothesized that ongoing p24 production is responsible for low level immune activation. Indeed, CD8 and CD4 T cells from individuals with detectable HIV p24 showed significantly increased expression of the activation marker CD38 compared to individuals without detectable p24 ($p < 0.05$). Interestingly, individuals with detectable HIV p24 had significantly higher HIV-specific CD8 T cell responses ($p<0.05$) despite ongoing treatment, indicating that they are still able to recognize HIV infected cells. We also determined HIV p24 concentration behavior before and after ART initiation as well as from acute to chronic infection. Therefore, we studied 43 people who initiated suppressive ART during acute HIV and remained virally suppressed over a 2-year period. Despite HIV-1 RNA that declined to undetectable levels (<30 copies/mL), p24 levels remained detectable in 25% of individuals one year and 19% of individuals two years after ART start.
Conclusion: Despite continuous ART, we were able to detect ultra-low level of p24 production, suggesting either ongoing viral replication or active transcriptional HIV integration sites can be the primary driver of HIV immune activation.
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350 CARD8 Activation in Myeloid Cells as a Driver of Inflammation in HIV Infection

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Background: Myeloid cells play an essential role in HIV persistence and chronic inflammation. Inflammasome activation in response to "danger-associated stimuli" can lead to pyroptotic cell death and release of inflammatory cytokines such as IL-1ß and IL-18. HIV-1 protease has been shown to activate the CARD8 inflammasome in CD4 T cells, which undergo pyroptosis but do not produce IL-1ß and IL-18. We hypothesize that CARD8 can also be activated in myeloid cells upon exposure to HIV, which are poised to drive inflammation.
Methods: Monocyte-derived macrophages (MDMs) were cocultured with HIV-infected autologous CD4 T cells. In selected experiments, CARD8 knockout (KO) cells were used for coculture. Supernatants were collected at 8 hours for IL-1ß and IL-18 ELISA. P values were calculated using t test or ANOVA test.
Results: Coculture of MDMs with autologous CD4 T cells infected with CCR5-tropic HIV isolates resulted in increased release of IL-1ß compared to uninfected cocultures(n=4, 128 vs 5 ρg/mL, p=0.02) and MDM alone (128 vs. 3.8 ρg/mL, p=0.03) at 8 hours. Similar increases were observed for IL-18. Coculture with CD4 T cells infected with X4-tropic HIV did not increase IL-1ß or IL-18 release. The release of inflammatory cytokines was prevented by pre-incubation with the caspase-1 inhibitor VX-765 or maraviroc. Coculture using CARD8 KO cells resulted in significantly lower IL-1ß (43 vs. 292 ρg/mL, p=0.03) and IL-18 (224 vs. 1384 ρg/mL, p=0.0005) levels compared to Cas9 only controls.
Conclusion: Activation of the CARD8 inflammasome upon coculture with infected CD4 T cells results in release of inflammatory cytokines from autologous myeloid cells. This is abolished by CARD8 knockout as well as by use of drugs that either prevent HIV entry in myeloid cells or block the downstream signaling through caspase-1. Our findings offer novel clues into HIV pathogenesis by providing a mechanism for myeloid cell activation observed during untreated infection. Since some HIV proviruses remain translationally active even during effective antiretroviral therapy, it is possible that HIV proteins can continue to fuel inflammation by activating CARD8 in myeloid cells even when new rounds of infection are prevented. Therefore, it is important to understand whether CARD8 inhibition could decrease chronic inflammation in people living with HIV.

351 Increased Immune Activation Following Acute Sleep Deprivation in

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Background: Sleep disturbances are prevalent in people with HIV (PWH). The immunosuppressive adenosine (ADO) pathway is induced by inflammation and is integral in mediating homeostatic sleep drive. Dysregulation of the pathway exists in PWH. We evaluated the effects of acute sleep deprivation on the levels of immune activation and inflammation and determined whether it results in a compensatory increase in the expression of ectoenzymes responsible for extracellular ADO generation to mediate sleepiness and decrease inflammation.
Methods: Twenty PWH (75% men) who have been virally suppressed on antiretroviral therapy for at least one year underwent one week of regularized sleep with at least 8 hours of opportunity to sleep each night followed by 24 hours of sleep deprivation (SD). Blood was obtained pre- and post-SD to measure levels of T cell activation (HLA-DR+CD38+), cell cycling (Ki-67+), and T-cell ectoenzyme expression (CD39; CD73) using flow cytometry. Plasma levels of soluble inflammatory markers (IL-6, sCD14, sCD163) were measured using a multiplex assay.
Results: Participants had a median (IQR) age of 59.7(58.6,63.5) years and CD4 of 760(678,883) cells/mm^3. Levels of CD8+ T cell immune activation increased post-SD (median 8.6% to 9.4%; p=0.05, paired t-test). There were no differences in CD4+ T cell activation. In contrast, cell cycling post-SD decreased in both CD8+ (88.0% to 80.8%, p=0.03) and CD4+ (90.3% to 83.5%; p=0.02) T cells. There was a trend for increased sCD163 post SD (3587 to 3838 ng/mL, p=0.08), but no differences were observed in IL-6 and sCD14. Despite increases in CD8+ T cell activation, we did not observe compensatory increases in the expression of CD39 and/or CD73 on CD8+ or CD4+ T cells. Decreased CD73 expression on CD8+ T cells post SD was associated with increased CD8+ activation (Spearman ρ= 0.76, p <0.005) and a trend toward increased CD8+ cycling (ρ=-0.43, p=0.14) but not with measures of CD4+ T cell activation (p=0.49), cycling (p=0.18) or changes in sCD14 (p=0.33), CD163 (p=0.44) or IL-6 (p=0.25).
Conclusion: Our results suggest that among virally suppressed PWH, sleep deprivation could impact systemic inflammation by activation of CD8+ T cells and macrophages. However, there is no compensatory increase in ectoenzyme expression that can increase extracellular adenosine and counteract the inflammatory process.

352 Immunosuppressive Effects of LLDT-8 in ART-Treated SIV-Infected Rhesus Macaques

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Background: Chronic immune activation plays a significant role in the pathogenesis and disease progression of human immunodeficiency virus (HIV), and the existing interventions to address this issue are limited. In a phase II clinical trial, (5R)-5-hydroxytriptolide (LLDT-8) demonstrated promising potential in enhancing CD4+ T cell recovery. However, the precise mechanism of action of LLDT-8 remains to be explored.
Methods: To assess the treatment effects of LLDT-8, we conducted flow cytometry and RNA-seq analyses on eight Chinese rhesus monkeys infected with simian immunodeficiency virus (SIV). Additionally, we performed comprehensive transcriptomic analyses, including cross-sectional and longitudinal differentially expressed gene (DEG) analysis, gene set enrichment analysis (GSEA), weighted gene co-expression network analysis (WGCNA), and deconvolution analysis using peripheral blood mononuclear cell (PBMC) samples from 14-time points. These findings were further validated with RNA-seq analysis on patients who received LLDT-8 treatment, along with in vitro cellular experiments using human PBMCs.
Results: Flow cytometry analysis revealed that LLDT-8 treatment significantly reduced the percentage of HLA- DR+CD38+CD8+ T cells in SIV-infected rhesus monkeys (P=0.029). The cross-sectional and longitudinal analysis identified 2531 and 1809 DEGs, respectively. GSEA analysis indicated that LLDT-8 treatment led to significant downregulation of proliferation-related pathways, such as E2F targets, G2M checkpoint, and mitotic spindle pathways. WGCNA analysis identified two modules and 202 hub genes associated with CD8 activation levels. Deconvolution analysis showed a significant decrease in the proportion of CD8+ T cells and activated CD4+ T cells during LLDT-8 treatment. Gene ontology results demonstrated that the common DEGs between LLDT-8-treated patients and rhesus monkeys were primarily enriched in cell activation and cell cycle progression. Furthermore, in vitro cellular experiments validated the consistent impact of LLDT-8 in inhibiting proliferation, activation (HLA-DR and CD38 expression), exhaustion (PD-1 expression), and IFN-γ production in human CD4+ and CD8+ T cells.
Conclusion: LLDT-8 exhibited notable efficacy in alleviating immune activation in both an in vivo animal model and in vitro human cell experiments. These findings suggest that LLDT-8 may hold potential as a drug for managing systemic immune activation associated with SIV/HIV infection, warranting further prospective clinical explorati.

353 Circulating Immunoregulatory Proteins Indicative of Poor CD4 Recovery in People With HIV on ART

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Background: One-third of people with HIV (PWH) demonstrate poor CD4+ lymphocyte recovery (<200 cells/ml) despite suppressive anti-retroviral therapy (ART). Poor CD4 recovery is associated with persistent immune activation and inflammation, severe immune dysfunction, adverse comorbid outcomes, and mortality. Soluble immunoregulatory proteins and lymphocyte receptor/ligands that function in activation or inhibition are elevated in PWH, and associate with HIV-specific T cell function, HIV reservoir size, and comorbid outcomes during ART. The potential mechanism of poor immune reconstitution and relationship of poor CD4 recovery with lymphocyte-associated immunoregulatory proteins remains unclear. Here we assessed a panel of circulating immunoregulatory proteins and their association with poor CD4 recovery.
Methods: Study participants enrolled in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) cohort were stratified in poor CD4 recovery (CD4 <200, n=34) or CD4 count normalization (CD4 >500, n=82)

subgroups. Participants were evaluated at one-year post-ART during viral suppression (HIV RNA <400 copies/mL). We measured an exploratory panel of 37 immunoregulatory proteins in the plasma by Luminex assay. Differences among CD4 groups were evaluated by Mann-Whitney U tests and multivariate logistic regressions adjusted for pertinent covariates. A boosted decision tree machine learning algorithm was used to determine biomarker signatures classifying individuals by CD4 group.

Results: Circulating immunoregulatory proteins Galectin-1 (Gal-1), Galectin-9 (Gal-9), ICOS, CD276 (B7- H3), BAFF and OX40 were significantly higher in PWH with poor CD4 recovery as compared to those with normalized CD4 count (all p<0.05) [Figure 1A]. Gal-9, CD276, and OX40 remained significant in logistic regressions adjusted for age (all p<0.05). Further, a boosted decision tree model consisting of age and the six differential immunoregulatory proteins accurately classified individuals with poor CD4 recovery from those with reconstituted CD4 counts (AUC=0.902 +/- 0.078) [Figure 1B]. In this model, Gal-9, ICOS and Gal-9 had the highest feature importance [Figure 1B].

Conclusion: We found a novel signature of circulating lymphocyte-associated immunoregulatory proteins indicative of poor CD4 recovery and potential targets to monitor immune perturbations in PWH during suppressive ART.

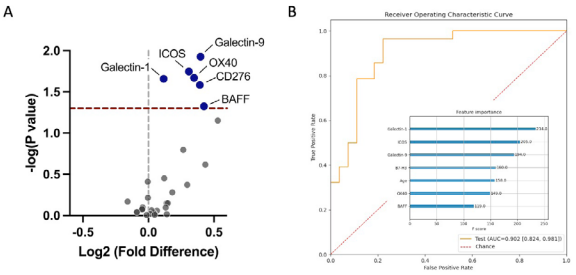

Figure 1 – A. Differential immunoregulatory proteins in PWH on ART with poor CD4 reconstitution compared to those with normalized CD4 counts determined by Mann-Whitney U tests. **B.** ROC curve for the boosted decision tree model consisting of age and six differential markers with their corresponding feature importance.

354 Suppressing Asymptomatic CMV With Letermovir Reshapes Cardiometabolic Proteome in Treated HIV

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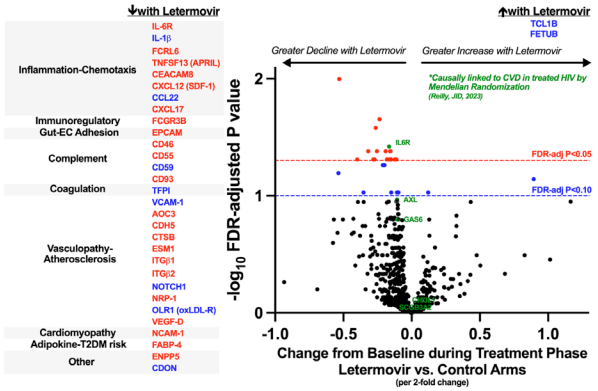
Background: People with HIV (PWH) and CMV have higher cardiometabolic disease risk than those without HIV despite antiretroviral therapy (ART), but mechanisms are unclear.

Methods: We performed a randomized trial of letermovir (CMV terminase inhibitor, 480 mg daily) in ART- suppressed CMV-seropositive PWH to assess whether letermovir therapy for 48 weeks reduced plasma sTNFR2 levels (primary endpoint) and other inflammation and cardiometabolic indices vs. no anti-CMV treatment. A planned futility analysis was performed after 40 (of planned 180) participants reached week 8. Continuous changes in plasma biomarkers (ELISA and Olink Inflammation and Cardiometabolic Explore panels) and binary CMV shedding in genital secretion and saliva were compared between arms with linear mixed or logistic models, adjusting proteomic analyses for False Discovery Rate (Benjamini-Hochberg).

Results: Of 42 participants enrolled, 40 contributed to the week 8 per-protocol analysis, stratified by CD4 count (45% <350 cells/mm³) and sex at birth (29% female). Adverse events were similar between arms. Letermovir suppressed CMV DNA at all on-treatment timepoints. Unexpectedly, plasma sTNFR2 levels increased in the letermovir arm at week 8 (P<0.001, between-arms P=0.059) and the trial was stopped for futility. We hypothesized that suppression of CMV's immunoregulatory viral IL-10 may have caused the increase in plasma sTNFR2. Consistent with this hypothesis, plasma IL-10RA – a marker of IL-10 receptor signaling – declined 28% more in the letermovir than control arms (P=0.009), while human IL-10 levels were unchanged. While sTNFR2 increased, 30 plasma inflammation (e.g., IL-6R, IL-1b) and cardiometabolic proteins (e.g., VEGF-D, VCAM-1, Neuropilin-1, FABP-4) declined more in the letermovir than control arms (FDR-adjusted P<0.05 [red] and P<0.10 [blue], Figure). Letermovir caused a greater decline in 3 of 5 proteins recently causally linked to vascular events in treated HIV by Mendelian Randomization (AXL, GAS6, and IL-6R; nominal P≤0.02).

Conclusion: Suppression of asymptomatic CMV in PWH on ART increased plasma sTNFR2, but decreased markers of IL-10 receptor signaling and several inflammation and cardiometabolic proteins, some of which are causally linked to cardiovascular risk. While the clinical significance remains unclear, this is the first study to show that a specific inhibitor of CMV – without direct activity against other herpesviruses – is safe and has broad impact on immunologic and cardiometabolic biomarkers in PWH.



355 DNA Methylation-Based Telomere Length Is Associated With HIV Infection and Cancer in Relation to HIV

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Background: Telomere length (TL) is an important indicator of cellular aging. Shorter TL is associated with several age-related diseases including coronary heart disease, heart failure, diabetes, increased cancer risk, and osteoporosis. However, due to technical issues, directly measuring TL remains a challenge. Recently, a DNA methylation-based TL (DNAmTL) estimator has been developed. In this study, we determined the association of DNAmTL with cancer prevalence and mortality risk among people with and without HIV.

Methods: Data analyzed were from the Veterans Aging Cohort Study Biomarker Cohort. DNAm was assessed from peripheral blood mononuclear cells (Illumina HumanMethylation450 BeadChip and Illumina Human Methylation EPIC BeadChip). DNAmTL was subsequently estimated based on methylation profiles of 140 CpGs that prior work identified by regressing measured leukocyte TL on blood methylation data. Cancer prevalence was estimated from electronic medical records and cancer registry data. Mortality risk was estimated by the VACS Index 2.0, a measure of physiologic frailty, and by deaths from any cause over time. We used multivariable linear regression to estimate the association between DNAmTL and cancer, and VACS Index 2.0. We utilized Cox Proportional Hazards models to assess how DNAmTL is associated with the risk of all-cause mortality. Models were adjusted for self-reported race/ethnicity, batch, smoking status, alcohol consumption, and six cell types (CD4, CD8, NK, B cell, Monocyte, and Granulocyte).

Results: People with HIV (N=1,147) had shorter average DNAmTL than those without HIV infection (N=104) [beta=-0.24, 95% confidence interval (-0.31, -0.17), p=4.54E-12]. VACS Index 2.0 [beta=-0.0023 (-0.0034, -0.0012), p=2.32E-05] and higher cancer prevalence [beta= -0.03 (-0.06, 0.00), p=4.49E-02] were associated with shortened DNAmTL. One unit decrease in DNAmTL was associated with a 40% increase in mortality risk [Hazard Ratio: 0.60 (0.44,0.82), p=1.42E-03].

Conclusion: Physiologic frailty, cancer, and mortality are associated with DNAmTL.

356 Methamphetamine Use in PWH on ART Is Associated With Inflammation and Residual HIV Transcription

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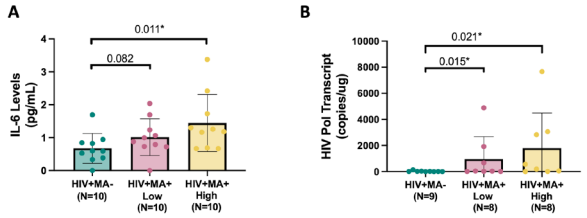
Background: High-risk people with HIV (PWH) such as individuals who use methamphetamine (MA) are most likely to benefit from HIV eradication strategies and yet they often have high rates of suboptimal ART adherence. No study to date has evaluated whether PWH with adequate viral suppression and who use MA have elevated levels of systemic inflammation and residual viral transcription during ART, which may pose additional challenges to HIV cure in this population.
Methods: We performed a pilot study of 20 PWH with and without MA use (10 HIV+MA+, 10 HIV+MA-). Inclusion criteria were confirmed HIV-1 infection and undetectable viral load (<40 copies/mL) for at least 1 year. HIV+MA+ participants were sampled at 2 timepoints, and MA concentrations were quantified from plasma using a clinically validated liquid-chromatography tandem mass spectrometry (LC-MS/MS) assay. Plasma samples were also used to quantify 43 analytes using a multi-plex chemiluminescence immunoassay (MesoScale Discovery). PBMCs were used to perform reverse transcription droplet digital PCR (RT-ddPCR) assays to quantify HIV RNA transcripts produced during sequential stages of viral transcription reflecting transcriptional initiation (TAR), elongation (Long LTR), mid-transcription (Pol), distal transcription (Nef), completion (PolyA), and multiple splicing (Tat-Rev) events. Wilcoxon rank sum and signed rank tests, as well as linear regression models, were used to perform across- and within-individual comparisons.
Results: HIV+MA+ and HIV+MA- groups were balanced by age, gender, race/ethnicity, nadir CD4+ T cell count, and duration of ART. Among the 43 analytes, only TNF-α, TNF-β, IL-6, and MIP-1α and IFN-β were significantly higher in HIV+MA+ vs. HIV+MA- individuals, and these associations (except IFN-β) remained statistically significant in multivariate models adjusted for nadir CD4+ T cell count and duration of ART (P<0.05). HIV RNA transcripts were detectable in a total of 17 participants. HIV Pol transcripts were significantly higher in 8 HIV+MA+ vs. 9 HIV+MA- participants.
Conclusion: To our knowledge, this small pilot study is the first human study to evaluate the impact of MA use on circulating cytokine levels and the HIV reservoir during suppressive ART. MA has been shown in animal and in vitro studies to increase T cell activation and exhaustion and enhance HIV transcription. Our findings suggest that even during ART suppression, PWH who use MA may have higher levels of systemic inflammation and residual HIV transcription.

Figure 1. Methamphetamine use in people with HIV on ART was associated with increased plasma markers of inflammation (A) and residual viral replication (B).



357 Singular CD4+ and CD8+ T-Cell Proteomic Profiles in PLHIV Immunological Non- Responders Before ART

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Background: A significant proportion of people living with HIV (PLHIV) who achieve virological suppression with antiretroviral therapy (ART) fail to recover CD4+ T-cell counts, these patients are known as immunological non-responders (INR). Multiple complex mechanisms are involved in the failure of immune recovery, and intracellular proteins of CD4+ and CD8+ T-cells may have an important role. The main aim is to identify proteins, or a group of proteins, that may explain the different immune response to antiretroviral therapy and to determine the metabolic pathways or biological processes that may be involved in the failure of the immune recovery process.
Methods: Untargeted CD4+ and CD8+ T-cell proteomic analyse has been performed on 100 HIV-infected adult patients recruited from 5 different hospitals and classified according to their baseline CD4+ T-cell count (cases < 200 CD4+ T-cells/µl, controls ≥ 200 CD4+ T-cells/µl). Cases were divided into immunological responders (IR) or immunological non-responders (INR) based on the CD4+ T-cell counts after 48 weeks of being on ART. IRs were defined by a CD4+ T-cell count greater than 250 CD4+ T-cells/µl after treatment, and INR patients were those that showed less or equal to 250 CD4+ T-cells/µl.
Results: Basal CD4+ T-cell count and CD4+/CD8+ ratio showed significant differences between groups (p<0.001 in both cases). Both CD4+ and CD8+ T-cells have shown a differential proteomic profile in INR compared to controls and IR. Alpha-1-antitrypsin (SERPINA1) and Isocitrate dehydrogenase 1 (IDH1) were two proteins with good discriminatory power between INR and IR in CD4+ T-cells using Random Forest analysis. The pathways associated with these two proteins may have a role in CD4+ T-cell death. Moreover, concerning CD8+ T-cells, Random Forest analysis has classified Carbonyl reductase [NADPH] 1 (CBR1) as a very important group differentiating variable. This protein is involved in the biosynthesis of folate, known to stimulate T-cell proliferation.
Conclusion: There is a specific CD4+ and CD8+ T-cell proteomic pattern in HIV-positives before undergoing ART that is distinctive among subjects initiating ART with good immune status (control), subjects initiating ART with low immune status but good immune recovery on ART (IR) and subjects initiating ART with low immune status that maintain poor immune recovery on ART (INR). The system inability to immune non-recovery of INR may include CD4+ T-cell death and CD8+ T-cell proliferation.

358 Evaluating Biomarkers and Mortality by Sex in People With Late HIV Starting Antiretroviral Therapy

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Background: In a large international study, we previously demonstrated an association between female sex and increased risk of mortality in people with HIV (PWH) with CD4 <100 cells/µL who were initiating antiretroviral therapy (ART). Our understanding of the factors underlying these differences remains incomplete.
Methods: We performed a secondary analysis of data from a prospective study that included ART-naïve PWH with CD4 <100 cells/µL in the U.S., Kenya, and Thailand, who initiated ART between December 2006 to March 2013, and were followed for 48 weeks. We compared baseline differences in biomarkers using multivariable regression models, associations between the odds of death and baseline biomarkers by sex using logistic regression models, and hazards of death using Cox proportional hazards models. All analyses were adjusted for site of enrollment.
Results: We assessed 506 PWH, 39.3% of whom were female (assigned sex at birth, N=199) with a median follow-up of 48 weeks. Baseline age, CD4 count, and HIV viral load were not significantly different by sex. Baseline biomarkers, including C-reactive protein (CRP), hyaluronic acid (HA), hepcidin, IP-10, IL-2, -6, -8, -10, -17, IFN-γ, myeloperoxidase (MPO), sCD14, sCD163, tissue factor, TNF, and d-dimer did not differ by sex after adjusting for multiple comparisons. The rate of CD4 recovery was higher in females than males (3 vs. 2.6 cells/µL/week, P=0.045). Within 6 months of initiating ART, 31 (6.5%) participants died, 17 of whom were female (55%). Female sex was associated with increased hazards of mortality, particularly in the first 30 days after ART initiation (HR 3.34, P=0.038). Increased CRP, increased IL-27, and decreased body mass index were associated with increased odds of death in both sexes; increased IL-8, -10, HA, MPO, and d-dimer were associated with increased odds of death in females but not males, while elevated white blood cell count and decreased hemoglobin were associated with increased odds in males but not females (Figure 1).
Conclusion: We found no significant differences by sex in biomarkers, CD4 count, or viral load in PWH with CD4 <100 cells/µL starting ART. Despite a slightly higher rate of CD4 recovery, female sex was associated with increased

mortality. The biomarkers associated with increased odds of mortality differed by sex. These findings suggest that there may be distinct pathophysiologic mechanisms that account for the observed increased risk of death seen in female PWH that warrant further investigation.

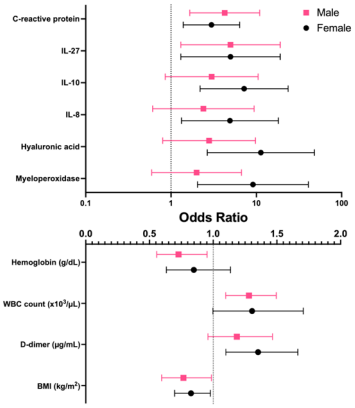

Figure 1: Results of multivariate logistic regression models for odds of death by biomarker stratified by sex. C-reactive protein, IL-27, IL-10, IL-8, hyaluronic acid, and myeloperoxidase were transformed from pg/mL to a $\log_{10}$ scale. Abbreviations: WBC: white blood cell, BMI: body mass index.

359 Glycomic Markers of Biological Aging in Trans Women With HIV Versus Cis Men and Cis Women With HIV

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Background: The effects of gender-affirming hormonal therapies (GAHT) on systemic markers of inflammation and aging among transgender women with HIV (TWWH) who are virally suppressed by antiretroviral therapy (ART) are unknown.
Methods: Plasma samples were collected from 22 transgender women with HIV (TWWH); all were on estrogen, 50% were on spironolactone/antiandrogen, and 32% having testosterone levels <50ng/dL. These samples were age (± 5 years), race/ethnicity, and body mass index category matched with samples from 20 cisgender men with HIV (CMWH) and 18 cisgender women with HIV (CWWH, 6 pre-menopausal and 12 post- menopausal). All participants were on ART and had viral load <50 copies/ml. We measured two categories of plasma-based markers of aging: 1) 20 markers of inflammatory aging (based on PMID: 34888528) using multiplex cytokine arrays, and 2) 31 IgG glycomic markers of biological aging (based on PMID: 24325898) using capillary electrophoresis. Kruskal-Wallis tests and Spearman correlations were used for analyses, and false discovery rates (FDR) were calculated to correct for multiple comparisons.
Results: While we observed no differences in levels of inflammation markers between TWWH and CMWH, there were significant differences in levels of several IgG glycomic markers of aging between the two groups. Notably, levels of several galactosylated glycans, which are linked to younger chronological and biological age, were higher in TWWH compared to CMWH (FDR<0.05; Fig. 1A). Conversely, several agalactosylated glycans, linked to older age, were lower in TWWH compared to CMWH (FDR<0.05; Fig. 1B). These effects were consistent among TWWH, regardless of whether they had testosterone suppression or not. The anti-aging glycomic profiles of TWWH resembled those of pre-menopausal CWWH, while the pro-aging profiles of CMWH resembled those of post-menopausal CWWH. The anti-aging profile, enriched in TWWH, was correlated with lower levels of several inflammation markers, including CXCL9, TNFα, and IP10, while the pro-aging profile, lower in TWWH, was associated with higher inflammation, especially in TWWH.
Conclusion: TWWH exhibit anti-aging glycomic profiles that resemble those of pre-menopausal CWWH. Longitudinal studies are needed to better understand the relationships between GAHT, biological aging, and the risk of developing age-associated diseases. Mechanistic investigation is also warranted to explore the potential impact of GAHT and sex hormones on aging processes.
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360 Signature of CD4 T Cells During Acute HIV-1 Infection Is Predictive of Disease Progression

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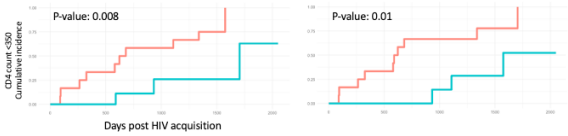
Background: Immune activation, a hallmark of chronic HIV infection, is a major contributor of HIV pathogenesis, even in the context of viral suppression by anti-retroviral therapy. The magnitude of immune activation during HIV infection is both established early and is more predictive of the rate of disease progression than plasma viral load. Elucidating the critical events in acute HIV infection (AHI) associated with disease progression will facilitate the design of new approaches to achieve HIV remission.
Methods: To investigate the dynamics of inflammation and immune activation during AHI, we utilized samples from 17 Thai and 26 East African participants in the RV217 AHI study. We measured the levels of 26 soluble markers of inflammation inclusive of chemokines, cytokines, and markers of microbial translocation starting from pre-infection through AHI. We determined the dynamics of cellular immune activation by assessing CD4 and CD8 T cell activation during AHI using flow cytometry. The level and frequency of immune activation was used to predict a CD4 T cell count <350 using nonparametric rank-based testing, logistic regression, and cumulative incidence. The prediction capability of identified markers was also examined by Area under the Receiver Operating Characteristic (AURCO) curve.
Results: The level of soluble and cellular markers of immune activation between East Africa and Thailand significantly differed between regions both before and during AHI. Similarly, variable signatures of immune activation were associated with peak and set point viral loads for each region. IP-10, IL-8 and IL-10 levels were associated with peak viral load in Africa but not in Thailand. Levels of IL-1β pre-infection in Thailand, but not in East Africa, were inversely associated with peak and set point viral loads. Combining datasets, higher levels of CCR5 and CD38 expression on CD4 T cells at 4.5 weeks post 1st HIV RNA positive test (around set point viral load) were predictive of reaching a CD4 count <350 independently of region or viral load.
Conclusion: Our results show that the frequency of CD4 T cells expressing CCR5 and CD38 at set point viral load is associated with faster disease progression independent of viral load. This suggests that CD4 T cells circulating with an activated phenotype associated with susceptibility to viral entry may be predictive of immune pathology.



Cumulative incidence curve showing faster progression to CD4 count <350 for participants with levels of CD38 MFI (left) and CCR5+ (right) CD4 T cells above the median and below the median at 4.5 weeks post HIV acquisition.

361 Distinct Plasma Protein Changes Precede Loss of Spontaneous HIV Control

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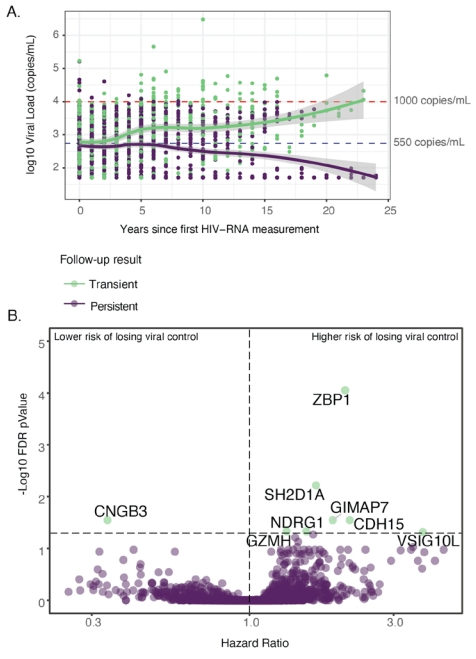
Background: Understanding antiretroviral therapy (ART)-independent control of HIV is of paramount importance and central for HIV cure. Some people living with HIV spontaneous regulate viral replication without ART and are categorized into 'elite controllers' (EC, HIV-RNA <50 c/mL) and 'viremic controllers' (VC, HIV-RNA between 50-10,000 c/ml). EC or VC may eventually lose controller status (HIV-RNA >10,000 copies/mL) and become transient controllers (TC), in contrast to persistent controllers (PC). Exploring plasma protein profiles of controllers that transition to TC may discern the intricacies of HIV pathogenesis and may ultimately yield new treatment strategies. Our aim was to scrutinize

whether circulating proteins of EC and VC at baseline were associated with loss and/or sustained viral control.
Methods: The Dutch national ATHENA cohort provided baseline blood samples from 36 ECs and 145 VCs, maintaining control status for >5 years. Serial viral load (VL) measurements were documented for up to 17 years. Expression of 3072 plasma proteins was measured using proximity extension assay coupled with next- generation sequencing, with 2420 proteins used for analysis after quality control. Only one EC lost control during follow-up; analysis was therefore applied on VC only.
Results: Loss of controller status occurred in 38% (55/145) of VCs after a median of 8.5 years. TC had similar demographics (age, sex, BMI, ethnicity), smoking status, and latest CD4 and VL compared to PCs. However, elevated initial VL was noted in TCs (median [Interquartile range] TCs 1347 [245, 4271] vs. PCs 443 [50, 1912.5] c/ml). Over time, TC exhibited an annual increase in VL by 1375 c/mL, while PCs exhibited stable VL. Proteomic analysis identified seven proteins (ZBP1, SH2D1A, CDH15, GIMAP7, VSIG10L, NDRG1, GZMH) associated with a higher risk of losing VC status, whereas CNGB3 was linked to a lower risk, observed over a median period of 4.2 years before loss of HIV control. Notably, certain proteins (SH2D1A, NDRG1) have been implicated in other viral infections, yet their association with HIV infections is scarce or absent in existing literature.
Conclusion: Several years before loss of spontaneous viral control, TC exhibited the upregulation of plasma proteins with known immune and cellular functions, including inflammation, apoptosis, and cell adhesion. Our findings advance our understanding of ART-independent control mechanisms, underscoring the prospect of identifying early biomarkers for impending loss of HIV control.



A. Yearly viral load dynamic comparing transient and persistent VC.
B. Association between baseline plasma protein concentrations with risk of loss of viral control in VC

362 HIV-Induced Lung Inflammation in Humanized Mice

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Background: HIV infection-related lung diseases continue to be one of the leading causes of morbidity and mortality for people living with HIV. The cross-sectional design of population studies has made it impossible to elucidate a causal relationship between immune biomarkers and lung disease. Therefore, we aim to establish an animal model to longitudinally monitor HIV infection and lung immune activation and perturbation.
Methods: We established HIV infection in a humanized mouse model named MISTRG-6-15, in which several human cytokine-coding genes, including M-CSF, IL-3/GM-CSF, SIRPα, TPO, IL-6, and IL-15, were knocked into their respective mouse loci to promote human hematopoietic stem and progenitor cells (HSPCs) for self- renewal and differentiation. We isolated human CD45+ cells from the lungs of HIV-infected and control mice and performed single-cell RNA sequencing and ex vivo functional analyses.
Results: MISTRG-6-15 mice engrafted with cord blood HSPCs developed human myeloid cells (monocytes, macrophages, and neutrophils), T cells, B cells, NK cells, and other innate lymphoid cells (ILCs) in the lungs. The HIV-infected MISTRG-6-15 mice had a systematic augment of interferon gamma and alpha pathways across all cell types in the blood, spleen, and lung tissues. We found significant depletions of lung effector and tissue-resident CD4+ T cells and CD4+ regulatory T cells, as well as many subsets of antigen presenting cells (APCs). By contrast, CD8+ T cells, NK cells, and ILCs expanded and produced inflammatory cytokines in the infected lungs, which was in line with human studies. Genes associated with cell proliferation and interferon responses were significantly upregulated in the lungs of HIV-infected mice. Compared to the blood and spleen, the lungs had a larger amount of differentially expressed genes between the infected and un-infected mice. Further subset analyses identified that T-cells (both CD4+ and CD8+ T cells) and myeloid cells specifically had significantly more differential expressed genes in the lungs than in the blood and spleen.
Conclusion: Our results demonstrated that MISTRG-6-15 mouse can be a useful model to evaluate lung inflammation driven by HIV infection. We identified unique features of HIV-induced immune perturbation in the lung. This humanized mouse model allows us to perform mechanical studies to better understand HIV-driven lung complications.

363 Exogenous Estrogen Increases HIV Target Cell Frequency in the Rectal Mucosa of Male Primates

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Background: Transgender women (TGW) are 49-66 times more likely to be infected with HIV than individuals over age 15. Considering TGW's high risk of contracting HIV, they stand to benefit greatly from anti-HIV therapeutics, but little is known about the immunomodulatory effects of feminizing hormone therapy (FHT). To relieve gender dysphoria and facilitate physical feminization, many TGW utilize FHT, consisting primarily of 17β-estradiol (E2), which has immune-enhancing effects. It is well established that estrogen can influence T-cell development and impart higher resistance to infection in women versus men. Since estrogen can also amplify antibody responses, FHT could have both positive and negative immune consequences to TGW. Hence, to advance our understanding of the immunomodulatory effects of FHT in TGW, we set out to model FHT in rhesus macaques.
Methods: Using slow-release subcutaneous E2 pellets, we developed a dosing regimen in male rhesus macaques that elevate levels of E2 and suppressed testosterone. We used flow cytometry to measure cellular dynamics and ELISA to evaluate the magnitude of LNP/mRNA vaccine-induced Env-binding IgG antibodies.
Results: The E2 regimen significantly increased serum E2 concentrations and suppressed endogenous testosterone levels, while also inducing physical traits associated with feminization, like enlarged nipples. Importantly, immunophenotyping analysis revealed that CCR5+ CD4+ T-cells, the primary targets of HIV infection, were significantly elevated in both blood and gut from the E2-treated animals. Although the female sex is associated with enhanced immune responses to vaccines, FHT did not significantly alter vaccine-induced anti-Env antibodies in the E2 group following mRNA vaccination.
Conclusion: These results demonstrate for the first time the feasibility of modeling gender affirming hormone therapy in rhesus macaques and implicate FHT as a potential driver of HIV susceptibility in TGW.

364 Enema Use Minimally Impacts Immunity and Does Not Affect Susceptibility to Low-Dose Intrarectal SIV

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Background: Men who have sex with men (MSM) are disproportionately affected by HIV. Increased susceptibility to HIV in MSM is attributed to high frequencies of susceptible CD4+ T-cells, GI epithelial barrier disruption, and dysbiosis of the intestinal microbiome. Although colorectal epithelial barrier damage is due, in part, to inflammation resulting from receptive anal intercourse, rectal douching has also been proposed as a significant contributor. The effects of repeated enema use on the composition of the GI tract

microbiome, intestinal immunity, and susceptibility to rectal HIV acquisition have not been empirically assessed.
Methods: We administered enemas (Normosol-R) to rhesus macaques (Control/Enema, n=6/6) thrice-weekly, prior to repeated low-dose intra-rectal SIVmac239X challenge. Before and 28 days after enema treatment initiation (n=12 enemas) we assessed the fecal microbiome by 16S Illumina sequencing and surveyed intestinal and systemic immunity by flow cytometry, multiplex immunologic transcript quantification (NanoString), and ELISA. Fifty-six days after enema initiation (n=24 enemas) we challenged animals with 4 $TCID_{50}$ SIVmac239X until infection was confirmed. Susceptibility to SIV infection in our animals was assessed both by time to SIV infection and number of acquired transmitter-founder (T/F) variants.
Results: Prior to SIV challenge, we observed that as compared to control animals, repeated enema administration was associated with fewer memory CD4+ T-cells in the jejunum ($p<0.001$) and fewer memory CD4+ ($p=0.032$) and CD8+ ($p=0.016$) T-cells in the peripheral blood of treated animals. Treatment was also associated with a trend for less IL-22 production from intestinal memory CD4+ T-cells. No post-treatment differences were observed in plasma sCD14 or iFABP2. Few differences were observed in the composition of the fecal microbiome, with enema treated animals displaying perturbations in the representation of some Oscillospirales species. Of animals infected thus far (n=3/6 each group), there are no differences in the number of challenges that resulted in successful infection nor in the number of acquired T/F variants.
Conclusion: Our analyses will provide a detailed assessment of how the microbiome and intestinal immunity change in response to repeated enema usage. Insight gained from our comprehensive study will inform the causes and consequences of repeated enema usage in MSM and will inform the design of improved bowel- clearing preparations for sexual and surgical use.

365 SIV Infection in Sooty Mangabeys Does Not Impact Survival but Changes Cause of Death

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Background: Sooty mangabeys (SMs) are natural host of simian immunodeficiency virus (SIV), and do not progress to AIDS despite high viral replication. The main factors involved in the benign nature of this infection are (i) low level of immune activation, (ii) relative preservation of specific CD4+ T-cell subsets from direct virus infection, and (iii) absence of microbial translocation from the gut to the systemic circulation. Extensive documentation supports the non-pathogenic nature of SIV infection in SMs, with no significant disparities observed between SIV-infected and uninfected SMs.
Methods: To better assess the long-term impact of SIV infection on the overall clinical conditions of SMs, we have conducted a systematic analysis of the causes of death in 307 SMs, of which 219 SIV-infected and 88 uninfected, that were housed at ENPRC and have died of natural (i.e., non- experimental) causes between1986 and 2022.
Results: We found that SIV-infected SMs live ~4 years longer than SIV-uninfected SMs, although this result is hard to interpret due to differences in the way animals were housed and included in specific experimental studies. While the causes of death were not different between SIV-infected and uninfected SMs that died before age 15, we found a significant differences in the relative frequency of specific causes of death in the geriatric population (≥15 y.o.). Specifically, we observed that SIV-infected SMs were more likely to die from infections (Odds Ratio (OR) +infinity, 95% CI 2.07- +infinity, $P = 0.0064$) but less likely to die from cardiovascular disease (OR 0.2326, 95% CI 0.104-0.675, $P = 0.00613$) as compared to uninfected animals. A similar trend was consistently observed within the subgroups categorized by sex, indicating that these findings were robust across sexes. No differences were observed for cancer, diabetes, trauma, and miscellaneous other causes.
Conclusion: While confirming the non-pathogenic nature of SIV infection in SMs, these data reveal, for the first time, a qualitative impact of SIV infection on the host physiology that induces a significant change in the pattern of mortality in these natural SIV hosts.

366 Positive Reinforcement Training Reduces Stress in SIV-Infected Macaque Models of HIV Infection

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Background: Work with SIV infected macaque models is essential to HIV pathogenesis, vaccine development and cure research. Positive reinforcement training (PRT) may be used rather than restraint or sedation to facilitate administration injectable antiretroviral therapy (ART) or obtain blood samples. The effect of PRT on data in these models has yet to be defined.
Methods: A subset of juvenile male rhesus (Macaca mulatta) and pigtailed (Macaca nemestrina) macaques were trained using PRT to voluntarily present a limb for ART injection and blood sampling prior to intravenous infection with SIVmac251 or SIV17E/Fr combined with SIV delta B670, respectively, and compared to untrained SIV infected macaques, and subsequently treated with ART to suppress viral replication. Regardless of training history, macaques were sedated throughout infection to obtain blood and cerebral spinal fluid. Viral loads, immune markers, and plasma cortisol levels were compared between trained and untrained SIV infected macaques (M. mulatta; $n = 24$ trained; $n = 8$ untrained; M. nemestrina $n = 6$ trained; $n = 29$ untrained) throughout the course of infection using a mixed effects model.
Results: No differences were observed between trained and untrained M. mulatta in peripheral or central nervous system (CNS) viral loads during acute infection, though trained M. nemestrina demonstrated significantly lower viral loads compared to untrained macaques; no differences in viral suppression were observed upon ART initiation in either species. CD4 T cell numbers declined in all animals during acute SIV infection, with trained rhesus macaques demonstrating a delay to decline compared to untrained animals. Though all macaques experienced increased plasma cortisol following SIV infection, trained macaques had a lesser increase compared to untrained animals.
Conclusion: PRT buffers the physiologic stress associated with SIV infection in macaques, as evidenced by a less pronounced cortisol response to infection. Further work needs to be completed to understand the extent to which PRT may affect viral load and immune parameters, and caution should be exercised when comparing data from animals that have engaged in PRT compared to untrained macaques.

367 HIV Rapid Intra-Host Evolution Allows Evasion From VRC01 Infusion via Positive Selection

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Background: One of the factors contributing to HIV's persistence is its rapid evolution. Understanding how the env gene evolves under antibody-mediated pressure is particularly important for efforts to use antibodies as therapies for HIV. In a previous clinical trial, infusion of the broadly-neutralizing antibody (bNAb) VRC01, which targets the CD4 receptor binding site, lowered plasma HIV viremia in a subset of participants, but was associated with the emergence of neutralization-resistant env variants. Here we sought to develop an analytical approach for identifying env mutations that confer escape from antibodies using single-genome sequence data from participants treated with VRC01.
Methods: We applied single-genome amplification and sequencing (HT-SGS) using unique molecular identifiers (UMIs) and the Pacific Biosciences long-read platform, to measure HIV env allele frequency changes over time in longitudinal samples from people with chronic, untreated HIV infection who received one dose of VRC01. Eight participants were studied, and a total of 29,433 sequences were analyzed. We used two approaches to identify changes adaptive to VRC01 escape: (1) a codon-based dN/dS approach executed by HYPHY with FUBAR (2) a population genetics approach where Tajima's D was used to identify positive selective sweeps along the env gene, and then a score for the selected allele favored in evolution (SAFE) was calculated.
Results: In six of eight hosts the viral populations pre and post infusion were distinct. Specifically, changes in the VRC01 epitope were observed. In two individuals, both FUBAR and SAFE approaches identified the same positions as adaptive. In another four individuals FUBAR and SAFE pointed to different residues as adaptive. Examining manually regions of selective sweeps as

identified by negative values of Tajima's D, revealed complex evolutionary scenarios, and suggested the existence of several adaptive mutations in each host. Furthermore, epistasis between positions is likely, due to existence of low frequency combinations, of the adaptive alleles, that do not grow in frequency. In two individuals, subpopulation structure correlating with sequence signatures of cell tropism is associated with different escape mutations.
Conclusion: These results suggest diverse adaptive pathways to bNAb escape among different individuals. While some mutations are easily identified as adaptive, multiple escape mutations, epistasis and tropism associated mutation are more challenging to identify and interpret.

368 A Rare Molecular Signature in HIV-1 Env V1 Associates With bNAb Evolution

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Background: Identifying traits of HIV-1 Envelope (Env) linked with broadly neutralizing antibody (bnAb) development is critical for designing bnAb vaccines. Here we report a rare twin cysteine (Cys) motif in the variable loop 1 (V1) region that is enriched among Env of bnAb inducers.
Methods: V1 Cys insertions were functionally characterized in vitro and quantified in Env sequence datasets from bnAb inducer cohorts (Swiss 4.5K), longitudinal cohorts (ZPHI, SHCS, CAPRISA) and the LANL sequence database. Factors associated with frequency of V1 Cys insertions were analyzed using logistic regression.
Results: Studying Env from 35 bnAb inducers from the Swiss 4.5K screen we noted a high overall neutralization resistance and observed a rare twin Cys motif in V1 in several Envs. Functional studies with bnAb inducer Envs and analysis of the CATNAP database showed that Envs with the V1 Cys motif had a modestly increased neutralization resistance pointing towards a compensatory stabilizing effect. Analyzing Env sequences from 1,105 Swiss 4.5K participants, we observed an independent association with neutralization where >20% of elite neutralizers carried the motif compared to 5% of non-neutralizers. Sequence simulations and comparison to >6000 Env sequences of the LANL database showed that the observed frequency of Env with two extra Cys in V1 is unlikely to occur by chance. Twin V1 Cys occur in recent transmission, suggesting no transmission bias, and show peak frequencies in later infection. Longitudinal Env profiles of 57 CAPRISA donors showed fluctuating frequencies of variants with extra V1 Cys, suggesting the motif alone provides a limited fitness advantage. Notably, a high proportion of Env with twin V1 Cys was transmitted in the AMP trial placebo arms (15% and 9% of participants in HVTN703 and 704, respectively) while breakthrough viruses showed a VRC01 treatment dose dependent reduction in twin V1 Cys, suggesting a fitness deficit of transmitted twin V1 Cys viruses.
Conclusion: Our data support a role of the V1 Cys motif in optimizing V1 stabilization and epitope shielding during neutralization escape. Gains in neutralization resistance and viral fitness through the motif may vary depending on the extent of virus nAb co-evolution. BnAb-experienced viruses are likely optimized for both fitness and resistance, while recently escaped variants may, despite twin V1 Cys insertions, still have fitness deficits and are rapidly counter-selected when new pressure arises as in the case of VRC01 prophylaxis.

369 Potent Cross-Reactive HIV-1 Neutralization in Fusion Peptide-Primed SHIV-Infected Macaques

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Background: An effective antibody-based HIV-1 vaccine will require the consistent induction of potent cross- reactive HIV-1-neutralizing responses. Epitope-focusing approaches have elicited consistent, but low titer, cross-clade neutralizing responses against multiple sites of vulnerability. However, consistent, broad, and potent neutralizing responses against HIV-1 have not been achieved by vaccination.
Methods: To demonstrate feasibility towards the consistent, broad, and potent neutralizing responses, we combined vaccination targeting the fusion peptide-site of vulnerability with infection by simian-human immunodeficiency virus (SHIV).
Results: In four macaques with vaccine-induced neutralizing responses, SHIV infection boosted plasma neutralization to 45-77% breadth on a cross-clade panel of 208 strains with geometric mean ID_{50} titers of ~100, a level of potency recently shown to protect against mucosal SHIV challenge from fusion peptide-directed antibodies. Neutralization fingerprinting identified epitope-specific signatures in plasma and observed higher estimates for fusion peptide-directed specificity versus other known specificities. By longitudinally plasma viral RNA sequencing, we observed evidence of strong viral selection by post-SHIV week 16 at the N terminus of the fusion peptide and at the structural adjacent regions, including residues nearby glycan 88. Molecular dissection of these responses into component antibody specificities by antibody isolation and cryo-EM structure determination revealed 15 of 16 isolated antibodies with cross-clade neutralization breadth to be directed towards the fusion peptide-site of vulnerability. In each macaque, isolated monoclonal antibodies recapitulated the plasma-neutralizing response (r =0.71-0.97), with fusion peptide-binding antibodies reaching breadths of 40- 60% (IC_{50} <50 µg/ml) on a 208 strains panel. Longitudinal phylogenetic analysis revealed each of the top macaques to have only 1-2 broadly neutralizing fusion peptide-binding lineages, each induced before SHIV infection.
Conclusion: These results provide explicit in-vivo molecular examples for one or few B-cell lineages affording potent cross-reactive plasma-neutralizing responses. While increased titers in the current study resulted from SHIV-infection boosting, it will be interesting to test fusion peptide-Env trimer immunogens not only with altered boosting regimens, but also with altered priming regimens, such as with the escalating prime, extended- boost regimen.

370 Maturation Pathway of Rhesus V3-Glycan Broadly Neutralizing Antibody Lineage

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Background: We previously isolated clonally-related HIV-1 envelope (Env)-reactive broadly neutralizing antibodies (bnAbs), termed DH1030, from a pathogenic SHIV-infected rhesus macaque (RM08N021). Rhesus DH1030 targeted the V3-glycan bnAb-epitope on HIV-1 Env using an arginine (R) residue acquired via an improbable mutation from glycine (G) in the HCDR2. Engineering HCDR2-G56R mutation into the DH1030 unmutated common ancestor (UCA) alone was insufficient to achieve neutralization activity. We hypothesized that DH1030 lineage maturation included a series of mutations that preceded G56R in the HCDR2. Defining mutations associated with maturation of DH1030 will inform prime-boosting strategies to select for key mutations that confer maturation to bnAb status.
Methods: We isolated 62 clonally-related DH1030 Abs from RM08N021 via Env-reactive B cell flow cytometry sorting and 10X Genomics single cell immune profiling assays. DH1030 Abs clustered into three phylogenetic clades. The majority of clade 1 Abs had HCDR2-G56; all clade 2 Abs had HCDR2-G56; and all clade 3 Abs had HCDR2-R56. Monoclonal (m) Abs were tested for binding specificities, structure, and function. We expressed 26 mAbs representative of all three clades, including the inferred intermediates and UCA.
Results: Of 8 mAbs tested from clade 1, two containing HCDR2-G56 neutralized only autologous HIV-1 strains, but two that contained HCDR2-R56 did not neutralize HIV-1 strains tested. None of six mAbs tested from clade 2 neutralized HIV-1. In contrast to results from clades 1 and 2, all 10 mAbs tested from clade 3 with HCDR2-R56 neutralized CH848 10.17DT and up to 6/9 heterologous tier 2 HIV-1 from the global panel. Sequence analysis of DH1030 Abs along the path to clade 3 bnAbs revealed mutations in the HCDRs that preceded G56R. All the clade 3 bnAbs had a serine-to-proline mutation at position 114 (S114P) in the HCDR3. Mutating S114P into an intermediate Ab (IA59) along the clade 3 bnAb path conferred Ab binding at similar levels to the clade 3 bnAbs in contrast with wild-type IA59 which showed no binding. Computational modeling of S114P on DH1030.1-Env complex suggested favorable neighboring contact residues facilitated by this mutation. Additionally, the light chain (VL) of DH1030UCA

paired with bnAb DH1030.1VH had no binding, in contrast to DH1030IA59VL + DH1030.1VH, suggestive of VL gene mutations in bnAb maturation.
Conclusion: The DH1030 maturation pathway occurs via a series of VH and VL mutations, including HCDR2- G56R and HCDR3-S114P.

371 An Efficient Envelope Genotypic Assay to Identify bNAb Susceptibility in Infants with HIV

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Background: HIV-1 envelope (Env)-specific broadly neutralizing antibodies (bNAbs) have several potential clinical benefits including in infants: Infants have limited tolerable antiretroviral treatment (ART) options, given daily for prevention and twice daily for treatment. In contrast, bNAbs with modified Leucine-Serine (LS) Fc receptors permit infrequent subcutaneous dosing. Moreover, unlike ART, bNAbs may facilitate viral reservoir reduction and contribute to functional cure. However, data on HIV-1 Env evolution and bNAb susceptibility in perinatally infected infants are limited.
Methods: The evolution of Clade C Env in five infants (4 female) born with HIV-1 and with intermittent viraemia despite early ART was investigated over 19.3 (range: 16.9 - 21) months. A single-genome sequencing approach using Oxford Nanopore Technologies (ONT) was developed and validated using Sanger Sequencing as reference. In short, consensus sequences were constructed for each single genome using NECAT, a published bioinformatics pipeline that corrects ONT error. Defective individual genomes containing stop codons were excluded. The susceptibility of the remaining genomes to 33 bNAbs were investigated using the bNAb- Resistance Predictor (bNAb-ReP) machine learning algorithm.
Results: The intra-patient average pairwise distances (APD) ranged from 0.08% - 1.29% (median: 0.43%). Different evolutionary patterns were observed. Env length variation emerged in 4 out of 5 infants. Phylogenetic trees showed temporal structure in four cases with new variants emerging either from majority or minority populations or apparent ancestral or archived variants. All variants were identified as CCR5-tropic by three genotypic prediction models. Predicted bNAb susceptibility showed much higher inter-patient than intra-patient variability with PGDM1400, PGT128 and 3BNC117 (Table 1) predicted to have the highest susceptibilities overall.
Conclusion: As phenotypic bNAb susceptibility testing is costly and has low reproducibility, we developed an efficient Env genotypic assay, combining single-genome sequencing with ONT to accommodate Env sequence length variation. Applying our workflow, the predicted susceptibility to bNAbs varied across individuals due to high levels of inter-patient Env diversity. Early ART-treated infants often have viraemia due to adherence challenges. However, early intra-patient Env evolution was limited and unlikely to impact bNAb susceptibility. Updated prediction algorithms require validation across HIV-1 subtypes.

Table 1. Investigation of HIV-1 Env of five infants and the highest predicted bNAb susceptibilities

Patient	Duration of observation (months)	Env APD# (%)	Length variation (base pairs)	Most susceptible bNAbs*	
				bNAb name	*Probability susceptibility*
SA-TY-012	16.9	1.02	2 550 – 2 571	PDGM1400	0.98
				PGT128	0.98
				10-1074	0.95
SA-TY-015	19.5	0.08	2 568	PDGM1400	0.99
				HJ16	0.77
				VRC13	0.71
SA-TY-025	19.1	0.36	2 565 – 2 568	PGT128	0.96
				10-1074	0.91
				3BNC117	0.89
SA-TY-032	19.3	1.29	2 568 – 2 583	3BNC117	0.98
				PG9	0.88
				PGDM1400	0.83
SA-TY-034	21.0	0.43	2 553 – 2 568	PGDM1400	0.96
				PGT145	0.85
				PG9	0.81

APD – average pairwise distance
* predicted by bNAb-ReP artificial intelligence algorithm

372 MHRP.01, an MPER Targeting bNAb, Enables Further Definition of the 4E10-Class of bNAbs

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Background: The membrane proximal external region (MPER) is a conserved site of vulnerability on the HIV- 1 gp41 envelope, targeted by highly potent broadly neutralizing monoclonal antibodies (bNAbs) such as 4E10, VRC42 and PGZL1. Although elicited by unrelated persons living with HIV (PLWH), from multiple different HIV-1 subtypes, these bNAbs have similar features. We report the isolation of 4E10-class bNAb, MHRP.01, from an untreated person living with subtype B HIV infection that had 100% neutralization breadth against a 34- pseudovirus (pSV) panel and predicted specificity for MPER binding mAbs. Using bNAbs 4E10, VRC42, and MHRP.01, we provide evidence of an amino acid signature pertaining to 4E10-class bNAbs.
Methods: CD19+/IgD-/IgM- B cells were sorted from donor PBMCs by flow cytometry and cultured in 384- well plates. Cultured supernatants were screened via microneutralization assays against HIV-1 pSVs. B cell receptors from wells with neutralization >70% were sequenced, followed by cloning and expression of heavy and light chain genes to produce monoclonal antibodies (mAbs). mAbs were characterized for binding, epitope mapping and neutralization assays against panels of diverse HIV-1 strains. Based on crystal diffraction analysis, mutations were introduced in the heavy chain of the MHRP.01 to generate a 4E10-like bNAb signature, and the resulting mutant mAbs were further characterized.
Results: MHRP.01 neutralized 99.5% of a globally diverse 208-pSV panel with IC_{50} of 1.49 µg/ml and demonstrated striking similarities to 4E10, VRC42, and PGZL1, including utilization of VH1-69 and VK3-20 gene usage and similar critical residue epitopes. Crystallization of MHRP.01 revealed residues important for MPER binding, which bound in the same conformation as 4E10 and VRC42. Mutation of glycine at 50 or proline at 108 locations within CDRH2 and CDRH3 respectively abolished binding to the MPER peptide and neutralization of autologous pSV (Fig 1), with further paratope residues contributing to a definable sequence signature.
Conclusion: MPER targeting bNAb, MHRP.01 contained identical germline usage, binding angle of approach and neutralization breadth as 4E10-class bNAbs. Structural analysis reveals a 4E10-like bNAb signature important for MPER binding and neutralization. MPER represents a common epitope which has the potential to elicit similar B cell responses from several PLWH, making it desirable for vaccine design.

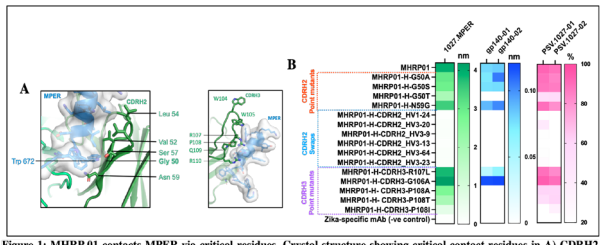

Figure 1: MHRP.01 contacts MPER via critical residues. Crystal structure showing critical contact residues in A) CDRH2 and B) CDRH3 region of MHRP.01. C) MHRP.01 heavy chain mutants were produced by site-directed mutagenesis and tested for binding against MPER and autologous gp140 via biolayer interferometry and neutralization against autologous pSV.

373 Mycobacterium tuberculosis Infection Dampens the HIV-1 Antibody Response

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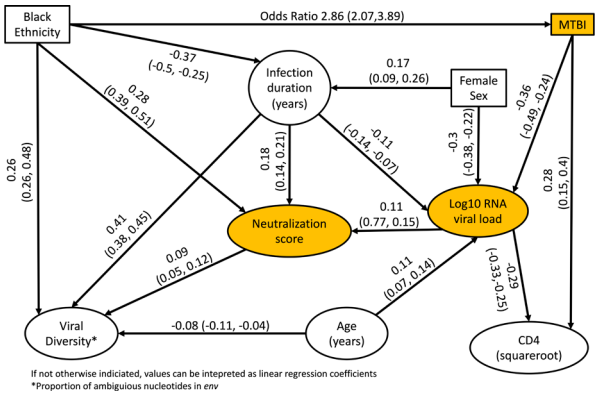
Background: In prior investigations, we uncovered the impact of *Mycobacterium tuberculosis* (MTB) infection on the innate immune system in people with HIV (PWH). We showed an improved ability to control HIV and less susceptibility to opportunistic infections in untreated PWH. Intriguingly, it also heightened the risk of non- communicable diseases such as diabetes mellitus. Our exploration of the transcriptome in PWH, with and without MTB infection, unveiled gene alterations associated with innate immunity and B cell upregulation. Additionally, another group showed that active TB enhances immune responses. Here we extend these investigations and determine the effects of MTB infection on the anti-HIV-1 antibody (Ab) response.

Methods: Using data from the Swiss HIV Cohort Study and the Swiss 4.5K neutralization Screen (Rusert, Nat Med, 2016), we assessed immune responses in PWH dependent on MTB status (excluding active TB and preventively treated). We examined two aspects: (i) plasma neutralization against eight HIV strains (activity/breadth score 0 to 24), and (ii) relative plasma Ab (IgG1/2/3) binding (score 0 to 1) to 20 HIV antigens. We determined the impact of MTB status by tobit and linear regression adjusting for ethnicity, age, sex, CD4, HIV viral load, viral diversity, and infection duration. We employed bayesian networks to elucidate interplays between factors, particularly disentangle direct and indirect effects.

Results: Our analysis included 2,823 PWH (211 MTB infected). MTB infection was associated with a -0.74 (-1.44,-0.05) neutralization reduction in multivariable tobit regression. Moreover, MTB infection was associated with a -0.04 (-0.07,-0.01) binding decrease of epitopes/IgG classes (IgG2 trimer, IgG1 gp140, IgG1 V3), previously shown to be predictive of high neutralization. Bayesian network analysis (Figure) showed MTB infection was associated with a -0.36 (-0.63,-0.08) $\log_{10}$ viral load decrease. In turn, one $\log_{10}$ viral load increase, was associated with a 0.11 (0.03,0.19) neutralization increase.

Conclusion: Consistent with our previous findings, our results underscore the immediate impact of MTB infection in reducing HIV-1 viral load. The resulting decreased exposure to HIV-1 antigen is likely the cause of the observed attenuated HIV-1 antibody response. While a modest decrease in binding Abs may be of limited consequence, a reduced ability to induce neutralizing Abs in untreated HIV and MTB co-infection may potentially counteract the gains in HIV-1 control induced by MTB.



If not otherwise indiciated, values can be intepreted as linear regression coefficients
*Proportion of ambiguious nucleotides in *env*

374 Temsavir Treatment Enhances bNAb Recognition and Subsequent Clearance of HIV-1– Infected Cells

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Background: HIV-1 gp120 is a viral envelope glycoprotein (Env) expressed on the surface of infected cells which renders it an attractive target for the clearance of the infected cells. However, Env is metastable and presents in multiple conformations, making it challenging for antibody-mediated clearance. Temsavir (TMR), the active form of the HIV-1 attachment inhibitor fostemsavir, binds to and stabilizes Env in a 'closed' conformation that may allow better targeting by broadly neutralizing antibodies (bnAbs).

Methods: To understand whether TMR can modulate bnAb binding to Env on the infected cells, we conducted experiments with primary CD4+T cells isolated from HIV negative donors infected with a broad panel of viruses that includes 26 clinical HIV isolates. Antibody binding to Env on the infected cell surface was determined after 24h treatment with a serial titration of TMR ranging from 0 to 25µM.

Results: We found that TMR treatment significantly enhances binding of bnAbs, including N6, to HIV-1 infected cells and leads to increased clearance of infected cells through antibody dependent cellular cytotoxicity (ADCC). This synergistic effect of N6 and TMR is most prominently observed on infected cells that maintain CD4 expression, the cells that are otherwise difficult to target by N6 and other bnAbs alone. The enhanced bnAb binding is diminished when tested against strains with reduced TMR sensitivity (clade AE), suggesting that it is an on-target MOA. We observed decreased bnAb binding to CD4 downregulated infected cells with some viruses. However, this effect only occurs at much higher TMR concentrations than required for neutralization and is not consistent across the panel. Alternatively, we saw significantly increased bnAb binding to the CD4 downregulated cells in 1/3 of isolates that are tested. Further analysis of HIV Env from infected cells demonstrated that the altered bnAb binding is not attributed to the modified gp160/gp120 processing by TMR.

Conclusion: We have demonstrated for the majority of viruses tested that TMR treatment leads to enhanced bnAb binding to the infected cells that maintain CD4 expression, and the reduced bnAb binding to the CD4 downregulated infected cells occurs at much higher concentrations than neutralization. These results suggest that combination of bnAb and TMR can expand the population of HIV-1 infected cells susceptible to bnAb mediated clearance and may increase the likelihood of reservoir reduction in the clinical setting.

375 AAV-1, -8, and -9 Seroprevalence in Healthy Donors and People Living With HIV in Sub- Saharan Africa

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Background: Adeno-associated virus (AAV)-vectored delivery of monoclonal (m) HIV-specific broadly (b) neutralizing (n) antibodies (Abs) holds promise for treating HIV infection. Because AAV is non-pathogenic and its genome persists in host cells, successful AAV/bnAb transduction of long-lived cells, such as myocytes, can result in continuous bnAb expression for years, possibly

decades. We set out to address a critical barrier to the clinical use of AAV/bnAb vectors: the high prevalence of pre-existing anti-AAV nAbs in humans. One way to maximize the impact of AAV/bnAb therapies is to determine the seroprevalence of muscle-tropic AAV capsids in areas with high incidence of HIV, so that people living with HIV (PLWH) who are seronegative for these AAV capsids can potentially benefit from AAV/bnAb therapies without any additional intervention. AAV epidemiology is well documented in developed countries but nearly absent for sub-Saharan Africa, home of most PLWH.

Methods: To address this deficit, we partnered with the HVTN (HIV Vaccine Trials Network) and ACTG (AIDS Clinical Trials Group) to establish the prevalence and titers of anti-AAV nAbs in South Africa and Zimbabwe. We used HEK293T cells and luciferase-expressing vectors to screen sera from 300 healthy adult donors (HD) and 277 PLWH for nAbs against AAV-1, -8, and -9.

Results: First, we screened sera at a 1:20 dilution and found that 15%, 79%, and 77% of HD samples displayed <50% neutralization of AAV-1, -8, and -9, respectively. We found no significant sex-specific differences in the prevalence of anti-AAV nAbs in this cohort. Among PLWH, 17%, 72%, and 73% of samples exhibited <50% neutralization of AAV-1, -8, and -9, respectively. Next, we determined the midpoint titers of anti-AAV-9 nAbs in the samples that exhibited >50% neutralization at a 1:20 dilution (i.e., AAV-9+). We selected AAV-9 for this in- depth analysis because of its superior performance to AAV-1 and -8 in promoting persistent mAb expression in nonhuman primates following intramuscular (IM) administration. Among HD, 75% of AAV-9+ donors exhibited titers of anti-AAV-9 nAbs below 1:160, a level that is not thought to impair IM AAV transduction in primates. We are currently determining the titers of anti-AAV9 nAbs among the AAV-9+ PLWH.

Conclusion: In summary, nearly three quarters of HD and PLWH in South Africa and Zimbabwe could be eligible to participate in clinical trials of bnAb-encoding AAV-9 vectors delivered by the IM route.

376 Machine Learning-Guided Generation of a Combination of Broadly Neutralizing Sarbecovirus Antibodies

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Background: Sarbecoviruses represent a subgenus of coronaviruses including strains mostly circulating in bats and at risk of zoonotic spillover as well as strains that can infect humans (SARS-CoV-1 and SARS-CoV-2). Over the past 20 years, SARS-CoV-1 was responsible for an outbreak in Asia while SARS-CoV-2 initiated a global pandemic and remains a continuous health threat especially for vulnerable populations. There is still the need to develop therapeutic measures that can effectively control human sarbecoviruses and potential zoonotic spillover events, thereby preventing future epidemics/pandemics. Several monoclonal antibodies have been discovered with broad neutralizing activity against sarbecoviruses by targeting conserved regions of the spike proteins such as class 3 and 4 RBD regions and S2 fusion machinery. Viral escape mutations accrued in the SARS-CoV-2 spike protein have rendered most of the antibodies targeting RBD regions ineffective. In addition, antibodies targeting the S2 fusion machinery have relatively low neutralization potency compared to anti-RBD antibodies and therefore their therapeutic utility has not been realized.

Methods: Here we used a machine learning-guided protein engineering approach to optimize broadly neutralizing antibodies against sarbecoviruses. We screened computationally designed sequence sets for binding to spike proteins, neutralization of pseudoviruses and developability parameters to select lead molecules. Additional characterization of lead molecules as single agents and combination included: epitope mapping through cryo-EM and X-ray crystallography, assessment of binding affinities to spike proteins, neutralization of pseudoviruses and live viruses, in vitro escape experiments and in vivo hamster challenge with SARS-CoV-2 BA.2.

Results: We rescued the neutralizing activity of a previously described class 4 anti-RBD antibody against Omicron variants. We also improved neutralization potency and efficacy of a previously described antibody with pan-sarbecovirus activity targeting the S2 stem helix peptide. Finally, we demonstrate that the combination of these optimized antibodies improves both neutralization of SARS-CoV-2 variants in vitro and suppression of viral replication in a hamster challenge model.

Conclusion: Our work highlights the successful use of machine learning-guided protein engineering for optimization of anti-viral antibodies and supports further evaluation of the described antibody combination for epidemic/pandemic response and preparedness.

377 Safety and Immunogenicity of Month 30 Boost of ALVAC+gp120/MF59 Preventive HIV Vaccines

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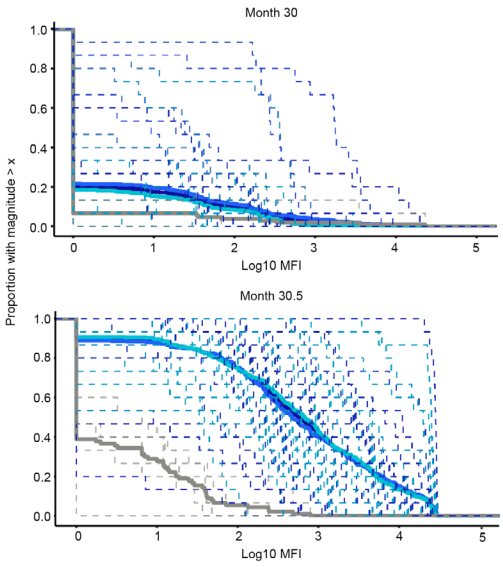
Background: HVTN 100, a phase 1-2 preventive HIV vaccine trial in South Africa, administered subtype C- containing ALVAC-HIV (vCP2438) at months 0 and 1, and ALVAC-HIV with bivalent subtype C gp120/MF59 at months 3, 6 and 12 in Part A. IgG binding antibody and T-cell responses were similar or greater at month 12.5 compared to month 6.5 then waned by month 18. In Part B we boosted after an 18-month interval at month 30.

Methods: Part B vaccinations were administered to eligible Part A participants, randomized to either ALVAC- HIV + gp120/MF59(n=32), or gp120/MF59 alone(n=31) and placebo group was re-administered placebo(n=7). At months 30, 30.5 and 36, we measured envelope (Env)-specific serum binding antibodies by binding antibody multiplex assay (BAMA) and HIV-specific CD4 T-cell responses by intracellular cytokine staining assay, and neutralization by reductions in Tat-regulated luciferase reporter gene expression in TZM-bl cells.

Results: Vaccine groups had an acceptable safety profile based on reactogenicity, adverse events and laboratory tests. There were no statistically significant differences in IgG binding antibody response rates or magnitudes between the two vaccine groups for any gp120, gp140, or V1V2 antigens at any timepoint. Vaccine groups had positive IgG responses to all V1V2(n=27), gp120(n=11) and gp140 antigens(n=9) at all timepoints but were more common for gp120 and gp140 antigens and highest at month 30.5. Booster vaccination restored the magnitude-breadth IgG response to V1V2 antigens at Month 30.5 which waned by month 36 with median area under the curves(AUCs) for combined vaccine groups 0.13, 2.55 and 0.40 for months 30, 30.5 and 36 respectively (Fig 1). Month 30 boosting increased magnitude and durability of tier 1A neutralization responses but did not induce tier 2 neutralization responses. Month 30.5 tier 1A response magnitudes for the pooled vaccine group increased significantly compared to month 12.5, median 331 versus 756, $p<0.0001$ for TV1c8.2; 886 vs. 1763, $p<0.0001$ for MW965.26). CD4+ Env responses, rate and magnitude, to vaccine-matched antigens were seen at month 30, boosted at month 30.5, waned by month 36, with no significant differences between vaccine groups.

Conclusion: Booster vaccination with gp120/MF59 given alone or with ALVAC after an 18-month interval was safe and induced binding, tier 1A neutralization and CD4+ T-cell responses similarly in both vaccine groups. Late boosting may increase breadth of responses and restore V1V2 binding antibody responses.



Magnitude-breadth of IgG binding antibody responses to subtype C Env V1V2 at the month 30 vaccination timepoint and at month 30.5.

378 Adenosine Deaminase-1 Enhances HIV-Specific Responses to a HIV Trimeric Envelope DNA Vaccine

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Background: Human immunodeficiency virus (HIV) remains a prominent global health threat for which no prophylactic vaccine is available. Extensive research efforts have resulted in immunogens, including SOSIP trimers, that closely mimic the native envelope (Env) glycoprotein conformation and consistently induce autologous neutralizing responses. Recently, a novel triple tandem trimer (TTT) platform has been used to generate a plasmid encoding Env immunogen (pBG505-TTT) that expresses only as trimers, making it more suitable for nucleic acid vaccines. We have demonstrated that adenosine deaminase-1 (ADA-1) is critical to the T follicular helper (TFH) function and survival. In fact, ADA-1-induced TFH function that improved the magnitude and durability of both cellular and humoral vaccine immune responses in vivo. We therefore hypothesized that ADA-1 combined with the improved HIV envelope antigen pBG505-TTT would result in enhanced qualitative and quantitative humoral and cellular HIV specific responses.

Methods: Mice were immunized intramuscularly with 1, 5, or 10µg of pBG505-TTTalone or were co- immunized with 10µg of plasmid encoded adenosine deaminase-1 (pADA). A separate group of mice were immunized with both DNA as described and 10ug of trimeric Env recombinant protein (rBG505-SOSIP) with adjuvants Alum or MF59. Mice were bled on day 21 post 2 immunizations (D21P2) and day 14 post 3 immunizations (D14P3) to evaluate humoral responses via ELISA, surface plasmon resonance, and neutralization assays. Cellular responses were evaluated on D14P3 via ELISpot assays, T cell intracellular cytokine staining and antigen specific memory B cell staining via flow cytometry.

Results: Mice co-immunized with pADA and 1µg pBG505-TTT displayed significantly increased Env specific antibody titers as early as D21P2. pADA and 10µg pBG505-TTTco-immunized mice exhibited Env specific antibody with enhanced affinity and increased Env specific memory B cells when compared to non-adjuvanted counterparts. Mice immunized with 10µg pBG505-TTT, pADA, rBG505-SOSIPand alum exhibited enhanced neutralization compared to their non-pADA adjuvanted counterparts. Mice receiving pADA and 1µg or 5 µg pBG505-TTT exhibited enhanced Env specific T cell activation, cytokine polyfunctionality, and degranulation.

Conclusion: These data demonstrate that pADA enhances both cellular and humoral immunity in a dose sparing manner against HIV Env making it a promising adjuvant for HIV targeting vaccines.

379 Sex-Based Differences in Antibody Responses Induced by a Native-Like HIV-1 Envelope Trimer Vaccine

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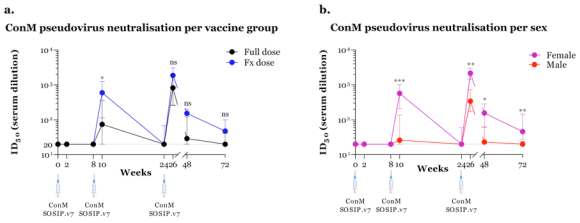
Background: A protective vaccine would be the most powerful tool towards reducing HIV-1 infections worldwide and sustainably ending the AIDS epidemic as a public health threat. We assessed the safety and immunogenicity of ConM SOSIP.v7, a native-like envelope trimer vaccine based on an HIV-1 group M consensus sequence, in HIV-negative adults.

Methods: 24 individuals were enrolled in a phase 1 clinical trial to receive three dosages of adjuvanted ConM SOSIP.v7 (baseline, eight and 24 weeks) and followed-up for one year thereafter. Out of 23 per-protocol vaccine recipients, 10 received a one-fifth fractional third dose, aimed to increase B cell somatic hypermutation. Outcomes included ConM-specific total immunoglobulin G (IgG), IgG subclasses, pseudovirus neutralisation and single B cell sequencing. Levels of sex hormones were measured over time.

Results: The majority of adverse events were mild to moderate, self-limiting and similar between dosage groups and sexes. No serious adverse events were reported. Similar to non-human primates, adjuvanted ConM SOSIP.v7 was consistently capable of inducing an autologous neutralising antibody response in humans, which remained detectable in half of the participants six months after the final vaccination. Antibody binding to several heterologous envelope proteins could be detected in the majority of participants, but no neutralisation breath. No differences in serological outcomes could be attributed to the fractional third dose. Female born participants had an earlier increase in neutralising antibodies than males and had a 6.3-fold higher neutralisation titer post third vaccination. Sex-based differences in IgG1 and IgG4 subtype responses were also observed. Subtle correlations, both positive and negative, were seen between ConM-neutralisation, IgG2 and IgG3 levels on one hand, and oestradiol and testosterone on the other hand, but the small sample size limits drawing strong conclusions. Single B cell sequencing should reveal whether the fractional dose and/or sex influence B cell affinity maturation.

Conclusion: The adjuvanted ConM SOSIP.v7 native-like trimer vaccine is safe and elicits a robust strain- specific neutralising response in nearly all recipients, making it an interesting boosting immunogen candidate. Females responded earlier and had a striking 6.3-fold higher neutralisation titer after the final vaccination. This study highlights that sex-based differences should be taken into consideration when assessing HIV-1 vaccine candidates and adjuvants.



Pseudovirus serum neutralisation. 50% inhibitor dilution (ID_{50}) values are depicted at each vaccination, two weeks post-vaccination and at 48 and 72 weeks. **a.** ConM-pseudovirus serum neutralisation (ID_{50}) per vaccine group. Full dose n=13. Fractional (Fx) dose n=10. **b.** ConM-pseudovirus serum neutralisation (ID_{50}) per sex at birth. Female n=13. Male n=10.

380 IgG and Fc Receptor Genetic Variation Associates With Functional Antibody Responses in HVTN 108

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Background: The HVTN108 trial evaluated the immunogenicity of a DNA prime, adjuvanted protein boost vaccine regimen in the US and South Africa. We defined the IgG antibody Fc and Fc receptor (FcR) genotypes in the study population to test our hypothesis that IgG and FcR genetic variation can affect vaccine-elicited functional antibody responses.

Methods: HVTN108 enrolled 334 participants in treatment (n=310) and placebo (n=24) groups. The genotypes of IgG Fc and FcRs were determined by targeted PCR amplification and Illumina next-generation sequencing. Vaccine-

elicited functional antibody responses, including binding antibody multiplex assay (BAMA), antibody- dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) assays, were measured by HVTN core labs. Pearson correlation analysis of IgG and FcR genetic variants was used to identify potential linkage disequilibrium (LD). Relationships between genotypes and antibody responses were identified by linear regression controlling for treatment group and region. Variants were deemed to be associated with antibody responses when the p-value was below 0.05 and the Benjamin-Hochberg false discovery rate (FDR) adjusted value below 0.2.

Results: In the study population, there was evidence of LD within IgG and FcR alleles, but no strong correlations between specific IgG and FcR alleles (all r values were <0.5). The distribution of many polymorphisms significantly differed between the US and South Africa. Within the subset of the cohort tested for functional antibody responses (IgG, n=41; FcR, n=55), we determined that IgG genotypes such as IgG1_12 (p=0.010, p=0.027), IgG3_11 (p=0.028, p=0.050), IgG2_02 (p=0.032, p=0.102), IgG4_07 (p=0.064, p=0.133), and others were associated with vaccine-elicited ADCC antibody titers and activity peaks when corrected for vaccine group and regional effects. In the same way, we identified that the FCER1A rs2427827 had a significant association with higher peak ADCC activity and the FCGR2A rs1801274 mutation was associated with a higher antibody binding to a subtype C V1V2 antigen.

Conclusion: Multiple IgG genotypes and FcR mutations were associated with ADCC and binding antibody levels after HVTN108 vaccination when controlling treatment and region. Genetic variation in both antibodies and FcRs contributes to vaccine-induced humoral responses but there were significant regional differences in their distribution, suggesting regional development of HIV vaccines may be scientifically appropriate.

381 Developing Novel HIV-1 Env Proteins That Efficiently Engage the Unmutated Forms of VRC01-Class Abs

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Background: VRC01-class antibodies are potent and broadly neutralizing antibodies (bnAbs) that protect animals from experimental S/HIV infection and have been shown to prevent HIV-1 acquisition in two phase 3 clinical trials. These antibodies target the CD4 binding site (CD4-BS) of the HIV-1 envelope glycoprotein (Env), but their predicted germline (gl) forms bind the Envs inefficiently. This is potentially why Env immunization has so far failed to elicit VRC01-class antibodies. We previously reported that specific modification of the clade C Env 426c lead to its binding by several glVRC01-class Abs.

Methods: Based on new structural information of Envs, we have now identified additional N-linked glycosylation site mutations that allow Envs from different clades to bind glVRC01-class antibodies (Biolayer Interferometry assays, BLI) and to activate B cells engineered to express glVRC01-class B cell receptors (Ca2+ flux assays) in vitro; and also activate the corresponding B cells in vivo when used as prime immunogens in knock-in mice expressing human VRC01-class B cell receptors.

Results: Importantly, our current studies suggest that although different gl-targeting Envs can engage glVRC01 B cells; because of differences in VRC01 epitope exposure on these gl-targeting Envs, different VRC01-cass antibodies are elicited by the different gl-targeting Envs.

Conclusion: These findings are central to efforts to engage a broad spectrum of VRC01-class precursors in clinical trials.

382 Enhancing HIV Vaccine Efficacy via Langerhans Cell-Targeted Env Trimers

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Background: Developing an effective HIV-1 vaccine is contingent on generating protective antibodies (Abs). Novel antigen delivery methods are needed to enhance immune responses. One promising approach involves directing antigens to dendritic cells (DC) through fused monoclonal antibodies (mAbs) to amplify both cellular and humoral responses. Previous studies have shown success in targeting skin Langerhans cells (LC) with anti- Langerin mAbs fused to HIV-1 Envelope (LC.Env), inducing antigen-specific humoral responses in mice and human LC:T/B co-cultures. In this study, we aimed to refine LC targeting by designing three Env monochains instead of 2 (LC3.Env3) mimicking natural Env conformation. We aim to investigate whether these new trimeric Env constructs could stimulate germinal center (GC) and Tfh cell reactions, ultimately leading to the production of Env-binding IgG and HIV neutralizing antibodies (NeutAb) in vivo.

Methods: B6 mice were intradermally immunized with LC3.Env3 or control LC.Env mAb (5 mcg of Env antigen) at day (D) 0 and D21, without adjuvant. Antibody (magnitude and affinity) and cellular responses were assessed post-prime (PP) and post-boost (PB) using Luminex and FACS, respectively. GC/Tfh reactions in draining lymph nodes (dLN) were monitored through immunofluorescence at various times. Additionally, rabbits were subcutaneously immunized with 50 mcg LC3.Env3 without adjuvants, and serum NeutAb levels were evaluated.

Results: Compared to LC.Env, LC3.Env3: (i) elicited a rapid and potent Env-IgG response, with mean titers measuring 22- and 37-fold higher at D14 PP and D7 PB, respectively. (ii) enhanced the avidity of anti-Env IgG, resulting in an index increase of 12% and 36% at D14 PP and D7 PB, respectively. This was accompanied by a marked expansion of Tfh and GC B cells (GL-7+/Fas+) at D7 PB. (iii) swiftly induced the formation of structured germinal centers in dLN, indicative of a robust immune response. Significant Tier-1 NeutAb induction was observed in rabbits immunized with LC3.Env3.

Conclusion: This study underscores that HIV Env antigen can be adeptly targeted to LC as a trimer, intensifying both the magnitude and quality of humoral responses without using any adjuvant and after only two shots. In addition, the strategy of targeting SOSIP-like trimeric Env to LC holds substantial promise for eliciting broadly neutralizing antibodies (bNAb) against HIV and will require an optimization of the vaccination regimen.

383 Mucosal HIV Vaccine Targeting Host Epithelial Stem Cells for Long-Term Immunity

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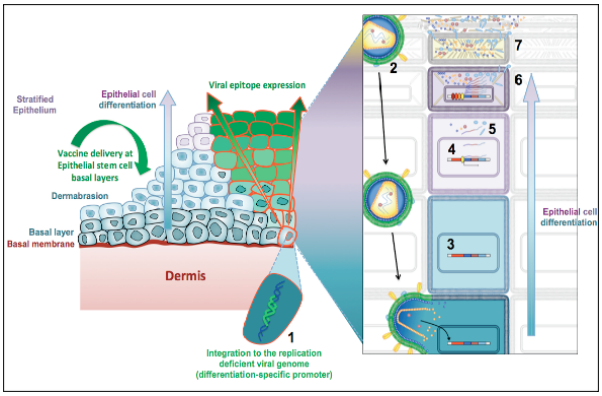
Background: HIV transmission occurs predominantly across mucosal surfaces; an ideal vaccine should be to target HIV at mucosal entry sites to prevent infection. We developed a SIV single-cycle replication- deficient vaccine under the control of the involucrin promoter, which was tested for its ability to drive SIV expression in terminally differentiated epithelial cells, induce mucosal immune responses, offering protection against SIV.

Methods: Sixteen macaques (8 females, 8 males) were immunized (1 dose: 50ng p27=$3x10^{11}$ RNA copies, atraumatic, needleless) at week 0 and monitored over time for specific immune responses in blood, mucosal secretions, and various lymphoid/non-lymphoid tissues. At weeks 12 (group 1) or 24 (group 2), animals were challenged with repeated low-doses SIVmac239 (intravaginal, 2500 $TCID_{50}$/ml; intrarectal at 300 $TCID_{50}$/ml) 4 females and 4 males per group. Sixteen additional animals (8 females, 8 males) served as unvaccinated SIV-infected Controls.

Results: Within two weeks post-vaccine, strong mucosal antibody responses (IgG, IgA) and specific CD8+ T-cells were detected. Immunohistofluorescence revealed antigens-expression in epithelia upper-layers. SIVenv was detected via anti-gp120 immunoPET/CT scans in female vagina and draining-LN as well as in male rectal and transversal. SIV-challenges demonstrated a significant delay and/or lower viremia (2-3 logs-reduction, peak; 4-5 logs-reduction, set-point) to undetectable viremia 10-20 weeks post-SIV in vaccinees. Robust SIV- specific T-cell responses were also detected in blood, lymph-nodes, and mucosa tissues. Controls had high viremia (log_{10}: 7.2-8.7 viral-RNA copies/ml, peak) and significant gut CD4+ T-cells depletion. We demonstrated a positive correlation between mucosal and systemic T-cell responses and control of viremia, and inverse associations between viremia and post-challenge vaginal antibody responses. All vaccinees manifested durable aviremic SIV-control for 2 years when CD8-depletion was performed. The dramatic fall in viremia coincided with the CD8+ T-cells recovery and significant increase of SIV-specific responses.

Conclusion: The study demonstrated the efficacy of an epithelial stem cell-based vaccine to serve as antigen delivery to generate specific mucosal antibody

and cellular immune responses leading to significant delays in infection followed by rapid and durable plasma viral control to undetectable.



384 **Naive B-Cells From Unvaccinated Rhesus Macaques Cross-React With HIV gp140 Protein**

Michelle Premazzi Papa[1], Andrew Wilson[1], Rosemarie Mason[2], Jennifer A. Manuzak[3], Nichole R. Klatt[4], Rebecca M. Lynch[1]

[1]George Washington University, Washington, DC, USA, [2]National Institutes of Health, Bethesda, MD, USA, [3]Tulane National Primate Research Center, Covington, LA, USA, [4]University of Minnesota, Minneapolis, MN, USA

Background: HIV causes a chronic infection that it is not cleared by the normal immune response, in part due to an ineffective early antibody response. Other groups have shown that early in infection, people with HIV-1 (PWH) develop anti-gp41 antibodies that cross-react with commensal bacteria but do not neutralize HIV, and that this same phenomenon occurs after vaccination. Here, we investigate if the baseline antibody response prior to HIV vaccination is comprised of antibodies targeting commensal bacterial that weakly target HIV, and if these antibodies are preferentially activated after subsequent infection.
Methods: To test this hypothesis, PBMC samples from a SIV/HIV DNA vaccine (SIV gag (p55), HIV env (gp160), and gp140 trimeric protein) and simian-human immunodeficiency virus (SHIV) challenge study in Rhesus Macaques (RhM; n=8) were collected prior to vaccination (week -7) and stained using an 11-color B cell panel. HIV-1 gp140-specific B cells from these SHIV-naïve RhM were sorted and nested-PCR was performed using specific primers for IgG, IgM, IgA heavy chains, and Kappa and Lambda light chains. PCR products were sequenced and compared to germline using IMGT/V-QUEST. Selected sequences were cloned as IgG1 and tested for function.
Results: A total of 120 cells were sorted (ranging from 1-44 cells per RhM). 95 heavy chains were amplified, and 70 had productive ORF sequences. 56 out of 70 were IgM, seven were IgA, and seven were IgG sequences. Analyzing light chains, a total of 110 were amplified and 63 had productive ORF sequences. 42 out 63 were Kappa and 21 were Lambda sequences. From these, 35 had productive heavy and light chain sequences. Fourteen cells that exhibited intermediate and high gp140 binding during cell sorting were selected for cloning. Monoclonal antibodies (mAbs) were generated and tested for binding to gp41, gp120, and gp140 proteins. Ten mAbs recognized gp41, two mAbs bound to gp120, and five recognized gp140. A total of four mAbs bound to MAPK14 with high and low affinities, the two with high affinity also bound to LPS (Fig 1). This data shows that these mAbs not only cross-react with bacteria but also bind to different cellular components suggesting that these are polyreactive antibodies.
Conclusion: Here, we show that B cells can recognize HIV without previous vaccination or infection, and they are mostly naïve (IgM+). Future directions include investigating if these clones are expanded after vaccination and/or SHIV infection trough deep sequencing..

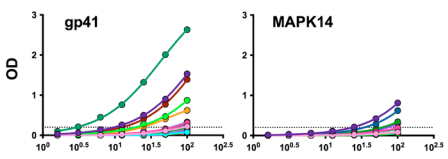


Fig 1. Binding to HIV gp41 and MAPK14. Fourteen mAbs were tested for binding to gp41 and MAPK14. Ten mAbs recognized gp41, and four mAbs bound to MAPK14 with high and low affinities.

385 **Complement Activation as a Mechanism of Protection by SARS-CoV-2 mRNA Vaccines in Men With HIV-1**

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Background: People living with HIV (PLWH) are recommended to be fully vaccinated against SARS-CoV-2. However, men with HIV-1 (MWH) respond to the COVID-19 vaccine with lower immunoglobulin binding and neutralization titers against SARS-CoV-2 than men without HIV-1 (MWOH). Although neutralization is an important protective mechanism against SARS-CoV-2, other mechanisms can play a key role in protection. Therefore, we assessed antigen-specific complement activation in vaccinated MWH and MWOH.
Methods: We quantified activation of the classical compliment cascade through C3 deposition by antibodies specific for SARS-CoV-2 S1 and for the receptor binding domain (RBD) in MWH and MWOH from the MACS/WIHS Combined Cohort Study using a bead-based flow cytometry assay and capture C3/C3a ELISA.
Results: When matched on anti-S1 IgG titer, MWH had 10-fold greater C3 deposition than MWOH against the Washington (WA) and Omicron strains. However, the level of complement activation was proportional to the IgG titer. MWH thus, had lower C3 deposition against the RBD of both WA and Omicron strains without titer matching, which is consistent with MWH having lower vaccine induced antibody titers than MWOH. For both MWH and MWOH, C3 deposition against the RBD and full S1 proteins were comparable. However, C3 deposition against the Omicron RBD was lower than for the WA RBD, indicating lower affinity of antibodies binding to the variant RBD. These antibodies still induced a strong activation of the classical complement cascade, even as neutralization titers against the Omicron strain are low, indicating that non-neutralizing antibodies that bind to Omicron can mediate protection through complement activation. Finally, we found that the C3 levels significantly declined post-vaccination in MWH, concomitant with a significant increase in C3a levels in serum, suggesting an elevation of the baseline complement activity in this group.
Conclusion: Collectively, these data suggest that complement activation is a mechanism of protection of SARS-CoV-2 vaccination, and that it can have a greater impact on protection against SARS-CoV-2 variants in the absence of neutralizing antibody titers. It also suggests that antibodies with greater complement activation potency in MWH can compensate for lower antibody titers. These results highlight a critical mechanism of protection in MWH that can inform further booster vaccination schedules.

386 **WITHDRAWN**

387 Sarbecovirus Ferritin Nanoparticle Vaccines as Protein or mRNA-LNP Elicit Broad Immunogenicity

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Background: The need for SARS-CoV-2 next-generation vaccines is clear. Early in the COVID-19 pandemic, we designed and characterized four categories of engineered ferritin nanoparticle immunogens based on the WA- 1 sequence that recapitulate the structural and antigenic properties of prefusion SARS-CoV-2 Spike (S), S1, and RBD. A lead candidate, Spike-Ferritin nanoparticle (SpFN) adjuvanted with a liposomal-saponin adjuvant (ALFQ) was subsequently assessed in a Phase I study in humans showing broad immunogenicity to VoCs. Building on that work, we have developed novel immunogen designs that have increased antigenic diversity and are delivered as mRNA-LNP immunogens. This study aims to understand the breadth of sarbecovirus immune response that can be elicited using either adjuvanted protein or mRNA platforms.
Methods: Designs based on Spike and RBD proteins contain antigenic matter from up to four different sarbecovirus strains. To further increase the vaccine immunogen diversity, formulations including two or more of these antigen designs were combined as cocktail or mosaic immunogens to further increase the vaccine immunogen diversity. These immunogens were either produced as proteins in mammalian cells or expressed in vivo as mRNA encapsulated in LNP. Groups of 8-10 naïve male and female C57BL/6 mice were immunized 2-3 times, followed by serum antigen binding and pseudovirus neutralization assessment.
Results: Immunogens in both protein-ALFQ or mRNA format elicited broad and robust neutralizing responses. The mRNA formulations containing BQ.1.1 immunogens (either singly or in combinations) elicited potent neutralizing responses against all Omicron virus strains assessed. Vaccine candidates combining antigens from three sarbecovirus strains elicited high ID_{50} GMT titers against all sarbecovirus strains tested, including heterologous pseudoviruses not included in the vaccine. Of further note, following two immunizations, ID_{50} GMT titers of 19,200 and 1,400 against heterologous Omicron BA.5 and XBB.1.5 respectively were observed in mice immunized with this trivalent combination.
Conclusion: The ferritin platform either as a protein or mRNA format provides a potent platform for pan- sarbecovirus vaccine development. Funding statement: This work was funded by the Walter Reed Army Research Institute, the Henry Jackson Foundation, Sanofi, and the National Institute of Health.
Disclosure: PD, MW, NC, AV, WW, NA, VL are Sanofi employees and may hold shares and/or stock options in the company.

388 Immune Responses to an Original/BA.4-5 Bivalent Booster of SARS-CoV-2 mRNA Vaccine in PWH on ART

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Background: In the current Omicron era of COVID-19 pandemic, boosters with variant-adapted mRNA vaccines are recommended for fragile populations to provide broad protection against newly emergent SARS- CoV-2 variants. While previous studies showed enhanced neutralization against Omicron sub-lineages after a bivalent booster, data on T-cell immunity are limited, especially in PWH. We assessed humoral and T-cell responses to an original/BA.4-5 booster in this population.
Methods: PWH on ART receiving a bivalent booster as fourth dose were enrolled. We measured immune responses against WT and BA.4-5 virus: RBD-binding Abs (ELISA); RBD-blocking Abs (RBD-ACE2 binding inhibition assay); Th1/Tc1 cytokine (IFN-γ/TNF-α/IL-2)-producing and cytotoxic (CD107a+) CD4/CD8 T-cells (flow cytometry after PBMCs stimulation with spike peptides) before (T0) and 1 month after (T1) the 4th dose. Wilcoxon test was used for statistical analyses.
Results: We included 30 PWH who received the 4th dose at a median time of 14.5 (IQR: 13.5–15) months after the 3rd one. Median CD4 T-cell count was 790/μL (IQR: 598–929) and HIV-RNA <20 copies/mL. Demographic and viro-immunologic features are reported in Fig.1A. The 4th dose led to an increase of RBD-binding/blocking Abs against both WT and BA.4-5. Interestingly, when compared to WT, BA.4-5–specific humoral immunity was lower at both T0 and T1. Frequencies of Th1/Tc1 and cytotoxic CD4/CD8 T-cells against WT and BA.4-5 did not increase after the booster, with similar values of WT– and BA.4-5–specific responses both before and after the booster administration (Fig.1D–G). Despite stable frequencies, polyfunctionality of WT/BA.4-5–specific T-cells was increased after the booster, and yet the proportion of BA.4-5–specific polyfunctional IFN-γ+TNF-α+IL-2+/IFN-γ+TNF-α+IL-2– CD4 T-cells and IFN- γ+TNF-α+IL-2– CD8 T-cells were lower than WT–specific ones at all time-points.
Conclusion: In PWH on effective ART, an original/BA.4-5 bivalent booster increases RBD-binding/blocking Abs and T-cell polyfunctionality against both WT and BA.4-5. However, humoral and polyfunctional T-cell responses hold higher against WT than BA.4-5 both before and after the booster, suggesting immune imprinting to the wild-type strain. By showing a strengthened antigen-specific immune response, our data reinforce the importance of a variant-adapted mRNA boosters in PWH, possibly directed against the dominant variants alone to maximize the response to circulating strains
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389 Immune Response to SARS-CoV-2 Omicron Breakthrough is a Recall of Vaccine-Induced Memory

Jernej Pusnik[1], Jasmin Zorn[1], Werner O. Monzon Posadas[1], Kathrin Peters[1], Emmanuil Osypchuk[1], Sabine Blaschke[2], Hendrik Streeck[1]
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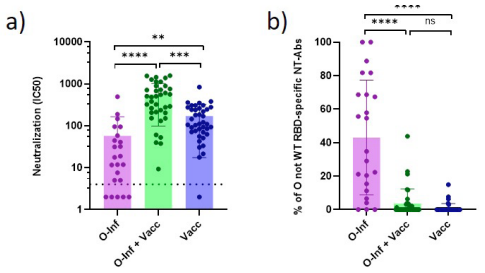
Background: The COVID-19 vaccination campaign is considered the largest in history with over 70% of the global population having received at least one vaccine dose. While vaccination demonstrated outstanding results in cutting down the severity of the disease, breakthrough infections with the Omicron-derived variants occur frequently. Others and we have previously shown that vaccinated individuals develop a potent B cell response following the Omicron breakthrough infection. It is however not clear whether this is due to the reactivation of vaccine-induced memory or de novo response specific for the mutated regions of the spike protein.
Methods: We compared the adaptive immune response of thrice-vaccinated individuals following Omicron breakthrough infection with those of unvaccinated Omicron-infected and thrice-vaccinated uninfected individuals. Plasma antibodies against Omicron were assessed by normal and competitive versions of ELISA and plaque reduction neutralization assay. Omicron-spike-specific memory B and T cells were assessed by flow cytometry.
Results: Our data demonstrate higher plasma neutralization potency in vaccinated individuals with Omicron breakthrough compared to the control groups ($p<0.001$). The levels of Omicron-spike-specific memory B and T cells were comparable between the groups. Importantly, the proportion of antibodies binding mutated regions of the Omicron spike protein was lower in the breakthrough infection group compared to the uninfected vaccinated group ($p<0.0001$) and equal compared to the vaccinated uninfected group. The same was also true for the proportions of spike-specific IgG+ B cells ($p<0.001$) and Omicron spike-specific CD4 T cells ($p<0.01$) targeting regions mutated in the Omicron variant. No significant differences were observed for CD8 T cells.
Conclusion: Our findings suggest that Omicron breakthrough infection increases the plasma neutralization potency but not Omicron-specific B and T cell levels in previously vaccinated individuals. Both humoral and cellular responses against the Omicron are mostly a recall of preexisting vaccine-induced memory rather than de novo response towards the mutated regions of the spike protein.



a) Plasma neutralization capacity against the Omicron (O) given as IC50 b) Leftover plasma neutralization capacity against the Omicron following incubation with wild type (WT) surface proteins. Compared are Omicron-infected (O-Inf+Vacc), unvaccinated Omicron-infected (O-Inf) and vaccinated uninfected individuals (Vacc)

390 Long-Term Immunodominant Profile of SARS-CoV-2 T-Cell Responses in Hybrid Immunity

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[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Hospital Germans Trias i Pujol, Badalona, Spain, [3]Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain

Background: Characterization of long-term T-cell immunity against SARS-CoV-2 proteome is critical for understanding the implications of virus-specific hybrid immunity in protecting against re-infection and advancing novel vaccine designs. Here, we conducted a high-resolution mapping of the breadth and magnitude of T-cell responses to the entire SARS-CoV-2 proteome over a 2-year follow-up period in individuals with hybrid immunity.

Methods: We selected cryopreserved PBMC from 38 healthcare workers, including 19 SARS-CoV-2 infected (CoV2+, tested at 124 days from symptoms onset, DfSO) and 19 uninfected (CoV2-) participants in the ProHEpiC-19 cohort study (NCT04885478). Longitudinal PBMC were available from 18 individuals after a 3- dose mRNA vaccination, including 13 CoV2+ (CoV2+Vac+, 825 DfSO) and 5 CoV2- who became infected during the follow-up period (Vac+CoV2+, 302 DfSO). We measured the breadth and magnitude of IFN-γ T-cell responses by ELISpot assay using a 15-mer overlapping peptide (OLP) library of 2,790 SARS-CoV-2 peptides in 100 pools using a Mega Matrix approach, and we deconvoluted the matrix using single peptides by ELISpot assay.

Results: We identified immunodominant T-cell responses to 13 regions across the SARS-CoV-2 proteome within S, Nsp3, NC, Env, and M proteins across groups and time. In addition, we observed a booster vaccination effect in these immunodominant regions with the strongest responses targeting S and Nsp3 proteins. In addition, CoV2+Vac+ individuals had broader T-cell responses than Vac+CoV2+ and showed an exclusive targeting of ORF3a, M, upORFs, Nsp2, 3C_LP, Nsp10 and Hel regions across the SARS-CoV-2 proteome. At the single peptide level, we identified differential frequency in the optimal T-cell responses across groups as the CoV2+Vac+ showed a preferential targeting of S1 (58%), S2 (17%) and ORF1ab/8 (25%) compared to Vac+CoV2+ with almost exclusive recognition of S2 (86%).

Conclusion: Our results define immunodominant long-term T-cell responses in S, Nsp3, NC, Env, and M proteins in SARS-CoV2 proteome in the context of hybrid immunity. Our data demonstrate broader and exclusive T-cell responses in CoV2+Vac+ individuals compared to Vac+CoV2+. Overall, we identify differences in long-term T-cell hybrid immunity primed by infection or vaccination with implications for protection from re- infection and future vaccine design.

391 Bivalent mRNA COVID Vaccines Elicit Predominantly Cross-Reactive CD4+ T-Cell Clonotypes

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Background: The emergence of the Omicron BA.5 sublineage in February 2022 raised concerns due to its ability to escape neutralizing antibodies induced by ancestral spike mRNA vaccines and natural infection with prior SARS-CoV-2 variants. Bivalent COVID-19 vaccines, containing mRNA for both ancestral and Omicron BA.5 spike proteins, were developed to enhance immune responses against the BA.5 sublineage. However, studies have shown that these bivalent vaccines do not induce stronger T cell responses to the BA.5 spike protein than monovalent vaccines containing only ancestral spike mRNA. We tested the hypothesis that this was due to the preferential expansion of cross-reactive memory T cells rather than naive BA.5 mono-reactive T cells.

Methods: We used the ELISpot assay to determine the targeted epitopes and the functional expansion of specific T Cells (FEST) assay to assess the percentage of CD4+ T cells that cross-recognized both ancestral and BA.5 spike proteins compared to those that were mono-reactive for each protein. We conducted this analysis in two distinct cohorts: 20 healthy donors (HDs) and 20 people living with HIV (PLWH) on suppressive antiretroviral therapy. All the participants received either the Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) SARS-CoV-2 ancestral spike/BA.5 spike bivalent vaccine.

Results: We found robust T cell responses to both ancestral and BA.5 spike proteins in both HDs and PLWH. Importantly, the FEST assay revealed that a predominant percentage of these responses were cross-reactive CD4+ T cells. Specifically, only 8.9% and 3.8% of spike-specific CD4+ T cell receptors were mono-reactive to BA.5 spike protein in HDs and PLWH respectively. Additionally, we conducted an in-depth analysis of the individual ancestral spike protein epitopes targeted by T cells in bivalent vaccine recipients. We found that more than 80% of these epitopes were ones that did not contain BA.5 mutations.

Conclusion: In conclusion, our study suggests that the current bivalent vaccines do not effectively induce substantial BA.5-mono-reactive T cell responses; instead, cross-reactive T cells dominate the spike-specific T cell response. These findings have significant implications for future COVID vaccine strategies.

392 Spike-V987H Vaccination Protects Animal Models From SARS-COV-2–Induced Severe Disease

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Background: Most SARS-CoV-2 vaccines are based on a two-prolines (K986P and V987P) stabilized Spike (S) glycoprotein (S-2P). Although these mutations improve S stability and immunogenicity, S-2P is produced at low levels yet. Here we explored new S protein stabilization approaches.

Methods: We have investigated the immunogenicity and efficacy of a novel set of stabilizing mutations selected by computational modelling and screened by recombinant S yield and RBD exposure. S variants were produced by transient transfection in Expi293 cells, and yield and RBD exposure were analyzed by ELISA. Immunogenicity and efficacy studies were conducted in K18-hACE2 mice and golden Syrian hamsters (GSH) challenged with SARS-CoV-2 D614G, Beta or Omicrom BQ1.1 variants. We measured weight changes, and viral loads in different biological samples: oropharyngeal swab, nasal turbinate, lung and brain. In addition, we performed histopathological analysis of tissue samples. Humoral and T cell responses were analyzed by ELISA and neutralizing assays, and by ELISPOT, respectively.

Results: When compared with the S-2P, a single V987H mutation increased RBD exposure and production, and showed equivalent immunogenicity (determined as anti-RBD, anti-S IgG levels, and IFN-g ELIspot). S-V987H- immunization induced neutralizing antibodies against Wuhan, Beta and Delta variants and gained activity against Omicron after viral challenge. S-V987H immunized mice showed lower viral loads and immunohistochemistry score than non-immunized animals and were protected from severe disease induced by SARS-CoV-2. These results were confirmed in the GSH model.

Conclusion: Here, we identified a novel single mutation that increased the yield of S protein, maintaining its immunogenicity and improving the protective efficacy against the development of SARS-CoV-2-induced severe disease in two animal models. These results could contribute to the development of novel vaccines for other respiratory viruses.

393 Prior COVID-19 Alters Antibody Function in ART-Suppressed PWH Receiving SARS- CoV-2 Vaccination

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Background: People with HIV infection (PWH) receiving suppressive antiretroviral therapy (ART) develop vaccine-driven immune responses (anti-RBD antibodies, RBD/ACE binding competition and neutralization) to early SARS-CoV-2 isolates similar to the general population. However, the impact of previous SARS-CoV-2 infection on the humoral and cellular immune response after a two-dose SARS-CoV-2 RNA vaccination in PWH on ART is unknown.
Methods: We collected peripheral blood from 44 PWH on ART (n=24 with prior SARS-CoV-2 infection; HIV^{POS}/$COVID^{POS}$ and n=20 who did not report prior SARS-CoV-2 infection; 24: HIV^{POS}/$COVID^{NEG}$) at four time points: 1) before the 1st and 2nd dose of RNA-based vaccine, and 3 and 6 months after 2nd dose. We assessed total spike (S), RBD, and nucleocapsid (N) titers and neutralizing antibody titers (ELISA; Spike/ACE2 HTRF against Wuhan, β, δ, λ, and o variants; pseudo-neutralization of o BA.1 and BA.2), Fc-mediated antibody-dependent cytotoxicity (ADCC), complement deposition (ADCD), and cellular phagocytosis (ADCP), SARS-Cov-2 and HIV-specific T cell responses (IFN-γ ELISPOT), and T cell and monocyte activation (Flow cytometry). Changes from baseline and between visits were assessed using the Wilcoxon signed rank test.
Results: Neutralizing antibody titers against spike protein (all variants) were elicited by vaccination in both groups, but were significantly higher and better retained in the HIV^{POS}/$COVID^{POS}$ group, including antibody titers against o BA.1 and BA.2 pseudotypes, compared to HIV^{POS}/$COVID^{NEG}$ group. Non-neutralizing antibody responses (ADCC and ADCP) were induced in both group; however, ADCD was significantly enhanced in the HIV^{POS}/$COVID^{POS}$ group than the HIV^{POS}/$COVID^{NEG}$ group. Both groups showed persistent increase in T-cell and monocyte activation following vaccination, yet without a parallel increase in T-cell-specific responses to HIV Gag or Nef.
Conclusion: Prior SARS-CoV-2 infection is associated with greater non-neutralizing antibody innate immune effector functions and a broader anti-SARS-CoV-2 immune response (including greater activity against Omicron variants) in PWH on ART following Wuhan strain RNA vaccination. Further studies are needed to examine the impact of vaccination-induced, Fc-mediated innate immune functions on re-infection and/or disease course.

394 Distinct Absence of Post-Boost S-IgG Surge in Sub-Saharan African COVID-19 Vaccine Responses

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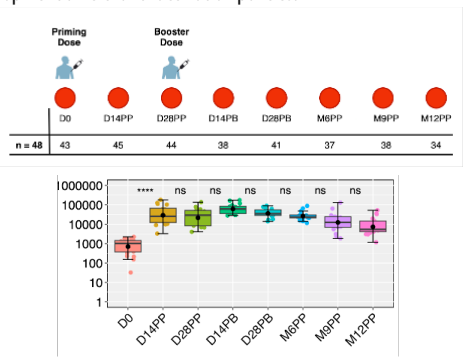
Background: This study investigated the longitudinal antibody response profiles and their durability after administering various COVID-19 vaccines to a subset of the Ugandan population within Sub-Saharan Africa (SSA). The hypothesis was that these profiles in SSA may exhibit unique characteristics due to genetic, environmental, or serological variations, thereby addressing significant gaps in global datasets and contributing insights specific to response patterns within this demographic.
Methods: Participants were enrolled to assess the temporal evolution and persistence of antibody responses for 12 months post-initial vaccination. These included 48 individuals vaccinated with Pfizer, 67 with AstraZeneca, and 21 with Moderna, all receiving two doses 28-30 days apart. Additionally, 60 participants who received the Sinovac vaccine were included, with their doses administered three months apart. A validated enzyme-linked immunosorbent assay (ELISA) was used to measure concentrations and optical densities (ODs) of SARS-CoV-2-specific IgG, IgM, and IgA binding antibodies. The OD threshold values for determining antibody positivity in this population were S-directed IgG at 0.432, IgM at 0.459, and IgA at 0.226. Statistical analyses included box plots, diverging bar graphs, and the Wilcoxon test with a Bonferroni correction for multiple analysis.
Results: All four vaccines demonstrated a significant increase in Spike-directed IgG antibody concentrations within 14 days of the initial vaccine dose declining by six months, mirroring global observations. A significant observation was the lack of the anticipated surge in S-IgG levels following the booster dose. This trend starkly contrasted findings noted in various other global populations. The S-IgM response was transient and mostly subsided below the established thresholds, illustrating its initial early emergence and subsequent decline. S-IgA highlighted the temporal dynamics of mucosal immunity, showing an initial increase and then a reduction by six months post-vaccination. Breakthrough infections occurred at similar levels across all vaccines studied; however, they were all asymptomatic.
Conclusion: These data emphasise the critical need for inclusion of region-specific research to formulate vaccination strategies attuned to regions like SSA's unique environmental, genetic, and serological landscapes, ensuring the development of relevant vaccination policies.



395 Disparities in Anti-SARS-CoV-2 Reactivity According to Vaccines in the Era of Omicron in Cameroon

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Background: Anti-SARS-CoV-2 vaccine remains a global health priority, but evidence on its significance within tropical settings like Cameroon is limited. Our objective was to assess the overall rate of COVID-19 antibodies, its disparity according to vaccine-status and types of vaccines administered in Cameroon during the active phase of Omicron variants.
Methods: A cross-sectional sero-survey was conducted from february throughout July-2022 (active phase of Omicron circulation) among individuals tested for COVID-19 in Yaoundé-Cameroon. Socio-demographic and detailed clinical data were collected; SARS-CoV-2 antibodies were tested on plasma using Ninonasal™ and ABBEXA™ COVID-19 IgG/IgM assays. Statistical analyses were performed with $p<0.05$ statistically significant.
Results: A total of 2449 participants were enrolled: median [IQR] age was 40 [31–48], 56.4%(1382/2449) men, 2.2%(54/2449) with flu-like symptoms and 19.6%(481/2449) reporting previous SARS-CoV-2 positivity (confirmed with PCR). Regarding COVID-19 vaccination, 67.5%(1652/2449) had received at least one dose (48.7% Pfizer, 24.8% Johnson&Johnson, 18.2% Moderna; 8.1% AstraZeneca, 4.8% Sinopharm and 0.2% Sputnik-light) ; among these, 55.0%(909/1652) were fully vaccinated and 37.1%(613/1652) received additional boost doses. Median duration from vaccination to phlebotomy was 5 [3–8] months (min: 1; max: 20). Overall, rate of COVID-19 antibodies was 81.13%(1987/2449), with 1.2% IgM, 73.9% IgG and 6.5% IgM/IgG. Following univariate analysis, high prevalence of antibodies was associated to vaccination (OR=1.9; $p<0.0001$). Among the vaccinated, those who received boost doses had higher odds for COVID-19 antibodies (OR=2.5; $p<0.0001$) and regarding the vaccines, Pfizer induced the greater immunogenicity (OR=2.4; $p<0.0001$); and post vaccination time ≤5months (OR=2.3; $p=0.001$) was also a determinant of high COVID-19 antibodies. Following multivariate analysis, the vaccine-status, Pfizer vaccine, booster doses and post vaccination time remained statistically associated with the high prevalence of COVID-19 antibodies (aOR=3.1, OR=2.5, aOR=2.1, and aOR=3.04 respectively; with all $p<0.001$).
Conclusion: The high-rate of COVID-19 antibodies suggests herd immunity at community-level in Cameroon, during the wide circulation of Omicron. Furthermore, vaccination with Pfizer appears with higher Covid-19 antibody response, supporting the need for vaccine update with novel variants, especially with the rapid antibody weaning (~5months) in this tropical setting.

396 Uptake of 3+ COVID-19 Vaccine Doses Among People Living With HIV in Ontario, Canada

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Background: In Canada, important socio-demographic differences exist between males and females living with HIV which may impact uptake of COVID-19 vaccines. While most people living with HIV are recommended a 2-dose primary series, a 3-dose primary series is recommended for moderately/severely immunocompromised individuals including people living with HIV with AIDS-defining illness, recent TB diagnosis, CD4 count <200 cells/uL, or not virally suppressed. Using a population-based approach, we examined uptake of 3+ COVID-19 vaccine doses among people living with HIV in Ontario, Canada.
Methods: Community-dwelling adults living with HIV aged ≥19 years were identified using a validated algorithm based on physician billing claims for HIV diagnoses in the past 3 years. Data on COVID-19 vaccine doses and administration dates were ascertained from the Ontario COVID-19 vaccine registry (COVaxON) from December 14, 2020, to August 31, 2022. We used modified Poisson regression with robust standard errors to calculate predictors of 3+ COVID-19 vaccine dose uptake, and report these as adjusted risk ratios and 95% confidence intervals and stratified by sex.
Results: Among 20,825 people living with HIV, most received at least one (87.2%) or two (85.3%) COVID-19 vaccine doses as of August 31, 2022, with 64.5% receiving a third dose and 24.4% receiving a fourth dose. While uptake of the first 2 doses was similar among males (85.9%) compared with females (83.0%), there were disparities in 3+ dose uptake by sex (3rd dose: 68.3% vs 50.8%; 4th dose: 27.6% vs 12.5%). Among both males and females, predictors of 3+ dose uptake included older age, being born in Canada, and receiving ≥1 influenza vaccine within the past 2 seasons (see Table). Living in an urban region and having at least 1 comorbidity were predictors among males, while having ≥1 COVID-19 test episode in the 3 months prior to December 14, 2020, was a predictor among females. Positivity for SARS-CoV-2 prior to Dec. 14, 2020, was not associated with 3+ dose uptake.
Conclusion: Nearly two thirds of people living with HIV received at least 3 doses of a COVID-19 vaccine, compared with approximately half of the general Ontario population. Yet disparities in uptake remain, especially by sex; this needs further exploration due to differences in social determinants of health between males and females living with HIV. Continued monitoring of COVID-19 vaccine uptake for people living with HIV is critical to inform prevention efforts.

Table. Adjusted risk ratios (95% confidence intervals) for uptake of 3+ COVID-19 vaccine doses among people living with HIV in Ontario, Canada, as of August 31, 2022, stratified by sex.

	Total Cohort* (n=20,825)	Males only* (n=16,360)	Females only* (n=4,465)
Sex (Male) Reference: Female	**1.22 (1.18,1.25)**	n/a	n/a
Age (≥65 years) Reference: <65 years	**1.10 (1.08,1.12)**	**1.08 (1.06,1.10)**	**1.23 (1.17,1.30)**
Not born in Canada Reference: Born in Canada	**0.88 (0.86,0.90)**	**0.89 (0.87,0.91)**	**0.86 (0.82,0.91)**
Geography (Urban) Reference: Rural	**1.05 (1.04,1.07)**	**1.07 (1.05,1.09)**	1.01 (0.96,1.07)
At least 1 COVID-19 test in the 3 months prior to December 14, 2020 Reference: No COVID-19 test	**1.04 (1.02,1.06)**	1.01 (0.99,1.03)	**1.16 (1.10,1.23)**
At least 1 influenza vaccine in the past 2 seasons Reference: No influenza vaccine	**1.30 (1.28,1.33)**	**1.27 (1.25,1.29)**	**1.46 (1.38,1.53)**
Any comorbidity Reference: No comorbidities	**1.02 (1.01,1.04)**	**1.02 (1.00, 1.04)**	1.05 (1.00,1.11)

*Model additionally adjusted for testing positive for SARS-CoV-2 prior to December 14, 2020.

397 COVID-19 Breakthrough Infections Among People With and Without HIV: A Statewide Cohort Analysis

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Background: Evidence is limited regarding the COVID-19 vaccine effectiveness among people with HIV. This study aims to characterize and compare the COVID-19 breakthrough infections between people with and without HIV across different phases of the pandemic.
Methods: Using a statewide HIV cohort data, the study population was adult residents (>18 years old) who were fully vaccinated (i.e., receipt of the second vaccine dose of Pfizer-BioNTech or Moderna or the single-dose of the Janssen vaccine) between January 2, 2021 to April 14, 2022 when Alpha, Delta, or Omicron variant circulating in South Carolina. Vaccinated people with HIV (PWH) was matched with the vaccinated people without HIV (PWoH) via propensity score matching (PSM) with 1:2 rate. A vaccine breakthrough infection was defined as SARS-CoV-2 infection ≥14 days after fully vaccination. We used Cox proportional hazard model to investigate the association between HIV infection and breakthrough infections, adjusting for relevant covariates.
Results: Among 2,144,415 vaccinated individuals, 8,335 were PWH and 2,136,080 were PWoH. Over the 18- month observation period, the percentage of breakthrough infections among PWH and PWoH was 5.22% and 4.61% (p=0.0084), respectively. After PSM matching, HIV infection was not significantly associated with breakthrough infection rate. However, when comparing breakthrough infections among individuals without any booster dose, PWH had a higher risk of breakthrough infections (adjusted Hazard Ration [aHR]: 1.19; 95%CI: 1.03, 1.39). Individuals who resided in a county with higher COVID-19 incidence (aHR: 1.05; 95%CI: 1.02, 1.07), being vaccinated during the Omicron dominant period vs Alpha dominant period (aHR: 7.02; 95%CI: 3.12, 15.80), being Black (aHR: 1.20; 95%CI: 1.04, 1.39), or who had chronic pulmonary disease (aHR: 1.36; 95%CI: 1.10, 1.68) were associated with higher odds of breakthrough infections, while prior COVID-19 infection (aHR: 0.37; 95%CI: 0.28, 0.48) and being vaccinated with Moderna vs Pfizer (aHR: 0.77; 95%CI: 0.66, 0.90) was negatively associated with the outcome. Comparing with PWoH, PWH with high levels of CD4 count or viral suppression were not associated with breakthrough infections.
Conclusion: We did not find an increased risk of breakthrough infections of PWH compared with PWoH. Receipt of a booster dose conferred further

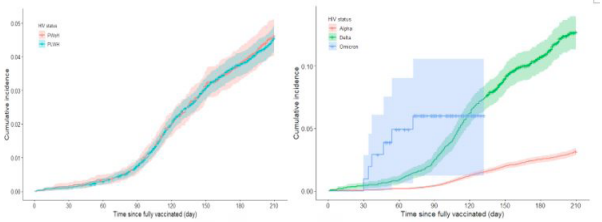

Figure 1 Cumulative incidence of COVID-19 breakthrough infections stratified by HIV status and different variants of concerns

398 Effectiveness and Safety of SARS-CoV-2 mRNA Vaccines in Children: A Population-Based Study in Madrid

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Background: Decisions about COVID-19 vaccination in children require an assessment of benefits such as prevention of COVID-19 hospitalization and multisystem inflammatory syndrome in children (MIS-C), as well as of risks such as myocarditis. In the absence of large, randomized trials, this evidence needs to be obtained from prospective observational studies conducted in large populations over more than 6 months.
Methods: We emulated target trials of COVID-19 vaccination among children using the population-wide databases of the Madrid Health Service, which include demographic information, primary care records, hospital data, and pharmacy data. Eligible children were residents of the Madrid region who were aged 6-11 years after 7 December 2021 and 12-17 years after 31 May 2021 (when vaccination was first recommended in each age group), had not been previously vaccinated, and had no prior evidence of SARS-CoV-2 infection. We emulated sequential trials by identifying eligible children who received the first dose of an mRNA vaccine each day between the start of eligibility and December 2022 and matching them (on sex, age, and postcode) with five controls who had remained unvaccinated through that day. After censoring matched sets at vaccination of an unvaccinated child, we estimated the 240-day cumulative incidence (risk) of COVID-19 hospitalization, MIS-C, and myocarditis. We used percentile-based bootstrapping to obtain 95% confidence intervals.
Results: The age group 6-11 years included 183,430 vaccinated children and 917,150 controls. Over 240 days, the estimated effectiveness (95% CI) of

vaccination was 10% (-40 to 50) for COVID-19 hospitalization and 30% (-40 to 80) for MIS-C. No cases of myocarditis occurred. The age group 12-17 years included 277,758 vaccinated children and 1,388,790 controls. Over 240 days, the estimated effectiveness (95% CI) of vaccination was 50% (20 to 70) for COVID-19 hospitalization and 50% (-20 to 90) for MIS-C. The risk ratio of myocarditis was 1.1 (95% CI: 0.7, 1,7) for vaccinated vs. controls.

Conclusion: In this population-based study, including over 2.8 million children, the estimated effectiveness of mRNA vaccines against COVID-19 hospitalization was modest in the age group 12-17 years and lower in the age group 6-11 years. The absolute risks of MISC-C and myocarditis were small, and under conventional statistical criteria, both increased and decreased risks after vaccination were highly compatible with the data.

399 Heterologous mRNA-1273 Boost After Ad26.CoV2.S Prime in Health Workers in South Africa: SHERPA Trial

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Background: Given limited data on safety and effectiveness of heterologous Covid-19 vaccine boosting in lower income settings with high HIV prevalence, we evaluated an ancestral strain mRNA-1273 vaccine boost after priming with Ad26.COV2.S in South Africa.

Methods: SHERPA was a single-arm, open-label, phase 3 study nested in the national Sisonke implementation trial of 500000 health workers. Sisonke participants were offered mRNA-1273 boosters between May and November 2022, a period of circulating Omicron sublineages. Adverse events (AE) were self-reported. Covid-19 co-primary endpoints (1. SARS-CoV-2 infections, 2. Severe Covid-19 of hospitalizations or deaths) were identified through national databases. We used Cox regression models with mRNA-1273 booster status as a time-varying covariate to determine the relative vaccine effectiveness (rVE) of a mRNA-1273 boost among SHERPA participants compared to Sisonke participants who did not receive the booster. 200 participants contributed to an immunogenicity substudy.

Results: Of 11248 SHERPA participants in the rVE analysis cohort (79.3% female, median age 41), 45.4% had previously received one and 54.6% two Ad26.COV2.S vaccines. Self-reported comorbidities included HIV (18.7%), hypertension (12.9%) and diabetes (4.6%). In multivariable analysis including 413161 unboosted Sisonke participants, rVE of the booster was 59% (95%CI 29-76%) against SARS-CoV-2 infection: 77% (95%CI 9–94%) for participants with one, and 52% (95%CI 13-73%) for those with two prior Ad26.COV2.S (Table 1). There were 148 adjudicated severe COVID-19 cases among unboosted participants, and only one among SHERPA participants, a person with severe HIV-related immunosuppression. Of 11798 SHERPA participants in the safety cohort, 271 (2.3%) reported a reactogenicity events or unsolicited AEs, more in those with prior SARS-CoV-2 infections (adjusted odds ratio [aOR] 2.03, 95%CI 1.59-2.59) and less in persons with HIV (PWH) (aOR 0.49, 95%CI 0.34-0.69). No related serious AEs were reported. Antibody functions were higher 4 weeks after boosting regardless of prior Ad26.COV2.S dosing, or HIV status. mRNA-1273 increased T- cell responses and generated spike-specific responses that were durable and cross-reactive against circulating Omicron sublineages, irrespective of HIV status.

Conclusion: mRNA-1273 boosters after one or two doses of Ad26.COV2.S were well tolerated, immunogenic and effective against SARS-CoV-2 infections with Omicron sub-lineages in a diverse health worker population and PWH.

Table 1: Relative Vaccine Effectiveness of mRNA-1273 booster against SARS-CoV-2 infection after Ad26.COV2.S prime

	Unadjusted	Adjusted*
	VE (95% CI)	VE (95% CI)
Primary Endpoint		
SARS-CoV-2 Infection	59% (29 -76%)	59% (29 - 76%)
Secondary Endpoints		
SARS-CoV-2 infections after 1 previous Ad26.COV2.S	77% (8 - 94%)	77% (9 - 94%)
SARS-CoV-2 infections after 2 previous Ad26.COV2.S	51% (13 - 73%)	52% (13 - 73%)

*Adjusted for age, sex, presence of comorbidities (yes/no), prior Covid-19 (yes/no), prior Covid-19 vaccination (single or two doses of Ad26.COV2.S), geographical location

400 Peripheral Immune Progression to Long COVID (LC) Is Driven by Mitochondrial Gene Transcription

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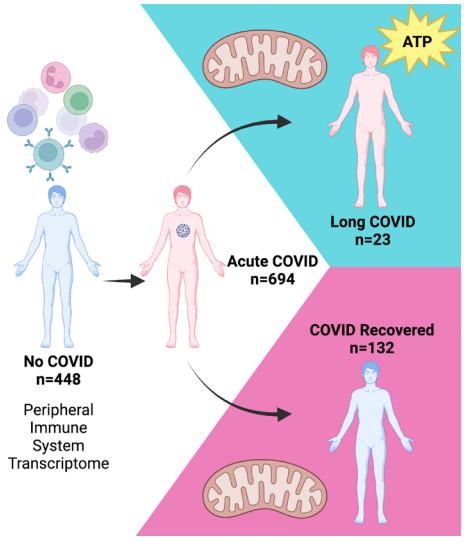
Background: Long COVID (LC) affects about 10% of persons infected with severe acute respiratory coronavirus 2 (SARS-CoV-2) and can have serious clinical consequences. Whereas the pathophysiology of LC is likely multifactorial, several hypotheses have been proposed, including viral persistence in some individuals for months following the acute phase of COVID-19. Herein, we analyzed existing human RNA transcriptome datasets from people with and without LC to identify unique phenotypic fingerprints of LC.

Methods: We analyzed 28 publicly available RNAseq datasets from COVID-19 acute and convalescent studies. Differentially expressed genes and gene ontology analysis between No known COVID (NC) (n = 448), Acute COVID (AC) (n = 694), COVID Recovered (CR) (n = 123), and LC (n = 23) were examined. All samples underwent processing using the STAR Aligner and GRCh38 reference genome. DESeq2 identified differentially expressed genes, and the most significant genes were distilled through Gene Ontology and Reactome to identify pathways. We accounted for batch effects between the studies by including 'study' as a covariate in the DESeq2 analysis.

Results: The cohort comparison between NC and AC revealed global changes in nucleosome assembly (p.adj = 1.23e-24), chromatin remodeling (p.adj = 1.39e-13), and defense response to virus (p.adj = 0.0027), among others. Comparisons of AC to CR or LC showed a transcriptome signature enriched in mitochondrial genes. LC differed from CR in an increase in genes explicitly related to the electron transport chain and ATP synthesis. Further, the most significantly over-expressed gene in the comparison of AC to LC was MGAT2 (Log Fold Change [LFC] = 6.02; p.adj. = 3.85e-22); which was considerably less expressed in AC compared to CR (LFC = 1.55; p.adj. = 1.45e-17). Reactome analysis additionally points to inhibited CASP8 activity in LC (p = 0.0358).

Conclusion: RNA profiling of peripheral immune cells suggests that recovery from AC is driven by mitochondrial gene transcription. In contrast to recovery, LC correlated with electron transport chain-specific genes. These findings support our previous findings of increased oxygen consumption and ATP production in the peripheral immune cells in people with LC and further implies that host gene transcription drives this phenotype.



401 ERAPs Control In Vitro and Ex Vivo SARS-CoV-2 Infection by Triggering Antiviral Immune Response

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Background: ERAP1 and ERAP2 (ERAPs) are two endoplasmic reticulum aminopeptidases which control susceptibility/progression of different infectious diseases. Beyond their canonical role in antigen processing and presentation,

following inflammatory stimuli ERAPs can be secreted and modulate both the acquired and natural immune response. We investigated in an in vitro model whether exogenous recombinant human (rh) ERAP can play a role in modulating SARS-CoV-2 infection/replication by boosting the antiviral potential of immunocompetent cells.
Methods: Granulocytes isolated from 10 healthy controls were stimulated with 300ng/mL of rhERAP1, rhERAP2 or rhERAP1+rhERAP2. After 24h, these cells were co-cultured with in vitro SARS-CoV-2 infected A549-ACE2 cell line and the following parameters were assessed: 1) viral replication; 2) neutrophil activation; 3) cytokine secretion;4) Phagocytosis and cell migration. In parallel, ERAP1 and ERAP2 mRNA concentration were quantified in unstimulated and Spike-stimulated PBMCs as well as in plasma of 10 mild (MD) and 10 severe (SD) COVID-19 patients.
Results: Granulocytes incubation with rhERAPs significantly reduced SARS-CoV-2 replication in A549-ACE2 infected cells (rhERAP1 $p<0.05$; rhERAP2 $p<0.05$; COMBO $p<0.01$). This antiviral activity was associated with: neutrophil activation and degranulation (CD15+CD16+CD66b++MPO) ($p<0.05$); increased neutrophil migration ($p<0.001$) and reduction of SARS-CoV-2 neutrophils internalization ($p<0.05$), and the release of several cytokines/chemokines, mainly IL-8 ($p<0.01$). Ex vivo analyses showed that ERAP mRNA expression was drastically reduced in both unstimulated ($p<0.05$) and Spike-stimulated ($p<0.05$) PBMCs of SD compared to MD. Conversely, a higher ERAP concentration was detected in plasma of SD compared MD ($p<0.05$).
Conclusion: ERAPs trigger several antiviral mechanisms in neutrophils suggesting that their anti-SARS-CoV-2 potential is not limited to their canonical role in Ag presentation and CD8+ T cell activation. These findings pose the premise to further investigate potential use of ERAP in novel preventive and therapeutic approaches against viral infections.

402 Innate Immune Response Through NOD1 Agonists Prevents SARS-CoV-2 Infection in Lung Epithelial Cells

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Background: The difficulty to exert a direct antiviral activity in the lung, is one of the major roadblocks for the management of respiratory infections, such as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV- 2). Boosting the innate immune response of the respiratory mucosa at early stages of the infection is a potential alternative intervention for the treatment of respiratory infections.
Methods: Ability to induce innate immune response was evaluated by flow cytometry, measuring IL8 production upon 24h incubation with distinct immunomodulators targeting the main pattern recognition receptors (PPRs), in lung epithelial A549 or myeloid THP-1 cells. NOD-like receptor (NLR) agonists were characterized through their proinflammatory profile in A549 and the activation of the NF-κB and the Interferon- sensitive response element (ISRE) pathways in A549-DualTM hACE2-TMPRSS2 cells (A549-Dual). Specificity of TriDAP (NOD1) and M-TriDAP (NOD1/2) agonists in lung epithelial cells was assessed by transient downregulation of NOD1 gene expression (siRNA) and selective NOD1 and NOD1/2 inhibitors. Systemic activation by NOD agonists was evaluated in PBMCs. Antiviral activity of NOD agonists was determined in A549-Dual cells in vitro challenged with SARS-CoV-2-GFP as measured by the percentage GFP+ by flow cytometry at 48 h infection.
Results: Amongst the immunomodulators tested, NLR agonists TriDAP (NOD1) and M-TriDAP (dual NOD1/2) showed the best potency and selectivity, inducing up to 3.3-fold increase of IL8+ cells in a dose- dependent manner, without impairing cell viability. Response to NOD1 and dual NOD1/2 agonists was 2-fold- higher compared to LPS control. NOD1 and dual NOD1/2 agonist activity involved NF-κB and ISRE pathways induction. NOD1 downregulation (siRNA) resulted in a 93% reduction of IL-8+ cells cocultured with TriDAP or M-TriDAP. Selective NOD1 and NOD1/2 inhibitors impaired the NOD1-induced activation of NF-κB and ISRE pathways. PBMCs were unresponsive to NOD1 agonists, suggesting tissue specific activity of NOD1 in lung epithelial cells, without a global systemic activation. Finally, NOD1 agonist Tri-DAP and dual NOD1/2 agonist M-TriDAP, promoted an antiviral environment that prevented SARS-CoV-2 replication in lung epithelial cells (57% protection).
Conclusion: This work provides the biological basis for the development of host-directed therapies based on the NLR pathway to boost the innate immune system for an early viral clearance and infection resolution.

403 SARS-CoV-2 Natural Infection Elicits Cross-Reactive Immunity to OC43

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Background: The recent SARS-CoV-2 pandemic renewed interest in other previously discovered non-severe acute respiratory syndrome human coronaviruses. Among these, OC43 is a seasonal human coronaviruses widely diffused in the global population (90% seroprevalence in adults), mostly responsible for mild respiratory symptoms. As OC43 protective immunity is short lasting the aim of this study was to verify if systemic and mucosal SARS-CoV-2 humoral immunity elicited by both natural infection and/or vaccination is able to confer protection against a new OC43 re-infection.
Methods: Neutralization assay of plasma and saliva samples from 49 uninfected SARS-CoV-2-vaccinated subjects (SV), and 25 SARS-CoV-2-infected and vaccinated subjects (SIV) were performed against "wild type" SARS-CoV-2 lineage B.1 (EU) and OC43 in VeroE6 cell lines. Sampling was carried out immediately before (T0) and 15 days (T1) post third-dose administration (SV) or 15 days post-infection (SIV).
Results: Neutralizing activity (NA) against SARS-CoV-2 significantly increased after third dose administration in plasma ($p<0.0001$) but not in saliva from SV; however, it doesn't seem to protect against OC43. On the other hand, SARS-CoV-2 NA triggered by natural infection was able to defend against OC43 infection in both plasma ($p<0.05$) and saliva ($p<0.01$) samples.
Conclusion: Our data suggest that compared to vaccine administration, SARS-CoV-2 natural infection is able to elicit a broader and cross-reactive immunity, which results in protection from OC43 at both systemic and mucosal level. As the oral cavity represents the main entry route for coronaviruses, these results support the development of a pan-coronavirus vaccine to prevent new infections and re-infections

404 SARS-CoV-2-Specific T-Cells Correlate With Airway Virus Control During Early Acute Infection

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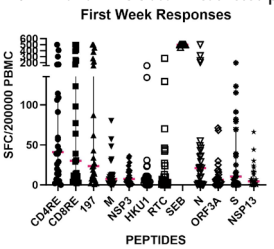
Background: SARS-CoV-2-specific T cell responses, including those targeting the Nucleocapsid (N) and the conserved Replication-Transcription Complex (RTC), have been associated with protection from infection and airway virus control.
Methods: We studied the specificity and magnitude of SARS-CoV-2 T cell responses within the first week of symptom onset in previously unexposed individuals before seroconversion, using an IFN-γ ELISPOT assay and peptides pools spanning the SARS-CoV-2 virion structural proteins N, membrane (M) and spike (S), as well as the nonstructural proteins NSP3, ORF3a, and the RTC (consisting of NSP7, NSP8, NSP12 and NSP13). Moreover, pools of MHC Class I- and II-restricted peptides (CD8RE and CD4RE, respectively) spanning the entire SARS-CoV-2 proteome (excluding the S region), as well as a custom pool of 197 non-overlapping 8- to 14mer peptides, selected for their predicted binding affinity to the five most common MHC Class I HLA-A and B alle groups in Europe, were also investigated. To investigate cross-reactivity of the acute SARS-CoV-2 T cell response with the common cold coronavirus HCoV-HKU1, the dominant strain during late 2019/early 2020, an HCoV-HKU1 whole-proteome peptide pool was tested.
Results: Within the first week of symptom onset, N-specific T cells had the highest median response magnitude (105 Spot Forming Colonies/106 PBMC), followed by S (52.5 SFC/106 PBMC), NSP3, M, ORF3a and RTC (32.5 - 37.5 SFC/106 PBMC) and NSP13 (22.5 SFC/106 PBMC). The megapools CD4RE, CD8RE, and custom MHC Class I pool exhibited a median response of 205, 150 and 117.5 SFC/106 PBMC, respectively, indicating a comparable magnitude of CD4 vs. CD8 T cell responses. Upper airway viral load inversely correlated with N-, S-, RTC-, NSP13-, ORF3a and CD4RE-specific T cell response magnitudes ($p<0.05$,

-0.65≤r≤-0.4). Non-significant inverse associations were detected for CD8RE, the custom MHC Class I pool, NSP3 and the HCoV-HKU1 peptide pool (p>0.05, -0.37≤r≤0.18).

Conclusion: SARS-CoV-2-specific T cell responses targeting the structural and nonstructural virus proteins, (including the RTC), were associated with airway virus control during early, acute infection before seroconversion. Results show an inverse correlation between the Upper Airway Viral Load (UA-VL) and circulating viral N, ORF3a, RTC, and NSP13-specific T cells, as well as an inverse correlation between UA-VL and MHC Class II-restricted peptides.



405 Sex-Specific Transcriptional Profiles Associate With Severe SARS-CoV-2 Infection

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Background: Rates of severe disease and death from SARS-CoV-2 infection are higher in males than in females, but the mechanisms are unclear. We interrogated the transcriptional profile associated with severe disease in males and females to investigate differences in pathogenesis.

Methods: Individuals with SARS-CoV-2 in the CCPSEI cohort from 4-7/2020(Cohort 1) and 7/2020- 1/2021(Cohort 2) were enrolled; Cohort 2 all received dexamethasone. Whole blood RNA was extracted from cryopreserved Paxgene tubes from the earliest timepoint and sequenced (NovaSeq). Plasma N antigen level was measured (Simoa,Quanterix). Participants were classified as mild-moderate and severe by the WHO scale. Differentially expressed genes(DEGs) and pathways and N antigen levels were compared between mild-moderate and severe in the full cohorts and within sex adjusted for age and BMI. A publicly available data set of bulk neutrophil sequencing was used to assess neutrophil phenotype by sex.

Results: Cohort 1: n=95, 48% male, median age 53, median sample 4 days after test. Cohort 2: n=59, 56% male, median age 56, median sample 3 days after test+, and on day of dexamethasone. In Cohort 1 there were 3173 DEGs in severe versus mild-moderate, enriching pathways associated with hypoxia. 54% of DEGs were shared in Cohort 1 males. Male DEGs enriched neutrophil activation/degranulation and granule pathways. In Cohort 1 females, there were few DEGs(n=111)between severe and mild-moderate; female specific DEGs enriched unfolded protein response and ER stress pathways. In Cohort 2, administration of dexamethasone ablated differential gene expression in males(n=1 DEG), but had minimal impact on DEG in females(n=149). CIBERSORT identified quantitative differences in neutrophil enrichment. Sex-stratified analysis of bulk neutrophil sequencing from 370 individuals with SARS-CoV-2 identified increased immature neutrophils in males and increased PDL1+ISG+ neutrophils in females with severe disease. Plasma N antigen level was linked to antiviral responses, and detection was less frequent in males with severe disease.

Conclusion: Whole blood transcriptional responses show marked upregulation of neutrophil response genes in severe disease in males. Dexamethasone treatment ablates the transcriptional response in males with severe disease, with less impact in females. Both quantitative and qualitative differences in neutrophils contribute, and N antigen levels suggest that severe disease in males was linked to inflammation.

406 Regulatory T-Cell Manipulation Is Limited by Anti-Antibody Responses in HIV-1 Env- Immunized RMs

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Background: CD25+FoxP3+CD4+ regulatory T (Treg) cells help mediate antigen tolerance in immune responses. We aimed to dissect the influence of anti-CD25 monoclonal antibody (mAb) on the germinal center response to immunization. We tested three mAb treatment arms: inhibiting CD25+ Treg cells (Basiliximab), depleting that population (Anti-Tac), and a control (anti-influenza CH65). We immunized a cohort of rhesus macaques (RMs) with sequential gp120CH505 Envelopes (Envs) that mimicked the mutational pattern observed during HIV-1 infection and tested for the development of HIV-1 broadly neutralizing antibodies (bnAbs).

Methods: Nine RMs were randomly divided into three groups that received 1 mg per infusion of Basiliximab, Anti-Tac, or CH65. Plasma antibody responses were assayed by ELISA. Linear epitope mapping of plasma antibodies was performed by peptide microarray. Immune cell phenotypes were evaluated by flow cytometry. Single-cell PCR and sequencing were conducted to define the antibody spectrum of HIV-1 Env-specific memory B cells derived from lymph nodes. IgM anti-IgG in RMs was assayed by ELISA.

Results: All RMs developed antibodies that blocked CH106 or sCD4 binding to gp120CH505TF and gp12063521. Binding to HIV-1 Env-specific linear epitopes trended lower after each immunization and infusion
in RMs that received anti-CD25 treatment, compared to those received CH65. Treg cell and CXCR5-expressing follicular Treg cell frequency was slightly decreased after the first anti-CD25 infusion but was similar after later infusions. Plasma anti-CD25 activity was detectable after the first infusion but limited after later infusions; CH65 infusion did not show the same pattern. We hypothesized that an anti-antibody immune response developed in anti-CD25 infused RMs; these RMs developed rheumatoid factor after anti-CD25 mAb infusion that matched loss of anti-CD25 plasma activity. Notably, the transient Treg cell disruption that we observed was associated with a change in germinal center responses, as assessed by the size and number of vaccine-elicited B- cell clonal lineages in lymphoid tissue.

Conclusion: Transient Treg perturbation strategies to break immune tolerance and increase poly-reactive anti-Env antibodies in immunized RMs were limited by anti-antibody responses, indicating that immune manipulation strategies to drive the development of protective bnAbs may have off target effects.

407 Characterizing New and Boosted HIV-Specific T-Cell Responses Elicited by an HIV Therapeutic Vaccine

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Background: Little is known about the capacity of HIV therapeutic vaccines to overcome pre-existing immunodominance hierarchies and elicit functional, long-lived new or boosted HIV-specific CD8+ T cell responses. We previously reported therapeutic vaccine-induced new and boosted HIV-specific T cell responses in people with HIV on ART in the PENNVAX trial. We now characterize the magnitude, proliferative capacity, and durability of these responses.

Methods: Participants received gag+pol+IL-12 DNA (GP, n=11), gag+pol+env+IL-12 DNA (GPE, n=15), or placebo (n=13) vaccination via intramuscular electroporation. Individual Gag peptide-specific T cell responses (vaccine-matched 15-mer peptides) were measured via IFNγ ELISpot at baseline (BL), 2 weeks after the last vaccine (Week [Wk] 14), and at Wk48. Responses were defined as "new" at Wk14 if they were absent at BL with a fold change (FC)≥2, and "boosted" if present at BL and Wk14 with FC≥2. We then performed a 6-day in vitro peptide stimulation assay with Cell Trace Violet (CTV) to discern CD4+/CD8+ identity and quantify the proliferative capacity of the responses (%CTVlo of total CD4+ or CD8+ T cells).

Results: At Wk14 versus BL, 10 new Gag-specific T cell responses formed in 5 vaccinated participants (4 in GP arm, 1 in GPE) and 26 Gag-specific T cell responses were boosted in 8 vaccinated participants (4 in GP, 4 in GPE; Fig 1A); there were no new or boosted responses in the placebo group. CD8+ T cells responded to 4 of the new and 20 of the boosted peptides. New responses had a median [IQR] magnitude of 48 [36-95] SFU/1e6 PBMC and proliferation of 1.89% [1.13-4.43%]. Between BL and Wk14, boosted response magnitude increased from 23 [17-70] to 114 [60-179] SFU/1e6 PBMC (p=0.02 boosted vs new at Wk14). Proliferation of boosted responses was unchanged (0.70% [0.41-1.00%] at BL, 0.91% [0.39-2.27%] at Wk14). At Wk48, 5 of the new responses

remained detectable, and 11 of the boosted responses remained ≥2 fold above BL magnitude (Fig. 1B).

Conclusion: HIV DNA therapeutic vaccination both boosted pre-existing T cell responses and also elicited responses against new epitopes. The higher magnitude of boosted responses by IFNγ ELISpot post-vaccination yet similar proliferative responses suggest their per-cell proliferative capacity is lower than that of new responses. Eliciting new T cell responses may be required in order for HIV therapeutic vaccines to enhance T cell function.

Fig 1A. New and boosted Gag-specific T cell responses amongst participants with detectable Wk14 responses. Stable responses (present BL and Wk14, FC<2) in placebo also shown.

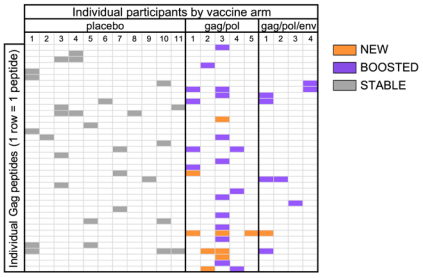
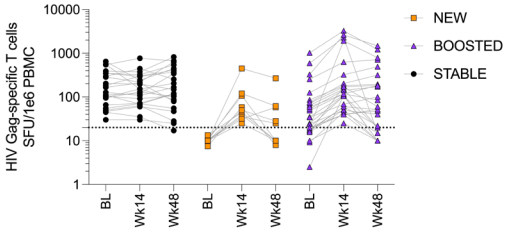


Fig 1B. Change in IFNγ ELISpot magnitude of new and boosted responses. Stable placebo responses also shown.



408 Safety of Therapeutic HIV-1 Vaccine for Adolescents with Early Treated Perinatal HIV Infection

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Background: HVRRICANE is a phase I, proof of concept, open-label, randomized clinical trial to evaluate safety, immunogenicity and efficacy in HIV reservoir reduction of a prime-boost strategy with a multigene, multi-subtype A, B, C HIV-DNA vaccine (HIVIS DNA) and modified vaccinia Ankara Chiang Mai Double Recombinant (MVA-CMDR) vaccine ± co-administration of Toll-like Receptor 4 agonist (within Cervarix® human papilloma vaccine) in adolescents and youth living with perinatally acquired HIV-1.

Methods: Twenty-five South African adolescents living with perinatal HIV, 14 to 16 years of age were enrolled. All started antiretroviral therapy prior to 6 months of age, with continuous viral suppression through enrollment, and randomized to HIV vaccines only (n=10, Arm 1), HIV vaccines and Cervarix® (n=10, Arm 2) or Cervarix® only (n=5, Arm 3). The HIV DNA vaccines were administered through a needle free device (PharmaJet Stratis®) at weeks 0 and 4 ± Cervarix® and the MVA-CMDR at 24 (± Cervarix®) and 36 weeks (MVA-CMDR only). Local and systemic reactions were captured 30 minutes after vaccination and on diary cards for seven days. Pregnancy was screened at each visit.

Results: Two participants missed week 24 immunization (due to TB and pregnancy). There were no loss to follow up, no deaths and 15 participants have completed their week 60 visits. Local and systemic reactogenicity reported as mild or moderate in all 25 participants: 24 (96%) had local and 21 (84%) systemic reactions. Five participants with severe reactogenicity all reduced to moderate, mild or resolved within 2 days. There was one serious adverse event (SAE) and 2 adverse events (AEs) above Grade 2, all in Arm 2. The SAE (acute appendicitis) was unrelated to study participation. One Grade 3 AE (reduced estimated glomerular filtration rate) was considered tenofovir- and not vaccine-related. The other Grade 3 AE was headache for 10 days that was severe on days 1 and 2. A pregnancy during the study was noted (Arm 2) and was electively terminated. The first MVA-CMDR vaccine was omitted due to the pregnancy, but the final CMDR was given after termination. No vaccine related AE prompted discontinuation of investigational product. All participants are expected to complete the study by mid-October 2023.

Conclusion: This study represents the first combined therapeutic HIV vaccine study in pediatrics. While all participants reported local and/or systemic reactions to vaccination, most events were self-limiting and no dose limiting AEs were reported.

Table 1 Severe reaction after vaccination

Reaction type	Arm	Week 0, Vaccination 1 N (%)	Week 4, Vaccination 2 N (%)	Week 24, Vaccination 3 N (%)	Week 36, Vaccination 4 N (%)	Participants with Reactions n (%)
Local	Arm 1 (n=10)	0/10 (0.0%)	0/10 (0.0%)	0/9 (0.0%)	0/9 (0.0%)	
	Arm 2 (n=10)	0/10 (0.0%)	0/10 (0.0%)	1/9 (11.1%)	0/9 (0.0%)	1/10 (10%)
	Arm 3 (n=5)	0/5 (0.0%)	0/5 (0.0%)	0/5 (0.0%)		
Systemic	Arm 1 (n=10)	0/10 (0.0%)	1/10 (10.0%)	0/9 (0.0%)	0/9 (0.0%)	1/10 (10%)
	Arm 2 (n=10)	0/10 (0.0%)	1/10 (10.0%)	2/9 (22.2%)	1/9 (11.1%)	3/10 (30%)
	Arm 3 (n=5)	0/5 (0.0%)	0/5 (0.0%)	1/5 (20.0%)		1/5 (20%)
Total	(N=25)	0/25 (0.0%)	2/25 (8.0%)	4/23 (17.3%)	1/18 (5.5%)	5/25 (20.0%)

409 WITHDRAWN

410 Linking TCR αβ Chains to Costimulatory Signaling Domains Enhances HIV-Specific CD8 T-Cell Function

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Background: The addition of costimulatory signalling domains to the CAR construct has dramatically increased the functional capacity of CAR-T cells to kill cancer cells. We hypothesized that we could augment the functional anti-HIV activity and persistence of cytotoxic CD8 T cells (CTLs) engineered to express HIV-specific TCRs used as an adoptive therapy to provide a functional HIV cure by incorporating the intracellular activation domain of costimulatory signalling domains into the TCR construct, termed TCR-costim.

Methods: As a proof-of-concept, we constructed a lentiviral vector (LV) encoding chimeric α and β TCR chains containing the well described HIV-1 Gag epitope SL9 human variable TCR region fused to the murine constant region, to prevent TCR mispairing with the endogenous TCR. We added the signal transduction domain of either the CD28 or 41BB to the α and/or β TCR chains. Jurkat/MA-NFAT-luciferase reporter (Jurma) cells were transduced with the LV to evaluate SL9-TCR activation by quantification of the luciferase reporter. SL9-TCR expression in CTLs from seronegative donors was determined by tetramer staining; and their cytotoxic activity, activation, and IFNγ and TNFα production by flow cytometry.

Results: In Jurma cells transduced with the different SL9-TCR LV constructs, TCR was highly expressed (95- 99%). Jurkat/Ma transduced with the SL9-CD28 LV displayed 1.47 or 2.2-fold greater TCR activation than SL9- TCR or SL9-41BB, respectively, after coculturing with SL9-loaded T2 cells. Donor CD8 T cells were effectively transduced (15-30%) with all LV contructs and SL9-TCR expression reached 80% of the transduced cells. SL9 reactivity was demonstrated by increased LAG3 and CD25 expression in SL9-TCR, SL9-CD28 and SL9-41BB CTLs incubated with SL9-loaded T2 cells but not with T2 cells alone. Of great interest was the increased cytotoxic activity (figure 1A) and IFNγ and TNFα production of SL9-CD28 and SL9-41BB CTLs as compared with SL9-TCR CTLs (figure 1B).

Conclusion: Incorporating costimulatory signalling domains with the TCR construct (TCR-costim) provides an increased downstream activation of the TCR and an improved functional activity of CTLs. Because TCRs require recognition of far fewer HIV peptides than CARs to activate their effector functions, adoptive therapy with TCR-costim CTLs may overcome CAR-T cell limitations in recognizing and killing latent HIV infected cells which produce low levels of HIV proteins, and provide the sustained CTLs response required for a functional HIV cure.

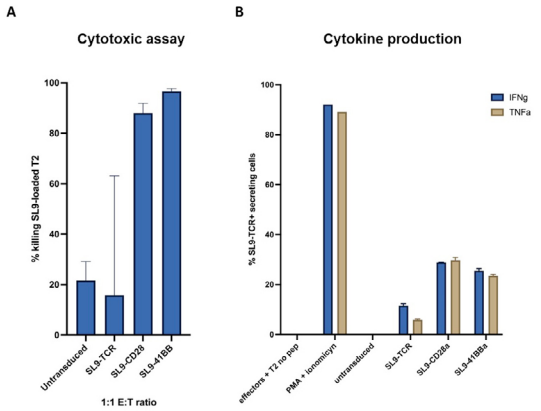

Figure 1. A. SL9-TCR-costim T cells showed an enhanced cytotoxic activity when T2 cells presented SL9 peptide respect to no peptide. **B.** Increased production of IFNγ and TNFα was detected in SL9-TCR-costim T cells after 5 hours stimulation with SL9-loaded T2 cells by intracellular staining.

411 ABBV-382, an Anti-α4β7 Ab That Enhances HIV-1 Antigen Presentation for Immune- Mediated Viral Control

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Background: The α4β7 integrin plays an important role in the pathogenesis of HIV-1 infection. It is a heterodimeric receptor expressed on different immune cells. Expression of α4β7 on peripheral CD4+ T cells predicts HIV-1 acquisition and disease progression. Recent study showed that α4β7 is present on the envelope of HIV-1 virions, which suggests that α4β7 could be a highly conserved target for HIV-1 treatment.
Methods: ABBV-382, a humanized mouse anti-human α4β7 mAb, has been evaluated in different biochemical, virological, immunosafety, and immunopeptidomics studies to characterize its properties and determine its mechanisms of action for HIV-1 intervention.
Results: ABBV-382 demonstrated high binding affinity to α4β7 and blocked the interaction of α4β7 with its ligand MAdCAM-1. The binding profile of ABBV-382 to human FcγRs was similar to that of a typical human IgG1 mAb, but it did not induce ADCC or ADCP activity in vitro. ABBV-382 blocked the MAdCAM-1- mediated co-stimulation of CD4+ T cells, and HIV-1 replication in these treated cells. It also inhibited the interaction of α4β7 with HIV-1 gp120, and is therefore proposed to inhibit the cell-to-cell viral spread mediated by this interaction. Consistent with the report that α4β7 is present on the surface of HIV-1 virions, ABBV-382 could bind to virions from different HIV-1 strains to form immune complexes (ICs). These ICs could engage different FcγRs through the Fc domain of ABBV-382 in vitro. When the ICs were incubated with antigen presenting cells (APCs), they were phagocytosed in a Fc-dependent manner. Immunopeptidomics analyses demonstrated that the internalized ICs were processed, and HIV-1 peptides were presented by MHC class II on APCs, a mechanism that is proposed to enhance HIV-1 antigen presentation to T cells.
Conclusion: Our study results provide evidence of the antiviral and immunomodulatory properties of ABBV-382 through two main mechanisms: (1) Direct antagonism of the interaction of α4β7 with its ligand MAdCAM-1 or HIV-1 gp120, leading to inhibition of HIV-1 replication or cell-to cell viral spread, respectively, and (2) Enhanced viral antigen presentation to T cells enabled by the Fc-dependent uptake of ICs (HIV-1 virions and ABBV-382) by APCs. Taken together, ABBV-382 demonstrates favorable biological characteristics and novel mechanistic properties supporting its clinical evaluation as an immune-based intervention for HIV-1 viral control. Disclosure: The design, study conduct, & financial support were provided by AbbVie.

412 10e8.4/iMAb Bispecific Antibody for Immunoprophylaxis Against High-Dose Intravenous SHIV Exposure

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Background: A lead strategy for preventing HIV transmission is the passive provision of broadly neutralizing antibodies (bNAbs). Various investigators have validated this approach in nonhuman primate (NHP) models of HIV exposure. Experiments in NHPs have primarily focused on preventing viral transmission across anogenital mucosae. In humans, the antibody-mediated prevention (AMP) trial demonstrated that passively administered VRC01 bNAb prevents the transmission of neutralization-sensitive but not resistant HIV strains, emphasizing the urgent need for bNAbs with greater breadth and potency for immunoprophylaxis strategies.
Methods: We developed a nonhuman primate model of immunoprophylaxis in the context of high-dose intravenous HIV exposure. We assessed the 10e8.4/iMAb bispecific antibody, which targets the membrane- proximal external region of the HIV envelope and the CD4 receptor, as an immunoprophylaxis agent. We measured the in vitro neutralization activity of 10e8.4/iMAb using the TZM-bl cell line-based neutralization assay. We intravenously infused three animals with 30mg/kg of 10e8.4/iMAb and three control animals with PBS. One hour later, we challenged all animals intravenously with a high dose (~50,000 $TCID_{50}$) of SHIV- BG505. We performed antibody-mediated CD8+ lymphocyte depletions eight weeks after the viral challenge in aviremic animals to assess for subclinical/occult infections.
Results: The SHIV-BG505 challenge virus was sensitive to 10e8.4/iMAb (IC_{50} <0.01 ug/ml). Control animals developed plasma viremia one week after high-dose intravenous viral challenge (peak: 8.7E6 – 1.1E7 copies/ml). Animals passively administered 10e8.4/iMAb exhibited no evidence of viral infection, even five weeks after systemic depletion of CD8+ lymphocytes.
Conclusion: Passive intravenous provision of potent anti-HIV bispecific bN Abs is a highly promising immunoprophylaxis strategy for high-dose intravenous HIV exposure.

413 Long Half-Life Broadly Neutralizing Killer Bispecifics Against HIV-1: Harnessing the Immune System

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Background: HIV-1 remains significant global health challenge, requiring continuous efforts to develop innovative therapeutic approaches. Clinical use of mAb needs multiple infusions and for BiTEs is limited by short half-life in blood, demanding continuous infusion resulting in high costs inconvenience and time- consumption. We describe the development of DNA-launched, bispecific T cell engagers that redirect T cells towards killing target HIV infected cells. These are highly specific Broadly neutralizing Killers (BnKs) that demonstrate long half-lives (LHL) in-vivo.
Methods: We designed DNA-launched LHL- BnKs with bispecific scFvs and a Fc fragment having Fc effector- null mutations to abrogate Fcγ receptor binding. We evaluated in-vitro and in-vivo expression of DNA launched LHL-BnKs and characterized functionality. ELISA and flow cytometry were used to demonstrate binding studies, pseudo-neutralization assays to test neutralizing potential against a global virus panel. A novel cell based Xcelligence assay was designed which uses impedance as a readout for killing activity. In-vivo pharmacokinetics were evaluated by inoculating the DNA launched LHL-BnKs in BALB/c mice.
Results: DNA launched PGDM1400, 3BNC117 and PGT121 LHL-BnKs respectively were designed and optimized for expression both in-vitro and in-vivo. Binding studies demonstrate that these molecules bind to CD3 in a concentration dependent manner. They also demonstrated binding to CD3+T cells and neutralized a global panel of HIV-1 Tier 2/3 viruses with high potency and specificity. The LHL-BnKs displayed potent killing of HIV-1 infected target cells with nanogram/ml IC_{50} for killing. Combination therapy of 10-1074 and 3BNC117 did significantly reduce viral rebound in clinical trials where the groups received up to 8 infusions of 3BNC117 during the 24-week period. Our data suggests that after single inoculation of 50ug DNA, plasma concentration of ~10ug/ml was

achieved in vivo with peak serum expression around day 21 and expressed for extended duration.
Conclusion: Our data highlights the design and characterization of novel DNA launched immunotherapeutic against HIV-1, which possess significant characteristics of a promising immunotherapy having broad neutralization capacities of a Tier 2/3 global virus panel, specific engagement of effector cells and killing of the infected target cells and longer serum half-life in comparison to conventional bispecific T cell engaging molecules. Delivery of LHL-BnKs as combination therapy.

414 Targeting HIV-Infected Cells for Immunotherapy Through HLA-E

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Background: Cytolytic T lymphocytes (CTLs) help control viremia in people with HIV. HIV evades this response through escape mutations in CTL epitopes and downregulation of HLA molecules. The dimorphic non-canonical HLA-E molecules, however, are upregulated during infection, making them promising targets for CTL-engaging reagents such as single-chain diabodies (scDbs) provided that they present HIV epitopes. Here, we show that HIV-infected cells can be targeted for CTL-mediated lysis using novel scDbs specific for HLA-E-bound epitopes.
Methods: To validate HLA-E as a suitable scDb target, we used the previously characterized M. tuberculosis- derived peptide Mtb44 that binds with high affinity to HLA-E. Through phage biopanning, we isolated a novel scDb (RLP13) that recognizes this epitope bound to HLA-E. This scDB also recognizes CD3 and is able to induce CTL activation. The specificity of RLP13 was tested through killing assays with CD8+ effector T cells and target cells presenting cognate Mtb44 peptide or the irrelevant canonical HLA-E epitope VL9. To test whether HIV-encoded peptides can be targeted, an Mtb44-encoding DNA segment was inserted into an HIV reporter virus (NL4.3 ΔEnv-GFP). Target cells were infected with this virus and co-cultured with RLP13 scDb and autologous CTLs to assess killing of infected cells.
Results: RLP13 scDb induced antigen-specific lysis of Mtb44-presenting target cells, regardless of the donor HLA type, in an scDb- and antigen-dose-dependent manner. Furthermore, addition of the RLP13 scDb to co- cultures of primary CD8+ T cells and autologous CD4+ T cells infected with viral reporter constructs carrying the Mtb44 epitope led to a 50% reduction of the HIV+ population, indicating that targeting of HIV-1 peptides presented on HLA-E can potentially lead to the elimination of infected cells.
Conclusion: Our findings with scDb RLP13 demonstrate that virally encoded peptides presented in the context of HLA-E can be targeted by scDbs to induce CTL-mediated lysis of infected cells, regardless of HLA-genotype. The development of novel scDbs recognizing HIV-derived epitopes that bind HLA-E would provide a universal reagent that could be used to promote the killing of HIV-1 infected cells in shock and kill strategies for HIV cure.

415 Instability of the HLA-E Peptidome of HIV Presents a Major Barrier to Therapeutic Targeting

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Background: Human leukocyte antigen (HLA) class Ia molecules present peptides derived from the ER for recognition by cytotoxic T lymphocytes. As such, HLA class Ia-restricted peptides are well characterised drug targets for infectious diseases. However, their clinical potential is limited by the high polymorphism of the HLA class I genes within the population. In contrast, the HLA class Ib molecule, HLA-E, has only two alleles and thus offers the potential to develop donor-unrestricted therapies. With only a few reported HIV-derived HLA-E restricted peptides, there is limited understanding of the composition and druggability of the HIV HLA-E 'ligandome.' We therefore sought to systematically interrogate the HIV HLA-E ligandome to identify stably presented peptides as drug targets for a potential HIV cure strategy.
Methods: The HIV proteome of in vitro infected cells was interrogated for HLA-E presented peptides using both immunopeptidomic (mass spectrometry) and bioinformatic (predictive) approaches. Putative ligands were then ranked based on stability using a panel of biochemical assays as well as an HLA-E cell surface stabilization assay. The stability of the highest ranked peptide, Gag275-283, was further assessed using an affinity-enhanced T cell receptor bispecific molecule (ImmTAX). The ImmTAX was used as a probe for peptide-HLA-E complexes on antigen-presenting cells (peptide-pulsed targets or HIV-infected cells) in T cell redirection assays.
Results: Tandem mass spectrometry analysis of 1 billion infected C8166 cells (19.4% Gag+ by intracellular staining) failed to identify any HIV HLA-E peptides. Of >80 bioinformatically predicted ligands, all were characterised by low or unmeasurable complex thermostability and half-lives and performed poorly in the cell surface stabilisation assay. In T cell redirection assays using the ImmTAX, consistent presentation of Gag275-283 by HLA-E was only demonstrated when peptide was supplied exogenously (peptide pulsing model). Only sporadic and inconsistent peptide presentation was detected when the peptide source was endogenously expressed HIV Gag protein (infected cells).
Conclusion: This study provides biochemical and biological evidence for the failure of HIV-derived peptides to form a stable complex with HLA-E, highlighting a major challenge for HLA-E targeted drug or vaccine development.

416 Immune Responses Associated With Mpox Viral Clearance in People With and Without HIV Coinfection

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Background: During the emergence of the global mpox outbreak in May 2022, over 90,000 cases were diagnosed, disproportionately affecting those living with HIV. Milder re-infections have been recently reported. Here, we extensively characterized cellular and humoral responses in people without HIV (PWoH) and with HIV (PWH) at acute mpox, determined their impact on disease severity and viral clearance dynamics, and assessed post-infection immunity 6 months after mpox virus (MPXV) diagnosis.
Methods: Thirty-three men (PWoH n=19; PWH n=14, all with CD4 T cell>400) from a prospective, observational cohort study (NCT0547674) were included. Samples from skin lesions were collected weekly to estimate the time to clear MPXV. Blood samples were taken at diagnosis and 29, 91, and 182 days later for immune analysis. IgG and IgA against A35L, H3R and A29L MPXV proteins were quantified by ELISA, and in-vitro neutralization capacity was measured in Vero E6 cells. T-cell responses were characterized upon antigen recall by IFNγ ELISpot and multiparametric flow cytometry.
Results: PWoH and PWH had similar clinical severity and time to MPXV clearance in skin lesions. Both PWoH and PWH had comparable levels of anti-MPXV IgG and broad IgA-mediated responses. Whilst in-vitro neutralization was not fully observed until 91 days after infection, both titers and breadth of antibodies induced early after infection were associated with reduced clinical severity, lower levels of virus in skin lesions and a shorter and more rapid viral clearance. Levels of antibodies increased one month after MPXV infection and waned thereafter, while frequencies of mpox-specific T-cells were sustained up to 6 months, regardless of HIV status. Although no major differences were observed in cellular activation or cytokine production between study groups, a delay in the contribution of multifunctional CD4+ T-cells was only observed in PWH. Overall, GzmB+ CD4+ and CD8+ T-cells were the predominant subsets contributing across all timepoints in both groups.
Conclusion: Although PWoH and PWH had comparable immune responses at acute mpox, a delay on functional T-cell diversity and a faster wane of antibodies was observed in PWH. Mpox-specific antibodies may play a key role in the initial control of infection via non-neutralizing pathways, and a durable cellular immunity is induced following infection, which might help to contain viral spread, contribute to a faster clearance, and reduce severity in future re-infections.

417 Orthopoxvirus-Specific IgG Upon Mpox Vaccination Among People With and Those Without HIV

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Background: In Taiwan, nationwide routine and compulsory smallpox vaccination with Lister strain had been stopped in 1979. As Mpox continued to spread worldwide, a two-dose Mpox vaccination, with an interval of at least 28

days, is currently recommended as pre- and post-exposure prophylaxis in the high-risk populations. However, orthopoxvirus-specific (OPXV) IgG remains less investigated in people with HIV (PWH), especially for those born after 1979.
Methods: Men who have sex with men (MSM) planning to receive two doses of MVA-BN vaccine were enrolled. Blood samples were collected on D0, 28±7, and 96±7 for all individuals after each dose. All serum specimens were tested for the presence of OPXV-specific IgG. Those testing positive for OPXV-specific IgG and being infected with Mpox were excluded from subsequent analysis.
Results: A total of 299 participants, including 188 PWH and 111 people without HIV (PWoH), were included. The median age of the participants for PWH and PWoH 38 and 31 years, respectively; 51 PWH and 3 PWoH were born before 1979. Most of the included PWH (97.9%) were virologically suppressed with antiretroviral therapy and had a median CD4 count of 648 cells/mm³. Overall, 16 (8.5%) of 188 PWH and 8 (7.2%) of 111 PWoH had seroconversion of OPXV-specific IgG 28 days after the first dose, while 31 (24.8%) of 125 PWH and 12 (19.4%) of 62 PWoH had a seroconversion 28 days after the second dose of Mpox vaccination. The median titer of OPXV-specific IgG for PWH and PWoH was 3.8 and 6.4 ng/mL. respectively. Those born before 1979 were more likely to seroconvert after Mpox vaccination than those born after 1979 (51.3% vs 16%; adjusted odds ratio [aOR], 5.54; 95% CI, 2.54-12.07). After excluding PWH born before 1979, PWH tended to have a lower seroconversion rate than PWoH (14.6% vs 18.0%; aOR, 0.78; 95% CI, 0.32-1.87).
Conclusion: The median OPXV-specific IgG titer among individuals who received two doses of Mpox vaccine was higher in those who had had prior smallpox vaccination. For those born after 1979, OPXV-specific IgG was higher in PWoH compared to virologically-suppressed PWH, though the differences between the two groups did not reach statistical significance, probably related to a relatively small case number.

418 MPXV Replication Induces an IFN Response and Is Suppressed by IFN-γ

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Background: Poxviruses have developed strategies to evade host antiviral immunity, particularly the Interferon (IFN) response, but limited data are available for Monkeypox virus (MPXV). To better understand how MPXV affects the IFN response, we analyzed type I, II and III IFNs and IFN stimulated genes (ISGs) expression in different MPXV-infected anatomical sites from male patients. Also, we investigate MPXV in vitro sensitivity to different type of IFNs.
Methods: Eighteen samples from different anatomical sites [Skin lesions (SL), anal canal brushing (ACB) and nasopharyngeal swabs (NSP)] were collected from MPXV-infected male patients. Gene expression of type I (IFN-α/β/ω), type II (IFN-γ), type III IFNs (IFN-λ1/2/3) and ISGs (ISG15, ISG56 and PKR) was measured by quantitative RT-PCR assays. MPXV-DNA levels were evaluated by Bioperfectus Monkeypox Virus Real Time PCR kit. Antiviral assays were performed to evaluate MPXV (MOI=0.1) sensitivity to different types of IFNs (IFN-α, IFN-α natural, IFN-β, IFN-ω and IFN-γ) on different cell lines (human lung adenocarcinoma epithelial A549 cells, cervival carcinoma HeLa cells and african green monkey kidney VeroE6 cells). Viral yield after IFN treatment was quantified in VeroE6 cells.
Results: Examination of IFN-related genes across anatomical sites revealed that IFN-α, IFN-λ1, and PKR were significantly upregulated in ACB compared to other clinical samples. Conversely, levels of IFN-β and IFN-ω increased in SL ($p<0.05$). IFN-I/III and ISGs showed higher expression in samples with low MPXV-DNA Ct values, while the opposite trend was observed for IFN-γ production ($p<0.05$ for all the genes). Pre-treatment of A549, HeLa, and VeroE6 cells with high concentrations of IFN-α, IFN-αn, and IFN-ω (greater than or equal to 300,000 IU/mL) did not significantly inhibit MPXV replication, while MPXV exhibited moderate sensitivity to the antiviral action of IFN-β. In contrast, IFN-γ strongly inhibited MPXV replication in all the cell lines used.
Conclusion: This study provides evidence that MPXV infection triggers the production of various types of IFNs and ISGs, with IFN-γ being particularly effective in inhibiting MPXV replication in vitro. These findings contribute to a better understanding of how MPXV evades the host immune response and may inform potential therapeutic strategies for MPXV infections.

419 Early Tecovirimat Treatment for Mpox Disease Among People With HIV: A Matched Cohort Analysis

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Background: Despite a lack of efficacy data in humans, tecovirimat was widely prescribed to people with HIV (PWH) with mpox during the 2022 mpox epidemic, particularly among those with low CD4+ T-cell counts or severe mpox clinical manifestations.
Methods: This is a matched cohort study of PWH diagnosed with mpox at four hospitals in Atlanta, Georgia between 6/1/2022 and 10/7/2022. The exposure cohort ("early tecovirimat") included PWH with mpox who were treated with tecovirimat within 7 days of symptom onset. The unexposed cohort ("late/no tecovirimat") included PWH diagnosed with mpox who did not receive tecovirimat or who received tecovirimat >7 days after symptom onset. Multivariate logistic regression models were used to identify factors associated with progression of mpox disease, defined as development of at least one severe mpox criteria after symptom day 7. The 2 cohorts were matched 1:1 using propensity scores based on the identified predictors.
Results: Each cohort included 56 matched individuals. Predictors selected for inclusion in the final propensity score estimation model included age, race, HIV viral load suppression, involvement of any mucosal site(s), and hospitalization at day 7. Mpox progression occurred in 3 (5.4%) individuals in the early tecovirimat cohort and in 13 (23.2%) individuals in the late/no tecovirimat cohort (paired odds ratio 11.0 (95% CI 1.4, 85.1), exact binomial test $p = 0.006$).
Conclusion: PWH with mpox who were prescribed tecovirimat within 7 days of symptom onset were less likely to have mpox progression compared with matched PWH who didn't receive early tecovirimat. While awaiting the completion of randomized controlled trials of tecovirimat efficacy for mpox, these results favor starting tecovirimat in all PWH as soon as a mpox diagnosis is suspected.

Table 1: Matched Cohorts: Covariates and Outcome

Baseline characteristics; median (IQR) or N (%)	Tecovirimat on/ before symptom day #7: (n = 56)	No tecovirimat on/ before symptom day #7: (n = 56)	p-value*
Age (years)	35 (30-42)	36 (32-43)	0.52
Race: Black	46 (82.1%)	49 (87.5%)	0.60
HIV viral load: < 200 copies/mL	33 (58.9%)	33 (58.9%)	1.0
Number of mucosal sites involved at presentation: 0	21 (37.5%)	22 (39.3%)	1.0
Hospitalized at symptom day #7: Yes	15 (26.8%)	15 (26.8%)	1.0
Development of severe mpox after symptom day 7	3 (5.4%)	13 (23.2%)	0.006

*P-values were calculated using Wilcoxon rank sum testing for continuous variables, Fisher's Exact testing for categorical variables, and an exact binomial proportion-based McNemar's test for the primary outcome. P-values based on categories for race "Black vs. other" and for mucosal sites "any vs. none."

420 Combination of Extended Antivirals With Antiretrovirals for Severe Mpox in Advanced HIV Infection

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Background: Appropriate therapeutic management of mpox in people with advanced HIV remains challenging given an absence of clinical trial evidence. This case series aims to provide our experience during the 2022 outbreak for patients with severe mpox treated aggressively with a combination of extended tecovirimat and cidofovir with antiretrovirals (ART).
Methods: This is a retrospective review of cases at the University of Pennsylania during the 2022 mpox outbreak collecting clinical data and evaluating effectiveness and safety of combination antivirals in people with advanced HIV and disseminated mpox.
Results: We identified four male patients with mpox and advanced HIV (CD4 count 0-53 cells/mm³, viral load 2,104-217,000 copies/ml, age range 30s-50s). They exhibited necrotic skin lesions across the face, trunk, groin and extremities, with one developing keratitis and conjunctival ulcers. Three cases were associated with super- and co-infections: HSV1/2, severe COVID-19 and MRSA. All patients started/resumed ART and began daily oral tecovirimat and cidofovir infusions with probenecid/fluids every 2 weeks. While one patient exhibited full recovery after a single 6-week course of tecovirimat, 6 doses of cidofovir and ART, the other three had a more complicated course including two with

insufficient daily nutrition affecting oral tecovirimat absorption and another lacking consistent housing and wound care that led to recurrent presentations that required extended tecovirimat (5-16 weeks) and cidofovir (1-12 doses). We stopped cidofovir after 7 months on one patient based on IgG+/IgM– orthopoxvirus serology. Ocular lesions were treated with trifluridine (3 weeks). Two patients required adjustments of ART. After ART, all cases had markedly lower HIV load (0-138 copies/ml). All patients had improved mpox lesions at follow-up and renal function remained stable.

Conclusion: This report illustrates that prolonged cidofovir with tecovirimat can be safely administered to manage severe mpox infections in people with advanced HIV. Our case series underscores the multifaceted challenges this population faces, extending beyond clinical manifestations, to include social determinants such as housing stability, nutritional intake essential for effective tecovirimat absorption and presence of concurrent infections. Our findings advocate for a comprehensive approach integrating ART with multiple antivirals, while simultaneously addressing contextual and socio-environmental factors.

Table. Summary of clinical cases with mpox and advanced HIV at our institution.

Age and Sex	Presentation and Factors affecting Recurrence	HIV VL and CD4 from Start → End	Mpox Treatment	HIV Treatment	Prophylaxis and Treatment of Co-Infections
40s M	Recurrent diffuse mpox skin ulcers with keratitis and conjunctival lesions due to inadequate caloric intake for PO absorption and ART. HSV1/2+.	VL 43,100→65 copies/ml CD4 53 →61 cells/mm³	PO/IV tecovirimat (16 weeks), IV cidofovir (9 doses), GTT trifluridine (3 weeks)	B/FTC/TAF with DRV/COBI →DOR	TMP-SMX, mupirocin, GTT erythromycin, ACV→VACV
50s M	Recurrent, diffuse mpox skin lesions related to inconsistent housing and wound care. MRSA+.	VL 2,104→138 copies/ml CD4 41→71 cells/mm³	PO tecovirimat (5 weeks), partial IV cidofovir (1 dose)	B/FTC/TAF	Atovaquone, vancomycin →doxycycline
30s M	Recurrent, diffuse mpox skin ulcers from difficulties in caloric intake, adherence and ART management.	CD4 <35→65 cells/mm³	PO/IV tecovirimat (8 weeks), IV cidofovir (7 months)	B/FTC/TAF → CBG/RPV and LEN	
30s M	Multiple mpox skin lesions and dysphagia. No recurrences. COVID+.	VL 217,000→0 copies/ml CD4 0 cells/mm³ on admission	PO tecovirimat (6 weeks), IV cidofovir (6 doses)	B/FTC/TAF	Remdesivir

Abbreviations: VL viral load. PO oral. IV intravenous. GTT eye drops. B/FTC/TAF bictegravir/emtricitabine/tenofovir alafenamide. DRV/COBI darunavir/cobicistat. DOR doravirine. CBG/RPV cabotegravir/rilpivirine. LEN lenacapavir. TMP-SMX trimethoprim-sulfamethoxazole. ACV/VACV: acyclovir/valacyclovir.

421 Mpox Virus Model of Sexual Transmission in Cynomolgus Macaque

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Background: The Monkeypox virus (MPXV) responsible for 2022 outbreak belongs to clade IIb which derives from the less virulent clade and whose exact mode transmission needs to be established. Monkeypox (Mpox) mainly affects male population and evidence suggest that Mpox could be a sexually transmitted disease. Today, the animal models of Mpox and more particularly the non-human primate models (NHP) available remains limited; and do not fully reflect the pathophysiology of the virus infection. In particular, there are no precise evidence and model on the potential sexual transmission of MPox.

Methods: We mimicked virus transmission during sexual activities by challenging Cynomolgus macaques by intradermal (ID) or intrarectal (IR) route alone or in combination with a MPXV strain isolated on a French patient in 2022. Infection of NHPs was documented clinically (clinical score and photographs) and monitored by blood count. Virus dissemination was tested by qRT-PCR and viral isolation, and the humoral immune response was assessed by specific IgG quantification and seroneutralisation. The virus was tested in various compartments, including blood, seminal fluid, rectal secretions and saliva. In a second time, we focused on the IR transmission and have mapped the virus-infected organs and performed large histology analysis.

Results: We observed a moderate disease whatever the route of infection with clinical symptoms similar to human including fever episodes, lymphodenomegaly and skin lesions. Interestingly, the kinetics of clinical symptoms appearance is also very similar to human. The infection was characterized by marked lymphopenia, combined with monocytosis and a drop in Hemoglobin as reported in patients. Virus was detected in skin lesions, blood, rectal mucosa and semen. Sexual fluids contain infectious virus during 2 weeks after IR transmission. We also observed that IR challenge provoked a systemic infection with virus dissemination in organs including digestive tract and genital tract but a very limited seroconversion. Histological analysis also revealed remarkable inflammation and infiltration in the infected organs such as rectum and genital tract.

Conclusion: We have set up a non-lethal model of MPox in NHPs by intrarectal route and validated that Mpox can be considered as a sexually transmitted disease disseminated by sexual fluids. We established a pathophysiological model of Mpox with symptoms similar to human that will allow to assess vaccines and therapeutics against this emerging disease.

422 Tecovirimat Plasma Concentrations, Mpox Resistance Mutations Selection, and Clinical Outcomes

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Background: During the recent Mpox outbreak, Tecovirimat was used to treat patients with severe disease. There are few studies characterizing Tecovirimat resistance mutations and none describing concomitant drug plasma concentrations.

Methods: Two HIV-1 infected patients hospitalized for severe and persistent Mpox clinical manifestations were studied. Sequential sampling of several anatomic compartments were screened for Mpox by PCR. Positive samples were sequenced using whole genome sequencing. Plasma concentrations of Tecovirimat were determined using LC-MS/MS (lower limit of quantification - LLOQ: 1 mg/L).

Results: Patient 1 with a low CD4+ cells count (198 CD4+/mm³) despite an undetectable viral load, presented multiple Mpox skin lesions, evolving with fever and associated with extensive bilateral pulmonary, hepatic Mpox lesions and persistent Mpox viremia, motivating a Tecovirimat treatment. Mpox clinical evolution was very slow but favorable after 90 days of Tecovirimat (600mg BID). Whole genome sequencing showed no resistance associated mutations (RAMs) and Tecovirimat plasma concentrations were in the expected range (177 and 1635 mg/L) during all the follow-up. Patient 2 presenting an uncontrolled HIV-1 replication (30,000 copies/mL) and a deep immunodeficiency (43 CD4+/mm³) with a high BMI (48.5 kg/m²) was treated by Tecovirimat (600mg BID) during 14 days due to a disseminated mucocutaneous Mpox. Evolution during treatment was marked by a clear improvement of the cutaneous lesions. Nevertheless, three days after the tecovirimat cessation, two new cutaneous lesions appeared and evolved within abscess aspects. Whole genome sequencing showed the appearance of previously described Tecovirimat RAMs (A290V, D294V, I372N) and a new one (Y252C) with anatomic compartmentalization patterns. Tecovirimat plasma concentrations were always below the expected range or below the LLOQ during the treatment period.

Conclusion: Persistent replication of Mpox under Tecovirimat pressure in an immunosuppressed patient harboring adequate plasma drug concentrations was not associated with RAM selection. However, in case of suboptimal Tecovirimat plasma concentrations, we observed in another patient a rapid selection of RAMs associated to a clinical and virological rebound. These low plasma concentrations could be due to adherence issues, malabsorption or high BMI. This study highlights the interest of the Therapeutic Drug Monitoring of Tecovirimat in special populations and raises the discussion of dose adjustment.

Table: Clinical, virological and Tecovirimat trough concentrations characteristics of the two Mpox cases

Patient number	CD4+ T-cell count (cells/mm³)	HIV viral load (copies/ml)	Tecovirimat cure number	Sampling time	Mutation in the F13L gene of the Mpox virus	Tecovirimat trough concentrations (mg/L)
#1		54	1 (14 days)	D0		
	198	<20		D+5/ post cure	None	
			2 (90 days)	D0	None	
	177	<20	2	D16	None	376.0
			2	D46		531.5
			2	D61		858.0
	111	<20	2	D75		669.6
			2	D81		314.0
#2	53	4,120	1 (14 days)	D6		79.5
			1 - cessation	D14	I372N	< 1
	78	938		D+3 post cure	A290V ; I372N	< 1
		390		D+11	Y252C ; A290V ; I372N	
	79	155		D+37	Y252C ; D294V ; I372N	

423 Predictors of Treatment With Tecovirimat and Hospitalization Among People With Mpox and HIV

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Background: Thousands of mpox cases have been reported in the US since 2022, disproportionately affecting people with HIV (PWH), but epidemiologic data on mpox among PWH are limited. We examined demographic and clinical characteristics of PWH with mpox across the US in the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort.

Methods: We studied all PWH in care at 9 CNICS sites and identified mpox cases based on: a positive mpox PCR value, a documented mpox diagnosis, or tecovirimat prescription without accompanying negative mpox PCR result between June-December 2022. We examined the most proximal CD4 count and HIV viral load (VL), as well as antiretroviral therapy (ART) status prior to mpox diagnosis. We used generalized linear models with Poisson distribution and robust variance to estimate associations of demographic and clinical characteristics with tecovirimat prescription and hospitalization within 2 weeks of mpox diagnosis, adjusting for age and site.

Results: We identified 381 PWH who had mpox, all assigned male at birth, with median age of 39 years; 30.7% identified as non-Hispanic White, 22.3% as non-Hispanic Black, and 29.9% as Hispanic. A majority of mpox cases were prescribed ART (95%, Table), had undetectable HIV VL (77%), and a CD4 count ≥500 (55%) at mpox diagnosis. Most mpox diagnoses (77%) were confirmed by PCR and 13% of cases had received ≥1 doses of JYNNEOS vaccine prior to mpox diagnosis. PWH with mpox who had CD4 count <200 were twice as likely to receive Tecovirimat compared to those with CD4≥500 (adjusted prevalence ratio [aPR]: 2.0, 95% confidence interval [CI]: 1.5-2.8). Race/ethnicity, detectable HIV VL, and ART status were not associated with Tecovirimat receipt. Cases with lower CD4 count were more likely to be hospitalized within 2 weeks of mpox diagnosis compared to those with CD4 ≥500 (CD4<200:aPR: 2.1, 95%CI: 0.7-6.6; CD4 200-350: aPR: 2.6, 95% CI: 1.2- 5.8); those not on ART were nearly 4 times more likely to be hospitalized (aPR: 3.9, 95% CI: 1.7-8.9) compared to those prescribed ART; and those with detectable HIV VL were twice as likely to be hospitalized (aPR: 2.1, 95% CI: 1.1-4.3) as those with viral suppression.

Conclusion: Among PWH at HIV care centers across the US, we observed notable associations between CD4 count ≤350, detectable VL, lack of ART and hospitalization following mpox diagnosis, suggesting that immunologic risk may extend beyond those with CD4 <200, the threshold at which many PWH are prescribed tecovirimat.

Clinical characteristics of PWH with mpox across 9 sites of the CFAR Network of Integrated Clinical Systems diagnosed from June – December 2022.

Characteristic	N=381	%
CD4 count < 200, cells/mm^2	25	6.6
CD4 count 200-349 cells/mm^2	47	12.3
Detectable HIV viral load	75	19.7
On ART	353	94.6
Tecovirimat prescribed	165	43.3
Received 1 JYNNEOS dose prior to mpox diagnosis	34	8.9
Received 2 JYNNEOS doses prior to mpox diagnosis	17	4.5
Hospitalized within 2 weeks following mpox diagnosis	35	9.2

CNICS sites contributing to this cohort were in Baltimore, Birmingham, Boston, Chapel Hill, Cleveland, Nashville, San Francisco, San Diego, and Seattle

424 Predictors of Mpox Duration and Severity in the Italian Multicenter Mpox Icona Cohort

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Background: The mpox 2022 outbreak was characterized by novel clinical presentation and new routes of transmission. We explored potential predictors of mpox severity and duration and described mpox virus (MPXV) persistence in relevant biological fluids after healing.

Methods: Italian multicenter study in the network of Icona cohort. Severe mpox cases were defined as hospitalized or proctitis, pharyngotonsillitis, ocular lesion, or >20 skin lesions; recovery as the resolution of all mucocutaneous lesions. Mixed effect regression models with a random intercept for clinical center assessed predictors of mpox duration (linear model) and severity (logistic model). A stepwise backward process (with p=0.200) was fitted for the selection of variables in both multivariate models, using HIV status as a priori predictor. Assessment of early MPXV viral load (VL) as a predictor of severity was done by Student T-Test and mixed effect logistic regression model including random intercept on clinical center.

Results: 541 pts: 99.2% male, median age 38 (IQR 33-44), 43,5% PLWH (see Fig1A). Mean mpox duration was 23.1 days (95% CI 21.9-24.3), significantly longer in pts with lymphadenopathy (+2.47 days), sore throat (+3.12), proctitis (+4.78), diffuse rash (+3.42) and in PLWH with <350 CD4 (+12.51) (Fig1B). Caucasian race (OR 1.82), fever (OR 1.95; p<0.002), lymphadenopathy (OR 2.30), sore throat (OR 2.14), and peri-anal lesions (OR 2.91) at onset were significantly associated with severe mpox (Fig1C). Quantitative determination of VL in the upper respiratory tract (URT) was available for 233 pts (136 mild and 97 severe). Mean Ct-value was 37.3 (33.9-40.8) and 34.6 (30.9-38.3) in mild and severe cases, respectively (P<0.005), and the probability of developing severe disease was inversely associated with Ct-value, dropping by 5% per Ct (OR 0.95; 0.91-0.98; p<0.005; Fig1D). We found no association between severity and VL in other fluids. Detectable MPXV was found in sperm (14/60 pts), urine (5/86), anorectal (10/72), and URT (24/160) up to 46 days after recovery with a minimum Ct value of 26.

Conclusion: In the event of proctitis, sore throat, lymphadenopathy, and disseminated skin lesions, mpox may last longer, as well as in PLWH with a low CD4 count. Caucasian race and presentation with fever, sore throat, lymphadenopathy, and peri-anal lesions predicted disease severity directly associated with VL in URT. Still unclear if viral shedding after recovery in several anatomical sites could lead to persistent infectivity.

425 Molecular Epidemiology of Human Mpox in Chicago

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Background: Mpox (formerly known as monkeypox) is a syndrome of fever, rash, and lymphadenopathy caused by the mpox virus (MPXV), a zoonotic double-stranded DNA orthopoxvirus. The virus was first isolated in monkeys from Singapore in 1959 and is now known to have several animal reservoirs. Since its emergence in humans in the 1970's, MPXV has become endemic in central and western Africa. In 2022, an outbreak of Mpox consisting of over 88 thousand cases across 113 countries prompted the World Health Organization to declare a public health emergency of international concern. High-risk populations for transmission were prioritized for vaccination with the JYNNEOS MPXV/smallpox vaccine. Global case counts peaked in early September of 2022 before tapering off in January 2023. In April 2023, a small resurgence of cases was noted in Chicago, including several vaccinated individuals, raising concerns of immune escape.

Methods: In this study, we investigated the genetic variation and evolution of the virus throughout the 2022- 2023 outbreaks in Chicago. Between July 1, 2022 and September 1, 2023 residual diagnostic specimens were collected from Northwestern Memorial Hospital and affiliated clinics for DNA extraction and whole genome sequencing. In total, 139 specimens from 98 patients were collected, and 101 specimens from 77 patients were of sufficient viral load for whole genome sequencing.

Results: We observed a rapid increase in viral population size and diversity peaking in August 2022, comprised of eleven lineages, indicative of a high degree of viral circulation. On the contrary, all of the 2023 cases belonged to the same lineage, B.1.20, defined by three synonymous mutations. These most likely arose from a single transmission cluster, which was supported by traditional epidemiological follow up.

Conclusion: The circumstances underlying the unprecedented, international outbreak of Mpox in 2022 remain to be fully elucidated. The reemergence of MPVX in 2023 suggests continued circulation in the human population, which is supported by the virus' continued evolution. Ongoing and robust epidemiological and genomic surveillance is required to determine if MPVX has become endemic in populations outside of West Africa. Continued monitoring of the genetic variation of the virus will allow for development of new antivirals and vaccinations with increased efficacy.

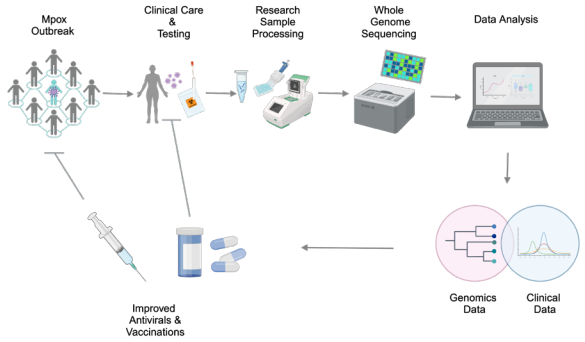

Figure detailing the molecular epidemiology pipeline utilized for this study and the impact of the findings on future treatment and vaccine development

426 Plausibility of Sexual Behavior Changes and Role of Vaccination in Mpox Outbreak Control Among MSM

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Background: The European mpox exponential increase during the early summer 2022 was believed to be linked to major LGBTQI+ sex-related events. However, it inexplicably faded in the last months of the year: main proposed reasons included behavioural changes in sexual habits and immunization through vaccination campaigns started during summer. We compared the trends of mpox and classical STIs in MSM PLWH and PrEP-users in relation to sex-related events and vaccination campaigns in highly-involved European countries over 2022.
Methods: We enrolled consecutive self-identified MSM attending two large sexual health clinics in Milan, Italy, from January to December 2022, who underwent an STIs screening and mpox evaluation. We focused on PLWH and PrEP-users for their strict link to healthcare and regular STIs screening. *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and mpox were detected through Nucleic Acids Amplification Tests while a serologic Rapid Plasma Reagin test was used to identify new syphilis cases. Also, we noted the timing for major European LGBTQI+ sex-related events and for the beginning of the mpox vaccination campaign.
Results: 1281 STIs were diagnosed from January to December 2022, of whom 654 in PLWH, 627 in PrEP- users. STIs peaked as follows: Chlamydia infection in October (49 cases), followed by January and July (42 and 45 cases), gonorrhoea in June (38), November (37) and January (36), syphilis in August (35 cases), February and March (34 each); mpox in June and July (49 cases) [Figure 1].
Conclusion: We found that classical STIs had a fluctuating, still constant presence throughout the year, while mpox showed a decline even if, in the same period, the mentioned events continued to be held. These findings suggest the unlikeliness of a behavioural change in influencing such a decline, putting in a new light the role of vaccination in the MSM community.

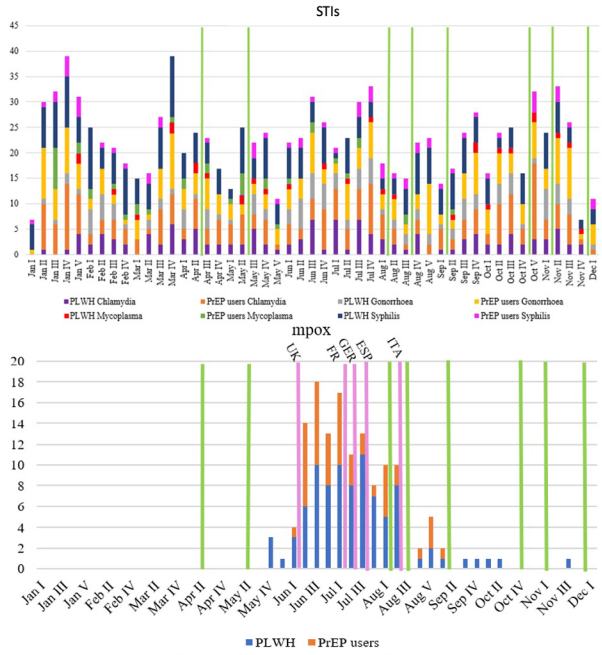

Figure 1. Cumulative STIs and mpox cases among MSM. Charts bars represent vaccination start (pink) and LGBTQI+ sex-related events (green; April: Revolver, Berlin; May: Maspalomas Pride, Grar Canaria; August: Circuit, Barcelona; August: XLsior, Mykonos; September: Folsom, Berlin; October: LaDemance, Brussels; November: Winter Pride, Gran Canaria; December: Snax, Berlin).

427 Mpox Vaccination Uptake Among MSM During the 2022 Epidemic: A Single-Center Retrospective Study

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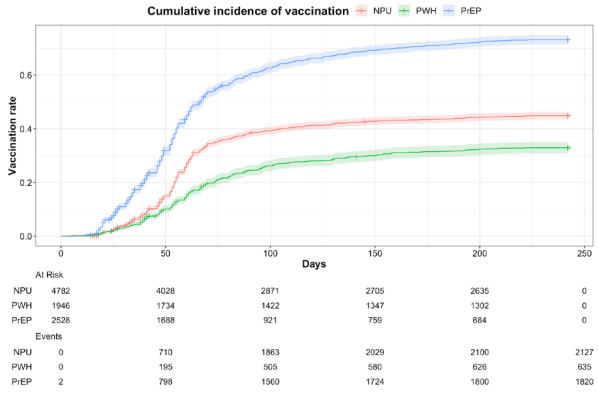
Background: During the 2022-2023 Mpox outbreak, 5010 cases were reported in France. Among them, an estimated 85% occurred in men who have sex with men (MSM). Smallpox vaccination was offered to at-risk populations in France, including MSM, starting July 2022. We sought to assess the vaccination uptake rate in MSM and the factors associated with vaccination uptake in different MSM risk-groups: people living with HIV (PWH), people who use pre-exposure HIV prophylaxis (PrEP) and other individuals (NPU, non-PrEP users).
Methods: A retrospective observational study was conducted in Lyon, France, enrolling MSM presenting at the sexual health clinics of the University Hospital between July 1st, 2022 and February 28th 2023. Data regarding HIV infection, PrEP use, Mpox infection and Mpox vaccination (first dose received) were collected from electronic medical records. All patients gave informed consent regarding vaccination and the use of their data for analysis.
Results: A total of 9256 MSM were enrolled, including 1946 PWH, 2528 PrEP users and 4782 NPU. The median age of each group was respectively 51, 34 and 29 years. The vaccination rate of all participants at the end of follow-up was 49.6%. Compared to NPU, it was significantly higher for PrEP users (72.2%) with a relative risk estimate of 1.62 (95%CI 1.56-1.69), and significantly lower for PWH (32.7%) with a relative risk estimate of 0.73 (95%CI 0.68-0.79). Of note, half of PrEP users were vaccinated by day 66 of the vaccination campaign. In multivariate cumulative risk analysis, HIV infection/PrEP use, age and chemsex were all independently correlated with vaccination uptake.
Conclusion: Our study demonstrates Mpox vaccination uptake in MSM during the 2022 outbreak in France was high, especially in PrEP users. This could be explained either by the closer follow-up of this group, or their proactive engagement in STI prevention strategies. In contrast, PWH, although regularly followed-up, were less receptive to the vaccination campaign. It is likely that sexual behavior of PWH, hence exposure risk, are noticeably different. Although vaccination is probably not the only explanation, these successful results mirror the sharp decrease of Mpox cases reported after August 2022 in France.



428 Pharmacokinetics of Tecovirimat in Persons With Mpox: Results From ACTG 5418

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Background: Tecovirimat is an FDA-approved oral antiviral medication for human smallpox and is being used widely for mpox treatment. The pharmacokinetics (PK) of tecovirimat has been assessed in animal models and healthy human volunteers, but data in people with mpox are limited.

Methods: The Study of Tecovirimat for mpox (STOMP/ACTG 5418, NCT05534984) is an ongoing international randomized (2:1) clinical trial of the efficacy of tecovirimat for mpox. STOMP includes an open-label arm of participants with severe disease, immunosuppression, pregnancy and those aged <18 years, which is the focus of this report. Intensive PK assessments were conducted in a subset of participants on study day 8 (steady-state) following an observed dose of tecovirimat with a meal. All received 600 mg twice daily. Blood samples were collected pre-dose (time 0), 1, 2, 3, 4, 6, 8, and 10 hours post-dose. Tecovirimat concentrations were quantified by LC-MS/MS. PK were analyzed via noncompartmental analysis with predicted AUC0-12h and C12h determined from the terminal phase of the post-dose curve. AUC0-12h and C12h were compared to predicted exposures in fed healthy adults receiving the same doses (data from the U.S. FDA) and mean Cmin values associated with survival and clinical/virologic response in non-human primates (NHP) (minimum and maximum effective doses of 3 and 10 mg/kg/day, respectively).

Results: PK data were generated in 13 participants (11 non-pregnant adults; 1 adolescent; 1 pregnant female adult). Of 12 non-pregnant participants, 11 were male, 5 were Black; 7 were persons with HIV of whom 4 had HIV-1 RNA <200 copies/mL, 2 were not on ART, and 2/6 had CD4 counts <200 cells/mm^3; median (range) age and weight were 35 (<18-51) years and 77 (57-103) kg, respectively. Comparable PK was observed between non-pregnant participants and the pregnant participant and by HIV status (Table). Median tecovirimat AUC0-12h and C12h in non-pregnant adults were 38% and 72% lower than 50th percentile exposures in healthy adults. Despite lower tecovirimat exposures, C12h across all participants exceeded mean effective Cmin values in NHPs receiving 3 and 10 mg/kg/day.

Conclusion: Persons with mpox had lower tecovirimat exposures vs. healthy adults, although concentrations remained above the minimally effective Cmin in NHPs. Future work will explore factors associated with tecovirimat PK and assess relationships with clinical and virologic outcomes to evaluate the clinical relevance of these PK differences.

Table. Tecovirimat PK in Open-Label Arm

PK Parameter	Pregnant (n=1)	Non-Pregnant			Healthy Adults[a]	Non-Pregnant vs. Healthy Adults[b]
		With HIV (n=7)	Without HIV (n=5)	Total (n=12)		
$AUC_{0\text{-}12h}$ (mg*h/L)[c]	9.23	9.13 (6.95, 13.1)	10.9 (10.7, 12.5)	10.7 (6.95, 13.1)	17.33	0.62
C_{max} (mg/L)	1.42	1.75 (0.97, 2.84)	1.78 (1.44, 1.83)	1.77 (0.97, 2.84)	1.93	0.92
C_{12h} (mg/L)[c]	0.18	0.24 (0.19, 0.43)	0.30 (0.22, 0.36)	0.26 (0.19, 0.43)	0.94	0.28
Ratio of A5418 C_{12h} / NHP C_{min}						
NHP 3 mg/kg/day C_{min} (0.037 mg/L) (n=6)	4.86	6.5 (5.0, 11.7)	8.07 (6.03, 9.76)	7.13 (5.01, 11.7)	25.4	--
NHP 10 mg/kg/day C_{min} (0.169 mg/L) (n=6)	1.07	1.43 (1.10, 2.55)	1.77 (1.32, 2.14)	1.56 (1.10, 2.55)	5.56	--

Data presented as median (minimum, maximum) [a]50th percentile exposures from 19,900 simulations in humans under fed conditions [b]Ratio of median values [c]Reported in 5 with HIV, 4 without HIV.

429 Evaluation of a Protocol for Managing Cyclosporine and Nirmatrelvir/Ritonavir Drug- Drug Interaction

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Background: Morbidity and mortality of COVID-19 is higher in immunocompromised people including kidney transplant recipients (KTR). Nirmatrelvir/ritonavir (NRMr) interacts with many medications, in particular calcineurin inhibitors (CNI). Limited evidence exists for reinitiating CNIs post-NRMr. We created a protocol to manage the NRMr-cyclosporine (CsA) interaction. This study aims to describe the application of the protocol and deviations, evaluate its impact on cyclosporine levels, and analyze safety outcomes.

Methods: This is a retrospective study between May 2022 and Nov 2023. As per protocol, CsA dose was reduced by 80% at NRMr start and up to 2 days post-NRMr. CsA levels were drawn 2 days post-NRMr. If the 1st level was sub/therapeutic, CsA was resumed at 100% and level repeated 1 week later. If supratherapeutic, the dose reduction was maintained for another 2 days, then reinitiated at 100% pre-NRMr dose. Acute kidney injury (AKI), hospitalization and death were collected through 30-days post-NRMr therapy.

Results: Forty-two KTR were identified, of which 35 started NRMr and met eligibility criteria and were analyzed. Nine KTR did not follow the protocol instructions. At baseline, 83% of patients were in therapeutic range, with a mean CsA level of 258 µg/L. Median dose reduction at initiation of NRMr was 80% [IQR 76-83]. At the first follow-up (FU) 2 days post-NRMr, the average CsA level was higher by 23 µg/L (P=0.51). There was a greater proportion of patients with sub and supratherapeutic levels compared to baseline (20% vs 9% and 31% vs 9%). Nonadherence to the protocol was observed in 5/18 levels outside therapeutic range. At the second FU, there was a correction of sub and supratherapeutic levels (14% and 14%) as patients shifted to therapeutic range. Of the 16 patients requiring additional monitoring, levels returned to baseline values within 30 days. Two KTR experienced AKI for unrelated reasons to COVID-19 treatment (unstable atrial flutter, gastroenteritis) and one that resolved with increased fluid intake. There were 4 hospitalizations, but none related to the initial COVID-19 treatment management. There was no graft rejection or death 30 days post-NRMr.

Conclusion: Though CsA levels outside therapeutic range were common immediately post-NRMr treatment, levels were restored rapidly. No clinically relevant safety events related to NRMr treatment occurred within the 30-days. Adherence to the protocol is crucial.

	Baseline N=35	1st FU N=35	2nd FU N=35	3rd FU N=16
Median time [IQR], days	ref	2 [1,2]	9 [8,12]	18 [12,23]
Serum level change, µg/L Median [IQR]	ref	26 [-43,96]	5 [-19, 39]	-3.5 [-21, 76.5]
Subtherapeutic, #	3	7	5	2
Therapeutic, #	29	17	25	11
Supratherapeutic, #	3	11	5	3

FU: Follow up, IQR: Interquartile range

430 Disparities in Mpox Vaccination Among Cis Men and Trans Persons With HIV in Los Angeles County

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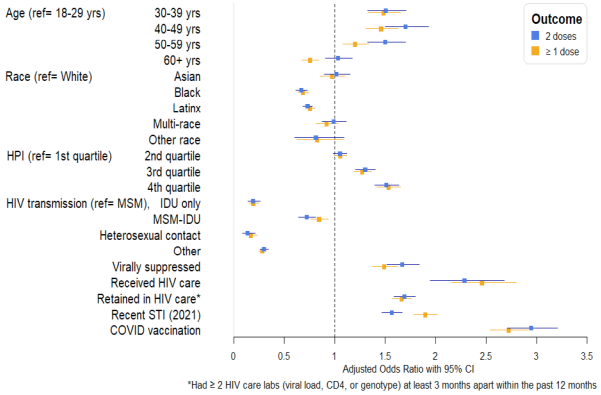
Background: The CDC recommends the 2-dose JYNNEOS vaccine for protection against mpox for people with HIV (PWH) due to a high proportion of US mpox cases occurring in PWH and an increased risk of severe mpox disease among those with uncontrolled HIV infection. In Los Angeles County (LAC), 45% of mpox cases have occurred in PWH, primarily among cis-men and transgender persons. We aim to identify demographic and health-related predictors of JYNNEOS vaccination among cis-men and transgender PWH in LAC.
Methods: Cis-men and transgender adults aged ≥ 18 years with diagnosed HIV in LAC were included. Unvaccinated PWH with a prior mpox diagnosis were excluded. Potential predictors of JYNNEOS vaccination included: demographics, viral suppression, CD4 count, HIV transmission mode, receipt of HIV care (past 12 months), retention in HIV care*, recent STI (in 2021), and ≥ 1 prior COVID-19 vaccination (proxy for individual vaccine confidence). Fully nonproportional odds models were used to measure the associations between predictor variables and the outcome (2, 1 or 0 doses of JYNNEOS).
Results: Among 37,613 cis-men or transgender PWH, 8,757 (23.3%) were fully vaccinated, 3,473 (9.2%) had received 1 dose, and 25,383 (67.5%) were unvaccinated. Disparities by age group, race/ethnicity, and healthy places index (HPI) were observed. Full vaccination was lowest among PWH who were aged 18-29 (14.5% vs 26.2% aged 40-49), Black (17% vs 30.3% Asian and 28.8% White), or living in zip codes in the lowest quartile of HPI (20% vs 31% highest). Prior COVID vaccination (adjusted odds ratio [aOR] 2.9, confidence interval [CI] 2.7-3.2), receipt of HIV care in the past 12 months (aOR 2.3, CI 1.9-2.7), recent STI diagnosis (aOR 1.6, CI 1.5- 1.7), and living in the highest HPI quartile (aOR 1.5, CI 1.4-1.6) were significant predictors of JYNNEOS vaccination (Figure). Black (aOR = 0.67, CI: 0.62-0.73) and Latinx (aOR = 0.73, CI: 0.68-0.78) PWH were less likely to be fully vaccinated against mpox compared to White PWH.
Conclusion: Patients engaged in HIV care or who had a recent STI diagnosis were significantly more likely to receive the JYNNEOS vaccine; this may be attributable to vaccine receipt during an HIV/STI visit or underlying individual healthcare seeking behaviors. These findings also highlight the importance of tailoring vaccine outreach efforts to improve vaccine confidence and access, especially for younger individuals, underserved neighborhoods, and Black and Latinx communities.

Figure. Adjusted odds ratios of vaccination with JYNNEOS among cis-gender men and trans-persons with HIV.



*Had ≥ 2 HIV care labs (viral load, CD4, or genotype) at least 3 months apart within the past 12 months

431 A Novel Non-Invasive Approach to Sample Female Genital Tract Immune Cell Populations

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Background: An increased understanding of immune cell populations in the female genital tract (FGT) is essential for efforts to decrease risk of HIV and other sexually transmitted infections and to develop vaccines that induce mucosal responses. To-date, FGT immune cell collection has utilized techniques that require a healthcare provider and a speculum exam, creating a barrier to participation and limiting longitudinal studies. To overcome these challenges, we developed a novel method to collect leukocytes from cervicovaginal fluid (CVF) utilizing Softdiscs.
Methods: Non-menstruating persons with vaginas of reproductive age were asked to self-insert disposable Softdiscs and wear for up to 4 hours on three sequential days. After self-retrieval, CVF was removed from the disk via washing, followed by treatment with DTT to thin mucus, passage through a cell strainer, and cryopreservation. Cells were subsequently thawed, enriched for CD45+ cells using magnetic cell separation, and stained with a 28-color antibody panel focused on T cell phenotyping.
Results: Across 15 samples (5 participants x 3 days) we recovered high numbers of CD45+ cells (median: 6,233; range: 212-57,703), CD3+ T cells (median: 1,182; range: 12-11,554), and CD19+ B cells (median: 1,072, range: 8-4,690). Of CD3+ T cells, frequencies ranged from 37-87% for CD4+ T cells and 7-55% for CD8+ T cells. Within CD4s there were both regulatory (Tregs) and conventional subsets and within CD8s both tissue resident (TRM) and migratory populations. To demonstrate reproducibility, we compared populations across days and found that within individuals the distribution was strongly conserved. For example, comparing the first and last day of sampling, the frequency of CD4s (R2=0.78, p=0.12) and CD8s (R2=0.90, p=0.04) of CD3s, Tregs of CD4s (R2=0.75, p=0.15), and TRM of CD8s (R2=0.93, p=0.02) were all correlated. Of note, while population distributions were strongly conserved within individuals, they were unique across individuals (Fig 1).
Conclusion: Collection of CVF from Softdiscs represents a novel, non-invasive approach to study FGT immune cell populations, including both tissue resident and migratory memory T cell subsets. This approach yielded high quality immune cells which could be cryopreserved and had reproducible population structure and phenotype across multiple days. This self-collected sampling will empower a more diverse population of individuals to participate in future studies of FGT immunity.

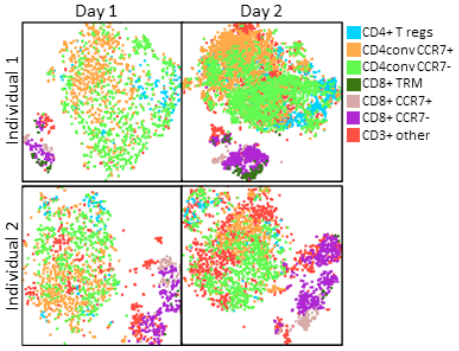

Figure 1. Distribution of FGT T cell populations varies across individuals but is preserved within individuals. Example t-SNE plots of FGT T cell populations from two individuals sampled on two days. T cell subset distribution was highly conserved within individuals but varied across individuals.

432 Identification of Innate Lymphoid Cell Subsets in the Human Female Genital Tract That Respond to HIV

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Background: Women acquire HIV mainly through sexual contact. Identification of innate immune mechanisms that protect against infection in the female genital tract (FGT) will enable strategies to prevent HIV acquisition. Innate lymphoid cells (ILCs) are tissue-resident cells specialized in cytokine secretion that provide mucosal protection against infections in mice. However, human ILCs remain poorly characterized and their potential role in HIV prevention is unknown.
Methods: Human hysterectomies (n=35) were enzymatically digested to generate mixed-cell suspensions from endometrium, endocervix, and ectocervix. ILC phenotype and function was assessed with high-dimensional spectral flow cytometry for surface and intracellular molecules (22-parameters). To define ILC-mediated anti- HIV responses, genital mixed-cell suspensions were stimulated with HIV for 30 minutes in vitro, and cytokine content (IL-22 and IFNγ) and degranulation (CD107a) were analyzed by flow cytometry.

Results: Genital ILCs represented <5% of mononuclear immune cells. Subset distribution was compartmentalized, with ILC3s predominant in the endometrium (63% of ILCs), and ILC1s in the ectocervix (48%). In the absence of stimulation, ILC1s constitutively produced IFNγ (14%), while ILC3s produced IL-22 (46%), important for barrier maintenance. We identified two ILC3 subsets at steady state, CCR6+CD103+ and CCR6+CD103-, with the highest IL-22 content (63%; p=0.003), and highest degranulation (CD107a, 10.4%; p=0.002), respectively. Genital ILCs expressed HIV coreceptors (CCR5, CXCR4), but CD4 expression was restricted to ILC1s (p<0.0001). In vitro HIV stimulation increased the percentage of CD107a+ ILC1s (p=0.03), concomitant with a decrease in intracellular IFNγ (p=0.02), indicating IFNγ release and degranulation in response to HIV. For ILC3s, in vitro HIV stimulation induced a significant decrease in the percentage of CCR6+IL22+ cells, regardless of CD103 expression (p=0.03), while CD107a+ cells specifically increased in the CCR6+CD103- population (p=0.06), indicating a response to HIV through IL-22 release.
Conclusion: Our findings demonstrate that ILCs reside in the FGT, produce antiviral cytokines under steady-state, and ILC1s and CCR6+CD103- ILC3s degranulate in response to HIV stimulation, indicating a major role in the maintenance of an antiviral environment and the ability to mount an antiviral response. Our investigation suggests ILCs could represent a novel mechanism for protection against HIV acquisition in the FGT.

433 The Cervicovaginal Neutrophil Protein CRISP3 Is a Correlate of HIV Protection

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Background: Identifying immune correlates of HIV protection in the female genital tract is important for HIV prevention efforts. We performed discovery proteomics to identify vaginal mucosal immune predictors of HIV acquisition from 1190 women enrolled in two HIV prevention trials.
Methods: We employed a case-control study design including women in the VOICE (MTN-003) trial as the discovery cohort (121 cases, 381 controls) and CAPRISA 004 trial as the validation cohort (62 cases, 626 controls). Mucosal swab and lavage samples from the last seronegative timepoint of HIV cases, and at a comparable time point in controls who remained uninfected during the trials, were analyzed by tandem mass spectrometry, identifying 1051 human proteins. HIV risk associations were determined using logistic regression and machine learning approaches. Biomarker-immune cell associations were studied using cervical samples collected from healthy donors.
Results: LASSO regression identified CRISP3 as the strongest correlate of HIV protection in both cohorts (P<0.0001), where above median levels associated with a 3.5-fold reduced risk of HIV acquisition (VOICE: OR=0.28, 95% CI=0.18-0.45, P=3.44E-9; CAPRISA004: OR=0.31, 95% CI=0.16-0.57, P=5.55E-5), and 5-fold when comparing highest vs. lowest tertiles (OR = 0.19960, 95% CI=0.09-0.41, P=6.38E-07). CRISP3 was protective in both Lactobacillus and non-Lactobacillus dominant vaginal microbiomes (OR=0.39, 95% CI=0.19-0.75, P=2.36E-3; OR=0.23,95%CI=0.12-0.43, P=4.11E-7, respectively). Similar estimates for CRISP3 and HIV were obtained in models adjusting for study arm, sexual behavior, and concurrent STIs. Using fluorescence immunohistochemistry, CRISP3 localized to the basal layer of the cervical epithelium. By flow cytometry, CRISP3 was highly expressed intracellularly in cervical neutrophils (CD66b+), including activated subsets (CD11b+CD62L-/dim). Mucosal CRISP3 levels were negatively associated with activated cervical CD4+ T cells (CD3+CD4+CD38+HLA-DR+, *r*=-0.36, P=0.03), and higher CRISP3 expression was associated with innate immune and antiviral molecular pathways (P<0.001).
Conclusion: CRISP3 is a mucosal neutrophil protein associated with lower risk of HIV infection, which may be mediated by reduced HIV target cell activation and innate antiviral immunity. More research on CRISP3 function and associated neutrophil phenotypes in the context of HIV prevention trials and strategies is warranted.

434 CD101 Variants Are Associated With Lower Levels of Genital HIV-Inhibiting and Tissue Repair Factors

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Background: We previously demonstrated that Africans with variants in the Ig-like domain of CD101 are associated with an increased risk of heterosexually acquired HIV infection. Recognizing that CD101 has known immunoregulatory functions, we had shown that these CD101 Ig-like variants are associated with reduced regulatory T cell function and increased proinflammatory T cell responses in the circulation. We had not previously examined the effects of these variants on the genital mucosa - the portal of entry for sexually acquired HIV. Here, we explore associations between CD101 Ig-like variants and the level of soluble immune factors in genital secretions that may suggest a mechanism for how these variants impact HIV risk.
Methods: We enrolled women without HIV in HIV serodifferent heterosexual couples (with a male partner with HIV, N=44) or HIV seroconcordant negative couples (N=296) in Thika, Kenya consenting to collection of blood and genital samples. We used a custom Open Array (Thermo Fisher) to genotype ten candidate CD101 variants including six Ig-like variants (minor allele frequencies 0.007 – 0.11) and a Luminex assay (Eve Technologies) to measure 71 cytokines and chemokines in enrollment softcup and serum samples from 245 women. We used multivariable linear regression (controlling for frequency of condomless sex, for softcup) to compare the $\log_{10}$ cytokine and chemokine level in genital secretions or serum from women having one or more Ig-like variants (N=60/245=24%) to women with none of the ten candidate CD101 variants (N=59).
Results: Between these two groups, median age 29 (18-54) years, women with one or more vs no CD101 Ig-like variants were associated with a significant reduction in levels of LIF (β= -0.41, p=0.001), G-CSF (β= -0.46, p=0.006), as well as IL-1a, PDGF-AB/BB, RANTES, Eotaxin-2, Eotaxin-3, IL-16, IL-33, and TPO (p=0.025– 0.044) in genital softcup samples. In contrast, we found no significant association of CD101 Ig-like variants with any factors in serum.
Conclusion: Our exploratory findings suggest that CD101 Ig-like variants have immunoregulatory impact in the genital mucosa. Notably, RANTES, IL-16, and LIF have demonstrated HIV inhibitory activity. The reduction in these factors observed in genital secretions associated with CD101 Ig-like variants could underlie increased HIV infection risk. Additionally, G-CSF, PDGF-AB/BB, IL-33, and LIF facilitate tissue homeostasis and repair, so reduced levels could compromise mucosal tissue barrier and facilitate pathogen entry.

435 Synergistic Effects of HIV, HPV, and Polyomaviruses on Interferon Response in Male Anal Mucosa

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Background: Viral persistence is a crucial prerequisite for high-risk (HR) HPV-associated tumor growth, such as anal squamous cell carcinoma (SCC). Men living with HIV (MLWH) are more likely to be co-infected with HPV. Moreover, HIV may alter epithelial integrity, thereby favoring not only HPV but also Polyomaviruses (HPyVs) infections in basal cells, where they dysregulate cell division and local immunity. Indeed, HPyVs have garnered interest due to their carcinogenic potential and their possible presence in the anal mucosa, which could promote transmission through sexual intercourse. To explore the innate response of the anal mucosa in relation to HPV and HPyVs infections, we analyzed the expression of type I/III interferon (IFN)-related genes in anal cells from MLWH and non-MLWH.
Methods: Sixty-one anal canal brushing samples were collected from men attending a proctology clinic. Detection of HPV and HPyVs [i. Merkel cell PyV (MCPyV), ii. JCPyV, iii. BKPyV] DNA was performed by PCR, and genotyping by sequencing. From purified cellular RNA, transcripts of genes encoding IFN-I (α, β), IFN-III (λ1-3), and TLR9 were measured by quantitative RT-PCR assays and normalized to the housekeeping GUS gene.
Results: Thirty-five MLWH (mean age 47.7 years, SD 11.4), on long-term ART, and twenty-six controls (mean age 47.4 years, SD 15.3) were enrolled in this

study. Out of the 61 men, 47 were HPV-positive, while 24 were HPyV-positive, with 87.5% specifically testing positive for MCPyV. HPV infections were associated with lower IFN-I mRNA levels compared to the HPV-negative group [Mann-Whitney (MW) test, $p<0.05$]. Notably, IFN-α levels decreased in HPV/HIV co-infected patients [Jonckheere-Terpstra test (JT), $p<0.006$]. Furthermore, HPV/HIV co-infections and the presence of Low-grade Squamous Intraepithelial Lesion (LSIL) were associated with lower expression of TLR9 (JT, $p<0.026$). When comparing HPV/HIV-positive and HPV/HPyVs positive men, IFN-α showed lower mRNA levels in the HPV/HIV group (MW, $p<0.037$), while IFN-λ2 was more produced in the HPV/HPyVs group (MW, $p<0.008$).

Conclusion: The findings highlight the potential synergy between HIV and HPV infections in compromising mucosal innate immunity and promoting viral co-infections, such as HPyVs, in the anal mucosa. Alterations in IFN and TLR-9 genes provide insights into complex mechanisms behind viral persistence, enhancing the understanding of innate immunity, viral infections, and HPV-related malignancies, with implications for future research and therapies.

436 Circulating Acyl-CoA-Binding Protein Abates T-Cell Function in People Living With HIV

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Background: Autophagy, a cytosolic-structure degradation pathway producing energy, allows efficient anti- HIV T-cell responses. Autophagy enables IL21 production in anti-HIV CD4 T-cells, which in turn stimulates lipophagy and enhances CD8 T-cell anti-HIV responses. Extracellular Acyl-CoA-Binding Protein (ACBP) inhibits autophagy, tricarboxylic acid (TCA) cycle and oxidative phosphorylation in mouse models. Herein, we assessed the levels of circulating ACBP and its influence on T-cell function in people living with HIV (PLWH) on antiretroviral therapy (ART).

Methods: Plasma ACBP and cytokines were quantified by ELISA in 50 PLWH on effective ART (mean duration 14.7 years) and 30 controls with similar age. Metabolomic analyses were performed on serum samples by GC-MS (10 participants with high and low ACBP). In vitro, recombinant ACBP (recACBP) was added at increasing concentration up to 10µg/mL on PBMCs from PLWH on ART and controls, T-cell responses were assessed by flow cytometry. Intracellular LC3B was visualized by microscopy.

Results: ACBP levels were higher in PLWH on ART compared to controls (median 127.5 vs 78.1 ng/mL, $p=0.03$), independently of age and sex. In ART-treated PLWH, plasma ACBP levels were neither associated with CD4 nor CD8 T-cell counts, however they correlated with levels of growth factors (EGF, G-CSF, GRO), pro- inflammatory cytokines (IFNα2, IFNγ, IL1β) and homeostatic factors (IL7 and IL15) ($r>0.3$, $p<0.05$ for all comparisons). Conversely, ACBP levels were inversely associated with plasma IL21 levels ($r=-0.54$, $p<0.01$). PLWH with high ACBP had higher serum levels of TCA intermediates glutamate (2-fold, $p=0.02$) and α- ketoglutarate (1.5-fold, $p=0.09$), respectively. We added recACBP to PBMCs stimulated with either anti-CD3 antibodies or HIV Gag, Nef and Env peptides for 16 h, and observed a decrease in IFNγ, IL2 and TNFα production in CD4 and CD8 T-cells ($p<0.03$ for all). Upon anti-CD3 stimulation, IL17A and IL21 production were also decreased in CD4 T-cells while IL10 levels remained unaffected. RecACBP decreased intracellular levels of the autophagy marker LC3B without affecting cell viability.

Conclusion: Higher plasma ACBP levels in PLWH on ART were associated with inflammation, unfit metabolism, and markers of T-cell dysfunction. Our findings indicate that circulating ACBP directly abates autophagy and anti-HIV T-cell functions, compelling the development of circulating ACBP inhibitors aiming at improving anti-HIV T-cell responses in PLWH, towards an HIV cure.

437 Immunological Non-Responders Have CD4+ Immunosenescense and Impaired Lymphocyte Cytokine Production

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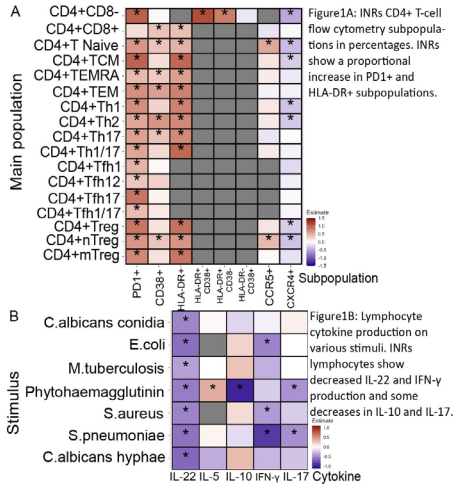
Background: Immunological non-responders (INRs) are people living with HIV (PLHIV) that fail to restore CD4+ T-cell counts despite suppressive antiretroviral therapy (ART). INRs are at a higher risk for non-HIV related mortality and morbidity, such as non-aids malignancies. IL-2 induced CD4+ T-cell count increases did not effect clinical endpoints in previous trials, indicating a persistent qualitative defect despite increases in absolute CD4 counts.

Methods: PLHIV with CD42 years of suppressive ART were defined as INRs, and were compared to immunological responders (IRs) with CD4>500 during ART. The 2000HIV study (clinicaltrials NTC03994835) enrolled 1895 PLHIV, which were divided into a discovery and a validation cohort. We used logistic, and rank based regression to analyze clinical data, extensive flow cytometry panels for monocytes, DC-, NK-, B-, CD4+T- and CD8+T- cells, and monocyte, and lymphocyte cytokine production capacity after stimulation with various stimuli in INRs compared to IRs. Analyses were corrected for sex at birth and age (all), seasonality (flow cytometry), and current monocyte/lymphocyte count (cytokine production).

Results: The discovery cohort consisted of 62 INRs and 1224 IRs, the validation cohort of 26 INRs and 243 IRs. INRs were older, had more advanced HIV disease before starting ART and more often had a history of non- AIDS related malignancy. INRs had lower absolute CD4+ T-cells in all subsets analyzed. Activated and immunosenescent related subpopulations (HLA-DR+, CD38+; PD1+) were proportionally increased throughout CD4+ T-cell subsets (Figure 1A). CD8+ cells had proportionally increased HLD-DR+ subsets. Results were confirmed in the validation cohort. Monocyte and granulocyte phenotypes were not different between INRs and IRs in both cohorts. Moreover, INRs lymphocytes produced less IL-22 and IFN-γ in response to most stimuli, and less IL-10 and IL-17 to some stimuli (Figure 1B) indicating impaired cytokine production capacity. In contrast, monocyte cytokine production was comparable between INRs and IRs. Findings in the validation cohort were consistent. Proportional CD4+CD38+HLA-DR+ and CD4+PD1+ subsets were inversely correlated to lymphocyte cytokine production.

Conclusion: We show an increase in immunosenescence CD4+ subsets and impaired lymphocyte function in INRs in a large cohort of PLHIV. These qualitative immune defects may therefore contribute to the observed increased morbidity in INRs.



438 Phenotype of Gamma-Delta T-Cells in Acute HIV-1 Infection Predict Neutralization Breadth

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Background: New HIV vaccine approaches are focused on eliciting broadly neutralizing antibodies (bNABs). Leveraging the U.S. Military HIV Research Program's (MHRP) therapy naïve RV217 cohort comprised of study participants monitored for HIV acquisition and progression, we have previously shown that B cell engagement and activation within the first 14-43 days of viremia are predictive of bNAB development. We therefore hypothesized that innate immune cells might provide signals to B cells during acute HIV-1 (AHI) infection resulting in neutralization breadth years later. This study characterized early innate immune responses in RV217 participants previously investigated for bNAB development.

Methods: Flow cytometry was performed on PBMC samples from 22 RV217 study participants previously studied for neutralization breadth development. Four timepoints per participant were utilized: pre-infection, days 14-25 post-infection (peak viral load), days 30-60 post infection (viral set point), and >365 days post-infection (chronic infection). Data was analyzed utilizing global heat map analysis, univariate summary of marker analysis, longitudinal analysis of markers of interest, logistic regression analysis, cumulative incidence curves analysis, and area under receiver operating characteristic curve analysis.

Results: Flow cytometry analysis showed significant differences in gamma-delta (γδ) T cell surface marker expression in participants that developed neutralization breadth and those that did not. Levels of CD16 on γδ1 T cells were found to be significantly higher in broad neutralizers at set point viral load while levels of CD57 on γδ2 T cells were found to be significantly higher in broad neutralizers at both pre-infection and set point viral load. CD16 and CD57 are two markers associated with effector functions suggesting that more differentiated γδ T cells may contribute to the development of bNabs. Further analysis of these results revealed that these specific markers are significantly associated with the probability of bNAb development and are predictive of neutralization breadth accuracy at almost 80%. Our results identify CD16+ γδ1 T cells and CD57+ γδ2 T as potential key populations involved in the neutralization breadth development.

Conclusion: γδ T cells may play an important role in bNAB development during AHI and these results could inform HIV vaccine design.

439 NK Cells During Acute HIV Infection Are Associated With Slow Disease Progression in Subtype A

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Background: Understanding immune responses linked with viral control during early HIV-1 infection is critical to develop new prophylactic and therapeutic strategies. HIV-1 subtypes impact disease outcomes, but their association with diverse immune responses during acute HIV-1 infection (AHI) is unclear. Natural killer (NK) cells contribute to HIV-1 control and may influence the pathogenesis of AHI. Using longitudinal samples collected during and after peak HIV-1 viral load (VL) in a prospective unique cohort of ART-naïve individuals, we studied evolving NK cell responses in patients with different HIV-1 subtypes in relation to disease progression

Methods: Participants with subtype A (n=28) and non-A subtype (n=17 subtype C and n=7 subtype D) were recruited from Kenya, Rwanda, Zambia, and Uganda between 2006-2011 under "IAVI Protocol C". Samples were collected at two weeks (median=18 days), 1-month (median= 32 days), and 3-month (median=91 days) post-HIV-1 infection. Multiparameter flow cytometry was used for phenotypic characterisation. ADCC responses were determined against Raji cells. Soluble markers were evaluated using multiplexed assays

Results: AHI induced expansion of NK cell subset with adaptive/memory features, as early as two weeks post- infection, increasing in magnitude after resolution of peak VL. This adaptive NK cell signature was delineated by lower expression of the signaling molecule FcεRγ and higher expression of the activating receptors NKG2C and CD2. The kinetics of NK cell responses differed based on the infecting HIV-1 subtype, with patients with subtype A exhibiting a higher magnitude of adaptive NK cells than those with non-A subtype infection (p=0.036). A stronger innate immune response induced by subtype A, including IL-15 (p=0.021) and IL-12 (p=0.009), correlated with the enrichment of adaptive NK cells. This early increase in adaptive NK cells was associated with enhanced ADCC (p=0.002) and correlated with higher levels of CD8+ T-cell activation during AHI (r=0.621, p=0.015).Notably higher frequencies of adaptive NK cells during the first month of infection were associated with future viral control in patients who maintained a persistently undetectable or low viral load (<10,000 copies/ml) up to six years post-infection

Conclusion: These data provide insights into the beneficial role of adaptive NK cells during AHI, revealing previously unappreciated diversity of NK cell responses to different HIV-1 subtypes, thereby informing strategies toward NK-cell-directed therapies.

440 PWH on ART and Tyrosine Kinase Inhibitors Show High Cytotoxic Activity Against HIV- 1–Infected Cells

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Background: We evaluated if PWH with chronic myeloid leukemia (CML) on antiretrovirals (ART) and tyrosine kinase inhibitors (TKI) had cell populations with high antiviral capacity that may explain the reduced reservoir size observed in these individuals.

Methods: Blood samples were obtained from 6 PWH with CML on ART and TKI (n=3 imatinib; n=3 dasatinib) and 18 PWH on ART recruited as controls. Cell immunophenotyping was performed by flow cytometry. Cytotoxic activity was determined using NK-specific target cells K562 and HIV-1-infected TZM-bl. Cytokine release was measured after stimulation with HIV-1 peptide pool. Statistical analysis was performed with Mann-Whitney or unpaired t-test.

Results: 1)Most participants were male (100% PWH on ART+TKI and 73% of controls). Median age was 53 (IQR 42-51) and 54 years-old (IQR 47-62), respectively. Age at HIV+ diagnosis was 39 (IQR 32-45) and 31 years-old (IQR 25-36); age at CML diagnosis was 47 years-old (42-63). Time with HIV-1 infection was 22 (IQR 15-30) and 23 years (15-30). Nadir CD4 and CD4 count was 97 (IQR 63-382) and 370 cells/µl (186-843) in PWH on ART+TKI and 292 (IQR 176-385) and 983 cells/µl (IQR 798-1174) in controls. CD4/CD8 was 0.6 (IQR 0.3-1.5) and 1.0 (IQR 0.7-1.5), respectively. PWH on ART+TKI showed CML molecular response of 5.0 log (IQR 4.1-5.1) and they were on imatinib or dasatinib for median 3.3 years (IQR 1.7-9.6). All participants were on standard ART. 2)PBMCs from PWH on ART+TKI showed higher cytotoxicity against NK-specific (p=0.0050) and HIV-1-infected target cells (p=0.0205) than controls. 3)PWH on ART+TKI had higher levels of NK cells (p=0.0179) with higher expression of maturation/memory marker CD57. 4)PWH on ART+TKI showed increased levels of CD8 (p=0.0325) with higher degranulation capacity (CD107a+; p=0.0084) and increased release of GZB (p=0.0002). No changes were observed in the release of IFNγ. 5)CD8 from PWH on ART+TKI released lower levels of TNFα (p=0.0469), which is essential in HIV-1-associated chronic inflammation. 6)No differences were found in the expression of immunosenescence/exhaustion markers in CD4 and CD8 except for KLRG1 that was increased in PWH on ART+TKI (p=0.0176 and p<0.0001, respectively).

Conclusion: PWH on ART+TKI show low HIV-1 reservoir size, which may be partly related to higher levels of cytotoxic cells with antiviral activity. These cell populations may have been stimulated by the presence of cancerous cells, so these results have to be confirmed in clinical trials with PWH without CML.

441 A Skewed NK Cell Repertoire Persists in People With HIV-1 Despite Long-Term ART

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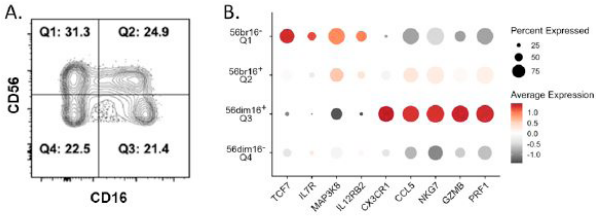
Background: HIV-1 infection can greatly impact the NK cell phenotypic and functional repertoire. This is highlighted by the expansion of a rare population of FcRγ−NK cells exhibiting adaptive immune characteristics in people with HIV-1 (PWH). While current antiretroviral therapy (ART) effectively controls HIV-1 viremia and disease progression, its impact on HIV-associated NK cell abnormalities remains unclear.

Methods: We performed a 4-year longitudinal analysis characterizing conventional and memory-like NK cells from PWH (n=60) participating in the AIDS Clinical Trials Group (ACTG) A5321 study, all of whom initiated ART in ACTG trials during chronic infection and had well-documented consistent HIV-1 suppression. Peripheral blood mononuclear cells collected at 4 weeks, 1 year, and 4 years post-initiation of ART were characterized. The phenotypic and functional profiles of NK cells, as well as frequencies of FcRγ−NK cells, were determined by flow cytometry analysis at baseline and following a 24h exposure to rhIL-18 (500 ng/ml) and rhIL-12p70 (50 ng/ml). Plasma CMV/EBV IgG antibody titers were measured by ELISA, and CMV/EBV viremia was determined by real-time qPCR. The BD Rhapsody™ Express System was used for single-cell multiomic analysis.

Results: Throughout the first 4 years of ART, a skewed repertoire of highly specialized antibody responsive but rhIL-18/IL-12 unresponsive FcRγ− memory-like NK cells persisted. This was accompanied by an increase in both CD57 and KLRG1 expression and a decrease in NKp46 within the total NK cell population, indicative of a progressive differentiation toward senescence. These characteristics were linked to increasing antibody titers to CMV, with CMV viremia detected in 35% and 29% of PWH at years 1 and 4 of ART. Interestingly, 40% of PWH displayed an atypical NK cell subset distribution based on differential expression patterns of CD56 and CD16. Single-cell multiomic trajectory analysis (Figure) revealed that these abnormal subsets likely represent intermediate stages of NK-poiesis, a phenomenon partially corrected between 1 to 4 years of ART.

Conclusion: Our findings indicate that HIV-associated NK cell irregularities persist in PWH despite long-term, effective ART. This underscores the need to better understand the causative mechanisms contributing to these immune irregularities. The study also provides a rationale for exploiting in HIV remission trials the selectively expanded antibody responsive FcRγ−NK cells that are maintained in PWH during ART.



Multiomic trajectory analysis corroborates intermediate stages of NK-poesis in PWH. A) FACS plot illustrating presence of CD56bright/CD16+ (Q2) and CD56dim/CD16− (Q4) NK cells in a PWH at 1y on ART, representing intermediate developmental stages. **B)** Gene expression associated with NK cell development determined via scRNA-seq, grouped by CD56/CD16 Ab-seq labeling.

442 Trained Immunity in Monocytes Is Associated With Persistent Elite Controller Status

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Background: The protective role of trained innate immunity in various infections is well known, but its impact on HIV control has not been investigated. We hypothesized that trained monocytes, as induced by b-glucan, are crucial in orchestrating a beneficial antiviral immune response associated with long-term spontaneous HIV control.

Methods: 1895 people living with HIV, among which 114 HIV controllers (HIC) classified as Elite controller (EC), viremic controllers (VC) and transient controllers (TC), were included (2000HIV study - NTC03994835). First degree family members (FAM) of HIV controllers and non-HIV controllers (non-HIC) were part of the 2000HIV-trained study (NCT04968717). We analyzed multi-omics data consisting of: 1) cytokine/chemokine production upon stimulation, 2) circulating concentrations of b-glucans, 3) trained immunity induction through the exposure of monocytes to b-glucan and restimulation with LPS, 4) genome-wide association study (GWAS), 5) single-cell and bulk RNA seq expression in PBMCs, 6) epigenomic profile using H3K4me3 ChiP- and ATAC- seq.

Results: Monocytes of HIC and their FAM showed increased production of IL-1b, IL-6 and MCP-1 upon viral and bacterial stimulation compared to non-HIC and their FAM, respectively. Difference in monocytes responsiveness was stronger in ECs but not different between TCs and non-HIC. b-glucan induced trained immunity responses in all groups, yet upregulation of TNF and IL-6 production was highest in HIC and their FAM. Genetic data (GWAS) showed no link between SNPs associated with HIV control and monocyte responsiveness of HIC. Interestingly, HIC and their relatives displayed higher circulating concentrations of b- glucan, suggesting a trained phenotype in their monocytes. scRNA-seq demonstrated that monocytes of HIC displayed upregulation of type I IFN and antigen processing and presentation genes, as well as downregulation of genes associated with chronic inflammation and regulation of DNA transcription. Moreover, changes in gene expression levels and cytokine production of HIC, more prominently in EC, were sustained by changes in chromatin accessibility in innate immune genes, among which NF-kB and type I IFN were reported.

Conclusion: Monocyte responsiveness is increased in HIV controllers and their relatives, which is associated with trained immunity and related epigenetic regulation. These traits are stronger in EC compared to transient controllers, suggesting the importance of a trained program in monocytes in maintaining HIV control.

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443 Effective Elimination of HIV-1 Infected CD4+ T-Cells by NKG2C+ "Memory-Like" NK Mediated by Trail

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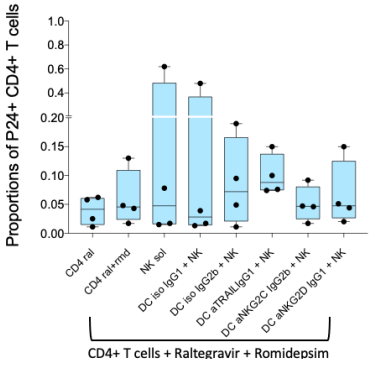
Background: "Memory-like" NKG2C+ Natural Killer (NK) cells from people with HIV-1 (PLWH) induced in the presence of dendritic cells (DC) are associated with a more effective elimination of autologous latently HIV- 1 infected CD4+ T cells. TRAIL is a TNF family receptor that can induce cytotoxic function. In this study, we evaluated the expression of this receptor and its potential role in function of memory-like NK cells eliminating HIV-1 infected CD4+ T cells.

Methods: NK cells were isolated from the blood of n=19 PLWH on ART and activated in the presence of autologous monocyte-derived DC pre-treated with nanoparticles loaded poly I:C (Nano-PIC DC). Expression of TRAIL in different memory and effector NK cell subsets defined by NKG2C vs CD57 expression was tested and associated with functional ability to kill HIV-1 infected cells. In addition, expression of the TRAIL ligand DR4 was also tested in PHA+IL-2 reactivated p24+ isolated CD4+ T cells. Finally, impact of anti-TRAIL, anti-NKG2C and anti-NKG2D or isotypic mAbs in NK cell-mediated elimination of p24+ HIV-1 infected CD4+ T cells from PLWH was tested in the presence of Romidepsin and Raltegravir.

Results: CD56dim and CD56- CD16+ NK cells from PLWH exposed to nano-PIC DC displayed increased levels of TRAIL compared to cells stimulated with control nano DC (p=0.0039). Induction of TRAIL expression was higher in CD56dim and CD56- CD16+ NK cells from PLWH characterized by effective elimination of infected CD4+ T cells at baseline (p=0.0076; p= 0.0133) and after activation with nano-PIC DC (p=0.0076; p= 0.0133), respectively. Notably, higher levels of TRAIL were enriched in NKG2C+ cells from good compared to bad PLWH responders after nano-DC stimulation. Moreover, TRAIL was enriched in NKG2C+ CD57- NK cells, compared to NK cells expressing CD57 (p=0.0391). In this regard, TRAIL negatively associated with expression of TIGIT in CD56dim CD16+ NK cells

(p=0.0125; r=-0.55). By the other hand, p24+ CD4+ T cells from PLWH showed higher expression of the TRAIL ligand DR4 than p24- CD4+ T cells. Finally, cytotoxic NK function against HIV-1 infected p24+ CD4+ T cells was abrogated in presence of an anti-TRAIL blocking mAbs, in contrast to anti- NKG2C and anti-NKG2D.

Conclusion: In conclusion, cytotoxic function of memory-like NKG2C+ CD57- NK cells associated with good functional elimination of HIV-1 reservoir CD4+ T cells is mediated by TRAIL.



444 Single-Cell, Multi-Omics Analysis of SIV-Specific CD8 T-Cells Across Multiple Anatomical Sites

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Background: CD8+ T cells contribute to the antiviral response in simian immunodeficiency virus (SIV) infection in nonhuman primates. CD8+ T cells recognize viral epitopes via the T cell receptor (TCR). In previous studies, we examined the TCR repertoire of CD8+ T cells specific for a single SIV immunodominant epitope, Gag-CM9 (CTPYDINQM), throughout SIV infection. We identified tissue specific TCR sequences and TCRs shared by multiple anatomical sites. We now sought to evaluate if the tissue localization or TCR sequence of a CM9 specific CD8+ T cell corresponds with a transcriptional phenotype.

Methods: CM9 specific CD8+ T cells were sorted from blood, lymph nodes, spleen, and liver from SIV infected rhesus macaques. The cells were processed through the 10x Genomics single cell sequencing protocol, creating a TCR amplified library and an RNA gene expression library for each cell. The sequenced libraries were demultiplexed and integrated using Cell Ranger and Seurat software. Clonotypes that reside within specific tissue specific and shared across multiple sites and clonotypes shared across multiple individuals (public) were identified.

Results: Clustering analysis on the transcriptional profiles of CM9 specific CD8+ T cells revealed no obvious clustering by animal, or the presence of a public TCR sequence and minimal clustering was observed by tissue. Cells with tissue specific TCRs were most numerous in the liver. CM9 specific CD8+ T cells with a tissue specific TCR had higher expression of the tissue resident maker gene ITGA1. Multidimensional scaling analysis of CM9 specific CD8+ T cell transcription within the same tissue showed distinct distances between cells with shared and tissue specific TCRs in the blood, lymph nodes and liver. Interestingly, most of the transcriptional variation was captured by the spleen, rather than CM9 specific CD8+ T cells from peripheral blood.

Conclusion: These data suggest that the tissue of origin of a CM9 specific CD8+ T cell, or the presence of a public TCR sequence does not associate with a distinct transcriptional profile across multiple anatomic sites. However, within the same tissue, whether a cell has a shared or tissue specific TCR sequence does appear to associate with a different transcriptional profile. Importantly, analysis of antigen specific CD8+ T cells from peripheral blood does not capture immunological phenomena occurring within tissues.

445 Revealing the Role of Tissue-Resident NK Cells in HIV Infection Using Tissue Explant Models

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Background: Tissue-resident NK cells participate in immune clearance of tumor and infections, yet their response against HIV infection may vary across tissue microenvironments. Here, we characterized NK cells by their memory-like and residency properties, and assessed their functionality in killing HIV-infected cells in relevant tissue models of HIV infection.

Methods: We obtained tissue resections from tonsils (n=38) and colons (n=32) from routine surgeries. Flow cytometry was used to quantify residency markers (CD49a, CD69, CD103), the memory-related marker NKG2C, and Killer-cell immunoglobulin-like receptors (KIRs) (KIR2DL1, S1, L2, L3, S2). Additionally, we measured natural cytotoxicity (CD107a, IFN-γ) after coculturing tissue cells with HLA-negative K562 cells in suspension, 2D coatings and 3D gels with collagen I and IV. Using tonsil and colon explants, we additionally characterized NK cells following ex vivo HIV(BaL) infection for 5-7 days.

Results: Both tissues shared similar NK cell residency patterns, predominantly CD16-CD69+. Among these, CD49a-CD103- and CD49a+CD103+/- subpopulations exhibited the highest and lowest preactivation levels, respectively (median % of CD107a+IFN-γ- in tonsil: 70.60% vs 9.26%; colon: 77.90% vs 18.35%). However, robust natural cytotoxicity was exclusive to tonsillar NK cells, with CD16-CD49a+ "adaptive" (KIR+NKG2C+) cells showing a median 9.85-fold higher CD107a+IFN-γ+ cells upon stimulation. Of note, we observed that coculture on 2D coatings with collagen I or IV increased the IFN-γ in this subset, and K562 killing in 3D collagen I was enhanced in both tissues (tonsil: 1.75-fold; gut: 1.37). After 5-7 days of HIV infection, tonsils exhibited 10% more KIRs expression on CD16+CD69+CD49a+CD103- NK cells (p=0.032), yet the presence of CD69+KIRs+ NK cells correlated with lower levels of HIV infection (Fig. 1A). Conversely, in the colon, the CD16-CD103+ population significantly expanded (1.27-fold, p=0.001), correlating with reduced HIV infection levels when expressing NKG2C (p=0.017). Moreover, more CD16-CD69+CD49a-CD103+/- tonsillar NK cells were activated (% CD107a+IFN-γ-) after ex vivo HIV infection than in uninfected tissue explants, and CD16- KIRs+ and multiple resident NK cells showed increased CD107a expression upon K562 stimulation post-HIV exposure (Fig. 1B).

Conclusion: This study underscores tissue-specific NK cell responses to HIV and their potential role in limiting HIV establishment in tissues, offering insights for future research and therapies.

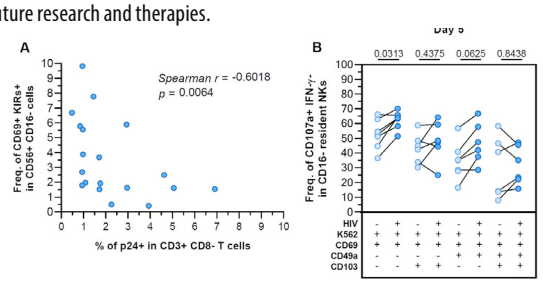

Fig. 1. A. Spearman correlation between the frequency of resident CD69+ KIR+ NK cells and frequency of HIV infection in the tonsil tissue. **B.** Frequency of CD107a+ IFN-γ- tonsillar NK cells expressing different residency markers, upon K562 cell stimulation post-HIV exposure.

446 Post-Intervention HIV Control Linked to Early In Vivo CD8+ T-Cell Proliferative Response to Rebound

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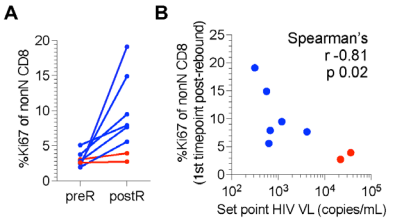
Background: The mechanisms by which emerging immunotherapies (e.g., broadly neutralizing antibodies [bNAbs], vaccines) contribute to post-ART control are unknown. Robust HIV-specific CD8+ T cell proliferation (after in vitro peptide stimulation) has been consistently associated with sustained (elite) virus control. To determine the relevance of this relationship in vivo, we studied early T cell proliferation in response to reactivating virus in two prospective studies with an analytic treatment interruption (ATI).

Methods: We previously reported a higher-than-expected rate of post-intervention control after a single-arm combination clinical trial (NCT04357821) in which people with treated HIV received a DNA/MVA vaccine regimen, followed by two bNAbs (10-1074, VRC07-523LS) plus a TLR-9 agonist (lefitolimod), then two bNAbs at the time of ATI. Seven of 10 participants achieved a low viral load (VL) set point ~1000 copies/mL while three had typical rebound (median set point 48,043 cpm). Before rebound and at an early timepoint (within 1 month) after rebound (median VL 775 cpm; n=8), we performed intracellular cytokine staining (by flow cytometry with overlapping peptide pools) and CyTOF on PBMCs. In a second study (NCT04359186), we performed single cell transcriptional analysis (10X 5' scRNA/TCRseq) of lymph node (LN) mononuclear cells before an ATI and at or near the time of rebound in 5 participants, two of whom had controlled HIV pre-ART and then re-controlled post-ATI.
Results: In the trial, early post-rebound, the frequency of IFNg+ HIV-specific CD8+ T cells (sum: Gag+Pol+Nef+Env) increased in those who exhibited control (median fold-change [FC] vs pre-rebound: 1.8x) but not in those who failed to control (FC 0.9x). Similarly, the frequency of proliferating (Ki67+) non-naïve CD8+ T cells increased robustly in controllers (FC 2.8x; 2.7 to 8.8%) but not in non-controllers (FC 1.2x; 2.8 to 3.3%). Higher %Ki67+ non-naïve CD8+ T cells early post-rebound was associated with lower VL set point (r=-0.81, p=0.02). Similarly, post-ATI in the second study, the fraction of proliferating CD8+ T cells (expressing MKI67) in the LN was higher in controllers vs non-controllers (3.6% vs 0.8%).
Conclusion: To our knowledge, these studies are the first to demonstrate a relationship between the early in vivo CD8+ T cell proliferative response to viral reactivation and HIV control post-ART. The results support continued focus on developing HIV cure strategies that enhance HIV-specific CD8+ T cell proliferative capacity.



Post-rebound CD8+ T cell proliferation after combination immunotherapy.
(A) Proliferation (%Ki67+) of non-naïve CD8+ T cells pre- vs within 1m post-rebound.
(B) Correlation: post-rebound CD8+ T cell proliferation vs set point VL.
Red = non-controllers, Blue = controllers

447 HIV Post-Treatment Controllers Show Enhanced CD8+ T-Cell Proliferative Capacity After ART Cessation

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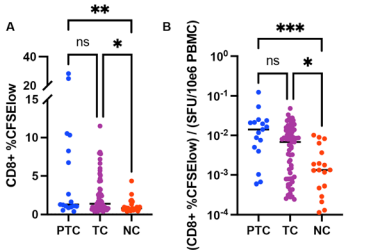
Background: HIV post-treatment controllers (PTCs) are individuals who control viremia to low or undetectable levels following ART discontinuation. While functional CD8+ T cell responses have been shown to be a defining feature of spontaneous ("elite") control of HIV, characterization of features of CD8+ T cell responses in PTCs has been limited. Here, we aimed to characterize the frequency, functionality, and specificity of CD8+ T cells in PTCs following ART cessation.
Methods: We evaluated HIV-specific CD8+ T cell responses of 7 PTCs alongside a group of 8 spontaneous controllers who had received and later discontinued ART (treated controllers, TC) and 11 non-controllers (NC) during the post-treatment interruption (TI) period. Both PTCs and TCs were defined as having plasma viral loads <10,000 copies/mL for at least 52 weeks post-TI; individuals meeting these criteria were defined as TC if their viral load immediately preceding ART initiation was <10,000 copies/mL, and PTC if otherwise. Ex-vivo CD8+ T cell reactivity was evaluated by IFN-γ ELISpot and functional proliferative capacity through a six-day CFSE-based proliferation assay with individual optimal clade B epitopes matched to each participant's HLA haplotype.
Results: HIV-specific CD8+ T cell reactivity post-TI as measured by ELISpot was significantly lower in PTCs compared to TCs (P<0.01), with no significant differences observed between TCs and NCs. Of note, median plasma viral loads at time of analysis were 50, 638, and 36200 copies/mL in the PTCs, TCs, and NCs respectively. In contrast, both PTCs and TCs had significantly stronger proliferative responses to HIV epitopes than NCs (P<0.01 and P<0.05, respectively). Additionally, we calculated the capacity for antigen-specific CD8+ T cells to expand after antigen exposure by normalizing the magnitude of proliferation to direct ex vivo ELISpot magnitude and observed an even substantially higher proliferative capacity in both PTCs and TCs compared to NCs (P<0.001 and P<0.05, respectively).
Conclusion: Compared to NCs, PTCs exhibited a distinct HIV-specific CD8+ T cell profile, with less direct ex vivo reactivity but greater proliferative capacity following antigen exposure. These findings warrant further investigation into the mechanisms by which highly expandible antigen-specific CD8+ T cell populations are formed and maintained, and lend further support to therapeutic vaccine strategies aimed at inducing T cell responses that retain high proliferative capacity.



(A) Proliferative responses to individual immunogenic clade B HIV epitopes (%CFSElow CD8+ T cells after six-day incubation). **(B)** Proliferative capacity defined as proliferative response magnitude normalized to magnitude of *ex-vivo* ELISpot response to same epitope. Statistical comparison by Kruskall-Wallis test with Dunn's multiple comparisons test (*P<0.05, **P< 0.01, ***P<0.01, ns P>0.05).

448 Cannabis-Induced DNA Methylation Changes Mediate Immune Response in PLHIV

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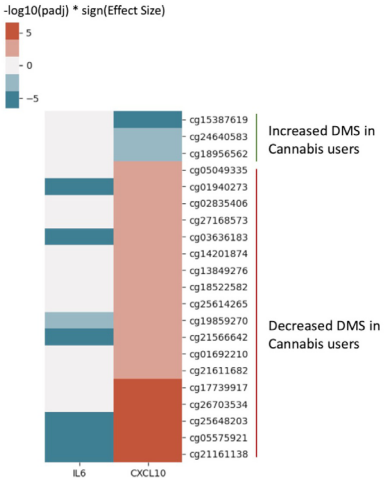
Background: Cannabis use is prevalent among people living with HIV (PLHIV). Cannabis is mostly smoked leading to inhalation of the psychoactive tetrahydrocannabinol as well as reactive particles, toxins, and oxidants that may induce epigenetic changes and affect immune responses. We therefore analyzed the effect of cannabis on DNA methylation and immune function in PLHIV.
Methods: Participants were recruited from the 2000HIV study (NTC03994835), a Dutch multi-center study amongst virally suppressed PLHIV, separated into a discovery cohort (n=1512, 280 cannabis users) and a validation cohort (n=317, 47 cannabis users). Cannabis use and tobacco smoking were recorded through a self- reported questionnaire. Genome-wide DNA methylation data was obtained using the Illumina Infinium MethylationEPIC array. Plasma proteins were assessed by targeted proteomics (Olink Explore). PBMC ex vivo cytokine production capacity was measured upon bacterial, fungal, and viral stimulation. The differential DNA Methylation Sites (DMSs) were identified by an epigenome-wide association study, followed by integration with the proteomics, and cytokine secretion data from the same individuals.
Results: In the discovery cohort, 3741 cannabis-associated DMSs were identified, with 293 DMSs being replicated in the validation cohort. The most significant DMS is cg01940273 (p=1.3e-50) also strongly associated with tobacco smoking in 2000HIV and other studies. After accounting for tobacco smoking effects, 98% DMSs showed reduced significance but the methylation trend remained consistent and 81% DMSs were demethylated. Validated DMSs associated genes were enriched in nervous system development and leukocyte differentiation. The DMS-associated plasma proteins suggested that DMSs are associated with leukocyte differentiation and cytokine expression, such as IL6 upregulation and CXCL10 downregulation (Figure1). The causal inference test suggested that cannabis-induced DMSs may modulate immune response in PLHIV, such as increased IL22 and decreased INF-γ production after PBMC stimulation.

Conclusion: Cannabis inhalation induces significant DNA methylation changes in PLHIV. Such modifications may lead to systematic changes in plasma (inflammatory) protein levels, and cytokine secretion of circulating immune cells. Downregulation of INF-γ and INF-γ induced protein CXCL10 may influence host response to HIV and co-pathogens. Our data indicate that cannabis use needs to be recorded and corrected for reporting inflammation in PLHIV.



449 Immunomodulatory Effects of Cannabis Use in PLHIV

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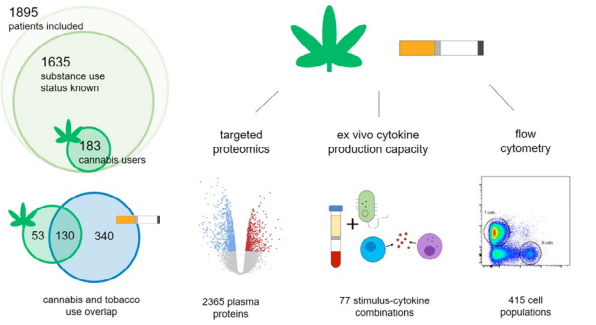
Background: Cannabis is one of the most commonly used psychoactive substances worldwide. Cannabinoids are known to have anti-inflammatory effects. However, cannabis is mainly used by smoking, which results in exposure to reactive particles, toxins and oxidants, inducing pro-inflammatory effects. The effect of cannabis inhalation on systemic inflammation and immune function has barely been studied in humans. Therefore, we assessed the effects of cannabis inhalation on systemic inflammation and immune function in a large cohort of people living with HIV (PLHIV), while taking into account the effects of tobacco inhalation.

Methods: This cross-sectional study was performed in 1896 PLHIV using antiretroviral treatment. Cannabis and tobacco use were assessed by self-questionnaire MATE-Q, and cannabis use was validated by metabolomic mass spectrometry. Systemic inflammation was assessed using targeted proteomics to assess a total of 2365 plasma proteins. Immune function was assessed by extensive phenotyping of circulating immune cells using flow cytometry, and assessing ex vivo cytokine production capacity of peripheral blood mononuclear upon bacterial, fungal and viral stimulation. The relation between these omics data and the use of cannabis was assessed correcting for age, sex, tobacco use and multiple hypothesis testing.

Results: Cannabis use was associated with an upregulation of 15 and a downregulation of 50 proteins. Downregulated proteins in cannabis users were involved in leukocyte-mediated cytotoxicity and NK cell- mediated cytotoxicity. Regarding immune function, the production of monocyte- and lymphocyte-derived cytokines did not differ between cannabis users and non-users, apart from increased MCP-1 production upon stimulation with IL1A. Extensive flow cytometry showed that cannabis use was associated with increased levels of CD27+CD21- B-cells only. In contrast, tobacco use was associated with an extensive upregulation of systemic immune-related proteins, increased ex vivo production of various cytokines, as well as extensive alternations in immune cell phenotypes.

Conclusion: Our results suggest that cannabis has systemic anti-inflammatory effects, and little effect on immune function, even when used by inhalation. Based on our data, no conclusions can be drawn regarding local immunological effect of cannabis in the airways. Given the increasing legalization of cannabis use worldwide, future research on the health effects of cannabis inhalation is of crucial importance, especially for PLHIV.



Overview of study methods. Out of the 1896 participants included in the 200HIV study, 1635 completed the questionnaire on substance use. 183 participants used cannabis, of which 130 concurrently used tobacco. Effects on immune function were assessed by evaluating targeted proteomics, *ex vivo* cytokine production capacity and extensive flow cytometry.

450 Impact of Hormone Therapy and HIV on the Immunometabolic Landscape in a Cohort of Transgender Women

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Background: Studies of HIV-1 pathogenesis have found differences in set point viral load, immune activation, and latency reversal between cisgender men and women. Although mechanisms are unclear, sex steroid hormone 17-beta estradiol impacts HIV transcription, and sex chromosome genes including TLR7 impact HIV imunopathogenesis. Little is known about the relative influence of these factors in transfeminine individuals. We sought to investigate the impact of exogenous estrogens on markers of inflammation and metabolism in immune cells in a cohort of transgender women (TGW) living with HIV (TGWLWH) or HIV-negative.

Methods: To parse the role of feminizing hormone therapy (FHT) versus a lived feminine gender identity in individuals with an XY chromosome complement, we recruited 120 TGW in Brazil through the Transcendendo cohort in 4 groups: HIV-negative on FHT(Group 1) HIV-negative not currently on FHT (Group 2), TGWLWH on FHT(Group 3), TGWLWH not currently on FHT (Group 4). We collected demographic data including depression, substance use, injected fillers, and biospecimens. Cryopreserved PBMCs were immunophenotyped with a 32 color panel using the Cytek Aurora and data were analyzed with FlowJo. Metabolic capacity was assessed using Single Cell ENergetIc metabolism by profiling Translation inhibition (SCENITH) to determine dependence on different metabolic pathways. T cells were isolated from individuals with HIV and qPCR was performed to determine mRNA expression levels of CPT1a.

Results: Median age of participants was 37.5. Among TGWLWH, 99.17% had undetectable viral load. In TGWLWH, we saw expected decrease in CD4:CD8 T cell ratios and an increase in HLADR+CD38+ memory CD8 T cells, slightly attenuated by feminizing hormone therapy. Feminizing hormone therapy was linked to decreased expression of CPT1a (a metabolic marker associated with acetylation and fatty acid oxidation) in CD4 and CD8 T cells. Likewise, in PWH CPT1a gene expression levels were significantly lower in individuals on FHT. SCENITH assays performed on HIV- on hormone therapy (Group 1) indicated an increased glucose dependence after ex vivo T cell activation.

Conclusion: The combined impact of HIV infection and FHT was associated with differences in mRNA and protein expression of CPT1a in T cells. Additionally, FHT leads to an increase in glucose dependence. These findings suggest that FHT directly impacts immunometabolic phenotypes and that HIV modulates these effects.

451 IRF5 Mediates Persistent Inflammatory Responses in HIV-1–Infected Macrophages

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Background: People living with HIV (PWH) experience chronic inflammation, which can contribute to HIV- associated co-morbidities. Long-lived HIV-1-infected macrophages are important mediators of chronic innate immune activation. Additive effects of aging and persistent HIV-1 infection can promote macrophage dysfunction, contributing to chronic inflammation, or "inflammaging". We previously reported that nuclear export and cytoplasmic expression of HIV-1 intron-containing RNA (icRNA) activates MAVS-dependent

innate immune sensing and persistent type I IFN responses in macrophages. However, the signaling pathways downstream of HIV-1 icRNA sensing have not been fully elucidated. In this study, we show that IRF5 mediates type I IFN responses downstream of icRNA sensing in HIV-1 infected macrophages, and that persistent IRF5 activation in older PWH may contribute to inflammaging.
Methods: THP-1/PMA macrophages or monocyte-derived macrophages (MDMs) with selective abrogation of MAVS signalosome members, IRF3, IRF5, IRF7, TRAF6, and IKK-β were infected with a single cycle HIV-1 reporter. MDMs were also differentiated from CD14+monocytes derived from a primary patient cohort, stratified by age into younger (<35 yo) and older (>50 yo) donors. Cells were harvested at 2-3 days post infection and analyzed for infection establishment by flow cytometry, RT-qPCR for ISG expression, while cell-free supernatants were harvested for type I IFN and IP-10 production by bioassay and ELISA, respectively. Infected macrophages were also fixed on coverslips for determining nuclear-cytoplasmic IRF5 localization using immuno-fluorescence microscopy.
Results: Though initiation of MAVS signaling can activate transcription factors, IRF3, IRF5 and IRF7, disruption of IRF5 expression had the highest impact on HIV-1 icRNA-induced type I IFN and IP-10 expression. Furthermore, attenuation of TRAF6 (necessary for IRF5 ubiquitination and nuclear localization) expression, but not IKK-β, abrogated IP-10 production in macrophages. Interestingly, expression and nuclear localization of IRF5 was constitutively upregulated in older MDMs which translated to higher IFN-β and IP-10 expression, though infection establishment and HIV-1 icRNA expression was similar in MDMs from both younger and older donors.
Conclusion: Collectively, these results elucidate the mechanism of icRNA sensing in HIV-1 infected macrophages and offer insight into potential targets for therapeutics to alleviate chronic immune activation in PWH.

452 Expression of Unspliced HIV-1 RNA Induces NLRP1 Inflammasome Activation in Myeloid Cells

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Background: Despite the success of combination antiretroviral therapy (ART), chronic HIV-1 infection in long-lived tissue-resident cells such as macrophages and CNS-resident microglia and associated chronic inflammation remain a major barrier to successful HIV-1 management strategies. Inflammasome activation is a critical checkpoint in innate immune responses and HIV-1 has been proposed to activate multiple inflammasome sensors, including NLRP3 and CARD8 (activated by HIV-1 protease). Recent work in our laboratory has shown that expression of HIV-1 intron-containing RNAs (icRNA) is sufficient to activate innate immune responses. As ART does not affect viral RNA expression in long-lived infected cells, persistent expression of HIV-1 icRNA thus presents a novel mechanism for inflammasome activation and chronic inflammation observed in people living with HIV (PWH).
Methods: Primary human monocyte-derived macrophages (MDMs, differentiated from CD14+ monocytes) or phorbol 12-myristate 13-acetate (PMA)-differentiated THP-1 macrophages were infected with HIV-1. Supernatants from infected cells were collected and assayed by ELISA for IL-1β. Transfected siRNAs were used to knock down putative sensors in MDMs, while lentiviral constructs were used to knock down or overexpress putative sensors in THP-1/PMA macrophages.
Results: We found that inflammasome activation in MDMs was dependent on the nuclear export of HIV-1 icRNA, similar to the activation of type I interferon. Surprisingly, unlike induction of type I IFN responses, MAVS-signaling was not required for inflammasome activation and IL-1β secretion. IL-1β secretion was dependent on caspase-1 and the inflammasome sensor NLRP1, but unlike HIV-1-mediated activation of CARD8 inflammasome, not dependent on viral protease or enzymatic activity. Furthermore, knockdown of NLRP1 did not affect the activation of type I IFN responses in MDMs, suggesting cytosolic icRNA expression engages divergent innate immune sensing pathways. Finally, HIV-1 infection also induced inflammasome activation and IL-1β secretion in NLRP1-overexpressing THP1/PMA macrophages, confirming that NLRP1 senses HIV-1 icRNA expression.
Conclusion: Persistent expression of HIV-1 icRNA in long-lived infected cells may contribute to persistent immune activation in PWH via NLRP1 activation. Future studies in our laboratory will address the mechanism of HIV-mediated NLRP1 activation.

453 Type I Interferons Drive Sustained Dominance of CCR5-Tropic Variants During HIV Infection In Vivo

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Background: A curious phenomenon is observed in people living with HIV (PLWH) who are not on antiretroviral therapy. Despite there being no difference in viral fitness between CXCR4(X4)-tropic and CCR5(R5)-tropic HIV viruses in vitro, R5-tropic viruses typically dominate in the early clinical stages. While R5 tropic viruses are selected during transmission events, it is surprising that X4 tropic virus takes years to emerge, if at all. CXCR4, the co-receptor for X4 tropic viruses, is expressed by the vast majority of CD4+ T cells while CCR5 is expressed by ~15% of total CD4+ T cells. In addition, it only takes a few amino acid changes to switch tropism. Even under maraviroc treatment, a CCR5 antagonist, X4 tropic viruses rarely emerge. Instead, resistant viruses arise that can bind to the maraviroc bound CCR5, which requires generation of multiple simultaneous mutations. These studies suggest that X4 viruses are stably suppressed by the immune system in vivo beyond transmission. We aimed to understand the molecular mechanism of X4-specific immune control in vivo.
Methods: In vitro models are not suited to explore the mechanism of R5 dominance. To better understand tropism specific immune control of HIV, an interferon-α/β receptor knockout (IFNAR-KO) human immune system was reconstituted in mice. Briefly, human CD34+ cells were transduced with Cas9 protein and guiding RNAs targeting the IFNAR coding gene or scrambled controls by electroporation before injection into 1-3 day old pups. Nine weeks post engraftment, these mice were infected with X4- or R5-tropic HIV isolates.
Results: In humanized mice engrafted with unmodified CD34+ cells, X4- and R5-tropic viruses replicate equally well when present alone. In contrast, when mice were infected with both viruses, there was a near complete suppression of X4 viral replication and sustained dominance of R5 viral replication, recapitulating what is observed in patients. This restriction of X4 viral replication was lost in mice with an IFNAR-KO immune system. High levels of type 1 IFN production was observed in mice challenged with both X4- and R5-tropic viruses, which resulted in selective suppression of X4-tropic viruses. These results suggest that emergence of X4-tropic viruses post viral transmission is likely blocked by type 1 IFNs.
Conclusion: Our work reveals that X4 tropic virus is selectively restricted by type I interferon (IFN) beyond the transmission event. We will explore how this restriction is lost in the later clinical stages.

454 Crosstalk Between TLR-8 and RLR Enhanced Antiviral Immunity Against Acute HIV-1 and PWH

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Background: Achieving an HIV-1 cure requires both reactivation of the viral reservoir and antiviral immunity. In HIV negative individuals we showed that crosstalk between TLR8 and RLR enhances antiviral immunity by increasing production of IL12, IL27 and type I IFNs, promoting Th1 and Tfh differentiation and boosting CD8+ cytotoxicity. Targeting TLR8 and RLR could elicit antiviral immunity required in a HIV-1 cure strategy. We investigated whether this crosstalk persists in the context of HIV-1, in acute infected, treated, individuals as well as individuals who started ART in the chronic phase.
Methods: Four distinct participant groups were included: age matched HIV-negative (n=28), HIV-positive individuals treated in the chronic phase of infection (n=28) (ART initiated at CD4 <300), and individuals that initiated ART during the acute phase of infection (24-weeks (n=17) post-treatment initiation and three years (n=11) post-treatment initiation). PBMCs were stimulated with TLR8 and RLR agonists alone or in combination for 24 hours. Immune responses; cytokine levels, type I IFN responses, and co-stimulatory molecules, were assessed.
Results: TLR8 agonist GS9688 induced pro-inflammatory cytokines IL6 and IL12. Poly(I:C)-lyovec, a RLR agonist, induced IL27 in PBMCs in all 4 groups. In HIV-negative individuals combination of the TLR8 agonist and RLR agonist resulted in a two-fold increase of IL12 and IL27, while IL6 secretion was decreased compared to single-stimulation. In the acutely treated individuals (24 weeks, 3 year post treatment initiation) crosstalk was largely preserved when

comparing to HIV-negative individuals. However, notably, in individuals treated during chronic infection as compared to HIV negative individuals, TLR/RLR crosstalk was impaired: the level of IL12 and IL27 was 2 to 1.5 fold lower and, and IL6 restriction decreased from 1.9 to 1.2 fold.
Conclusion: Crosstalk between TLR8 and RLR is disrupted following chronic infection with HIV-1, initiation of ART in the acute phase of infection preserves this crosstalk to a large extent. Our data suggest that HIV- related monocyte dysfunction might underlie this lack of crosstalk, as monocytes respond to this form of TLR8 and RLR stimulation. Differences between treated acute and chronic infection suggest that this phenomenon is more pronounced during chronically treated infection. Deciphering these alterations in crosstalk is paramount for pioneering strategies that bolster immunity and eradicate reservoirs, especially in a chronic setting.

455 The Effect of HIV Infection at Pre-ART Initiation on the Early Innate Immune System

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Background: Despite the advent of antiretroviral therapy (ART), perinatal HIV infection still occurs, mostly in low-income countries. The nature of the innate immune response to HIV infection in infants is relatively unknown, as is an understanding of the effect of HIV replication on the development of the early innate immune system.
Methods: 68 perinatally HIV exposed infants from Maputo, Mozambique were diagnosed as infected (HEI, n=33) not (HEU, n=35) at 1 month of age, prescribed ART for HEI and followed until 24 months. PBMC were isolated from blood at the clinical site and cryopreserved before being shipped to Miami. Flow cytometry was performed using a 27-color panel on PBMC to investigate the effect of HIV on innate immune cells (NK and monocytes). NK cell subsets were defined based on CD56 and CD16 expression on lineage negative lymphocytes. Monocytes were identified based on CD14 and CD16 expression on lineage negative and HLA- DR positive cells. These cell types were analyzed for markers of immune activation (IA), immune regulation, and trafficking. A flow cytometry based assay was implemented to investigate the killing potential and degranulation of NK cells utilizing a highly sensitive in vitro target (K562) and HIV-Infected target cell line (HUT78/SF2) in a small subset of the cohort.
Results: At study entry pre-ART, NK cells in HEI infants exhibited an altered profile of activation, inhibitory, and trafficking receptors suggestive of a more activated profile when compared to HEU such as increased activation (CD38) and trafficking (CCR2) with decreased inhibition (NKG2A). In addition, similar alterations were observed in the monocyte compartment but to a lesser extent. CCR2 on NK cells and intermediate monocytes were highly correlated with pre-ART viral load. NK cells of HEI had a similar cytotoxic capacity as HEU towards both cell lines but increased degranulation towards the K562 cell line. By 10 months of age, disturbances in subset distribution and markers of activation, inhibition, and trafficking were partially reversed in both viremic and aviremic infants.
Conclusion: The data suggests that NK cells and monocytes of HEI have an activated profile that appears to diminish with age. In addition, these cells are associated with viral replication at pre-ART initiation. These observations warrant further investigation on the impact of HIV on development of the innate immune system and the role of Intermediate monocytes and NK cells on viral replication and reservoir establishment.

456 Inflammatory Monocytes Increase During HIV-1 Treatment Interruption Before Detectable Viremia

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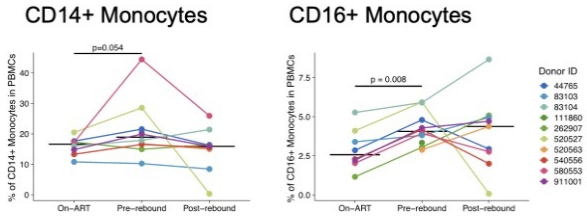
Background: When antiretroviral therapy (ART) is interrupted, most people living with HIV (PLWH) experience rapid viral rebound within a few weeks. We currently have no reliable non-viral biomarkers of imminent viral rebound. Rebound viremia is defined by circulating HIV RNA, but we hypothesize that low levels of virus replicating in tissues may create measurable biological changes in the immune landscape prior to detectable viremia. These changes may be most detectable directly preceding rebound viremia, when the viral load has not reached the limit of detection and is still under tentative immune control.
Methods: To investigate changes in the immune system indicative of the first signs of viral rebound, we performed two separate analyses on a cohort of donors with HIV-1 who participated in an observational analytical treatment interruption (ATI). We performed single cell RNAseq on peripheral blood mononuclear cells (PBMCs) from a subset of 10 donors and analyzed soluble protein levels in plasma using three Olink 92-plex panels on 19 donors. For the purposes of analysis, we compared three distinct timepoints: on-ART (before ATI), pre-rebound (during ATI, before detectable viremia), and post-rebound (detectable viremia). scRNAseq data was analyzed using the Seurat integration workflow. Pathway analysis using MSigDB hallmark gene sets collection was performed on scRNAseq data. Olink protein levels were log-normalized and assessed with a paired Wilcox test.
Results: In these PLWH, we found a significant increase in monocyte subsets prior to detectable viral rebound. Non-classical inflammatory CD14-CD16++ monocytes increased in proportion by 1.9% (p=0.008) while classical CD14++CD16- monocytes increased in proportion by 3.6% (p=0.054) (Fig. 1). Pathway analysis indicated enrichment for IFNγ, IFNα, and inflammatory response pathways within monocyte subsets. Olink analysis indicated an increase in soluble inflammatory plasma proteins post-rebound related to immune activation (PD-L2, TRAIL), cytokine signaling (TNF, LAG3, GZMB), and NFkB signaling (CXCL9, CXCL10, IL12).
Conclusion: Our data suggest that prior to detectable viremia, a subset of circulating monocytes activate and expand in response to low level viral replication. These cells shift to a more inflammatory phenotype, indicating innate immune sensing of early viral rebound activity. This has the potential to be a non-viral biomarker of imminent viral rebound.



457 Intact Proviruses Persist in Expressed Genes in People With Non-Suppressible HIV on Long-Term ART

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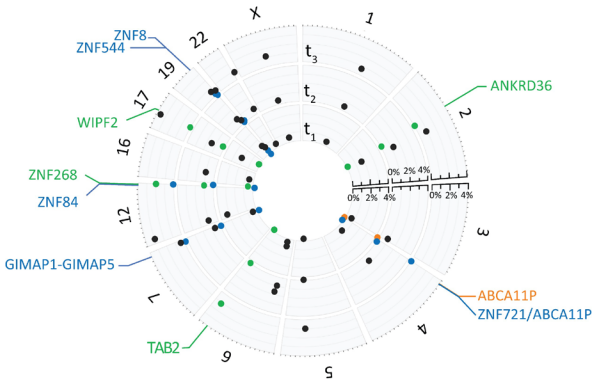
Background: The persistence of replication-competent proviruses during ART is a key barrier to an HIV cure. A previous study identified 3 cell clones carrying replication-competent proviruses that were integrated in genes and were the sources of non-suppressible viremia (NSV). Here, we asked if additional clones carrying intact proviruses were present in these 3 individuals; and, if so, where the proviruses were integrated in the host genome.
Methods: Three donors on ART for 10-20 years who recently developed NSV were sampled over 1-4 years. PBMCs were subjected to endpoint diluted multiple displacement amplification (MDA). MDA wells were screened for HIV LTR, psi (Ψ), and RRE. Proviruses that were positive for LTR, Ψ, and RRE underwent full-length HIV sequencing and integration sites analysis. The % predicted-intact proviruses were calculated as in the IPDA and also using HIV LTR+ MDA wells as the denominator. A custom pipeline was used to map both discrete and non-discrete (e.g., centromeric) integration sites. Gene expression levels in memory CD4+ T cells were determined using the Human Protein Atlas Database (www.proteinatlas.org).
Results: We identified 7 additional clones carrying sequence-intact HIV proviruses (10 total). All 10 integration sites mapped to expressed genes (Figure) and 4 were in the same orientation as the gene. Five were in KRAB-ZNF genes (50%), compared to the 3.7% of total proviruses (which are mostly defective) in KRAB-ZNF genes in one of the donors ($p<10^{-4}$). Reported gene expression levels were not significantly different for the genes with intact vs defective proviruses (median=33.9 vs 61.0 TPM; p=0.3). Predicted-intact proviruses (Ψ+RRE) comprised 9-10% of the total population using the IPDA approach and

2-4% using LTR as the denominator. Proviruses that were confirmed intact by full-length sequencing comprised 0.07-2% of the LTR+ MDA wells. Two of the 10 clones carrying sequence-intact proviruses increased in size, one decreased, and seven did not change significantly over 1-4 years.

Conclusion: In 3 donors with non-suppressible viremia on ART, we identified 10 clones carrying sequence-intact proviruses comprising <2% of the total proviral population. All 10 intact proviruses were integrated in genes that are normally expressed in memory CD4+ T cells, including the 5 in KRAB-ZNF genes. Only 1/10 clones declined in size on long-term ART. These results indicate that a stable pool of intact proviruses integrated in expressed genes can persist on long-term ART.



Proviruses mapped to human genome. Location of sequence-intact (colored) and a subset of defective (black). Size of each clone shown for each timepoint (t_1, t_2, t_3).

458 Host Gene Activation at the Integration Site Reduces HIV Expression by Transcriptional Interference

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Background: The integration site affects HIV persistence in vivo. A provirus shares and competes with local host genes for transcription machinery that regulates expression. How host promoter activity at the integration site affects HIV expression remains unsettled. We postulated that host promoter activation increases local chromatin accessibility to transcription factors and increases HIV expression.

Methods: We isolated 9 Jurkat T cell clones, each with HIV provirus (NL4-3-d6-dE-dsGFP) stably integrated into (a) introns of an actively transcribed gene in the same orientation (*VAV1, RAP1B, SPECC1*), (b) introns of an actively transcribed gene in the opposite orientation (*INPPL1, FNBP1, KLF12, EEF2K*), and (c) intergenic regions. Using CRISPR-mediated activation or inhibition (CRISPRa/CRISPRi), we activated or inhibited the local host promoter using host-targeting sgRNA. We used nontargeting sgRNA as a control. We examined how host promoter activity affects HIV gene expression using ATAC-seq, RNA-seq, and qRT-PCR. We assessed differential gene expression and chromatin accessibility using edgeR and chromatin footprints with TOBIAS.

Results: Activation of the host promoter dominantly decreased HIV gene expression in 4 out of 7 cell line clones: *SPECC1, KLF12, EEF2K* (each FDR<10^{-6}), and *VAV1* (FDR<10^{-3}), in both orientations of HIV integration. A smaller trend was seen with *RAP1B* (FDR=0.07). For the cell line clone in which HIV integrated 7kb from the host promoter, activation of the host promoter *INPPL1* increased HIV expression. The two clones harboring a provirus in intergenic regions expressed substantial proviral RNA despite lower chromatin accessibility. We next examined whether host promoter activity changes chromatin accessibility and transcription factor binding to the HIV LTR. Activating the host promoter of *VAV1*, *RAP1B*, *SPECC1*, and *EEF2K* significantly reduced chromatin accessibility of the downstream HIV 5' LTR (FDR<10^{-6}; *KLF12* n.s.) and displaced HIV transcription factors. In contrast, activating host promoter *INPPL1* increased HIV LTR chromatin accessibility.

Conclusion: We identified transcriptional interference at the HIV integration site. Activation of host genes harboring an HIV integration site displaces transcription factors bound to the HIV 5' LTR and inhibits HIV expression. In vivo studies to understand or modulate latency should account for transcriptional interference.

459 Role of HIV Integration Site on Clonal Expansion of Infected Cells and Maintenance of Latency

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Background: Latent reservoirs of HIV-1 are the major barrier to achieving a cure. Because latently infected cells are rare in humans there is a paucity of understanding of how latent reservoirs survive and expand, escape immune clearance, and reactivate upon ART cessation. The site of HIV-1 proviral DNA integration into the host genome could (i) determine the transcription status of the provirus and (ii) influence the expansion of infected clones during ART. In this study we are interested in the characterizing proviral integration landscape associated with clonal expansion and latency of HIV-1 infected cells in an in vivo model.

Methods: Primary memory CD4+ T cells isolated from healthy human donors were infected with dual reporter tagged, defective HIV-1 to generate large populations (millions) of human memory CD4+ T cells each presumptively carrying a single reporter provirus at a distinct integration site. These cells were grafted into NSG mice and analyzed for proviral transcriptional dynamics over a period of time. HIV-1 integration sites were characterized by PCR based amplification of host-viral junction and next-generation sequencing.

Results: Our preliminary analysis of HIV-1 integration sites in these long-term persistent HIV-1 infected cells led to the identification of 1777 unique integration sites (UIS). Consistent with previous reports, HIV-1 integration was favored in genic regions (60%) of human chromosomes as compared to non-genic regions (40%). Genic HIV-1 integrations were primarily in introns (94%). We found 84 genes that harbored HIV-1 integrations in multiple different clones and in most cases these integrations were clustered within a single intron, suggesting possible hotspots within a gene for integration or for clone survival. Two different mice had clones with HIV-1 integrants in the same 25 genes suggesting a growth or survival advantage for clones harboring HIV-1 integration in these genes. Overall, 641 UIS were associated with expanded clones persisting in vivo and clonally expanded cells were more likely to have HIV-1 integration inside genes than cells where clonal expansion was not detected. The genes in which HIV-1 integration was associated with clonal expansion belonged to pathways with roles in cell component biogenesis, mitosis, regulation of cell cycle, and chromatin remodeling.

Conclusion: Clonal expansion of HIV-1 infected cells in this model system is associated with proviral integration in a set of genes which provide selective growth advantage in vivo.

460 HIV Integration Site Features Associated With Persistence of Infected Cells Under CD8 Pressure

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Background: HIV integration sites (IS) in elite controllers and after long-term ART are highly clonal and skewed towards transcriptionally silent genomic loci. The mechanisms contributing to this IS landscape remain unclear, hampering the design of cure therapeutics. Using a participant-derived xenograft mouse model, we observed that CD8+ T-cell pressure was sufficient to recapitulate key features of this IS profile, including enrichment for large clones and integrations distal from genes. Here, we expand our dataset and assess whether prolonged elite controller CD8+ T-cell pressure is associated with integrations into specific gene pathways.

Methods: NSG mice were engrafted with memory CD4+ T-cells from two HLA-B27+ HIV male elite controllers and infected with HIVJRCSF to test the effect of autologous memory CD8+ T-cell engraftment on the proviral landscape. T cell responses and HIV viral loads were monitored weekly by flow cytometry with a Gag-KK10 tetramer and by qPCR. At week 8, splenic DNA was subjected to linker-mediated PCR for IS sequencing. IS were identified with the AAvengeR software pipeline. We performed Reactome pathway analysis on 6,402 and 12,406 unique IS from 18 CD8+ and 9 CD8- mice respectively. A

Bayesian mixture model was developed to incorporate different IS associated characteristics of CD8+ T-cell pressure.
Results: The top 10% of expanded clones harbored integrations in recurrent integration genes previously identified in clinical studies, such as STAT5B, BACH2, MKL1, as well as genes observed in rare HIV-related tumors, including STAT3 and LCK. In the absence of CD8+ T cell pressure, HIV integrations were enriched in genes involved in cell cycle and cellular signaling pathways (p.adj<1e-6). In the presence of CD8+ T-cells, integrations frequently targeted genes involved in chromatin organization, mRNA processing, modification, and trafficking, as well as SUMOylation (p.adj<1e-9). The Bayesian model determined a CD8+ T-cell selection score of each mouse, thus functioning as a tool for quantifying CD8+ T-cell selective pressure, and highlighted clonality as a prominent characteristic associated with CD8+ T-cell selection.
Conclusion: Our findings support a role for CD8+ T-cell pressure in selecting for particular clones of infected cells. Enrichments in gene pathways may reflect accessibility for integration, but also raises the possibility of CD8+ T-cell selection for insertional mutagenesis events that might modulate the transcription of genes involved in HIV expression.

461 HIV Proviruses Among CMV-Reactive Cells Are Abundant, Defective, and Polyclonal After 4 Years of ART

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Background: Since clonal expansion plays a major role in the maintenance of HIV-infected CD4+ T cells, antigen exposure and immune reconstitution can affect reservoir dynamics. Chronic CMV infection is characterized by percolating antigen expression and progressive inflationary T-cell memory. Although HIV-infected, CMV-reactive cells are often dominated by large clones, which factors lead to their selection remain unclear. We assessed the contribution of immune reconstitution, CMV-related disease, and CMV-DNAemia to HIV persistence.
Methods: We studied 16 participants living with HIV and CMV, enrolled in two NIAID clinical trials. All had a CD4 nadir <50cells/μL. CMV-driven immune reconstitution inflammatory syndrome (IRIS) and end-organ disease were present in 3 and 3 participants, respectively. PBMCs from week 192 on ART were CD8-depleted and stimulated with CMV antigens. Reactive cells (positive for CD69/CD154/CD137) were plate-sorted at limiting dilution and subjected to whole genome amplification. HIV+ wells were tested for LTR, IPDA, proviral sequencing, and integration site analysis. Bulk TCRseq was performed on cells reactive to CMV and CD3/CD28.
Results: CMV DNAemia was detected in 11/16 participants but decreased below LOD upon CD4 recovery. Only 4/16 participants reached CD4 counts >500 cells/uL by week 192. CMV-reactive cells were highly variable but detectable in 15/16 participants (median 2.7%, range 0.6-18.6%). We observed a high frequency of HIV DNA among CMV-reactive cells, with a median of 4328 [2464-5654] proviruses/million cells. IPDA showed 2-fold lower total DNA (p=0.0006) and rare intact genomes, suggesting that the majority of proviruses are highly defective or solo LTR. Based on gag and env sequencing, we detected only a few identical proviruses in most individuals. Among those expanded, we found proviruses in loci linked to heterochromatin (ZNF84) and insertional mutagenesis (STAT5B). TCR sequencing revealed marked clonality of CMV-reactive cells compared to the CD3/CD28 control (p<0.0001). Across all analyses, we detected no correlation with CMV DNAemia, IRIS, or CMV disease.
Conclusion: We observed high infection frequency among CMV-reactive cells regardless of immune reconstitution and CMV DNAemia. The discrepancy in clonality between total CMV-responding cells and those infected suggests a preferential expansion of uninfected cells, likely selected during ART, while older infected clones may require longer time to be substantially shaped by proliferation.

462 Differential Gene-Specific Selection Pressures on HIV-1 Defective Proviruses During ART

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Background: The error-prone nature of HIV-1 replication and host factors generate defective genomes. Defective proviruses persist, can be transcribed, and translated contributing to HIV-1 pathogenesis. During antiretroviral therapy (ART), most defective proviruses contain large deletions and hypermutations precluding the investigation of gene-specific selection pressures. We studied selection pressures on whole HIV-1 genomes and subgenomes of >7kb near-full length (NFL) defective proviruses prior to following ART.
Methods: Blood cells were collected from 11 HIV-1 suppressed participants prior to and at multiple timepoints on ART (4-20 years). We performed single genome sequencing of >7kb proviruses and identified defective proviruses with stop codons, insertions/deletions or hypermutations. We collapsed identical sequences and compared the whole genomic and subgenomic characteristics of defective proviruses from pretherapy to ART. We predicted the Major Histocompatibility (MHC) class I binding, immunogenicity, and sensitivity to Broadly Neutralizing Antibodies (bNabs)
Results: We obtained 705 NFL defective sequences. Proportions of hypermutant proviruses were not significantly different prior (median 38.38%) to following ART (26.86%). We observed significant selection for proviruses with defects on major spliced donor/packaging signal (MSD/PSI) (33.33% prior to 84.44% on ART) and gag (40% to 75%) but against proviruses with defects on env (66.67% to 21.25%) (p-values: 0.001-0.006). However, Rev-response elements (RRE) remained very conserved during ART; a median (interquartile range) of 0 (0-5.8%) proviruses carried RRE defects. Patterns of gag defects mainly involved start codon or deletion while deletion was the only defect pattern on env. HLA-associated mutations emerged or significantly shifted in env of 5/11 participants, but these mutations did not cause changes in the predicted MHC binding affinity or immunogenicity. Significant changes in predicted bNAbs sensitivity were observed for env of 2/11 participants.
Conclusion: NFL defective proviruses are subjected to significant differential selection pressures on MSD/PSI, gag and env under ART. Gag defects are likely linked to deletions on MSD/PSI suggesting the selection for proviruses with impaired replication and infectivity. Selection against deletions on env is possibly linked to HLA escape mechanism but did not lead to significant changes in MHC binding or immunogenicity suggesting the possible involvement of other immune and viral factors.

463 In-Depth Proviral Sequence Analysis Reveals Conserved Reservoir Landscape Composition Across Group M

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Background: The biology of HIV-1 replication and epidemiology of transmission led to a diverse landscape of viral subtypes heterogeneously distributed across the globe. The majority of people with HIV-1 (PWH) are infected with non-subtype B virus, yet the landscape of persistent HIV-1 is understudied outside of subtype B. In-depth analysis of persistent HIV-1 in PWH across subtypes is essential to globalize HIV-1 cure research and clinical trials. Critically, such analysis is also foundational to the design and validation of molecular assays for latent HIV-1, such as a cross-Group M IPDA.
Methods: We performed an extensive proviral sequencing campaign on samples from hundreds of PWH on ART with broad geographic and Group M coverage. We optimized and employed a new semi-automated, high-throughput, near-full length single-genome PCR (NFL-PCR) workflow to generate proviral amplicons paired with improved pipelines for proviral assembly, alignment, and defect mapping. Proviral quantity and landscape composition were compared between subtypes and CRFs across Group M.
Results: Our analysis revealed highly consistent proviral landscapes across Group M. In all subtypes, the majority of proviruses analyzed harbored fatal deletions, which on average spanned half the genome and most frequently

impacted the env gene. A subset of proviruses were extensively hypermutated in all subtypes. Initial sliding window analysis of deletion position and frequency suggests comparable IPDA proviral discrimination across subtypes using psi and env targets. Optimization of NFL-PCR resulted in substantially increased overall provirus recovery efficiency, and genetically intact proviruses were quantified at a higher frequency in all subtypes (including B) compared with other reports.
Conclusion: The consistency in HIV-1 provirus deletion frequency and position across Group M suggests that conserved mechanisms drive formation of defective proviruses. The dominance of env deletions has important implications for antibody-mediated reservoir immune selection and for global deployment of env-targeting therapeutics. Our improvements to long-range proviral PCR reduce the bias against intact proviruses, resulting in a more accurate analysis of proviral landscape composition in PWH on ART, and will enable comparison of short- and long-range PCR-based reservoir quantification assays. Importantly, our results support the feasibility of a unified IPDA version 2 design with robust performance across Group M for global use.

464 Solo LTR Formation Promotes Elimination of Proviruses in Persons Living With HIV

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Background: A major obstacle for curing persons living with HIV (PLWH) is persistence of HIV-infected cells during combination antiretroviral therapy (ART). Most persistent cells harbor defective proviruses, including solo LTRs, which are the result of cellular homologous recombination during DNA replication and clonal expansion; the recombination event excises the entire coding sequence of HIV, leaving only a solo LTR provirus. Solo HIV LTRs are reported (Anderson et al., 2020; Botha et al. 2023) and may dominate proviral populations, but little is known about their frequency and persistence during ART. We combined a new screen for solo LTR with single genome sequencing (SGS) and integration site analysis (ISA) to identify and characterize solo LTR in PLWH.
Methods: Peripheral blood lymphocytes (PBLs) from adults undergoing ART in clinical protocols at NIH were screened using multiplexed droplet digital PCR (ddPCR) that targets LTR and sequences downstream from the 5' LTR or upstream of the 3'LTR. A high ratio of LTR to non-LTR sequence implies an excess of LTRs and the potential presence of solo LTR proviruses. We developed specific ddPCR to characterize and quantify levels of HIV clones, and designed bridging PCR strategies that amplify solo LTR to validate provirus structure. Integration sites and single genome sequencing were performed in PBL and autopsy tissue when available.
Results: Analysis of PBL from PLWH (N=48) with LTR/gag ddPCR revealed > 90% had excess LTRs (median: 832 excess LTRs/million CD4 cells; range <1-21651). Large clones of solo LTRs were identified in two PLWH; quantification of one clone integrated in HORMAD2 (Anderson et al., 2020) with bridging ddPCR demonstrated this clone now persists 10% of total proviruses >20 years after first identified during early ART. In a second PLWH, analysis of PBL and neoplastic tissue revealed a solo LTR integrated near the FAM9C gene on the X chromosome; As FAM9C is not located pseudoautosomal recombination regions (PARs) where homologous recombination on the X chromosome is restricted, these data demonstrate that cellular mechanisms responsible for homologous recombination are functional outside of PARs.
Conclusion: Screening for highly deleted proviruses will be useful in identifying solo LTR proviruses. HIV solo LTR provirus form in vivo and may be prevalent among proviral populations in adults. Understanding solo LTR formation provides a new insight into requirements for eliminating functional viral sequences from host genome.

465 Longitudinal Evaluation of Viral Tropism in Archived Intact DNA Genomes in Acute HIV-1 Infections

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Background: HIV-1 tropism refers to the ability of the virus to infect CCR5- and/or CXCR4-expressing CD4+ cells. Since CXCR4 expression is associated with naïve T cells, whereas CCR5 is associated with memory T cells, viral tropism has direct implications in the composition of the persistence viral reservoir. Here, we longitudinally evaluate viral tropism using V3-loop sequences derived from an acute infection cohort.
Methods: The FRESH cohort in Durban, South Africa enrolls young women at high risk for acquiring HIV infection who undergo HIV-1 RNA surveillance testing twice a week. We studied 24 women who were detected during acute HIV-1 infection and were followed up to 1102 days: 11 were subsequently treated after >1 year, and 13 were treated 1-3 days post-first-detection. Near-full-length single-genome HIV-1 DNA sequencing (HXB2 638-9632) was performed on longitudinal PBMC samples, and genomes were classified as intact or defective using HIVSeqinR. Viral subtyping was performed with RIP 3.0. Viral tropism was inferred using V3-loop sequences with a subtype-specific algorithm PhenoSeq.
Results: We obtained 697 viral DNA genomes, of which 320 contained full-length Env (247 intact and 73 defective) representing all 24 donors. Intact viral DNA genomes were detected in 23 out of 24 donors: V3-loop analysis revealed that 61% donors were entirely R5-tropic (n=13 subtype C, n=1 A1/K), 26% donors were entirely X4-tropic (n=6, all subtype C), and 13% donors had a mix of R5- and X4-tropic viral DNA genomes (n=3 all subtype C). Tropism remained stable in 82% (14/17) of donors who had longitudinal data, including six who initiated antiretroviral therapy within 1-2 days post-detection, as well as eight who initiated treatment during chronic infection due historic treatment guidelines and remained viremic for a median of 332 days (IQR 330-441). Mixed-tropic populations were observed only in donors who were untreated during acute infection (n=3).
Conclusion: We detected an unexpected high prevalence of X4-tropic archived intact HIV-1 DNA in acute infections in FRESH by PhenoSeq, confirmed by geno2pheno[coreceptor] and C-PSSM (results not shown). Given that previous studies have associated subtype C and acute infections with mostly R5-tropic variants, our results suggest phenotypic studies are needed to further assess the extent and roles of archived X4-tropic variants in intact HIV-1 DNA genomes, which may have implications in the types of cells that would fuel virologic rebound during treatment interruptions.

466 Multiomics Profiling of HIV-Transcribing Cells in People With HIV on Suppressive ART

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Background: HIV reservoir cells actively transcribing HIV persist despite ART, but remain poorly characterized since standard single cell (sc)RNAseq approaches inefficiently identify these cells. In this study, we devised a comprehensive scRNAseq-based approach that increases identification of HIV-transcribing cells, enabling a deep characterization of these cells.
Methods: We developed HIV-seq, an approach whereby HIV primers targeting multiple regions of the HIV genome are added during scRNAseq library preparation to increase our ability to identify HIV RNA+ cells from people with HIV (PWH) under suppressive ART. We paired HIV-seq with a new bioinformatics pipeline, named 2-Step HIV Alignment, to further increase our ability to identify HIV transcripts from scRNAseq datasets. This entailed realigning initially unmapped reads to 1) a subtype B consensus sequence under reduced stringency conditions, and 2) participant-autologous viral sequences. HIV-seq combined with 2-Step HIV Alignment were implemented in the context of multi-omic single-cell sequencing analyses where transcriptomic (scRNAseq), surface phenotypic (CITEseq), and clonal expansion (TCR analysis) data were simultaneously captured on the same cells. A total of 18 PWH under ART were recruited for this study, and 4 of them also provided viremic samples.
Results: Using this combined approach, we were able to increase by up to 40% our ability to detect HIV RNA+ cells from PWH. HIV RNA+ cells were identified from all blood samples and 7 tissue sites (spleen, lymph nodes, ileum, colon, rectum, endometrium, and endocervix) of 15 donors on suppressive ART. The host transcriptome of these HIV RNA+ cells differed in a tissue site-dependent manner, and included Th17 and Trm cells. Unlike HIV RNA+ cells from viremic individuals, those from suppressed individuals did not preferentially exhibit a cytolytic phenotype characterized by higher expression levels of granzymes,

perforin, and granulysin. Shared clonotypes of HIV RNA+ cells (expressing the same TCR) were found in multiple tissue compartments; these cells showed distinct surface phenotypes and transcriptional profiles characteristic of their tissue site of residence.
Conclusion: Our study presents new tools that improve detection of HIV RNA+ cells at the single-cell level, enabling us to establish an atlas of HIV-transcribing cells from PWH on suppressive ART. HIV-transcribing cells clonally expand and disseminate to multiple tissue sites where they adopt tissue site-specific features.

467 HIV-1 Transcriptional Activity Is Largely Driven by Defective Proviruses

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Background: The majority of cells that are latently infected with HIV-1 do not produce viral RNA, making it difficult for the immune system and current antiretroviral therapy (ART) to target them. To study the underlying mechanisms governing latent HIV-1 infection, a panel of reverse transcription droplet digital polymerase chain reaction (RT-ddPCR) assays specific for different HIV-1 transcripts has been described that define distinct blocks to transcription.
Methods: We designed the Rainbow transcriptional HIV-1 RNA 4-plex digital PCR assay, compatible with the QIAcuity 5-plex system, to quantify elongated (long LTR), unspliced (pol), multiple-spliced (Tat-Rev) and completed transcripts (polyA). To evaluate technical performance, a 2-fold dilution curve was prepared containing J-Lat copy DNA (cDNA), ranging from 0.005 to 2.5 ng input, and measured in 20 replicates. This assay was then applied to samples from 40 people living with HIV (PLWH) on ART. Additionally, the HIV-1 DNA reservoir was quantified by the Rainbow proviral HIV-1 DNA assay. Intactness levels were defined by two target regions: psi and env (IPDA), and by four target regions: psi, env, gag and pol (D4PCR). Levels of defective proviruses were measured by the difference between total and intact HIV-1 DNA levels (D4PCR).
Results: Linear quantification was observed for each HIV transcript (slope: 0.98). The Limit of Detection (LoD) was <10 copies/well for all HIV-1 RNA transcripts, except poly A (average: 11.1 copies/well, range: 5.6-24). The Limit of Blank (LoB) was calculated by using 90 negative template control (NTC) samples, resulting in an LoB of 1 copy/well or less in long LTR, pol and Tat-Rev. The LoB of polyA was 15.75 copies/well. In samples from 40 PLWH, HIV-1 RNA levels were compared to total and intact HIV-1 DNA levels (Figure 1). We found that intactness levels by IPDA correlated better with HIV-1 RNA transcripts than intactness levels by D4PCR. Interestingly, defective proviruses showed a stronger correlation with HIV-1 RNA transcripts compared to intact proviruses.
Conclusion: The Rainbow proviral HIV-1 DNA and transcriptional HIV-1 RNA assay allow us to map the characteristics of the viral reservoir by using a minimal amount of sample. This analysis resulted in a strong correlation between defective proviruses and HIV-1 RNA transcripts, suggesting that the HIV transcriptional activity is largely driven by defective proviruses.

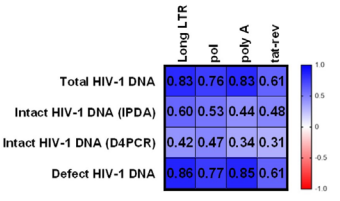

Figure 1: Total, intact and defect HIV-1 DNA levels correlate with HIV-1 RNA transcripts. This heatmap represents the Spearman correlation factors between total/intact/defective HIV-1 DNA levels (copies/million CD4+ T cells) and HIV-1 RNA transcripts (copies per µG RNA). All correlations are significant (P < 0.05).

468 Dynamics of Different Proviruses and HIV Transcripts After Acute ART Treatment

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Background: Different subsets of HIV-transcribing cells may contribute to immune activation and rebound. We investigated the dynamics of proviruses and different HIV transcripts after initiation of ART during acute infection. We hypothesized that completed, multiply spliced, and intact HIV RNA will decay at a faster rate than initiated, 5'elongated, or defective HIV RNA.
Methods: CD4+T cells were isolated from blood before ART (T1) and 6 mo (T2) ± 1 year after suppressive ART from 9 PWH (Treat Acute Cohort). U3-U5, TAR, R-U5/Gag and Pol HIV DNA regions, as well as 5'defective (Psi−RRE+), 3'defective (Psi+RRE-), and intact (Psi+RRE+) proviruses, were measured by ddPCR. HIV transcripts, including total initiated (TAR), 5'elongated (R-U5/Gag), mid-transcribed (Pol, unspliced), completed (U3-polyadenylated), multiply spliced (Tat-Rev), 5'defective, 3'defective, and intact HIV RNA, were measured by RT-ddPCR. We also calculated ratios of each HIV RNA to the corresponding HIV DNA (to account for proviral mutations) and ratios of one HIV RNA to another (to measure blocks to transcription).
Results: In untreated infection, we observed an excess of initiated over 5'elongated HIV RNA (median 5'elongated/initiated=0.19; P=0.03) but no significant difference between levels of 5'elongated and completed HIV transcripts. ART induced progressive reductions in initiated (median T1/T2=11; P=0.06), 5'elongated (84; P=0.03), mid-transcribed (143; P=0.03) and completed (503; P=0.03) HIV transcripts. These trends persisted after normalization to the corresponding HIV DNA. Completed transcripts decayed faster than initiated (P=0.03) or 5'elongated transcripts (P=0.03). The ratio of completed/5'elongated HIV RNA was lower at T2 than T1 (P=0.03). ART also reduced intact, 3'defective, and 5'defective HIV RNA (P<0.05 for all). Intact transcripts tended to decay faster than Psi+RRE- HIV RNA (P=0.06). After normalizing to the corresponding HIV DNA, ART reduced Psi+RRE- HIV RNA/DNA (median T1/T2=11.3; P=0.03) and tended to reduce intact HIV RNA/DNA (376.9; P=0.09).
Conclusion: Although ART does not target HIV transcription, the pattern of HIV transcriptional processivity differed between untreated infection (less of a block to completion) and early ART suppression. ART reduced completed HIV RNA more than initiated or 5'elongated HIV RNA, and tended to reduce intact HIV RNA more than 3'defective HIV RNA. These findings suggest distinct clearance of cells depending upon HIV RNA processivity and absence of proviral mutations.

469 Multiomics of Detectable vs Undetectable Monocyte Cell-Associated HIV RNA During Acute HIV

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Background: Monocytes play a significant role in the early immune response during acute HIV infection (AHI), and the extent myeloid cell dysregulation has implications for long-term central nervous system (CNS) outcomes. We hypothesized that monocytes carrying HIV RNA would show increased transcriptional dysregulation during AHI.
Methods: We isolated ultra-high purity monocytes from 25-40 million PBMC aliquots of 17 participants in the Thai RV254/SEARCH010 AHI cohort obtained prior to ART during AHI (Fiebig I-V) to measure genome-wide transcriptome expression and epigenetic profiles and assess the detection of cell-associated (CA-) HIV RNA. Mann Whitney and T tests examined demographic differences between those with detectable and undetectable monocyte CA-HIV RNA. Differential expression analyses compared participants with detectable versus undetectable HIV RNA using an FDR adjusted P value.
Results: Participants had a median age of 26 yrs, median $\log_{10}$ plasma viral load of 5.55 copies/mL (IQR: 4.87-6.51), CD4+ T cell count of 451 cells/mm^3 (324.5-644), and CD4/CD8 ratio of 0.64 (0.37-1.09). 11/17 participants had detectable CSF HIV RNA levels in supernatant. 41% were in Fiebig stages I/II, and 59% in stages III-V. 8/17 (47%) had detectable monocyte HIV CA-RNA. Those with detectable monocyte HIV RNA trended higher in plasma viral load (6.17 vs 4.79; p=0.05) and lower in CD4/CD8 ratio (0.52 vs 1.02; p=0.06), but there was no difference in CD4 count or Fiebig stage between groups. 70 genes were significantly differentially expressed in monocytes comparing participants with detectable versus undetectable monocyte HIV RNA at an FDR adjusted P < 0.05. Notably, expression of immunomodulatory inflammatory gene CD38, cell surface receptor gene CD40, interferon-induced gene MX1, and viral RNA sensor IFIH1 were significantly higher in participants with detectable versus undetectable monocyte cell-associated HIV RNA. Moreover, we identified that expression of pro-apoptotic BCL-2 protein family gene PMAIP1 and transcription

factors SP3 and ETV3 were significantly decreased in participants with detectable versus undetectable monocyte CA-HIV RNA.
Conclusion: In AHI, detectable monocyte HIV RNA is linked to notable transcriptional dysregulation, potentially impacting long-term myeloid cell programming and CNS outcomes. Identifying individuals with a higher transcriptionally active HIV myeloid reservoir warrants further study to guide early myeloid targeted treatment strategies and prevention of inflammation.

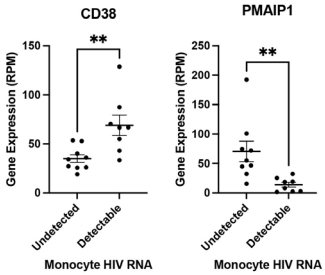

Figure. Top differentially expressed genes in monocytes from participants with undetectable and detectable cell-associated HIV RNA during AHI **P<0.01

470 Antiretroviral Therapy Within 2 Years of HIV Acquisition Is Associated With Fewer Viral Blips

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Background: Viral blips may represent bursts of HIV replication or clonal expansion from reservoirs. Antiretroviral therapy (ART) started within days of HIV acquisition may limit reservoirs, thereby decreasing blips, but is uncommon. We evaluated the impact of ART initiation within months to years after HIV acquisition on the occurrence of viral blips.
Methods: The ongoing U.S. Military HIV Natural History Study enrolls adult U.S. Department of Defense beneficiaries with HIV. HIV RNA results and ART medications are extracted from centralized electronic medical records. These analyses included participants who had an estimated HIV seroconversion date (midpoint of documented negative and positive test dates), achieved viral suppression (VS) ≤400 copies/mL within 1 year after starting ART, and had at least 3 HIV RNA measurements after achieving VS. A blip was any HIV RNA 401-1000 copies/mL immediately preceded and followed by HIV RNA ≤400 copies/mL without a change in ART. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for factors potentially associated with the time from VS to first viral blip.
Results: From January 1996 to December 2022, 1,413 participants on suppressive ART met inclusion criteria for these analyses. Their median age at HIV diagnosis was 29.2 years (interquartile range 24.9-35.4) and a majority were males (96.3%). Viral blips were observed in 88 (6.2%) participants. Of these, 68 (77.3%) had a single blip, 13 (14.8%) had two blips, four (4.5%) had three blips, and three (3.4%) had four blips. The overall incidence of blips was 1.2 blips per 100 person-years (95% CI 0.9-1.4) and blip incidence decreased over time (Panel A). ART initiation within 24 months of estimated HIV acquisition was associated with decreased hazard of viral blips as compared to ART initiation after more than 24 months (0-6 months HR 0.32 [95% CI 0.20-0.52]; 6-12 months HR 0.48 [95% CI 0.35-0.67]; 12-24 months HR 0.52 [95% CI 0.40-0.69]; controlling for age, sex, race, time-updated ART regimen, time-updated CD4, HIV RNA at ART initiation, ART adherence [proportion of days covered >90%], history of hepatitis B, and history of hepatitis C; unadjusted in Panel B).
Conclusion: Participants who initiated ART within two years of HIV acquisition had lower hazard of blips. Further research to characterize the clinical implications of blips and how they relate to HIV reservoir dynamics is ongoing. HIV reservoir plasticity may extend beyond the period of acute HIV.

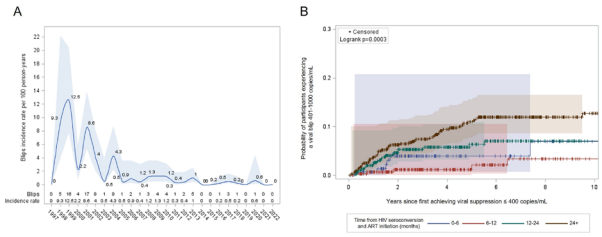

Figure. (A) Blip incidence rate (blips per 100 person-year) among U.S. Service members and their medical beneficiaries living with HIV, by year. (B) Kaplan-Meier survival curves by ART initiation group

471 Reduced HIV RNA Transcription During Long-Term ART Is Associated With Increased Ki67+ CD8+ T-Cells

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Background: Sex-based differences affect HIV infection and immune responses. We investigate longitudinal T cell phenotypes and their association to HIV reservoir in men and women during long term suppressive ART.
Methods: From the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials, we identified 52 cisgender women and 29 age-matched men. Participants were between the ages of 40-53 at time of ART initiation and virally suppressed (<20cp/ml) throughout the entire study period (318 timepoints, median 4 per participant). At each timepoint we measured markers of activation (HLA-DR+CD38+), cytotoxicity (CD107a+), cycling (Ki67+), exhaustion (TIGIT+PD-1) on T cell memory subsets (central memory, effector memory, terminally differentiated) and cellular HIV DNA and RNA (by ddPCR). Immune cell trajectories were analyzed with a negative binomial generalized additive model. Association between immune cells and HIV reservoir measures were analyzed using a similar model with a gaussian distribution. All p-values were adjusted for multiple comparisons (FDR).
Results: At baseline, median CD4+ T cells were 218 cells/uL for women and 238 for men. Median follow up was 106 months for women and 83 for men. As expected, total CD4+ T cells increased, whereas CD8+ T cells decreased over time (p<0.001). Overall, we found a significant decrease in cellular markers of cycling (Ki67+) and activation (CD38+HLA-DR+) across all memory subtypes in CD4+ and CD8+ T cells (p<0.001). Similarly, we found a significant decrease in cellular markers of exhaustion (TIGIT+PD-1+) in all CD4+ T cell subtypes (p<0.01) but not in CD8+ T cells. Markers of T cell cytotoxicity (CD107a+) remained elevated over time. We did not observe any significant sex-difference in T cell dynamics. Increased proportions of effector memory and terminally differentiated CD8+ T cells expressing Ki67 were associated with lower cellular HIV RNA (p=0.037), and lower HIV DNA (p=0.016).
Conclusion: While markers of T cell activation and cycling keep decreasing, cytotoxic CD4+ and CD8+ T cells and exhausted CD8+ T cells remain elevated in people with HIV despite years-long HIV suppression, as a possible consequence of ongoing antigen exposure. In both sexes, increased Ki67+CD8+ T cells correlate with reduced cellular HIV RNA and DNA. Although women showed a slower decline in HIV reservoir than men in this cohort (PMID:34612493), we did not detect any sex-differences in T cell phenotypes, suggesting that deeper phenotypic analysis might be needed.

472 HIV-2 Transcription in Blood CD4+ T-Cells Is Inhibited by Blocks to Elongation and Completion

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Background: HIV-2 differs from HIV-1 in sequence, transmissibility, and pathogenicity. Both can establish a latent infection that prevents cure, but it is unclear if the mechanisms that inhibit viral expression are the same for both viruses. As with HIV-1, we hypothesized that HIV-2 expression may be inhibited by blocks to transcriptional elongation, completion, and splicing.

Methods: CD4+ T-cells were isolated from blood of 6 ART-suppressed HIV-2 infected individuals. Levels of cell-associated U3-U5 [Read-Through], initiated [TAR], 5'elongated [R-U5-pre-Gag], Gag, Nef, completed [PolyA] and multiply spliced [Tat-Rev] HIV-2 transcripts were measured by HIV-2 specific RT-ddPCR assays. U3-U5, TAR, R-U5-pre-Gag, Gag, and Nef HIV-2 DNAs were also quantified by ddPCR. For some individuals, primers and probes were matched to pre-existing proviral sequence data.
Results: HIV-2 TAR DNA levels (median=1163 copies/1e6 cells) were similar to U3-U5 (1112) and were higher than R-U5-pre-gag (314), gag (211), and nef (86) HIV-2 DNA levels (P<0.04 for all). Levels of HIV-2 initiated transcripts (median=6339 copies/µg) were greater than 5'elongated transcripts (316; P<0.04). 5'elongated HIV-2 RNA levels were higher than Gag transcripts (median=71; P<0.04) and tended to be higher than Nef (13; P=0.063) and Poly A (4; P=0.063) HIV-2 transcripts. These trends persisted after normalization to the corresponding HIV-2 DNA regions. Ratios of 5'elongated/initiated HIV-2 RNAs (5'elongation) were higher than Gag/initiated (P<0.04) and Read-Through/initiated (P<0.04). The ratios of 5'elongated/initiated (median=0.069) HIV-2 RNAs also tended to be higher than Nef/initiated (distal elongation, 0.0022) and PolyA/initiated (completion, 0.0015; P= 0.063 for both). We calculated that a median of 86% of HIV-2 transcripts are blocked at elongation, while 99% of transcripts are blocked at completion.
Conclusion: Differences in the levels of HIV-2 transcripts and ratios suggest that HIV-2 expression is inhibited by blocks to elongation and completion of HIV-2 transcription. These mechanisms, which are also observed in HIV-1 infection, likely contribute to latent infection with both viruses. Future studies aimed at curing HIV-2 should focus on determining the cellular factors underlying these blocks to transcriptional elongation and completion.

473 Variable Persistence of Non-Suppressible Viremia on Antiretroviral Therapy

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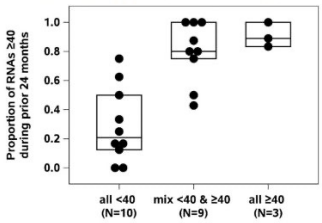
Background: Nonsuppressible viremia (NSV) on antiretroviral therapy (ART) has been shown to originate from infected T-cell clones rather than viral replication. The variation and longitudinal persistence of NSV have not been well defined. To address this knowledge gap, we enrolled a longitudinal cohort of persons with NSV on stable ART.
Methods: We enrolled individuals living with HIV into a longitudinal ACTG cohort study of NSV who met the following inclusion criteria: At least 2 HIV-1 RNA values ≥20 and ≤1500 copies (c)/mL within 24 months prior to entry, at least 1 documented HIV-1 RNA value ≥20 and ≤1500 c/mL within 12 months prior to entry and on uninterrupted ART for at least 12 months. Persistence of NSV was categorized into three groups among those without ART changes or interruptions using RNAs at week 0 (entry), week 24, 48 (all 3 required): 1) all RNAs <40 c/mL, 2) mix of RNAs <40 and ≥40 c/mL, and 3) all RNAs ≥40 c/mL. Analyses of participant characteristics at study entry compared the 3 groups by age, sex, gender, pre-ART plasma HIV-1 RNA (log_{10} c/mL), pre-ART and entry CD4+ T-cell count (cells/mm³), entry CD8+ T-cell count (cells/mm³), entry CD4:CD8 ratio, years on ART at entry, and the proportion of RNAs ≥40 c/mL during 24 months on ART prior to entry
Results: 22 participants were analyzed: 1 (5%) female; median age 58 (range 24-75); median years on ART 9.5 (range, 2.9-26.8). The reported pre-study duration of NSV ranged to 10+ years. At week 48, 8 of 22 (36%) still had quantifiable viremia (≥40 c/mL). Only 3 (14%) participants had RNA ≥40 c/mL at weeks 0, 24 and 48; 10 (45%) had RNA <40 c/mL at all three weeks and 9 (41%) had mix of <40 and ≥40 c/mL. The median pre-ART CD4 T-cell count for groups 1, 2 and 3 were 98, 121 and 164 cells/mm³, respectively. The only factor significantly associated with persistence of NSV ≥40 c/mL was the proportion of plasma HIV RNA measurements that were ≥40 c/mL during the 24 months on ART prior to entry (p=0.001, Kruskal-Wallis Test) (Figure).
Conclusion: NSV was dynamic and consistently ≥40 c/mL at 0-48 weeks in only 14% of participants. Persistence of NSV over 48 weeks was only associated with the proportion of RNAs ≥40 c/mL prior to entry. These results are consistent with variable persistence of clones producing virus with the minority being stable, and the majority declining in size and/or producing less virus.

Figure: The proportion of HIV RNAs ≥40 c/mL on ART during the 24 months prior to study entry, by the three groups defined by study week 0, 24, 48 HIV RNAs (p=0.001 across groups)



474 Different Impact of Latency Reversal in Cells From People With HIV Viremia and With ART Suppression

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Background: Induction of viral transcription using latency reversing agents (LRAs) is a promising approach to reduce the HIV reservoir but has shown modest effects in virally suppressed people with HIV (PWH) on ART. The administration of LRAs at the time of ART initiation may enhance the efficacy of this approach, since latently infected cells may be more sensitive to latency reversal in a viremic setting. However, the effect of LRAs on infected cells isolated from untreated PWH is largely unknown. Here, we compared the effect of the ingenol-based PKC agonist GSK445A alone or in combination with the HDACi romidepsin (RMD) on HIV transcription in cells from viremic and virally suppressed individuals.
Methods: We measured the effect GSK445A +/- RMD on HIV transcription in CD4+ T cells isolated from the blood of 10 PWH on ART with undetectable plasma viral load as well as in 18 untreated individuals (median = $3.31x10^5$ HIV RNA copies/mL). CD4+ T cells were conditioned or not for 4h with RMD (40nM) and pulsed for 30min with GSK445A (5nM) in the presence of antiretroviral drugs. HIV transcription was assessed 18h post-stimulation by RT-qPCR for cell-associated LTR-gag RNA.
Results: As expected, the addition of RMD enhanced the GSK445A-mediated induction of HIV transcription in cells from ART-suppressed PWH (mean fold change over GSK445A alone 35.4, p=0.06). In cells from viremic participants, stimulation with GSK445A also led to a robust induction of HIV transcription (mean fold change 4.1, p<0.0001). However, the addition of RMD inhibited the induction of HIV transcription mediated by GSK445A (mean fold change 0.62, p=0.0003). To determine whether this apparent decrease could be attributed to the death of infected cells upon latency reversal, we used the pan-caspase inhibitor Q-VD-OPh 20µM. Inhibition of apoptosis not only rescued but also enhanced the levels of HIV transcripts measured in cells from viremic participants (mean fold increase in HIV RNA 2.1).
Conclusion: The combination of GSK445A and RMD leads to an apparent reduction in the levels of HIV transcripts in cells isolated from viremic PWH. This decrease is abrogated by a caspase inhibitor, suggesting that latency reversal in a viremic setting leads to the death of the infected cells. Our results suggest that the administration of LRAs at the time of ART initiation, when the bulk of the reservoir is established, may reduce the frequency of persistently infected cells.

475 Strong Latency Reversal by *C. megalobotrys* Extract in ART-Suppressed PBMC and Humanized Mice

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Background: Latency reversing agents (LRAs) have had limited success in vivo, indicating a need for more potent agents. "Mukungulu," an extract prepared from the bark of Croton megalobotrys and traditionally used for HIV/AIDS management in Northern Botswana (Africa), is an LRA in latent HIV cell lines and contains protein kinase C-activating phorbol esters (PMID: 28970153). However, the properties of Mukungulu ex vivo in ART suppressed cells from PLWH and/or in vivo are not known.

Methods: Using cells from 12 PLWH suppressed on ART for > 3 years cell pellets and culture supernatants from 20 million PBMC in triplicate independent tests were assessed for p24 protein by Simoa (PMID: 33796087) after 72 hours treatment with Mukungulu (1 µg/mL) or anti-CD3/CD28 positive control. Isolated CD4 T-cells (5 million) were also tested in 3 donors. Intact and defective proviral DNA were assessed by IPDA (PMID: 30700913). 12 BLT-Humanized male mice were infected with HIVSUMA, suppressed with ART for 7 weeks (PMID: 36460646), and injected i.p. with 5 µg/mL Mukungulu (N=7) or PBS vehicle (N=5) and measured after 24 hours for pVL and vRNA from human cells. Analysis was done with Prism software.
Results: In PBMC from 12 ART suppressed donors, Mukungulu induced 0.30 ± 0.15 and 0.46 ± 0.24 pg/mL of p24 protein in pellets and supernatants, respectively, without cytotoxicity, compared to only 0.11 ± 0.06 and 0.17 ± 0.08 pg/mL of p24 induced by anti-CD3/CD28 (p = 0.06 and 0.07). In contrast, Mukungulu induced no detectable p24 in pellets or supernatants in isolated CD4+ cells, compared to anti-CD3/CD28 inducing 0.49 ± 0.12 and 0.38 ± 0.14 pg/mL of p24. Notably, p24 levels from PBMC pellets and supernatants induced by Mukungulu correlated well with intact provirus reservoir size (r2 = 0.60 and 0.74, respectively) but not with defective provirus reservoir size (r2 = 0.03 and 0.08). Finally, in humanized mice, Mukungulu induced 1336 ± 402 vRNA copies / million human cells plus a pVL of 391 ± 394 copies / mL, compared to no change by PBS, without obvious toxicities.
Conclusion: Mukungulu is a potent LRA ex vivo and in vivo. It induces virus production from the intact viral reservoir of CD4+ cells with ~2.5 more activity than anti-CD3/CD28. However, this reactivation is dependent on PBMC and not isolated CD4+ cells, indicating that additional cell-types contribute to its mechanism of latency reversal.

Table 1. HIV-1 p24 Induction by *C. megalobotrys* Extract

p24 simoa (pg/mL)		PBMC	CD4+ cells	PBMC correlation with IPDA (r^2) (N=10)			
N donors		12	3	Intact provirus	p value	Defective provirus	p value
pellets	No treatment	0.01 ± 0.01	0.02 ± 0.02				
	anti-CD3/CD28	0.11 ± 0.06	0.49 ± 0.12	0.74	0.001	0.15	0.27
	1 ug/mL Mukungulu	0.30 ± 0.15	0.03 ± 0.03	0.60	0.008	0.03	0.63
super-natants	No treatment	0.07 ± 0.04	0.03 ± 0.03				
	anti-CD3/CD28	0.17 ± 0.08	0.38 ± 0.14	0.71	0.002	0.54	0.02
	1 ug/mL Mukungulu	0.46 ± 0.24	0.01 ± 0.00	0.74	0.001	0.08	0.43

476 Transcriptomic HIV Reservoir Profiling Reveals a Role for Mitochondrial Functionality in HIV Latency

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Background: Improved characterization of the HIV reservoir is crucial for devising effective cure strategies. We developed a strategy for isolating and characterizing the viral reservoir in peripheral blood from people with HIV (PWH). We hypothesize that short abortive HIV transcripts are present in latently infected cells, and based on this we developed an innovative flow cytometry-fluorescent in situ hybridization (flow-FISH) allowing HIV reservoir detection and cell sorting without prior activation. This method was used for direct ex vivo detection and isolation of HIV+ CD4 T cells harboring transcriptionally latent or active HIV and allowed for transcriptomic analysis of the viral reservoir.
Methods: Peripheral blood mononuclear cells (PBMCs) from 21 ART-naïve PWH from the Amsterdam Cohort Studies were used for this study. Flow-FISH was performed with probes targeting either abortive (TAR+Gag–) or elongated HIV transcripts (TAR+Gag+), representing latently and productively infected cells, respectively. Flow cytometry sorting was used to isolate three distinct cell populations (i.e. TAR+Gag–, TAR+Gag+, and probe-negative) from CD4 T cells of five PWH. The transcriptomic profile was determined by 3' RNA sequencing (RNAseq).
Results: Our flow-FISH method detected between 10-751 HIV+ cells per 10^4 CD4 T cells in PBMCs from PWH, of which 1-47 per 10^4 CD4 T cells harbored transcriptionally latent HIV (TAR+Gag–) and 7-727 per 10^4 CD4 T cells harbored transcriptionally active HIV (TAR+Gag+; Figure A). Supervised RNAseq analysis allowed for the identification of transcriptomic signatures that separate the isolated populations independently of person-related characteristics. Notably, we identified several differentially expressed mitochondrial genes in latently infected (TAR+Gag-) compared to productively infected (TAR+Gag+) CD4 T cells (Figure B). Interestingly, enhancing mitochondrial function increased HIV transcriptional activity in latently infected CD4 T cells from PWH.
Conclusion: Our flow-FISH approach was able to detect and differentiate between cells with transcriptionally latent or active HIV in PBMCs from PWH without the need for ex vivo stimulation. Transcriptomic profiling showed an association between diminished mitochondrial functioning and the transcriptional activity of the viral reservoir. These findings underline the relevance of altered cellular metabolism in HIV infection, and support the development of therapeutics that take this into consideration.

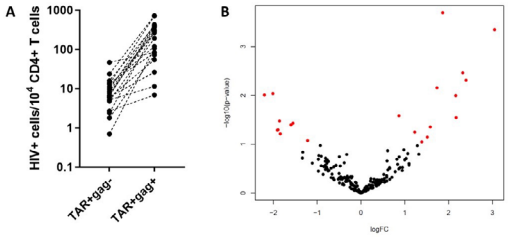

Figure. (A) Total number of detected transcriptionally latent (TAR+Gag-) and transcriptionally active (TAR+Gag+) HIV+ CD4 T cells by flow-FISH and (B) paired differential gene expression analysis of TAR+Gag- compared to TAR+Gag+ HIV+ CD4 T cells from PBMCs of PWH, with differentially expressed genes shown in red (log FC>0.5 and p-value<0.1).

477 Investigating the Effects of Chromatin Spatial Folding on HIV-1 Latency

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Background: Persistence of HIV-1 in latent reservoirs is a major obstacle that prevents its eradication and cure. Understanding the mechanisms governing HIV-1 latency is crucial to eliminate this reservoir. Spatial folding of chromatin governs cellular gene expression. However how 3D genome organization affects HIV-1 latency is unknown
Methods: To investigate the impact of chromatin spatial folding on HIV-1 latency, we used a comparative approach that takes advantage of the different integration profiles of wild type (WT) HIV-1 and a capsid mutant virus N74D. We mapped unique integration sites (UISs) for HIV-1 WT and N74D to DamID and HiC data. Next, to investigate how different integration site distribution may affect latency, jurkat cells were transduced with either WT or N74D single cycle HIV-1 vectors expressing GFP from the LTR. GFP+ cells were sorted after 48 hrs, and latency was established. Lastly, to identify UISs functionally relevant for latency, latently infected cells (WT and N74D) were stimulated serially by TCR engagement followed by inhibition of HDAC6 and sorted into reversible (GFP+) and deep (GFP-) latency populations at each step
Results: We observed that WT HIV-1 integrated more frequently in A1 compartment, whereas N74D virus integrated more frequently into lamina associated domains (LADs). These results were confirmed in ART-treated patients' cells. We found that WT virus becomes latent more slowly and can be reactivated more efficiently than N74D virus by TCR stimulation or PMA. Epigenetic profiling showed that the pan histone deacetylase inhibitor SAHA and the G9a inhibitor BIX-0124 reversed both WT and N74D latency with equal efficiency; however, selective inhibition of HDAC6, inhibition of FOXO-1 or AzadC reversed WT more potently than N74D latency. Integration site analysis on sorted GFP+ and GFP- cell populations revealed that, in WT HIV-1 infected cells, latency was associated with significantly fewer UISs in the A1 compartment and significantly more UISs in the B1 compartment. Deep latency was associated with more UISs in intergenic regions and fewer UISs in exonic regions than reversible latency. In N74D virus infected latent cells, deep latency was associated with greater distance of UISs from transcriptional start sites
Conclusion: We propose that deep latency may be linked to integration into particular 3D chromatin regions enriched for certain epigenetic marks and gene clusters, which might be specifically targeted to either induce, or prevent, virus reactivation.

478 Modulation of IRF7-Driven Transcription as a Strategy to Control HIV-1 Latency

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Background: The persistence of a latent viral reservoir represents a major barrier shared by current HIV cure strategies. Emerging evidence suggests that

modulation of innate immunity could impact viral latency and contribute to the clearing of HIV reservoir. Our previous data indicated that IRF7 expression correlates with HIV latency reversal. Here, we demonstrate the key role of IRF7 in HIV-1 transcription and latency, identifying also novel therapeutic agents useful in HIV eradication.

Methods: Latency was evaluated by non-clonal models drug-treated, alone or in combination with known LRAs. qPCR and WB were used to assess gene and protein expression. IRF7 loss and gain-of-function models were developed by siRNA or plasmid overexpression. IRF7 role in HIV-1 transcription was evaluated by measuring LTR-driven transactivation in TZM-bl cells and co-immunoprecipitation. Immunophenotyping of ex vivo treated CD4+ T-cells from ART-suppressed HIV+ subjects was performed by flow cytometry and latency reactivation/promoting activity was measured by qPCR in cell supernatant.

Results: IRF7 expression correlates with latency reversal/promoting capacity of LRAs/LPAs, including PMA, PNB, JQ1 and the JAK2inhibitors fedratinib and pacritinib among others (r2= 0.8; p-value=0.0012). Downregulation of IRF7 impaired the latency reversal capacity of LRAs (p=0.005). On the contrary, overexpression of IRF7 enhances Tat-mediated transactivation of integrated HIV in the presence of LRAs (at least 50% increase, p=0.05). Coimmunoprecipitation studies showed physiological interaction between Tat protein and IRF7, relating IRF7 to HIV-1 transcription control. The JAK2 inhibitor pacritinib dowregulated IRF7 expression and thus, was used to further explore IRF7 role in HIV latency. Pacritinib significantly blocked HIV-1 reactivation both alone or in combination with PMA or VOR in non-clonal models of HIV-1 latency (50% reduction, p=0.05) and ex vivo in CD4+ T cells from ART-suppressed HIV+ subjects (1log reduction). Immunophenotypic characterization of pacritinib-treated primary CD4+ T cells from PLWH showed no major changes on CD4+ T cell subsets nor activation markers. Moreover, pacritinib significantly reduced the presence of multispliced HIV transcripts in primary CD4 T cells.

Conclusion: IRF7 controls latent HIV-1 transcription and plays a role in both HIV-1 reactivation or blockade. Moreover, modulation of IRF7 expression through pharmacological agents might represent an asset to current HIV-1 cure strategies.

479 Reversing HIV-1 Latency by Targeting RasGRP1-Dependent Biogenesis of P-TEFb

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Background: The deliberate reactivation of latent HIV-1 to enable clearance of persisting latently infected memory T cells – the Shock and Kill strategy – has had limited success because efficient, non-toxic latency-reversing agents (LRAs) remain to be discovered. We are taking a direct approach to LRA development based on the principle that proviral reactivation is tightly coupled to the posttranscriptional biogenesis of P-TEFb, a cellular transcription elongation factor whose expression is highly restricted in resting memory T cells. Recently, we reported that naturally occurring diacylglycerol (DAG)-mimicking protein kinase C (PKC) agonists stimulate the posttranscriptional expression of the cyclin T1 (CycT1) subunit of P-TEFb to reactivate latent HIV-1 primarily via the RasGRP1-Ras-Raf-MEK-MAPK ERK1/2 signaling pathway rather than through PKC enzymes. Here we describe synthetic agonists that preferentially bind RasGRP1 over PKC and can safely activate P-TEFb to reverse HIV-1 latency in primary CD4+ T cells.

Methods: Synthetic DAG indololactones, with known differential affinities for PKC and RasGRP, were tested for their ability to stimulate P-TEFb expression in healthy donor-derived memory CD4+ T cells. Combinatorial LRA studies were performed in a primary CD4+ T-cell latency model to examine the effectiveness of DAG indololactones at synergizing with LRAs that target proviral transcription initiation.

Results: Three of the 4 DAG indololactones we tested were more effective at inducing CycT1 and active P-TEFb than the T-cell activation markers CD69 and CD25. The DAG indololactone 2A-127, which preferentially binds RasGRP1 over PKC more than 60-fold, synergized with the HDACi SAHA in reactivating latent HIV-1 in primary T cells. DAG indololactones and other DAG-mimicking agonists stimulate CycT1 protein synthesis by activating mTORC1 kinase through ERK1/2 MAPK signaling.

Conclusion: DAG indololactones can stimulate the posttranscriptional expression of P-TEFb in memory T cells at concentrations below the threshold needed to induce T-cell activation through a RasGRP1-mediated ERK1/2-mTORC1-S6K-rpS6 pathway. These agents can synergize with HDAC inhibitors, thereby bolstering the hypothesis that a two-pronged strategy that targets P-TEFb biogenesis and stimulates RNA polymerase II recruitment to the HIV-1 promoter is needed to reverse HIV-1 latency efficiently.

480 Monovalent and Bivalent SMAC Mimetics Reverse HIV Latency and Decreases the HIV Reservoir

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Background: Latently infected CD4+ T cells persist in people living with HIV (PLWH) despite suppressive antiretroviral therapy (ART). This persistence may be due to the over-expression of pro-survival proteins such as the inhibitors of apoptosis (IAP) proteins. SMAC mimetics (SMACm) are small molecule compounds that inhibit IAPs, leading to their degradation and ultimately the activation of apoptosis. While bivalent SMACm are known to be more potent than monovalent SMACm, they cause significant toxicities, which have not been seen in clinical trials of monovalent SMACm. Here we investigated whether monovalent and bivalent SMACm could reverse latency and/or deplete the reservoir.

Methods: Latency reversal by monovalent (GDC0197, GDC0152, LCL161, Xevinapant) and bivalent (AZD5582, BV6) SMACm was assessed in J-Lat 10.6 cells (flow cytometry for GFP expression); the dual-reporter primary CD4+ T cell latency model Morpheus (flow cytometry for productive marker mCherry); and ex vivo CD4+ T cells from PLWH on ART (using HIV transcriptional profiling by digital PCR). Depletion of infected cells in ex vivo cultures was measured by the Intact Proviral DNA assay. Proliferation and function of HIV-specific CD8+ T cells following treatment with SMACm was measured using HIV-specific tetramers and flow cytometry.

Results: The bivalent SMACm AZD5582 (100nM) was the most potent latency reversal agent in J-Lat10.6 cells (fold change (FC) reactivation over untreated=22.92, p=0.03) and in the primary cell latency model (FC=1.43, p=0.03). AZD5582 partially overcame all blocks in HIV RNA transcription inducing multiply spliced HIV transcripts (FC over untreated=2.35, p=0.03). AZD5582 treatment also led to a decline in intact HIV provirus (FC=0.51, p=0.02). The monovalent SMACm GDC0197 reversed latency in cell lines (FC=1.82) and primary T cells (FC=1.30, p=0.001); but could only induce HIV RNA transcription initiation (FC=4.26, p=0.03), and not elongation or completion. GDC0197 induced the proliferation of tetramer positive cells (FC=5.63 over untreated, p=0.0001) and enhanced killing of Gag peptide-loaded target cells (FC=1.47 killing over untreated). This was not observed with AZD5582.

Conclusion: Bivalent SMACm can reactivate latent HIV and deplete the reservoir. Monovalent SMACm although less potent in latency reversal, may have a novel role in enhancing clearance of the reservoir through altering antigen presentation and inducing greater CD8+ T cell mediated killing.

481 Optimal Administration Timing of Latency Reversal Agents to Reduce Effectively the HIV Reservoir

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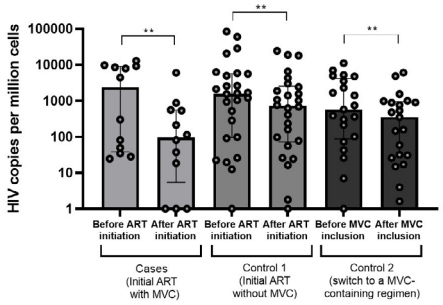
Background: The administration timing of Latency Reversal Agents (LRA) may impact the success of strategies aimed to HIV functional cure. Maraviroc (MVC) is an antiretroviral drug that exhibits HIV latency-reversing properties by activating viral transcription through NF-κB pathway. We aimed to evaluate the efficacy on HIV-DNA reduction following MVC administration at the time of ART initiation (with detectable viral load), or in patients under suppressive ART.

Methods: We compared people with HIV initiating ART with a regimen including MVC (Cases, n=12) to two different control groups: Control 1

(n=26), who initiated ART not containing MVC; and Control 2 (n=21), who had undetectable HIV-RNA on ART and switched to a MVC-containing regimen. Cases and Control 1 groups were matched by age, sex, and the number and type of drugs in ART regimen (excluding MVC). We determined the HIV reservoir size by measuring integrated HIV-DNA in stored PBMCs. We estimated the HIV reservoir variation with multivariate linear regression models adjusted for age, baseline CD4 counts, baseline HIV-RNA and baseline HIV-DNA.

Results: Pre-ART, median CD4 counts (cells/mm^3) were 96 (IQR: 36.5-204.0) in Cases and 351.5 (IQR: 237.0-494.0) in Control 1, and 456.0 (IQR: 264.5-598.5) prior MVC inclusion in Control 2. Pre-ART, the HIV reservoir size (median copies of integrated HIV/million cells) was 2368.0 [IQR: 38.6-9101.0] in Cases and 1583.0 [IQR: 97.3-5720.0] in Control 1. After a median of 79.7 weeks (IQR: 72.0-116.0) from ART initiation, the HIV reservoir size decreased significantly in both groups (97.5 [IQR: 5.4-552.9] in Cases and 720.5 [IQR: 72.6-2578.0] in Control 1, p<0.01). Control 2 group displayed an HIV reservoir size of 661.3 [IQR: 130.0-4499.0] and 416.0 [IQR: 31.2-965.5] before and after switching to a MVC-containing regimen, respectively (p<0.01). Multivariate analysis showed that Cases had a 12-fold and 11-fold greater HIV reservoir decline than Control 1 and Control 2, respectively (p<0.01).

Conclusion: Administering an LRA during ART initiation with detectable viremia more effectively reduces the HIV reservoir size than in patients with undetectable viral load. This finding can inform the design of clinical trials based on the shock and kill strategy.



Effect of timing administration of LRA on the HIV reservoir size.
All measures were summarized as median and interquartile range of integrated HIV copies per million cells. MVC, maraviroc; ART, antiretroviral treatment. **p ≤ 0.01.

482 The Fraction of HIV Reservoir Variants Neutralized by Autologous IgG Correlates With Time to Rebound

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Background: During untreated infection, HIV-1 rapidly evolves to escape contemporaneous, autologous neutralizing antibodies (anAbs). At the time of ART initiation, archived reservoir isolates may be sensitive or resistant to anAbs. Factors such as time to rebound, and the genotype of rebound virus are difficult to predict amongst analytical treatment interruption (ATI) cohorts. Elucidating the factors that govern these phenomena can inform cure strategies aiming for ART-free virologic control. We hypothesize that (1) anAb-resistant virus detected in the reservoir prior to an ATI may be identical, or genetically similar, to virus that rebounds post ART, and (2) higher percentages of anAb-sensitive reservoir variants may be associated with a longer time to rebound post ART.

Methods: Among 9 study participants who underwent an ATI without intervention, we measured inhibition of outgrowth by contemporaneous anAbs in a modified quantitative viral outgrowth assay (mQVOA). The mQVOAs were conducted using donor-derived resting CD4+ T (rCD4) cells isolated prior to the ATI. These rCD4 cells were activated by PHA, then cultured in the presence of contemporaneous autologous IgG, HIV-negative donor IgG, or no IgG for 14 days. Viral outgrowth was scored by HIV-1 p24 ELISA.

Results: With samples obtained prior to the ATI, we observed donor-to-donor variation in the ability of contemporaneous autologous IgG to neutralize inducible, replication-competent reservoir isolates. In the cohort analyzed, the fraction of outgrowth isolates neutralized by anAbs ranged from 0 to 44%, and it was observed that participants with more neutralizable reservoir variants had delayed times to viral rebound. Overall, the fraction of anAb-sensitive viruses detected in the latent HIV-1 reservoir prior to ART interruption significantly correlates (p=0.0150) with the time to viral rebound.

Conclusion: We report that autologous IgG antibodies can neutralize inducible, replication-competent HIV-1 prior to an ATI, and higher percentages of variants susceptible to anAbs are associated with a longer time to rebound post ART. These results suggest that inducing a potent immune response against anAb-resistant virus could eventually lead to sustained virological control in the absence of ART. The mQVOA may serve as a useful pre-screening tool for selective ATI enrollment. Lastly, ATI studies using time to viral rebound as an outcome measurement should consider the anAb response when designing trials and interpreting results.

483 Plasma Correlates of Rebound After Discontinuation of ART in Persons Living With HIV-1 (PLWH)

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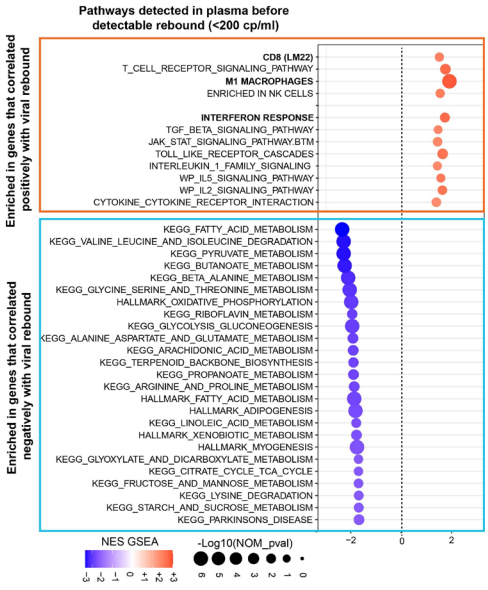
Background: The discovery of biomarkers that predict viral rebound after ATI would significantly contribute to the HIV cure field. Further, the discovery of biomarkers predicting viral rebound after ART discontinuation will inform and guide ATI studies to understand who is more likely to experience a viral rebound and could help select participants for ART interruption studies to make ART discontinuation safer and more effective.

Methods: We initiated a multi-center, open-label trial of three monthly intravenous (IV) administration of 20 mg/kg each of PGT121, PGDM1400, and VRC07-523LS (n=12) in persons living with HIV-1 (PLWH) following discontinuation of antiretroviral therapy (ART). ART was interrupted 2 days after the first broadly neutralizing monoclonal antibodies (bNAb) infusion. We collected plasma from all participants two days before ATI, multiple times off ART, and after rebound. We conducted high-throughput transcriptomics, proteomics, and metabolomics at all time points in all participants.

Results: We investigated protein signatures modulated after ATI, before detectable rebound (VL< 200cp/ml), and after rebound (VL>200cp/ml) compared with baseline (pre-ATI). We observed a significant increase (FDR q value < 0.05) of T cells, immune activation, and proinflammatory signatures preceding detectable rebound (VL<200 cp/ml) that were augmented after rebound. Signatures of activated proinflammatory macrophage M1, response to interferon-alpha and gamma as well as proinflammatory cytokines and chemokines (CXCL10, CXCL9, TNFRSF1B, CD14, CSF1) were elevated before detectable rebound compared with pre-ATI. Metabolic pathways show dysregulation or a decrease after analytical treatment interruption (ATI) and before detectable rebound, indicating metabolic changes associated with the rebound virus (Fig 1).

Conclusion: Our preliminary observations highlight the role of proinflammatory signatures and macrophages as potential plasma biomarkers to predict imminent rebound following ATI.



484 Common T-Cell Features Predicting Time to Rebound in Interventional and Non-Interventional Treatment

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Background: Immunological features predicting time-to-rebound during analytical treatment interruption (ATI) may differ between cohorts, and be impacted by whether or not therapeutic interventions were used. Here, we used CyTOF to identify shared and unique pre-ATI features of T cells associated with time-to-rebound in the non-interventional ACTG A5345 cohort and 3 interventional Danish cohorts.
Methods: A 40-parameter CyTOF T cell phenotyping panel was applied on pre-ATI blood specimens from 33 chronic-treated and 11 acute-treated individuals from the non-interventional ACTG A5345 cohort, and 3 chronic-treated Danish cohorts receiving therapy prior to ATI: CLEAR (Panobinostat intervention, n=9), TEACH (TLR9 agonist intervention, n=9), and REDUC (therapeutic vaccination + romidepsin intervention, n=16). Clustering analysis was performed to identify T cell phenotypes associated with time-to-rebound upon ATI.
Results: Using cluster-resolution optimization, nine and five clusters were identified from the A5345 and the 3 collective Danish cohorts, respectively. Cluster 9 from A5345 and Cluster 3 from TEACH were both significantly ($p<0.01$) positively associated with longer time-to-rebound. Cluster 9 consisted of memory T cells expressing high levels of the T resident memory (Trm) marker CD103, and high levels of the homeostatic proliferation marker CD127 and the Th17 marker CCR6. As Cluster 9 consisted of both CD4+ and CD8+ T cells, we split it into subclusters 9a (CD8+) and 9b (CD4+). Cluster 9a expressed high levels of the pro-survival factor BIRC5, and low levels of the integrin component CD29. By contrast, Cluster 9b expressed low levels of BIRC5 and high levels of the co-stimulatory molecule CD28. Cluster 3 from the Danish cohorts consisted of CD8+ T cells expressing high levels of BIRC5 and low levels of CD29. These cells also expressed high levels of CXCR4 and CCR7, suggesting homing to inflamed and lymphoid tissues. Our observation that CD8+ T cells from both A5345 Cluster 9a and Danish Cluster 3 expressed high levels of BIRC5 and low levels of CD29 suggest that phenotypic features predicting longer time-to-rebound can be shared among non-interventional and interventional ATI cohorts.
Conclusion: CD8+ T cells expressing high levels of BIRC5 and low levels of CD29 predict longer time-to-rebound in both interventional and non-interventional ATI cohorts. These "pro-survival" CD8+ T cells may be better able to survive during the early post-ART period and thereby slow down viral rebound upon ATI.

485 Dynamics of the Intact HIV Reservoir During ART Following Analytical Treatment Interruption

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Background: To assess efficacy, clinical trials evaluating therapeutic agents aimed at achieving HIV cure or sustained virologic remission require analytical treatment interruption (ATI). It has been shown that ATI results in the expansion of HIV reservoirs in people living with HIV (PLWH) with rebounding plasma viremia; however, the dynamics of the intact HIV reservoir during ART in PLWH who underwent ATI has not been fully delineated. We conducted longitudinal measurements of intact HIV proviral DNA, residual plasma viremia, and biomarkers before ATI and following re-initiation of ART in PLWH who participated in previous ATI trials.
Methods: We studied two cohorts of PLWH who initiated ART during the acute/early (A/E, n=25) or the chronic (Chronic, n=19) phase of infection. We determined the levels of intact HIV proviral DNA, residual plasma viremia, and biomarkers before and during ATI, and 24 and 52 weeks following the re-initiation of ART. Levels of intact HIV DNA were determined using the intact proviral DNA assay (IPDA). Residual plasma viremia was measured using an automated instrument. Levels of plasma biomarkers were measured by an automated ELISA.
Results: Both groups experienced a significant increase in the level of intact HIV proviral DNA following ATI. After the re-initiation of ART (Post-ATI), the intact HIV DNA burden in the A/E group normalized to the baseline level ($P=0.1245$) by Week 24. However, in the Chronic group, the level of intact HIV DNA remained elevated at Post-ATI Week 24 and 52 ($P=0.0069$ and $P=0.0042$, respectively) compared to that of baseline. There was no difference in the residual plasma viremia between the baseline and Post-ATI Week 24 in the A/E group ($P=0.1556$). However, in the Chronic group, the level of residual plasma viremia was significantly higher at Post-ATI Week 24 compared to baseline ($P=0.0181$). There were significant increases in the levels of soluble PD-L1 ($P=0.0066$) and perforin ($P=0.0094$) from baseline to Post-ATI Week 24 in the Chronic but not in the A/E group.
Conclusion: We conclude that ATI differentially affects the dynamics of the HIV reservoir, residual plasma viremia, and certain biomarkers following the re-initiation of ART in PLWH who initiated ART during the acute/early versus chronic phase of infection. Thus, delineating the underlying mechanisms by which the A/E group achieved faster normalization compared to the Chronic group of immunologic and virologic markers could be informative for the development of future therapies.

486 Immune Responses and HIV Reservoir Evolution From Pre-ART to 5 Years Into Post-Treatment Control

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Background: In the randomized-controlled eCLEAR study focusing on the administration of the broadly neutralizing antibody 3BNC117 at the time of ART initiation, one post-treatment controller was identified. He initiated ART and 3BNC117 during primary HIV-1 infection (plasma viral load of 188,945 copies/mL and CD4 counts of 470 cells/mm^3) and has had sustained virologic control for 5.3 years following ART interruption (ATI). However, immunological and virological mechanisms in this post-treatment controller are poorly understood.
Methods: Viral reservoir cells were evaluated using quantitative in vitro viral outgrowth assays, duplex ddPCR (3dPCR), near full-genome proviral sequencing (FLIP-Seq) and matched integration site and proviral sequencing (MIP-Seq). Single cell transcriptome, surface protein and T-cell receptor profiling of 14,230 CD4 T cells were performed with the 10x platform. HIV-1-specific CD8 T cells were analyzed using the activation-induced marker (AIM) assay.
Results: The person did not have any known protective HLA alleles and plasma samples repeatedly tested negative for antiretroviral drugs. Replication-competent proviruses were detected during ATI at a frequency of 0.2-0.5 infectious units/ million CD4 T cells. Intact proviruses/million CD4 T cells declined during ATI. PreART intact proviruses were predominantly (85%) located in ordinary genic locations, although 2 clones of intact proviruses in ZNF genes on chromosome 19 were already observed at this time. During the ATI stage, two large clones of intact proviruses were observed, one integrated in the centromere region of chromosome 4, and one in the peri centromere region of chromosome Y; one single provirus integrated in the centromere region of chromosome 9 was also noted. A strong HIV-1-specific CD8 T response towards Gag was maintained during the ATI, whereas responses towards Pol, Nef and Env decreased. Single cell analysis showed widespread CD4 T cell activation during ATI compared to pre-ATI and upregulation of cytotoxic and antiviral markers (GZMA, CX3CR1, APOBEC3G) by a subset of highly clonally expanded Th1 CD4 T cells.
Conclusion: Post-treatment control in this individual was associated with persistence of genome-intact HIV-1 proviruses that grew out under in vitro tissue culture assays but not under physiological in vivo conditions. This is possibly due to a strong immune-mediated selection of intact proviruses in heterochromatin locations that may have a weaker ability to drive rebound in vivo.

487 Intact HIV Reservoir Levels Are Stable After Short-Term ART Interruption

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Background: As HIV cure remains a high priority for HIV research, analytical treatment interruption (ATI) in clinical studies remain vital to understand mechanisms for ART-free HIV remission. However, the impact of short-term treatment interruption on the intact HIV reservoir remains unclear.
Methods: We evaluated participants who underwent treatment interruption as part of the ACTG A5345 trial. Participants had been on suppressive ART ≥2 years and comprised two groups: individuals who initiated ART during chronic infection (n=33) and during early infection (n=12). HIV reservoir levels were measured at three time points: pre-ATI, during the ATI and ~ 24 weeks of viral resuppression on ART (Step 3). We quantified levels of unspliced cell-associated RNA (CA-RNA), intact, defective, and total proviruses by the intact proviral DNA assay (IPDA). Residual viremia was measured by the integrase single-copy assay (iSCA). Wilcoxon rank-sum test was used for between-group comparison and Wilcoxon signed-ranks test for within-person comparison.
Results: The median duration of ATI was 4 weeks in the study. Compared to the pre-ATI time point, levels of intact, defective, and total HIV DNA levels were significantly increased during the ATI for both the early and chronic-treated groups. Approximately 24 weeks after viral resuppression on ART, almost all levels of proviral measures (including intact and total HIV DNA) had returned to their baseline levels with no significant differences compared to the pre-ATI time point for both early and chronic-treated participants (Figure). Compared to pre-ATI, there was also no significant increase in CA-RNA levels 24 weeks after viral resuppression on ART. At all time points, levels of CA-RNA, intact, defective, and total HIV DNA levels were higher in chronic-treated compared to early-treated individuals. Early after ATI (median 1 week), higher levels of residual viremia by the iSCA was significantly associated with a shorter time to viral rebound ≥1000 HIV-1 RNA copies/mL amongst all participants (Spearman r = -0.60, p<0.01).
Conclusion: Short-term ATI does not irreversibly change the reservoir size as reflected by stable levels of CA-RNA, or intact and total HIV DNA after viral resuppression. High-level viral rebound can be predicted by early signals of very low viremia. .

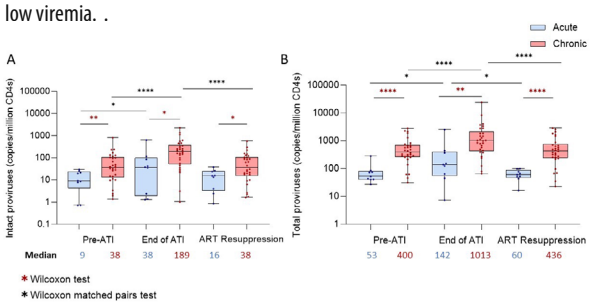

Figure. A) Intact and B) total proviral size at pre-ATI, end of ATI, and ~24 weeks after viral re-suppression upon ART restart. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

488 Clonal Expansion and Driving Forces of HIV-1 Persistence in Anatomic Compartments

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Background: Upon infection, HIV quickly disseminates and establishes persistent infection throughout the body. The persistence mechanisms of HIV in tissues are complex, with viral and local environment interaction contributing to tissue-specific pathogenesis. To investigate the distribution of HIV populations in anatomic compartments, we characterized HIV-infected populations in tissues obtained at autopsy from individuals on suppressive therapy.
Methods: HIV-DNA in tissues was quantified by single copy and multiplexed LTR/gag digital droplet PCR. Single genome sequences of proviral gag or pol were assessed by average pairwise distance (APD) (genetic diversity) and Slatkin-Maddison analyses. Proviral integration sites (IS) were obtained to assess diversity and clonal expansion rate/patterns; alpha (Simpson) and beta diversity (Bray-Curtis) indices were calculated to quantify intra- and inter-tissue diversity of clones.
Results: Eight donors(median age = 50 y) expired from comorbid illnesses(5 neoplasms, 1 cardiac disease, 2 infection) underwent autopsy within 3-48 hours. HIV-DNA was present in all tissues with highest concentrations in lymph node (43-720 copies/1e6 cells), and lowest in brain (1-9 copies). HIV-LTR/gag quantification revealed diverse proviral structures with variable proportions of gag-deleted proviruses (0.1%-87.4%). Across tissues, proviruses harbored variable levels of hypermutations (6.2-44.4%) but were not compartmentalized (APD=0.2%-0.9%) and intermingled if hypermutated sequences were discarded. We obtained 914 IS from 3 donors with median (range) of 26 (3-163) IS per tissue. In 2/3 donors, clonal expansion rates were significantly different but not tissue-specific with 0-91.9% of clonal proviruses per tissue. Median (range) intra- and inter-tissue diversity indexes were 0.95 (0.53-0.1) and 0.93 (0.84-1) suggesting non-diverse but distinct proviral populations across tissues. In one donor with >15 tissues analyzed for IS, we observed significant difference in intra-tissue diversity between neoplastic and non-neoplastic (p=0.03) and in inter-tissue diversity between lymphoid vs non-lymphoid tissues (p=0.002).
Conclusion: During therapy, HIV-infected cells are widely distributed in tissues but subject to differential pressures allowing the selection of proviruses with variable levels of defects and hypermutations. Clonal expansion significantly contributes to the proviral landscape. Our data suggests the role of local immune responses in shaping the anatomic proviral landscape.

489 Impact of BACH2 on the Formation of HIV Latent Reservoirs in Humanized Mouse Model

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Background: A pivotal challenge in achieving a cure for HIV is the limited understanding of the mechanisms governing the formation of latent reservoirs. Intriguingly, HIV integration site analysis studies have revealed unusually frequent integrations into the BACH2 gene. More importantly, inserted proviruses are nearly exclusively located upstream of the BACH2 start codon and share the same transcriptional orientation as the host gene, which leads to an increase in BACH2 transcription. The recurrent HIV-1 integration at the BACH2 locus and upregulation of the host gene expression suggest that BACH2 plays an important role in HIV reservoir seeding and maintenance.
Methods: To investigate the impact of BACH2 on the HIV latent reservoir in vivo, humanized mice engrafted with BACH2 knockout (BACH2-KO) or control CD34+ cells were generated. Engrafted mice were infected with HIV followed by the administration of ART for six weeks. Subsequently, the frequency of tissue HIV DNA was assessed, and a portion of the splenic cells were transferred to immunodeficient mice for viral rebound analysis. In addition, we evaluated the influence of BACH2 on the conversion of $CCR5^+$ $CD4^+$ T cells into memory cells.
Results: As expected, we observed a notable reduction in total B cells in mice reconstituted with a BACH2-KO immune system in comparison to the control animals. Concurrently, BACH2-KO group had a slight decline in the number of naïve T cells. Notwithstanding, BACH2 deficiency did not affect the quantities of CD4+ central and effector memory cells. In HIV-infected mice, the viral loads were comparable between the BACH2-KO and control groups. In mice on ART, a lower frequency of HIV DNA was observed in the BACH2-KO group. In splenic cell transfer experiments, a 100% rebound was detected in the control mice (5/5), contrasted by a 50% rebound (4/8) in the BACH2-KO group. Mechanistically, we found that BACH2-KO CCR5+ cells were unable to convert into long-lived central memory cells.
Conclusion: Our study shows that BACH2 is required for the conversion of CCR5+ cells to central memory cells, and the formation of HIV reservoirs in long-lived central memory cells was abrogated in the absence of BACH2. Our study provides insight into the mechanisms underlying the establishment and stability of HIV latent reservoirs and identifies avenues for targeted interventions.

490 Tissue-Resident TCR Repertoires Linked to HIV Persistence

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Background: Clonal expansion of infected CD4+ T cells is a mechanism of HIV persistence, driven by homeostatic, integration site-driven, and antigen-driven proliferation. We profiled the composition and diversity of TCR repertoires across 18 tissues and blood of 19 people with HIV (PWH) from the Last Gift cohort.
Methods: Blood and tissues were collected by rapid autopsy in PWH on suppressive ART (N=19, 179 sites). Bulk TCR sequencing (Immunoverse TCR kit) was performed across gastrointestinal (GI, 5 sites), central nervous (CNS, 6 sites), lymphoid (6 sites) and vascular systems (2 sites). Data were analyzed using the mixcr bioinformatic platform. HIV reservoir size (HIV DNA) and activity (HIV RNA) was measured by ddPCR. HIV molecular diversity was obtained from single genome env sequencing. HIV integration site (IS) sequencing was performed for one participant in selected tissues. The VDJdb and McPASTCR databases were used to determine TCR specificities. Generalized mixed effects models were used to examine the association between outcomes (proportion of hyperexpanded clones, TCR diversity) with negative binomial for counts, and gaussian for continuous outcomes, and tissue and HIV reservoir measures as predictors.
Results: We observed shared clonotypes in all tissues suggesting migration within and across systems, and substantial expansions of TCR clonotypes in all systems. The CNS exhibited more hyperexpanded TCR clones (mean: 45% [34-61]), compared to GI tract (18% [34-61], p=0.004), lymphoid (13% [8-23], p=0.001) and vascular (24% [16-38], p=0.24). The CNS exhibited significantly lower TCR Chao and HIV DNA diversity compared to other systems (FigA,middle-right). Higher transcriptional activity (HIV RNA) and HIV DNA diversity in tissues were associated with increased TCR diversity and lower proportion of hyperexpanded clones (p<0.001). IS sequencing confirmed that proportion of HIV-infected clonally expanded cells was negatively associated with TCR diversity and positively with the proportion of expanded TCR clones. We did not find any evidence for TCR expansions driven by cytomegalovirus or other pathogens.
Conclusion: This is the first comprehensive analysis of TCR repertoire landscape across the tissues of PWH. Our findings unveil the expansion and cross-tissue migration of clonal T cells, which are linked to the dynamics of the HIV reservoir. This work sheds light on the interplay between HIV infection and the T cell response, offering insights into the pathogenesis of HIV.
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491 Single-Cell Multiomics Reveals Trafficking and Enrichment of HIV RNA+ CD4+ T-Cells in Gut Th17

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Background: Persistence of HIV RNA+ CD4+ T cells under ART is a major barrier to cure. We examined T cell polarization, clonal expansion, and migration of HIV RNA+ cells between the blood and gut.
Methods: We used ECCITE-seq to examine transcriptome, 131 surface protein, T cell receptor (TCR), and HIV RNA in the same single cells using paired blood and gut samples from 11 ART suppressed people with HIV, before and after 20 weeks of interferon alpha2b (Peg-IFN-α2b). Plasma viral load was undetectable at both sampling points, with no change in the size of the reservoir as measured by IPDA. Blood and gut samples from 4 uninfected individuals served as negative controls.
Results: We analyzed 245,928 CD4+ T cells from blood and 58,895 from the gut. We found that cytotoxic CD4+ T cells (CD4-CTL) were more abundant in the blood (4.9%) compared to the gut (0.9%)(p=0.019), while Th17 cells were more abundant in the gut (17.4%) than in the blood (8.1%) (p=0.001, paired Wilcoxon rank sum test). Similar distributions were observed in control participants. We detected 75 HIV RNA+ CD4+ cells (mean 452/million) in the blood and 31 HIV RNA+ CD4+ T cells (mean 578/million) in the gut. HIV RNA+ cells were enriched in blood Th17 (22 cells, mean 1639/million blood Th17) and the gut Th17 (14 cells, 1317/million gut Th17). There were more clonal cells in the gut (24.1%) than the blood (16.9%). Of the top 100 largest T cell clones, 72 were only in the blood, 11 were only in the gut, and 17 were identified in both blood and gut. The top 10 blood-only T cell clones were almost exclusively cytotoxic CD4+ T cells (96.8%), consistent with our previous finding. Notably, T cell clones in the gut were highly heterogeneous within clones and between clones, including a mixture of Th1 (42.7%), Trm (15.8%), and Th17 (11.1%) in the 11 gut-only T cell clones, and Th1 (44.4.%), CTL (40.4%) and Th17 (5.4%) in the 17 clones in both blood and gut. Among them, HIV+ T cell clones were mainly CTL (92.2%) in the blood-only clones, Th17 (46.3) and Th1 (36.6%) in the gut-only clones, and Th17 (53.8%) and Th1 (30.8%) in the clones migrated between blood and gut.
Conclusion: While expansion within CD4-CTL clones contributes to the persistence of the HIV reservoir in the blood, the gut showcases a diverse landscape of CD4+ T cells, especially Th17 cells. This distinction between blood and gut emphasizes the gut's unique role in HIV persistence and highlights the necessity for specialized therapeutic approaches for each reservoir.

492 Intact Proviruses From Lymph Nodes Are a Preferential Source of Viral Rebound in SHIV- Infected NHP

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Background: The persistence of SIV/HIV reservoirs is the main obstacle to a cure and the cause of viral rebound after ART cessation. However, the source of viral rebound remains elusive. We characterized the proviral landscape in various tissues of virally suppressed SHIV-infected rhesus macaques before ART interruption (ATI) and matched it with the env sequences from plasma viruses during rebound.
Methods: We used a highly processive and accurate polymerase and PacBio sequencing to obtain near full-length (NFL) genome sequences from blood, lymph node, and gut biopsies in 5 SHIV-infected rhesus macaques who started ART 8 weeks post infection and remained on therapy for 28 weeks. Env sequences (2,554 pb) from plasma rebound viruses 4 weeks after ATI were obtained by single genome sequencing and analyzed using the ElimDupes tool from the HIV Sequences Database to identify matches between intact NFL proviruses and plasma env sequences.
Results: Using our novel NFL sequencing approach, a total of 144 proviral sequences were obtained (49 from blood, 63 from lymph nodes and 32 from the gut). 35% of all viral sequences were genetically intact, with a lower proportion in the gut (26%) compared to the blood (42%, p=0.04) and the lymph nodes (41%, p=0.04). Overall, only 2.8% of the proviral sequences were 100% identical, indicating that the SHIV reservoir was mainly composed of unique sequences. Overall, we found that rebounding viruses recovered from plasma more frequently matched with pre-ATI intact proviruses derived from lymph nodes (4 pairs of matched sequences) compared to sequences from blood and the gut (1 and 1 pairs of matched sequences, respectively).
Conclusion: The SHIV reservoir is largely composed of non-clonal proviral sequences, suggesting that clonal expansion of the SHIV reservoir has a minor contribution to viral persistence in this model. Our results further suggest that intact proviruses persisting in the lymph nodes may be a preferential source of viral rebound upon ATI in this model.

493 Minimally Invasive Autopsy Confirms HIV Persistence in Multiple Compartments Despite Prolonged cART

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Background: HIV cure strategies require sophisticated knowledge of the formation and maintenance of latent and active reservoirs of HIV-infected cells. However, the overall paucity of individuals undergoing autopsy have hampered investigation of the anatomical distribution of infected cells during prolonged combination antiretroviral therapy (cART). We report on the largest post mortem study using minimally invasive autopsy on deceased virologically suppressed and unsuppressed adult persons with HIV (PWH) to characterise viral reservoirs.

Methods: Admitted adult PWH who died at Klerksdorp Tshepong Hospital, North West Province, South Africa were included in this study. Relatives of eligible deceased PWH provided informed consent. Causes of death were documented. Ultrasound-guided core needle biopsies were used to sample a broad range of body fluids and organs ≤16hrs after death. Trocars were used for minimal contamination. Organs were verified by histopathological analyses. HIV reservoir analysis from stored fluid and organ samples was conducted by digital droplet PCR, as HIV copies per million cells (cpm).
Results: Sixty recently deceased PWH (38 virally suppressed; 22 unsuppressed of whom 13 were cART-naive) were enrolled with a median time to autopsy of 10.4hrs (IQR 6.9). FIND046 was COVID-19 positive and excluded. Most patients were of Black African descent (94.9%), male (57.6%) 50 y/o (IQR 18), with a median VL<24 RNA copies/ml (IQR 2,401). Virally suppressed PWH were on cART for a median of 66.6 months (IQR 80.3). A total of 489 unique specimens from 11 anatomically distinct compartments were analyzed for HIV proviral DNA, including bone marrow aspirate and trephine, brain, bronchioalveolar lavage, cervicovaginal lavage, kidney, lymph nodes, liver, lung, spleen and whole blood. Overall, all anatomical compartments of suppressed and unsuppressed PWH were positive for HIV proviral DNA. Highest copy numbers were detected in lymph nodes (7,384±28,669cpm) and lowest copies in brain (513.7±866cpm) and bone marrow trephine (416±814cpm). No statistically significant differences in HIV proviral DNA concentrations between compartments, irrespective of viremic status were noted. However there was an overall trend of higher proviral DNA in all compartments of viremic patients. Sequence analysis showed viral compartmentalization.
Conclusion: Findings provide new insights on anatomical location of HIV-infected cells that persist despite prolonged cART that should be targeted for effective cure interventions.

494 The Extended Survival of Infected Brain Myeloid Cells Contributes to HIV Persistence During ART

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Background: HIV spreads in the Central Nervous System (CNS) and establishes a persistent viral infection. Recently, we demonstrated that the replication-competent HIV persists in long-lived brain myeloid cells (BrMCs) as a definitive proof of HIV persistence in the CNS (PMID: 37317962). We found that HIV lies dormant within BrMCs (mainly microglia), rather than CNS T cells. In BrMCs during suppressive antiretroviral therapy (ART), HIV mainly persists as a latent infection but residual HIV transcription exists. Here, we investigate BrMC cell type-specific mechanisms of persistent HIV expression in the brains of Last Gift participants.
Methods: Brain tissues were obtained through a rapid autopsy from 4 people with HIV (PWH) on suppressive ART and one PWH after ART interruption (plasma viral load 68,007 copies/ml). HIV RNA expression and spatial distribution in brain tissue were examined by RNAscope. Isolated BrMCs were studied ex vivo to characterize their responses to ART and inhibitors of HIV transcription machinery to define the cell type-specific mechanisms that modulate persistent HIV expression during ART.
Results: We consistently detected low levels of HIV RNA in the brains by quantitative RNAscope. The levels ranged from 0.67 to 16.67 RNA dots per 1000 nuclei in the brains of four ART-suppressed donors while it was 117.3 HIV RNA dots per 1000 nuclei in the brain of viremic PWH . Co-staining with the myeloid cell marker CD68, HIV RNA expression was colocalized with BrMCs. When examining BrMCs isolated from the viremic PWH, it became evident that ART alone lacked efficacy in inhibiting HIV expression. However, when combined with an HIV Tat inhibitor (Triptolide), ART demonstrated a remarkable capacity to significantly reduce HIV transcription (Figure A). In vitro, although ART was effective in inhibiting new infection by HIV recovered from BrMCs of PWH, it failed to suppress the established HIV infection in BrMCs. In contrast, in PHA-stimulated PBMC blasts, ART blocked both new and established infections of the same viral strain. Further studies showed that BrMCs were resistant to the cytopathic effects after viral infection, and cell viability remained comparable between infected cells and mock-infected wells (Figure B). This was in contrast with observations of virus-induced cytopathic effects in PBMCs.
Conclusion: The long survival of infected BrMCs leads to ineffectiveness of ART, which can be controlled by the addition of HIV transcription inhibitors into the current ART regimen.

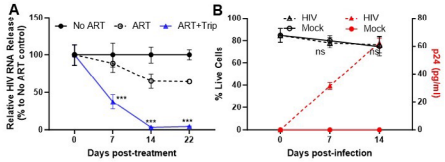

Figure. (A) ART was less effective in blocking HIV in BrMCs isolated from PWH, which was augmented by a Tat inhibitor Triptolide (Trip) to eliminate HIV production. ***, p<0.0001 compared with ART. (B) BrMCs sustained cellular viability after infection. ns, no significance compared with mock infection.

495 HIV Infection and Reactivation Heterogeneity in Tonsillar and Intestinal Models of HIV Persistence

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Background: Tissue reservoirs constitute a significant source of latent and persistent HIV infection in people living with HIV (PLWH) on antiretroviral treatment (ART). While extensive research has focused on understanding HIV reservoirs in the blood, the intrinsic characteristics of viral reservoirs within tissue compartments remain largely unknown. In this study, using tonsillar and intestinal explant models of HIV persistence, we characterized the cellular composition of these anatomical reservoirs and evaluated the effectiveness of latency reversal agents (LRAs) in inducing viral reactivation after ART.
Methods: Human tonsillar (n=5) and intestinal (n=7) tissue resections from uninfected donors were ex vivo infected with HIVBAL for 5-6 days, followed by ART treatment for 2 days to establish persistent viral infection. CD4+ T cells were then isolated and cultured for 22 hours in the presence of various LRAs. Using unsupervised clustering analysis (FlowSOM) we identified distinct CD4+ T subsets. We confirmed the presence of viral reservoirs and assessed the effectiveness of LRAs by quantifying intracellular p24 levels after viral reactivation.
Results: We identified fifteen CD4+ T cell clusters exhibiting significant inter-tissue variations in the proportions of the majority of these subsets ($p<0.05$). In both tonsillar and intestinal tissues, viral infection predominantly occurred in various populations of effector memory (TEM: C06, C09, C11 and C14), central memory (TCM: C03 and C07) and T follicular helper (TFH: C10 and C12) cells. However, we found differential enrichment of infected CD4+ T subpopulations between tissues (Fig. 1A). Intestinal latently infected CD4+ T cells exhibited greater reactivation with IL15 and AZD5582; whereas the tonsillar reservoirs responded better to ingenol (ING) and the combination of ingenol and romidepsin (ING+RMD). Notably, IL-15 induced potent reactivation in intestinal C06 and C10 (Fig. 1B) while ING and ING+RMD in tonsillar C09. Notably, we observed no significant differences in the proportion of these clusters before and after LRA treatment. Furthermore, no significant changes were observed for the LRAs RMD and panobinostat.
Conclusion: In our tonsillar and intestinal tissue models of HIV persistence, CD4+ T cell populations exhibited varying susceptibility to viral infection and reactivation, showing significant differences between tissues. Further research is required to identify LRAs effective against distinct HIV cellular reservoirs within these tissues.

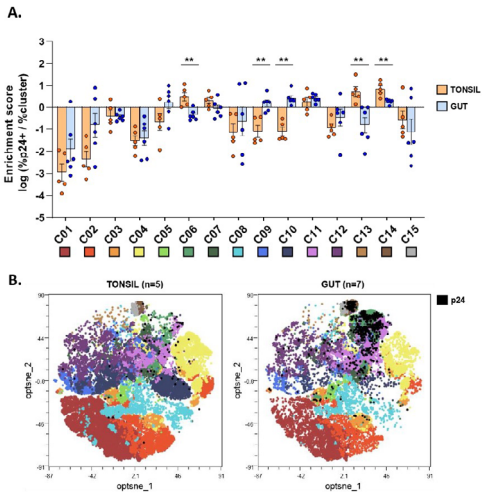

Figure 1. Differential infection and reactivation permissiveness in tonsillar and intestinal CD4⁺ T populations. (**A**) Enrichment score of infection for each cluster. Mann-Whitney T- test. **p<0.005. (**B**) Opt SNE representations displaying HIV reactivation in the fifteen CD4⁺ T subpopulations in response to IL-15 treatment.

496 Development of a Single-Cell Multiomic Assay to Phenotype SIV/SHIV Infected Rhesus Macaque Cells

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Background: SIV infection recapitulates many aspects of HIV-1 infection. However, the SIV reservoir at the single-cell resolution remains to be defined. Here, we adapted our single-cell viral Assay for Transposase Accessible Chromatin with Select Antigen Profiling by sequencing (viral ASAPseq) to rhesus macaque SIV infection model, to characterize SIV/SHIV reservoir epigenetics and phenotype.

Methods: To adapt viral ASAPseq to the nonhuman primate model, we compiled, titrated, and characterized a rhesus cross-reactive antibody panel consisting of 62 immune-related markers using custom and commercially available oligo-tagged antibodies from Biolegend. Using this cocktail, we performed viral ASAPseq on purified lymph node CD4+ T cells at day 13 post-SIVmac251 infection. Finally, we developed a customized bioinformatics analysis pipeline to assess infected cells after viral alignments were made against the SIVmac251 sequence.

Results: From this pilot test, we identified 81 SIV+ cells out of 15,334 cells (0.5%); of these, 42 cells had 2 or more reads aligned to multiple regions of the provirus. Using both the epigenetic and surface antigen profiles, we found that 67% of infected cells had characteristics of T follicular helper, T follicular regulatory, or T regulatory cells. The remaining infected cells appeared to have effector, activated, and/or resident memory characteristics.

Conclusion: These initial findings demonstrate that NHP viral single-cell ASAPseq can be used to identify SIV+ cells and determine the unperturbed epigenetics and phenotype of these cells. Notably, this assay allows an unprecedented view into the SIV/SHIV reservoir to understand the perturbations associated with various cure strategies.

497 Pure CD32+CD4+ Cells Are Cytotoxic Memory CD4+ T-Lymphocytes Highly Enriched for HIV-1 DNA

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Background: Whether CD32 is a cellular marker of HIV-1 reservoir is a matter of ongoing debate. Despite intensive research, isolation of pure CD32+CD4+ T cells has not been reported thus far. Therefore, the biology of this cellular subset remains ill-defined. Here we present a novel purification strategy that allowed in-depth characterization of this subset in healthy donors as well as in HIV-1 infected individuals.

Methods: A purification strategy was developed combining MACS pre-purification of CD4+ T cells with subsequent double FACS sorting, validated by imaging cytometry. Single-cell RNA sequencing and in depth FACS phenotyping was performed followed by unsupervised analysis pipelines. Real time PCR was applied to quantify total HIV-1 DNA.

Results: Post-purification sample characterization by imaging cytometry revealed a small (median of 0,015% of CD4+ T cells express CD32) and pure (>96%) CD32+CD4+ T-cell population. CD32 protein expression on these cells was evidenced by a dim but homogeneous signal, spread over the cellular membrane. To characterize this subset, we performed single-cell RNA sequencing and observed clustering in the memory T cell compartment with Th1, Th2, and cytotoxic gene signatures. These transcriptional traits were confirmed on protein level, as significant increases in Perforin, Granzyme A and K, as well as IFN-γ, IL4, and IL10 production were measured after short-term in vitro stimulation (all p-values <0.05). Detailed FACS phenotyping revealed that 80% of CD32+CD4+ T cells make part of the central memory, effector memory and transitional memory compartment the latter expressing high levels of CD31, a protein with a key role in leukocyte transmigration. Median fluorescence intensity on CD32+CD4+ cells was significantly increased for HLA-DR, PD-1 and CD95 (all p values <0.05). Importantly, in HIV-1 infected individuals on ART, these pure CD32+CD4+ T cells were on average 284-fold enriched for HIV-1 DNA.

Conclusion: We found that CD32+CD4+ T cells are memory CD4+ T cells with traits of activation harboring cytotoxic gene and protein signatures. The tremendous enrichment in HIV-1 DNA suggests that these cellular traits represent an ideal niche for HIV-1 to persist during ART.

498 Persistence of HIV-RNA in Autopsy Tissue Samples From Persons With HIV With Suppressed Viral Loads

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Background: The rapid viral rebound observed following treatment interruption, despite prolonged time on ART with plasma HIV-RNA levels <40 copies/ml, suggests persistent HIV-1 reservoirs outside of the blood. However, the relative contribution of different anatomical compartments to the HIV-1 reservoir is not well understood.

Methods: Autopsy specimens were collected from 10 donors: 3 with active HIV-1 replication (blood HIV-RNA levels ≥5 copies/1 µg host-genomic RNA) ("Active") and 7 with suppressed HIV-1 replication (blood HIV-RNA levels <5 copies/1 µg host-genomic RNA)("Suppressed") at the time of death. Specimens were collected from 31 different tissues compartments including blood. Levels of HIV-DNA and HIV-RNA were determined using quantitative PCR. HIV-1 proviruses were analyzed by 5'LTR-to-3'LTR PCR single-genome amplification of near full-length HIV-1 (9 kb in size) and direct amplicon sequencing. A total of 1,902 HIV-1 sequences derived from the 10 donors (median: 128, range: 42 - 697 sequences per donor) were obtained and used for analyses.

Results: HIV-DNA and HIV-RNA species were detected in all 10 donors in 31 different tissue compartments. No statistically significant differences were noted between the Active and Suppressed groups when comparing levels of HIV-DNA in blood or tissues. The same was true for levels of HIV-RNA species in tissues other than blood. The frequencies of full-length intact HIV-1 provirus (encoding replication-competent virus) were similar between the Active and Suppressed groups (5.9% vs. 3.7%, p=0.18). In both populations, the highest levels of HIV-RNA expression were within lymphoid tissues and the ileum. Multiple copies of identical full-length intact HIV-1 provirus were found in one donor in the Suppressed group. The expanded clone was detected in the blood, the kidney and the liver but not associated with HIV-RNA expression.

Conclusion: Outside of peripheral blood, similar levels of HIV-DNA and HIV-RNA expression were noted in autopsy samples from persons with HIV with either active or suppressed HIV-1. These data imply that the substantial seeding of tissues with cells harboring proviral DNA seen in the setting of HIV-1 infection does not change despite ART and that many of these cells are actively transcribing HIV-RNA. While it is likely that the majority of this HIV-RNA is coming from cells harboring defective proviruses in the suppressed population, these findings highlight one of the challenges in achieving an HIV cure.

499 Gut Microbiome Associations With Intestinal HIV Persistence in ART-Suppressed Pediatric Macaques

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Background: Currently, ~1.5 million children are living with HIV, worldwide. ART cannot clear the HIV reservoir, resulting in the need for life-long adherence to therapy. Using SHIV-infected pediatric rhesus macaques (RMs) on long-term ART, we recently demonstrated transcriptionally active HIV in the gastrointestinal (GI) tract. Interestingly, the GI tract was also the first anatomic site of HIV reactivation after ART interruption. However, factors contributing to viral persistence in the GI tract remain unknown. Here, we tested whether pediatric GI microbiome can influence transcriptionally active HIV in this compartment.

Methods: Feces were obtained from SHIV.CH505-infected virally-suppressed infant RMs. All RMs received the same triple-drug ART regimen (TFV+FTC+DTG) and were categorized into early ART (n=7, ART start: 4 days post-infection, pi), intermediate ART (n=9, ART start: 2 wks pi), late ART (n=14, ART start: 8 wks pi) and late ART+ therapeutic vaccine (n=8, ART start: 8 wks pi, vaccine on ART) groups. The fecal microbiome was profiled using 16s rRNA sequencing. Levels of 21 bile acids and 162 polar metabolites in feces were measured by LC-MS. To determine the impact of microbiome on cell-associated (CA)-RNA, we used Analysis of Compositions of Microbiomes with Bias Correction (bacterial taxa) and linear regression models (metabolites).

Results: Irrespective of the regimen and duration of treatment, the ratio of SHIV CA-RNA/DNA was higher in the CD4+ T cells of rectal biopsies, compared to blood or lymph nodes. Treatment impacted both fecal-microbial and -metabolomic profiles. After correcting for therapy-based differences, we identified bacterial species Sarcina ventriculi, Lactococcus lactis and Treponema succinifaciens and metabolite adenosine diphosphate to be directly associated with increased SHIV CA-RNA. Additionally, the levels of Eubacterium hallii, Ruminococcus bromii, Terrisporobacter mayombei, D-glucose, D-glucuronic acid, citric acid, D-fructose and 4-hydroxyproline were inversely correlated with CA-RNA in the GI tract. Finally, a statistical mediation analysis indicated that the association of commensal Eubacterium hallii with reduced viral persistence was mediated via D-glucose.

Conclusion: In the pediatric RM model, gut microbiome appeared to impact intestinal SHIV persistence. Building a GI microbiome from early life that can dampen HIV persistence and prevent reactivation may contribute to the goal of ART-free viral suppression in children living with HIV.

500 Decreased Frequency of Colon-Resident Memory T-Cells Is Associated With HIV-1 Persistence on ART

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Background: The gut is a major target for HIV-1 replication and persistence. Tissue-resident memory (TRM) cells play a crucial role in mucosal immunity but this cell population could be affected by HIV-1 replication in mucosa. Their depletion may contribute to a persistent imbalance in mucosal homeostasis and the persistence of HIV-1 in the gut on ART.

Methods: 42 virologically suppressed people living with HIV-1 (PLWH) and 42 uninfected controls were recruited in the ANRS EP61 GALT study. Duodenal, ileal, and colonic biopsies and blood samples were obtained. The frequency and activation/exhaustion phenotype of intestinal-TRM cells was assessed by FACS. Total HIV-1 DNA and residual HIV-1 RNA were quantified in gut samples, and the genetic complexity of HIV-1 quasispecies was assessed by single-molecule real-time next-generation sequencing of env. Recirculating intestinal-TRM cells were defined as CD103+β7hiCD8+ T cells in peripheral blood. The frequency of HIV-1–specific CD8+ T cells among recirculating TRM cells was assessed in 15 PLWH after stimulation with HIV-1 peptide pools and measurement of IFNγ production, degranulation (CD107a), and cell proliferation (CFSE).

Results: CD4+ and CD8+ TRM cells were significantly depleted in the colonic mucosa of PLWH versus uninfected controls (P=0.015 and P=0.006 for CD4+ and CD8+ TRM cells, respectively), and their frequency correlated negatively with CD4 nadir (ρ=0.41, P=0.020 and ρ=0.37, P=0.037 for CD4+ and CD8+ TRM cells, respectively). TRM cells express overall lower levels of PD-1, TIGIT, KLRG1 and CD57 than non-TRM cells in all 3 gut segments, but levels are highest in the colon. CD4+ and CD8+ TRM cell frequencies were negatively associated with total HIV-1 DNA and residual HIV-1 RNA, while non-TRM cells were associated with quasispecies genetic complexity (Figure). Recirculating CD8+ TRM cells were enriched in HIV-1-specific T cells (P<0.01 for IFNγ+, CD107a+, and CFSEdim cells in recirculating TRM vs total CD8+ T cells).

Conclusion: The frequencies of CD4+ and CD8+ TRM cells remained reduced in PLWH on ART, particularly in the colon. Irreversible damage may have been inflicted on these cell populations prior to initiation of ART. The loss of these cells could promote the persistence of HIV-1 in the colon. Enrichment of HIV-1-specific cells in recirculating TRM supports persistent antigenic stimulation by HIV-1 antigens in the gut mucosa of PLWH on suppressive ART.

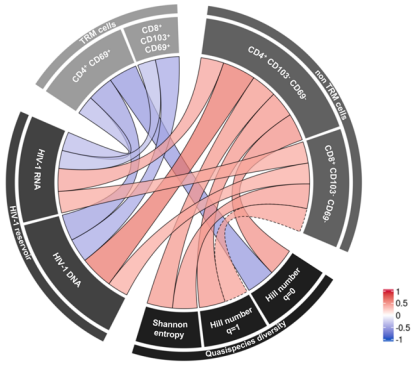

Figure. Associations between HIV-1 reservoir in the colon, viral quasispecies complexity, and the phenotype of colon-TRM or non-TRM cells. The color scale indicates Spearman's correlation coefficient. Solid lines indicate significant correlations (P<0.05) and dashed lines indicate correlation trends (P<0.1)

501 Monocytes/Macrophages Contribute Only Marginally to the Gut Reservoir of HIV-1 on ART

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Background: Current antiretroviral treatments (ART) are unable to cure HIV-1 infection due to the persistence of latently infected cells. The gut mucosa contains numerous target cells, and high levels of HIV-1 DNA persist in this compartment under ART. CD4+ T cells are the best-characterized reservoir for HIV-1. However, macrophages are abundant long-lived cells in the gut, but their involvement in HIV-1 persistence under ART remains debated.

Methods: To investigate the contribution of intestinal monocytes/macrophages to the HIV-1 reservoir, we collected duodenal (N=8) and colonic (N=8) biopsies from 12 people living with HIV (PLWH) under suppressive ART (viral load <30 copies/mL) for 8 years, included in the ANRS EP61 GALT study. T cells were isolated by positive CD2 magnetic sorting, and monocytes/macrophages (CD3-CD19-CD56-CD66- CD11c+ HLA-DR+ CD33+ CD14+/–) were sorted by flow cytometry. Cellular DNA was extracted and amplified by REPLI-g. We quantified total HIV-1 DNA by qPCR in the LTR region and integrated proviral DNA by Alu-LTR qPCR. We used the Intact Proviral DNA Assay (IPDA) to estimate the frequency of intact, 5' defective and 3' defective HIV-1 proviruses in monocytes/macrophages and T cells.

Results: Total HIV-1 DNA levels in intestinal T cells (positive samples: 8/8 in the duodenum and 8/8 in the colon, median 3,398 copies/10^6 CD4+ T cells [IQR, 1,208-12,312]) were much greater than those in monocytes/macrophages (positive samples: 4/8 in the duodenum and 3/8 in the colon, median 12 copies/10^6 monocytes/macrophages [IQR, 8-22]) (P<0.001). Unintegrated HIV-1 DNA was detected in a third of T cell and monocytes/macrophages positive samples. Using the IPDA assay, we detected intact HIV-1 proviruses in 4/16 of T cell samples but in only 1/6 of monocyte/macrophage samples.

Conclusion: We showed that monocytes/macrophages from the intestinal mucosa of both the duodenum and colon of PLWH under suppressive ART can contain HIV-1 DNA, even intact or unintegrated, but at much lower levels (300-fold lower) than those found in T cells. These findings provide further evidence that monocytes/macrophages contribute only marginally to the HIV-1 reservoir in the gut of ART-treated individuals.

Background: While HIV-1 group M is responsible for the large majority of HIV infections worldwide, 3 others groups named O, N and P (HIV-1 non-M) are more genetically divergent and concentrated in West-central Africa

with sporadic cases in Europe, America and Canada. Previous works have demonstrated the limited number of therapeutic options due to the natural genetic polymorphisms associated with HIV-1 non-M. Thus, our work aimed to determine the in vitro susceptibility of these particular strains to Ibalizumab, a first-in-class long-acting CD4-directed post-attachment inhibitor.

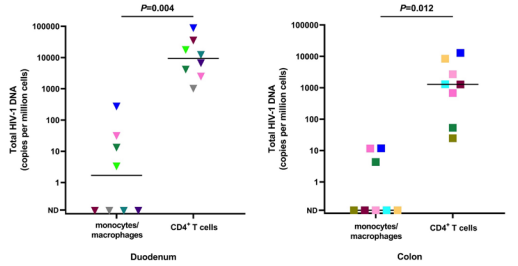

Figure. Levels of total HIV-1 DNA in monocytes/macrophages and CD4+ T cells sorted from the duodenum (n=8, triangle) and the colon (n=8, square) of 12 PLWH. Each color corresponds to samples from the same PLWH. ND: not detected. Mann-Whitney test was used for statistical comparison.

502 Non-Invasive Imaging Identifies Elevated Metabolic Activity in Lymphoid Tissue During Long-Term ART

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Background: Mechanisms of HIV persistence in anatomic compartments remain poorly understood. Positron Emission Tomography (PET) is a non-invasive technique that may provide insights to the spatial distribution and microenvironment of HIV persistence and identify sites for tissue sampling. Early 18F-fluorodeoxyglucose PET (FDG-PET) techniques did not detect elevated metabolic activity during long-term antiretroviral therapy (ART), though increased metabolic activity was observed with rebound viremia. To investigate whether new technologically advanced PET imaging with improved resolution detects metabolic activity in lymphoid tissues during long-term ART, we used FDG-PET co-registered with computed tomography (CT) followed by fusion guided lymph node biopsy to obtain samples for characterization.
Methods: Participants recruited through NIH study NCT05419024 (Imaging and Biopsy of HIV-Infected Individuals Undergoing Analytic Treatment Interruption (ATI)) underwent FDG-PET-CT and FDG uptake was quantified as standardized uptake value (SUV; FDG uptake normalized to injected activity/weight). Tissue was sampled with ultrasound fusion guidance and aspiration. HIV RNA in plasma and cell-associated (CA) HIV DNA and RNA in cells from blood and lymphoid tissue were quantified by single copy assays (Somsouk et al., 2014).
Results: Study participants (N=2; HIV RNA <50 copies/ml plasma for >3 y, CD4 562-590) underwent imaging and guided biopsy. Imaging noted lymph nodes were all ≤ 1cm diameter; although most nodes had minimal FDG signal, increased uptake was detected in c. 3-10 lymph nodes in both participants (SUVmax 1.14 - 6.4), indicating increased metabolic activity was present in these tissues. Metabolically active nodes were present in mediastinal, axillary and inguinal distributions. Nodes accessible to fusion guided sampling yielded 104-105 cells. Levels of HIV DNA in biopsies (610-900 HIV DNA copies/1e6 cells) were c. 5 -15-fold higher than levels in peripheral blood mononuclear cells (PBMC). HIV RNA was quantifiable in both nodal tissue and PBMC; levels of HIV RNA/DNA (0.4-1.2 RNA copies/DNA copy) were comparable in blood and nodal sampling.
Conclusion: New non-invasive imaging approaches identify increased metabolic activity in subsets of lymph nodes during long term ART, and directed biopsy recovers sufficient HIV DNA and RNA for analysis even in nodes < 1cm size. Image guided approaches will advance understanding of HIV persistence in tissues.

503 Inducible, Infectious HIV-1 Resistance to Autologous Neutralizing Antibodies After Long-Term ART

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Background: ART reduces HIV-1 viral loads below the detection limit, but ART cessation leads to rapid viral rebound due to a population of latently infected CD4+ T cells carrying inducible, replication-competent proviruses. Current HIV cure strategies aim to delay or prevent viral rebound. Previously, we showed that autologous neutralizing antibodies (aNAbs) can prevent ex vivo outgrowth of some viruses in the latent reservoir of people with HIV (PWH; Bertagnolli et al., PNAS 2020) and that the reservoir remains stable for decades (McMyn et al., JCI 2023). However, it is not understood whether viruses persisting over long times on ART are sensitive to aNAbs.
Methods: Using samples of outgrowth viruses from nine PWH on long-term ART for a mean of 22 years and four PWH on ART for 11 years, we generated HIV pseudoviruses with the env sequences of inducible, replication-competent outgrowth viruses. Pseudoviruses of viral variants from each person were incubated with contemporaneous aNAbs and tested in a TZM-bl-based neutralization assay. Viral variants were also tested against three clinically relevant broadly neutralizing antibodies (bNAbs) targeting different neutralizing epitopes.
Results: Most outgrowth viruses from PWH on long-term ART were resistant to neutralization by aNAbs, with 85% of 34 isolates being resistant (IC_{50} >100 ug/mL). Conversely, PWH on ART under 20 years had more sensitive isolates (IC_{50}: 3 to 99 ug/mL), as only 22% of 55 viral isolates were resistant to aNAbs (IC_{50} >100 ug/mL). Viral isolates from both groups demonstrated similar sensitivities to the three bNAbs (VRC01, 10-1074, PGDM1400; IC_{50}: <.03 to >10). 89% of PWH on long-term ART had all tested viral isolates sensitive to at least one bNAb and 56% sensitive to two bNAbs, while 100% of PWH on short-term ART were sensitive to at least one bNAb and 50% sensitive to two bNAbs.
Conclusion: We demonstrated that in PWH on long-term ART, outgrowth viruses including large clones are more resistant to neutralization by aNAbs than proviruses induced in CD4+ T cells of PWH on ART for 11 years. This suggests a selection process may occur over two decades of ART. These aNAb resistant outgrowth viruses may contribute to viral rebound during treatment interruption, but this data may inform cure strategies with therapeutic vaccines that induce antibodies to neutralization-resistant viruses. Additionally, the large proportion of viral isolates sensitive to at least one bNAb could aid in the design of immunotherapy trials involving bNAbs.

504 Immune Selection of HIV-1 Reservoir Cells After Early ART Initiation

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Background: HIV reservoirs are established shortly after infection, but little is known about immune effects that influence viral reservoir cell evolution in early-treated people living with HIV (PLH). Here, we analyzed the proviral landscape and phenotypic features of HIV reservoir cells in the RIVER study, a randomized-controlled study evaluating effects of a ChAd63-vectored therapeutic vaccine (HIV.consv) given prior to a histone deacetylase inhibitor, Vorinostat, in PLH started on ART at the time of acute/early HIV diagnosis.
Methods: 10 RIVER study participants (n=5 from ART-only group, n=5 from the treatment group) were studied, using PBMC samples from randomization, the primary endpoint (18 weeks after randomization), and 1 year after study completion. Proviral landscapes were analyzed by near full-length proviral sequencing (FLIP-seq) and matched integration site and proviral sequencing (MIP-seq). Phenotypic and proviral sequencing (PheP-seq) was used to investigate the phenotype of memory CD4 T cells from 3 participants.
Results: In total, n=2763 proviral sequences were detected from 122.03 million PBMCs in all 10 participants combined; n=295 sequences (10.68%) were genome-intact. The mean numbers of intact HIV proviruses from randomization, primary endpoint and 1 year follow-up were 6.27, 2.39, 8.84 per million PBMC in the ART-only group versus 4.42, 2.37, and 5.46 per million cells in vaccine group (p=n.s.). 138 integration sites (IS) of intact proviruses were identified; among these, 54 (39.13%) were located in non-genic DNA, centromeric satellite DNA and genes encoding for members of the Zinc Finger Protein family. The proportion of intact proviruses integrated in these heterochromatin regions increased during longitudinal evaluations from 26% at randomization to 54% at the 1-year follow-up timepoint, but did not differ between the study arms. A total of n= 116,023 individual mCD4 T cells were analyzed by PheP-seq: n=648 represented HIV-infected cells and n=128 cells harbored genome-intact HIV-1. Notably, HLA-G, HLA-F, HLA-C, CCR6 and TGFB-R

were upregulated on HIV-1 reservoir cells with intact proviruses, consistent with immune selection primarily mediated by innate immune responses.
Conclusion: These data suggest accelerated and more efficient immune selection of HIV-1 reservoir cells when ART is started during early disease. Immune selection appears to be predominantly driven by innate immune responses in early infection, while the therapeutic T cell vaccine had no detectable effect.

505 Identification and Targeting of Metabolic Profiles in CTL-Resistant, HIV-Infected CD4+ T-Cells

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Background: HIV-specific CTL responses remain present even under long term ART, in association with residual HIV expression. Selection of CTL-resistant reservoir-harboring clones may contribute to HIV persistence, with BCL-2 overexpression being a previously reported mechanism. To identify additional mechanisms of resistance, we developed an in vitro model that compares infected cells surviving CTL pressure to non-targeted infected bystander cells in the same environment. Here, we highlight a specific metabolic profile enriched in CTL-resistant infected cells.
Methods: CD4+ T-cells were infected with HIVJRSCF (WT) or a variant containing an escape mutation in the Gag-TW10 epitope (TW10esc). Killing assays were performed by labeling infected T-cells with CTFR (WT) or CFSE (TW10esc) dyes, then culturing these together with a TW10-specific CTL clone. Surviving WT-infected and bystander TW10esc-infected cells were sorted based on HIV-Env expression and profiled by RNAseq, CITEseq and flow cytometry. Killing assays were also performed with pre-treatment of infected cells with the FDA approved antimalarial Atovaquone (ATQ) and iron chelator Deferoxamine (DFO).
Results: WT-infected survivors exhibited distinctive transcriptional and protein expression profiles, relative to bystanders (Figure 1). GSEA analysis of RNAseq data revealed that among several dysregulated pathways, WT-survivors were negatively enriched for Hallmark Glycolysis (n=4, NES = -1.74, Padj = 2.96e-05) and byproducts of active metabolism such as Hallmark Hypoxia (NES = -1.79, Padj = 1e-05). Flow cytometry on WT-survivors showed enrichment of cells expressing lower levels of cellular reactive oxygen species (ROS) (n=4, mean = -24.41% +/- 13.62, P=0.037). Pre-treatment of infected cells with ATQ, to increase ROS accumulation, and DFO, to induce hypoxia, modestly and robustly enhanced susceptibilities of infected cells to elimination by CTL respectively (ATQ: n=5, P = 0.09 ; DFO: n=4, P = 0.015; ATQ+DFO: n=4, P = 0.051).
Conclusion: Oxidative disbalance contributes to CTL mediated killing. Our results suggest that lower levels of ROS and hypoxic responses in HIV-infected cells with particular metabolic features renders these cells less susceptible to killing by CTL. Treatment with FDA-approved and well-tolerated ROS inducer ATQ and hypoxia-inducing iron-chelator DFO increased CTL mediated elimination of infected cells in vitro. Targeting metabolic balance may be a strategy to enhance elimination of persistent HIV-infected cells.

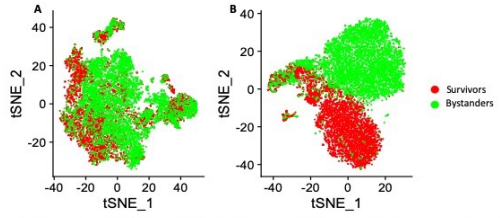

Figure 1: CTL-resistant, HIV-infected CD4+ T-cell survivors display an enriched gene expression and distinct surface protein profile at the single cell level compared to infected bystanders.
A. Unsupervised gene expression based clustering of WT-infected survivors (red) and TW10esc-infected bystanders (green) from scRNA-seq reveals enriched transcriptional states in survivors. **B.** CITE-seq analysis of survivors and bystanders captures distinct surface protein expression patterns defining CTL-resistant infected cells.

506 Immune Profile During ATI in AELIX-002 HTI Vaccine Trial and Its Role in Post-Intervention Control

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[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Hospital Germans Trias i Pujol, Badalona, Spain, [3]Hospital Germans Trias i Pujol, Bandalona, Spain, [4]Institut Universitari Fundació Parc Taulí, Sabadell, Spain, [5]Gilead Sciences, Inc, Foster City, CA, USA, [6]Aelix Therapeutics, Barcelona, Spain

Background: Autologous neutralizing antibodies (aNAb) are able to apply selective pressure on rebounding viruses after ART interruption (ATI). Recent findings in CHAMP cohort also show higher frequencies of activated natural killer (NK) cells in post-treatment controllers (PTC). In AELIX-002, a randomized controlled clinical trial testing HTI T-cell vaccines in early-treated PWH, all participants experienced detectable viral rebound during ATI, but lower viremia and longer ART-free periods (>12 weeks) were observed in vaccine recipients in whom vaccination induced robust cytotoxic HTI responses pre-ATI. Here, we explore humoral, innate, and T cell responses during ATI.
Methods: We used plasma and PBMC from 41 AELIX-002 participants (1) before ART was initiated (pre-ART), (2) at study entry (BL), (3) at first recrudescence timepoint (ATI-Rc), at peak viremia (ATI-Pk), (5) at viral setpoint (ATI-Setp) and (6) at the end of ATI (ATI-end). Neutralizing antibodies were measured against a panel of 6 HIV-1 pseudoviruses (Tier 1 and 2) and the pre-ART autologous virus in a standard TZM-bl cell-based assay. T, B and NK cell composition, activation and exhaustion were measured by flow cytometry. Total HIV- and HTI-specific responses were measured by IFNg ELISpot.
Results: Pre-ART, only three participants showed low-to-moderate neutralization of NL4-3 pseudovirus and, one participant, of the autologous virus. At ATI-Pk, 27% placebo and 4% vaccinees neutralized NL4-3, while 21% placebo and 12% vaccinees had detectable neutralization to the pre-ART autologous virus. Despite viral recrudescence occurring in all participants, vaccinees who remained off ART > 12 weeks had stronger and more HTI-focused responses at ATI-end compared to the rest of participants and presented a unique immunological profile characterized by i) lower levels of plasma B cells, ii) lower levels of activated B and CD8 T cells, and iii) less exhaustion after peak viremia and up to ATI-end. Unlike PTC, no increase in activated NK was seen in vaccinees who remained off ART for >12 weeks at any timepoint.
Conclusion: After HTI-vaccination, the immune profile of participants remaining off ART for >12 weeks was different from those described in other studies on post-treatment controllers. While no significant contribution of humoral and innate responses was detected, durable HTI-specific responses and lower B- and T-cell activation profiles were maintained during ATI despite viral recrudescence.

507 IL-1β Blockade in PWH on ART Enhanced Host Antiviral Responses and Cytotoxic Effector Functions

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Background: Plasma IL-6 levels are amongst the strongest predictors of mortality in people with HIV (PWH) on ART, and IL-1β, an upstream regulator of IL-6, may be the major driver of this risk. In vivo IL-1β blockade with the monoclonal antibody, canakinumab, significantly reduced arterial and bone marrow inflammation in our prior pilot study of PWH on ART. Here we now identify the host immune mechanisms associated with IL-1β blockade, using single cell mass cytometry (CyTOF) and transcriptomic approaches.
Methods: A total of 10 PWH on ART with known cardiovascular disease (CVD) or 1 traditional CVD risk factor, were administered a single subcutaneous dose of 150 mg canakinumab and followed for 12 weeks. Biospecimens were collected at weeks 0, 4, and 8 weeks post-treatment. We performed bulk RNA sequencing from PBMCs, sorted CD4+ T cells, and CyTOF from PBMCs. We performed differential gene expression analysis with correction for multiple testing using the Benjamini-Hochberg method. Gene set enrichment analyses were performed using the MSigDB database.
Results: We observed a significant reduction in plasma IL-1β and IL-6 levels after canakinumab treatment. RNA-seq from bulk PBMCs showed significant induction of interferon signaling and downregulation of genes pathways reflecting CD8+ T cell exhaustion after canakinumab treatment. RNA-seq from

sorted peripheral CD4+ T cells showed a significant reduction in pathways of T cell activation, immune exhaustion (e.g.,PD-1), and cell cycling. While overall we did not observe a significant reduction in the HIV reservoir size after canakinumab, among 6 "virologic responders" (median -33% decrease in HIV total DNA copies/10^6 peripheral CD4+ T cells) we observed enhanced plasma IFN-β along with decreased expression, by CyTOF, of PD-1 on CD8+ T cells and Ki67 (a marker of cell cycling) on CD4+ T cells compared to 4 "non-responders" (no change in HIV total DNA). Single cell sequencing revealed significantly lower levels of the exhaustion markers (TOX, TIGIT and LAG3) in CD8+ T cells in virologic responders, although levels of granzyme and perforin were similar between groups.

Conclusion: Our multiomic analysis highlights three potential novel mechanisms to target HIV after in vivo IL-1β blockade: (1) augmenting antiviral immunity, (2) enhancing cytotoxic CD8+ T cell effector function, and (3) reversing dysregulated immune activation of CD4+ T cells. Thus, IL-1β, via a multi-faceted approach, may induce an immunologic milieu favorable for HIV reservoir clearance.

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508 Elevated Plasma IL-10 and Type I Interferon Predict Faster HIV Reservoir Decay in Acute Treated HIV

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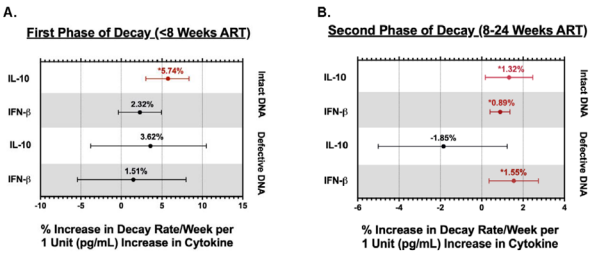
Background: The HIV reservoir largely consists of "defective" virus, but the elimination of the "intact" (replication-competent) reservoir is a major focus of HIV eradication strategies. There are limited data describing reservoir decay rates during the first few months of acute-treated HIV, nor the host immune responses that drive reservoir decay. We quantified plasma cytokine levels from >500 longitudinal samples from the UCSF Treat Acute HIV cohort to determine immunologic pathways that predict reservoir decay in people with HIV (PWH).

Methods: Individuals diagnosed with acute (<100 days) HIV were enrolled between 2015-2020, immediately initiated on ART (tenofovir/emtricitabine+dolutegravir), and followed monthly for the first 24 weeks of ART initiation. Frequencies of intact vs. defective provirus were quantified using the IPDA®. High-sensitivity multiplex plasma cytokine assays were performed from cryopreserved plasma samples (MesoScale Diagnostics). Multivariate nonlinear general additive models were adjusted for false discovery rate (FDR) using the Benjamini-Hochberg method.

Results: Among 67 PWH diagnosed <100 days from HIV acquisition, we observed an initial rapid (<8 weeks) decay, followed by second slower (8-24 weeks) decay of both intact and defective HIV proviral DNA during the first 24 weeks of ART. Among 20 plasma cytokines assayed across these same longitudinal timepoints (weeks 0, 2, 4, 8, 12, 16, 20, 24), IL-10 and type I interferons (IFN-β) significantly predicted accelerated reservoir decay even after adjustment for initial CD4+ T cell count, pre-ART viral load, age, and timing of ART initiation. IL-10 was significantly associated with faster decay rates for intact, but not defective virus, during both phases of decay (5.74% and 1.32% increase in decay rate/week per unit-increase in IL-10, respectively). IFN-β was significantly associated with faster decay rates during the second decay phase (0.89% intact and 1.55% defective HIV DNA).

Conclusion: Individuals with higher plasma IL-10 and type I IFN expression during the first 24 weeks of ART demonstrated accelerated HIV reservoir decay. These cytokines are well known to exert variable effects on the host immune response depending on stage of disease (e.g., favorable during acute but detrimental during chronic infection). Our findings add insight into the complexity of these pleiotropic cytokines and highlight the need for potential stage-specific targeting of these cytokines in future HIV cure strategies.

Figure 1. Among 20 cytokines assayed, IL-10 and IFN-β significantly predicted accelerated first (A) and second (B) phases of HIV reservoir decay. Bars= 95% confidence intervals. Red font= statistically significant in multivariate nonlinear models adjusted for initial CD4+ T cell count, pre-ART viral load, age, and timing of ART initiation (FDR q<0.05).



509 Labelled High Affinity TCRs for Detection of HIV Epitopes on Infected Cells: How Low Can We Go?

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Background: HIV proviruses persist in a non-productive state in CD4+ cells. There is no individual cell surface biomarker that uniquely identifies infected cells. However, some cells contain proviruses that are transcriptionally active and translationally competent, leading to expression of viral proteins and T cell epitopes. We used soluble affinity-enhanced T cell receptors (TCR) to investigate the level of expression of viral peptides presented by HLA class I molecules.

Methods: We developed T cell receptors with picomolar affinity (pM) for an HIV Gag epitope presented by HLA-A*02:01 and incorporated either a biotinylation tag or Fc fragment to enable fluorescence imaging. CD4+ T cell lines or primary cells with varying HLA expression levels were pulsed with peptide or infected with HIV and analysed for expression of viral peptide-HLA complexes by total internal reflection microscopy (TIRF; single molecule epitope counting).

Results: HIV Gag peptide-HLA complexes could be identified on peptide pulsed cells using a labelled TCR and TIRF microscopy. The signal/noise ratio was improved using the TCR-Fc format. T2 cells pulsed with a titration of peptide were then used to quantify pHLA copies/cell and determine the dynamic range of the assay (~10-200 pHLA/cell). pHLA could also be detected on the surface of HIV-infected HLA-A*02-transduced C8166 cells, albeit at copies/cell near the lower limit of detection of the assay. Similar results were obtained with primary CD4+ T cells infected in vitro with HIV. In parallel we showed that the same TCR, when used in a bispecific format (Gag x CD3) could eliminate infected C8166 cells at picomolar drug concentrations in a T cell redirection assay.

Conclusion: An affinity-enhanced TCR targeting a Gag peptide successfully detected pHLA complexes on the cell surface down to ~10 copies/cell and could redirect killing of infected cells when used in a bispecific format despite low pHLA expression, demonstrating its high sensitivity to antigen. Further work is ongoing to develop flow cytometry applications using labelled high affinity TCRs with the potential to isolate HIV-infected cells ex vivo for further analysis.

510 HIV T-Cell Immunity Predicts Intact Proviral DNA Decline in People Treated During Acute Infection

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Background: Starting antiretroviral therapy (ART) during acute HIV infection (AHI) is known to limit damage to the immune system and lower the size of the viral reservoir. In light of HIV cure interventions, it is important to understand the longitudinal dynamics of the early host immune responses in relation to the viral reservoir size. Therefore, we investigated the viral reservoir size and HIV specific immune responses in participants of the Netherlands Cohort Study on Acute HIV Infection (NOVA study), who initiated ART immediately after diagnosis of AHI.

Methods: Participants in the NOVA study diagnosed during Fiebig II-VI were included in the analysis (n=22). PBMC from leukapheresis at 24 and 156 weeks after initiation of ART were analyzed. Viral reservoir size was assessed by Intact Proviral DNA Assay and qPCR. HIV specific precursor T-cell responses after HIV peptide pool stimulation (Env, Gag, Nef, Pol) were determined by

flowcytometry. Correlations were determined using Pearson's correlations ($p<0.05$).

Results: A mean decline in intact proviral DNA (Fig.1A) and total HIV-DNA load, but not defective proviral DNA and cell-associated US-RNA between 24 and 156 weeks after ART initiation was observed. We measured a positive HIV specific CD4+ and CD8+ T-cell response to at least 3 different viral proteins in the majority of individuals at both time points (Fig.1 B+C). At 24 weeks, intact proviral DNA load was associated with CD4+ T-cell responses to Env ($p<0.001$, $R2=0.96$), Gag ($p=0.005$, $R2=0.6$), Nef ($p<0.001$, $R2=0.9$) and Pol ($p=0.002$, $R2=0.6$). At 156 weeks, intact proviral DNA load was correlated with CD8+ T-cell response to Gag ($p=0.034$, $R2=0.59$) and Pol ($p<0.001$, $R2=0.77$). Moreover, we observed a positive association between the decay of intact proviruses between 24 and 156 weeks with CD4+ T-cell responses to Env ($p=0.034$, $R2=0.64$) and Nef ($p=0.007$, $R2=0.76$). No associations between T-cell responses and other viral reservoir measurements (defective proviral DNA load, total HIV-DNA and US-RNA) were observed.

Conclusion: We detected a positive association between HIV specific T-cell responses and the decay of intact proviral DNA load in individuals treated during AHI. This implies that a potent HIV specific T-cell response, in addition to early ART, leads to a reduction of intact proviral DNA load. This finding potentially provides a promising avenue for cure interventions aimed at reservoir induction in combination with T-cell activating strategies.

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511 Lower ADCC After 26 Weeks of PEG-IFN-α2b and 2 bNAbs in Otherwise Suppressed HIV-1+

Emmanouil Papasavvas[1], Jessicamarie Morris[1], Brian N. Ross[1], Matthew Fair[1], Livio Azzoni[1], Karam Mounzer[2], Jay R. Kostman[2], Pablo Tebas[3], Luis J. Montaner[1]
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Background: Previous studies suggested that pegylated interferon α2b (peg-IFN-α2b) and the broadly neutralizing antibodies (bNabs) 3BNC117 and 10-1074 may contribute to cure-related strategies. We evaluated the effect of a 26-week immunotherapy course with peg-IFN-α2b+bNAbs in the cytotoxic function and activation of natural killer (NK) cell subsets in persons with HIV infection (PWH) that participated in the BEAT 2 study (NCT03588715).

Methods: Fourteen PWH receiving suppressive antiretroviral therapy (ART, <50 HIV-1 copies/ml) underwent ART interruption (ATI) while receiving a 26-week immunotherapy course of peg-IFN-α2b+bNAbs. Peripheral blood mononuclear cells (PBMC) were collected prior to ATI/immunotherapy (ART alone, time-point 1), on ART+4 weeks peg-IFN-α2b (time-point 2), and on ATI+26 weeks peg-IFN-α2b+bNAbs (time-point 3). Fresh PBMC were used in 51Cr release assays for assessment of antibody-dependent cell-mediated cytotoxicity (ADCC) against NK-resistant lymphoblastic target cell line prior and after in vitro stimulation with gp120, and for direct cytotoxicity against MHC-cell null cancer target cell line prior and after in vitro stimulation with IFN-α. Cryopreserved PBMC were used for immunophenotypic characterization by flow cytometry of NK cell subsets and of markers associated with NK activation, inhibition or maturation (e.g. CD38, NKp46, NKG2A, Siglec 7, Siglec 9, CD57). Statistics were performed by JMP 15.

Results: Immunotherapy did not affect IFN-α-induced NK direct cytotoxicity but resulted in a decrease in gp120-mediated ADDC. Reduced ADCC was observed together with an increase in the cytokine producing CD56hi and in CD56lo/+CD16- % of CD56+ NK cells, and a decrease in the cytotoxic CD56lo/+CD16+ % of CD56+, suggesting that decrease in the expression of Fc receptor CD16 on NK could be associated with lower ADCC function. These findings were supported by a negative correlation between ADCC and CD56lo/+CD16− % of lymphocytes after IFN-α immunotherapy (end of step 2). Finally, the gp120-induced ADCC decrease was observed together with a decrease in the maturation/cytotoxicity marker CD57 in CD56lo/+CD16+ NK cells, despite an increase in activation (CD38, NKp46) and inhibition (NKG2A, Siglec 7) markers.

Conclusion: In PWH, combined immunotherapy with peg-IFN-α2b+bNAbs resulted in no effect on IFN-α-induced NK direct cytotoxicity and an unexpected decrease in gp120-induced ADCC and in circulating CD16+ NK cell subsets.

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512 Slope of Neutralization Curve is Best Predictor of Viral Decay Response to 3BNC117 at ART Initiation

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Background: Broadly neutralizing anti-HIV-1 antibodies (bNAbs) are currently being tested as component in long-acting treatment of HIV-1 and curative strategies. bNAb sensitivity of plasma viruses and thus the proviral reservoir is crucial for the clinical outcome. Currently, there is no gold standard for analyzing nor categorizing bNAb sensitivity.

Methods: Plasma HIV-1 RNA from 59 eCLEAR ART-naïve participants were analyzed for 3BNC117 sensitivity post hoc using the PhenoSense assay and two genotypic prediction algorithms; the 'HIV screening analysis' developed at Rockefeller University and the 'bNAb-ReP' developed by VRC/NIH. We used mixed-effects linear regression models to calculate the second-phase (day 10 to 24 after ART initiation) plasma HIV-1 RNA decay among individuals receiving 3BNC117 to ART initiation compared to ART alone. A ROC curve was used to explore and identify the optimal characteristic among the three bNAb sensitivity assays for predicting second-phase viral decay.

Results: The IC values ($\geq IC_{50}$) on the neutralization curve obtained from the PhenoSense assay may be modelled using the Median Effect Principle. This implies that a logistic model can be used to estimate the slope of log(f_a/(1-f_a)) as a measure of inhibition increase with respect to 3BNC117 dose. There was a significant faster second-phase viral decay with steeper slope of the neutralization curve (-0.029 change in log(f_a/(1-f_a)) per $\log_{10}$ 3BNC117 concentration, 95% Confidence Interval: -0.049; -0.010, P=0.003). Among the three bNAb sensitivity assays, the slope of the logistic was the best predictor of second-phase viral decay outperforming any IC values or genotypic assessments. The sensitivity and specificity in predicting a faster second-phase viral decay with a slope of 2.25 was 62% and 75%. The next best predictors of plasma viral decay in the second phase were $IC_{90}<1.2$ µg ml−1 with a sensitivity and specificity of 78% and 63% on the PhenoSense assay and a threshold for single envelope sequences of 75% on the bNAb-ReP (90% of all sequences needed to be categorized as sensitive) with a sensitivity and specificity of 77% and 75%.

Conclusion: Whilst bNAb sensitivity is crucial for clinical outcome in clinical trials administering bNAbs, so far bNAb sensitivity threshold has been based on expert opinions. Using clinical data from the eCLEAR trial, we have shown that the best predictors of bNAb-mediated effects on plasma HIV-1 RNA decay are the slope of the neutralization curve from the PhenoSense assay.

513 HIV-1 Reservoir Dynamics in Children With Early Treated, Perinatally-Acquired HIV: Does Sex Matter?

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[1]Africa Health Research Institute, Durban, South Africa, [2]University College London, London, United Kingdom, [3]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [4]Hospital Universitario [12] de Octubre, Madrid, Spain, [5]Bambino Gesu Children's Hospital, Rome, Italy, [6]University of Padova, Padova, Italy, [7]University of the Witwatersrand, Johannesburg, South Africa, [8]Stellenbosch University, Cape Town, South Africa, [9]Fundação Ariel Glaser Contra o SIDA Pediátrico, Maputo, Mozambique, [10]Universitat de Barcelona, Barcelona, Spain

Background: Eliminating the HIV-1 reservoir is key to an effective HIV cure. Improved understanding of the size and nature of the viral reservoir will help the design of cure strategies. Here, we performed a longitudinal analysis of the total HIV reservoir in early treated, perinatally HIV-infected children.

Methods: Participants were infants from the Early AntiRetroviral Treatment in Children (EARTH) Cohort in South Africa, Mozambique, and Mali. HIV was diagnosed shortly after birth, followed by early ART initiation with up to 4 years of follow up. We analysed 34/52 infants, 18 females and 16 males, termed virological controllers with undetectable viral load during at least 12 months of follow up. Proviral DNA was measured from total PBMCs by droplet digital PCR from ART initiation through 4 years.

Results: ART was initiated at a median of 34 days of life (IQR, 26.0-73.0) and the median time to viral suppression in virological controllers was 363 days on ART (IQR, 317,0-552,0). There was a positive correlation with baseline viral load and proviral load each measured at ART initiation ($p=0.03$, $r=0.58$) and 1 year ($p=0.01$, $r=0.56$) and 2 years ($p=0.001$, $r=0.69$) of follow up. At ART initiation the median total HIV DNA level was 3.7 log copies/million cells (IQR, 3.2-4.1). The HIV DNA reservoir decreased slowly over the first 6 months (median=3.2 log c/10^6 cells, IQR, 2.6-3.7) of ART with significant decline after 1 year (median=2.6

log c/106 cells, IQR, 2.3-3.1) (p=0.002). There was a further steady decline over the next 3 years (median=2.05 log c/106 cells, IQR, 0.5-2.7) (p<0.0001). However, total HIV DNA remained detectable in 9/12 (75%) participants after 4 years. There was no difference in proviral load at ART initiation between sexes but after 4 years the HIV reservoir size decreased significantly in males (p=0.006) but not in females.

Conclusion: Decline in total HIV DNA is observed after 1 year of treatment and is still detectable after 4 years of treatment. The faster reservoir decay in males is novel, suggesting that sex differences should be considered to optimize HIV cure strategies in children.

514 Earlier Initiation of ART Reduces Intact Proviruses but Not Residual Viremia After 48 Weeks

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Background: The timing of antiretroviral therapy (ART) initiation during acute or early HIV infection (AEHI) may affect the size of the latent and expressed HIV reservoir but its specific influence on intact proviral DNA (IPD) or low-level viremia has not been fully described.

Methods: AIDS Clinical Trials Group study A5354 enrolled 192 adults who started ART during AEHI at 30 sites in the Americas, Africa, and Asia. Participants were retrospectively centrally categorized as Group 1 (Fiebig I-II), Group 2 (Fiebig III-IV), or Group 3 (Fiebig V) and measures of HIV persistence were evaluated on a subset of 106 US study participants or those with confirmed subtype B. The intact proviral DNA assay (IPDA®) was performed on CD4+ T cells isolated from peripheral blood at weeks 24 (not shown), 48, and 72 after ART initiation. Plasma HIV RNA was measured by automated single copy assay (SCA) at week 48. Wilcoxon rank-sum and Fisher's exact test were used for pairwise comparisons between Groups and Jonckheere-Terpstra test for trends across the 3 Groups.

Results: Participants had a median (IQR) age of 29 (24, 39) years, 11 (10%) were female, 3 (3%) identified as transgender, 58 (57%) were Black, and 103 (97%) initiated a regimen of EVG/COBI/FTC/TAF. Participants in Group 1 had a nominally lower level of total proviral DNA (IPD + defective DNA) than Groups 2 and 3 at weeks 24 and 48 (p≤0.038). Participants who started ART during the earliest study groups had significantly lower IPD levels at all three timepoints (trend tests p≤0.033) but with substantial variation and overlap in IPD copies per million CD4+ T cells (Figure 1). No significant longitudinal trends were observed in the decline of IPD across Groups. Persistent plasma HIV RNA was detected by SCA in >75% of participants at week 48 with no significant differences in the proportions with detectable HIV RNA (76-85%; p≥0.41) or the levels of HIV RNA between pairwise groups (p≥0.22). IPD and plasma HIV RNA at week 48 were significantly but modestly correlated (r=0.42, p<0.001).

Conclusion: Here we show that earlier ART lowers the levels of total and IPD in Groups 1 and 2 (Fiebig I-IV) compared with Group 3 (Fiebig V). Surprisingly, residual plasma HIV RNA was detected in >75% of participants at week 48 with no significant differences in proportions or levels between study Groups. These results provide new evidence that earlier ART does not affect the active HIV reservoir measured by plasma HIV RNA.

Figure 1 – Level of Intact Proviruses at Weeks 48 and 72 by Study Group

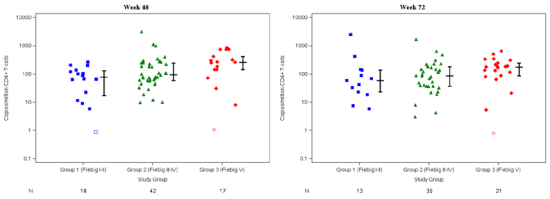

Figure 1. Log_{10} copies of IPD per 1M CD4+ T cells isolated from peripheral blood mononuclear cells across study groups at weeks 48 and 72. Week 24 data were used in the analysis but not shown here. IPDA measurements reported as 'undetectable' are indicated with open symbols, without any imputation.

515 Host and Viral Factors Shape the Composition of the HIV-1 Viral Reservoir in the 2000HIV Cohort

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Background: The HIV-1 host interaction exhibits remarkable diversity, resulting in various clinical profiles and virological traits, including coreceptor tropism. The 2000HIV study, which is a multi-omics study including 1895 people living with HIV-1 (PLWH) (NTC03994835), reflects this notable variability by including different clinical phenotypes, such as elite controllers (EC), viremic controllers (VC), transient controllers (TC), immunological non-responders (INR), rapid progressors (RP) and normal HIV-1 progressors (NP).

Methods: We quantified the total and intact HIV-1 reservoir by using the Rainbow proviral HIV-1 DNA digital PCR assay in CD4 T cells from blood in a subset of PLWH from the 2000HIV cohort (n = 863). In this study, we identified two distinct groups of PLWH, LoViReT-like and HiViReT-like, based on their total HIV-1 DNA levels (10% cut-off). Coreceptor tropism was determined by sequencing the viral env region and using the Geno2pheno algorithm (10% false positive rate).

Results: Quantification by the Rainbow HIV-1 DNA assay resulted in a median of 456.1 (CI95%: 410.2-521.4) total HIV-1 DNA copies/10^6 CD4+ T cells (n = 863) and 8.7 (CI95%: 6.7-10.6) intact HIV-1 DNA copies/10^6 CD4+ T cells (n = 565). Total HIV-1 DNA levels in EC and VC were significantly lower than the NP (P <0.0001), whereas total HIV-1 DNA levels in INR were higher than NP (P = 0.0097). Intactness levels were significantly lower in the different controller groups versus NP (P <0.05) (Figure1). The selected samples for the LoViReT-like PLWH and HiViReT-like PLWH harbor total HIV-1 DNA levels of <50 copies/10^6 CD4 T cells and >2170 copies/10^6 CD4 T cells, respectively. Clinical parameters associated with infection (CD4 nadir, latest CD4 count, plasma viral load before ART and viral zenith) were significantly different between both groups (Mann Whitney U test). In addition, PLWH infected by X4-tropic viruses (n = 144) harbor significantly higher levels of total and intact HIV-1 DNA compared to PLWH infected by R5-tropic viruses (n = 561) (P = 0.003 and P = 0.04).

Conclusion: Intactness levels differ significantly among controller groups and NP, highlighting the importance of intact HIV-1 DNA as a relevant virological parameter. Additionally, the study highlights the role of coreceptor tropism in influencing the reservoir size. This study marks a significant milestone in HIV research, as it represents a pioneering effort to comprehensively characterize the viral reservoir in a substantial number of PLWH.

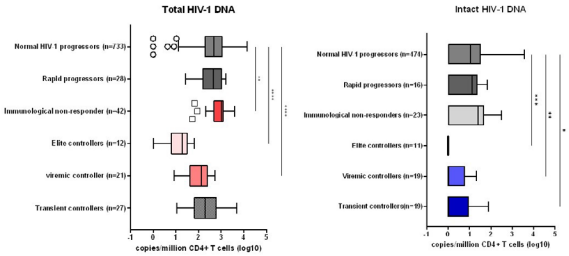

Figure 1: Reservoir levels differ between different HIV-1 clinical phenotypes. Horizontal boxplots demonstrating the differences in total HIV-1 DNA (left) and intact HIV-1 DNA (right) between the different groups. Dunnet's comparison test was used to compare the groups to the normal HIV-1 progressors.

516 Intact HIV DNA Decay During 15 Years of Suppressive ART: Comparisons by Timing of ART Initiation

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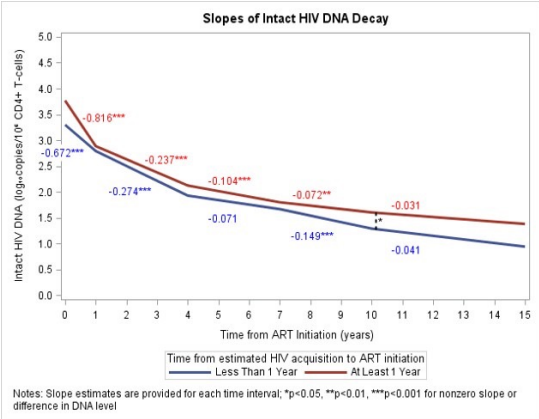
Background: People who initiate antiretroviral therapy (ART) during acute HIV may be ideal candidates for curative interventions due to small reservoirs

of proviral HIV DNA integrated into CD4+ T-cells, but this population is rare. We evaluated how the time between seroconversion and ART initiation impacts HIV reservoir decay during up to 15 years of suppressive ART to clarify reservoir pathogenesis and inform future studies of strategies to achieve HIV remission.
Methods: The U.S. Military HIV Natural History Study enrolls adult U.S. Department of Defense beneficiaries with HIV. We identified participants who achieved HIV RNA <400 copies/mL within 1 year of starting ART, maintained suppressive ART for at least 10 years, and had stored peripheral blood mononuclear cell (PBMC) specimens. PBMCs were analyzed using the intact proviral DNA assay (IPDA) to separately quantify intact and defective proviruses. We created linear spline models for intact HIV DNA, total HIV DNA, and proportion of intact HIV DNA based on time between estimated HIV seroconversion and ART initiation (<1 year vs. ≥1 year), with knots at 1, 4, 7, and 10 years on ART. Models were adjusted for age, race/ethnicity, CD4 count, and viral load at ART initiation. Correlations between intact and total HIV DNA were assessed using Spearman's rank correlation coefficient.
Results: Of 83 participants, median age at ART initiation was 34.3 years (IQR: 29.2-41.5), 23 (27.7%) started ART within one year of estimated HIV acquisition (21 within 3-12 months), and 82 (98.8%) were male. The first ART regimen was NNRTI-based for 49 (59.0%). There were similar patterns of decay of intact HIV DNA (Figure), total HIV DNA, and proportion of intact HIV DNA between time to ART initiation groups. Intact HIV DNA was consistently lower in the earlier ART initiation group (1.13 vs. 1.54 log_{10} copies/10^6 CD4+ T-cells at 10 years, p<0.05). Correlations between intact and total HIV DNA were strongly positive at all visits for both groups (range: 0.824-0.964; p<0.001).
Conclusion: Earlier ART initiation was associated with lower levels of intact proviral DNA in PBMCs that persisted through 10-15 years of suppressive ART, at which point they were about 30% smaller in the early-treated group. Significant reservoir decay was observed through 10 years of ART. Future studies of curative interventions may consider enrolling participants who initiated ART within one year of year of estimated HIV acquisition, particularly those with a long history of suppressive ART.



517 Intact HIV Remains Similar in Early- and Late-Treated Patients With Comparable Immunological Status

Paula Suanzes[1], Judith Grau-Expósito[2], Jordi Navarro[1], Joan Rey Cano[2], Adrià Curran[1], Joaquín Burgos[1], Arnau Monforte[1], Meritxell Genescà[2], Vicenç Falcó[1], María Buzón[2]
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Background: The HIV reservoir stablished in the early stages of the acute HIV infection (AHI) and at the time of ART initiation is a major barrier to curing HIV. In this study, our objective was to assess the longitudinal impact of initiating ART during early HIV infection on the composition of the viral reservoir, in comparison to a cohort of individuals with similar immunological status treated during the chronic phase of the infection.
Methods: The VHAHI cohort is an ongoing ambispective cohort (n=147) including patients with confirmed AHI in Barcelona (Suanzes et al, IJID, 2023). We included 25 participants from the VHAHI cohort that started ART within 180 days (early treated: ET), and 16 individuals with similar immunological status that started ART during the chronic phase of HIV infection (late treated: LT). We performed a longitudinal analysis after 0, 6, 12 and 36 months of ART in 13 ET and 7 LT participants. Moreover, a cross-sectional analysis using samples from 23 ET and 14 LT participants who had been on ART a median of 68 months (45-101) was performed. We measured total HIV DNA using qPCR, and frequencies of intact and defective proviruses using the IPDA.
Results: Thirty-eight (92.7%) participants were men. The median time from the estimated date of infection to ART initiation was 75 days (42-128) in the ET group and >180 days in the LT group. Pre-ART HIV viral load was higher in the ET group (p=0.035), but there were no significant differences in CD4+ and CD8+ counts, or CD4+/CD8+ ratio pre-ART (p>0.05). In the longitudinal analysis, all viral forms, included intact, declined over time in both cohorts. However, defective proviruses plateaued after 6-12 months of ART in LT participants, while continuous decay was observed in the ET group (p=0.01). Participants in the cross-sectional analysis maintained virological suppression for a median of 63 months (39-95) without significant differences between ET and LT (p>0.05). Total HIV DNA and defective proviral DNA levels were significantly higher in LT participants (Fig.1A). Although we did not observed differences in intact proviral DNA between groups (Fig.1A), the contribution of the intact form to the total pool of HIV-DNA was significantly higher in ET participants (Fig.1B).
Conclusion: The intact HIV reservoir after ART remains similar between ET and LT individuals with comparable immunological status. Further research is necessary to determine the implications of these findings for HIV cure strategies.

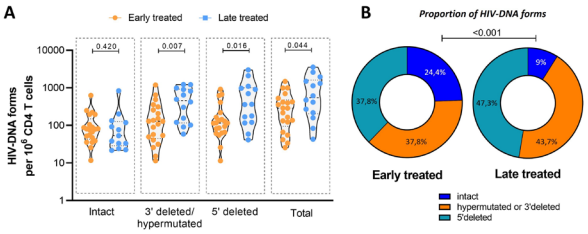

Figure 1. Composition of the HIV reservoir. **A)** Total, intact and defective proviruses were measured by qPCR or IPDA in early and late treated individuals after ≥36 months of ART. **B)** Proportions of proviral forms are shown.

518 Tumor Suppressor and Innate/Inflammatory Pathways are Associated With the HIV Reservoir Size

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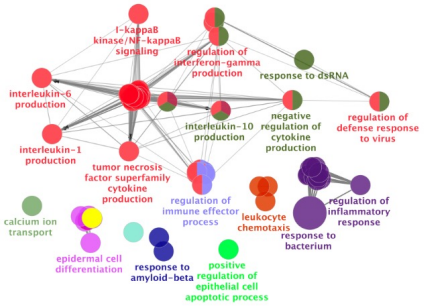
Background: The major barrier to an HIV cure is the HIV reservoir: latently-infected cells that persist despite effective antiretroviral therapy (ART). Most prior studies of host genetic predictors of HIV control have focused on "elite controllers," rare individuals able to control virus in the absence of ART. However, there have been few genetic studies among ART-suppressed non-controllers, who make up the majority of people with HIV (PWH).
Methods: We performed a large cross-sectional study of 191 PWH on ART and measured host gene expression (RNA-seq) and HIV reservoir from peripheral blood CD4+ T cells. HIV reservoir was quantified as total DNA (tDNA), unspliced RNA (usRNA), and intact DNA.
Results: After adjusting for nadir CD4+ count, timing of ART initiation, and genetic ancestry, we identified two host genes for which higher expression was significantly associated with smaller total DNA viral reservoir size, *P3H3* and *NBL1*, both known tumor suppressor genes. We then identified 17 host genes for which lower expression was associated with higher residual transcription (HIV usRNA). These included novel associations with membrane channel (*KCNJ2*, *GJB2*), inflammasome (*IL1A*, *CSF3*, *TNFAIP5*, *TNFAIP6*, *TNFAIP9*, *CXCL3*, *CXCL10*), and innate immunity (*TLR7*) genes (FDR-adjusted q<0.05). Gene set enrichment analyses further identified significant associations of HIV usRNA with TLR4/microbial translocation (q=0.006), IL-1/NRLP3 inflammasome (q=0.008), and IL-10 (q=0.037) signaling. Protein validation assays using ELISA and multiplex cytokine assays supported these observed inverse host gene correlations, with P3H3, IL-10, and TNF-α protein associations achieving statistical significance (p<0.05). Of note plasma IL-10 was also significantly inversely associated with HIV DNA (p=0.016). HIV intact DNA was not associated with differential host gene expression, although this may have been due to a large number of undetectable values in our study.

Conclusion: To our knowledge, this is the largest cohort-based transcriptomic study of host genetic predictors of the HIV reservoir. Further studies are needed to validate these findings, ideally with dedicated functional genomic and intracellular protein assays using longitudinal samples to demonstrate causality of these observed associations. Our findings add important clinical and immunologic data to the limited host genomic HIV reservoir studies to date.



Unbiased gene set enrichment analyses (GSEA) of the entire transcriptome (rank-ordered by q-value) in association with HIV unspliced RNA. Host gene sets involving interferon, IL-10, TNF, NLRP3 inflammasome activation, and bacterial translocation signaling were significantly associated with HIV usRNA. A Benjamini-Hochberg FDR of q<0.05 was used to generate nodes (circles).

519 Taming the Viral Reservoir Over 3 Decades of Advancements in HIV Treatment

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Background: Since the advent of antiretroviral therapy (ART), HIV clinical management has steadily improved, not only because of the availability of more potent and safer drugs, but also due to the recommendations for universal treatment at diagnosis, regardless of disease stage and CD4 count, and efforts to increase HIV diagnose at its earliest stage after HIV acquisition. However, little is known about the effects of such improvements on the establishment of the latent HIV reservoir. Here, we characterize a group of people with HIV (PWH) on ART to determine the influence of multiple factors on the HIV reservoir evolution.
Methods: We analyzed the reservoir of 893 PWH treated and virologically suppressed for >3 years by measuring total HIV-DNA in PBMCs by ddPCR. Those with <50 HIV-DNA copies/10^6 PBMCs were classified as LoViReT. 40 demographic, clinical, virologic, and immunologic variables were collected to explore their association with the LoViReT status using the Random Forest machine learning algorithm, along with LOESS and logistic regression, or PCA.
Results: 180 (20%) of the 893 PWH were classified as LoViReTs. Minimum CD4 count, maximum viremia during clinical follow-up, shorter time from ART initiation to viral suppression, and longer time on an integrase strand transfer inhibitor (INSTI)-based regimen predicted LoViReT status (classification error=30%). The multiple logistic regression model estimation of the effect of these parameters was: minimum CD4 count OR=1.52 (per 100 cells/µL), maximum viremia OR=0.73 (log_{10} plasma HIV-RNA copies/mL), and time to suppression OR=0.59 (years). We further analyzed how those factors vary based on ART start date. We observed a decrease in total HIV-DNA and a greater percentage of LoViReTs when ART was started after 2007. Indeed, time from treatment to suppression changed from 1.7 years in 1998 to <4 months in 2020. Since INSTIs were introduced in 2007, we performed a sub-analysis of the effect of INSTI-based regimens on HIV proviral levels, noting that individuals initiating ART with INSTIs had lower reservoir levels (p=0.001) and shorter times to undetectable viremia ($p=2.2x10^{-16}$).
Conclusion: ART guidelines constant improvement and the introduction of new generation drugs are related to the establishment of lower HIV reservoir levels in PWH and, therefore, to the increase in the LoViReT phenotype among the individuals examined, which could facilitate the future success of medical strategies aimed at achieving a functional cure.

520 Vectored Delivery of Closer-to-Germline Antibodies Can Mediate Long-Term SHIV Suppression

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Background: Delivery of potent broadly neutralizing antibodies by recombinant adeno-associated virus (AAV) vectors can strongly and durably suppress ongoing viral replication after a single vector administration. We have successfully and durably suppressed viral replication in three SHIV-infected monkeys with this approach, including the "Miami monkey" with well over 7 years of plasma viremia below 15 copies/mL of SHIV RNA. However, the generation of anti-drug antibody responses (ADAs) against the AAV-delivered antibodies often limits the efficacy of this approach. Due to extensive affinity maturation, most potent broadly neutralizing antibodies exhibit unusually high levels of somatic hypermutation that can be seen as 'non-self' by the recipient's immune system. To overcome this important challenge, delivery of less extensively mutated (i.e., closer-to-germline) antibodies was evaluated.
Methods: In a pilot experiment, four Indian-origin rhesus macaques were experimentally infected with SHIV-AD8. At week 14 post-infection, and with plasma viremias ranging from 5,100 to 130,000 copies/mL of SHIV RNA, all four monkeys received AAV vectors expressing anti-HIV antibodies DH270, PCIN63 and DH511. These antibodies are naturally closer-to-germline than those we had previously used.
Results: Three of the four macaques showed high levels (20-320 µg/mL) of two AAV-delivered antibodies through 70 weeks of follow up measurements. Sustained viral load suppression was achieved in two of these three monkeys. Only transient effects on viral load levels were observed in the third monkey suggesting viral escape mutations; sequencing to confirm escape is currently in progress. The fourth monkey showed low levels of AAV-delivered antibodies due to ADAs and little or no virologic suppression.
Conclusion: Our results indicate that potent broadly neutralizing antibodies which are closer-to-germline can mediate long-term virologic suppression following gene therapy with AAV vectors with potentially lower incidence of ADA responses, but also highlight the difficulties associated with achieving long-term, antibody-mediated suppression.

521 Ruxolitinib-Mediated HIV-1 Reservoir Decay in A5336 Phase IIa Trial

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Background: Ruxolitinib is FDA approved for myelofibrosis, polycythemia vera, atopic dermatitis and chronic graft-versus-host disease. We evaluated ruxolitinib's impact on the peripheral HIV-1 reservoir and key immunomodulatory events driving HIV-1 persistence in people with HIV-1 (PWH) in an AIDS Clinical Trial (ACTG) sponsored open-label randomized Phase 2a multi-site trial (n=60).
Methods: Inclusion criteria: ≥18 age ≤75, background ART regimen (NNRTI or INSTI without cobicistat for ≥2 years), continuously virologically suppressed, CD4+ T-cell count >350 cells/mm^3; no significant medical condition besides HIV or hypertension. Participants were randomized to ruxolitinib 10 mg bid plus ART (n=40) or ART alone (n=20) from week 0 through 5. Both groups were observed through week 12. Cellular markers, integrated DNA, and IPDA were measured on peripheral blood from weeks 0, 5, and 12. A sequential series of Mann-Whitney U tests were performed to understand how biomarker changes across weeks impact reservoir decay. We evaluated 1) biomarkers within the ruxolitinib-treated (RUX) group which were altered from baseline, 2) which markers determined in round 1 were differential versus control (CNT) group, and 3) which of these were associated with participants who experienced reservoir growth or decay independent of treatment. Significance was further confirmed through Benjamini-Hochberg testing to minimize the false discovery rate (15%).
Results: Integrated DNA and IPDA reservoir measurements were highly correlated to one another throughout trial. HIV-1 reservoir significantly decayed in the RUX group by week 12 versus CNT (p=0.0471). Cellular markers altered by ruxolitinib, possessing a different expression profile from CNT, and associated with reservoir decay were determined: pSTAT5+ monocytes in low baseline reservoir and total RUX groups at week 12, pSTAT3+ monocytes in low baseline

reservoir at week 12, BCL-2+KI67+ CD4+ TN cells in the total RUX group at week 5, CD127+ CD8+ TTD cells in the total RUX group at week 5, and CD25+ CD8+ TTM cells in the total RUX group at week 5.

Conclusion: Ruxolitinib decays the HIV-1 reservoir and resets immune balance in PWH on ART. Based on observed reservoir decay (week 5 to 12), our model predicts a 99.99% decay in 2.83 years, should rate of decay remain constant. These data are foundational for further human trials with Jak 1/2 inhibitors such as ruxolitinib towards HIV-1 elimination.

522 Short-Term BCL-2 Inhibition at ART Initiation Transiently Reduces SIV Reservoir in Rhesus Macaques

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Background: In spite of the success of antiretroviral therapy ART in suppressing HIV replication, effective strategies to limit the establishment and maintenance of the HIV reservoir are needed. Recent data highlighted BCL-2 as a key regulator for the establishment, persistence, and expansion of the CD4+ T cell reservoir, protecting infected cells from virus or CD8 T cell-induced cell death. Thus, there is a strong rationale behind promoting apoptosis of latently HIV-infected cells via BCL-2 inhibition. Herein, we evaluate in SIV-infected, ART-treated rhesus macaques (RMs) the effect of the BCL-2 inhibitor venetoclax, alone or combined with a latency-reversing strategy (CD8a cell depletion), on cellular dynamics and the size of the SIV reservoir.

Methods: 12 RMs were intravenously infected with barcoded SIVmac239 and initiated ART 2 weeks post-infection. RMs were distributed into 3 arms: 4 RMs received only ART; 4 RMs received 10 daily doses of venetoclax as a subcutaneous injection starting at ART initiation; and 4 RMs received venetoclax in conjunction with a single dose of the anti-CD8a depleting antibody MT807R1 at ART initiation. Animals were followed until day 70 post-infection.

Results: Venetoclax and venetoclax plus MT807R1 treated RMs had a slower viral plasma load decay rate than control RMs, with prolonged on-ART viremia. In blood, venetoclax depleted CD4+ T cells, including their central and effector memory subsets. This was accompanied by decreased total SIV-DNA in peripheral blood mononuclear cells and intact SIV-DNA in sorted CD4+ T cells, consistent with a preferential loss of infected cells following venetoclax administration. Furthermore, and despite the slower plasma viral load decay, venetoclax-treated animals showed a faster intact SIV-DNA decay rate, consistent with killing of SIV-DNA harboring cells. This effect was specific to the treatment and not sustained after the interruption of Venetoclax.

Conclusion: This study shows that BCL-2 inhibition at ART initiation can delay the establishment of latency and transiently deplete infected cells by promoting the elimination of SIV-infected circulating CD4+ T cells. The results support the concept that BCL-2 expression favors the survival of infected cells and represents a potential therapeutic target. Further studies are needed to explore the effect of BCL-2 inhibition during long-term ART and prolonged exposure to BCL-2 inhibitors.

523 CD4-Targeted mRNA Delivery of Tat Reverses HIV-1 Latency

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Background: Interventions that reverse viral latency are needed for an HIV cure. The viral protein Tat drives HIV expression but is toxic and difficult to deliver in a targeted manner. We tested whether CD4-targeted delivery of Tat encoding mRNA could safely reverse latency.

Methods: mRNA encoding wildtype and nontoxic Subtype B and D Tat variants were made and transfected into TZM-bls to assess transactivation. Five J-Lat clones were treated with Tat mRNA-LNPs or small molecule agents (romidepsin, prostratin, pabinostat, or AZD5582) and evaluated using flow cytometry, live cell imaging, or single cell multiomic (RNA+ATAC) profiling. Ibalizumab (anti-CD4) was conjugated to mRNA-LNPs to generate CD4-targeted mRNA-LNPs. Primary CD4 T cells were treated with CD4-targeted Tat or GFP mRNA-LNPs to assess mRNA expression, toxicity, and activation. PBMCs from people living with HIV (PLWH) on ART were treated with CD4-targeted Tat mRNA-LNPs and assayed for p24 expression.

Results: A nontoxic Tat variant demonstrated similar transactivation activity when compared to wildtype variants and drove HIV expression in neighboring, nontransfected cells, indicating secretion of active Tat. Tat mRNA transfection of J-Lat 10.6 resulted in dose-dependent viral reactivation. Multiomic analysis of treated J-Lat 10.6 revealed significant changes in expression of four genes ($|\log_2\text{-fold change}| > 0.25$, $p < 0.05$): HIV-1 (0.37 $\log_2$-fold increase), MTRNR2L12 (0.33 $\log_2$-fold decrease), RPS10 (0.31 $\log_2$-fold decrease), and SNHG25 (0.26 $\log_2$-fold decrease). Minimal changes to ATAC accessibility of the proviral genome 2-3 days post-treatment were seen despite GFP signal in ~60% of cells. All J-Lat clones reactivated, albeit heterogeneously, upon treatment with Tat mRNA-LNPs or Romidepsin, but less so with other agents. Ibalizumab-targeting of Tat or GFP mRNA-LNPs resulted in efficient mRNA delivery and expression in rhesus and human CD4 T cells, with no observed cytotoxicity (Live/Dead, Annexin V), change in activation markers (CD69, CD25, CD38, HLA-DR), or widespread changes to gene expression in bulk RNAseq. CD4-targeted Tat mRNA-LNP treatment of PBMCs from three PLWH with inducible reservoirs resulted in p24 expression in both cellular pellet (0.05-0.5 pg/ml) and supernatant (0.15-0.2 pg/ml).

Conclusion: CD4-targeted Tat mRNA-LNPs selectively drive viral gene expression without cytotoxicity. These findings show that viral transcriptional programs, such as latency, can be modified using cell-targeted mRNA gene therapy.

524 Potent HIV Latency Reversal by Lipid Nanoparticles Encapsulating HIV Tat mRNA

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Background: One approach to eliminating the HIV reservoir is to upregulate proviral transcription and protein production, to induce the clearance of latently infected cells. To date, latency reversal agents (LRAs) have demonstrated poor efficacy in reversing latency and exhibited off-target effects. This is likely due to targeting host pathways and transcription factors. Here we developed lipid nanoparticles (LNPs) encapsulating mRNA encoding for the HIV Trans-activator of Transcription (Tat) protein, and characterised their ability to reverse latency in a potent, HIV-specific manner.

Methods: LNPs encapsulating mRNA encoding either Tat (Tat-LNP) or mCherry reporter protein (mCherry-LNP) were formulated through microfluidic mixing. Transfection efficiency was assessed in non-stimulated CD4+ T cells from HIV-negative donors. HIV latency reversal was assessed in the latently infected J-Lat A2 cell line by measuring GFP induction, and ex vivo in CD4+ T cells isolated from people living with HIV (PLWH) on suppressive antiretroviral therapy (ART) using digital RT-PCR measuring various HIV transcripts. Cellular activation and viability were characterised ex vivo by assessing CD69, CD25 and HLA/DR expression by flow cytometry.

Results: mCherry-LNPs potently transfected non-stimulated CD4+ T cells (75±3.6% mean±SEM mCherry+ cells). Tat-LNPs induced HIV reactivation in J-Lat A2 cells, with a fold increase of 68.2±10.3 (mean±SEM; EC_{50}=5.3ng/mL) relative to untreated. In ex vivo CD4+ T cells from PLWH on suppressive ART (n=5), treatment with Tat-LNPs for 48-72 hours induced a 3.3-fold (median) increase in HIV transcription initiation (measured by TAR transcripts); 23.5-fold increase in elongated transcripts (Long-LTR); 36.1-fold increase in completed transcripts (polyadenylated transcripts); and 105.9-fold increase in multiply-spliced transcripts (Tat-Rev), relative to untreated. Tat-LNPs outperformed the PMA/PHA positive control for elongation, polyadenylation and splicing. Treatment with Tat-LNPs did not cause T cell activation or toxicity (median 85.5% viability).

Conclusion: Our mRNA encoding the HIV Tat protein can be encapsulated into LNPs and delivered to latently infected CD4+ T cells. Tat-LNPs reverse latency in a potent, HIV-specific manner, thereby overcoming the limitations of current LRAs which infrequently upregulate multiply-spliced transcripts and exhibit toxicities. These data warrant the further development of Tat-LNPs as a novel LRA

525 Nanoparticle Delivery of Tat Synergizes With Latency Reversal Agents to Express HIV Antigen

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Background: Latency reversal and clearance of persistently infected CD4 T cells during antiretroviral therapy (ART) is a major strategy for HIV cure. Minimal induction of HIV protein antigens by latency reversal agents (LRAs) is at least partially due to limiting intracellular levels of HIV Tat. Here, lipid nanoparticles containing tat mRNA (Tat LNPs) were evaluated for latency reversal activity alone and in combination with well-characterized LRAs.

Methods: Tat LNPs, inhibitor of apoptosis protein antagonists (IAPi), bromodomain and extra-terminal motif inhibitors (BETi), and histone deacetylase inhibitors (HDACi) were assessed for latency reversal activity in cell line models of HIV latency (J89♂, E4♂, 2D10♂, J-Lat 6.3♂, 2B2D♂ and ACH-2♀) via quantification of proviral reporters. Findings in cell lines were confirmed in CD4 T cells from ART-suppressed people with HIV (PWH) via digital PCR measurement of HIV cell-associated transcripts and ultrasensitive digital ELISA quantification of p24 protein in the culture supernatant.

Results: Tat LNPs alone demonstrated dose-responsive latency reversal, with variable maximal activity across cell line models of HIV latency. Control experiments demonstrated that Tat LNPs induced latency reversal in 2B2D cells (Tat ΔC22G) and were inactive in ACH-2 cells (TAR ΔC37T), confirming the specificity of the reagent. Tat LNPs in combination with IAPi, BETi, and HDACi demonstrated synergistic latency reversal activity that approached 100% proviral GFP reporter expression in J89, E4, 2D10 and 2B2D cell lines, with more limited activity in the J-Lat 6.3 line. In ex vivo studies of CD4+ T cells from aviremic PWH, Tat LNPs alone and in combination with IAPi, HDACi, and BETi resulted in tens to hundreds-fold inductions of unspliced, multiply-spliced, and polyadenylated HIV transcripts. Tat LNPs alone, but not other LRAs, induced detectable HIV p24 protein in the culture supernatants in a fraction of PWH. Remarkably, without toxicity or T cell activation, Tat LNPs combined with LRAs induced p24 protein at a frequency and magnitude similar to T cell mitogens.

Conclusion: Tat LNPs induced HIV RNA and p24 protein expression in CD4 T cells from ART-suppressed PWH ex vivo, and synergized with IAPi, HDACi, and BETi LRAs. Further characterization and optimization of Tat LNPs and combinations for in vivo testing is warranted.

526 Non-Neutralizing Antibody Therapeutics to Eliminate HIV-Infected Cells In Vitro and In Vivo via ADCC

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Background: In HIV-1 infection, a significant fraction of antibodies (Abs) is induced to epitopes occluded in the Env trimer at the surface of infected cells and viral particles that are exposed only upon Env interaction with CD4 (CD4-induced or CD4i). Most CD4i Abs are weakly or non-neutralizing (nnAbs) but their FcR activities, including antibody dependent cytoxicity (ADCC), are usually potent, but strictly dependent on epitope exposure. Studies have shown that HIV-1 evolved to restrict Env's contact with CD4 to avoid ADCC induced by CD4i nnAbs. Interestingly, some CD4i epitopes, including the co-receptor binding site (CoRBS) or gp120 Cluster A, represent the most conserved Env regions, suggesting their great potential as targets for Ab-based approaches.

Methods: We developed CoRBS and Cluster A Abs into Ab-CD4 hybrids or Ab-CD4 mimetic (mc) conjugates in which an Ab (e.g. 17b or A32) is linked via a (G4S)6(G4T)2-linker to d1d2 of CD4, or small compound CD4 antagonist, CJF-III-288, via a (PEG)23-linker, respectively. Ab therapeutics were evaluated for binding and ADCC-mediated elimination of HIV-1-infected primary CD4+ T cells, and in vivo for their ability to eliminate infected cells in HIV-1JRFL-infected humanized mice supporting NK cell functions.

Results: In in vitro and ex vivo settings, the Ab-CD4 hybrids of both specificities efficiently eliminated cells infected with HIV-1JRFL with potencies outcompeting the best-in-class bnAbs. In addition, these Ab-CD4s were also able to synergize with nnAbs present in HIV+ plasma, further enhancing their ADCC activity. Our experiments utilizing single molecule FRET (smFRET) imaging confirmed that the activity of the Ab-CD4s directly results from their ability to stabilize State 2A, an Env conformation known to be ADCC vulnerable. Furthermore, results in humanized mice showed that A32-CD4 can control HIV-1 replication and substantially reduce the level of integrated HIV DNA in an FcR-dependent manner. Finally, our data also indicates that the CD4 moiety in an Ab-CD4 hybrid can be replaced by a small molecule CD4 mimetic. Our preliminary data confirm in vitro activity to eliminate HIV-1 infected cells with an Ab- CJF-III-288 conjugate utilizing an Ab of the CoRBS specificity.

Conclusion: Our data confirm the utility of engineered CD4i Abs as therapeutics capable of overcoming obstacles to eliminate HIV-1 infected cells via ADCC. CD4i Ab therapeutics could be utilized in strategies to reduce or eliminate the viral reservoir in people living with HIV-1.

527 A New CD4mc Enables Fc-Mediated Reservoir Reduction for Durable Post-ART HIV-1 Control in Hu-Mice

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Background: Persistently-infected HIV-1-positive cells are heterogeneous, rare, and inherently difficult to eliminate; shock-and-kill approaches have thus far proven inefficient in measurably reducing infected cell frequencies in clinical trials. CD4-mimetic compounds (CD4mcs) sensitize HIV-1-infected cells to antibody-dependent cellular cytotoxicity (ADCC) mediated by CD4-induced (CD4i) non-neutralizing antibodies (nnAb) that are frequently found in plasma of people living with HIV (PLWH) (Richard et al., PNAS 2015, PMID: 25941367; Rajashekar, Richard et al., Cell Host Microbe 2021, PMID: 34019804). The development of a new indoline CD4mc, CJF-III-288, with improved potency in neutralization and ADCC (Fritschi et al., PNAS 2023, PMID: 36961924), prompted us to investigate the impact of treatment, administrated at ART initiation or ART cessation, on viral tissue reservoirs and post-ART virus rebound dynamics in humanized mice (hu-mice) that support antibody effector function.

Methods: NSG-Tg(IL15) hu-mice were treated with CJF-III-288 in combination with CD4i A32 (anti-cluster A) and 17b (anti-coreceptor binding site) nnAbs either at ART initiation or at ART withdrawal. Post-ART plasma viremia and tissue viral reservoir size were analyzed by longitudinal measurements of HIV-1 RNA and DNA respectively. We also analyzed the contributions of natural killer (NK) and CD8 T cells to the observed effects in in vivo cell-depletion studies.

Results: Striking differences in HIV-1 rebound dynamics were observed depending on the timing of CJF-III-288/CD4i nnAb treatment. While treatment at ART cessation resulted in a significant delay of viral rebound (up to 1 month), treatment at ART initiation had an even greater effect, delaying viral rebound by more than twice as long as treatment at ART cessation. Remarkably, durable control of plasma viral loads (in spite of transient viremic blips) with a highly significant reduction of the viral reservoir led to ART-free viral remission in a subset of mice treated during the viremic phase of infection, concomitant with initiation of ART. While the outcome was primarily mediated by NK cells supporting the major contribution of ADCC effects, a role for CD8+ T cells in the continued suppression of viral loads and control of viral rebound was suggested from the results of in in vivo cell-depletion experiments.

Conclusion: The overall results indicate that CD4mc have therapeutic potential in the presence of anti-Env CD4i antibodies, especially when administered at early stage.

528 Combination CAR T-Cell Therapy Restricts HIV Escape and Durably Suppresses HIV Replication In Vivo

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Background: In most cases, the cellular immune response is unable to durably control HIV replication. Chimeric antigen receptor (CAR) T cell therapy provides an avenue to engineer a more potent T cell response. Broadly neutralizing antibodies (bNAbs) targeting conserved regions of HIV Envelope may further facilitate the creation of a CAR T cell therapy effective against the majority of HIV isolates.

Methods: A panel of 4-1BB costimulated CAR T cells expressing 18 distinct bNAb-based CARs were generated against all well-characterized epitopes on HIV Env: V1/V2 apex, V3-glycan supersite, CD4 binding site, gp120-gp41 interface, fusion peptide, silent face, and MPER. CAR T products manufactured from primary human T cells were screened for potency via degranulation when cocultured with Env-expressing K562 (K.Env) cells, as well as K.Env killing assays and HIV suppression assays in the GXR25 cell line using the Incucyte SX5 live-cell imaging system. To map escape pathways and determine CAR efficacy, donor-matched CAR T products were adoptively transferred into HIV-infected, BLT humanized mice. CAR expansion and HIV viral loads were monitored weekly in the blood by flow cytometry and qRT-PCR, and HIV env sequences were amplified from plasma at >6-weeks post infection using nested PCR and deep sequenced to identify putative escape mutations.
Results: Potency hierarchy, as measured by degranulation potential, K.Env killing kinetics, and effective suppression of virus replication in vitro was heterogeneous among bNAb CAR constructs, but clustered between epitope specificities. Notably, Env epitopes most distal (V1/V2 apex, V3-glycan supersite) from the plasma membrane were associated with greater killing potency. Deep sequencing of HIV env derived from bNAb CAR T-treated HIV-infected humanized mice identified bNAb CARs with overlapping versus orthogonal associated escape pathways. This data guided the design of bNAb CAR combinations hypothesized to restrict escape. Using this approach, we demonstrate that a triple combination of V1/V2 apex, V3-glycan supersite, and CD4 binding site-directed CARs were able to durably suppress acute viremia to undetectable levels in humanized mice.
Conclusion: Distinct in vitro assays identified bNAb CARs with superior potency (PGT128, PGDM1400). HIV escape from individual bNAb CARs can be restricted when CARs associated with orthogonal escape pathways are combined, and restriction of HIV escape leads to durable suppression of HIV replication in vivo.

529 Vaccination Combined With PD-1 Blockade Provides Sustained SIV Suppression in Mamu-A01(+) Macaques

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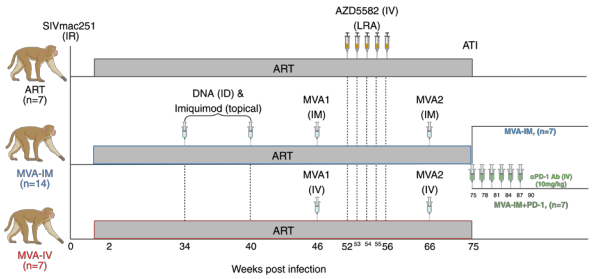
Background: Dysfunctional T cells and persistent viral reservoir under anti-retroviral therapy (ART) are the two major challenges to HIV cure. Towards this, here we evaluated therapeutic potential of intramuscular (IM) or intravenous (IV) vaccination combined with a latency reversal agent (LRA) and PD-1 blockade in SIV infected macaques.
Methods: A total of 28 RMs were infected with SIVmac251, placed on daily ART at 2 weeks post infection (wpi) and divided into three groups. Two groups received two DNA/SIV vaccinations (34, 40 wpi; ID) followed by two modified vaccinia Ankara (MVA)/SIV vaccines (46, 66 wpi) via either IM (MVA-IM, n=14) or IV (MVA-IV, n=7), and the third group did not receive any vaccination (ART, n=7). All RMs received five weekly IV infusions of AZD5582 from weeks 52 to 56 under ART as an LRA after the 1st MVA. On the day of ATI (75 wpi), 7 RMs from MVA-IM group received six infusions of a primatized anti-PD-1 antibody (10mg/kg body wt.) at three-week intervals (MVA-IM+PD-1). Viral rebound kinetics were studied for up to 32 weeks post ATI. In-depth immunological, virological, and reservoir analyses were performed throughout the study.
Results: Both IM and IV routes of therapeutic vaccination generated broad and polyfunctional SIV specific CD4 and CD8 T cells in blood and lymph nodes. Surprisingly, administration of AZD5582 under ART led to a significant loss of vaccine-induced effector CD8 T cells but were restored to high frequencies following the 2nd MVA. Post ATI, all animals showed a strong viral rebound. The ART, MVA-IM and MVA-IV animals, irrespective of Mamu-A01 status, did not control rebounding viremia. However, anti-PD-1 Ab treated Mamu-A01(+) animals (n=4) showed a profound suppression (below 60 copies with small blips under 1000 copies/ml) of reemerging viremia up to 32 weeks post ATI. The PD-1 blockade also induced high frequencies of polyfunctional SIV-specific cytolytic (granzyme B+, perforin+) CD8 T cells in the T-cell zone and B cell follicles of LNs, which were associated with sustained viral control.
Conclusion: A combination of vaccination during ART and PD-1 blockade post ATI can achieve a sustained functional cure for SIV in the presence of a potent anti-viral CD8 T cell response. These results also highlight the need for optimization of AZD5582 treatments in conjunction with vaccination to prevent the loss of vaccine-induced CD8 T cells.



530 The Impact of HIV Cure-Related Study Drugs and Treatment Interruption on Viral Resuppression Rates

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Background: To assess the effectiveness of novel HIV curative strategies, "cure" trials require periods of closely monitored antiretroviral therapy (ART) analytical treatment interruptions (ATI). We performed a systematic review and meta-analysis to identify the impact of ATI with or without novel therapeutics in cure-related studies on the time to viral resuppression following ART restart.
Methods: Medline and Embase databases were searched for human studies involving ATIs from January 2015 to March 2023. The primary outcome was proportion of participants who experienced viral resuppression (plasma HIV viral load (VL) <50 copies/mL) by 12 weeks post-ATI, stratified by receipt of interventional drug with ATI (IA) or ATI-only groups. A random-effects proportional meta-analysis and multivariable Cox proportional hazards analysis were performed using R.
Results: Of 1049 studies screened, 12 were relevant with available data and included in the analysis (n=180 participants). 96% of participants achieved viral suppression within 12 weeks (95% confidence interval (CI): 83% - 99%), with no difference between ATI-only and IA subgroups (97% vs 96%, p=0·79) (Figure 1). In the adjusted time-to-event analysis, age (adjusted Hazard Ratio (aHR) 0·97, 95%CI 0·96 – 0·99, p < 0·001), greater VL at ART restart (aHR 0·47, 95%CI 0·38 – 0·59, p<0·001), use of protease inhibitors (aHR 0·34, p= 0·19 – 0·73, p = 0·004), duration of ATI (aHR 0·96, 95%CI 0·94 – 0·98), and longer intervals between HIV VL monitoring (aHR 0·66, 95%CI 0·59 – 0·74, p<0·001) were associated with a decreased likelihood over time of achieving viral suppression after restarting ART, but not receipt of trial interventions (HR 0·89, 95%CI 0·57 – 1·40, p=0·612).
Conclusion: 96% of study participants who underwent ATIs achieved viral suppression by 12 weeks after restarting ART and this outcome did not differ with or without the receipt of any interventional drugs. When designing studies involving ATIs, time to viral resuppression after restarting ART should be regularly monitored and reported, to assess the impact and safety of specific trial interventions in ATI studies.
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531 Blockade of IFN-beta Reactivates HIV Reservoir in ART-Suppressed HIV-Infected BLT Humanized Mice

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Background: Despite the efficient suppression of HIV-1 replication can be achieved with combined antiretroviral therapy (cART), viral latency and low levels of type I interferon (IFN-I) signaling persist during chronic infection. This sustained signaling may promote T cell exhaustion and foster viral persistence. Using cloned human neutralizing antibodies specifically against IFNα or IFNβ, here we test the effects of blocking IFNα or IFNβ in ART suppressed BLT humanized mice to determine the role each Type I IFN in suppression.
Methods: Antibodies used for infusions against IFNα or IFNβ were characterized by ELISA, STAT-1 phosphorylation, dimerization assay, and western blot to

confirm specificity. Tissues and plasma from BLT humanized mice were used to measure IFNα and IFNβ expression as well as ISGs expression after HIV infection through qPCR, western, ELISA, IHC and RNAscope. BLT hu-mice were infected with transmitted/ founder (T/F) virus HIVsuma and following 4 to 5 weeks of viremia were suppressed on cART (FTC+TDF+RAL). Infusions of anti- IFNα/β-specific or IgG control antibodies were administered to the HIV fully suppressed animals intraperitoneally over three independent studies. Viral measures (plasma viral load, proviral DNA load), leukocyte subset activation, and HIV-antigen specific T cell function were measured by flow cytometry. Analysis was done with Prism software.

Results: Neutralizing anti-IFNα or anti-IFNβ-specific antibodies are capable of specifically blocking IFNα or IFNβ signaling in vitro and in vivo. We confirmed IFNα and IFNβ expression in BLT humanized mice, and the increase in ISGs expression after HIV infection. We found the infusions of anti-IFN-beta but not IFNα or IgG control can repeatedly elicit repeated low level viremic blimps under ART. HIV proviral/total DNA size were increased right after the IFNβ-specific antibody treatment supporting viral expression. HIV gag-specific CD8+ T cell frequency (IFN-gamma and CD107a) was also increased on ART after anti-IFNβ-specific antibody treatment consistent with HIV antigen expression. However, no change in viral rebound after stopping ART was detected between groups.

Conclusion: Blockade of IFN-beta signaling can reactivate HIV reservoir and stimulate HIV-specific T cells under ART in HIV infected BLT humanized mice. The potential use of anti-IFNβ strategies together with direct anti-HIV "kill" or clearance strategies should be further investigated.

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532 Treatment With AZD5582 + hetIL-15 Disrupts the Reservoir Establishment in SIV-Infected Macaques

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Background: HIV infection cannot be cured despite suppressive antiretroviral therapy (ART) due to a persistent reservoir of latently-infected memory CD4 T cells harboring replication competent virus. Here, we tested the SMACm/cIAP antagonist AZD5582 in combination with the heterodimeric interleukin-15 (hetIL-15), the native form of the cytokine that activates and expands cytotoxic T and NK cells, as a novel approach to prevent the establishment of the virus reservoir during the early stages of infection and/or ART.

Methods: 31 rhesus macaques (RMs) were infected with genetically barcoded SIVmac239M and started ART at 2-weeks p.i.. 9 RMs received hetIL-15 via sq injections of escalating dose of 10-40 ug/kg (weekly for 10 weeks) starting 3 days before ART initiation; 9 RMs received iv AZD5582 at 0.1 mg/kg weekly for 10 weeks starting at ART initiation; 9 RMs received the combination of hetIL-15 and AZD5582 over the same experimental phase as outlined above. 4 animals served as treatment-naïve, ART-only controls. Plasma viral loads were measured longitudinally for 16 weeks and the reservoir size was estimated in PBMC and lymph nodes (LN) by IPDA. CD8 T cells, CD4 T cells, and NK cells phenotypes were characterized by flow cytometry.

Results: Treatment with AZD5582, alone or in combination with hetIL-15, resulted in slower decline of plasma viremia after ART initiation, and SIV viral load was significantly higher at day14-15-17-21-25-49 and 70p.i. in AZD5582 treated RMs, indicating that treatment with the SMACm was associated with a longer lifespan of the productively infected cells. Levels of peripheral and LN CD4 T cell intact proviral SIV DNA declined in all the groups over the treatment course. The frequency of IPDA+ CD4 T cells tended to be lower in the animals receiving the SMACm, alone or in combination with hetIL-15, with a statistically significant difference at day25p.i in both PBMC and LN. Interestingly, levels of granzyme B at day25p.i. were higher in LN CD8 T cells of the treated animals compared to the controls.

Conclusion: Altogether, these findings suggest that treatment with AZD5582, alone or in combination with hetIL-15, may reduce the size of virus reservoir when administered at the time of ART initiation during acute SIV infection, thus suggesting a disruptive effect on the reservoir establishment. These data are consistent with previous work on the latency reversing activity of AZD5582 and provides rationale for further exploring this compound as a curative agent for HIV infection.

533 Drug-Controlled Anti-PD-1 CAR T-Cells to Target the Replication-Competent Reservoir in Tfh Cells

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Background: Programmed cell death protein 1 (PD-1) is an immune checkpoint marker expressed on memory T cells and enriched in latently-infected CD4+ T cells and T follicular helper cells (TFH) containing replication-competent human immune deficiency virus 1 (HIV) provirus in people with HIV on antiretroviral therapy (ART). We recently tested a novel anti-PD-1 chimeric antigen receptor (CAR) T cell approach in vivo in simian immunodeficiency virus (SIV) mac239-infected and SIV-naïve rhesus macaques (RM) to assess the impact of PD-1 depletion on viral reservoirs and rebound dynamics. We found that anti-PD-1 CAR T cells expanded efficiently and rapidly eradicated all TFH cells from the germinal centers with concomitant depletion of detectable SIV RNA from this sanctuary site. This occurred even before release from ART. The anti PD-1 Car T cells persisted for up to 100 days concomitant with the depletion of PD-1+ memory T cells in blood and tissues, resulting in off target immune depletion and a marked increase in SIV replication in extrafollicular portions of lymph nodes, a 2-log higher plasma viremia relative to controls and accelerated disease progression, associated with the acute depletion of CD8+ memory T cells after CAR T expansion. The rapid depletion of TFH sanctuary site in GC while on ART offered the potential to an important advance in the quest for HIV cure if we could develop a second-generation product that had less off target long tern effects.

Methods: Towards these ends, we integrated a Hepatitis C virus-derived non-structural protein 3 (NS3)-based ON switch into the intracellular domain of our anti-PD-1 CAR (NS3) T cell platform that can be controlled exogenously by administration of a NS3-specific protease inhibitor Grazoprevir (GZV).

Results: Mechanistically, the NS3 domain undergoes autocleavage in absence of GZV, thus abrogating any CAR signaling and CAR T cell function. In vitro, primary T cells expressing the anti-PD-1 CAR NS3 kill PD-1+ cells and secret IFNg in presence of GZV in a dose-dependent manner indicating that the NS3 domain functions as an ON switch.

Conclusion: Combined, these data indicate that a drug-controlled anti-PD-1 CAR NS3 is highly functional and can be controlled exogenously through administration or withdrawal of GZV. These data warrant further investigation of drug controlled-anti-PD-1 CAR T cells in ART-treated SIVmac239-infected rhesus macaques to transiently deplete TFH cells to determine their contribution to the latent reservoir.

534 Refractoriness to SIV Reinfection Is Induced by Anti-IL-10/PD-1 Therapy in Rhesus Macaques

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Background: IL10 and PD1 contribute to HIV reservoir persistence impeding HIV eradication. We hypothesized that the dual blockade of IL10 and PD1 could synergize and lead to SIV-functional cure by triggering intrinsic antiviral immunity in monocytes and CD4 T cells resulting in lack of viral re-seeding post-ATI (Analytical Treatment Interruption) and by boosting innate and adaptive cellular effector function.

Methods: 18 rhesus macaques (RMs) infected with SIVmac239 under antiretroviral therapy (ART) for 14 months started at 42 days post-infection received Rhesusized aIL10/aPD1 (Combo n=10) or vehicle (control n=8), administered every 3-weeks between 12 weeks pre-ATI and 14-weeks post-ATI. Animals were followed longitudinally for biospecimen collections.

Results: Durable viral load control post-ATI (<1000 cps/mL in 9/10 animals) was observed in the combo treated RMs up to 6 months post-ATI (Fig 1). Post-ATI stable IPDA and 2LTR readouts was also observed in combo-treated animals as compared to the control group. Gene expression analysis revealed significantly elevated restriction factor machinery in the lymph nodes (LN) cells from the

combo treated group pre-ATI (APOBECs, SAMDH, ISGs) that was persistent till the end of the follow up (6 months post-ATI). Monocytes, CD8 and CD4 T cells presented significantly higher protein-expression of pIRF3 and pIRF7. Use of multi-ome platform that allows simultaneous single cell assessment of transcription and epigenetic profiles showed that the enhanced expression of antiviral ISGs was concomitant with the increased chromatin accessibility of the IRF3, IRF7 and Stat1 transcription factors known to confer refractoriness to viral infections by inducing Interferon antiviral genes. Moreover, pre-ATI, the accessibility of the Tbet locus and its target genes such as granzyme B, perforin and IFNg, in CD4 and CD8 T cells from combo treated animals was observed. This poised antiviral environment was associated with viral rebound control.
Conclusion: The combo therapy triggers an epigenetic reprogramming of innate and adaptive immune cells highlighted by poised intrinsic antiviral machinery and poised effector molecules of T cell function that together synergize to block the de novo CD4 T cell infection post-ATI and viral dissemination.
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535 Disrupting SIV Reservoir Seeding by Targeting Stemness Pathways in Rhesus Macaques

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Background: Latently HIV-infected CD4+ T cells persist indefinitely through proliferation. We previously showed that inhibition of proliferation and induction of differentiation of the long-lived, self-renewing central (CM) and stem cell memory (SCM) CD4+ T cells can be achieved in ART-treated SIV-infected rhesus macaques (RMs) through modulation of the Wnt pathway. Here, we evaluated a combined approach targeting Wnt and Notch pathways during acute SIV infection of RMs to disrupt viral reservoir establishment.
Methods: Five RMs were infected i.v. with SIVmac239 before receiving 8 weeks of treatment with the Wnt inhibitor PRI-724 administered subcutaneously daily at 18-20 mg/kg in combination with the Notch inhibitor LY3039478 administered orally at 2.5 mg/kg three times per week. ART was initiated 8 weeks post-infection (wpi) and PBMC were collected longitudinally on ART to FACS sort subpopulations of naïve, SCM, CM, transitional memory (TM) and effector memory (EM) CD4+ T cells. Levels of cell-associated total SIVgag DNA and unintegrated 2-LTR circles were measured by multiplex qPCR in sorted cells. A group of 7 RMs infected with SIVmac239 and treated with ART alone served as controls.
Results: The combined treatment PRI-724+LY3039478 demonstrated an acceptable safety profile and did not alter plasma viral load dynamics in SIV-infected RMs. After ART initiation, the decay in the SIV 2-LTR circles, that are diluted with proliferation, was greater in the CM ($p=0.005$ at 12wpi) and TM ($p=0.018$ at 12wpi, $p=0.003$ at 20wpi) CD4+ T cells from the PRI-724+LY3039478-treated RMs as compared to controls. The ratio of SIVgag/2-LTR was higher in all subsets of memory CD4+ T cells from the treated RMs versus controls at 8 ($p<0.035$) and 12wpi ($p<0.073$). Interestingly, a reduced contribution of CM to the total SIV reservoir in CD4+ T cells was observed in the treated RMs as compared to controls at both 8 and 12wpi ($p=0.010$ for both). This reduction was attributed to lower levels of SIVgag DNA in CM CD4+ T cells at 12wpi ($p=0.048$) and decreased frequencies of CM cells within the CD4+ T cell pool at 8 and 12wpi ($p=0.004$ and 0.018) in PRI-724+LY3039478-treated RMs versus controls.
Conclusion: This proof-of-concept study suggests that the combined pharmacological modulation of Wnt and Notch pathways during acute SIV infection of RMs impacts viral reservoir seeding by transiently reducing the relative contribution of the CM cells to the peripheral CD4+ T cell compartment and to the pool of the infected CD4+ T cells.

536 Impact of Gender-Affirming Hormone Therapy on HIV Reservoirs and Inflammation in Transgender Women

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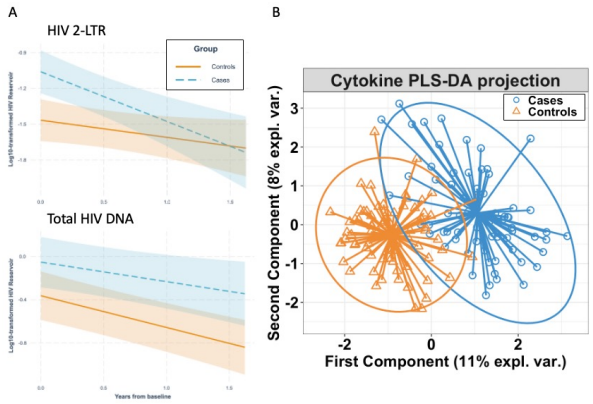
Background: Transgender women (TW) are at increased risk for HIV but are underrepresented in research. We investigated how the initiation of gender affirming hormone therapy (GAHT) impacts HIV reservoir (size and activity) and inflammation.
Methods: TW with HIV starting estradiol-based GAHT were recruited at two clinics in San Diego, CA and Houston, TX. Participants were on antiretroviral therapy (ART) and had suppressed HIV-1 RNA during the study. Blood and plasma were collected prior to starting GAHT and longitudinally 2, 4, 6, 9, 12, and 18 months post GAHT initiation. Historical samples from cisgender men with HIV were matched by age, CD4+ T cell count, duration of HIV, and time on ART. At each timepoint, we measured estradiol and testosterone by ELISA, cell-associated HIV RNA (unspliced and multiple spliced) and HIV DNA (total and 2-LTR) by ddPCR, and 41 cytokine/chemokines by Luminex. We used a linear mixed effects model with HIV reservoir values as outcomes, and time, group, and their interaction as predictors along with a random intercept. Partial least squares-discriminant analysis (PLS-DA) was used to predict gender groups using cytokine/chemokines. Error rates were estimated using k-fold cross-validation.
Results: A total of 22 TW were enrolled. Nine were lost to follow-up including one suicide, one homicide, and two imprisonments. A total of 77 samples from TW and 79 samples from cisgender controls were analyzed. Compared to cisgender controls, TG women had higher overall estradiol (145.83 vs 45.62 pg/mL, $p<0.001$), and lower testosterone concentrations (226 vs. 436 ng/dL, $p<0.001$) with a sharp decrease after baseline. Overall, TW had higher HIV DNA levels (both total and 2LTR). We observed a significant interaction between time and gender group for 2-LTR but not for total HIV DNA (Panel A). There was no difference in unstimulated cellular HIV RNA between groups. Using our cytokine/chemokines dataset, we accurately predicted gender group in the PLS-DA model with an error rate of 10% (Panel B).
Conclusion: TW had increased HIV DNA with faster decline in 2-LTR circle after initiating GAHT compared to cisgender men, supporting estradiol's inhibition of residual HIV replication. TW had unique immune signatures, which might impact HIV disease outcomes and comorbidities. Our study underscores the challenges associated with recruiting and studying this unique population, emphasizing the need for trauma-informed care and tailored research efforts.

Figure: (A) HIV 2-LTR and total HIV DNA over time; (B) Cytokine partial least squares-discriminant analysis projection with confidence ellipses.



537 Potent Indoline CD4 Mimetics Enable Anti-Coreceptor Binding Site Antibodies to Mediate ADCC

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Background: Antiretroviral therapy efficiently supresses HIV-1 replication but does not eradicate the virus. New approaches aimed at eliminating infected cells represent an appealing avenue to achieve this goal. Non-neutralizing antibodies (nnAbs) naturally present in the plasma of people living with HIV-1 (PLWH) have the potential to eliminate HIV-1-infected cells via antibody-dependent cellular cytotoxicity (ADCC). However, these nnAbs largely recognize epitopes only accessible upon interaction of the envelope glycoproteins (Env) with CD4. HIV-1 limits surface Env-CD4 interaction by downregulating CD4, thus protecting infected cells from CD4-induced (CD4i) nnAb-mediated ADCC responses. CD4-mimetic compounds (CD4mcs) can "open-up" Env and sensitize HIV-1-infected cells to ADCC mediated by HIV+ plasma. We have shown that two families of CD4i nnAbs contribute to eliminate infected cells in the presence of CD4mc: the anti-cluster A and the anti-coreceptor binding site (CoRBS) Abs. Of note, while indane CD4mcs significantly enhance the recognition of infected cells by anti-CoRBS Abs, these nnAbs mediate ADCC poorly. The combination of anti-CoRBS Abs together with CD4mc and anti-Cluster A is required to mediate ADCC. This combination reduces the size of the HIV-1 reservoir and delays viral rebound after ART interruption in humanized mice. The development of new indoline CD4mc with improved neutralization potency and breath enabled us to revisit the capacity of anti-CoRBS Abs to mediate ADCC.
Methods: The capacity of anti-CoRBS Abs to mediate ADCC against HIV-1-infected cells in the presence of indane and indoline CD4mcs was assessed in vitro, while their capacity to delay viral rebound in vivo was evaluated in infected humanized mice.
Results: Contrary to indane CD4mcs, we found that the lead indoline CD4mc, CJF-III-288, sensitizes HIV-1-infected cells to ADCC mediated by anti-CoRBS Abs. This was observed with multiple HIV-1 primary strains and using various anti-CoRBS Abs. Accordingly, treatment of humanized mice with CJF-III-288 and an CoRBS Ab alone was sufficient to delay viral rebound after ART interruption, and notably, for much longer when administered prior to ART initiation. These results suggest that the indoline CD4mc "open" the Env trimer in such a way that favors Fc gamma receptor engagement on effector cells.
Conclusion: More potent indoline CD4mc have the ability to sensitize HIV-1-infected cells to CoRBS Abs-mediated ADCC responses, thereby improving their therapeutic potential.

538 Lipid Composition and CXCR4 Decoration Facilitate HIV-1 CRISPR Delivery and Viral Excision

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Background: A principal limitation in achieving HIV cure rests, first, in locating and then eliminating integrated proviral DNA from viral target cells (CD4+ T and myeloid cells). In recent reports, the development of viral vector to deliver clustered regularly interspaced short palindromic repeats (CRISPR) guide RNAs (gRNAs) provided a proof of concept that HIV-1 elimination could be achieved. Our goal is to extend and improve those results by creating: (1) multiple viral exons (gp41, tat, and rev) gRNAs; (2) viral tissue reservoir targeted lipid nanoparticles (LNPs); and (3) decorating LNPs with CXC chemokine receptor-4 (CXCR4) for targeting cellular reservoir. The biodistribution of LNPs was evaluated in humanized mice. We posit that effective gRNA delivery and, subsequently, viral DNA elimination can be achieved with our approach.
Methods: A library of gRNAs was designed to disrupt five HIV-1 exons (tat1-2/rev1-2/gp41). These were derived from a consensus sequence of the transcriptional regulator tat from 4004 HIV-1 strains. CXCR4-targeting cyclic-peptide (CycPep) was conjugated with PEG-lipid to make DSPE-PEG-CycPep and LNP was formulated by microfluidic mixing. The specificity of the CXCR4 receptor was shown by blocking the CXCR4 receptor to demonstrate lymphoid targeting. CRISPR gRNA delivery and excision were tested in lymphocytic (JLat 8.4, Jurkat E6) and monocytic (U1) cell lines and confirmed in primary human lymphoblasts.
Results: A compositionally unique CXCR4 targeted LNP (T-LNP) was formulated with CRISPR gRNA-Cas9, D-Lin-MC3-DMA, DOPE, DOPS, DSPE-PEG-CycPep, DMG-PEG and β-sitosterol. T-LNP showed a significant shift in tropism in hu-mice from the liver to the spleen - one of the major HIV reservoirs. Further analysis revealed a substantially high mRNA expression in primary CD4+ T cells compared to nontargeted LNP. T-LNP demonstrated nearly 60% excision of viral DNA in lymphocytic cell lines; however, it was only 15% in myeloid cells. Moreover, in the presence of the CXCR4 blocker, T-LNP demonstrated decreased DNA excision, confirming CXCR4-specificity as compared to the control- LNP which lacked CXCR4 targeting.
Conclusion: This work introduces a novel, non-viral delivery system to target HIV reservoirs. Our preliminary work shows that CXCR4-targeted LNP reached HIV reservoirs and enabled excision of integrated latent HIV-1 DNA, potentially leading to its elimination.
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539 The Humanized DRAGA Mouse as a Model for HIV Latency and Cure

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Background: HIV infection is now a chronic disease due to the availability of antiretroviral therapy (ART) which suppresses plasma viral loads to below the limit of detection and prevents AIDS. However, the virus establishes latency and persists, a clear barrier to curing HIV. Interruption of ART causes viral rebound and thus requires a lifetime of medication for these individuals. We have previously demonstrated that the humanized DRAGA (hDRAGA) mouse (HLA-A2.HLA-DR4.RAG1 KO.IL-2RycKO.NOD) generated by engrafting CD34+ hematopoietic stem cells from human cord blood is a suitable model to study HIV infection. Subsequently, we evaluated if this mouse could also serve as a model for HIV cure and latency studies. We examined the effects of NU611 in HIV infected hDRAGA mice on viral rebound following ART interruption (ATI). NU611 is a compound that boosts the expression of APOBEC3G, a human antiviral protein that decreases virion infectivity in cells.
Methods: Humanized DRAGA mice (n=11) were intravaginally infected with HIV. Three weeks post-infection the standard 3-drug regimen: TDF, FTC, DTG in chow was administered for 6-10 weeks and then removed for observation of viral rebound. One week prior to ATI, 6 mice were administered NU611 intraperitoneally weekly and plasma viral loads were monitored by qRT-PCR. The tissues were also evaluated for viral RNA and DNA. Cellular profiles examining any changes in the human immune cells in the blood were performed using flow cytometry. Statistics were performed using Mann-Whitney analyses.
Results: The plasma viral load decreased within a week of ART administration to below the limit of detection (700 copies/mL) within 5 weeks and remained suppressed while on ART for up to 10 weeks with no viral blips. Following ATI, the viral rebound in all 5 control mice was either higher than or similar to levels before ART administration. In mice treated with NU611, although viral rebound was observed in the plasma 2 weeks post ATI, plasma viral set points were 1 log lower in 5/6 treated mice compared to 5/5 untreated control mice.
Conclusion: These results demonstrate the persistence of a viral reservoir in this model and the suitability of an APOBEC3G booster to contribute to the control of viral replication. The hDRAGA mice recapitulate some key aspects of HIV remission and rebound following ATI. This knowledge is important as it establishes the hDRAGA mouse as a model for HIV latency and can be utilized to investigate potential therapeutics for HIV cure.

540 Retinoids Enhance NK Natural and Antibody-Dependent Cell Cytotoxicity of HIV-Infected CD4 T-Cells

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Background: Novel approaches to sensitize latently infected cells to apoptosis may provide additional methods to eliminate latent reservoirs. Prior research identified several retinoids as potential drugs that increase the sensitivity of

HIV-infected cells to cell death. Retinoids are derivatives of Vitamin A that target retinoic receptors causing antiproliferative and proapoptotic activity. Several are FDA-approved or in clinical trials for different etiologies. The aim of this study was to evaluate the ability of retinol, 3 of its natural metabolites and 9 synthetic derivatives to sensitize HIV infected CD4 T cells to NK cell killing.
Methods: Naïve CD4 T cells isolated from PBMCs from male and female donors were activated, expanded and then infected with the replication competent HIV molecular clone NL43. CD4 T cells were cocultured overnight with autologous NK cells in the presence of 1µM of a retinoid and antiretroviral therapy, with or without 100ng/mL of IL15. We used three retinoids: alitretinoin, tazarotene acid and AM80 to assess their ability to enhance Antibody-Dependent Cell Cytotoxicity (ADCC) by using the same procedure with the broadly neutralizing antibody N6 (1µg/mL). To assess the mechanisms by which these retinoids enhance NK killing of HIV-infected cells, we measured changes of MHC Class I receptor expression on CD4 T cells and cytotoxicity markers on NK cells.
Results: None of the retinoids were toxic alone or with IL15. Without IL15, none of the retinoids influenced NK natural cytotoxicity. With IL15, alitretinoin (n=8, $p<0.001$), tazarotene, tazarotene acid and AM80 (n=8, $p<0.05$), significantly enhanced natural cytotoxicity of HIV-infected cells compared to DMSO control. Mechanistically, these four retinoids increased NK degranulation upon target recognition in the presence of IL15 (n=8, $p<0.05$). In initial studies, all three retinoids enhance HLA-F expression on CD4 T cells, previously known to enhance recognition by NK cells. Furthermore, these three retinoids significantly enhanced the ability of N6 to promote ADCC compared to DMSO control regardless of IL15 by increasing CD16 expression on NK cells (n=8, $p<0.0001$).
Conclusion: We identified three retinoids capable of enhancing HIV-infected cells to NK natural cytotoxicity and ADCC. We are conducting experiments to confirm the mechanism/s associated with this phenotype. Our studies may provide further evidence of small molecules that could be used clinically to reduce persistent reservoirs.

541 Comparison of Anti-HIV ADC and Immunotoxin Shows Clinically Relevant Differences in Cytotoxic Effect

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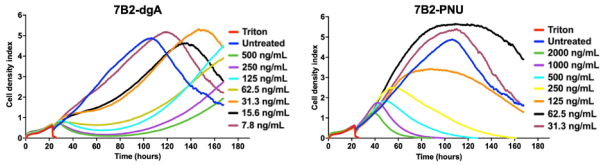
Background: The persistent reservoir of cells carrying a functional provirus is the barrier to HIV eradication. One approach to reservoir depletion is sequential activation of latent virus, followed by purging of HIV-expressing cells. initially it was hoped that once cells were activated, viral cytopathic effect or host immune responses would clear the reservoir, but recent studies using mAbs have shown greater effects. We have armed antibodies with cytotoxic agents to enhance killing of HIV-infected cells, independent of ADCC or complement activity. We screened >200 mAbs to identify those most effective at delivering the toxic moiety, and found that the anti-gp41 mAb 7B2, conjugated to ricin A chain, is safe and effective in SHIV-infected macaques. However, it was immunogenic, limiting its utility. We therefore sought to develop less immunogenic immunotoxins (ITs) and antibody drug conjugates (ADCs).
Methods: We screened drugs for cytotoxicity on resting lymphocytes . ADCs were prepared by chemical conjugation to 7B2. Cytotoxicity of ADCs was compared to ITs on Env-expressing cells. Antiviral effects were measured in tissue culture. The effect of ADCs and ITs on metabolism and transcription in HIV-infected cells was studied by NMR-based metabolomics and RNAseq.
Results: PNU-159682, an anthracycline, killed resting cells. We compared 7B2-PNU (ADC) to 7B2-ricin A (IT) in vitro. Cytotoxicity of the IT was 10X greater than the ADC on Env+ target cells, whereas neither IT nor ADC killed Env- cells. The ADC required >24 hr to initiate cytotoxicity; IT killing began within 6 hr. The ADC elicited bystander killing of ENV- cells when mixed with Env+ cells, the IT did not. At 6 hours, metabolomic analyses of IT-treated cells, but not ADC-treated or untreated cells, demonstrated elevated amino acids and choline and depressed taurine, creatine, and fumarate. At 24 hr the metabolic profiles of all three groups diverged. Similarly, the transcriptome of IT-treated cells diverged at 6 hr, while at 24 hours, the three transcriptional profiles were distinct. Pathway analysis indicated significant up-regulation of transcriptional control and death pathways in both IT and ADC treated cells
Conclusion: Cytotoxic immunoconjugates (ICs) targeted by anti-gp160 mAbs are potent killers of cells expressing HIV Env, work independently of Fc-effector functions, and are potentially useful in HIV eradication. Understanding how different ICs kill cells will guide their clinical application.



Cytotoxic efficacy of immunotoxin compared to antibody drug conjugate. Cell density was measured by electrical impedance. Results show a more rapid response to 7B2-dgA, but more complete killing with 7B2-PNU.

542 Type I IFN Signaling and Regulation in Vesatolimod-Treated Virally Suppressed Adults With HIV-1

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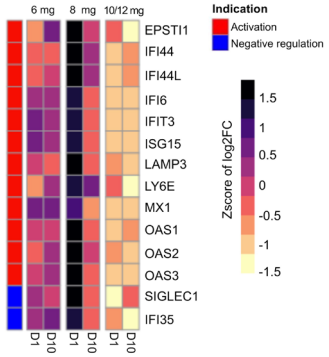
Background: Vesatolimod (VES) is a well tolerated and selective toll-like receptor-7 agonist under development as part of an HIV cure regimen. VES treatment increases interferon-stimulated gene (ISG) expression and immune cell activation in people with HIV (PWH); additionally, VES monotherapy promotes a modest delay in HIV rebound in HIV controllers, and VES pharmacodynamic response is higher with 8 mg compared with 10-12 mg doses in PWH treated during chronic infection. We used mRNA-Seq to further investigate the immune mechanism and regulation of type I interferon (IFN) signaling pathways in response to VES in a phase 1b, double-blind, placebo-controlled trial (NCT02858401; GS-US-382-1450).
Methods: The study enrolled virally suppressed PWH (age ≥18 years, plasma HIV-1 RNA <50 copies/mL) and randomized 6:2 to receive VES or placebo biweekly for 10 doses. Whole blood mRNA collected pre-dose and 24 hours after doses 1 and 10 from participants who received VES 6 mg, 8 mg, or 10-12 mg (n=24) was used for mRNA-Seq (Illumina Stranded mRNA Prep; NovaSeq 6000). A linear mixed-effects and placebo-adjusted model was used to test for differentially expressed genes (DEGs) associated with type I IFN regulation and regulators of pattern recognition receptors (FDR<0.1).
Results: VES consistently upregulated DEGs associated with type I IFN signaling after doses 1 and 10 in all 3 doses evaluated (Figure). After dose 1, the highest number of DEGs, including those associated with activation and inhibition, was observed with VES 8 mg (38 genes), followed by VES 6 mg (21 genes) and VES 10/12 mg (15 genes); type I IFN activation was most pronounced with VES 8 mg versus the other doses. After dose 10, VES 6 mg induced the highest type I IFN activation and numbers of genes (49), followed by VES 8 mg (31) and VES 10/12 mg (27), respectively. Also, a lower induction in type I IFN activation was observed by post dose 10 versus post dose 1 in all but the 6 mg dose group, with the greatest reduction in the 8 mg group. VES-mediated type I IFN activation was greatest after dose 1 at 8 mg, followed by dose 10 at 6 mg.
Conclusion: Whole blood transcriptome analysis identified pronounced differences in gene expression based on VES dose and administration order. The results suggest that a cumulative effect of multiple VES doses could modulate VES pharmacodynamic response, which should be taken into account in future combination studies with VES.



D1, 24 h post dose 1; D10, 24 h post dose 10; FC, fold change; EPSTI, epithelial stromal interaction; IFI, IFN-induced protein; IFI44L, IFN-induced protein like; LAMP, lysosome-associated membrane glycoprotein; LY6E, lymphocyte antigen 6 family member E; MX, myxovirus resistance protein; OAS, 2'-5' oligoadenylate synthetase; SIGLEC, sialic acid-binding Ig-like lectin.

543 Evaluation of a Bispecific Antibody Targeting NK Cells for the Elimination of HIV Reservoirs

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Background: "Shock and kill" strategies for HIV cure involve reactivating latent virus (i.e. using latency reversal agents), followed by immune-mediated clearance. HIV impairs NK function, hampering their ability to eliminate infected cells, highlighting the need for immunotherapies to enhance NK cytolytic activity against HIV.
Methods: We designed a tetravalent bispecific antibody (Bi-Ab32/16), which targets the gp120 HIV protein (Ab A32) and CD16a. We assessed its functionality through ADCC and cytotoxicity assays (n=7). Killing of viral reactivated cells (n=4) and changes in the intact proviral DNA (n=5) were evaluated in CD4+ T cells from ART-treated PLWH. Preclinical evaluation was conducted in humanized mice expressing IL15 (NSG-Hu-IL15). HIV-infected mice received ART from 6 to 9 weeks post-infection (wpi) and were randomized (n=6 per group) to receive immunotherapy at 10 mg/kg (Bi-Ab32/16 or A32) from 8 to 10 wpi. Mice were euthanized at 11 and 13 wpi. Immune subsets and NK activation were assessed by flow cytometry. HIV RNA was quantified by RT-qPCR.
Results: Bi-Ab32/16 enhanced NK activation, degranulation, and cytotoxicity against HIV-infected cells in vitro ($p<0.05$). Further, the EC_{50} (0.01±0.003 µg/ml) was 55-fold lower than the parental A32 Ab (0.55±2.5E-5 µg/ml). Following viral reactivation, Bi-Ab32/16 improved killing of HIV-infected cells (median reduction 55%, $p<0.01$), and mediated the clearance of cells harboring intact proviruses in 3/5 PLWH (median reduction 50.7%). HIV viral loads were detected at 3 wpi (10^3-10^5 copies/ml) in 24/34 animals. HIV-infected mice showed decreased CD4 counts and CD4/CD8 ratios ($p<0.05$), and increased frequencies of CD16+ NK ($p<0.001$), which were all normalized after ART initiation ($p<0.001$). Higher IFNg-expressing NK memory-like subsets were observed at 13 wpi with Bi-Ab32/16 compared to A32 and control groups ($p<0.05$). However, Bi-Ab32/16 reduced CD16+ NK counts ($p<0.05$) (Fig.1A), which was inversely associated with infection after ART interruption ($p<0.05$, $r=-0.58$). Furthermore, Bi-Ab32/16 animals had a shorter time to viral rebound versus A32 and control groups ($p<0.05$) (Fig.1B).
Conclusion: Bi-Ab32/16 activates NK, enhances ADCC, and diminishes latent HIV infection after viral reactivation in samples from PLWH. However, persistent in vivo NK stimulation with Bi-Ab32/16 reduces CD16+ NK, negatively impacting HIV control. Cellular in vivo therapies involving NK preloaded with Bi-Ab32/16 might offer a promising strategy for HIV elimination.

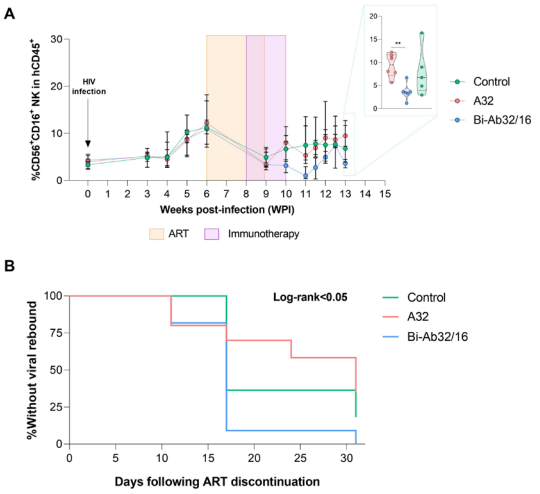

Fig1. Preclinical evaluation of Bi-Ab32/16. A) Evolution of CD56+CD16+NK frequencies by timepoint and group. Mann-Whitney t test. *p<0.05,**p<0.01. B) Kaplan-Meier curve depicting the proportion of animals experiencing viral rebound following ART discontinuation, stratified by group. Log-rank (Mantel-Cox) test. *p<0.05.

544 Associations Between Nadir CD4 and Subsequent Immune Measures With Long-Term Cognitive Function

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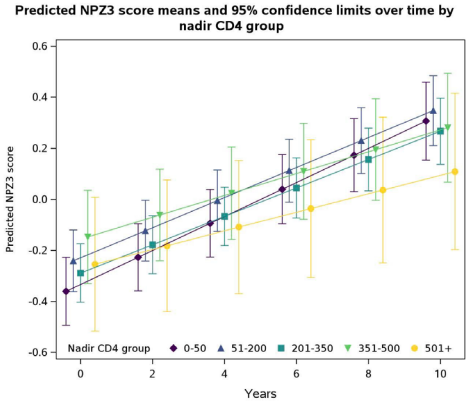
Background: Relationships between immune measures and neurocognition in persons with HIV (PWH) on ART are unclear.
Methods: We analyzed data, including nadir and current CD4 cells/µl (CD4), CD4%, and CD4:CD8 ratios, from virally suppressed PWH (HIV RNA <200 copies/ml >75% of time since ART start) with >2 NPZ3 scores in ALLRT (ACTG 5001) and HAILO (ACTG 5322). We used longitudinal linear mixed models with fixed and random effects to assess associations between NPZ3 (measured ≥96 weeks post ART start, baseline) and immune measures. We adjusted models for age, sex, and race/ethnicity, with and without adjustment for HIV RNA (>200 vs ≤200 copies/ml), type and years of ART use, and HCV infection.
Results: Among 885 PWH seen 1/1/2000-12/30/2021, median (Q1, Q3) age at ART start was 44 (39, 48) years, 81% were male, 50% were White, 29% Black, 21% Hispanic or other. CD4 nadir was 0-50 (22%), 51-200 (29%), 201-350 (33%), 351-500 (11%), 501+(5%). Baseline median CD4 was 486, CD4:CD8 0.66 and NPZ3 score -0.10 (Q1, Q3)(-0.70, 0.53). Higher nadir CD4 was associated with higher baseline NPZ3 but slower NPZ3 increase: PWH with nadir CD4 0-50 had mean NPZ3 increases of 0.067 per year (95% CL = (0.056, 0.077); PWH with nadir CD4>501 had smaller increases (0.030 fewer points) per year (95% CL=(-0.054, -0.007)). Adding any time-updated CD4 measure attenuated nadir CD4 associations with NPZ3, often rendering them non-significant. A standard deviation (1SD) (309 cells/µl) increase in maximum CD4 was associated with an increase in NPZ3 score of 0.034 (95% CL=-0.011, 0.080), and a reduction in NPZ3 score slope of -0.007 (-0.013, -0.002). A 1SD (10.4) increase in CD4% was associated with a 0.074 (0.034, 0.113) increase in NPZ3 score and a decrease of -0.009 (-0.015, -0.004) in NPZ3 slope. A 1SD (0.527) increase in CD4:CD8 ratio was associated with an increase in NPZ3 score 0.060 (0.020, 0.099) and reduction in NPZ3 score slope of -0.007 (-0.012, -0.001). When nadir and current CD4 were modeled together, their effects were not statistically significant. Effects were similar in fully-adjusted models; current CD4% and CD4:CD8 remained most strongly associated with current NPZ3 score and change over time; NPZ scores converged at 6-8 years after baseline for the lower 4 nadir CD4 groups.
Conclusion: Lower nadir CD4 was associated with lower NPZ3 score at baseline but greater increases over time. Current CD4% and CD4:CD8, but not absolute CD4, had the strongest associations with current NPZ3 score and change over time.



Adjusted for nadir CD4 group, age group, race/ethnicity, and birth sex, and inverse probability weighted for dropout.
Mean NPZ scores converged 6-8 years after baseline for the lower 4 nadir CD4 groups.

545 Predictors of CD4/CD8 T-Cell Inversion After 96 Weeks of ART Initiated During Acute HIV

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Background: >50% of people with HIV (PWH) do not achieve CD4/CD8 T-cell ratio normalization (ratio>1.0) on antiretroviral therapy (ART). Recent findings from RV254/SEARCH 010, a longitudinal investigation of acute HIV infection (AHI) and long-term response to ART, identified a combination of immune and behavioral factors (e.g., mental health) that predicted CD4/CD8 T-cell ratio inversion at week 144 of ART. This study examined a larger array of potential predictors of CD4/CD8 T-cell inversion, including multimodal indices of brain structure/function quantified using 3T MRI before ART initiation.
Methods: Archival data from RV254/SEARCH 010 were examined for individuals who completed neuroimaging (volumetrics, diffusion tensor imaging (DTI), and resting state connectivity) at enrollment followed by 144 weeks of sustained ART. Gradient boosted multivariate (GBM) regression with repeated cross validation was utilized to identify predictors for persistent CD4/CD8 T-cell ratio inversion at week 144 from baseline neuroimaging, demographic, immune, viral, cognitive, and mental/behavioral health indices.
Results: 74 Thai males with an average duration of HIV infection of 19.5 (7.2) days were included in the analysis. Study participants were of 27.4 (6.0) years of age and had a median viral load (log_{10}) of 6.01 (IQR 5.43-6.79) copies/mL, CD4+ T-cell count of 330, CD8+ T-cell count of 526, and a CD4/CD8 T-cell ratio of 0.64. After 144 weeks of ART, all study participants were virally suppressed. 34 individuals had a CD4/CD8 T-cell ratio <1.0. The GBM analysis identified 10 baseline features that predicted CD4/CD8 T-cell ratio inversion at 144 weeks (average model performance of .72). The algorithm included larger volumes in 6 brain regions (medial superior frontal gyrus, superior temporal gyrus, rectus gyrus, nucleus accumbens, cerebellar lobes IV-V, pallidum), lower connectivity between the salience and visuospatial network, lower high-density lipoprotein (HDL) levels, lower radial diffusivity in the external capsule, and higher IL-1α.
Conclusion: Perturbations in brain structure and function, possibly reflecting early inflammatory mechanisms, dyslipidemia, and inflammation prior to ART commenced in acute infection stratify individual risk for persistent CD4/CD8 T-cell inversion following sustained use of ART. Further investigation of potential causal pathways is needed to establish mechanisms and therapeutic opportunities.

Figure. Classifier of CD4/CD8 T-cell ratio inversion after ART.

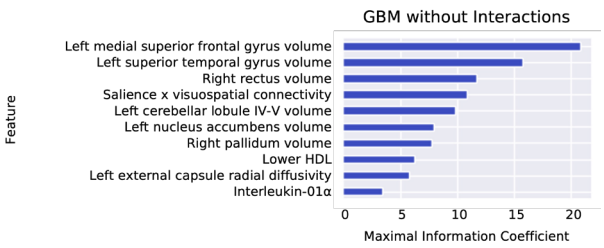

Figure. Larger regional brain volumes, lower resting state connectivity, higher levels of IL-1α, and HDL levels < 40 predicted CD4/CD8 T-cell inversion at week 96.

546 Assessing Blood-Based Biomarkers as Predictors of Cognitive Decline in PWH: ACTG A5322 (HAILO)

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[1]Harvard Medical School, Boston, MA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]Harvard TH Chan School of Public Health, Boston, MA, USA, [5]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: Blood-based markers (BBMs) show promise in evaluations of Alzheimer's disease and other cognitive disorders. We examined plasma neurofilament light chain (NFL) and glial fibrillary acid protein (GFAP) and their relationship to cognitive function in people with HIV (PWH) enrolled in the ACTG aging cohort study, HAILO.
Methods: Clinical data and plasma were obtained from 550 PWH aged ≥45y with ≥2 neuropsychological tests (NP) and HIV RNA<200 copies/ml. Four NP scores (Trail Making Test Part A and B, Digit Symbol, and Hopkins Verbal Learning Test-Revised) were standardized as z-scores. The average of these z-scores (NPZ4) at plasma collection or subsequent visits were provided by HAILO and used as primary outcomes; longitudinal scores were summarized by calculating the slope for each participant. We used a single molecule array platform to quantify NFL and GFAP. Associations between BBMs and baseline NPZ4 scores or slopes were assessed with linear regression. Longitudinal analyses were done for the total cohort and a subset with NPZ4 decline (slope <0). Models were adjusted for age, sex at birth, race, and years of education; regressions of slopes were also adjusted for baseline NPZ4 and weighted by number of visits.
Results: Mean age was 53y (range 45-77y), and observation time was 6.2y, 19.6% were female, and 28.4% non-Hispanic Black. Median [IQR] baseline NFL, GFAP, and NPZ4 scores were 10.7 pg/ml [7.98, 14.62], 77.5 pg/ml [58.80, 107.86], and 0.11 [-0.48, 0.75], respectively; median [IQR] NPZ4 slope was 0 [-0.06, 0.06]. In adjusted models, higher NFL or GFAP was associated with worse baseline NPZ4 (-0.05 per 10pg/ml NFL; p=0.06; -0.14 per 100 pg/ml GFAP; p=0.04) and became significant after excluding outliers NFL≥25 (p=0.03) but not GFAP≥200 (p=0.2). While baseline NFL (p=0.11) and GFAP (p=0.053) showed a weak relationship with NPZ4 slope in the total cohort, NFL had a stronger association in the subset with cognitive decline (n=263; -0.02 annual decrease per 10pg/ml NFL, p<0.01; Figure 1). The variance explained was ≤10% in all models.
Conclusion: In this cohort of PWH, with the majority in mid-life and cognitively stable, NFL and GFAP were associated with a minor decrement in cross-sectional NPZ4, and NFL was weakly associated with longitudinal NPZ4. NFL more strongly predicted NPZ4 slope in a prespecified subset with cognitive decline. Overall, results highlight the limitations of NFL and GFAP as predictive biomarkers of cognitive decline in this age range.

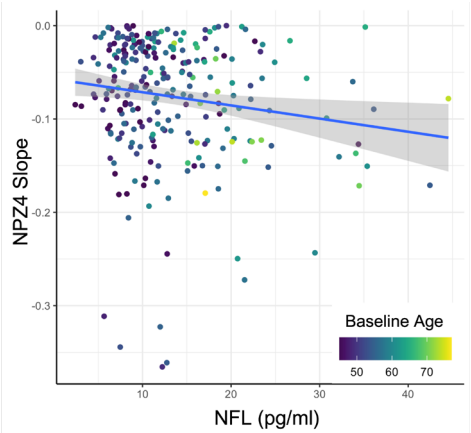

FIGURE 1: Relationship between neurofilament light chain (NFL) and slope for longitudinal NPZ4 in PWH aged ≥45. The scatter plot shows the regression line with 95% confidence band around the predicted value between NPZ4 slope and baseline NFL in the subset with slope<0. Each dot represents a participant, and color denotes age.

547 CD4 Count Predicts Longitudinal Trajectories of Central Executive Network Connectivity in PLWH

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Background: The brain's central executive network (CEN) plays a key role in the pathogenesis of depression, problematic substance use, and cognitive impairment, all of which are common comorbidities of HIV. Previous cross-sectional research has reported that resting-state functional connectivity (rsFC) in the CEN is lower in people living with HIV (PLWH) compared to participants without HIV, suggesting reduced integrity of the CEN in PLWH. But it is unclear when these alterations emerge and what clinical markers predict their emergence.
Methods: Resting state functional magnetic resonance imaging scans were conducted at baseline and two-year follow-up in a cohort (median age=29) of PLWH in early HIV infection (n=49) and healthy controls (n=20). A sub-sample (n=50, six female, 44 male) completed scans at both timepoints. Blood samples were collected to measure clinical immune markers and plasma HIV RNA.

Regression models adjusting for age and sex were used to predict longitudinal change scores for CEN rsFC.

Results: In the overall sample, CEN rsFC increased from baseline to follow-up (mean change=+13.4% ; 95% confidence interval [CI]: +2.2%, +25.1%). We detected no differences by HIV status in CEN rsFC at baseline or follow-up and no differences by HIV status in CEN rsFC change scores. Among PLWH, those infected longer at baseline (i.e., with detectable HIV antibodies and no longer in acute HIV) exhibited more negative CEN rsFC change scores (β=-0.78; 95% CI:-1.50, -0.06). Higher absolute CD4 counts at baseline predicted more positive CEN rsFC change scores (β=0.5; 95% CI:0.17, 0.83). Due to the small number of female participants, it was not possible to calculate sex-stratified effect estimates.

Conclusion: In the overall sample, CEN rsFC increased over time. Among PLWH, these gains in CEN rsFC were substantially weaker among those with evidence of greater immunopathology at baseline, as indexed by lower CD4 count. Gains in CEN rsFC were weaker among those infected longer at baseline, as indicated by the presence of detectable HIV antibodies. These findings suggest that HIV-related differences in CEN rsFC not yet apparent in early infection, but greater immunopathology in early infection alters early longitudinal trajectories of CEN rsFC. CD4 nadir may be an important prognostic marker for reduced CEN rsFC later in life in PLWH. Interventions that preserve CEN rsFC (e.g., non-invasive neuromodulation) may protect against emergence of psychiatric and neurocognitive comorbidities in PLWH.

548 Inflammation and Cognition Associations in Young Adults With Perinatal HIV Exposure and/or Infection

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Background: Children with perinatal HIV exposure, particularly those with HIV infection, are at risk for worse cognitive outcomes compared to unexposed children. Inflammation is a potential risk factor for worse cognitive outcomes in populations with HIV, but no studies have evaluated this association within young adults with perinatal HIV (YAPHIV) or perinatal HIV exposure but uninfected (YAPHEU). We evaluated the association between inflammatory biomarkers and NIH Toolbox cognitive outcomes in YAPHIV and YAPHEU.

Methods: Participants with available plasma samples and NIH Toolbox cognitive scores at entry into the PHACS AMP Up study were included in the analysis. Principal Component Analysis (PCA) was used to derive factor scores from biomarkers for monocyte activation (sCD14, sCD163), acute phase inflammation (CRP, fibrinogen, TNF-α), proinflammatory/Th1/Th17 (IFN-γ , IL-1β, IL-2, IL-12p70, IL-17a), or anti-inflammatory/Th2 (IL-4, IL-6, IL-10) cytokines and homeostasis (GM-CSF, Fractalkine). We computed Pearson correlations of individual log-transformed biomarkers and four PCA factors with Composite Standard Scores for Total (TC), Fluid (FC; e.g., processing speed, executive functions), and Crystallized Cognition (CC; e.g., word knowledge), separately by HIV status.

Results: 638 participants (YAPHIV: n=521, mean age 22.7 (SD:4.2) years; YAPHEU: n=117, mean age 19.0 (SD:1.4) years) were included. Mean TC, FC, and CC were similar for YAPHIV and YAPHEU. Compared to YAPHEU, YAPHIV had higher levels of TNF-α, sCD14 and sCD163 and lower levels of IL-2, IL-4, IL-6, IL-10, IL-1β, IL-12p70, IL-17a, Fractalkine, and GM-CSF. YAPHIV had weak negative correlations of FC with CRP, sCD163, and Fibrinogen (r=-0.08 to -0.09) and of CC and TC with sCD163 (r=-0.09). YAPHEU had positive correlations of FC with IL-2, IL-12p70, and IL-17a (r=0.18 to 0.24) and negative correlations of CC with Fractalkine and IL-10 (r=-0.17). Factor 3 (primarily sCD14, CRP, Fibrinogen) was weakly negatively correlated with both FC and TC in YAPHIV (r=-0.10) and Factor 1 (primarily GM-CSF, Fractalkine, IL-2, IL-1β, IL-12p70, IFN-γ, IL-17a) was positively correlated with FC in YAPHEU (r=0.19) (Table).

Conclusion: Cognition weakly correlated with different summary PCA factor scores in YAPHIV (monocyte and acute inflammation) and YAPHEU (Pro-inflammatory/Th1/Th17 cytokines). Further research is needed to understand the role of inflammatory profiles, perinatal HIV exposure or infection and other factors in cognition.

Table : Pearson correlations of principal component factor scores of log-transformed biomarkers with NIHT age-corrected composite scores by HIV status

		Fluid Composite Score		Crystalized Composite Score		Total Composite Score	
Factor		YAPHIV n=499	YAPHEU n=106	YAPHIV n=509	YAPHEU n=116	YAPHIV n=491	YAPHEU n=106
Factor 1	Correlation	-0.020	0.188	-0.047	-0.106	-0.034	0.028
**IFN γ, IL 12p70, IL 1β, IL-2, IL-1 ra, Fractalkine*	95% CI	(-0.108, 0.068)	(-0.003, 0.365)	(-0.133, 0.041)	(-0.283, 0.078)	(-0.122, 0.055)	(-0.163, 0.218)
Factor 2	Correlation	0.019	-0.030	0.033	-0.067	0.019	-0.029
**IL-4, IL-6 and IL-10;*	95% CI	(-0.069, 0.108)	(-0.220, 0.162)	(-0.054, 0.119)	(-0.246, 0.117)	(-0.070, 0.107)	(-0.218, 0.163)
Factor 3	Correlation	-0.104	0.058	-0.068	0.013	-0.100	0.053
**CRP, Fibrinogen, sCD14*	95% CI	(-0.190, -0.017)	(-0.135, 0.246)	(-0.154, 0.019)	(-0.170, 0.195)	(-0.186, -0.011)	(-0.139, 0.242)
Factor 4	Correlation	-0.044	-0.043	-0.019	-0.007	-0.038	-0.072
** TNF-α, sCD163*	95% CI	(-0.132, 0.044)	(-0.232, 0.149)	(-0.105, 0.068)	(-0.189, 0.175)	(-0.126, 0.051)	(-0.200, 0.120)

**Biomarkers listed have the highest loading for each factor:*
95% CI: 95% confidence interval of correlation which was obtained based on Fisher's Z transformation.

549 Pro-Inflammatory Glycomic Dysregulations Define HIV-Associated Neurocognitive Impairments

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Background: In the general population, host glycomic alterations drive inflammation and precede onset of inflammation-associated diseases. However, it remains unclear whether glycomic alterations are associated with development of inflammation-associated diseases, including neurocognitive impairment, in people with HIV (PWH) on suppressive antiretroviral therapy (ART).

Methods: In this analysis conducted within the ACTG A5322 (HAILO), 20 PWH on ART (10 men and 10 women) who were cognitively impaired over 8 years of follow-up were matched by sex, age, and ethnicity to 20 controls without impairment. Cognitive function was assessed using the Trail Making A and B tests, the Wechsler Adult Intelligence Scale-Revised Digit Symbol test, and the Hopkins Verbal Learning Test–Revised. NPZ4 scores, calculated as the mean of these test scores. Cognitive impairment was defined as ≥2 z-scores ≤1 SD from the mean or one z-score ≤2 SD from the mean. Longitudinal samples, collected over 8 years (5-9 per participant), were analyzed for 133 IgG and plasma glycans (using capillary electrophoresis) and 10 inflammation markers (using multiplex arrays). Longitudinal associations between neurological impairment or NPZ4 scores and glycans and inflammation markers were assessed using mixed-effects models.

Results: Cognitive impairment was associated with higher levels of total bisected GlcNAc glycans, as well as several glycomic traits containing bisected GlcNAc, such as (G0FB and G1FB) on IgGs, pro-inflammatory glycans that increase with age (Fig. 1A). Higher NPZ4 scores were associated with lower levels of these glycans (Fig. 1B). Consistent with their pro-inflammatory roles, these glycans, specifically G0FB, correlated with higher levels of the inflammatory marker TNFα (P<0.01; rho=0.4). Conversely, cognitive impairment was associated with lower levels, and NPZ4 scores with higher levels, of glycans that contain the anti-inflammatory sialic acid and fucose (such as FA2G2S1 and FA2G2S2). Finally, among inflammation markers, IL-10 and sCD14 exhibited positive correlations with neurocognitive impairment and negative correlations with NPZ4 scores.

Conclusion: Aging- and inflammation-associated host glycomic dysregulations are linked to the presence of neurological impairments in PWH on ART. Future studies are warranted to validate these exploratory findings and to examine potential prognostic and functional significance of host glycans and inflammatory markers in the pathogenesis of neurological impairments in PWH.

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550 WITHDRAWN

551 Immune Checkpoint Signatures Associated With Impaired Cognition in People Living With HIV

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Background: HIV-associated brain injury (HABI) persists among people with HIV (PWH) despite suppressive antiretroviral therapy (ART). Immune checkpoints (IC) interactions have been associated with HIV comorbidities in PWH on ART and IC blockade has been shown to restore immune function in the field of Oncology. Given the absence of effective interventions for HABI, we assessed for relationships with measures of IC pathways and neurocognitive deficits in PWH on suppressive ART.

Methods: A cross sectional study of PWH (n=50) living on stable ART (>12 months) with undetectable plasma HIV RNA (<50 copies/mL) and HIV-uninfected (n=50) demographically-matched controls were recruited in Metro Manila, Philippines to participant in the study and provide blood and undergo cognitive assessments. We assessed expression of ICs (PD-1, TIGIT, TIM-3, LAG-3) and their cognate ligands on immune cells using multiparametric flow cytometry. Neuropsychological (NP) performance tests were conducted and assessed for association with ICs and ligand expression. Non-parametric comparisons between the two groups were performed and Spearman's correlations.

Results: We observed an expansion of single and multiple ICs on both CD4 and CD8 T cells in PWH compared to HIV-uninfected controls. No differences were observed in cognate ligand expression. Only verbal memory and fine motor performance tests were impaired in PWH compared to controls ($p<0.05$). Higher PD-1+ CD4 T cell frequencies correlated with better verbal memory ($r=0.41$, $p=0.003$) and worse fine motor ($r=-0.39$, $p=0.005$) performance, while higher TIGIT+ CD4 T cells correlated with worse verbal memory ($r=-0.35$, $p=0.01$) in PWH but not in the control group. Given that neuronal cells have been known to express PD-L1 and PVR, a known TIGIT ligand, we further confirm the expression of PD-L1 and PVR on neuroblastoma cells and assessed the interaction of IC-expressing CD4+ T cells with neuroblastoma cells. We observed that PD-1High CD4+ T cells in vitro increased PD-L1 expression on neuroblastoma cells and this was associated with an increase in TNF-α production. PD-L1 blockade reduced neuronal expression of PD-L1 but was insufficient to reverse the inflammatory response.

Conclusion: Our findings suggest that interactions of immune checkpoints on T cells with neuronal cells may drive a neuroinflammatory process leading to cognitive deficits in PWH despite viral suppression and additional intervention beyond IC blockade may be necessary.

552 No Neurocognitive Benefit of Tesamorelin Immediate vs Delayed Treatment in Virally-Suppressed PWH

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Background: In people with HIV (PWH) who are virally suppressed (VS) on antiretroviral therapy (ART), abdominal obesity (AO) is associated with neurocognitive impairment (NCI). The likely mechanisms involve visceral adiposity, inflammation, and reductions in insulin-like growth factor type 1 (IGF-1), a neurotrophin. Tesamorelin (Tesa) is a synthetic growth hormone-releasing hormone that reduces AO and increases IGF-1, suggesting it may mitigate NCI in VS PWH.

Methods: We conducted a randomized clinical trial of immediate versus delayed treatment with Tesa with NCI in PWH. Entry criteria were PWH with VS, NCI (global deficit score [GDS] >0.5 on a comprehensive NC battery), and AO as indexed by elevated waist circumference (WC). Exclusions were other confounding conditions other than HIV accounting for NCI, active substance use disorder, and active malignancy. Participants were randomized 3:2 to receive either immediate or delayed Tesa 2 mg SC for 6 months. The primary outcome was the change in NC performance at 6 months by the published summary regression-based change score (sRCS) method, which corrects for the effects of repeated testing.

Results: We enrolled 73 participants who met the entry criteria. Per the study design, 43 were randomized to immediate Tesa and 30 to deferred treatment. The groups were well matched on baseline characteristics as follows: mean (95% CI) baseline GDS 0.939 (0.717, 1.161) in the immediate and 0.861 (0.653, 1.069) in the deferred Tesa arms, $p=0.619$. Mean WC was 111.0 (108.0, 114.0) cm in the immediate and 110.0 (106.1, 113.8) cm in the deferred Tesa arms, $p=0.655$. The immediate but not deferred Tesa arm showed improved NC performance, mean (95%CI) 0.155 (0.001, 0.309), $p=0.048$ in immediate, 0.103 (-0.095, 0.301), $p=0.295$ in deferred Tesa; but the difference for immediate Tesa compared to no treatment (delayed initiation) was not significant ($p = 0.673$). The immediate arm showed a higher reduction in WC at 6 months compared to the delayed arm (median difference -2.7 [-4.7, -0.7] cm, $p=0.015$).

Conclusion: These findings indicate that Tesa did not significantly improve NCI in VS PWH with AO compared to delayed initiation, but the study was underpowered to confidently show a relationship. Other limitations were that the study was unblinded and did not include a concomitant placebo arm. These findings do not support the hypothesis that AO contributes significantly to NCI in PWH.

553 Changes in Cognition, Mood, and Sleep Following EFV-DTG Switch in South Africa: The CONNECT study

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Background: Both efavirenz (EFV) and dolutegravir (DTG) have been associated with neuropsychiatric side effects. Rates of cognitive impairment and CSF escape have not been comprehensively studied in African populations, and the effect of EFV-DTG switch on cerebral function is not known.

Methods: 178 virally supressed PWH on EFV-based ART were studied at baseline, and 145 followed up at 1-year following switch to DTG. 95 people without HIV (PWoH) were recruited from the same area, matched for age and sex, and 40 followed up at 1-year. Participants underwent comprehensive cognitive testing over 7 domains, measures of mood (Center for Epidemiologic Studies Depression Scale (CESD)), anxiety (State-Trait Anxiety Inventory) and sleep (Pittsburgh Sleep Quality Index). PWH had cerebrospinal fluid (CSF) sampling for HIV RNA quantification. Global cognition was assessed by T-scores and low cognitive performance by global deficit score ≥0.5. Mixed effects regression models were used to investigate the effects of switch on cerebral function parameters.

Results: Global cognitive performance was 2.57 T-score points lower in PWH than PWoH at baseline ($p<.001$), but was not significantly different between groups at follow-up (figure). Rates of low cognitive performance were higher in

PWH at baseline (30.1 vs. 11.7%, p<.001), but not different to PWoH at follow-up (8.28 vs. 7.50%, p=1). Mixed effects models showed PWH improved 1.40 points more than PWoH (CI 0.21-2.58, p=.021). Overall sleep quality improved following switch (OR 0.37, p=.001), driven mainly by indicators of disturbed sleep. Rates of depressive symptoms (CESD ≥16) worsened (OR 6.53, p=.016), although baseline differences between PWH and PWoH were present (9.55% vs. 22.11%, p=.004). 104/113 (92.0%) plasma and 93/94 (98.9%) CSF samples were supressed <50 copies/ml at baseline, and 103/122 (84.4%) and 73/77 (94.8%) at follow up. There was 1 case (1.1%) of CSF HIV RNA escape (CSF HIV RNA > plasma) at baseline and 3 (3.9%) at follow up; 3/4 were at low levels (CSF HIV RNA <200 copies/ml) and 1/4 resolved on repeat sampling without change in ART.

Conclusion: Rates of low cognitive performance were lower than previously reported in this setting, and no different to PWoH once switched to DTG. Observed improvements in cognitive performance and sleep were likely related to switching away from EFV. The increase in depressive symptoms on DTG is inconclusive due to baseline differences, but warrants further investigation. CSF escape was uncommon on both EFV and DTG.

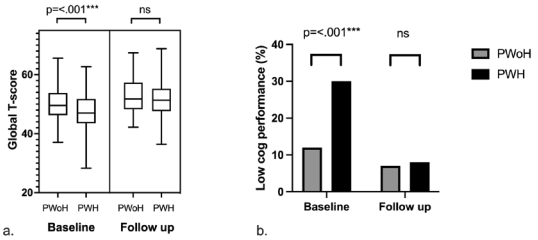

Figure. Cognitive performance by a) global T-score and b) GDS at baseline (on EFV) and follow up (on DTG). Improvements in PWoH over time relate to practice effects.

554 Antiretroviral Regimens Are Associated With Cognitive Function in People With HIV

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Background: While modern antiretroviral therapy (ART) is highly effective and safe overall, ART medications can cause neuropsychiatric adverse effects (e.g., poorer cognition). Observational studies addressing cognition have mainly focused on individual ART drugs rather than ART regimens, partly due to statistical limitations. We developed a novel statistical approach to examine the relationship between common ART regimens and cognition in people with HIV (PWH).

Methods: We leveraged longitudinal data collected between 2014-2020 from PWH enrolled in CHARTER, NNTC, or NeuroHIV cohorts at UCSD with available ART regimen data concurrent with comprehensive neuropsychological (NP) testing. Novel Bayesian machine learning methods building upon a subset-tree kernel approach were developed to estimate the combined effects of ART regimens on NP performance after controlling for relevant covariates.

Results: Among 1,702 individuals who participated in 1,928 (mean 1.13) visits, the mean age was 55 (interquartile range [IQR] 49-63) years; 26% were female, 23% were black; 23% were Hispanic; and 72% had HIV RNA <50 copies/mL at study entry. The most common ART regimens used were: 1) dolutegravir (DTG)+abacavir (ABC)+lamivudine (3TC) at 22%, 2) elvitegravir (EVG)+cobicistat (COBI)+tenofovir alafenamide (TAF)+emtricitabine (FTC) at 14%; and 3) efavirenz (EFV)+tenofovir disoproxil fumarate (TDF)+ FTC at 10%. Darunavir (DRV)+COBI+TAF+FTC was associated with worse executive function, learning and memory, while no association was observed with other protease inhibitors. Rilpivirine (RPV)+TAF+FTC and EFV+TDF+FTC were also associated with poorer executive function and memory without effects on learning. DTG+TDF+FTC, DTG+ABC+3TC, and EVG+COBI+TDF+FTC were associated with better learning, memory, and motor function, respectively.

Conclusion: Specific ART regimens are associated with worse domain-specific cognitive function. Tenofovir (including TAF or TDF) and FTC were common in such regimens in combination with either DRV+COBI, RPV, or EFV. Our findings suggest complex associations between ART regimens and cognition, such that specific ART combinations rather than individual agents are associated with cognition. Future studies should consider complete drug regimens when assessing the risk of long-term neuropsychiatric complications of ART, with attention to the highlighted drug combinations.

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555 Phenotyping Risk of Polypharmacy and Cognitive Impairment in ACTG A5322: "HAILO"

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Background: Polypharmacy is associated with worse cognitive health among people with HIV (PWH), however explanatory models have not been established. This study leveraged data from a large and well characterized cohort of virally suppressed individuals age 40 and older to identify risk factors that explain the association between polypharmacy and cognitive impairment among PWH.

Methods: Data obtained at enrollment into ACTG A5322 ("HAILO") were included. Cognitive performance was measured using four tests of verbal learning, attention/psychomotor speed, and fine motor speed and dexterity. Hierarchical density-based spatial clustering, an unsupervised machine learning based algorithm, was used to identify sub-groups based on cognitive performance. Polypharmacy (≥5 non-ART medications), and hyperpolypharmacy (≥10 medications) as well as demographic, clinical, and psychosocial variables were compared across clusters using multinomial regression, adjusted for multiple comparisons.

Results: Participants were 870 PWH (18.4% female, 52.2% non-White), with a median age of 51. Analyses identified 8 cognitive clusters. There were no differences in average age across clusters. Cluster 1 (33% of the sample) included participants with the best test scores whereas clusters 6, 7, and 8 (collectively 48%) had the worst test scores. Polypharmacy was more common in clusters 6 and 8 compared to cluster 1 (reference group) and hyperpolypharmacy was more common in clusters 7 and 8 compared to cluster 1 (ps<.05; Table). Participants in clusters 6, 7, and 8 were also more likely to be women, Black or Hispanic, less educated, and have higher rates of cardiovascular disease, diabetes, hepatitis C, peripheral neuropathy, and substance use compared to participants in cluster 1 (ps<.05). Participants in clusters 6, 7, and 8 also reported a shorter duration of ART, lower CD4+ T-cell count and nadir, and lower CD4/CD8 ratio compared to cluster 1. Use of psychoactive medications did not differ between the clusters. Black or Hispanic women were more likely to have polypharmacy or hyperpolypharmacy (OR=1.4; 95th CI [.97-2.0]) and cognitive impairment (OR=2.8; 95th CI [1.7-4.6]) compared to any other demographic group.

Conclusion: Psychosocial determinants of health, particularly those that disproportionately impact Black and Hispanic females with HIV, associate with an increased risk for polypharmacy/hyperpolypharmacy and cognitive impairment. Intervention/prevention efforts aimed at these high risk groups are warranted.

Table. Differences in polypharmacy, hyperpolypharmacy, demographic, psychosocial, and medical comorbidities between cognitive clusters.

	Cluster 1 (n=291)	Cluster 6 (n=222)	Cluster 7 (n=92)	Cluster 8 (n=104)
Polypharmacy	32% [a]	41.4% [b]	34.8% [a, b]	41.3% [b]
Hyperpolypharmacy	6.2% [a]	7.2% [a,b]	12% [b]	13.5% [b]
Female sex	11.3% [a]	22.1% [b]	19.6% [b]	33.7% [c]
Education, median (IQR)	16 (14-17) [a]	14 (12-16) [b]	12 (12-14) [b]	11 (6-12) [c]
Non-White race	28.9% [a]	63.5% [b]	73.9% [b]	87.5% [c]
Diabetes	6.9% [a]	13.1% [b]	14.1% [b,c]	25% [c]
Hepatitis C	7.6% [a]	15.8% [b]	14.1% [a,b]	19.2% [b]

Cells that share a superscript do not differ significantly. Results for clusters 2 through 5 are not included due to space restrictions and small cell sizes. Cluster 1: highest scores; clusters 6-8: lowest scores.

556 Pharmacogenetics of Early Neuropsychiatric Adverse Events After Switching to DTG in Second-Line ART

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Background: Dolutegravir is associated with neuropsychiatric adverse events (NPAEs). We characterised associations between genetic polymorphisms

and early NPAEs in adults failing efavirenz-based antiretroviral therapy and switching to a dolutegravir-based regimen.
Methods: We conducted a pharmacogenetic sub-study of participants enrolled into the ARTIST clinical trial, who were switched from tenofovir-emtricitabine-efavirenz to tenofovir-lamivudine-dolutegravir and randomised to supplementary dolutegravir 50 mg dose or placebo for the first 2 weeks. Primary outcome was change in sleep quality from baseline to week 2. NPAEs were assessed by questionnaires and neuropsychological testing before and after the switch. Plasma dolutegravir trough concentrations were collected at week 2. We genotyped polymorphisms relevant to efavirenz disposition [CYP2B6 (rs3745274 G→T, rs28399499 T→C and rs4803419 C→T), and CYP2A6 rs28399433 A→C], dolutegravir disposition (UGT1A1 rs887829 C→T), and dolutegravir toxicity (SLC22A2 rs316019 C→A). Multivariate logistic regression analyses were used to determine associations between genetic polymorphisms and early NPAEs.
Results: 128 participants were evaluable for genetic analyses. The median age was 38 years (IQR 32–45), 68% female, median duration on ART was 85 months (IQR 50–119), and median baseline HIV-1 RNA was 4.0 $\log_{10}$ copies/mL (IQR 3.5–4.7). Insomnia events occurred in 17 (13%) participants. There were no statistically significant associations between genetic polymorphisms and worsening sleep quality. UGT1A1 rs887829 homozygous TT genotype was associated with higher dolutegravir exposure [$\beta = 0.841$ (95% CI -0.030 to 1.711), $P = 0.058$]. CYP2B6 slow efavirenz metaboliser genotype was associated with lower dolutegravir exposure in both arms, but this was only statistically significant in the supplementary dolutegravir arm [$\beta = -1.457$ (95% CI -2.467 to -0.447), $P = 0.006$; Figure 1].
Conclusion: Among participants who switched from efavirenz to dolutegravir, early insomnia events were common, but these were not associated with known functional polymorphisms. CYP2B6 slow metaboliser genotype was associated with lower dolutegravir exposure, reflecting prolonged efavirenz induction effect.

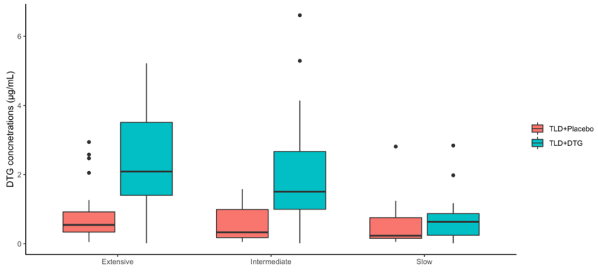

Figure 1: Dolutegravir trough concentrations at week 2 by efavirenz metaboliser genotypes in the supplementary dolutegravir arm and the placebo arm. Boxes indicate interquartile range, horizontal solid lines are medians, vertical lines are ranges, solid circles are outliers. TLD = tenofovir-lamivudine-dolutegravir, DTG = dolutegravir.

557 Long-Acting Dolutegravir Formulation Reduces Fetal Drug Exposure

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Background: Dolutegravir (DTG) is a preferred first-line antiretroviral for the treatment of people living with human immunodeficiency virus type one (PLWHIV). Fifteen million PLWHIV world-wide are expected to be treated with DTG regimen by 2025. This includes pregnant women, who remain a significant infected population. Widespread DTG usage is linked to its high potency, barrier to resistance, and cost-effectiveness. Despite such benefits, potential risks of DTG-linked fetal neurodevelopmental toxicity remain a concern. To this end, novel formulation strategies are timely to maximize DTG's therapeutic potentials while limiting adverse events during pregnancy. Thus, we posit that injectable long-acting (LA) nanoformulated DTG (NDTG) could provide improved safety by reducing fetal drug exposures compared to orally administered drug.
Methods: Pregnant C3H/HeJ mice were treated with daily oral DTG at a human equivalent dosage (5 mg/kg). These were compared against pregnant mice injected with intramuscular (IM) NDTG given at 45 or 25 mg/kg at one or two doses, respectively. Treatment began at gestation day (GD) 0.5. DTG levels were measured in plasma of dams and in whole brain tissues of embryos at GD 17.5 using mass spectrometry. Magnetic resonance imaging (MRI) and non-targeted proteomic tests were performed on embryo brains at GD 17.5 to cross-validate pathobiological pathways.
Results: Single (45 mg/kg) or two (25 mg/kg) IM injections of NDTG, or daily oral DTG administration (5 mg/kg) achieved equivalent therapeutic plasma DTG levels (4000-6500 ng/mL) in pregnant dams. However, five-fold lower DTG levels were observed in embryo brain following NDTG injections. For daily oral DTG, average concentrations of 196 ng/g were recorded compared to 34 ng/g and 45 ng/g for single or two IM injections of NDTG, respectively. MRI scanning of live dams was performed to acquire T1 maps of the embryo brain to assess oxidative stress. Significantly lower T1 values were noted in daily oral DTG-treated mice, whereas comparative T1 values were noted between control and NDTG-treated mice, indicating prevention of DTG-induced oxidative stress when delivered as NDTG. Proteomic profiling of embryo brain tissues demonstrated reductions in oxidative stress, mitochondrial impairments, and amelioration of impaired neurogenesis and synaptogenesis in NDTG-treated group.
Conclusion: This work suggests that long-acting drug delivery can prevent DTG-linked neurodevelopmental deficits by limiting drug exposure to the embryo brain.
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558 A New Measure of ART Activity in CSF and Association With Persistence and Cognitive Function

Sean N. Avedissian[1], Caitlyn McCarthy[2], Ronald J. Bosch[2], Ying Mu[1], Serena Spudich[3], Leah H. Rubin[4], Lee Winchester[1], Timothy Mykris[1], Jonathan A. Weinhold[1], Joshua C. Cyktor[5], Joseph J. Eron[6], John W. Mellors[5], Rajesh T. Gandhi[7], Deborah K. McMahon[5], Courtney V. Fletcher[1]
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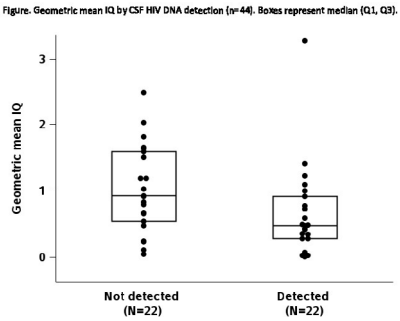
Background: ACTG A5321, a prospective study of HIV-1 reservoirs among persons with HIV on antiretroviral therapy (ART), previously showed detection of HIV DNA in cells from cerebrospinal fluid (CSF) was associated with poorer global cognitive function. We conducted a cross-sectional analysis of antiretroviral (ARV) pharmacokinetics (PK) in CSF and investigated relationships among a novel measure of ART regimen activity and HIV persistence in CSF and cognitive function.
Methods: Participants were on ART for a median of 8.1 years with sustained plasma HIV suppression at time of lumbar puncture (LP). CSF ARV concentrations, cell-associated HIV DNA and inflammatory biomarkers were measured; a neuropsychological test battery (outcome=global deficit score, GDS) was administered just prior to or at LP. ARV levels were quantified by LC/MS/MS. Population PK modeling was used to estimate CSF drug exposure. CSF inhibitory quotients (IQ) were calculated for each ARV in a regimen as ratio of predicted CSF trough to literature values for in vitro HIV inhibitory concentration (i.e., IC_{50}, IC_{90}). The geometric mean of CSF IQs of all drugs in each participant's ARV regimen was calculated (ART-IQ-GeoM). Statistical analyses evaluated associations among the ART-IQ-GeoM and CSF HIV DNA, biomarkers and GDS.
Results: CSF ARV levels were measured in 44 chronic-treated participants on TDF/FTC-based ART: 43 (98%) male sex at birth; 36 (97% of 37) male gender; 33 (75%) white non-Hispanic, 6 (14%) black non-Hispanic; median age, 49 yrs; median CD4 count, 642 cells/µL; 43 (98%) with plasma HIV RNA <40 copies/mL. Third drugs in ARV regimens were: EFV (n=17), ATV/r (8), RAL (8), EVG/c (5), DRV/r (4) and DTG (2). The median (Q1, Q3) ART-IQ-GeoM was higher in those with undetectable vs detectable CSF HIV DNA 0.9 (0.5, 1.6) vs 0.5 (0.3, 0.9), p=0.027 (Figure). A rank-based analysis gave similar findings. Higher ART-IQ-GeoM was associated with lower GDS (i.e., better global cognitive function, Spearman: -0.30, p=0.05). There was no association between CSF inflammatory biomarkers and ART-IQ-GeoM.
Conclusion:\ The ART IQ metric is a new approach to assess ART regimen activity. Higher ART-IQ-GeoM was associated with a lack of detection of CSF HIV DNA and better global cognitive function. These findings suggest ART regimen activity affects HIV persistence in CSF. This tool provides a basis for further investigations of relationships between regimen activity and biomarkers of HIV persistence in the CSF and other viral reservoirs.



559 The Association Between Prior SARS-CoV-2 Infection and Incidence of Stroke

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Background: Individuals with COVID-19 have an increased incidence of several comorbid conditions including diabetes and acute myocardial infarction. The association of COVID-19 infection with stroke is controversial, with some studies demonstrating a higher risk and other studies showing no association or even a protective effect. We sought to determine the association between COVID-19 infection and subsequent incidence of stroke at a national level in Qatar.

Methods: We used the Qatar Stroke Database to identify individuals who were admitted with acute ischemic or hemorrhagic stroke to the tertiary care referral hospital in Qatar, which accounts for 98% of all acute stroke admissions in Qatar. For the current study, we included individuals admitted with acute stroke between March 1, 2020 and April 11, 2023. We linked the Qatar Stroke Database to the Qatar National COVID-19 database to retrieve the information on COVID-19 testing and vaccination. This database contains all records of RT-PCR and medically-supervised antigen testing and vaccination in the State of Qatar. Eligible individuals with stroke diagnosis were exactly matched 1:1 on 10-year age group, sex, nationality, type of comorbid condition, and number of vaccine doses received, to eligible controls who tested SARS-CoV-2-negative during the same week of the stroke diagnosis. We utilized a case-control design to determine the association of COVID-19 diagnosis with acute stroke. Adjusted odds ratios and corresponding 95% confidence intervals were calculated for the entire study population and subgroups by age, nationality, and prior infection variant period (infection in the pre-omicron era, omicron era, or in both eras).

Results: A total of 1,640 matched pairs were analyzed. Median age was 49 years, 85% were male, 11% were Qatari nationals, 58% had no comorbidities, and 48% were unvaccinated at the time of first stroke diagnosis. Any prior infection was associated with a lower risk of stroke (aOR 0.48, 95% CI 0.40,0.58). The protective association was consistent across older age groups, among unvaccinated and vaccinated, the infection era (pre-Omicron or Omicron eras) and regardless of the time from infection. (Table)

Conclusion: Prior COVID-19 infection is associated with a lower risk of stroke. This association is independent of age, vaccination status, infection era by predominant COVID-19 variant, and time from infection. The reason for this effect is unclear and requires further investigation.

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560 Focal Cerebral Hypoperfusion in Individuals With Cognitive Impairment After COVID-19

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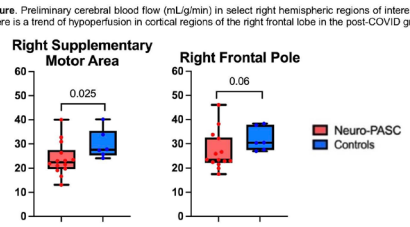
Background: Cognitive impairment is a common symptom of neuropsychiatric post-acute sequelae of COVID-19 (N-PASC), characterized by neuropsychological deficits including impaired executive functioning, processing speed, motor speed, attention, recall, and verbal fluency. Little is known about the underlying mechanism of cognitive N-PASC. We report preliminary analyses of noninvasive MRI measurements of brain perfusion in individuals with and without N-PASC.

Methods: Participants with cognitive N-PASC (self-reported symptoms of cognitive impairment >3 months after COVID-19) referred from a NeuroCOVID Clinic and controls with prior COVID without PASC underwent an MRI protocol, which included Arterial Spin Labeling (ASL) to assess perfusion (Cerebral Blood Flow; CBF). All imaging was performed on a Siemens 3T MRI scanner. A standard 3D ASL sequence was used (TA: 4:59, voxel: 1.5×1.5×3.0 mmRel, SNR: 1.00, TR: 4600ms, TE: 16.18ms). Post-processing was completed using MATLAB and the Harvard-Oxford atlas to generate CBF for 48 cortical and 21 subcortical regions of interest (ROI). Group comparisons used non-parametric statistics.

Results: 14 participants with cognitive N-PASC (median age 43 [IQR 37 – 55], 79% female, median 450 days after COVID-19 symptom onset [IQR 354 – 694]) and 6 controls (median age 34 [30 – 40], 67% female) underwent MRI. The groups did not differ in age, gender, race, or cardiovascular risk factors, which were low in prevalence. CBF was lower in N-PASC compared to controls (C) in the right supplementary motor area (N-PASC: median of 22.5 mL/g/min and C: 27.7 mL/g/min; $p = 0.025$). a trend of hypoperfusion that did not reach significance was identified in three other ROIs in the right hemisphere: the frontal pole (N-PASC: 23.5 mL/g/min and C: 30.4 mL/g/min; $p = 0.06$), middle frontal gyrus (N-PASC: 24.8 mL/g/min and C: 31.3 mL/g/min; $p = 0.06$), and post-central gyrus (N-PASC: 22.5 mL/g/min and C: 27.7 mL/g/min; $p = 0.06$). There was no difference in CBF between groups in the remaining ROIs.

Conclusion: We report preliminary evidence of focal hypoperfusion in the right frontal lobe and a trend of hypoperfusion in the right parietal lobe in individuals with N-PASC. These findings suggest that altered perfusion in the non-dominant hemisphere may play a role in cognitive N-PASC symptoms, possibly by affecting motor speed and motor control of speech. We look forward to collecting additional data to investigate the mechanism of decreased cortical perfusion in cognitive N-PASC.



561 CSF Biomarker Evidence of Synaptic Dysfunction in Acute, but Not Post-Acute COVID-19

Arvid Edén, Johanna Nilsson, Anna Grahn, Nelly Kanberg, Erika Stentoft, Daniel Bremell, Aylin Yilmaz, Marie Studahl, Staffan Nilsson, Michael Schöll, Iris Bosch, Kaj Blennow, Ann Brinkmalm, Henrik Zetterberg, Magnus Gisslén
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Background: CNS immune activation and neurocognitive symptoms are common in severe COVID-19, but mechanisms of persisting CNS dysfunction in post COVID-19 conditions (PCC; "long covid") are unclear. We used a panel of CSF markers, several of whom have been implicated in Alzheimer's disease (AD) and other neurodegenerative diseases to investigate synaptic and lysosomal dysfunction in acute and post-acute COVID-19.

Methods: Lumbar punctures were performed on 76 (49 male) patients and 20 (6 male) healthy controls from longitudinal studies, sampled during acute (46), ≥3 (39 [31 PCC]) and/or ≥12 (25 [19 PCC]) months after COVID-19. PCC symptoms at follow-up were evaluated by interview and self-report. The 37-marker CSF panel included cathepsins, calsyntenins, contactins, granins, glutamate receptor 4 (GRIA4), VGF, APP, neurogranin, syntaxins, LAMPs, beta-hexosaminidase subunit beta (HEXB), GM2A, dipeptidyl peptidase 2 (DPP-2), NCAM2, NSF, synapsin-1, CAMK2A, Thy-1, VAMP2, AP2B1, complexins, synucleins, GDI-1, neuronal pentraxins, PEBP-1, and members of the 14-3-3 protein family. A micro-high performance liquid chromatography mass spectrometry system (6495 Triple Quadrupole LC/MS system, Agilent Technologies) equipped with a Hypersil Gold reversed-phase C18 column (dim.=100 × 2.1 mm, particle size=1.9 µm, Thermo Fisher Scientific) was used for quantitation. Group comparisons of biomarker concentrations were analyzed by Kruskal-Wallis (Dunn's post hoc) test.

Results: Patients had mild (15), moderate (hospitalized with oxygen; 33) or severe (ICU; 28) COVID-19. Self-reported PCC symptom severity was mild or moderate. Significant alterations of GRIA4, DPP-2, cathepsin F, HEXB (all decreased) and 14-3-3 zeta/delta (increased), were seen in acute compared with post-acute COVID-19 and controls (all $p<0.005$ [Figure 1]). No significant differences in any biomarkers were seen between patients and controls, or between patients with PCC compared with fully recovered patients ≥3 or ≥12 months after acute infection.

Conclusion: Several markers previously associated with neurodegenerative and psychiatric diseases were significantly altered during acute COVID-19. Notably, neuronal pentraxin-2 (a sensitive marker of cognitive decline in AD) remained unaffected. Importantly, no biomarker evidence of persisting CNS pathology was seen at follow-up either between patients and controls, or between patients with or without PCC indicating that PCC is not associated with progressive postinfectious neurodegeneration.
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562 SARS-CoV-2 Nucleocapsid Antigen is Not Detected in the CSF During Long COVID

Shelli Farhadian[1], Allison Grubman[1], Lindsay S. McAlpine[1], Bibhuprasad Das[1], Jennifer Chiarella[1], Benjamin Orlinick[1], Hailey Reisert[1], Allison Nelson[1], Priya Kosana[1], Meenakshi Khare[2], Serena Spudich[1]
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Background: SARS-CoV-2 viral protein persistence has been suggested as a possible cause of post acute sequelae of COVID-19. We previously showed that some individuals with neuropsychiatric symptoms after COVID-19 had persistent anti-SARS-CoV-2 nucleocapsid antibodies in the cerebrospinal fluid (CSF) several months after COVID-19. However, it is unknown whether this is driven by persistence of SARS-CoV-2 antigen in the CSF.
Methods: CSF and plasma was collected from participants in four groups: acute COVID (hospitalized with acute-infection, n=5); post-COVID with neuropsychiatric symptoms (Neuro-PASC, n=31); post-COVID asymptomatic (n=8), and pre-pandemic never-COVID controls (n=20). Tissue samples were measured for SARS-CoV-2 Nucleocapsid (N) antigen levels via a Single Molecular Array (Simoa) immunoassay, a paramagnetic microbead-based sandwich ELISA (Quanterix, Billerica, MA, USA). Samples were run in duplicate, and the results were averaged. CSF was run undiluted and plasma samples were diluted 1:4 per manufacturer protocol, with results corrected for dilutions.
Results: Sixty-four participants' samples were analyzed: sixty-one paired CSF and plasma samples and three CSF samples. Acute COVID participants were sampled a median of 7 days (range 1-14) after symptom onset. Neuro-PASC and post-COVID asymptomatic participants were sampled a median of 381 days (range 81-1157) after acute infection. SARS-CoV-2 N-antigen was not detected in any of the post-COVID (Neuro-PASC or asymptomatic) or pre-pandemic participants, in CSF or plasma. SARS-CoV-2 N-antigen was detected in the CSF or plasma of three participants, all of whom were from the acute COVID cohort. Of these three participants, one had antigen present in the CSF sample (1.40 pg/mL), one had antigen present in the plasma sample (29.9 pg/mL), and one had antigen present in both the CSF and plasma samples (12.6 pg/mL and 785 pg/mL, respectively).
Conclusion: We found SARS-CoV-2 N-antigen is undetectable in the plasma and CSF of post-COVID participants, those with Neuro-PASC and those without PASC. Neuro-PASC is unlikely to be caused by persistent SARS-CoV-2 N-antigen in the CNS.

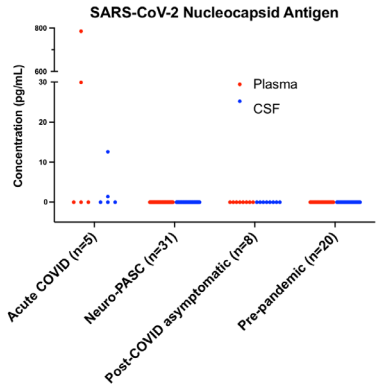

Figure. CSF and Plasma Dilution Corrected Concentrations among acute COVID (n=5), Neuro-PASC (n=31), post-COVID asymptomatic (n=8), and pre-pandemic groups (n=20). Individual SARS-CoV-2 Nucleocapsid antigen levels (pg/mL) were measured in the plasma (red) and CSF (blue). Black lines connect CSF and plasma taken from the same individual.

563 Gut Microbiome Dysbiosis and Lower Abundance of Butyrate Producing Bacteria in Neurologic PASC

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Background: Neurologic post-acute sequelae of COVID-19 (PASC) affects a growing population of individuals, with symptoms including myalgic encephalomyelitis chronic fatigue syndrome (ME-CFS), cognitive dysfunction, dysautonomia, and neuropathy. Gut microbiome dysbiosis has been reported in the early convalescent period after SARS-COV-2 infection (<1 year) in hospitalized patients, with lower alpha diversity and decreased abundance of butyrate-producing species. Butyrate has a protective effect in the gut by supporting the mucosal barrier and has systemic anti-inflammatory and immunomodulatory effects. Notably, in long-term ME-CFS patients (symptoms >10 years), metabolic dysfunction persists despite recovery of relative abundance of bacterial species. To date, the longitudinal role of gut dysbiosis in neurologic PASC remains unknown, especially in patients with mild acute COVID-19.
Methods: The COVID-19 Persistent and Immunology Cohort (C-PIC) is an observational cohort study with over 650 participants, with and without PASC. Rectal swabs or stool samples are collected at 3-6 month intervals, with matched clinical metadata. Neurologic PASC is defined as self-reported fatigue, cognitive dysfunction, or dysautonomia. DNA was extracted using the Zymo MagBead DNA/RNA kit and the MiSeq platform was used to sequence the V3/V4 region of the bacterial16s rRNA gene. DESeq2 was used to assess species-level differential abundance testing and alpha diversity was measured using Chao scores for richness. Differences between participants with and without neurologic PASC were compared in C-PIC participants with mild acute COVID-19 not requiring hospitalization.
Results: 151 C-PIC participants with mild acute COVID-19 were included in the analysis. Fecal samples collected at study enrollment demonstrated lower relative abundance of butyrate-producing species (Faecalibacterium prausnitzii, Eubacterium spp, Bacteroides spp) in participants reporting neurologic PASC ($p<0.05$). We also report a trend toward increasing alpha diversity (chao) over time across 371 longitudinal samples (figure).
Conclusion: Our findings of decreased abundance of butyrate-producing bacterial species in patients reporting neurologic PASC and a trend towards improving alpha diversity after recovery from SARS-CoV-2 align with late convalescent findings in ME-CFS. These data provide support for the role of gut microbiome in neurologic PASC. Further research is needed to identify gut microbiome targets for diagnostics and therapeutics.

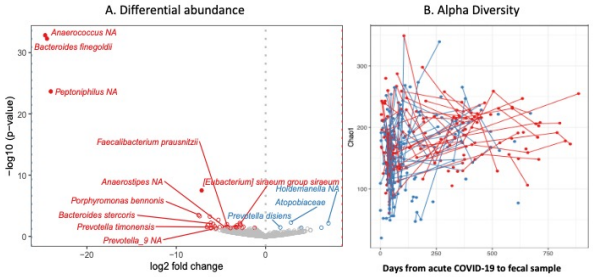


Figure. Volcano plot with differential abundance testing at enrollment (A) and longitudinal alpha diversity testing (B) in C-PIC participants with mild acute COVID-19, with neurologic PASC (red) and without (blue).

564 Brain White Matter Hyperintensity Accumulation in an Acute HIV Cohort Over 2 Years

Kathryn Holroyd[1], Jacob Bolzenius[2], Carlo P. Sacdalan[3], Netsiri Dumrongpisutikul[4], Somchai Sriplienchan[3], Pathariya Promsena[3], Sandhya Vasan[5], Lydie Trautmann[5], Serena Spudich[1], Phillip Chan[1], Robert Paul[2], RV254/SEARCH 010 Study Team[3]
[1]Yale University, New Haven, CT, USA, [2]University of Missouri St Louis, St Louis, MO, USA, [3]SEARCH, Bangkok, Thailand, [4]Chulalongkorn University, Bangkok, Thailand, [5]US Military HIV Research Program, Silver Spring, MD, USA

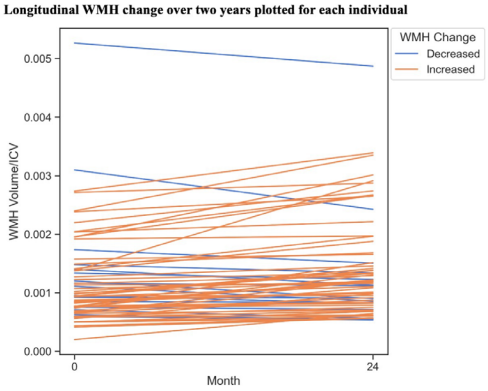
Background: Development and progression of cerebral white matter hyperintensities (WMH) are associated with increased risk of stroke and cognitive impairment for people with (PWH) and without HIV (PWOH). Individuals with chronic HIV have greater WMH burden compared to PWOH

despite viral suppression. Progression of WMH in relation to outcomes following onset of early antiretroviral therapy (ART) remains poorly understood.

Methods: We identified participants enrolled in the SEARCH010/RV254 cohort in Thailand. Multimodal 3T MRI and cognitive testing was performed at week 0 (Fiebig I-V, at ART onset) and week 96 post-ART initiation for all participants. WMH data were extracted from T2 FLAIR sequences using an automated k-nearest neighbor approach. Total WMH volume was computed as both a raw index and as a standardized percentage of the intracranial volume (ICV) for each individual. A composite cognitive score (NPZ-4) was created by averaging Z-scores for Color Trails 1 & 2, Grooved Pegboard Non-dominant, and Trail Making A. HIV disease indices, vascular comorbidities, and cognitive scores were compared to WMH indices using nonparametric testing.

Results: We identified 71 participants (70 male) with AHI and median age 27 years (IQR 24-33). Median CD4+ T-cell count was 348 (IQR 251, 481) and 674 (IQR 486, 908) at week 0 and 96. Median VL at week 0 was 6.16 logcopies/mL (IQR 5.43, 6.78). 96% of participants were virally suppressed (VL <50 copies/mL) at week 96. We observed a mean increase in standardized WMH volume of 22% from week 0 to 96, with 53 individuals (75%) showing an absolute increase and 18 individuals (25%) showing an absolute decrease. While presence of vascular comorbidities was low (9% hypertension, 1% diabetes, 7% hyperlipidemia, and 3% migraine), we found positive associations between WMH % change and history of smoking and systolic blood pressure at week 0, as well as between raw WMH change and BMI, pulse pressure, systolic blood pressure, and hypertension at week 0 (all p<0.05). We did not find an association between WMH burden and cognitive test scores.

Conclusion: Individuals with AHI showed an increase in WMH volume over two years following initiation of ART. Modifiable vascular risk factors during AHI correlated with WMH progression despite successful ART. These findings implicate vulnerability of white matter following acute infection despite early and effective initiation of ART. Further studies comparing these patterns to PWOH and individuals with chronic HIV are needed.



565 Atherosclerotic Cardiovascular Disease Risk Score and Cognition by HIV Serostatus and Sex

Hannah Begna[1], Ali Mirzazadeh[1], Maria L. Alcaide[2], Monica M. Diaz[3], Cecile D. Lahiri[4], Gypsyamber D'Souza[5], Deborah Gustafson[6], Seble Kassaye[7], Jeremy Martinson[8], Matthew J. Mimiaga[9], Kathleen Weber[10], Pariya Wheeler[11], Leah H. Rubin[12], **Felicia C. Chow**[1]

[1]University of California San Francisco, San Francisco, CA, USA, [2]University of Miami, Miami, FL, USA, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Emory University, Atlanta, GA, USA, [5]The Johns Hopkins University, Baltimore, MD, USA, [6]State University of New York Downstate Medical Center Downstate Medical Center, Brooklyn, NY, USA, [7]Georgetown University, Washington, DC, USA, [8]University of Pittsburgh, Pittsburgh, PA, USA, [9]University of California Los Angeles, Los Angeles, CA, USA, [10]Hektoen Institute of Medicine, Chicago, IL, USA, [11]University of Alabama at Birmingham, Birmingham, AL, USA, [12]The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: Higher cardiovascular risk is associated with poorer cognitive health, including in people with HIV (PWH). We examined whether HIV modifies the association between the Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator and subsequent cognition in the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS).

Methods: Participants followed in the MACS (N=1773 men, 2005 to 2019) and WIHS (N=1264 women, 2009 to 2019) who had available CVD risk data and underwent neuropsychological (NP) testing at least 1 year after calculated ASCVD risk score were included. Demographically-adjusted T-scores for the cognitive tests that overlapped between the two cohorts were averaged as a global NP score and in 4 domains (motor function: Dominant/Non-dominant Grooved Pegboard; executive function: Trail-Making Part B, Stroop Color-Word; attention: Trail-Making Part A, Stroop Word-Reading; processing speed: Symbol Digit Modalities, Stroop Color Naming). We constructed random-effects panel linear regression models to estimate the overall, HIV, and sex-stratified associations of ASCVD risk with subsequent cognitive function (NP testing performed median 2 years later, range 1-14 years) in the combined and separate cohorts.

Results: In the combined cohort (mean age 46 years, 39% women), median ASCVD risk score was 3.4% (IQR 1.2-7.6%). ASCVD risk score was higher in people without HIV (3.8%, IQR 1.3-8.6%) than in PWH (3.1%, IQR 1.1-6.8%; p<0.001). Higher ASCVD risk score (per IQR for all results) predicted lower subsequent global cognition (β -0.41, SE 0.04, p<0.001). HIV did not modify the association between ASCVD risk and cognitive function (interaction p=0.465). In men, no difference in the association between ASCVD risk and subsequent cognition (global or in domains) was observed by HIV. In women, higher ASCVD risk significantly predicted lower subsequent global cognition (β -0.20, SE 0.02, p=0.016) and motor function (β -0.68, SE 0.05, p=0.009) in women with HIV but not in women without HIV (Table).

Conclusion: The ASCVD risk score predicted subsequent cognitive function in PWH and people without HIV, although the magnitude of these associations was modest overall and particularly among women. These findings underscore the complex relationship between HIV and ASCVD risk on cognition. Future studies should examine the cause of these observed differences between women and men.

Table. Association between ASCVD risk score and subsequent cognitive function[1]

β(Standard Error)[2]	Men not living with HIV (n=821)	*p*	Men living with HIV (n=1009)	*p*
Global Cognition	-1.16 (0.01)	<0.001	-0.69 (0.01)	<0.001
Motor Function	-3.38 (0.02)	<0.001	-2.28 (0.02)	<0.001
Executive Function	-2.64 (0.02)	<0.001	-1.14 (0.02)	<0.001
	Women not living with HIV (n=443)	*p*	**Women living with HIV** (n = 764)	*p*
Global Cognition	-0.16 (0.02)	0.08	-0.20 (0.02)	0.016
Motor Function	-0.30 (0.06)	0.358	-0.68 (0.05)	0.009
Executive Function	-0.84 (0.05)	0.002	-0.73 (0.05)	0.003

[1]Adjusted for number of test administrations, baseline test score, age, education level, race, ethnicity, history of depression, hepatitis C; current alcohol, cocaine, marijuana, methamphetamine, or injection drug use.
[2]The effect of one interquartile range increase in ASCVD risk score on cognition.

566 Cumulative Exposure to CVD Risk Factors More Adversely Affects Cognition in Women With & Without HIV

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Background: The adverse effect of cardiovascular disease (CVD) risk factors on cognitive health may be greater for women than men. We evaluated if sex and HIV modify the effect of CVD risk on cognition in the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS).

Methods: People living with HIV (PWH) and without HIV who underwent neuropsychological testing at least once beginning in 2005 in the MACS and in 2009 in the WIHS were eligible. We examined performance on overlapping tests (TrailMaking A and B, Symbol Digit Modalities, Stroop Color Word Trials 1-3, Grooved Pegboard) in the two cohorts and averaged demographically-adjusted T scores into a global summary score and within domains. We calculated cumulative years of exposure for binary CVD risk factors and the average cumulative level of continuous CVD risk factors at each follow-up visit. We constructed adjusted mixed-effects linear regression models (Figure) to estimate separate and interactive associations of each time-dependent CVD risk factor with sex and HIV on cognition.

Results: Among 2,993 women from WIHS (mean follow-up 4.4 y), 2098 were living with HIV, 54% on ART at baseline. Among 2,702 men from MACS (mean follow-up 9.0 y), 1,477 were living with HIV, 44% on ART at baseline. BMI (-0.89 per 5 kg/m^2/yr [95% CI -1.27, -0.52], p<0.001), LDL (-0.24 per 10 mg/dL/yr [-0.36, -0.11], p<0.001), and methamphetamine (-0.74 per yr exposure [-1.36, -0.12], p=0.020) had a greater negative association with global cognition in women than men. Statins (0.39/yr exposure [0.11, 0.67], p=0.006),

antihypertensives (0.28/yr exposure [0.13, 0.43], p<0.001), and antidepressants (1.58/yr exposure [0.02, 3.13], p=0.047) had a greater positive association with global cognition for women than men. We observed a 3-way sex*LDL*HIV interaction, with a greater negative association of the sex*LDL interaction on motor function assessed by Grooved Pegboard test (-0.59 per 10 mg/dL/yr [-0.99, -0.19], p=0.004) and global cognition (-0.23 per 10 mg/dL/yr [-0.50, 0.04], p=0.09) in PWH than without HIV (Figure).

Conclusion: BMI, LDL, and methamphetamine use had greater negative associations with cognition in women, including women with HIV, though the clinical significance of these modest differences is unclear. Future directions include evaluating interactive effects of sex and CVD risk factors on cognition in the combined cohort of PWH, accounting for HIV-related factors including ART use and viral load.

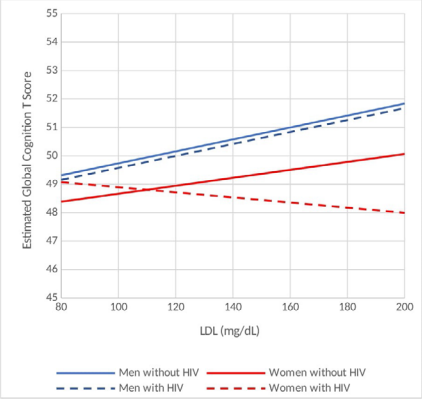

Figure: Association between LDL and global cognition by HIV and sex. The differential association between LDL and cognition by sex was more pronounced in PWH than people without HIV. Model adjusted for age, race/ethnicity, education, number of test administrations, BMI, diabetes, stroke, statins, anti-hypertensives, hepatitis C, depression, smoking, alcohol/cocaine/methamphetamine/marijuana use.

567 Circulating Endothelial Microvesicles With HIV-1 Promote Cerebral Endothelial Cell Stroke Profile

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Background: The incidence of ischemic stroke in adults living with HIV (ALWH) is three times higher than healthy adults. Circulating endothelial cell-derived microvesicles (EMVs) have been linked to cerebrovascular events. We have previously reported that EMVs isolated from ALWH receiving antiretroviral therapy (ART) impair brain endothelial cell nitric oxide (NO) production and fibrinolytic capacity, central etiologic mechanisms in the pathogenesis of ischemic stroke. However, it is unknown whether the pathologic EMV phenotype is a consequence of HIV-1 per se or ART. The experimental aim of this study was to determine the effect of EMVs isolated from treatment naïve ALWH on brain endothelial cell nitric oxide NO production and fibrinolytic capacity.

Methods: Circulating EMVs (CD 144-PE) were isolated (flow cytometry) from 16 young and middle-aged men (age range: 21-43 yr): 8 healthy (age 33±3 yr; BMI: 26.0±1.2 kg/m²; BP: 113/7±22/2 mmHg) and 8 treatment naïve ALWH (10M/2F; 36±2 yr; 25.3±1.5 kg/m²; BP: 117/76±3/3 mmHg; viral load: 5525 copies/mL). All men were free of overt cardiometabolic disease and not taking any medication. Human cerebral microvascular endothelial cells (hCMECs) were cultured and separately treated with EMVs from each subject.

Results: Circulating EMVs were significantly higher in the treatment naïve ALWH (229±23 EMV/µL) compared with healthy adults (133±13 EMV/µL). Although total endothelial nitric oxide synthase (eNOS) expression was not significantly altered (60.1±2.3 vs 65.3±2.1 AU); active eNOS (pSer1177) (19.0±0.8 vs 26.6±1.5 AU) and, in turn, NO production (5.7±0.2 vs 6.7±0.3 µmol/L) was lower (P<0.05) in cells treated with EMVs from treatment naïve ALWH vs EMVs from healthy adults. HIV-associated EMVs also significantly reduced tissue-type plasminogen activator (t-PA) (25.5±1.2 vs 34.7±1.7 AU) and increased plasminogen activator inhibitor (PAI)-1 (146.0±4.5 vs 110.0± 3.8 AU) protein expression in hCMECs. The t-PA:PAI-1 intracellular protein ratio (5.9±0.3 vs 3.3±0.1 AU; P<0.05) was higher in HIV-1 EMV treated cells, indicative of decreased fibrinolytic capacity.

Conclusion: HIV-1, independent of traditional risk factors and ART, is associated with a pathologic circulating EMV phenotype. Reduced NO bioavailability and impaired fibrinolytic capacity in brain endothelial cells heighten the risk and accelerated rate of ischemic stroke. EMVs represent a mechanistic factor underlying HIV-1-related cerebrovascular risk.

568 Vascular Inflammation in Neuropsychiatric Post-Acute Sequelae of COVID-19

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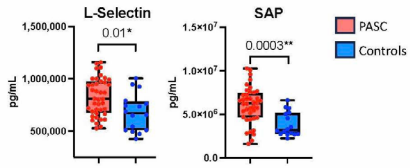
Background: Neuropsychiatric post-acute sequelae of COVID-19 (N-PASC) include cognitive impairment, mood changes, headache, and neuropathy. Biomarkers of endothelial and platelet dysfunction are elevated in patients with acute COVID-19, but it is unknown if this persists in individuals with N-PASC. We investigated for vascular inflammation in N-PASC and controls.

Methods: Participants with N-PASC (ongoing neuropsychiatric symptoms >3 months after COVID-19) and controls underwent cross sectional clinical assessment and blood collection. Plasma samples were tested via multiplex bead-based ELISA for the following analytes: a-2 macroglobulin, α1-acid glycoprotein (AGP), C-reactive protein (CRP), Fetuin A36, haptoglobin, L-selectin, platelet factor 4 (PF4), and serum amyloid protein (SAP) A (Eve Technologies). Non-parametric multiple Mann-Whitney testing was used with False Discovery Rate adjustment made to address multiple comparisons.

Results: The N-PASC (N; n=40) and control (C; n=16) groups were similar in age (N: 45 years, C: 40 years, p=0.15), gender (N: 73% female, C: 69% female, p=0.76), race (N: 20% non-white, C: 37% non-white, p=0.19) and cardiovascular risk factors (diabetes, smoking, hypertension, obesity, and cardiac disease, p>0.05). The groups had similar time from acute COVID-19 to study visit (N:325 days, C:418, p=0.95). N-PASC symptoms included cognitive issues (72%), new or worsening anxiety or depression (67%), and headache (61%). Five markers were elevated in N-PASC: a-2 macroglobulin (N: 994,143 ng/mL, C: 749,109, p=0.04), CRP (N: 8,851,400 pg/mL, C: 3,625,000, p=0.01), haptoglobin (N: 194,735 ng/mL, C: 99,319, p=0.046), L-selectin (N: 808,346 pg/mL, C: 670,940, p=0.01), and SAP (N: 6,252,000 pg/mL, C: 3,186,650, p=0.0003) (Figure). Fetuin A36 was reduced (N: 132,476 ng/mL, C: 207,355, p=0.05). There were no differences in the other biomarkers tested.

Conclusion: We report key differences in vascular inflammatory plasma biomarkers in individuals with N-PASC, including elevations in plasma proteins that indicate ongoing systemic inflammation (CRP, haptoglobin, SAP), endothelial dysfunction (a-2 macroglobulin), and atherosclerosis (L-selectin, fetuin A36, SAP). These findings suggest the N-PASC population may be at risk of persistent vascular inflammation and/or atherosclerosis. Further studies should longitudinally investigate endothelial inflammation and atherosclerosis in individuals with N-PASC.



569 Verbal Learning and Memory in Well-Controlled HIV Is Similar to People Without HIV in Uganda

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Background: Cognitive impairment is common among people with HIV (PWH) in the United States especially in verbal learning and memory. Notably, cardiometabolic risk factors and complications and substance misuse have been associated with cognition. In Rakai, Uganda, these complications are less common in middle-aged PWH. We examined the degree to which HIV-serostatus affects learning and memory in PWH and people without HIV (PWoH) in Rakai, Uganda.

Methods: Participants enrolled through the Rakai Community Cohort Study (350 PWH; 250 PWoH) were administered a neuropsychological assessment which included the WHO–Auditory Verbal Learning Test, a list-learning task where participants are asked to recall as many words as possible across five learning trials. The test was administered in Luganda by trained research staff. For delay recall, the participant is asked to recall the original list after a 20-minute delay. Primary outcome measures include total learning across trials and total correct words recalled on the delay recall trial. Demographically-adjusted (age, sex, education) z-scores were established using data from PWoH. Impairment was defined as one standard deviation below PWoH (z-score <1). The two groups were compared using a Chi-Square Test.
Results: PWH were demographically-similar to PWoH in terms of age (44 vs. 43 years, P=.53), sex (48% vs. 54% male, P=.11), and education (6 vs. 5.8 years, P=.31). Cardiovascular and metabolic comorbidities were low in each group, including obesity (9% vs. 12%, P=.01), history of diabetes (.6% vs. 3%, P=.03) or hypertension (5% vs. 6%, P=.41), as was substance use for the study group (<2%). 94% of PWH were virally suppressed (HIV RNA <40 cp/mL) with the majority (83%) on efavirenz, lamivudine, and tenofovir. Notably, there was no difference in the proportion of impairment on total learning (PWH 14.9% vs. PWoH 15.3%, P=.89) or delayed recall (PWH 14.6% vs. PWoH 14.0%, P=.84) between the two groups.
Conclusion: PWH on long term ART with relatively few comorbidities in Uganda demonstrate a low prevalence of verbal learning or memory impairment which is similar to that of PWoH. Possibly, the level of health care for PWH in Uganda may serve as a protective factor for HIV cognitive decline however, as the Rakai cohort ages it may be at risk for developing cognitive impairment and the emergence of age-related health comorbidities.

570 Prevalence of Stigma, Depression and Anxiety in a Cohort of PLWH in Lebanon: A Cross-Sectional Study

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Background: Adherence to Antiretroviral Therapy (ART) is associated with an improved quality of life and increased life expectancy for People Living with HIV (PLWH). Moreover, compliance with treatment ensures virological success, which, in turn, leads to reduced transmission. The Middle East and North Africa (MENA) region is witnessing a rise in new HIV infections. Stigma, anxiety, and depression are prevalent among PLWH and are often linked to noncompliance with ART. However, there is a lack of research on mental health issues among PLWH in the MENA. Our study aimed to assess the prevalence of anxiety, depression, and stigma in a cohort of PLWH in Lebanon and explore potential correlations between these factors.
Methods: We conducted a cross-sectional study between June 2022 and June 2023 at a tertiary care center in Lebanon. The study included adult PLWH with an undetectable viral load for at least six months. We collected demographic and HIV-related data and used the Generalized Anxiety Disorder (GAD-7) assessment, Patient-Health Questionnaire (PHQ-9), and HIV Stigma Scale to measure anxiety, depression, and stigma, respectively. We employed statistical methods such as the Spearman correlation test, multiple regression, and descriptive analysis to characterize the cohort and examine the prevalence of and correlations between stigma, depression, and anxiety. Statistical significance was set at $p<0.05$.
Results: Our analysis included 39 participants, with the majority being males (87.5%) and single (75%). The mean age was 38±9 years, with mean GAD-7, PHQ-9, and stigma scores of 6±5.5, 6±4.7, and 25±9.5, respectively. Approximately 46.2% experienced anxiety (GAD-7 score>5), and 61.5% reported depression (PHQ-9 score>5). The Spearman test revealed a significant positive correlation between anxiety and stigma ($p<0.001$, rho=0.665), as well as between depression and stigma ($p=0.021$, rho=0.400). Notably, the correlation between anxiety and stigma remained significant even after adjusting for age (B= 4.3, p=0.033).
Conclusion: In our cohort of PLWH, we observed correlations between stigma, anxiety, and depression. Furthermore, anxiety and depression were found to be prevalent among the participants. Considering the socio-cultural context of the MENA region, there is a pressing need for more extensive studies examining the intersection of HIV and mental health. Such research is essential for the development of tailored policies and strategies aimed at mitigating the escalating epidemic in this region.

571 Plasma Inflammatory Biomarkers Link to Worse Cognition Among Africans Living With HIV

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Background: Sub-Saharan Africa (SSA) accounts for nearly two-thirds of global HIV infections. Despite access to therapy, comorbidities in the region remain prevalent, including cognitive impairment (CI). The neuropathogenesis of CI among treated people with HIV is thought to be driven by inflammation, particularly that linked to monocytes.
Methods: We characterized the relationship between inflammatory plasma biomarkers (CXCL10, CCL2, sCD163, and sCD25) and cognitive performance in a Sub-Saharan African cohort of people living with HIV and people without HIV at sites in Kenya, Nigeria, Tanzania, and Uganda (AFRICOS). All assessments were completed at the time of enrollment into the AFRICOS cohort. Neuropsychological tests included the WHO/NIMH Auditory Verbal Learning task with recall and recognition trials, Trails A, Action Fluency and the Grooved Pegboard tests. Analyses were completed using linear regression models of the mean (NPZ) summary z-score of individual tests.
Results: In all, 473 (17%) were living without HIV, 1393 (51%) were living with HIV and suppressed plasma viremia, whereas 871 (32%) had unsuppressed plasma viremia (>1000 copies/mL). Compared to controls, the group of people living with HIV was older ($p<0.001$) and less literate ($p=0.013$). We found inverse relationships (see Table)) between plasma biomarkers and cognitive performance on all measures except sCD163 in the people living with HIV, particularly in the suppressed group. Inflammation was not associated with cognitive performance among controls. The Grooved Pegboard test appeared to have the strongest associations between inflammatory markers and worse cognitive performance.
Conclusion: In the sub-Saharan African context, chronic inflammation among people living with HIV is linked to worse cognitive performance. This association persists even in those with suppressed plasma viral load. *First and second authors contributed equally

	HIV-Uninfected		HIV-Infected Suppressed		HIV-Infected Unsuppressed	
Biomarker	**Coefficient**	***p*-value**	**Coefficient**	***p*-value**	**Coefficient**	***p*-value**
CCL2	0.072	0.450	-0.146	0.015	-0.030	0.684
sCD25	-0.146	0.175	-0.241	0.001	-0.081	0.362
CXCL10	-0.039	0.691	-0.223	<0.001	-0.136	0.045*

*Significance level < .05
**Significance level < .01

572 Improving Diagnosis of Central Nervous System Infections in High-HIV Prevalence African Settings

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Background: Central nervous system infections (CNSI) account for approximately 30% of early mortality in ART programmes. The epidemiology of CNSI in high-HIV prevalence African settings is poorly understood making presumptive diagnosis and empiric treatment challenging. Patients with CNSI who do not receive a diagnosis have mortality rates of up to 40% at 10 weeks indicating the presence of serious underlying pathology that needs appropriate diagnosis to guide effective treatment.
Methods: Enhanced diagnostic packages were introduced into routine CSF analysis at Princess Marina Hospital, Gaborone, Botswana in June 2021 and Parirenyatwa Hospital, Harare, Zimbabwe in October 2022. BioFIRE FilmArray-Meningitis/Encephalitis (FilmArray-ME) & Xpert MTB/RIF Ultra were performed on all samples and results returned to clinicians in real-time. Retrospective analysis was performed on stored samples with Toxoplasma gondii PCR &

rapid plasma reagin, Treponema pallidum particle agglutination assay, and metagenomic sequencing.

Results: Sequential CSF samples from 465 people living with HIV with suspected CNSI underwent analysis with FilmArray-ME and 454 had analysis with Xpert MTB/RIF Ultra. The median age of study participants was 40 (IQR 34-48), 54.4% were male, and the median CD4 count was 114 cells/μL (IQR 43-325); 49.0% (220/465) were established on ART the remainder were either ART naïve or had cycled out of treatment services. Through routine CSF analysis alone there were 99 microbiologically confirmed CNSIs; with the addition of enhanced diagnostics this increased to 155 (Figure 1), a relative increase of 57%. Detection of Mycobacterium tuberculosis, T. gondii and viral pathogens was only achieved through the addition of enhanced diagnostics. Cryptococcal meningitis was the most commonly diagnosed CNSI in 97/465 patients with 92/97 diagnoses made through cryptococcal antigen (CrAg) testing or India ink, figure 1. Restricting analysis to CrAg negative patients, only 11 CNSI diagnoses were made through routine analysis compared to 62 diagnoses made with the addition of enhanced diagnostics, a relative increase of 464%.

Conclusion: Enhanced diagnostic platforms substantially increased diagnostic yield in patients with suspected CNSI in Botswana and Zimbabwe. There was significant variation between population groups suggesting targeted use may be possible. The most clinically and cost-effective diagnostic algorithms need to be defined.

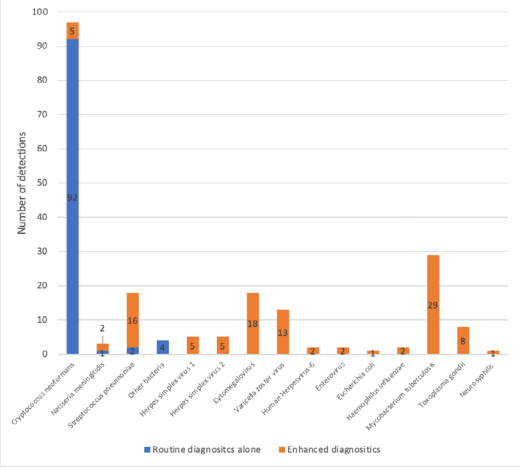

Figure 1 *Potential CNSI pathogens detected through routine and enhanced testing at Princess Marina Hospital, Gaborone and Parirenyatwa Hospital, Harare.*

573 Mental Health Phenotypes of Well-Controlled HIV in Uganda

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Background: HIV and mental health (MH) disorders, particularly depression, anxiety, and post-traumatic stress disorder (PTSD), are among the top 10 causes of disability among people with HIV (PWH) in Uganda. Most studies of PWH have focused on MH disorders as unidimensional constructs. However, the phenotypic expression and clinical course of MH conditions among PWH in Uganda and worldwide are heterogeneous. Accordingly, there has been a shift towards identifying MH phenotypes using data driven methods capable of identifying novel insights into mechanisms of divergent MH phenotypes among PWH. We leverage the analytic strengths of machine learning combined with inferential methods to identify novel MH phenotypes among PWH and the underlying explanatory features, with a particular interest in early life stress (ELS) as a determinant of MH phenotypes.

Methods: 277 PWH (46% female, median age=44; 93% undetectable viral load [<50copies/mL]) were included in the analyses. Participants were enrolled in an observational community-based cohort residing in the Rakai region of Uganda. Participants completed the Patient Health Questionnaire (PHQ-9), Beck Anxiety Inventory (BAI), and the PTSD Checklist-Civilian (PCL-C). Hierarchical clustering was used to identify MH subtypes using total symptom scores on the questionnaires. Inferential statistics (with false discovery rate) compared demographic and clinical factors between clusters (e.g., ELS).

Results: We identified four MH phenotypes (Fig. 1). Cluster 1 (n=76; PTSD phenotype) endorsed clinically significant PTSD symptoms, with an average PCL-C total score >33. Clusters 2 (n=32; anxiety phenotype) and 3 (n=130; mixed anxiety/depression phenotype) reported minimal PTSD symptoms, with modest BAI (Cluster 2) and PHQ-9 (Cluster 3) elevations. Cluster 4 (n=39; normative MH phenotype) reported no clinical MH symptom elevations. Comparisons of explanatory factors between MH phenotypes revealed a modestly higher rate of physical (14.5% vs. 5.1%; P=0.13) and sexual (27.6% vs. 12.8%; P=0.07) abuse among the PTSD phenotype (Cluster 1) vs. the normative MH phenotype (Cluster 4).

Conclusion: We identified unique MH phenotypes among PWH and confirmed the importance of ELS, particularly sexual abuse, as an early risk determinant for unfavorable MH among PWH in adulthood. Notably, PWH in the normative MH phenotype also reported a history of sexual abuse, consistent with resilience. Follow-up analyses will investigate these groups to further examine mechanisms of risk vs resi.

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574 Asymptomatic CSF HIV-1 Escape: Incidence and Effects on CNS Biomarkers

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Background: Elevated levels of HIV RNA can occasionally be detected in cerebrospinal fluid (CSF) despite viral suppression in plasma by antiretroviral therapy (ART), a condition termed CSF HIV-1 escape (CSF-E). In rare cases CSF-E is associated with clinical neurological disease (symptomatic CSF-E) but more commonly, no neurological symptoms are evident (asymptomatic CSF-E). Previous studies on asymptomatic CSF-E have been limited in size, leaving its incidence and clinical relevance unclear. Our objectives were to determine the incidence of CSF-E in a large, well-characterized Swedish cohort of people with HIV (PWH), and to evaluate its impact on biomarkers indicative of CNS inflammation and injury.

Methods: We retrospectively included neuroasymtomatic PWH from a longitudinal cohort who had been successfully treated with ART for >6 months (plasma HIV RNA <50 copies/mL prior to inclusion) and had undergone CSF examinations for research purposes between 2016–2022. CSF-E was defined as either increased CSF HIV RNA with concurrent plasma suppression or as CSF HIV RNA exceeding that in plasma when both were detectable. HIV RNA, neopterin, neurofilament light protein (NfL) and albumin ratio were analyzed in paired CSF and plasma samples.

Results: In total, 452 samples from 174 PWH (65% male) were included. Mean number of samples per participant was 2.6 (range 1–7) where ≥2 samples were collected from 115 PWH. CSF-E was present in 15/174 PWH (8.6%) with a median (interquartile range, IQR) CSF HIV RNA of 34 (26–52) copies/mL. Of 452 samples, CSF-E was present in 4% (1% with the cut-off ≥50 copies/mL) and 13% had detectable HIV RNA in plasma (3% with the cut-off ≥50 copies/mL). One individual had ≥2 consecutive samples with an isolated increase in CSF HIV RNA but remained clinically stable and did not require any treatment adjustment. None of the PWH with CSF-E developed subsequent viral failure (defined as a single plasma viral load >500 copies/mL or two consecutive samples ≥50 copies/mL drawn >6 weeks apart). CSF HIV RNA levels were weakly, but significantly, correlated with CSF neopterin concentrations ($r = 0.21$, $p < 0.001$). No significant association was found between increased CSF viral load and elevated levels of either CSF NfL or albumin ratio.

Conclusion: In this cohort, CSF-E was rare and usually resolved without treatment adjustments. A weak association exists between CSF-E and intrathecal immune activation, but no correlations were found with biomarkers of neuronal or blood-brain barrier damage.

575 HIV-1 Infection and Alzheimer's Disease Pathobiology in a Novel Humanized APP-Knock in Mouse Model

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Background: The prevalence of aged-associated Alzheimer's-like disease is increasing in people living with HIV. Disease mechanisms are linked to interactions between progressive HIV infection, neuroinflammation, CD4+ T cell depletion, and aggregation of misfolded proteins. Sustained viral replication in the brain and immune dysfunction accelerates neuroinflammation. Simultaneous HIV and Alzheimer's disease (AD)studies have been limited due to the lack of appropriate animal models. A relevant animal model would require human microglia and a robust adaptive immune system in an immune-deficient background amenable to human cell reconstitution.
Methods: We created a novel humanized AD mouse using CRISPR-Cas9 technology to address the need for an appropriate animal model to study HIV and AD simultaneously. This was accomplished by knocking in (KI) human APPKM670,671NL, PS1M146V, or MAPTP301S in an immunodeficient NOG mouse (Fig 1A). The APP-KI mice were crossed with NOG/hIL34 [NOG/Tg (CMV-IL34], supporting the development of human microglia. This allows the reconstitution of a human innate and adaptive immune system in the brain and periphery (APP/NOG/hIL34 mice). APP-KI/NOG/hIL34 mice were reconstituted with human hematopoietic progenitor cells to evaluate progressive HIV-1 infection. Four-month-old, humanized mice were infected with a macrophage-tropic HIV-1ADA at a tissue culture infectious dose ($TCID_{50}$) of 10e4/mice. Mice were sacrificed at four and eight weeks after viral infection.
Results: After four weeks of infection, plasma viral load demonstrated productive HIV-1 infection with an average of plasma HIV-1 RNA levels of 8.96E+03 at 2 weeks and 2.82E+05 at 8 weeks after infection. HIV-1p24 was readily detected in the brain (Fig 1B). After four weeks, the insoluble amyloid burden in HIV-1 -infected mice was markedly increased compared to uninfected controls as determined by amyloid-beta42 (Aβ42) ELISA (Fig 1C). Immunofluorescence staining revealed co-localization of Aβ fibrils and human IBA1+ microglia. Similarly, IHC staining of the brain showed more reactive microglia in the HIV-infected mice compared to the control mice.
Conclusion: We observed that HIV-1 infection accelerates AD pathology by increasing Aβ accumulation. Our results highlight, for the first time, the utility of this humanized CRISPR AD mouse model for evaluating the interconnections between progressive HIV infection and AD pathobiology.

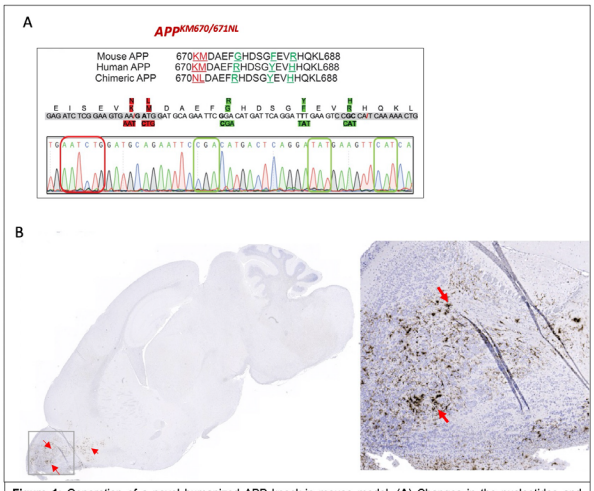

Figure 1: Generation of a novel humanized APP knock-in mouse model. (**A**) Changes in the nucleotides and corresponding amino acid sequences to confirm the replacement of pathological (red) and humanized (green) nucleotides in mouse APP. **(B)** Detection of HIV-1 P24 in the brain section (left) and enlarged olfactory bulb (right).

576 Increased mtDNA Level in Neuron-Derived Extracellular Vesicles in African Americans With HIV

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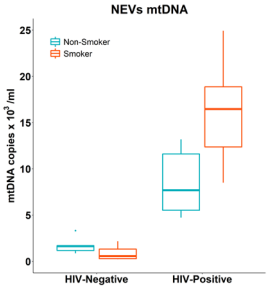
Background: HIV-associated neurocognitive disorders (HAND) remain common among people with HIV (PWH). Cigarette smoking induces mitochondrial damage and is more prevalent among PWH. Mitochondrial DNA (mtDNA) content reduction often occurs before neuronal degeneration. Our objective was to determine the effect of smoking on mtDNA content in neuron-derived extracellular vesicles (NEVs) isolated from the peripheral blood of African Americans (AAs), according to smoking and HIV status. We hypothesized that smoking exacerbates neuronal mtDNA damage in virally suppressed AA PWH, leading to increased release of mtDNA in NEVs.
Methods: Twenty-four AA men, aged 45-64, were recruited from Meharry outpatient clinics: HIV-negative non-smokers (NNS), HIV-negative smokers (NS), HIV-positive non-smokers (PNS), and HIV-positive smokers (PS). HIV-positive participants had plasma RNA ≤20 copies/ml. Blood plasma was obtained by centrifugation, and the total pool of EVs was isolated from 3 ml of plasma by ultracentrifugation. NEVs expressing neuron specific L1CAM antigen were isolated from a total pool of EVs. mtDNA content in NEVs was analyzed by qPCR using primer sets that amplify mtDNA's unique region (D-loop). The copy number of mtDNA amplicons was quantitated using a standard curve. Welch's One-way ANOVA was applied to determine differences in mean mtDNA content and multiple comparisons done with Games-Howell test, which considers heteroscedasticity. We used multiple linear regression and tested for interaction to determine the association between HIV and mtDNA content, adjusting for smoking status.
Results: NEVs mtDNA content were heteroscedastic (P-Value < 0.001). We found significant pairwise differences among NEVs mtDNA groups: between NNS and PNS (P-Value = 0.022), NS and PNS (P-Value = 0.014), NNS and PS (P-Value = 0.006), and NS and PS (P-Value = 0.005). Smoking did not significantly contribute to the linear model. Significance was found in HIV status (P-Value = 0.006) and the interaction term between HIV and smoking status (P-Value = 0.011).
Conclusion: We found a significant increase in mtDNA level in NEVs of AA PWH compared to HIV-negative counterparts. Smoking increased mtDNA levels in NEVs from AA PWH compared to non-smokers. mtDNA content in NEVs represents a potential biomarker for mitochondrial dysfunction that may precede neuronal damage in virally suppressed AA PWH.



577 Cerebrospinal Fluid NfL Decreases After Initiation of ART, but Slower Than Inflammatory Biomarkers

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Background: Persistent intrathecal immune activation and signs of neuronal disturbances are present in many HIV-infected individuals despite effective antiretroviral treatment (ART). We have studied the decay characteristics of neurofilament light (NfL) protein, a marker of neuronal injury, in cerebrospinal fluid (CSF) after initiation of ART in a large cohort of HIV-infected individuals.
Methods: In this longitudinal study, we assessed the levels of NfL, and a panel of neuroinflammatory biomarkers, including YKL-40, sTREM-2, neopterin and GFAp, in consecutive archived CSF samples from 99 people with HIV (PWH) who had achieved viral suppression. Participants were followed from before treatment initiation and up to at least one year on ART. Comparison of means was performed using t-test and partial correlations were calculated adjusting for age.

Results: Twenty-five percent of the study participants had CSF NfL levels above normal reference limits prior to initiation of ART. Following 12 months of ART, a significant reduction in mean NfL levels was observed (-27 %, $p < 0.005$); however, no significant decline was noted after three months of treatment (-12 %, $p > 0.05$). No further change in NfL levels was observed after 24 or 36 months of ART. CSF levels of YKL-40, sTREM2 and neopterin significantly declined after both 3 and 12 months while GFAp did not decline significantly at neither 3 nor 12 months. Notably, strong correlations were observed between all evaluated biomarkers at baseline and all except neopterin at 12 months.
Conclusion: The decrease of NfL as well as biomarkers of immune activation suggests that ART significantly reduces axonal injury as well as neuroinflammation within one year of treatment initiation. The significant decrease of inflammatory biomarkers, but not NfL, after three months indicate that reduction of neuroinflammation precedes reduction of neuronal harm.

578 Protein Modifications by Lactate Associate With Lower Risks of Neurocognitive Impairment and Death

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Background: In response to diverse infections, macrophages shift their main metabolism from oxidative phosphorylation to aerobic glycolysis, with lactate as the end-product. Ensuing increases in glycolytic flux promote the production of advanced glycation end products (AGEs), reactive glucose metabolites that alter protein function via non enzymatic, post-translational modifications (PTMs). These PTMs can modify cellular metabolism and they associate with adverse clinical outcomes. Lysine (Lys) lactoylation is a PTM that is derived from the transfer of a lactate moiety from the glyoxalase cycle intermediate, lactoylglutathione (LGSH), to a free Lys residue (hence 'lactoyl Lys'). These modifications are elevated during periods of increased glycolytic flux. In human cell cultures, this PTM was recently shown to inhibit glycolysis by disproportionally affecting glycolytic enzymes. We hypothesized that metabolic reprogramming from HIV-1 infection induces similar PTMs that contribute to enhanced AGEs-associated morbidities. Herein, we examined associations by plasma concentrations of selected AGEs and glutathione species with incident neurocognitive impairment (NCI) and all-cause mortality.
Methods: Plasma concentrations of 12 AGEs and 3 glutathione species were assayed by liquid chromatography–mass spectrometry, in stored specimens collected at entry from 376 randomly selected participants of a prospective AIDS Clinical Trials Group cohort of PWH (HAILO). Cox PH models explored associations with clinical outcomes, adjusted for possible confounders. Cognition was assessed by Trailmaking A&B, Digit Symbol and Hopkins Verbal Learning tests at entry and every 48 wks.
Results: Among 376 participants, with a mean f/u of 244 wks, there were 10 deaths and 104 incident NCI cases. Higher LGSH concentrations associated with a lower hazard of NCI [aHR 0.80; 0.65-0.99] while higher lactoyl Lys protein concentrations associated with lower hazard of both NCI [aHR 0.74; 0.58-0.96] and death [aHR 0.29; 0.09-0.93].
Conclusion: The observed protective associations by LGSH and lactoly Lys proteins may represent a counter-regulatory response to the adverse effects of enhanced glycolysis, supporting a possible role by metabolic reprograming to the enhanced NCI and mortality risks of PWH. Future studies within this nested cohort will examine associations by AGEs with additional comorbidities.

579 Tryptophan and Kynurenine Pathway Activation and Cognition in Virally-Suppressed Women With HIV

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Background: Dysregulated immune function and cognitive complications persist in people with HIV (PWH) despite viral suppression. Inflammatory cytokines and HIV proteins induce the enzyme IDO (indoleamine 2, 3-dioxygenase) to convert tryptophan (T) to kynurenine (K) while producing reactive oxygen species and downstream neurotoxic metabolites, which may lead to cognitive complications. Using the KT ratio as a surrogate marker, we investigated the relationship between IDO activation and cognition in virally suppressed women with HIV (VS-WWH) and women without HIV (WWoH).
Methods: 99 VS-WWH on stable antiretroviral therapy (median age = 54, 73% Black) and 102 (median age = 52, 75% Black) demographically similar WWoH from Chicago and New York sites of the Women's Interagency HIV Study (WIHS) completed a neuropsychological test battery assessing motor function, processing speed, attention/working memory, verbal fluency, verbal learning and memory, and executive function. Plasma tryptophan and kynurenine were measured using liquid chromatography-tandem mass spectrometry, and targeted plasma monocyte-derived (sCD163, sCD14, MCP-1/CCL2) and general inflammatory markers (TNFR-II, hsCRP, hsIL-6) were measured using enzyme-linked immunosorbent assay (ELISA).
Results: VS-WWH had a higher KT ratio ($P<0.01$) and higher sCD14 levels ($P<0.05$) compared to WWoH. In false discovery rate-corrected multivariable regression analyses, higher KT ratio was related to worse motor function in VS-WWH ($r = -0.33$, $P<0.05$). This relationship was independent of inflammatory markers. No relationship between IDO activation and motor function was observed in the WWoH.
Conclusion: IDO activation was associated with worse fine motor control in VS-WWH independent of measures of systemic inflammation. Further studies are required to investigate the biological mechanisms linking IDO activation to cognitive complications including poor fine motor function among PWH, despite having well-treated HIV.

580 Impact of Recombination on HIV-1 Evolutionary Dynamics in CSF and Plasma

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Background: HIV-1 is capable of establishing distinct viral populations within CNS, leading to a spectrum of neuronal complications. An improved understanding of HIV-1 evolutionary dynamics across the CNS and plasma is necessary to inform vaccine and cure efforts and longitudinal assessments are lacking.
Methods: We used single genome amplification to generate full-length HIV-1 env (>2.5Kb) clade B variants from the paired CSF and plasma of 13 chronically infected individuals living with HIV from the CHARTER cohort with no neurocognitive impairment (N=6) and asymptomatic or mild neurocognitive disease (N=7). Participants were viremic and either treatment naïve (N=6) or experienced (N=7). Each participant contributed viral samples from two time points separated by 6 to 48 months. We used phylogenetic analysis to determine viral compartmentalization and genetic divergence. Recombination was detected using both RDP and ClonalFrameML packages. dN/dS analysis was conducted in DnaSP6 software to assess selection force. BEAST software was used to estimate env DNA substitution rate.
Results: We analyzed 1300 confirmed single genome sequences. Compartmentalization between CSF and plasma was observed in 11 out of 13 participants in at least one of two time points. In analyses of combined time-points, plasma-derived variants showed higher sequence diversity (0.0302 vs 0.0247 in average nucleotide difference, p=0.016), divergence from the origin (0.0830 vs 0.0639 substitutions/site, p=0.041), recombinant frequency (0.147

vs 0.107/seq, p=0.046), and nucleotide substitution rate (5.53e-3 vs 1.07e-2 sub/site/year, p=0.017) when compared to those from paired CSF. Pervasive recombination was observed across env in plasma-derived variants. The ratio of recombination to point mutation (ρ/θ) was estimated to be 13.86±0.78. The ratio of nonsynonymous to synonymous substitution rate (dN/dS) was estimated to be 0.667±0.042 and 0.813± 0.044 in CSF and plasma subgroups, respectively, indicating stronger positive selection on env in plasma compared to CSF (p=0.001).
Conclusion: These findings revealed distinct intra-participant HIV-1 evolutionary dynamics between the CSF and plasma and suggest stronger immune selection on HIV-1 env in the peripheral blood than in the CSF. They also suggest that on average, recombination plays a larger role in HIV-1 env diversification in the plasma than in the CSF, and is the main driver of viral adaptive evolution in the plasma in this cohort with high rates of compartmentalized virus.

581 Effects of Recent Air Pollution Exposure on Cognition, Inflammation, and Neurodegeneration in HIV

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Background: Ambient air pollution, even within permissible levels, has been associated with greater risk of illness and mortality in the general population. People with HIV (PWH) may be more vulnerable to worsening climate- and pollution-associated outcomes. This study examined the association among common air pollutants on cognition and plasma biomarkers of inflammation and neurodegeneration in a cohort of community-dwelling PWH in the greater St. Louis, Missouri region.
Methods: 277 PWH (43% female) and 107 people without HIV (PWoH) (26% female) from the St. Louis region completed a comprehensive cognitive battery and a blood draw. Participant addresses were used to determine census tract-based location. Spatial interpolation was applied to publicly available EPA pollution monitoring data to calculate average exposure to pollutants (fine particulate matter (PM) 2.5, PM10, ozone, lead (Pb)) in the week prior to study visit. Average PM2.5 exposure over the past calendar year was also available for a subset of participants, using NASA satellite data. Pollution data were compared with cognition and plasma markers (sCD14, sCD163, CD14CD16 monocytes, neurofilament light protein (NfL), glial fibrillary acidic protein (GFAP)) using regression models.
Results: PWH and PWoH did not differ with regards to recent air pollutant exposure. Higher recent exposures to PM2.5, PM10, and Pb were associated with worse learning, delayed recall, executive functioning, and global cognition in both groups (p-values <.05). Within PWH, higher year's average PM2.5 exposure was associated with worse learning (p=.01), delayed recall (p=.02), executive functioning (p=.004), and global cognition (p<.001). Higher levels of plasma sCD163 and sCD14 positively associated with recent ozone exposure and PM2.5 in PWH (p-values <.05). Lower percentages of classical monocytes, and corresponding higher percentages of non-classical monocytes, were associated with higher PM2.5 in PWH (p=.001). Higher PM10 and ozone exposure was associated with higher NfL and GFAP in both groups (p-values <.01).
Conclusion: Recent exposures to common air pollutants were associated with poorer outcomes in cognition, inflammatory markers and monocytes, and markers of neurodegeneration in PWoH and PWH. Increases in ambient air pollution may trigger an immune response, particularly in PWH, that then may contribute to neurodegeneration and worse cognitive performance. However, longitudinal studies of air pollution with regards to these measures are needed in PWH.

582 Higher Mitochondrial DNA (mtDNA) Heteroplasmy Burden Associates With Depression in People With HIV

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Background: Depression is extremely common in people with HIV (PWH) and may involve immunometabolic dysfunction via mTOR hyperactivation. We tested the hypotheses that PWH acquire somatic mtDNA variants (linked to mitochondrial dysfunction) faster than people without HIV (PWOH) and that depression in PWH is associated with a higher burden of heteroplasmy (HP) (number of mtDNA loci with ≥2 somatic variants) across the mtDNA genome.
Methods: We performed Illumina deep mtDNA sequencing on genomic DNA sampled at 2 visits 10 years apart in 92 PWH and 37 PWOH from San Diego-based observational studies (mean coverage depth 3000X). Participants underwent serial neuromedical, mental health (Beck Depression Inventory-II, BDI-II), and comprehensive cognitive assessments. A BDI-II score and cognitive, apathy, affective and somatic depressive symptom scores were obtained; demographically adjusted cognitive T-scores were converted to domain deficit scores (DDS). Plasma MCP-1 was measured by immunoassay. Raw reads were mapped to revised Cambridge Reference Sequence, and HP was called at the 1-99% threshold using the GATK Mutect2 pipeline. Change in mtDNA HP burden at 10 years was compared by HIV status, adjusting for influential covariates (univariate p<0.05). Associations of HP burden at 10 years with BDI-II scores or depression (BDI-II score ≥14) were tested in backward-elimination Poisson regression models, using the Akaike Information Criterion.
Results: PWH (mean age 44, 11% female, 60% aviremic, 26% depressed) had higher plasma MCP-1 and more prevalent substance use than PWOH (mean age 45, 23% female). PWH did not acquire higher HP burdens over 10 years than PWOH (adjusted beta -2.75, p=0.337 for PWH). Higher mtDNA HP at 10 years associated with more depression (adjusted beta 0.320, p<0.001), and a higher BDI-II score (beta 0.014, p<0.001, adjusting for age, sex, race, mean coverage, HIV status, hemoglobin, smoking, plasma MCP-1, substance use, tenofovir alafenamide use, ±global cognitive impairment (DDS>0.5)), with similar results in PWH. In PWH, higher HP burden was also associated with higher BDI-II-based cognitive, apathy, affective, and somatic depressive symptom scores (adjusted betas 0.024-0.056, all p-values ≤0.01).
Conclusion: PWH do not accumulate HP across the mtDNA genome faster than PWOH over a decade, but higher overall mtDNA HP burden may confer increased risk for depressive symptoms and depression, regardless of HIV status. Future studies should define the mechanisms for these associations.

583 Sociodemographics Were Stronger Classifiers of Cognitive Profiles Than Neuroimaging in HIV

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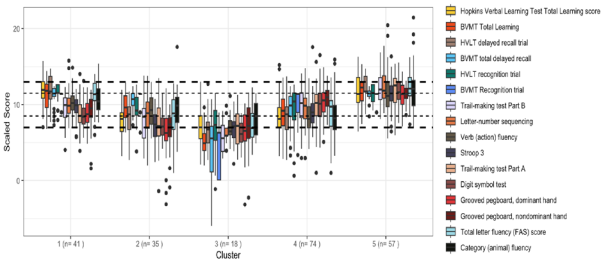
Background: Despite advancements in antiretroviral therapy, cognitive issues persist in some people with HIV (PWH) and are heterogeneous in nature. Recent research has focused on identifying cognitive profiles present in PWH and identifying factors that distinguish between these profiles; however, neuroimaging metrics of brain structure and function are rarely incorporated into these analyses.
Methods: We identified cognitive profiles among 225 PWH (mean age=51; 21% female, 67% African American/Black; mean years of education=13.3) from a single site (Washington University in St. Louis). Participants completed a standard neuropsychological test (NP) battery of 10 tests (16 outcomes) and magnetic resonance imaging (MRI), including structural MRI to measure regional volumes and resting-state functional MRI to assess brain connectivity. Raw NP test scores were converted to scaled scores and then Kohonen self-organizing maps were used to classify individuals with similar cognitive profiles. Socio-demographic features (including age, race, education, premorbid IQ (WRAT-3), and area deprivation index), HIV clinical factors (nadir and recent CD4 count, recent CD8 count, CD4/CD8 ratio, viral load), hepatitis C co-infection, depression, early life stress, brain volumes, and intra-network resting state values were compared between profiles using random forest models. Distinguishing variables were considered significant at P<0.001.
Results: Five cognitive profiles were identified: 1) strength in learning and memory (n=41; 18%), 2) weakness in motor and processing speed (n=35; 15%), 3) impaired globally (n=18; 8%), 4) average globally (n=74; 33%-referent group), and 5) strong globally (n=57; 25%)(Figure 1). Compared to profile 4, profile 1 (relative strength in learning and memory) had a higher premorbid IQ; profile 3 (impaired globally) was older, less educated, and had a lower premorbid IQ; and profile 5 (strong globally) was more highly educated, had a higher premorbid IQ, and was less likely to be Black. Although several

neuroimaging features distinguished profiles at P<.01, none reached the P<0.001 threshold.

Conclusion: Socio-demographic features, not clinical or neurologic features, distinguished cognitive profiles. Future studies are needed that incorporate additional neuroimaging methods that may be more sensitive to subtle changes in brain integrity that can impact cognition in order to evaluate their importance in distinguishing cognitive profiles.



584 MRI With T2 Maps and Spectroscopy Show Chronic Progressive Brain Damage Despite HIV Suppression

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Background: We used a 20-minute absolute single-voxel proton magnetic resonance spectroscopy (MRS) scan with relaxometry (T1 and T2 maps) to better quantify water as a reference for major brain metabolites in virally suppressed people living with HIV (PWH) who are aging and were assessed for HIV immune markers and cognitive functions.

Methods: 39 PWH, all male (mean age: 53 ± 14, 60+ years old: 35%, HIV duration: 18 years, 20% nadir CD4 <200 cp/mL) were enrolled into a prospective study investigating brain metabolites during long-term viral suppression. They completed a baseline and a two-year follow-up clinical visit for HIV biomarkers (CD4 and CD8 count, nadir CD4, HIV duration), a neuropsychological assessment, a structural brain MRI scan, and a 20-minute single-voxel MRS in the frontal white matter, right caudate, and posterior cingulate with whole brain T1 and T2 mapping to derive the absolute concentration of major brain metabolites. MRS data were fitted with the spant R package and scaled using partial volumes (derived from Freesurfer and FSL MRS tools structural volumes). Mixed effect models assessed associations and longitudinal changes to T1, T2, and metabolite concentrations with age, baseline HIV biomarkers, and HIV-associated cognitive disorder (HAND).

Results: Higher T2, but not T1 values, increased with age in white and grey matter ($p < 0.002$). HAND was associated with higher T2 values over time ($p < 0.03$). Older adults with HAND had higher T2 values than older adults without HAND ($p < 0.04$). Myo-Inositol concentration increased in all brain regions as a function of increased age ($p < 0.01$). There was a significant age-by-nadir CD4 interaction in frontal white matter for myo-Inositol ($p < 0.001$). Lower baseline CD4+ cell count and HAND were associated with lower glutamate in the cingulate ($p = 0.04$) and caudate ($p = 0.003$) of older participants, respectively.

Conclusion: Our results confirm and expand the evidence for chronic and slowly progressive structural and neurometabolic abnormalities including age-related loss of brain tissue density, age and HAND-related inflammation/glial activation, legacy-related (nadir CD4) inflammation/glial activation, but also age, current immune function (baseline CD4) and HAND related excitotoxicity in the cortex and basal ganglia. Our 20-minute absolute concentration MRI/S scan may be clinically scalable to monitor HAND stability or progression in virally suppressed PWH who are aging.

585 Functional Brain Network Changes Among People With HIV and Viral Suppression

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Background: The functional connectivity of global brain networks, quantified using graph theory metrics, provide insights into the efficiency and other characteristics of brain network functioning at a whole brain level. Such metrics are widely studied in numerous neurological and psychiatric conditions under a variety of task demands but have not yet been evaluated in virally-suppresesed people with HIV (VS-PWH). Here we examined global brain network organization in virally-suppressed people with HIV under three functional MRI conditions including resting state MRI (rsfMRI) and the performance of verbal memory and go/no-go tasks.

Methods: A total of 56 participants (69.6% VS-PWH; 51.7% female, 69.6% black) completed the MRI session and performed a battery of cognitive tests using the iPad-based platform Brain-Baseline Assessment of Cognition and Everyday Functioning. Graph theory metrics of the global functional brain network were computed in the weighted positive network, determined by positive correlations in the BOLD activity, to yield assortativity, characteristic path length (CPL), clustering coefficient (CC), global efficiency (GE), modularity (Q), and average node strength (ANS). Multiple regressions were performed to determine serostatus effects and associations with cognitive performance, adjusting for sex, age, race, ethnicity and education.

Results: In resting state, compared to controls, VS-PWH showed lower CC (p=.03), GE (p=.02), and ANS (p=.02) and higher CPL (p=.04) and Q (p=.04). In the verbal memory task, compared to controls, VS-PLWH also showed lower CC (p=.01), GE (p=.02), and ANS (p=.01) and higher CPL (p=.04) and Q (p=.005). No HIV-serostatus effects were observed in the go/no-go task. In the total sample, there were significant associations of CPL, CC, GE, and ANS with processing speed (reaction time on flanker, Stroop, Trail Making, and fine motor skills task), working memory (accuracy on n-back) and visual spatial learning test (total correct across trials).

Conclusion: During both the resting state and performance of a verbal memory task, VS-PLWH show less efficiently organized network structure (GE), less small-world network structure (CC, CPL), and less distributed connectivity (Q and ANS). These metrics relate to a number of cognitive processes including processing speed, working memory, and visual spatial learning. Here we show graph theory metrics may serve as biomarker for VS-PLWH to monitor disease progress and to evaluate new therapeutics.

586 HIV Status and APOE4 Differentially Impact White Matter Integrity in Adults With HIV

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Background: The median age of people with HIV (PWH) in USA is now over 50. This aging HIV+ population is facing increasingly significant risk of other neurodegenerative diseases-in addition to HIV brain disease-especially Alzheimer's disease. We investigated the potential impact of HIV-disease, APOE4 (E4), and their interactions on white matter (WM) microstructure in a cohort of middle-aged to older PWH.

Methods: Seventy-six adults (44-69 y.o. (56.4±6.3), 24 female, 58 PWH) participated in this study. All diffusion weighted images were preprocessed in FSL then analyzed using the automated fiber quantification (AFQ) software in Python. AFQ produced fractional anisotropy (FA) and mean diffusivity (MD) values at each of 100 equidistant nodes along each of 22 major WM bundles. We analyzed group differences along each tract for both FA and MD using pointwise t-tests with FDR correction to investigate the impact of HIV and E4 status on FA and MD values. Significant regions of group differences were defined by pFDR<0.05 with at least two adjacent nodes. Region-of-interest (ROI) based analyses were conducted on these significant regions to investigate the interactions between age, E4, and HIV-disease.

Results: Compared to controls, PWH showed trends of increased MD along all 22 bundles, with significant regions of group differences along the left inferior frontal occipital (Fig. A) and left uncinate tracts. ROI-based analyses revealed significant interactions between HIV-status and age in all these regions (at least p<.004), with a steeper age-related increase in MD in PWH. Across PWH and controls, E4 carriers had significantly reduced FA in multiple regions of the left arcuate fasciculus versus non-carriers (Fig. B). In PWH, the E4 effect remained significant (p<.001), and importantly, ROI-based analyses revealed significant interactions between E4 status and HIV disease duration in most of these regions, with a steeper disease duration-related decline in FA in PWH E4 carriers (after controlling for age, ps<.045).

Conclusion: HIV and APOE4 differentially impact white matter microstructure in middle-aged to older adults with HIV. Specifically, HIV-disease is associated

with wide-spread increases in MD, and older PWH are disproportionally affected. By contrast, E4-associated FA reduction is more localized, and PWH E4 carriers with long disease duration are at a greater risk. These findings warrant further examination of more localized WM changes along individual tracts in the rapidly aging HIV+ population.

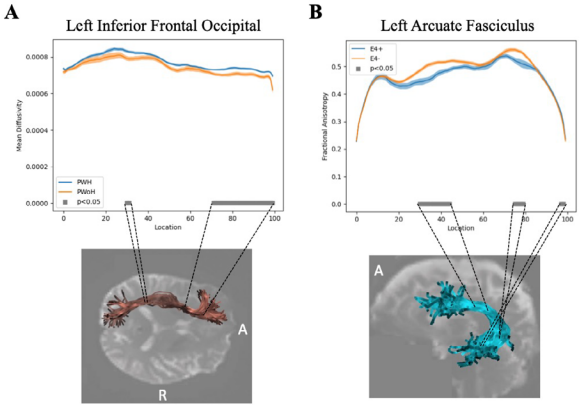

Figure. Tract profiles (top) with significant group differences ($p<0.05$, FDR corrected) in gray. Lines represent group mean values (MD on left, FA on right; ± SEM). Corresponding anatomical locations exemplified in bottom.

587 HIV Clinical Factors and Cardiovascular Disease Risk Predict White Matter Hyperintensity Burden

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Background: Cardiovascular disease (CVD) risk factors such as hypertension are highly prevalent in people with HIV (PWH) and have been shown to affect brain function and structure, including an elevated risk of white matter hyperintensity (WMH), a measure of small vessel disease. We investigated the factors associated with WMH burden (measured as total WMH volume, or WMHv) in adults with chronic HIV disease, focusing on CVD risk and HIV-clinical factors.

Methods: Participants were 134 adults (age range 40-70, 34 females, 82 African American, 97 PWH). CVD percent risk was calculated using the Framingham General Cardiovascular Risk Profile, including age, BMI, SBP status and treatment, smoking status, and diabetes status. High-resolution T1w structural MRI images (1x1x1mm^3) were acquired. The software package CAT12 (https://neuro-jena.github.io/cat/) was used to detect WMHs and obtain WMHv and gray matter volume (GMv). The effects of HIV status, age, sex, race, education, and CVD percent risk on WMH burden were examined using non-parametric ANCOVA. For PWH, potential impacts of CD4 nadir, current CD4/CD8 ratio, and disease duration on total WMHv were examined using non-parametric regressions separately for each clinical factor. Parametric multiple linear regressions investigated the effects of WMHv, HIV status, age, sex, race, education, and HIV clinical factors on total GMv. Total WMHv and GMv were normalized by intracranial volume.

Results: In the full study sample, higher CVD percent risk, older age, and African American race strongly predicted higher WMHv (at least p=.001), versus a marginal effect of education (p=.049) and HIV status (p=.057), while higher WMHv, male sex, and older age were associated with lower GMv (at least p=.001). In PWH, in addition to CVD percent risk, age, and race, lower CD4/CD8 ratio (p=.016) and longer HIV disease duration (p=.002) also strongly predicted higher WMHv.

Conclusion: Consistent with previous findings, WMH is prevalent in middle-aged to older PWH on cART and with successful viral suppression, and WMH burden strongly correlates with CVD risk and age. In addition, WMH burden correlates with current CD4/CD8 ratio and HIV disease duration, suggesting the need to improve immune function, control chronic neuroinflammation, and develop antiretroviral regimens that are less toxic to the CNS. Also, the significantly higher WMH burden in African Americans with and without HIV calls for actions to address health disparities.

588 Neurite Orientation Dispersion and Density Imaging in People With HIV on Stable Treatment

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Background: Neurite Orientation Dispersion and Density Imaging (NODDI) is a multi-compartmental diffusion MRI technique that characterizes brain microstructures by quantifying the packing density of axons or dendrites (neurite density index, NDI), the orientational coherence of neurites (orientation dispersion index, ODI) and the free water fraction (isotropic compartment, ISO). This preliminary study compares NODDI metrics cross-sectionally between virally suppressed people with HIV (PWH, plasma HIV RNA <20 cps/ml, median duration of treatment: 22 years) and people without HIV (PWOH), and longitudinally in the PWH group over a median duration of 32 months.

Methods: Eight PWH (age: 56 [IQR 53,59], 8/8 male) and eight PWOH (age: 57 [IQR 53,62], 3/8 male) underwent NODDI scans in a 3T Siemens Prisma scanner, employing a two-shell diffusion protocol tailored for NODDI (32,64 direction; b=700,2000 s/mm^2; 80 slices; TR/TE=4100/88ms). After performing distortion and eddy-current correction and FreeSurfer segmentations, NDI, ODI and ISO were measured in the primary region of interest (ROI), the frontostriatothalamic (FST) region, while NDI was measured in the secondary ROIs, including the frontal, parietal, temporal, and occipital lobes. Statistical assessments included the Mann-Whitney U Test for cross-sectional evaluations and the Wilcoxon Signed Rank Test for longitudinal changes.

Results: At the 1st scan, the CD4+ and CD8+ T-cell counts of PWH were 631 [IQR 412,831] and 576 [IQR 442,840] cells/mm^3, with a CD4/CD8 ratio of 0.96 [IQR 0.66,1.36]. Compared to PWOH, PWH had lower NDI (mean difference Δ=-13.6±6.6%, p=0.001) and ODI (Δ=-12.1±3.7%, p<0.001), but ISO showed no significant difference in the FST region. PWH also had lower NDI in all secondary ROIs when compared to PWOH (Table) (p<0.05). In the longitudinal analysis, PWH showed a decrease in NDI (Δ=-11.2±9.2%, p=0.02) and ISO (Δ=-17.2±7.6%, p=0.007) but statistically unchanged ODI (Δ=1.5±7.8%, p=0.547) in the FST region. Moreover, NDI decreased in all secondary ROIs (p<0.05).

Conclusion: Compared to PWOH, PWH with stable HIV suppression had lower NDI and ODI in the FST and lower NDI in major cortical regions, indicating a possible loss in microstructural integrity. The longitudinal decline of NDI in PWH may indicate ongoing changes at the axonal/dendritic level. Future inclusion of cognitive testing, multi-modal neuroimaging, and longitudinal PWOH controls will help validate and understand the observed NODDI changes.

Table: Neurite Density Index (NDI) by Region of Interest and Type of Analysis

	Cross-sectional (PWH vs. PWOH)			Longitudinal Analysis (PWH: 1st vs. 2nd scan)		
	% Difference (SD)	p value	Cohen's d	% Difference (SD)	p value	Cohen's d
Priamry Region of Interest						
Frontostriatothalamic	-13.6 (6.6)	0.001	-2.07	-11.2 (9.2)	0.023	-1.22
Secondary Regions of Interest						
Frontal Lobe	-15.6 (7.1)	0.001	-2.20	-14.4 (13.4)	0.039	-1.08
Occipital Lobe	-8.9 (6.8)	0.038	-1.30	-13.0 (12.9)	0.039	-1.01
Parietal Lobe	-15.3 (8.1)	0.007	-1.89	-16.6 (8.6)	0.008	-1.94
Temporal Lobe	-9.7 (7.6)	0.007	-1.28	-6.2 (5.4)	0.02	-1.15

Mann-Whitney U Test for cross-sectional evaluations.
Wilcoxon Signed Rank Test for longitudinal changes.
All p-values are uncorrected for multiple-comparison.
Abbreviations: PWH: People with HIV; PWOH: People Without HIV; SD: standard deviation

589 Associations Between a Polygenic Risk Score for Alzheimer's Disease and Brain Integrity in HIV

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Background: People living with HIV (PWH) continue to live to older ages making it difficult to differentiate between age-related neurocognitive disorders, such as Alzheimer disease (AD), and HIV-related neurocognitive impairment. Polygenic risk scores (PRS) allow for computing genetic risk for various diseases. This study leveraged a PRS calculated using the latest genome-wide association study for AD (AD-PRS) to evaluate if it was associated with the presence of HIV disease markers, HIV-related neurocognitive impairment, and brain integrity.

Methods: 115 PWH (age≥50; male n=94, female n=21) completed magnetic resonance imaging, a blood draw, and a comprehensive neuropsychological battery comprised of 15 tests covering 5 cognitive domains (learning, recall, executive functioning, psychomotor speed, and language). Participants were genotyped with an Illumina array platform (GSA), stringent quality control and imputation was performed following standard pipelines. AD-PRS was computed using the binary logarithm transformation of the reported OR from the sentinel SNPs from the latest AD GWAS, including the APOE region,

using PRSice. Regression analysis (adjusted for age, sex, and race) was used to examine relationships between PRS and cognitive test and domain Z-scores, inflammatory markers (sCD14, sCD163), brain volumes, cerebral blood flow (CBF), and HIV variables (CD4 t-cell count, CD8 t-cell count, CD4:CD8 ratio, duration of infection).
Results: Higher AD-PRS values were associated with worse cognitive test scores for letter number sequencing (p=0.015), animal fluency (p=0.039), verb fluency (p=0.001) and language domain (p=0.024). There was a negative correlation between AD-PRS and inflammatory markers sCD163 (p=0.043) and CD14 (p=0.03), and AD-PRS and total gray volume (p=0.032). A significant positive association between the AD-PRS and CBF in the caudate (p=0.047) and putamen volume (p=0.017) was found. No association was found between AD-PRS and HIV variables.
Conclusion: While no change in brain integrity was observed within cognitive domains or brain regions typically affected by AD, an elevated genetic risk measured by AD-PRS did associate with some worse cognitive performance. This mirrors patterns in the general population, implying that certain cognitive deficits among older PWH may result from aging rather than HIV-related factors. AD-PRS also had no association with HIV clinical markers, supporting previous work suggesting that HIV and AD affect brain integrity via different processes.

590 Further Evidence of Hypertrophy in Acute Infection Identified Using Machine Learning

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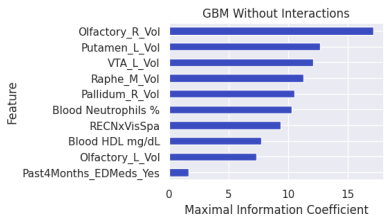
Background: A recent study of structural brain volumes during acute HIV infection (AHI) revealed evidence of hypertrophy among individuals in Fiebig stages III-V compared to Fiebig I-II. The present study incorporated multiple neuroimaging modalities (structure and function), blood markers of inflammation and immune dysregulation, and psychosocial determinants of health using ensemble machine learning to more comprehensively characterize brain integrity in late vs. early AHI and discover potential explanatory factors.
Methods: 112 Thai males with AHI (age 20-46) enrolled in RV254/SEARCH010 were included in the analysis. Features classifying individuals into early (Fiebig I-II; n=32) vs. late (Fiebig III-V; n=80) AHI were ranked using gradient-boosted multivariate regression (GBM) with repeated cross validation. Predictors included demographic, HIV disease, cognitive, neurologic exam, mental health, substance use, plasma immune/inflammatory, and multimodal 3T neuroimaging (i.e., volumes, resting state connectivity, diffusion, and spectroscopy) indices collected at enrollment.
Results: The GBM identified a combination of variables that classified individuals into early vs. late Fiebig with an average F1 score (a metric of model performance) of .82. Individuals in late Fiebig stages exhibited larger regional volumes in the olfactory cortex, putamen, raphe nucleus, and pallidum. Smaller volumes among late Fiebig individuals were noted in the ventral tegmental area, along with lower blood neutrophil percent and high-density lipoproteins, greater functional connectivity between the right executive control network and visuospatial networks, and lower use of erectile dysfunction medication.
Conclusion: Findings demonstrate that brain alterations in late vs. early stages of AHI associate with distinct multidimensional parameters: larger regional volumes observed together with lower immune levels (i.e., neutrophils) suggest that viral-immune dysregulation already underway in late Fiebig stages manifests as hypertrophy via neuroinflammation. Additionally, we reveal evidence of brain-behavior relationships via recent substance use and ventral tegmental area volume, a region implicated in addictive behaviors. Resting state connectivity differences may also reflect disrupted structural/functional integration. Psychosocial and immune processes operative during the first weeks of AHI and their effects on brain integrity may explain variability in long-term outcomes for those starting ART at later stages.



591 Beta-Amyloid PET Positivity Among Cognitively-Impaired People With HIV Over Age 60

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Background: Amyloid positron emission tomography (PET) imaging can stratify risk for Alzheimer's disease (AD). Limited data exist among people with HIV (PWH) and HIV-associated neurocognitive disorder (HAND) in older age groups. In this analysis, we sought to characterize frequency of amyloid PET positivity among older cognitively impaired PWH compared to cognitively healthy people without HIV (controls).
Methods: Virally suppressed PWH were enrolled in a study of HAND where PET positivity was used to exclude the possibility of AD (exclusion criteria). Participants underwent a standardized neuropsychological battery to diagnose HAND. Healthy controls were identified and matched by age from a separate cohort at our site. No participant from either group showed clinical signs and symptoms in a pattern that would be concerning for AD. We completed amyloid PET imaging using florbetapir F-18 among both groups which were visually read as amyloid positive (PET+) or negative (PET-).
Results: Compared to controls (n=65), the PWH group (n=74) was predominantly male (94.6% vs. 72.3%, p<0.001), of non-Hispanic white ethnicity (74.3% vs. 83.1%, p=0.211) and reported lower educational attainment (16.2 vs. 17.4 years, p<0.001). Among them, 6 (8.1%) had PET+ scans compared to 14 of 65 matched healthy controls (21.5 %, p=0.024). Within the PWH group, we did not identify differences in the neuropsychological testing pattern by PET status (all p-values >0.05).
Conclusion: Relative to healthy controls, this group of cognitively impaired PWH did not show increased frequency of amyloid PET+ compared to controls nor differences in patterns of cognitive performance.

592 Differential Expression Analysis Reveals Pervasive Transcriptional Changes in the Brains of PWH

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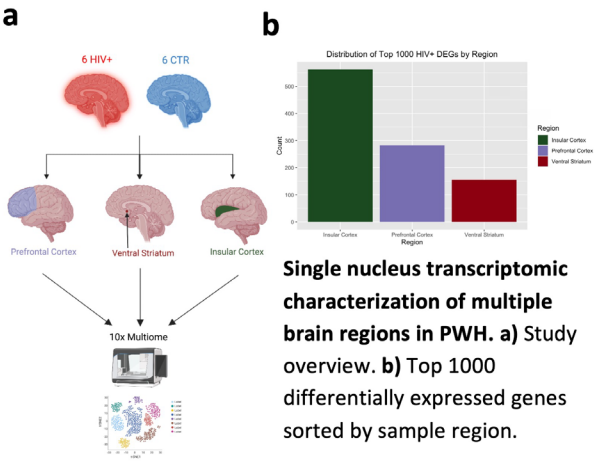
Background: Central nervous system (CNS) dysfunction is a common consequence in people with HIV (PWH). Understanding of the impact of HIV on the brain remains limited to select cell types and regions. We describe preliminary efforts to establish cell-type specific gene expression patterns across multiple regions in PWH using single cell transcriptomics.
Methods: Nuclei were isolated from frozen post-mortem tissue from insular cortex (INS), prefrontal cortex (PFC), and ventral striatum (VST) from 6 PWH and 6 HIV-negative control (CTR) donors. We profiled transcriptomes and chromatin accessibility profiles of these 36 samples using 10x Genomics Chromium Single Cell Multiome ATAC+Gene Expression. In total, we analyzed single-cell transcriptomes of 144,918 cells from PWH and 153,868 cells from CTR. An integrated single cell t-SNE embedding was created for each region, and cells were clustered using Louvain. These clusters were then manually annotated to identify major cell types. We also performed pseudobulk differential expression (DE) analysis between PWH and CTR within major cell types and regions using EdgeR.
Results: PWH and CTR donors were similar in age (median 45 and 39 years) and gender (33% vs 17% female) (p>.1). Canonical neuronal and non-neuronal cell types were detected in all regions. However, a population of putative T-like cells expressing CD247 and SKAP1 was identified in INS of 6 CTR and 5 HIV donors, with >80% of cells annotated as T-like originating from PWH. Consistent with their role as resident immune cells of the CNS, microglia exhibited the

largest gene expression changes in PWH, including upregulation of pathways related to cytokine signaling and innate immunity. On the other hand, many genes were significant on DE analysis ($p \leq .05$) across all regions (151 PWH, 55 CTR) and multiple cell types (567 PWH, 974 CTR). For example, SERPINA3 was differentially expressed in PWH in INS, VST, and PFC by astrocytes, endothelial cells, neuronal cells, oligodendrocyte precursor cells, oligodendrocytes, microglia, and pericytes. Despite these widespread trends, 562 of the top 1000 significant results were genes differentially expressed in INS.

Conclusion: We identified patterns of differential cell type abundance and gene/pathway expression in PWH. While our findings are consistent with previous single cell observations of glial cell involvement in PWH, our results indicate that many other cell types are affected by HIV and implicates the INS as a significant region for future exploration.



Single nucleus transcriptomic characterization of multiple brain regions in PWH. a) Study overview. **b)** Top 1000 differentially expressed genes sorted by sample region.

593 Epigenetic Impact in CSF Cells From 48 Weeks of Adjunctive Telmisartan in Acute HIV

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Background: Telmisartan, an angiotensin II receptor antagonist, is known to reduce inflammation. In a randomized trial, we examined whether 48 weeks of sustained adjunctive telmisartan initiated with antiretroviral therapy (ART) in acute HIV infection (AHI) would modify HIV's impact on the central nervous system (CNS). While we observed no significant changes in soluble makers of CNS inflammation or injury markers due to telmisartan, we did not evaluate its effects on CNS cells. Hence, we investigated whether telmisartan modified epigenetic states in cerebrospinal fluid (CSF) cells.

Methods: We utilized a new ultra-low DNA input assay to measure genome-wide DNA methylation (DNAm) epigenetic profiles in CSF cells at 48 and 72 weeks from 21 participants with AHI that were randomized 2:1 to initiate treatment with ART +/– telmisartan for 48 weeks. We used R statistical software to analyze DNA methylation data and identify differentially methylated loci using a linear model with FDR correction.

Results: The median age of participants was 29 years (IQR: 24-34), pre-ART median $\log_{10}$ plasma viral load was 5.95 copies/mL (5.36-6.48), pre-ART median CSF HIV RNA was 2.82 copies/mL (2.17-4.36), and pre-ART CD4+ T Cell count was 479 cells/mm^3 (95-688). Age, Fiebig stage, pre-ART plasma and CSF viral loads, and pre-ART CD4+ T cell count did not significantly differ between participants randomly assigned to ART+ telmisartan versus ART only groups. Comparing the DNAm states of CSF cells at Week 48 in participants receiving 48 weeks of ART+telmisartan versus ART, we identified 11,433 differentially methylated loci (DML) at a mean difference in DNAm of 10% or greater. Notably, DNAm levels of marker of proliferation Ki-67 MKI67, inflammatory gene IL1B, immune checkpoint receptor gene LAG3, central regulator of stress response gene CRH, and interferon stimulated gene IFI27 were significantly altered in CSF cells of participants receiving ART+ telmisartan versus ART only for 48 weeks. We examined the durability of telmisartan-associated changes in CSF cells at week 72 in participants who stopped telmisartan and continued ART only. We found that only 5.46% of DML identified at week 72 overlapped with changes observed at week 48.

Conclusion: Telmisartan initiated during AHI affects epigenetic states of genes related to inflammation, immune response, and cellular proliferation in CSF cells. Telmisartan's effects on long-term epigenetic reprogramming of CNS cells and CNS outcomes warrant further investigation.

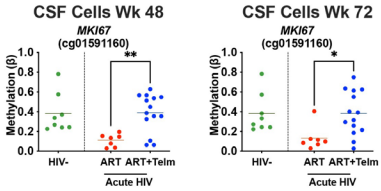

Figure. Top Telmisartan-associated DNA methylation change in CSF cells for marker of proliferation gene *MKI67* at Weeks 48 and 72 following ART initiation during AHI. **P<0.01, *P<0.05

594 Monocyte Epigenetic Age Relates to Non-Somatic Depressive Symptoms in Women With Undetectable HIV

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Background: HIV and its neuropsychiatric complications have been linked with accelerated biological aging using several DNA methylation-based epigenetic clocks. Monocytes, which are essential to the innate immune response, may contribute to this biological aging effect. A recently developed epigenetic clock derived from monocytes showed acceleration in people with HIV who were heavy alcohol users. However, its relationship with depression is unknown. As depression disproportionately affects women, we examine epigenetic clocks as biomarkers of depressive symptomatology in women with HIV (WWH) and women without HIV (WWoH). Specifically, we focus on the link between epigenetic age and dimensions of depression (non-somatic [affective or cognitive] vs. somatic [sleep or appetite]) as the phenotypic expression of depression is heterogeneous.

Methods: DNA methylation data and Center for Epidemiological Studies Depression Scale (CES-D) scores were available from 440 Women's Interagency HIV Study participants. Illumina MethylationEPIC microarrays were used to measure methylation levels in bisulfite-converted DNA from whole blood. Two estimates of biological age were calculated (Horvath age and monocyte age). Chronological age, Horvath age, and monocyte age were orthogonalized due to high mutual correlations. CES-D scores were used to quantify somatic and non-somatic depressive symptoms. In the full cohort (WWH+WWoH) and separately in WWH and WWoH, we used multiple linear regression to measure links between chronological or epigenetic age and depressive symptoms after confounder adjustment.

Results: We included 261 WWH (chronological age=43.7±8.9 years; 38% Black; 48% Hispanic; 84% undetectable viral load) and 179 WWoH (age=39.5±10.0; 31% Black; 49% Hispanic). In the full cohort, monocyte age was significantly associated with non-somatic depressive symptoms (P=0.003; Fig. 1), particularly CES-D items reflecting anhedonia (P's=0.01). This pattern was driven by WWH with undetectable viral load (depressive non-somatic: P=0.047; CES-D anhedonia items: P's<0.05). Horvath age was not associated with non-somatic depressive symptoms. Neither monocyte age nor Horvath age were associated with somatic depression.

Conclusion: Biological clocks reflecting the epigenetic age of immune cells may represent sensitive biomarkers of non-somatic depression in WWH. The relationship between morbidity and mortality-tuned epigenetic clocks (e.g., PhenoAge and GrimAge) and depression merits future study.

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595 Epigenetic Age Advancement Is Associated With Cognition, Frailty, and Mortality in Older PWH

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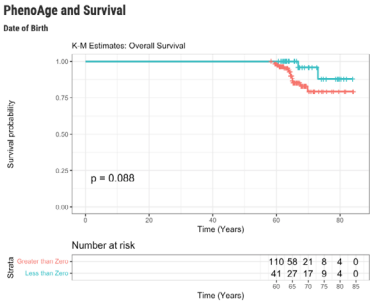
Background: DNA methylation (DNAm) patterns indicate a trend towards epigenetic age advancement in older persons with HIV (OPWH), however, data on relationships with phenotypic changes are limited. We investigated associations between phenotypic measures of cognition, frailty, and 7-year survival with epigenetic age estimates derived from the modification of DNAm in a population of OPWH.

Methods: OPWH aged 50 and older in clinical care for HIV management at Weill Cornell in NYC, were recruited to participate in a detailed biopsychosocial survey, and those age 55 and older were invited to complete an in-person study visit which included blood draw, Montreal Cognitive Assessment (MoCA) and Fried frailty phenotype testing. Genome-wide DNAm was measured from dried blood spots using the Illumina MethylationEPIC platform and analyzed using PhenoAge epigenetic age.

Results: A total of 164 participants enrolled in the study; 158 had available biospecimens for DNAm analysis. Median age was 60 years (IQR 56-64), 52 (33%) identified as female, and 76 (50%) identified as Black, median CD4 T-cell count was 588 cells/mm^3 (IQR: 323-811) and 93% were virally suppressed on ART. Epigenetic age analysis indicated an average epigenetic "age advancement" (EAA) of 5.4 years (SD 6.6). Median MoCA score was 24 (21-27) and 67% were pre-frail or frail. There were 17 deaths (10.7% mortality rate) from September 2016-September 2023. EAA was inversely related to chronologic age (ß= -0.31 [95%CI: -0.48, -0.14] (p<0.01)) and was associated with lower CD4 T-cell count (ß= -0.84 [95% CI: -1.14, -0.53] for every 100 CD4+ T-cells (p<0.01)) in an unadjusted linear regression model. EAA was associated with lower MoCA score in a linear regression model adjusted for age, sex and race (p<0.01), and there was a trend towards EAA association with more advanced frailty state in an ordinal logistic regression model adjusted for age, sex and race (p=0.07). Survival differed by EAA, and greater advancement was associated with 7-year mortality in a Cox Proportional Hazard model adjusted for age (HR 1.10 [95%CI: 1.02, 1.18] p=0.01) (Figure 1).

Conclusion: In OPWH the average EAA was 5.4 years, as calculated by PhenoAge, and was associated with cognitive dysfunction, more advanced frailty state, as well as 7-year mortality. These results suggest epigenetic clocks are a valuable biomarker of aging-related pathologies in OPWH and warrant further study.



596 Plasma Proteomics Identifies Variable Patterns of Association With Neuropsychiatric Dimensions

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Background: People with HIV (PWH) can suffer from neuropsychiatric conditions that have complex etiologies. We investigated the plasma proteome in 206 virally suppressed PWH on antiretroviral therapy (ART) and compared the results to multiple dimensions of a comprehensive neuropsychiatric assessment.

Methods: Neuropsychiatric dimensions included global and domain-specific neurocognitive impairment (NCI), Beck Depression Inventory (BDI)-II and subscales, and instrumental activities of daily living (IADL) dependence. Based on these and other data, 4 biopsychosocial phenotypes (BPSPs) were previously derived by machine learning analysis: healthy (BPSP1), mild NCI with moderate depressive symptoms (BPSP2), mild-to-moderate NCI with severe depressive symptoms and IADL dependence (BPSP3), and mild-to-moderate NCI without depressive symptoms or IADL dependence (BPSP4). Proteins were quantified by the Olink Target-96 Inflammation panel. Linear regression of normalized protein expression values analyzed group differences. Benjamini-Hochberg adjusted alpha was 0.003. Proteins with p<0.10 were next analyzed by multivariable regression adjusting for demographic, disease, and treatment characteristics. Classification accuracy was assessed by discriminant analysis.

Results: Cohort characteristics: mean age 45.0 years, 22.8% women, 51.5% Black, median CD4+ T-cells 480/µL, median duration: HIV 10.6 years, ART 5.7 years. An example volcano plot is shown in the Figure A. Across all dimensions, the most frequently associated proteins were CD8 antigen, IL-12B, IL-17C, FGF-21, FGF-23, and TGF-α. Adjusted multivariable models with R2>0.15 were found for global NCI, motor impairment, BDI-II somatic subscale, and all BPSPs (Table B). Among all dimensions, discriminant analysis correctly classified >75% of participants in only BPSP3 and BPSP4. The BPSP3 model included CCL19 and DNER and the BPSP4 model included CD8 antigen, IL-33, CCL3, TNFSF11, and stem cell factor.

Conclusion: Data-driven, cross-sectional analyses identified plasma proteins associated with multiple neuropsychiatric dimensions. While the results reinforce the complexity of neuropsychiatric disorders, novel, biologically plausible targets were identified for validation and future investigation. The BPSPs generally performed better in analyses, suggesting that they may be more inflammation-driven than other dimensions. The focus on inflammation is a limitation; future analyses that include other proteins (e.g., neuronal) should provide additional insights.

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597 Clinical Profiles Predicting Cognitive Decline Over 10 Years Among Older Adults With HIV in Canada

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Background: Correlates of cognitive impairment in older adults with HIV (OAWH) have been identified cross-sectionally, but much less is known about the clinical profiles predicting cognitive decline over several years among ART-treated OAWH.

Methods: The Positive Brain Health Now cohort included 856 individuals (mean age 53 years) from 5 HIV clinics in Canada between 2013-2016. Comprehensive cognitive and biopsychosocial characterization was conducted every 9-12 months for up to 10 years. Global cognitive ability was measured with the B-CAM, a computerized battery assessing cognitive domains known to be impacted by HIV and optimized to detect change. A longitudinal analysis was carried out on participants with ≥ 5 years of follow-up (n=229, 85% men). Group-based trajectory analysis was applied to centered B-CAM scores to identify distinct groups of individuals with a similar evolution over time. Recursive partitioning was used to identify profiles of participants with a declining trajectory.

Results: The sample was educated (70.5% post high-school education), predominantly aviremic (92.4%), had a mean B-CAM at baseline of 57.3/100 (SD: 13.8) and were followed for up to 9.3 years. Three trajectories of cognition emerged: 38.9% flat; 28.8% inverse U shaped; and 32.3% declining. The highest probably of decline was observed with a current CD4 count < 255 cells/µl (n=13, risk 77%). With CD4 count ≥ 255 cells/µl, a high probability of decline (59%) was observed with HDL cholesterol < 1.2 mmol/L plus a HADS-A ≥ 3.0 plus FIB-4 ≥ 1.5. Profiles of participants with lowest probability (18%) of being in the declining group included those with CD4 count ≥ 255 cells/µl, HDL cholesterol ≥ 1.2 mmol/L and HADS-A < 3.0 (very low anxiety). Some factors showed evidence of protection only when combined with others, e.g. CD4/CD8 ≥ 0.73 was protective only when combined with CD4 count ≥ 255 cells/µl.

Conclusion: In this cohort of primarily male, ART-treated OALH, cognition declined over 10 years in about one in three participants, who were characterized by low immune function, higher cardiovascular disease risk, and liver fibrosis. Recursive partitioning supported the identification of the interaction of several factors associated with cognitive decline. Early detection and optimal treatment of HIV and interventions to preserve vascular health could potentially prevent cognitive decline. Replication is required in a different sample.

598 High Plasma GFAP in Older PWH With Low Nadir CD4 Supports Legacy Brain Injury and Reactive Gliosis

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Background: Measuring cerebrospinal or plasma levels of brain injury markers may provide useful information on HIV neuropathogenesis and help characterize cognitive impairment in PWH. We compared plasma levels of these markers to cognitive function, physical performance and history of HIV in PWH≥50 years

Methods: 102 ART-treated PWH ≥50 years and 40 age-matched controls without HIV infection were prospectively assessed for Neurofilament Light Chain (NFL), Glial Fibrillar Acid Protein (GFAP), Tau and Ubiquitin C-terminal hydrolase-L1 (UCH-L1) by Simoa Human Neurology 4-Plex. PWH were evaluated for neurocognitive performance [TMT-A, TMT-B, Digit Symbol (DS)], depression and anxiety (Hospital Anxiety and Depression scale), physical function (handgrip, chair-stand test for muscle strength, mini-BEST test for balance and mobility), current and nadir CD4+ counts and years of HIV infection. Values are shown as median (IQR); group comparisons were analysed by Mann-Whitney test and correlations by Spearman's correlation test and linear regression

Results: No significant differences between PWH and controls were observed for age [60 (57-63) vs. 57 (52-62)] and any of the four markers [NFL: 11.5 (8.2-16.5) vs. 10.6 pg/µL (9.4-14.3); GFAP: 108.3 (76.2-144.2) vs. 95.4 (76.5-138.7); Tau: 2.69 (1.88-4.30) vs. 3.30 pg/mL (2.24-4.89); UCH-L1: 18.7 (10.6-28.8) vs. 19.5 pg/mL (11.4-34.2)]. In PWH, NFL and GFAP were highly correlated (p=0.0002, r=0.356); higher NFL and GFAP correlated to older age (both p<0.0001, r=0.356 and 0.496, respectively) and GFAP levels were higher in women (p=0.01); higher NFL was associated with lower performance at mini-BEST test (p<0.0001, r=-0.334), and higher GFAP with lower performance at DS (p=0.043, r=-0.201), handgrip (p=0.0001, r=-.0367) and mini-BEST test (p=0.015, r=-0.239), lower nadir CD4+ counts (p=0.0004, r=-0.343) and longer duration of infection (p=0.045, r=0.199). By multivariate analysis (Table), higher NFL levels were associated with older age and better performance at the Mini-BEST test; higher GFAP with older age, female gender and low nadir CD4+ count.

Conclusion: Beyond the expected correlation of higher GFAP and NFL with age, the specific association of high GFAP level with low nadir CD4+ counts and long infection duration may reflect a legacy injury with reactive gliosis, of a previous untreated CNS HIV infection. Practically, physical performance may help define the functional status associated with elevated markers of CNS cell injury

Table: Beta coefficients of the multivariable linear model of NFL and GFAP

	NFL		GFAP	
Variable	**Estimate (95% CI)**	**P value**	**Estimate (95% CI)**	**P value**
Female gender	-3.30 (-9.10, 2.51)	0.26	26.28 (2.90, 49.66)	0.03
Age (years)	0.63 (0.16, 1.09)	0.008	4.44 (2.57, 6.31)	<0.001
Digit Symbol (score)	0.06 (-0.18, 0.29)	0.64	-0.54 (-1.50, 0.41)	0.26
Mini-BEST test (score)	-0.88 (-1.76, 0.017)	0.05	1.49 (-2.10, 5.08)	0.41
Nadir CD4+ cells/µL	0.0006 (-0.014, 0.015)	0.92	-0.07 (-0.13, -0.01)	0.017

599 Pattern of Age-Related Cognitive Decline in People With HIV Depends on Viral Suppression

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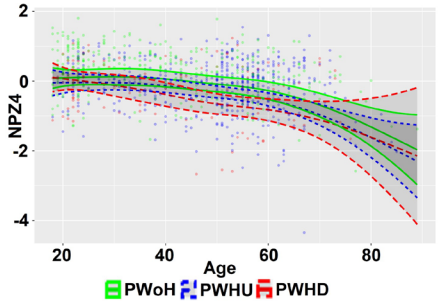
Background: The introduction of combination anti-retroviral therapy (cART) has led to increased life expectancy of persons living with HIV (PWH) and a reduction in the prevalence of HIV-associated neurocognitive disorder. As PWH grow older, it is important to understand the cognitive trajectories of PWH compared to people without HIV (PWoH) and how treatment efficacy impacts age related cognitive changes.

Methods: PWoH and PWH (virally undetectable; viral load ≤50/ml, PWHU; and detectable; PWHD) were recruited and repeatedly administered a simple cognitive battery – Category Fluency (language), Hopkins Verbal Learning Test (learning subtest), Trails A (psychomotor/processing speed), and Trails B (executive function) – that were combined to form a composite (NPZ4). The composite was formed by normalizing scores to baseline performance (flipping timed tests so that lower values means poorer performance), and averaging Z-scores. The association between cognition and age was assessed for each group in a generalized additive mixed model. Education, ethnicity, sex, and time since first cognitive test were included as covariates.

Results: A total of 679 participants (279 PWoH, mean (standard deviation) age 40 (17) years old; 305 PWHU, age 49 (14) years old; 95 PWHD, age 40 (17) years old), tested up to 6 times for a total of 968 data points, were analyzed. Age was associated with cognition in each group, with cognition worsening with increasing age. The overall effect significantly differed between all groups (PWoH > PWHU > PWHD). The shape of the age-cognition relationship was identical for PWoH and PWHU, only significantly shifted downward. Shape significantly differed in PWHD, resulting in a steeper, steadier decline in cognition with increasing age relative to PWoH and PWHU.

Conclusion: While there is a decrease in cognition associated with HIV, the age-cognition relationship mirrors PWoH when virologically controlled. Older, uncontrolled PWH are at greater risk for cognitive decline and should be the focus of future studies.



600 Hepcidin Modifies Effects of Age and Erythrocyte Indices on Cognitive Function in People With HIV

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Background: Cognitive impairment (CI) in people with HIV (PWH) is associated with abnormal erythrocyte indices, which may result from inflammation, disturbed iron metabolism, and other factors. Mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) are indices of erythrocyte volume and hemoglobinization, which help to classify anemia. Erythropoiesis requires bioavailable iron, levels of which are regulated by a complex system of peptide hormones, including the acute-phase peptide, hepcidin.

Methods: Iron biomarkers (hepcidin, erythropoietin, ferritin, erythroferrone, total iron-binding capacity, soluble transferrin receptor) and erythrocyte indices were quantified using commercial assays in 88 virally suppressed antiretroviral therapy (ART) treated PWH. All participants underwent comprehensive cognitive testing, and their performance was summarized by T-scores. Multivariable regression analysis of cognitive performance was performed using the Akaike Information Criterion and backward selection.

Results: Participants were mostly middle-aged (mean age 44 years), white (52.3%), and men (84.1%). Hepcidin levels were detectable (>1.0 ng/mL) in 42 (47.7%) and modified the relationship between global T-score and either age (interaction p-value=0.0072) or MCV (interaction p-value=0.0185). Stratified analyses identified that lower global T-scores were associated with older age (p=0.001) or higher MCV (p=0.0046) only when hepcidin was undetectable. A similar analysis was performed to assess interactions between anemia and iron indices in relation to global T-scores and this identified statistically significant interactions between anemia and either MCV (p=0.0119) or MCH (p=0.0127). Stratified analyses identified that lower global T-scores were associated with higher MCV (p=0.0015), and higher MCH (p=0.0026) only among anemic participants. These associations remained statistically significant after adjustment for sex, race, ethnicity, duration of HIV infection, CD4+ T-cell count and nadir, duration of ART, and HCV serostatus.

Conclusion: These findings suggest that a combination of iron-related (hepcidin, MCH) and iron-unrelated (age, higher MCV) mechanisms influence cognitive health. While these cross-sectional results require confirmation in larger, longitudinal studies with more women, they highlight hepcidin as a potential modifying factor in associations of age and erythrocyte indices in relation to cognitive performance in PWH.

601 VACS 2.0 Shows Improved Discrimination of Neurocognitive Impairment and Frailty in People With HIV

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Background: The Veterans Aging Cohort Study (VACS) 1.0 Index is a generalizable risk index that combines and weights age, CD4 count and human immunodeficiency virus (HIV) type 1 RNA alone (Restricted Index), hemoglobin, FIB-4 Index, hepatitis C virus, and estimated glomerular filtration rate. The VACS 1.0 index more accurately discriminates mortality risk among persons with HIV (PWH) prescribed antiretroviral therapy than traditional HIV markers and age alone. More recently, there have been revisions to VACS 1.0 index. This study examined whether the updated VACS 2.0 index (including serum albumin, body mass index (BMI), and white blood cell (WBC) count) had stronger correlations with cognitive function, brain volume, and frailty in older (≥50 years) PWH compared to the original VACS 1.0.

Methods: Neuropsychological performance (NP) Z-scores (learning, retention, executive functioning (EF), psychomotor function/processing speed (PM/PS), language, and global cognition), and neuroimaging measures (brain volumetrics) were analyzed in PWH (n=162, 88.17% male). A subset of the sample (n = 159) was defined as either frail (n = 18) or non-frail (n = 141) according to the Fried phenotype criteria. Brain volumes, NP scores, and frailty subgroups were analyzed with both VACS scores, albumin, BMI, and WBC count using Pearson's significance tests and independent T-tests.

Results: Based on values shown in Table 1, higher VACS scores significantly correlated with lower brain volumes. A higher VACS 2.0 score was associated with lower NP in the EF and PM/PS domains and was primarily driven by albumin. In contrast, VACS 1.0 scores did not correlate with cognition Z-scores. There was no relationship between frailty status and VACS 1.0. PWH who were frail had significantly greater VACS 2.0 scores than non-frail PWH.

Conclusion: The addition of serum albumin to the VACS index improved its correlations with NP and frailty in PWH. While low albumin levels may contribute to cognitive decline or frailty, the reverse causality should also be considered. For example, those with frailty or cognitive impairment may struggle to maintain proper nutrition, potentially resulting in decreased albumin levels. Regardless of the direction of causality, these findings suggest that the VACS 2.0 index and albumin are valuable measures for clinicians to improve outcomes in older PWH.

Table 1: Correlations of Brain Volume and Cognitive Z-Scores with VACS Indices and Serum Albumin

Domain	VACS 1.0 Score		VACS 2.0 Score		Albumin	
	r	p	r	p	r	p
Total Gray Matter	-0.36084	0.00001	-0.34752	0.00002	0.10489	0.20610
Executive Functioning	-0.14743	0.06117	-0.20575	0.00862	0.16268	0.03861
Psychomotor function/Processing speed	-0.09858	0.21200	-0.18609	0.01775	0.22874	0.00341
Overall Cognitive Function	-0.05221	0.50940	-0.13575	0.08499	0.13951	0.07663

602 Latent Viral Infections Are Associated With Veterans Aging Cohort Study Index in People With HIV

Patricia K. Riggs, Gordon Honerkamp Smith, Milenka Meneses, Antoine Chaillon, Gemma Caballero, Donald Franklin, Robert K. Heaton, Ronald J. Ellis, Scott L. Letendre, Sara Gianella Weibel
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Background: People with HIV (PWH) on ART have elevated risk for mortality, frailty, and cognitive impairment. The Veterans Aging Cohort Study (VACS) index is a validated risk score associated with these outcomes in PWH. CMV and EBV coinfections have been implicated in these outcomes and expansion of the HIV reservoir but it is unknown if this is a direct effect of the virus or the immune response. We sought to determine the relationships among quantitative cell associated viral DNA, IgG levels, and VACS index score.

Methods: Participants included 485 PWH with comprehensive neuromedical testing, HIV RNA<200 copies/mL on antiretroviral therapy, and stored blood. Digital droplet PCR quantified cell associated CMV, EBV, and HIV DNA in peripheral blood mononuclear cells (PBMCs). EBV VCA IgG and CMV IgG were measured in plasma by ELISA. Using linear regression, we tested the associations between VACS and viral DNA and IgG levels. Model estimates were adjusted for age, sex, race/ethnicity, estimated duration of HIV (EDI), CD4+ T-cells, and AIDS diagnosis.

Results: Cohort characteristics: mean age 53 years, 17% women, 59% White, median CD4+ T-cells 615/µL, 66% AIDS, and nearly all were seropositive for CMV (96.5%) and EBV (100%). CMV DNA was detected in PBMCs in 47.8%, EBV DNA in 95.6%, and HIV DNA in 99.2%. In simple regression, VACS was positively associated with CMV IgG (p<0.001), HIV DNA (p=0.013), EBV DNA (p=0.003), and EBV IgG (p=0.001). In adjusted models, VACS remained associated with CMV IgG (p=0.017, R2= 0.46) and HIV DNA (p=0.07, R2=0.45). VACS was not associated with CMV DNA. CMV IgG was associated with EBV IgG (p=0.008), but not HIV, CMV, or EBV DNA.

Conclusion: While limited by cross-sectional, observational design, our findings suggest the immune response to CMV (measured by IgG titers) is a more important predictor of adverse clinical outcomes in PWH than levels of CMV DNA in PBMCs. This may reflect the need for tissue level DNA or the immune dysregulation triggered by CMV may not be directly related to the burden of CMV. While CMV IgG correlated with EBV IgG levels, only CMV IgG was a significant predictor of VACS scores when adjusting for key confounders. This adds support for a CMV specific effect, rather than general hyperglobulinemia. Additional investigation is needed to identify potential therapeutic interventions and assess the relationship with CMV DNA within tissues.
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603 Changes in HAND Prevalence Among Medicaid Enrollees From 2016-2021 in the US

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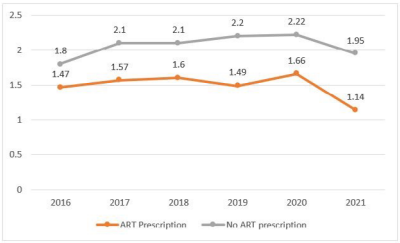
Background: HIV-associated neurocognitive disorder (HAND) is a range of progressively severe central nervous system complications associated with HIV infection. The range can be from mild problems with memory, language, and reasoning to the more severe HIV-associated dementia. HAND has declined with the advancement of antiretroviral therapy (ART), however, remains prevalent in older people with HIV (PWH). We describe the prevalence of HAND among PWH among Medicaid enrollees in the U.S. from 2016-2021.

Methods: We analyzed data from Truven Health MarketScan Claims and Encounters®, a large database derived from administrative claims for healthcare services provided to Medicaid enrollees. Among enrolled persons aged >18 years, we identified PWH with at least one inpatient or outpatient medical claim with an HIV and subsequent major to mild neurocognitive disorders (NDs) ICD-10-CM diagnosis codes. We used chi-square to compare PWH with an associated NDs diagnosis (HAND) to those without an associated ND diagnosis code (no-HAND) to investigate differences in HAND prevalence by age, sex, race/ethnicity, and by prescribed ART from 2016-2021.

Results: The annual crude prevalence of HAND ranged from 1.6% (512/31,897) in 2016 to 1.9% (558/29,967) in 2020. The prevalence of HAND significantly increased with age (p-value<0.001); highest prevalence was among ages 65+ years (range 3.7% in 2021;5.7% in 2017). Males had a significantly higher prevalence of HAND compared to females in 2016 (1.8% vs 1.4%; p-value= 0.007) and 2017 (1.9% vs 1.6%; p-value= 0.027) but from 2018-2021 there were no differences by sex. In 2016 and 2020 there were differences by race/ethnicity (p-value= 0.0002 and 0.001 respectively), with the highest prevalence of HAND among White persons in 2016 (1.9%) and Black persons in 2020 (2.1%) Among the 190,648 PWH from 2016-2021, the frequency of ART prescriptions ranged from 58% (18,671/31,897) in 2016 to 64% (21,018/32,820) in 2021. Prevalence of HAND was significantly higher among persons without an ART prescription (range 1.8% in 2016-2.2% in 2020) compared to those with an ART prescription (range 1.1% in 2021-1.7% in 2020) for each year (Figure).

Conclusion: In this large administrative database of PWH, HAND remains persistent, with some demographic disparities. With the aging population of PWH, strengthening interventions that improve access to ART, promote adherence, and address barriers to clinical care and supportive services for PWH is critical for reducing health disparities.

Figure: Prevalence of HAND by ART prescriptions among PWH enrolled in Medicaid in the U.S. from 2016-2021*.



*Significant differences (p-value < 0.05) were found for each year.

604 Implementation of an Online Drug-Drug Interaction Screener for STRIVE Ensitrelvir Trial for COVID

Josh Havens[1], Nayon Kang[2], Lucy Chung[2], Courtney V. Fletcher[1], Page Crew[2], Jacquie Nordwall[3], Birgit Grund[3], Marcelo Losso[4], Shikha Vasudeva[5], Adit Ginde[6], Jason Baker[3], for the INSIGHT STRIVE Ensitrelvir Study Group

[1]University of Nebraska Medical Center, Omaha, NE, USA, [2]National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, [3]University of Minnesota, Minneapolis, MN, USA, [4]Hospital JM Ramos Mejía, Buenos Aires, Argentina, [5]Salem VA Medical Center, Salem, VA, USA, [6]University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Background: Ensitrelvir (ESV) is an investigational oral protease inhibitor for SARS-CoV-2 infection currently being studied in a randomized placebo-controlled trial of patients hospitalized for COVID-19 within STRIVE (Strategies and Treatments for Respiratory Infections and Viral Treatments), a global network. ESV is associated with drug-drug interactions (DDI) due to its inhibition of CYP P450 3A, P-gp, BCRP, and OAT-3. We present the developmental framework and implementation of an online DDI screener for the STRIVE-1 ESV-trial.

Methods: A multidisciplinary team assessed DDI potential of commonly used drugs with ESV. Since the trial design is blinded (i.e. ESV or placebo), DDI recommendations considered implications for each participant as if they were assigned to ESV. DDI guidance was compiled into a database accessed by trial sites through an online web-portal (DDI screener). Drugs were categorized as permitted or prohibited. For each prohibited drug, a washout period before ESV administration and start/restart criteria were based on the drugs' characteristics (e.g., half-life, substrate sensitivity, etc). If applicable, alternative permitted drugs were recommended. Current guidance for some drugs supports enrollment with dose modification. Sites can request drugs not in the DDI screener be evaluated and added. Version updates were completed iteratively.

Results: The DDI team convened August 2022. Version (v) 1 of the DDI screener went live December 2022, with 615 drugs included. 4 sequential version updates were performed for a current total of 984 total drugs through v5 (Fig, 1A). Guidance for 11 prohibited medications (antihypertensives, antiinfectives, and psychiatric) was revised with permissive dosage adjustments (dose caps, 55%; dose reductions, 45%). To date, 132 participants have enrolled in STRIVE and 38,615 screener searches have been completed through initiation of v5. Top searched drug classes (% of total) include anti-infective, antihypertensive, psychiatric, and analgesic drugs (Fig, 1B). Anticoagulants, certain immunosuppressants, and emergency use drugs posed the greatest guidance challenges due to blinding considerations.

Conclusion: To our knowledge, this is the first online DDI management tool developed for a placebo-controlled trial of investigational agents. DDI resources for drugs like ESV with high DDI potential are essential for safe clinical trial conduct. Implementation requires a multidisciplinary and iterative approach that allows for feedback from trial sites.

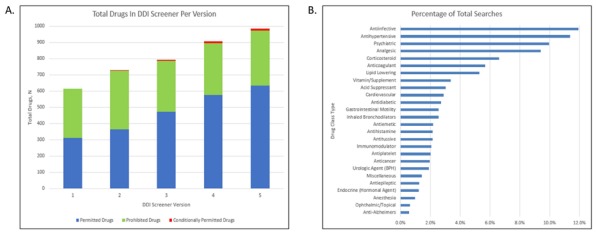


Figure 1. *A*, Total drugs added to DDI screener per version; *B*, Percentage of total searches by drug class.

Notes: The following drug classes represented smaller percentages of total searches; antigout agents, anticholinergic urologic agents, anti-Parkinson's agents, phosphodiesterase-5 inhibitors, illicit drugs, bisphosphonates, antimigraine agents, and herbals

Definitions: DDI, drug-drug interaction; Conditionally permitted drugs, drug guidance with dose reduction or caps; BPH, benign prostatic hypertrophy

605 Evidence for Safe Use of Doravirine With Hormonal Contraceptives in African Women Living With HIV

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Background: Prior to scale-up of new ART, exploring drug-drug interactions between ART and contraceptive methods is crucial. We are conducting EPIC, a parallel group pharmacokinetic study to examine interactions with doravirine (DOR)-containing ART among women of reproductive potential living with HIV in Johannesburg, South Africa.

Methods: EPIC began in November 2021 and is ongoing. A ≥6-week oral lead-in period was required after aviraemic participants switched from their existing ART to DOR-containing ART. Participants in the 3 intervention groups self-selected concomitant contraception: intramuscular depo-medroxyprogesterone acetate (IM DMPA; Group 1), etonogestrel implant (ETG; Group 2), or copper intrauterine device (IUD; Group 3). Comparator groups included a contemporaneous dolutegravir (DTG) + IM DMPA (Group 4) and a historical DTG + ETG implant (Group 5). Participants were followed up for 12 (Groups 1 & 4) or 24 (Groups 2, 3, & 5) weeks. We analyzed serum MPA and ETG concentrations per visit using validated LC-MS/MS assays. We evaluated DOR-containing ART's effect on MPA or ETG log-transformed C_{min} hormone concentrations with geometric mean ratios (GMR; 90% confidence interval), and a multivariate model adjusted for age and body mass index (BMI). We assessed safety (frequency, severity of adverse events (AE)) and tolerability (patient satisfaction, adherence) of DOR-containing ART.

Results: A total of 108 Black African women were enrolled (Table 1): Group 1 (n=21), Group 2 (n=23), Group 3 (n=19), Group 4 (n=21), and Group 5 (n=24). GM Cmin MPA concentrations for Groups 1 and 4 were 561 and 551 pg/mL, respectively (GMR 1.01, 90% CI 0.82, 1.24); adjusted GMR 1.05, 90% CI 0.83, 1.34). GM C_{min} ETG concentrations for Groups 2 and 5 were 312 and 225 pg/mL, respectively (GMR 1.15, 90% CI 1.04, 1.28; adjusted GMR 1.16, 90% CI 1.04, 1.30). Of all AEs reported to date (n=263), AEs attributable to DOR were at grade 1 or 2 and headaches were most frequent (n=31, 16%). Among the DOR groups, only 2 (3%) participants reported any dissatisfaction with this ART and adherence by pill count was 80% for >76% adherence.

Conclusion: We did not detect significant effects of DOR-containing ART on MPA or ETG contraceptives. DOR-containing ART appears to be safe and tolerable among women concomitantly using hormonal contraceptives. These data support the viability of this option for those living in resource-limited settings who are intolerant of or unable to take DTG-containing ART.

Table 1: Baseline characteristics of and pharmacokinetic results among African women living with HIV, EPIC study (n=108), Nov. 2021-Sept 2023

Baseline characteristics for groups, n (%) or median (IQR)					
Characteristic	**Group 1 DOR + IM DMPA (n=21)**	**Group 2 DOR + ETG implant (n=23)**	**Group 3 DOR + IUD (n=19)**	**Group 4 DTG + IM DPMA (n=21)**	**Group 5 DTG + ETG implant[1] (n=24)**
Age, years	35 (29, 38)	37 (28, 40)	37 (31, 42)	39 (35, 41)	35 (33, 37)
BMI kg/m^2	25.4 (21.3, 28.2)	22.5 (20.0, 24.6)	25.6 (24.7,27.3)	22.1 (19.8, 23.3)	23.5 (20.0, 26.0)
Duration on ART before study enrollment (years)	5 (2.5, 11.5)	9 (6.5, 10.5)	4 (3, 6)	7 (4, 11)	9 (8, 11)
Number of days since enrollment to study exit	141 (136, 146)	218 (215, 223)	219 (216, 227)	89 (87, 92)	168 (168, 169)

Pharmacokinetic results for contraceptive hormone concentrations							
Contraceptive method group	**ART group**	**# women (samples)**	**GM of C_{min} hormone concentrations (pg/mL) (IQR)[2]**	**Unadjusted Contraceptive + DOR: Contraceptive + DTG GMR[3] (90% CI)**	***p*-value**	**Adjusted Contraceptive + DOR: Contraceptive + DTG GMR[4] (90% CI)**	***p*-value**
IM DMPA	DOR (Group 1)	21 (102)	561 (415, 706)	1.01 (0.82, 1.24)	0.95	1.05 (0.83, 1.34)	0.70
	DTG (Group 4)	21 (104)	551 (401, 983)	Ref.	--	Ref.	--
ETG implant	DOR (Group 2)	23 (143)	312 (266, 464)	1.15 (1.04, 1.28)	0.03	1.16 (1.04, 1.30)	0.03
	DTG (Group 5)	24 (213)	225 (165, 279)	Ref.	--	Ref.	--

BMI=body mass index; ART=antiretroviral therapy; GM=geometric mean; GMR=geometric mean ratio; SD=standard deviation; DOR=doravirine; DTG=dolutegravir
[1]A historical control group
[2]The C_{min} for the IM DMPA groups was $C_{12weeks}$ and for the ETG implant groups was $C_{24weeks}$
[3]Unadjusted model conducted with linear mixed methods
[4]Adjusted model conducted with linear mixed methods adjusting for age and BMI

606 Pharmacogenetics of Dolutegravir During Rifapentine/Isoniazid Treatment of Latent TB in ACTG A5372

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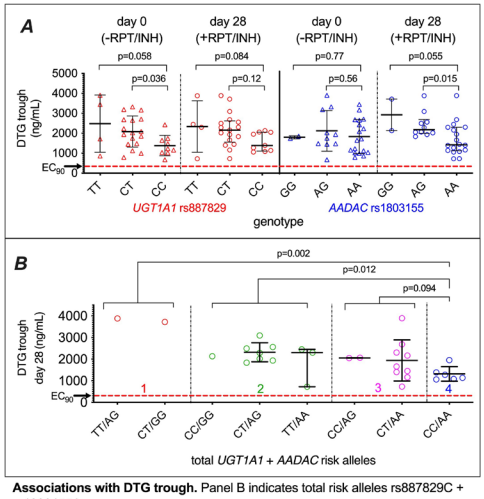
Background: The one-month 1HP regimen (daily rifapentine (RPT) + isoniazid (INH)) effectively treats latent TB in people with HIV (PWH). RPT induces hepatic enzymes that lower dolutegravir (DTG) exposure. A pharmacokinetic (PK) analysis of 32 PWH who received 1HP in ACTG A5372 showed that DTG 50 mg twice daily achieved day-28 DTG trough concentrations higher than those with 50 mg once daily without RPT/INH. We studied whether genetics that affect DTG (UGT1A1 rs887829) and RPT (AADAC rs1803155) PK impacted the RPT-DTG interaction.

Methods: In A5372, adult PWH on DTG-containing ART with HIV-1 RNA <50 c/mL and an indication to treat latent TB received daily RPT/INH (600mg/300mg) for 28 days. DTG was increased to 50 mg twice daily during 1HP. Intensive PK sampling was performed on day 0 (DTG 50 mg once daily without 1HP), and on day 28 (DTG 50 mg twice daily with 1HP). PK and demographics were summarized as median (Q1, Q3). Linear regression models for log-transformed observed DTG trough concentrations were adjusted for BMI. Models with AADAC also adjusted for UGT1A1.

Results: Thirty participants were evaluable for genetic associations, including 11 (37%) cis-gender females, 19 (63%) Black/Africans, 8 (27%) Asians; median BMI was 24 (22, 26) kg/m^2. Median day-0 DTG trough was 1745 (1099, 2694) ng/mL, and day-28 was 2146 (1412, 2484) ng/mL. UGT1A1 rs887829 was associated with DTG trough at days 0 and 28. At day 28, DTG trough was higher with TT (geometric mean ratio (GMR)=1.65; 90% CI 0.97, 2.78) and CT (GMR=1.38; 90% CI 1.02, 1.86) than with CC. AADAC rs1803155 was associated with day-28 DTG trough, which was higher with GG (GMR=1.79; 90% CI 1.09, 2.93) and AG (GMR=1.48; 90% CI 1.14, 1.90) than with AA (Figure, panel A). Considering both genes, participants with 4 risk alleles for lower DTG trough (UGT1A1 CC + AADAC AA) had median day-28 DTG trough of 1205 (1063, 1897) ng/mL. Those with 1 risk allele had day-28 DTG troughs of 3882 (TT/AG) and 3717 (CT/GG) ng/mL. Those with 2 or 3 risk alleles had intermediate troughs. (Figure, panel B).

Conclusion: In PWH receiving DTG 50 mg twice daily with 1HP, AADAC rs1803155 was associated with lower day-28 DTG trough (still >324 ng/mL, the DTG EC$_{90}$ for wild-type HIV-1), likely due to higher RPT concentrations causing greater hepatic enzyme induction. Individuals with concomitant AADAC slow metabolizer + UGT1A1 normal metabolizer genotypes (17% of Africans, 15-30% of people worldwide) may be at risk for low DTG trough concentrations with once daily DTG and RPT.



Associations with DTG trough. Panel B indicates total risk alleles rs887829C + rs1803155A.

607 Population Pharmacokinetic Approaches to Standardize Antiviral Exposure in the Cerebrospinal Fluid

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Background: HIV has been shown to persist in the central nervous system (CNS) in persons on antiretroviral therapy (ART). Consequently, CNS persistence may be linked to inadequate ART exposure. When assessing CNS drug levels in participants on ART, it is difficult to estimate drug exposure given sparse sampling and to standardize exposure given different sampling times among participants. We describe pharmacokinetic (PK) methods to estimate CNS exposure (maximum concentration [C_{max}] , area under the curve [AUC], and trough [C_{Trough}]) among individuals that allows a standardized evaluation of relative CNS drug exposure.

Methods: A5321 is a prospective study of HIV-1 reservoirs among persons with HIV on long-term virologically-suppressive ART. 59 participants had plasma and cerebrospinal fluid (CSF) concentrations measured ranging from 1 to 23hrs post ART dose. Population PK modeling was performed for FTC, TDF, EFV, 3TC, ATV/r, RAL, DTG, DRV/r, and EVG. The simplest PK model of plasma and CSF was considered for each ARV utilizing Pmetrics (version 1.5.0; Los Angeles, CA) for R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The final PK model was used to obtain predicted plasma and CSF estimates at 12-minute intervals from each participant's measured ARV plasma and CSF concentrations. Noncompartmental analysis was used to calculate AUC. Relative CNS penetration for each ARV was estimated by comparing CSF C_{max} and AUC to plasma C_{max} and AUC (i.e., relative CNS penetration= C_{max} _CSF/ C_{max}_Plasma and AUCCSF/ [Table 1]). The CSF CTrough for each ARV was compared to in vitro literature values of HIV inhibitory concentration values (IC_{50}or$_{90}$) for each ARV.

Results: Models converged for a combined plasma and CSF 3-compartment oral absorption model. FTC exhibited the highest median CSF penetration (C_{max}:46%, AUC:72%). The lowest median penetration was observed for both DRV/r (DRV C_{max}:0.95%, AUC:1%) and DTG (C_{max}:0.57%, AUC:0.57%). All ARVs had median CSF C^{T}_{rough} concentrations > IC_{50}or$_{90}$ except TFV: C_{Trough}:0.0016mg/L < IC_{50}:0.1437mg/L.

Conclusion: These methods demonstrate an approach of utilizing PK modeling to standardize drug levels to a given time point (i.e., C_{max} or C_{Trough}) and assess if desired therapeutic drug goals are obtainable in the CNS. Further studies are warranted to address whether CSF exposure as calculated using this method is associated with measures of HIV persistence in the CNS.

Table 1. Antiretroviral exposure summaries for all participants

ARV*	Observed CSF (mg/L) Median (IQR)	C_{max} (mg/L) CSF Median (IQR)	C_{Trough} (mg/L) CSF Median (IQR)	Median CSF% Penetration based off C_{max} ratio (CSF/Plasma)	Median CSF% Penetration based off AUC ratio (CSF/Plasma)
Emtricitabine N=59	0.09 (0.05-0.12)	0.426 (0.19-0.56)	0.04 (0.028-0.095)	46.3%	72%
Tenofovir (TDF) N=56	0.003 (0.002-0.005)	0.0073 (0.0067-0.008)	0.0016 (0.0003-0.0018)	3.33%	3.33%
Efavirenz N=20	0.019 (0.013-0.03)	0.041 (0.024-0.071)	0.012 (0.0080-0.022)	0.90%	0.92%
Lamivudine N=14	0.085 (0.05-0.112)	0.17 (0.11-0.20)	0.049 (0.02-0.056)	25%	26.53%
Atazanavir N=13	0.008 (0.004-0.01)	0.025 (0.01-0.043)	0.004 (0.0009-0.011)	1.16%	1.22%
Raltegravir N=9	0.04 (0.02-0.04)	0.055 (0.032-0.067)	0.0058 (0.003-0.023)	7.75%	6.90%
Dolutegravir N=8	0.013 (0.01-0.014	0.0254 (0.3252-0.0254)	0.0104 (0.01018-0.0108)	0.57%	0.57%
Darunavir N=5	0.02 (0.015-0.03)	0.038 (0.018-0.043)	0.015 (0.0058-0.015)	0.95%	1.00%

*Elvitegravir not shown.

Abbreviations: ARV, antiretroviral; CSF, cerebrospinal fluid; IQR, interquartile range (25%-75%); PL, plasma; AUC, area under the curve; C_{max}, maximum concentration predicted; C_{Trough}, minimum concentration predicted (based on interval); TDF, tenofovir disoproxil fumarate formulation

608 Antiretroviral Concentrations in Post-Mortem Tissues: Preliminary Results From the Last Gift Program

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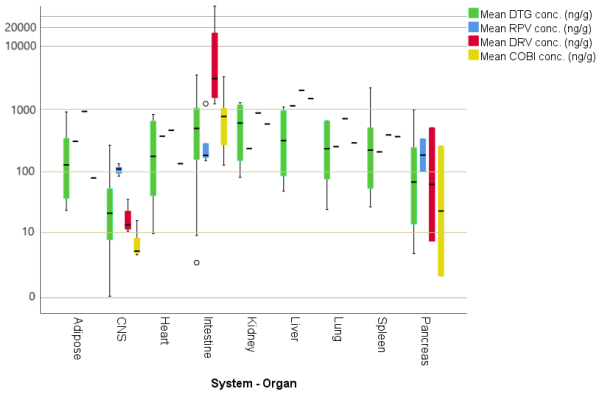
Background: Antiretroviral therapy (ART) successfully inhibits HIV replication but cannot eradicate the viral reservoir in various anatomic compartments. This is partially due to differential antiretroviral (ARV) drug penetration in different compartments. In humans, ARVs measurement in reservoirs is complicated by technical and ethical obstacles in performing tissue biopsies in vivo. Here

we present a map of ARVs penetration across different post-mortem tissue homogenates from altruistic participants recruited in the Last Gift program.
Methods: People with HIV with terminal illness who gave written informed consent were enrolled. All participants were on suppressive ART until the time of death. Tissue samples were collected through rapid research autopsy (<6h after death) and immediately snap frozen in liquid nitrogen. Non-nucleosidic ARVs intra-tissue concentrations were determined through an UHPLC-MS/MS validated method, with accuracy and precision within the requirements of FDA guidelines, after homogenization of 2 aliquots (about 30 mg) of tissue for each sample. The results were normalized by weight and the mean values were reported as results.
Results: 21 tissue biopsies per participant were isolated from different anatomical sites in 6 volunteers on different ART regimens: 3 on tenofovir alafenamide/emtricitabine (TAF/FTC) and dolutegravir (DTG), 1 on TAF/FTC+DTG plus rilpivirine (RPV), 1 on DTG and darunavir/cobicistat (DRV/c) and 1 on abacavir/lamivudine (ABC/3TC)/DTG. DTG had a higher exposure in intestine, kidney, and liver and lower in central nervous system (CNS) and pancreas ($p<0.001$ and $p=0.012$ compared to intestine, respectively). DRV, RPV and cobicistat (COBI), in a lower sample size (1 participant/drug), showed a higher exposure in liver and intestine, compared with other anatomical sites as reported in Fig.1. No statistical differences were observed in the overall ARVs penetration in different areas in the brain ($p=0.971$) and intestine tracts ($p=0.941$).
Conclusion: Scarce data on human intra-tissue ARV penetration are reported in literature. This is the first study to report different ARV concentrations in different anatomical sites in humans. Previous studies on non-human primates showed similar results about the poor, but rather uniform, concentrations of DTG in all the districts of the CNS, and higher concentrations in kidney and intestine.



609 Tenofovir Diphosphate Benchmarks in Dried Blood Spots in PWH Receiving TAF-Based ART (QUANTI-TAF)

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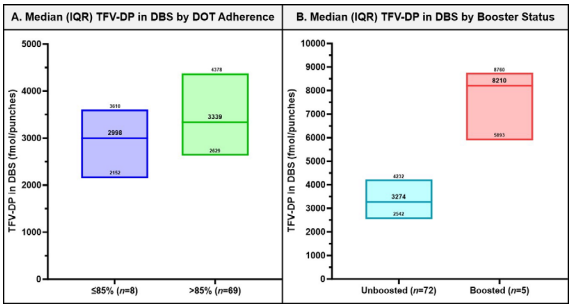
Background: Tenofovir diphosphate (TFV-DP) concentrations in dried blood spots (DBS) in people with HIV (PWH) receiving tenofovir alafenamide (TAF)-based antiretroviral therapy (ART) are not defined. QUANTI-TAF (NCT04065347) aimed to establish adherence:concentration benchmarks in PWH receiving TAF-based ART by quantifying TFV-DP concentrations in DBS, leveraging digital pills to organically capture directly observed therapy (DOT) adherence in a real-world clinical cohort.
Methods: PWH receiving TAF-based ART for ≥6 months were prospectively enrolled in a 16-week pharmacokinetic study. Digital pills captured DOT adherence by co-encapsulation of each TAF-based ART dose with an ingestible biosensor powered by gastric fluid. Blood for TFV-DP concentrations in DBS (fmol/2x7mm punches) was collected at each visit and quantified using a validated LC-MS/MS method. TFV-DP steady-state concentrations (Css) in DBS were assessed at weeks ≥12 overall, by DOT adherence, booster status, and HIV viral load (VL; all weeks), reported as median (IQR).
Results: N=84 participants (median age 54 [43, 59] years) receiving TAF for median 32 (18, 45) months were enrolled. Most were males (89%) receiving integrase strand transfer inhibitors (88%). Race/ethnicity was 55% White, 24% Black, and 21% Hispanic/Latino. TFV-DP Css in DBS (n=77) were median 3301 (2580, 4362) fmol/punches. PWH with ≤85% DOT adherence (n=8) had median 2998 (2152, 3610) fmol/punches; PWH with >85% DOT adherence (n=69) had median 3339 (2629, 4378) fmol/punches (A). TFV-DP Css in DBS were higher with boosted (b/) than unboosted (un/) ART. PWH receiving un/ART (n=72) had median 3274 (2542, 4232) fmol/punches; PWH receiving b/ART (n=5) had median 8210 (5893, 8760) fmol/punches (B). No HIV VL was >200 cps/mL. Low-level viremia (LLV) occurred at 60/335 (18%) visits from 33/84 (39%) participants (VL range: 20-149 cps/mL), with similar TFV-DP concentrations in DBS: median 3176 (2494, 4145) fmol/punches at LLV visits, median 3278 (2585, 4404) fmol/punches at suppressed (VL <20 cps/mL) visits. Digital pills were well tolerated.
Conclusion: We describe initial TFV-DP benchmarks in DBS in PWH receiving TAF-based ART as digital pills to capture DOT adherence in a real-world clinical study. We observed higher TFV-DP Css with b/ART than un/ART. The lack of relationship between LLV and TFV-DP concentrations in DBS in this cohort suggests mechanisms other than variable adherence for LLV. Future analyses will explore additional factors that may be associated with LLV.



610 Factors Affecting TFV-DP Concentrations in PBMC and Relationships With DBS in PWH on TAF-Based ART

Stefanie Schwab[1], Mary Morrow[1], Corwin Coppinger[1], Ryan P. Coyle[1], Vincent Mainella[1], Sarah C. Mann[1], Nicholas Barker[1], Lucas Ellison[1], Samuel L. Ellis[1], Pamela E. Alpert[2], Lane Bushman[1], Samantha MaWhinney[1], Kristina M. Brooks[1], Jose R. Castillo-Mancilla[1], Peter L. Anderson[1]
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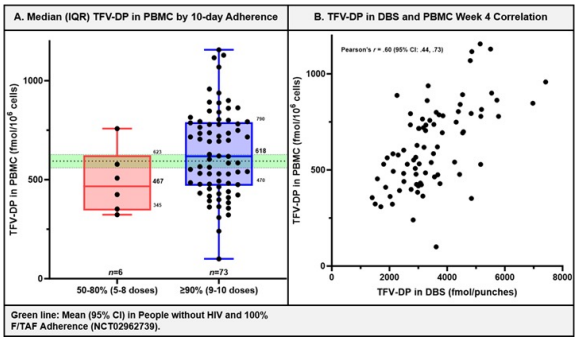
Background: Relationships between tenofovir-diphosphate (TFV-DP) steady-state concentrations (Css) in peripheral blood mononuclear cells (PBMCs), dried blood spots (DBS), and adherence have not been well-described in people with HIV (PWH) on tenofovir-alafenamide (TAF)-containing antiretroviral therapy (ART). Our objectives were to assess the influence of adherence and other factors on TFV-DP Css in PBMCs, and to examine relationships between TFV-DP Css in DBS and PBMC.
Methods: QUANTI-TAF was a 16-week observational study that enrolled PWH on TAF-based ART for >6 months. Study visits occurred at weeks 0, 4, 8, 12, and 16. Blood was collected for TFV-DP in DBS (2x7mm punches) and PBMC (per 106 cells) at each visit and quantified using validated LC-MS/MS methods. Adherence was quantified using TAF-based ART co-encapsulated with an ingestible biosensor (calculated as # ingestions in the 10 days before each visit). Week 4 TFV-DP Css in PBMC were dichotomized by 5-8 vs. 9-10 days of dosing in the 10-day window. A linear mixed-effects model with backward selection was used to evaluate factors associated with TFV-DP Css in PBMC (all visits), and included adherence, age, sex, weight, BMI, race, eGFR, CD4, and NNRTI or INSTI. Pearson correlation compared week 4 TFV-DP Css in DBS and PBMC.
Results: Data were available in 84 PWH (55% White, 24% Black, 21% Hispanic/Latino) on TAF for median (IQR) 32 (18, 45) months (79 unboosted [un/], 5 boosted [b/]). Median (IQR) age was 54 (43, 59) years; most were males (89%) on INSTIs (88%). Median TFV-DP Css in PBMC in PWH on un/ART were 32% higher for 9-10 vs. 5-8 days of dosing (Fig. A). Median TFV-DP Css for b/ART was 72% higher than un/ART (1007 [IQR: 868, 1297] vs. 585 [IQR: 459, 780] fmol/106 cells, respectively). Ten-day adherence was the only significant predictor, with every 10% adherence increase associated with an average TFV-DP in PBMC increase of 32 (95% CI: 14, 49; P=0.0005) fmol/106 cells. Week 4 TFV-DP Css in DBS and PBMC were moderately correlated (Fig. B).

Conclusion: 10-day digital pill adherence was a significant predictor of TFV-DP in PBMC. TFV-DP was higher in PWH on b/ART, which may enhance virologic effect, dose forgiveness, and/or side effects. TFV-DP in DBS and PBMC were moderately correlated, which may be due in part to TFV-DP in PBMC being more susceptible to recent non-adherence given the shorter half-life in PBMC vs. DBS (2 vs. 17 days). Further investigation of other factors contributing to variability in TFV-DP in PBMCs is warranted.



611 Adherence Markers for Doxy-PEP in Plasma and Urine

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Background: Clinical trials of Doxy-PEP demonstrated high efficacy in preventing bacterial sexually transmitted infections (STIs) among men who have sex with men but not in women. Low Doxy-PEP efficacy observed among women may be related to poor adherence highlighting the importance of objective adherence monitoring in future trials and implementation studies. We examined doxycycline (DOXY) concentrations in urine and plasma, two specimen types commonly collected for STI testing, following a single oral DOXY dose to identify objective adherence markers of Doxy-PEP dosing.

Methods: Eleven male and 9 female participants provided blood and urine up to 7 days after receiving a 200 mg oral DOXY dose. DOXY was measured in plasma and urine by liquid chromatography-mass spectrometry with a lower limit of quantification of 10 ng/mL. DOXY concentrations are reported as median and interquartile range. Adherence indicators were identified as the 10th percentile concentration at each time point.

Results: Plasma DOXY concentrations peaked 2 hours after dosing and declined to 0.487 µg/mL (0.402 – 0.682 µg/mL) 24 hours after dosing. Plasma DOXY remained measurable in all participants 96 hours after dosing (0.043 µg/mL; 0.032 – 0.067 µg/mL) but became undetectable in 13 of 16 participants by 7 days post dose. Urine DOXY concentrations were significantly greater than those in plasma with a urine to plasma ratio of 38:1 (9:1 – 103:1; $p < 0.001$). Urine DOXY concentrations also peaked 2 hours after dosing and declined to 13.1 µg/mL (6.8 – 28.5 µg/mL) 24 hours after dosing but remained measurable in 15 of 16 participants 7 days after dosing at 0.202 µg/mL (0.137 – 0.318 µg/mL). DOXY adherence indicators for plasma were determined to be 0.30 and 0.03 µg/mL at 1 and 4 days after dosing, respectively, while urine adherence indicators were determined to be 3.00, 0.35 and 0.07 µg/mL at 1, 4 and 7 days after dosing, respectively. Concentrations were not significantly different between male and female participants at each time point.

Conclusion: We identified adherence measures after a single DOXY dose within a pharmacologic tail of 4 and 7 days in plasma and urine, respectively. The data will inform and enable adherence testing in clinical studies to better assess Doxy-PEP efficacy.

612 Safety and PK/PD of a Tenofovir Rectal Douche Administered in Different Sequences, DREAM-03

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Background: On-demand and behaviorally congruent forms of HIV pre-exposure prophylaxis (PrEP) have long been requested by communities at risk of HIV, especially men who have sex with men (MSM). Previously in DREAM-01, we reported safety, acceptability, and pharmacokinetics/pharmacodynamics (PK/PD) of three single-dose tenofovir (TFV) rectal douche formulations in MSM and identified a lead formulation. Given that MSM report using multiple douches for cleanliness prior to receptive anal intercourse, DREAM-03 sought to report safety and PK/PD outcomes when using multiple TFV douches with and without water douches.

Methods: TFV douche products that consisted of 660 mg TFV in 125 mL hypo-osmolar saline were tested in three sequences: (A) three TFV douches, (B) one TFV douche then two tap water douches, and (C) two tap water douches then one TFV douche. We collected blood over 168 hours post-dose and rectal swabs/tissue biopsies over 72 hours. TFV and TFV diphosphate (TFV-DP) concentrations were quantified using validated methods. Anti-HIV effect was evaluated using an ex vivo colonic explant HIV challenge method with biopsies collected over 6 hours post-dose. An HIV p24 assay was used to quantify viral replication. Results among different sequences were compared using Wilcoxon signed-rank tests.

Results: Nine male participants were enrolled, with a median (range) age of 38 (29, 52) years and a median weight of 77 (64, 113) kg. No grade >2 study related adverse events were reported. Plasma TFV concentrations at 4 and 6 hours were significantly higher (4.9- and 6.5-fold, respectively) in sequence A than those in sequence B (Figure 1A). A trend of higher TFV-DP concentrations in rectal mucosal mononuclear cells (MMCs) at 24 and 72 hours in sequences A (12.0- and 3.5-fold, respectively) and C (5.1- and 4.2-fold, respectively) than those in sequence B were also observed (Figure 1B). Compared to pre-drug baseline, HIV replication after ex vivo HIV challenge demonstrated a concentration-response relationship with 2.8 log, 2.2 $\log_{10}$, and 2.2 $\log_{10}$ maximal effects for sequences A, B, and C, respectively.

Conclusion: Our result demonstrates that administering three TFV rectal douches are well tolerated. In addition, using non-medicated douches after a TFV douche may likely reduce both systemic and local TFV exposures, and may subsequently compromise anti-HIV effect of the TFV douche. Our study suggests that after non-medicated douches, a TFV douche should be used to provide better protection against HIV.

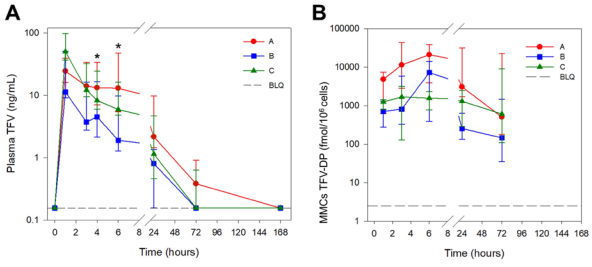

Figure 1. (A) TFV concentrations in plasma and (B) TFV-DP concentrations in rectal mucosal mononuclear cells (MMCs) over time. Data is represented as median (interquartile range); *p<0.05 comparing 4- and 6-hour data between sequences A and B; BLQ is set to LLOQ/2; no rectal MMCs collected at 168 hours.

613 Early Identification of ART Missed Doses: Baseline Data From the RETAIN Study

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Background: We present baseline data from "Improving RETention and viral load outcomes for people taking Antiretroviral therapy through early IdentificatioN of missed doses (RETAIN)", a cohort study exploring detailed adherence metrics [viral load (VL), electronic adherence monitoring (EAM);

tenofovir diphosphate (TFV-DP) concentrations and self-report (SR)] in people on ART, when initially flagged for reduced adherence.

Methods: ART-naïve people from three Cape Town ART clinics had adherence monitored by missed doses (EAM), missed clinic visits or by raised VL. At the time of first flagging by any measure, participants received an adherence support call, and were invited for blood draw for HIV-1 VL and TFV-DP (indicating dosing over 4-8 weeks); urine collected for tenofovir rapid assay (indicating dosing over 3-5 days). SR adherence and EAM data were collected for the prior 30 days. Initial adherence data at the time of first non-adherence are presented here.

Results: Between July22 and August23, 116 of 427 (27%) people were flagged for poor ART adherence; 93(80%) by missed doses, 20(17%) by missed visits and 3(3%) by raised viral load. 87 (75%) were women, with mean (±SD) age of 28 (±8) years. Median (IQR) self-reported adherence was 90% (83-97) doses taken in past 30 days; EAM showed reduced adherence across all groups 57% (16-77) doses taken over past 30 days; with suboptimal median (IQR) TFV-DP concentrations: 567 (263-864) fmol/punch (normal range >800fmol/punch)]. 89(76.7%) had tenofovir in their urine. 35 (30%) of all individuals had VL>50 copies/ml. The median VL was suppressed in all groups by the time of the blood draw. Missed doses and missed visit were flagged sooner: median (IQR) 39 (21-88) and 75(42-117) days than raised viral load: 134(94-194) days. Non-parametric analysis showed no significant associations between flagging method and TFV-DP concentrations, EAM or VL at this early stage of the study.

Conclusion: All those flagged for reduced adherence had poor adherence confirmed by objective measures, EAM and TFV-DP concentrations, despite self-reporting near perfect dosing. Positive urine tenofovir reflects reasonable dosing near to the study visit (white-coat dosing). A third of the cohort were viraemic. Poor adherence was noted most rapidly by detection of missed doses and missed visits; allowing time for adherence support before breakthrough viraemia occurs.

Table 1: Early Identification of ART missed doses: baseline data from the RETAIN study.

Flagged by:	n	Days from ART start to awareness of reduced adherence: median (IQR)	Self - reported 30-day adherence (%): median (IQR)	Individuals with positive urine tenofovir: (%)	Electronic adherence (%) over past 30-days: median (IQR)	TFV-DP in DBS (fmol/punch): median (IQR)	Individuals with viraemia (>50 copies/ml): N (%)
Missed doses	93	39 (21-88)	87 (83-96)	77	58 (20-74)	569 (262-815)	28 (30)
Missed visits	20	75 (42-117)	90 (83-95)	70	38 (16-80)	567 (288-871)	6 (30)
Raised viral load	3	134 (94-194)	100 (83-100)	100	0 (0-86)	229 (61-713)	1 (33)
Total	**116**	**42 (29-102)**	**90 (83-96)**	**77**	**57 (16-77)**	**567 (262-840)**	**35 (30)**

614 Baseline Urine Methamphetamine (UTOXM) Predicts ART Adherence and Poor Retention in Care Attributes

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Background: The CDC estimates 57% of US persons with HIV (PWH) achieve viral suppression. Early initiation of ART is recommended, but objective baseline tests with predictive ability to distinguish persons at risk of poor ART adherence and engagement in care are lacking. We evaluated the utility of baseline urine toxicology testing for methamphetamine (UTOXM) use in PWH starting oral ART in our West Coast US setting to predict adherence and characteristics associated with poor engagement in care.

Methods: PWH initiating ART with ingestible-sensor-enabled antiretroviral technology (IS-ARVs) to observe medication taking for the first 16 weeks of treatment had a baseline UTOXM, with demographics and self-report questionnaires obtained. UTOXM ability to predict IS-ARV-confirmed doses (taking & timing); persistence on study; and baseline demographics and questionnaires were analyzed using mixed-effects logistic regression; Kaplan-Meier curves; and linear models, respectively. No causal analyses were attempted.

Results: Sixty-three enrolled participants prescribed IS-ARVs had median age 37 (IQR 30-46) yrs, 82.5% were male, 33.3% White, 34.9% Hispanic, 22.2% African American, 3.2% Asian. UTOXM was negative in 42, positive in 21. Over 6049 observation days evaluated in longitudinal mixed effects logistic regression revealed a negative baseline UTOXM (compared to those who tested positive) was associated with a daily confirmed dose odds ratio (OR) of 3.12 (CI 1.71-5.71), P<0.001 and a regularity of dose timing OR of 5.05 (CL 2.43-10.6), P<0.001. A baseline positive UTOXM (vs negative) was associated with: higher homelessness/transient housing rate (52.4% vs 21.4% P=0.028); lower mean income $7,400 vs $31,500, P=0.042; more depression as measured by Mood PHQ8 11.8 vs 6.9, P=0.001 and higher Life Chaos score 14.2 vs 9.0, P=0.001. UTOXM positive 16-week persistence on study was 0.333 (0.182-0.610) vs negative 0.619 (95% CI 0.488-0.785), P=0.0098.

Conclusion: Baseline positive UTOXM in PWH starting oral ART predicted highly significant differences in treatment adherence & persistence on study (a surrogate for care retention); and identified a distinct subpopulation in our West Coast US setting with multiple attributes, including life chaos & depression, associated with poor care engagement. Baseline UTOX may be a useful, simple screening tool to identify PWH requiring differentiated care and adherence support on initiation of oral ART, and may be easily employed in mobile testing sites offering quick start care.

615 Preclinical to Human Scaling of Pharmacokinetics for Long-Acting Injectable Antiretrovirals

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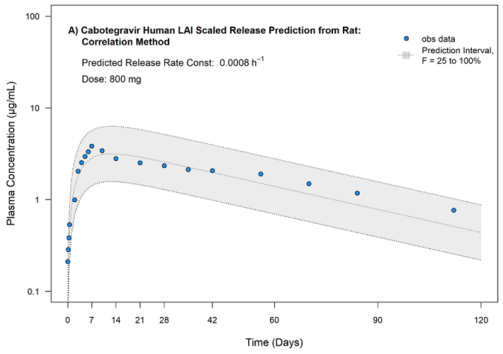
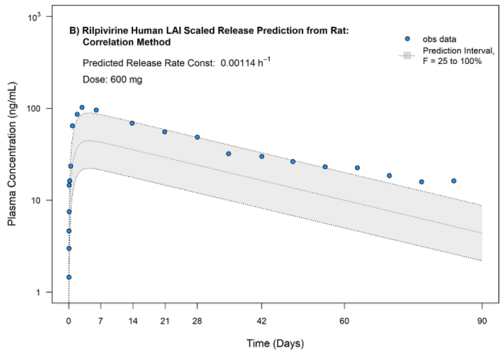
Background: Long-acting injectables (LAIs) have attracted interest for prevention and treatment of infection (including HIV, HCV and tuberculosis), addressing issues with pill burden and adherence. Better methods for scaling preclinical pharmacokinetics (PK) for prediction of human exposure are needed to aid decision making, and accelerate early clinical development through better human dose prediction.

Methods: Matching rat and human PK data were sourced from publications or in-house PK studies for 11 marketed intramuscular LAIs. Terminal depot release rates (KA) were determined from analysis of terminal phase, release-dependent, "flip-flop" half-lives. Two approaches for human KA prediction were: 1) Linear regression between human and rat KAs (Fig 1A). 2) Allometric scaling of KA by body size according to formula: KA (human, pred) ≈ KA (rat) x (70 kg/0.3 kg)-0.25 = KA (rat) x 0.255. Qualification was undertaken for cabotegravir and rilpivirine with human LAI PK profiles simulated for comparison with empirical human PK data. For this, human PK disposition was described by a minimal 1-compartment model parameterised with clearance (CL) and steady state volume of distribution (Vss) from published IV PK if available, or via PBPK where absent. This model was deemed sufficient under flip-flop PK due to slow LAI depot release masking multiphasic PK disposition. Depot release input was treated as a simplified 1st order process governed by KA. For qualification, the LAI of interest was removed from the regression used to predict the KA. Given that bioavailability (F) is unknown for novel LAIs and varies for approved LAIs, profiles were simulated assuming 25, 50 and 100% F.

Results: A variety of PK profile shapes were evident across LAIs and terminal flip-flop KAs trended faster in rat than human. A good correlation was observed between human and rat KA with all 11 LAIs included (R2 = 0.81, slope coeff. 0.38), and retained with the removal of cabotegravir (R2 = 0.82) or rilpivirine (R2 = 0.81). Reasonable concordance of resulting human PK predictions was observed for cabotegravir (assuming 50% F; Fig.1A) and rilpivirine (assuming 100% F; Fig.1B).

Conclusion: This simplified scaling may be useful to predict human terminal release PK from rat studies to inform phase I human dose prediction. More work is needed to predict LAI F, and understand relationships across other species and routes of administration. Final validation of the approach will require a priori application for a novel LAI.





616 Pharmacokinetics of Long-Acting Cabotegravir and Rilpivirine in Elderly Using PBPK Modelling

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Background: The quality of life of people with HIV (PWH) has significantly increased thanks to potent single pill antiretroviral regimens characterized by a good tolerability. Another milestone has been reached with long-acting (LA) formulations which enable infrequent dosing. Clinical trials of LA agents were mostly conducted in standard populations, leading to a lack of knowledge on their pharmacokinetics in elderly PWH. Physiologically based pharmacokinetic (PBPK) model is a mathematical tool approved by the regulatory authorities used to simulate clinical unknown scenarios. The aim of this study was to determine the pharmacokinetics of LA cabotegravir and rilpivirine in virtual elderly individuals.

Methods: Our in-house PBPK model built in Matlab®2020a and implemented with an intramuscular framework was verified against clinical observed data for cabotegravir and rilpivirine after oral and intramuscular administration. As for PBPK modelling guidelines, the model was considered verified when the predictions were within 2-fold of clinical observed data. The effect of ageing on the pharmacokinetics of LA cabotegravir and rilpivirine was evaluated by using two separate cohorts of virtual individuals aged 20-50 (50% female) and 65-85 (50% female), respectively. The design of the ATLAS/FLAIR and ATLAS-2M studies was reproduced in our PBPK model and the fold change in elderly relative to young was determined for area under the concentration-time curve (AUC) and trough concentration (C_{min}) at steady state.

Results: The PBPK model was successfully verified as all the predictions were within 2-fold of clinically observed data. Age related physiological changes did not significantly impact the C_{min} and AUC of LA cabotegravir administered every month (Q4W), and the AUC of LA rilpivirine Q4W since the ratios (elderly vs young) were predicted to be within the bioequivalence range (0.8-1.25 fold). On the other hand, the Cmin of LA rilpivirine administered Q4W was 28% higher in elderly relative to young. Additionally, the Cmin and AUC of LA cabotegravir administered every other month (Q8W) were predicted to be 29% and 26% higher in elderly relative to young, respectively. Similarly, the Cmin and AUC of rilpivirine Q8W were 46% and 41% higher in elderly (Fig. 1).

Conclusion: Age related physiological changes are predicted to modestly increase the AUC and Cmin of LA cabotegravir and rilpivirine. Thus, elderly PWH could possibly be at lower risk for sub-optimal drug exposure at the end of the dosing interval.

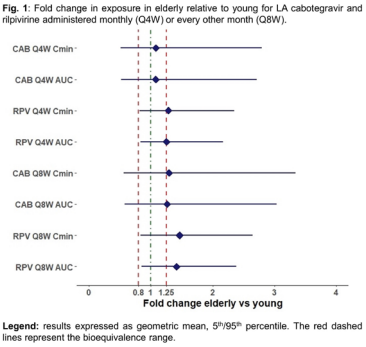

Fig. 1: Fold change in exposure in elderly relative to young for LA cabotegravir and rilpivirine administered monthly (Q4W) or every other month (Q8W).

Legend: results expressed as geometric mean, 5th/95th percentile. The red dashed lines represent the bioequivalence range.

617 Model-Based Comparison of Cabotegravir Pharmacokinetics Following Thigh and Gluteal Injections

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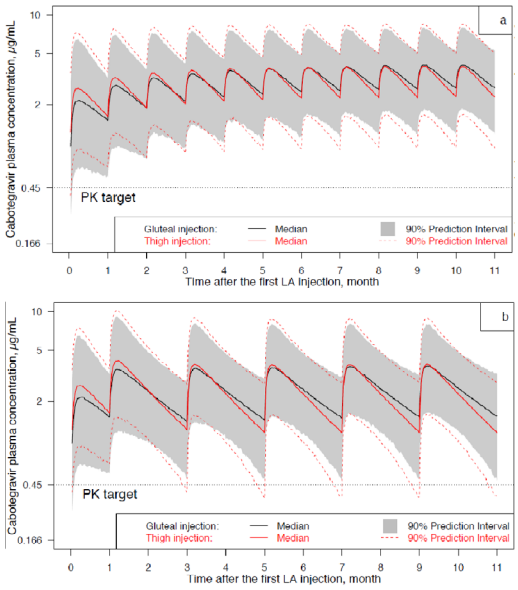
Background: Cabotegravir (CAB) long-acting (LA) intramuscular (IM) gluteal injections are approved for HIV-1 pre-exposure prophylaxis (PrEP) and combination treatment with rilpivirine. The *vastus lateralis* (lateral) thigh muscle is a potential alternative site of administration in cases of gluteal injection fatigue or physical obstruction. We aimed to characterize CAB pharmacokinetics (PK) and its association with demographics following thigh administration in comparison to gluteal administration using population PK (PPK) analysis.

Methods: Fourteen participants (pts) who were HIV-negative and received a 600mg single thigh injection in Phase 1 Study 208832 and 118 pts who were HIV-positive and received thigh injections [400mg monthly (QM) x 4 or 600mg every-2-months (Q2M) x 2] after >3 years of gluteal injections in Phase 3b Study 207966 (ATLAS-2M) provided CAB concentrations for the analysis. An established gluteal PPK model was fit to PK data following both gluteal and thigh injections, enabling within-person comparison in ATLAS-2M pts. Gluteal parameters were fixed. Thigh parameters including absorption rate constant (KA-thigh) and bioavailability (F-thigh) were estimated. CAB PK profiles following chronic or intermittent thigh injections administered QM and Q2M were simulated and compared to gluteal injections. PK target was that 95% of pts maintain concentrations >0.45 µg/mL, the 5th percentile of observed CAB trough concentration following the gluteal initiation injection in Phase 3 Studies.

Results: 1254 concentrations from 366 thigh injections and 2022 concentrations from 1631 gluteal injections were analyzed. Similar to gluteal administration, KA-thigh was associated with sex and BMI. KA-thigh was correlated with and was generally faster than KA-gluteal, described by the additive linear relationship: KA-thigh = KA-gluteal + 0.000253 h^{-1}. Terminal half-life of thigh administration was 26% (male) and 39% (female) shorter than for gluteal administration. F-thigh was 90% of gluteal injection. PK target was maintained following chronic QM thigh injections or alternating thigh-gluteal injections for either QM or Q2M regimens but not following chronic Q2M thigh injections. (Figure).

Conclusion: PPK modeling and simulation support chronic thigh administration of CAB LA QM and intermittent thigh injections for both QM and Q2M regimens. However, simulated chronic Q2M thigh administration did not maintain PK target established in pivotal trials and therefore is not recommended.

Figure. Simulated chronic CAB QM (a) and Q2M (b) administration to the lateral thigh and gluteal muscles (25% female population).



618 Effect of Broadly Neutralizing Antibody Exposure on HIV Rebound Following Combination Immunotherapy

Amelia N. Deitchman[1], Leonid Serebryannyy[2], Rowena Johnston[3], Lucio Gama[2], Marina Caskey[4], Elena Vendrame[5], Devi SenGupta[5], Romas Geleziunas[5], Jackie Reeves[6], Christos Petropoulos[6], Michel Nussenzweig[4], Rachel Rutishauser[1], Steven G. Deeks[1], Michael J. Peluso[1], for the UCSF-amfAR Study Team

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Background: Waning broadly neutralizing antibody (bNAb) levels and emergence of resistance have been associated with viral rebound during analytic treatment interruption (ATI) studies. In this pharmacokinetic/pharmacodynamic (PK/PD) analysis, we evaluated the impact of bNAb exposure, susceptibility, and antidrug antibody (ADA) formation on rebound kinetics following combination immunotherapy with a boosted DNA vaccine, lefitolimod, and bNAbs (10-1074 and VRC07-523LS) (NCT04357821), in which 7/10 individuals exhibited altered post-intervention rebound dynamics.
Methods: We described plasma bNAb PK using population PK modeling approaches in Monolix software. We performed Spearman correlations or Wilcox's test to determine the relationship between bnAb AUC, peak concentration (C_{max}), and bNAb level at time of rebound and rebound kinetics (time to rebound, post ATI setpoint). We evaluated susceptibility (IC_{90}) relative to bNAb level (i.e., IQ_{90}: bNAb level/IC_{90}). We performed competitive and functional ADA assays for both bNAbs.
Results: Time to Rebound: Greater bNAb exposure for 10 participants (9 cis men, 1 trans woman) was associated with later rebound (VRC07-523LS AUC ρ=0.76, p=0.04; 10-1074 C_{max} ρ =0.7, p=0.04). In those who rebounded later (>15 weeks), VRC07-523LS and 10-1074 levels were lower at the time of rebound (both p=0.01), with a similar trend observed for IQ_{90} (p=0.01 and p=0.03, for each bNAb). There was no association between IC_{90} and time to rebound.
Post intervention setpoints: Although there was no association between VRC07-523LS IC_{90} and setpoint, higher VRC07-523LS IQ_{90} at the time of rebound was associated with higher post-intervention setpoint (ρ = 0.85, p=0.006). No association between 10-1074 IQ_{90} or IC_{90} and setpoint were observed. Antidrug antibody: While ADA was detected for two participants for competitive assays for both bNAbs, no functional ADA impacting PK was observed.
Conclusion: Higher bNAb exposure (e.g., AUC, C_{max}) was consistently associated with delayed viral rebound. Our results suggest that post-treatment setpoint was not driven by bNAb susceptibility and that the association of IQ_{90} and setpoint is driven by higher VRC07-523LS levels at the time of rebound in those who rebounded earlier and had higher setpoints. Overall, bNAb PK-PD is likely not responsible for lower observed post-treatment setpoints during this trial, suggesting the effect is likely attributable to changes in anti-HIV immune function.
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619 A Randomized, Adaptive Phase I Study to Determine the Phase II Dose of VIR-7832: AGILE CST5

Richard J. FitzGerald[1], Chris Edwards[2], Jimstan Periselneris[3], Geoff Saunders[4], Nicky Downs[4], Rebecca Lyon[5], Danny Pratt[2], Helen Reynolds[1], Lauren Walker[1], Gareth Griffiths[4], Saye Khoo[1], Thomas Fletcher[6], for AGILE CST[5]

[1]University of Liverpool, Liverpool, United Kingdom, [2]NIHR Southampton Clinical Research Facility, Southampton, United Kingdom, [3]King's College Hospital NHS Foundation Trust, London, United Kingdom, [4]University of Southampton, Southampton, United Kingdom, [5]NIHR Liverpool Clinical Research Facility, Liverpool, United Kingdom, [6]Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Background: Despite widespread COVID-19 vaccination, anti-virals remain important for COVID-19 treatment. Early treatment is crucial to avoid progression and severe disease, with monoclonal antibodies (mAb) offering possible advantages in single dosing and duration of effect. VIR-7832 is a novel mAb derived from the same parental antibody as sotrovimab with addition of an Fc domain XX2 modification to enhance effector function and modulate immune response. Here we report data from the First-in-Human (FIH) trial of VIR-7832 in mild-moderate COVID-19 patients (AGILE CST5, NCT04746183).
Methods: Participants with PCR-confirmed mild-moderate COVID-19 infection, within 7 days of onset, were randomised (3:1, double-blind) to single dose VIR-7832 or placebo. Three cohorts of 8 participants were recruited, with dose escalation in between (Cohort 1-50mg, Cohort 2-150mg, Cohort 3-500mg) supported by a Bayesian dose-toxicity model. Participants were followed to day 253 post-dose, with assessments performed for safety (laboratory samples, electrocardiograms, vital signs), VIR-7832 pharmacokinetics (PK), patient reported outcomes (FLU-PRO PLUS) and viral swabs. The primary endpoint was safety & tolerability to day 8 (AEs, SAEs and dose-limiting toxicities (DLT, defined as CTCAE >/= grade 3)) with secondary endpoint of VIR-7832 PK and exploratory endpoint of SARS-CoV-2 viral dynamics (PCR swab at day 1,3,5,8,11,15,22,29).
Results: 24 individuals (8 female) were recruited. Median (range) age, BMI, number of days with Covid symptoms were 23.5 years (19-52), 22.9 Kg/m² (17.8-32.9), 5 days (2-7) respectively. For the primary endpoint, to day 8, 1 participant receiving 150mg VIR-7832 reported a DLT (syncope); beyond day 8, 2 more DLTs were reported in placebo group (diarrhoea, neutropenia). One SAE (dyspnoea, considered unrelated) was reported in a participant receiving 50mg VIR-7832. Skin rashes were reported by 2 participants receiving 150mg VIR-7832 (lichenoid reaction & maculopapular rash). Time to negative SARS-CoV-2 PCR in all participants in each cohort was 15 days for those receiving 50mg VIR-7832, 8 days for 150mg VIR-7832, 8 days for 500mg VIR-7832 and 22 days for placebo.
Conclusion: This is the first report of the safety, tolerability and viral outcomes for VIR-7832, a novel mAb for treating SARS-CoV-2. These data suggest VIR-7832 is safe and well tolerated at doses up to 500mg. SARS-CoV-2 PCR data are presented for each cohort; however, these data are limited by the small number of participants.

620 Gendered Inclusion in Studies Evaluating Injectable HIV Treatment and PrEP: A Scoping Review

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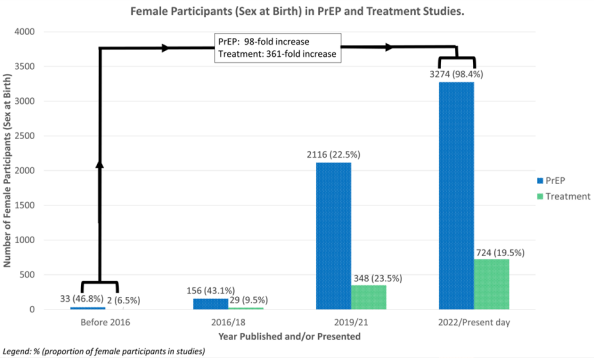
Background: Globally, 54% of people living with HIV (PLWH) are female (UNAIDS). Therapies containing long-acting injectable (LA-I) agents are included in treatment guidelines and licensed for pre-exposure prophylaxis (PrEP). In female participants, LA-I cabotegravir (CAB) is superior to oral PrEP. However, cisgender and transgender women are historically underrepresented in wider HIV research.
Methods: We report an ongoing scoping review to evaluate inclusion of women (cis/trans) and non-binary people (NBP) in Phase I-III clinical trials, implementation and real-world studies evaluating any LA-I agent for HIV treatment or PrEP. We searched electronic databases (PubMed, MEDLINE, Embase) and peer reviewed abstracts excluding studies with no report of sex or gender. Statistics were descriptive.
Results: We included 41 studies, 14 evaluated PrEP (34%) and 27 (66%) evaluated treatment. We included 27 clinical trials [Phase I (n=8); Phase II (n=12); Phase III (n=7)], 6 implementation and 8 real-world studies. 38 studies included sites in high-income countries and 13 included sites in low- and

middle-income countries. PrEP studies evaluated CAB 8 (57%), rilpivirine (RPV) 2(14%) and mono-clonal antibodies 4 (29%). Treatment studies evaluated CAB+RPV, lenacapavir, albuvirtide and monoclonal antibodies, [18 (67%), 5 (18%), 3 (11%), 1 (4%), respectively]. The number of female participants increased 98-fold in PrEP studies (2014-present), and 361-fold in treatment studies (2010-present). However, the percentage of female participants in LA-I treatment studies during 2022/3 remains disappointing [724/3709 (19%)]. From 2020, gender-targeted PrEP studies were established to ensure inclusive recruitment. Between 2019-2023, 42% of participants in PrEP studies were female (n=5390). Only 13/41 (32%) studies reported on self-identified gender. The number and proportion of transgender women, transgender men, and NBP included in treatment and PrEP studies was 728 (4%), 28 (0.2%) and 58 (0.3%), respectively.

Conclusion: The number of female participants in studies on LA-I treatment have significantly increased, but remain unacceptably low at 19% (2022/3) and do not reflect the global population. Gender-targeted PrEP studies have been effective at increasing numbers of females recruited. Transgender and NBP remain very poorly represented. A gender-targeted approach to inclusion in treatment studies is urgently needed and long overdue.



621 Implementing LA Cabotegravir (CAB)+Rilpivirine (RPV) Therapy in 6 UK Clinics & in the Community: ILANA

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Background: The feasibility of implementing CAB+RPV LA ART in the community has not yet been described. In the first UK-based study, we purposefully recruited participants more representative of the global population of PLWH to evaluate feasibility of implementation in 6 clinics (in & outside London) and in the community.

Methods: ILANA is a 1-year UK-based implementation study in PLWH who switched to CAB+RPV LA 2-monthly within the label. Participants receive CAB+RPV in the clinic for 6 months with an option to receive the drug in the clinic or community (eg home or community organization) from M6-M12. This prespecified M4 analysis evaluated PLWH perspectives on feasibility and acceptability of CAB+RPV LA and on potential community delivery through validated implementation questionnaires [Feasibility of Intervention Measure (FIM), Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), HIV Treatment Satisfaction Questionnaire (HIVTSQ-12)] at baseline and 4 months.

Results: Between May-December 2022 we enrolled 114 virally suppressed PLWH [53% female, 51% Black, 30% White, 40%> 50yrs, 68% heterosexual,75% employed]. Median time since diagnosis was 13 yrs (IQR 8, 19), time on ART was 11 yrs (IQR 7,16) with a mean of 3 prior regimens. 57% had received NNRTIs. 84% had other co-morbidities, and 80% (91/114) were taking non-ART medications. 75% (68/91) were on >2 non-ART drugs. 99% of injections were given within the 7-day window. There were 5 discontinuations by M4 (2 injection-related, 3 participant choice). 1 participant with VL 478 at M4 continued. Regarding injectable treatment: FIM, IAM and HIVTSQ scores improved significantly (baseline to M4) (Table). FIM, IAM and AIM scores regarding perceptions of the future prospect of receiving ART in the community setting (at M6) did not improve from baseline. 96% preferred injectable to oral ART at M4. At M4, IAM mean scores were significantly less favourable in Black participants than in White participants with respect to the injection (4.44 vs. 4.67; p=0.029) and the community setting (3 vs 3.75;p=0.003).

Conclusion: Over four months, participants found injections increasingly feasible, appropriate and satisfactory, and preferred them to oral ART. Pre-specified sub-group analyses based on gender and race and ethnicity revealed significant differences around perception of delivering LA ART in the community in Black participants. These findings will be further evaluated in relation to psychological challenges.

Table: Change from baseline to 4 months for FIM, AIM, IAM outcomes in relation to injection and community setting

Mean difference* (SD) in scores	Black N=54	Non-Black N=52	Women (cis/trans) Woman N=60	Men N=46	Total N=106	p-value for change from baseline
FIM change from baseline in relation to injection	+0.21 (0.53)	+0.02 (0.51)	+0.16 (0.57)	+0.06 (0.45)	+0.12 (0.52)	0.023
FIM change from baseline in relation to the alternative community-based location	-0.23 (1.24)	+0.04 (0.13)	-0.11 (1.08)	-0.08 (1.17)	-0.10 (1.12)	0.359
AIM change from baseline in relation to injection	+0.11 (0.67)	+0.04 (0.45)	+0.01 (0.62)	+0.16 (0.49)	+0.08 (0.57)	0.175
AIM change from baseline in relation to the alternative community-based location	-0.08 (1.35)	+0.13 (1.00)	-0.06 (1.21)	+0.13 (1.17)	+0.02 (1.19)	0.855
IAM change from baseline in relation to injection	+0.20 (0.58)	+0.07 (0.50)	+0.17 (0.58)	+0.09 (0.50)	+0.13 (0.55)	0.013
IAM change from baseline in relation to the alternative community-based location	-0.10 (0.17)	+0.17 (1.02)	-0.06 (1.09)	+0.16 (1.22)	+0.03 (1.15)	0.775
HIV-TSQ12 change from baseline	+5.43 (8.65)	+7.58 (11.85)	+5.32 (8.84)	+8.00 (11.97)	+6.48 (10.35)	<0.001

Ns with non-missing data (baseline data complete; missing for 3 participants at 4-months)

* Calculated as month 4 -baseline score; +ve mean differences indicate higher score at 4-months compared with baseline.

622 Acceptability of Long-Acting Cabotegravir & Rilpivirine in a Large Urban Ambulatory HIV Clinic

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Background: There are limited data regarding the acceptability of injectable long-acting cabotegravir and rilpivirine (LA-CAB/RPV) outside of randomized controlled trials (RCTs). We performed a mixed-methods analysis to describe patient-reported outcomes (PROs) of LA-CAB/RPV among a population often underrepresented in RCTs at one of the largest HIV/AIDS care centers in the United States.

Methods: We interviewed persons living with HIV (PLWH) who received at least one dose of LA-CAB/RPV at the Ruth M. Rothstein CORE Center in Chicago, Illinois. PRO endpoints included mean treatment satisfaction (1 [Very Unsatisfied] to 7 [Very Satisfied]), mean tolerability of injection site pain (1 [Not at All Bothered] to 10 [Very Bothered]), and reasons for switching to LA-CAB/RPV. Mean and standard deviations (mean±SD) and proportions (%) are reported.

Results: Among the respondents (N=136), 68.4% identified as Black/African American, 24.3% as Hispanic, 36.0% as female, 58.1% as male; the median age was 43 years (range 21-76), with 36.8% being ≥50 years old. Most respondents (92.6%) completed ≥3 injection appointments at the time of interview. The two most common reasons for switching from oral therapy to LA-CAB/RPV were no longer wanting to take pills (89.7%) and had trouble taking their pills daily (58.8%). Treatment satisfaction was high (6.7±0.4). Two-thirds (64.0%) reported an aspect of their life improved that was not expected after initiation. The majority (90.4%) reported pain from injections, with a mean pain level of 4.2±2.7. Among those reporting pain, half (48.8%) reported pain decreased after initial injection. Among those with a reported >6 level of pain (N=31), most (83.9%) reported no improvement since initial injection. One-fifth (19.1%) reported swelling from injections and one-third (33.1%) reported anxiety before injections.

Conclusion: We found high treatment satisfaction with LA-CAB/RPV in a population with a high proportion of people of color, women, and PLWH ≥50 years old. Patients reported moderate pain with injections, which improved with time. These results suggest that scaling up of injectable LA-CAB/RPV will be met with high patient acceptability across diverse patient populations.

623 Real-World Effectiveness of Cabotegravir + Rilpivirine vs Standard of Care Oral Regimens in the US

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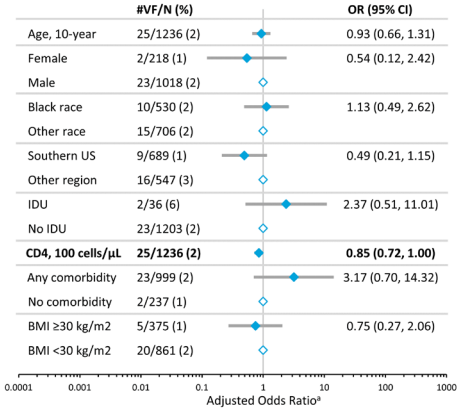
Background: In trials, long-acting (LA) injectable antiretroviral therapy (ART) with cabotegravir plus rilpivirine (CAB+RPV) was shown to be non-inferior to oral ART regimens in virologically suppressed (viral load [VL] <50 copies/mL) individuals. We assessed real world effectiveness after a switch to CAB+RPV or a new oral ART regimen.
Methods: From the OPERA cohort, ART-experienced, suppressed adults with HIV switching to CAB+RPV or a new oral ART regimen between 21Jan2021-31Dec2022 were followed through 30June2023. Confirmed virologic failure (VF; 2 VL ≥200 copies/mL or 1 VL ≥200 copies/mL + regimen change) was assessed among those with ≥1 follow-up VL. Logistic regression models were fit to assess the risk of VF by regimen, adjusted for age (linear & quadratic terms), sex, race, injection drug use (IDU), history of AIDS-defining events (ADE), CD4 count (linear & quadratic terms), comorbid conditions, and prior regimen class. In those receiving CAB+RPV injections, age, sex, race, US region, IDU, history of ADE, CD4 count (per 100 cells/μL), comorbid conditions, prior regimen class, and BMI were evaluated as potential predictors of VF.
Results: In OPERA, 1362 virologically suppressed adults switched to CAB+RPV injections and 2783 switched to a new oral ART regimen. CAB+RPV users were younger (aged ≥50 years: 29% vs. 41%), had been on their prior regimen for a shorter period (20 vs. 37 months), were more likely to switch from an INSTI (74% vs. 68%), but had similar median CD4 counts at initiation (686 [IQR 496-902] vs. 700 [524-913] cells/μL) compared to oral ART users. Risk of VF out of individuals with a follow-up VL (CAB+RPV: n=1236; oral ART: n=2432) did not statistically differ (adjusted OR: 0.64; 95% CI: 0.41, 1.02). Only baseline CD4 marginally predicted VF; every 100 CD4 cells/μL increase was associated with 15% lower risk of VF (Fig 1). Of the 25 CAB+RPV VF, 40% went to INSTI oral therapy, 40% remained on CAB+RPV, 16% went to multi-core agents, and 1 remained off therapy. Of the 19 with VL, 95% achieved <200 and 79% <50 after VF. In contrast, of the 78 oral VF, 69% stayed on the same ART, 23% went to INSTI regimen, 3 remained off therapy, and the remainder went on a variety of other regimens. Of the 43 with VL, 84% achieved <200 and 72% <50 after VF.
Conclusion: In routine clinical care in the US, the risk of VF did not differ between virologically suppressed adults switching to CAB+RPV injections or oral ART regimens. Lower CD4 count at initiation was the only predictor of VF with CAB+RPV.

Figure. Predictors of confirmed virologic failure among people switching to CAB+RPV LA with ≥1 follow-up viral load and no missing data (N=1236)



◊ reference; IDU, injection drug use; INSTI, integrase inhibitor; N, number; US, United States; VF, virologic failure
[a]Excluding 57 individuals without race or baseline CD4 cell count

624 Predictors of Injection Visit Adherence in Those Receiving Injectable Cabotegravir/Rilpivirine

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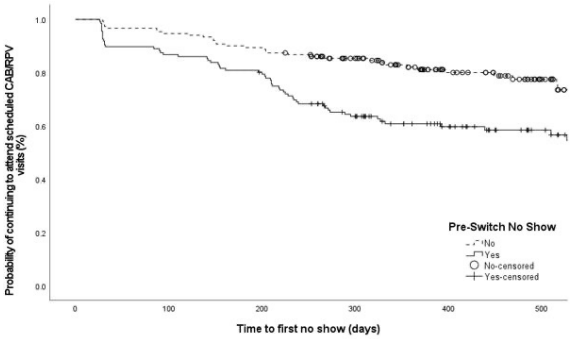
Background: Long-acting injectable (LAI) cabotegravir/rilpivirine (CAB/RPV) provides a novel treatment option for people with HIV (PWH). However, missed and late injections potentially jeopardize viral suppression, increases risk of resistance development, and requires extensive resources to track adherence and proactively reschedule missed injections.
Methods: We conducted a retrospective cohort study at the University of California San Diego Owen Clinic. Adult PWH who received LAI CAB/RPV for at least 6 months from May 2021 through August 2023 were included. Data collected included demographics, baseline HIV RNA and CD4 count, distance from the clinic, substance use, CAB/RPV dosing regimen, office visit no-shows one year prior to switching to LAI CAB/RPV, injection visit no-shows, injections outside of the dosing widow, and virologic outcomes. PWH were excluded if they had a late injection due to COVID-19 infection or planned/known travel. Cox-proportional hazards regression was performed to evaluate predictors of no-show to injection visits or late injections.
Results: A total of 287 PWH were included with median age of 42 years, 54.4% were non-white, 38% Hispanic ethnicity, and 15% female sex assigned at birth (SAB). Median follow up time (IQR) on LAI CAB/RPV was 450 days (344-548 days), and median distance to the clinic was 4.8 miles (2.5-11.8 miles). A total of 92 (32.1%) had at least one no-show to a scheduled injection visit and 44 (15.3%) had at least one injection outside the recommended dosing window. Younger age (HR 0.97, 95%CI 0.95-0.98) and ≥ 1 office visit no-show in the year prior to switch (HR 2.03, 95%CI 1.32-3.12) were independently associated with having a no-show to an injection visit (Figure 1). The number of pre-switch no-shows was also significantly associated with post-switch no-shows (p<0.001) and those with at least one injection visit no-show had a higher frequency of late injections, 30.4% vs. 8.2%, p<0.0001. Male SAB (HR 9.18, 95%CI 1.26-66.9) after adjustment for age, was independently associated with late injection visits. There was no relationship between no-shows to injection visits or late injections and having a detectable viral load or virologic failure (n=3) after switch to LAI CAB/RPV.
Conclusion: Evaluating attendance to office visits prior to switching to LAI CAB/RPV may help identify those more likely to miss injection visits, however it was not associated with late injections or having a detectable viral load or virologic failure.

Figure 1: Time-to-event analysis comparing probability of attendance to CAB/RPV injection visits in those with and without at least one office visit no-show in the year prior to switching to LAI CAB/RPV



625 Real-World Utilization of Cabotegravir + Rilpivirine in the US: Data From Trio Health Cohort

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Background: Cabotegravir+Rilpirivine (CAB+RPV) is the first complete long-acting (LA) antiretroviral regimen approved in the United States for the treatment of HIV for ART-experienced people with undetectable viral load (VL <50 copies/ml). This study examines the utilization and effectiveness of CAB+RPV in real-world settings in the US.
Methods: All ART-experienced adults with undetectable VL at initiation who received ≥1 documented CAB+RPV injection were identified from electronic health record data within the Trio Health Cohort between February 2021-July 2023. Discontinuation of CAB+RPV was defined as 2 consecutive missed injections or a regimen switch, while confirmed virologic failure (CVF) was

defined as 2 consecutive VLs > 200 copies/mL or 1 VL > 200 copies/mL with discontinuation within 4 months of last recorded injection. ARV resistance from HIV genotype results was available for a subset of individuals and was analyzed through Stanford HIVdb algorithm among those with identified CVF.
Results: The analysis included 278 ART-experienced individuals with undetectable VL who initiated CAB+RPV; initiators were a median of 44 years (IQR: 35-54) of age, predominately male (80%), non-Black (64%), and from the US South (73%). Median follow-up time after first injection was 10 months (IQR 5-13) with median of 5 injections (IQR: 3-7). There were 246 (88%) CAB+RPV initiators who remained on the regimen at end of follow-up; among those who discontinued CAB+RPV, none experienced injection site reaction. Among all initiators, 221 (80%) individuals had ≥1 recorded follow-up VL. Those with no follow-up VLs had median 1 injection (IQR: 1-2). Among individuals with VL data, 213 (96%) had all follow-up VL <200 copies/mL throughout follow-up, with 196 (89%) undetectable at last recorded VL. Only 2 (0.9%) individuals experienced CVF, both of whom discontinued CAB+RPV after one unsuppressed VL. Resistance data prior to initiation was available for 1 individual, who had extensive resistance to NNRTI and NRTI. Genotype results were not recorded for this individual at the time of CVF, and suppression had not been documented on subsequent therapy (DRV/c/FTC/TAF: 3 months).
Conclusion: Among ART-experienced adults with undetectable VL initiating CAB+RPV, the vast majority continued the regimen and maintained virologic suppression throughout the follow-up period. Additionally, confirmed virologic failure was rare, suggesting high effectiveness of CAB+RPV in real world settings.

Table: Characteristics of ART-experienced, virologically-suppressed PWH with ≥1 CAB+RPV LA injection

Study Population Characteristics	All CAB+RPV Initiators N = 278
Age, median (IQR)	44 (35, 55)
Male sex, n (%)	221 (79.5)
Black, n (%)	99 (35.6)
Geographic region, South, n (%)	204 (73.4)
On CAB+RPV regimen at end of follow-up, n (%)	246 (88.5)
CAB+RPV initiators with ≥1 recorded follow-up VL, n (%)	221 (79.5)
Maintained virologic suppression, n (%)	213 (96.3)
Confirmed virologic failure, n (%)	2 (0.9)

626 Real-World Virologic Outcomes of Cabotegravir/Rilpivirine in Patients With Elevated Body Mass Index

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Background: Injectable cabotegravir (CAB) and rilpivirine (RPV) is the first complete long-acting antiretroviral (ARV) regimen approved in persons with HIV with sustained virologic suppression (HIV RNA <50 copies/mL) on current ARV therapy. In a multivariable analysis, body mass index (BMI) > 30 kg/m² alone was not predictive of confirmed virologic failure; however, data are limited due to small sample sizes. The primary objective of this study is to determine the incidence proportion of participants with a plasma HIV-1 RNA > 50 copies/mL at last observed endpoint in those with and without body mass index > 30 kg/m². Secondary objectives evaluated include incidence proportion of virologic failure (VF: > 200 HIV-1 RNA copies/mL) in those with and without body mass index > 30 kg/m² and assessing the primary outcome stratified by BMI categories (> 40 kg/m², > 45 kg/m², and > 50 kg/m²).
Methods: We conducted a retrospective, multi-center cohort study from January 22, 2021 to February 15, 2023 for participants receiving either every 4 or 8 weeks dosing of CAB/RPV (Q4w or Q8w). We included participants who were >18 years of age, received at least one injection of CAB/RPV, had HIV RNA < 50 copies/mL at baseline, and had at least one follow up HIV RNA. We excluded those with no weight available within 90 days of first CAB/RPV injection. Baseline characteristics such as prior regimens, resistance history, smoking history, and history of gluteal implants were collected. HIV RNA > 50 copies/mL and virologic failure (VF: > 200 HIV RNA copies/mL) were collected. Data was pooled to determine the proportion of participants with HIV RNA >50 copies/mL in those with BMI >30 kg/m² compared to those who with BMI <30 kg/m².
Results: We analyzed 369 participants across 5 medical centers and 148 (40.1 %) had a BMI > 30 kg/m². Individuals received a median 202 days of therapy (range 22-664). Sixteen (4.3 %) were on q4w, 250 (67.8%) were on q8w, and 103 (27.9 %) were on a combination q4-q8w. For those with BMI > 30 the median BMI was 35.1 (range 30.0-67.4) kg/m². Eighteen individuals (4.8%) had HIV RNA > 50 copies/mL with BMI>30 kg/m² compared to 20 (5.4%) with a BMI < 30 kg/m². Additionally, we found that 3 individuals (0.08%) experienced VF at the last timepoint with BMI>30 kg/m² compared to 4 (1.04%) with a BMI < 30 kg/m².
Conclusion: Based on our analysis, the incidence of HIV RNA > 50 copies/mL and VF were similar between groups regardless of BMI category.

627 HIV-1 RNA Blips and Low-Level Viral Replication: SOLAR (CAB+RPV LA vs BIC/FTC/TAF)

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Background: Cabotegravir plus rilpivirine long-acting (CAB+RPV LA) administered every 2 months (Q2M) is the first and only complete LA regimen recommended for virologically suppressed people living with HIV-1. Here, we report HIV-1 RNA viral blips and target virus not detected (TND), as well as the impact of HIV-1 RNA blips on viral load measurements at Month 12 and confirmed virologic failure (CVF), in participants switching to CAB+RPV LA vs. continuing daily oral bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) through Month 12 in the SOLAR study.
Methods: SOLAR (NCT04542070) is a Phase 3b, randomized (2:1), open-label, multicenter, noninferiority study assessing switching virologically suppressed adults to CAB+RPV LA Q2M vs. continuing BIC/FTC/TAF. The analysis was based on the modified intention-to-treat exposed (mITT-E) population (exclusion of one trial site for non-compliance to protocol entry criteria). HIV-1 RNA viral blips were defined as a single HIV-1 RNA value between 50 and <200 c/mL with adjacent values <50 c/mL. CVF was defined as two consecutive HIV-1 RNA ≥200 c/mL values. Plasma samples were analyzed for HIV-1 RNA viral load using the Abbott RealTime HIV-1 assay, and TND outcomes were provided for HIV-1 RNA <40 c/mL.
Results: Of 670 participants (mITT-E), 447 (67%) switched to LA and 223 (33%) continued BIC/FTC/TAF. The proportion of participants with HIV-1 viral blips through Month 12 was 4% (n=19/447) in the CAB+RPV LA arm and 4% (n=9/223) in the BIC/FTC/TAF arm. Of participants with viral blips, 5% (n=1/19) and 11% (n=1/9) in the CAB+RPV LA and BIC/FTC/TAF arms, respectively, had HIV-1 RNA ≥50 c/mL at Month 12; no participants with HIV-1 RNA viral blips developed CVF. The proportions of participants with viral blips were consistently ≤1% of participants with available data across both treatment arms at any time point. TND outcomes at individual study visits were similar between study arms (CAB+RPV LA, 85–88%; BIC/FTC/TAF, 80–86%), and the proportions of participants with HIV-1 RNA <40 c/mL (CAB+RPV LA, 90–97%; BIC/FTC/TAF, 90–97%) were comparable between treatment arms through Month 12.
Conclusion: The proportions of study participants with HIV-1 RNA viral blips, TND, and HIV-1 RNA <40 c/mL were similar between CAB+RPV LA and BIC/FTC/TAF through Month 12. HIV-1 viral blips with CAB+RPV LA did not appear to be associated with CVF, consistent with prior CAB+RPV LA Phase 3 clinical study data.

Table. SOLAR Key Efficacy Outcomes at Month 12

Outcome at Month 12 (mITT-E)	CAB+RPV LA Q2M	BIC/FTC/TAF
Participants with HIV-1 blip* at any study visit	19/447 (4%)	9/223 (4%)
Participants with CVF†	2/447 (<1%)	0/223
With HIV-1 blip*	0/19	0/0
Without HIV-1 blip*	2/428 (<1%)	0/0
Participants with HIV-1 RNA ≥50 copies/mL (FDA Snapshot)	5/447 (1%)	1/223 (<1%)
With HIV-1 blip*	1/19 (5%)	1/9 (11%)
Without HIV-1 blip*	4/428 (<1%)	0/214

*A single HIV-1 RNA between 50 and <200 copies/mL with adjacent values <50 copies/mL.
†Two consecutive HIV-1 RNA ≥200 copies/mL.
BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB, cabotegravir; CVF, confirmed virologic failure; FDA, U.S. Food and Drug Administration; LA, long-acting; mITT-E, modified intention-to-treat exposed; Q2M, every 2 months; RPV, rilpivirine.

628 24-Week Viral Suppression in Patients Starting Long-Acting CAB/RPV Without HIV Viral Suppression

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Background: We previously demonstrated that initiation of long-acting cabotegravir/rilpivirine (LA-CAB/RPV) in people with HIV (PWH) with an unsuppressed HIV viral load (VL) at the Ward 86 clinic in San Francisco can rapidly lead to viral suppression (VS). We now seek to evaluate the durability of VS in this population.

Methods: We conducted a retrospective cohort study of PWH who started LA-CAB/RPV before 7/17/2023, focusing on those with HIV VL ≥50 copies/mL at initiation. Our primary outcome was VS (VL <50 copies/mL) and LA-CAB/RPV persistence (not discontinued or late by >14 days) at 24 weeks, using the closest VL to 24+/-8 weeks. We considered missing 24-week VL as 1) unsuppressed (primary analysis); and 2) suppressed if evidence of VS before and after the outcome window (sensitivity analysis). We also describe viral failure (VF), defined as <2-log viral load decline at 4 weeks or VL ≥200 copies/mL after initial VS with emergent CAB- or RPV-associated resistance mutations; discontinuations; and overall VS at week 24 including those who switched to oral ART.

Results: Among 243 PWH initiating LA-CAB/RPV, 88 (36%) had baseline VL ≥50 copies/mL and 60 had ≥32 weeks of follow-up time to assess the primary outcome (88% cisgender men, 47% age ≥50, 40% white, 28% Latino/a, 25% Black, 47% with housing instability, 43% using stimulants). At 24 weeks, 51 (85%) had VS, 4 had VL ≥50 copies/mL and 5 had missing VL data (table). Forty-nine met the primary outcome of LA-CAB/RPV persistence and VS (82%; 95%CI 69-90%), with this estimate rising to 85% (52/60) using imputed VLs in sensitivity analysis. Of the four with VL ≥50 copies/mL at week 24, two had VF with resistance (RT E138K, INSTI R263K; RT L100I, Y181I) and two had slow viral decay without resistance. After week 24, both patients with VF later attained VS on alternative regimens (lenacapavir(LEN)+BIC/TAF/FTC and CAB+LEN). Four other patients discontinued LA-CAB/RPV before week 24: two had VS on oral ART at week 24, one had VS after switch to oral ART but missing week 24 VL, and one was off ART and lost to follow-up due to psychosis. Week 24 VS on either LA-CAB/RPV or oral ART using imputed VL data was 92% (55/60).

Conclusion: In those initiating LA-CAB/RPV without viral suppression, 24-week VS estimates were at least 85%. Long-acting ART can be an important tool for improving VS among patients who face adherence challenges to oral ART.

	Week 24 HIV VL at week 24 (copies/mL)		
	<50 (N=51)	≥50 (N=4)	Missing (N=5)
Overall	51 (85.0%)	4 (6.7%)	5 (8.3%)
LA-CAB/RPV persistence	49 (81.7%)	2 (3.3%)[1]	3 (5.0%)[2]
Viral failure	0	2 (3.3%)	0
Patient-initiated discontinuation	1 (1.7%)[3]	0	1 (1.7%)[4]
Provider-initiated ART change[5]	1 (1.7%)	0	0
Lost to follow-up (LTFU)[6]	0	0	1 (1.7%)

1.Slow viral decay, no resistance. 2.VS before/after window. 3.Pregnancy. 4.Injection site pain, VS on oral ART before/after window. 5.Rebound after initial VS (due to use of standard-size needle with high BMI), re-suppression on oral ART, no resistance on HIV DNA. 6.VS by week 4, then LTFU (due to psychosis).

629 Case Series Examining the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial

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Background: Long-acting antiretroviral therapy (LA-ART) is novel and has been used for both virologically-suppressed (VS) and viremic patients with adherence challenges. The currently-approved LA-ART combination – cabotegravir (CAB) and rilpivirine (RPV) – is limited by the relatively high prevalence (up to 10%) of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistant virus globally and is not endorsed for low-and-middle-income-countries (LMICs). The combination of LA lenacapavir (LEN) and CAB has not been studied in a clinical trial but poses promise for LMICs.

Methods: Providers (MDs/pharmacists) at the UCSF Ward 86 Clinic, the UCSD Owen Clinic, MetroHealth in Cleveland, and the UPenn HIV Clinic used LEN subcutaneously every 6 months after oral loading in combination with CAB administered intramuscularly every 4 or 8 weeks in patients with adherence challenges to oral ART. A case series was assembled with the following data points: gender, age, housing insecurity and/or substance use, viral load (VL) prior to starting LEN/CAB, duration between CAB doses (every 4 or 8 weeks), whether RPV was maintained, viral mutations, whether VS (VL <75 copies/ml) was achieved on LEN/CAB, and if so, time to VS.

Results: The Table shows patients in the case series (n=34; 76% male 24% cis/trans female; 41% Black; 38% Latino/a; median age 47 (range 28-75) years; 71% with CAB every 8 weeks). All patients had difficulty adhering to oral ART, with 56% reporting housing insecurity, substance use, or both. The reason(s) for either adding LA LEN to CAB/RPV (68%) or using LEN/CAB without RPV (32%) were documented/suspected NNRTI mutations (n= 21, 59%), INSTI mutations (n=5, 15%), high VL when switching or starting LA ART (n=6, 18%) or continued viremia on CAB/RPV alone (n=4, 12%). One patient was started on LEN + CAB/RPV due to a high body mass index and another had LA RPV intolerance. Injection sites reactions on LEN were reported in 44% (32% grade I, 12% grade 2). All patients but 2 suppressed (VL <75) after starting LEN (94%) at a median of 8 weeks (4-16), with only 16 (47%) being suppressed at baseline.

Conclusion: In this case series of 34 patients started on LEN every 6 months in combination with CAB every 4 or 8 weeks (with or without RPV), high rates of VS (94%) were seen. Reasons for using this combination included adherence challenges, underlying ART resistance (mostly to NNRTIs) or low-level viremia on CAB/RPV. This data supports a clinical trial of LEN/CAB to study this combination for global use.

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630 Lenacapavir Efficacy in CAPELLA Patients With No Fully Active Agents in Optimized Background Regimen

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Background: Lenacapavir (LEN), a long-acting HIV-1 capsid inhibitor, is approved for the treatment of heavily treatment-experienced (HTE) people with HIV (PWH) with multidrug resistance (MDR) in combination with other antiretrovirals (ARVs). LEN is highly potent with no overlapping resistance with other ARVs. In CAPELLA, LEN in combination with an optimized background regimen (OBR) led to high virologic suppression: 78% (n=56/72; week [W] 52). We assessed LEN efficacy in participants whose OBR had no fully active ARVs.

Methods: The Phase 2/3 CAPELLA study enrolled HTE PWH with MDR. Eligible participants had resistance to ≥2 ARVs in ≥3 of the 4 main ARV classes (NRTI, NNRTI, PI, INSTI). After oral loading, SC LEN was administered every 6 months. OBRs were selected by the clinicians; other investigational drugs were permitted. OBR overall susceptibility score was the sum of susceptibility scores for each OBR ARV; 0 (no susceptibility), 0.5 (partial susceptibility) and 1 (full susceptibility). Efficacy data (HIV-1 RNA copies/mL; FDA Snapshot algorithm) were assessed at W26, 52, and 104. LEN and OBR ARV resistance analyses were done at virologic failure (virologic rebound ≥50 copies/mL or <1 $\log_{10}$ decline vs baseline).

Results: Of the enrolled 72 participants, 12 (17%) had no fully active ARVs in their OBR; 6/12 and 1/12 had 1 or 2 partially active (score 0.5 each) ARVs, respectively. Median (range) number of OBR ARVs was 4 (2–6). Overall, OBR comprised NRTI (9 participants), INSTI (8), PI (7) or NNRTI (6); 5, 2, and 2 participants were on a CD4 post-attachment inhibitor (ibalizumab), CCR5 inhibitor (maraviroc), or attachment inhibitor (fostemsavir), respectively. Treatment outcomes: 8 participants had HIV-1 RNA <50 copies/mL at all 3 visits (W26, 52, and 104), including 1 participant with LEN resistance (R; M66I) at W10 and an OBR change at W25. 1 participant with missing W104 data was

suppressed at a later visit; 1 participant not suppressed at W26 developed LEN-R (M66I) but was suppressed at W52 and 104 (OBR changed at W25); and 2 participants had HIV-1 RNA ≥50 copies/mL throughout, but with a stable, low level viral load (1 with <600 copies/mL, OBR changed at W30; 1 with <3000 copies/mL despite emerging LEN-R at W4 [M66M/I]). None of the 12 participants discontinued the study drug.
Conclusion: In HTE PWH with MDR on an OBR with no fully active ARVs, LEN led to sustained virologic suppression over 104 weeks for most participants. LEN is an important option for treating HTE PWH with MDR.

631 Intramuscular Injection vs Intravenous Infusion of Ibalizumab for HTE PWH: The Results of TMB-302

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Background: Ibalizumab (IBA) is a monoclonal antibody approved for the treatment of multi-drug resistant HIV-1 infection in heavily treatment experienced (HTE) people with HIV (PWH) in combination with an optimized background regimen. The efficacy of ibalizumab (IBA) in combination with an optimized background regimen has been demonstrated in clinical trials previously. IBA is currently administered every two weeks (Q2W) via intravenous infusion (IVI) over 15-30 minutes, or via undiluted intravenous push over 30 seconds. This requires a peripheral IV catheter for administration by trained staff, which can limit access. Altering the mechanism of administration of IBA will expand and simply access for HTE PWH in need of new therapies to achieve their treatment goals.
Methods: TMB-302 (ClinicalTrials.gov Identifier: NCT03913195) is a phase 3 study of the safety and efficacy of IBA administered as an intramuscular (IM) injection in clinically stable HIV-1 infected IBA experienced patients and healthy HIV-uninfected volunteers. All subjects in this study received at least two IVI infusions of IBA prior to administration via IM injection for 8 weeks. The HIV treatment satisfaction questionnaire – status (HIVTSQS) and study medication satisfaction questionnaire - status (SMQs) were administered at the last IVI administration (day 29) and after 8 weeks of IM administration (day 85) and the HIV treatment satisfaction questionnaire – change (HIVTSQC) and study medication questionnaire - change (SMQc) were also administered on day 85. All study participants were also asked to answer a one-question Preference Assessment at Day 85 comparing the experience on IM injections with IV infusion.
Results: Administration of IBA via both IVI and IM were well-tolerated by study participants. Although there was no statistically significant difference in either the HIVTSQS or SMQs between day 29 and 85, 83% of HIV-uninfected volunteers and 67% of HIV-infected clinical stable participants preferred administration of IBA IM compared to IVI. Importantly, no PWH lost viral suppression throughout the course of the study. No new or unexpected safety signals were identified.
Conclusion: Administration of IBA via IM injection was safe, well-tolerated, did not result in the loss of viral suppression among HTE PWH, and was the preferred method of administration of all participants in the TMB-302 study. Expanding the administration options for IBA is an important step to increasing access and agency for PWH.

632 Discovery of Next-Generation CD4 Mimetic-Based Long-Acting Entry Inhibitors

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Background: CD4 mimetics have shown promise for HIV prevention and treatment because of the broadest HIV neutralization profiles and high barrier to virus escape stemming from the essential role of CD4 in HIV entry. Their development has been limited, however, by rapid in vivo clearance, possibly related to major histocompatibility complex (MHC) class II binding. An optimal CD4 mimetic construct would retain neutralization breadth and have a long in vivo half-life requiring infrequent administration. To this end, we have engineered CD4 mimetics to reduce/abrogate MHC II binding, increase neutralization potency and prolong in vivo half-life.
Methods: Candidate CD4 mimetic constructs exhibiting increased stability were engineered using molecular modeling, DNA mutagenesis and phage display selection. Promising variants were assessed for MHC Class II binding by biolayer interferometry assays, antiviral potency by TZM-bl neutralization assays and plasma PK following intravenous injection in wild type Balb/c mice.
Results: Engineered CD4 mimetic constructs eliminated MHC II binding without reducing binding to gp120 or loss of neutralization potency against both CCR5 and CXCR4 tropic viruses (IC_{50} of 130 and 953 ng/ml, respectively). The plasma half-life ($t_{1/2}$ = 129 hours) in wild-type mice following IV injection was markedly prolonged compared to the prototypic CD4 mimetic construct, LSEVhLS-F and comparable to the long-lasting IgG1 bnAb 10-1074 ($t_{1/2}$ = 174 hours).
Conclusion: We have successfully engineered CD4 mimetics to prolong their in vivo half-life without affecting antiviral potency. These new constructs are promising candidates as long-acting entry inhibitors for HIV prevention and treatment.
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633 The Preclinical Profile of Maturation Inhibitor VH3739937

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Background: VH3739937 (VH937) is a next generation maturation inhibitor (MI) currently in clinical trials. We report here on its preclinical profile.
Methods: Replication competent and single cycle inhibition assays were performed using a cohort of clinical isolates or site-directed mutant (SDM) viruses. Biochemical experiments using purified viral like particles (VLPs) were performed, while a radiolabeled surrogate compound was used to examine binding kinetics to viral-like particles (VLPs). Resistance selection was carried out using NL4-3 virus at escalating concentrations of VH937. DMPK studies were also carried out.
Results: Biochemical experiments showed VH937 to be a bona fide MI. VH937 is a pan-genotypic MI that was active against all HIV-1 viruses examined. EC_{50}s of 1-5 nM were obtained against 8 laboratory strains and 43 clinical isolates. VH937 was also highly potent against all SDM polymorphisms previously identified as causing reduced susceptibility to first generation MIs. VH937 was partially active against a replication competent A364V mutant, with an EC_{50} of 5 nM and a maximum percent inhibition (MPI) of 95%. However, A364V could be selected under escalating VH937 conditions in cell culture, potentially explained by its weaker activity in a single cycle inhibition assay (EC_{50}=32 nM; MPI=57%). Other mutations selected by VH937 included T332P, L363W or the triple mutant H144Y/V362I/R384K. However, whereas each of these mutations induced highly reduced susceptibility in a single cycle assay, incorporation of any of these mutations into a replicating virus clone did not produce functional virus. The surrogate compound bound to an NL_{4-3} VLP with a binding affinity of 3.3 ± 0.8 nM and had a dissociative half-life of 4125 minutes (almost 3 days), showing the compound binds avidly and dissociates slowly. This was in agreement with SP1 cleavage data obtained with VLPs. Finally, VH937 was ~93.3% protein bound in 100% human serum and exhibited DMPK profiles suitable for clinical development.
Conclusion: The pre-clinical virology profile of VH937 supported the progression of this MI into clinical development.

634 Next-Generation Maturation Inhibitor GSK3640254 Showed Broad Spectrum Potency Without MI Resistance

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Background: HIV-1 maturation inhibitors (MI) offer a novel mechanism of action but have suffered from gag polymorphisms and decreased antiviral potency. GSK3640254 (GSK'254) is a next-generation MI that demonstrated broad spectrum coverage of gag polymorphisms in vitro (Dicker et al. AAC 2022;66:e0187621). GSK'254 + 2 nucleoside-reverse transcriptase inhibitors (NRTIs) demonstrated comparable efficacy to DTG + 2 NRTIs with no treatment-emergent resistance across all doses and a comparable safety/tolerability profile in the DOMINO Phase 2b dose-ranging study (Joshi et al. EACS 2023. Oral RA2.01.). HIV-1 gag/protease from day 1 baseline and on-treatment samples were tested for sensitivity to GSK'254 and gag sequences generated to identify polymorphisms and/or treatment emergent resistance mutations.
Methods: Plasma samples from study participants at day 1 pre-dose, week 4 on-study and any time point at protocol defined virologic failure (PDVF) were sent to Monogram Biosciences for phenotypic analysis using the Phenosense gag-pro assay. Gag genotypic data were generated using the gag next-generation sequencing (NGS) assay.

Results: Day 1 baseline samples were sensitive to GSK'254 with IC_{50} values ranging from 0.39 – 18.4nM. No on-treatment week 4 samples had greater than a 4-fold shift in IC_{50} compared to day 1 baseline samples. Two samples with low infectivity are continuing to be explored. No sample from any participant that met PDVF criteria resulted in phenotypic resistance. The MI resistance associated mutation A364V was not detected in any sample with data at the level of sensitivity for the NGS assay.
Conclusions: In vitro analysis of GSK'254 predicted activity against a broad array of gag polymorphisms, including those hindering prior MI class compounds. Clinical data from the DOMINO study supported the efficacy of this novel MI, GSK'254, as no virus tested from the study demonstrated a decrease in potency to GSK'254 at baseline, through week 4 on treatment, or at any time of protocol defined virologic failure. The clinical durability observed for GSK'254 in this study suggests a sufficient genetic barrier without emergence of resistance. Overall, these data provide clinical evidence that newer MI class compounds offer future options for HIV-1 treatment without the issue of gag polymorphisms observed with prior MI compounds. Finally, the learnings from this Phase 2b study will support the development of future MI compounds in the ViiV pipeline

635 Structure-Guided Optimization of InSTIs to Increase Antiviral Potencies Against HIV-1 IN Mutants

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Background: There are at least four distinct resistance pathways that emerge against second-generation INSTIs: G118R, G140A/S + Q148H/K/R, N155H, and R263K. Although it is critical to develop INSTIs that retain potency against all four resistance pathways, an important aspect of our research has been directed at overcoming resistance associated with G140S/Q148H mutants, a pathway common in PLWH who have undergone virological failure. We are using combinations of our most promising compounds to develop new INSTIs with improved antiviral potencies against the IN G140S/Q148H mutants.
Methods: Compound AK-01 was generated by combining some of the best structural features of our previous compounds 4d and 5j to produce a naphthyridine scaffold with modifications at the 4' and 5' positions. Single round infectivity assays were used to measure EC_{50} values against a panel of clinically relevant IN mutants. We compared the antiviral potencies of AK-01 with the potencies of parent compounds, 4d, 5j, another naphthyridine-based prototype INSTI (4a), and FDA-approved second-generation INSTIs.
Results: AK-01 exhibited high antiviral potencies against WT HIV-1 (1.2 ± 0.4 nM) and several well-characterized IN mutants (G118R = 3.8 ± 0.7, N155H = 2.3 ± 0.2 nM, and R263K = 2.8 ± 0.6 nM). Importantly, AK-01 showed only a modest loss in potency against the key IN mutant G140S/Q148H (17.9 ± 4.2 nM). However, there was a more pronounced loss of antiviral potency when AK-01 was challenged with some other well-known IN double and triple mutants.
Conclusion: Although AK-01 is not a fully optimized compound, our results show that combining structural modifications of promising naphthyridine-based INSTIs can be used to produce new compounds that are effective against some of the known drug-resistant mutants. Importantly, AK-01 had an improved antiviral profile when compared to cabotegravir. We are currently using the available structural and virological data to design and evaluate additional INSTIs.

636 Preclinical Characterization of GS-5894, a Potent NNRTI With Once-Weekly Oral Dosing Potential

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Background: Non-nucleoside reverse transcriptase inhibitors (NNRTIs) target an allosteric binding pocket near the polymerase active site of HIV-1 reverse transcriptase (RT) to prevent viral replication. To date, all approved NNRTIs must be dosed once-daily as part of a highly active antiretroviral regimen. Due to their physiochemical properties such as low solubility and high logD, NNRTIs are good candidates for long-acting regimens. Here we describe a novel and potent NNRTI with metabolic stability supportive of once-weekly (QW) oral dosing for the treatment of HIV-1 infection.
Methods: Antiviral activity against IIIB WT virus and drug resistant variants was measured in cytopathic assays using the MT-2 and MT-4 T-cell lines. Cross-resistance was assessed against a Monogram panel of HIV-1 reporter viruses containing NNRTI resistance-associated mutations. Mutations that emerged under selective drug pressure were identified by dose-escalation and fixed-drug concentration resistance selections. Compound binding to rat, dog and human plasma was measured by equilibrium dialysis. Predicted clearance (CL) was measured by metabolic stability in human hepatocytes. Additional oral and intravenous pharmacokinetic studies were conducted in rat and dog.
Results: GS-5894 is a potent and selective inhibitor of HIV-1 replication in the MT-4 T-cell line, in primary human CD4+ T lymphocytes, and in monocyte-derived macrophages, with EC_{50} and selectivity index (CC_{50}/EC_{50}) values ranging from 1.5 to 4.2 nM and 5,152 to >66,000, respectively. The antiviral activity of GS-5894 against a panel of 32 NNRTI-resistant reporter HIV-1 variants derived from treatment-experienced people with HIV (PWH) was superior to that of other marketed NNRTIs. GS-5894 dose escalating resistance selections resulted in the emergence of an HIV-1 triple RT variant (I125V+E138K+P236T) that was cross-resistant to EFV and RPV. GS-5894 is tightly bound to plasma across species though the human binding-adjusted EC95 is 122 nM. The human predicted CL for GS-5894 (uncorrected for plasma binding) is 0.17 L/h/kg. GS-5894 has oral bioavailabilities of 34% and 31% (dosed as a solution), and mean-residence times of 2.9 and 23 hours in rat and dog, respectively.
Conclusion: GS-5894 is a novel and potent NNRTI with an improved resistance profile compared to other NNRTIs. Given the high plasma binding and low predicted metabolic clearance, GS-5894 has the potential for once-weekly oral dosing in PWH for the treatment of HIV-1 infection.

637 Discovery of GS-9770: A Novel Unboosted Once Daily Oral HIV Protease Inhibitor

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Background: HIV protease was one of the first biochemical targets identified to inhibit HIV replication. Nine HIV-protease inhibitors (PIs) have been approved since the first, saquinavir, in 1995. The latest generation showing high efficacy and barrier to resistance. However, these agents have poor metabolic stability and a short human half-life on their own. As a result, HIV-PIs need to be co-administered with a CYP-inhibitor or pharmacokinetic (PK) booster, such as Cobicistat, to extend their half-life long enough to achieve daily oral dosing, hampering their broad utility.
Methods: To meet this need, it was our goal to discover a novel HIV-PI that could be administered without the need of a PK booster. Attributing the poor metabolic stability of known HIV protease inhibitors to their peptidomimetic nature and inspired by the guanidine scaffold which was used in the discovery of non-peptidomimetic, and unboosted, β-secretase 1 (BACE1) inhibitors, we selected an iminohydantoin pharmacophore to initiate a structure-enabled optimization to GS-9770.
Results: GS-9770 is exquisitely potent (Ki = 0.14 nM, EC_{50} = 7 nM) and metabolically stable (3H hLM pred CL = 0.09 L/h/kg). Pre-clinical in vivo PK studies showed that GS-9770 had good oral bioavailability (46 – 100 %) and long half-life (7 – 12 hours).
Conclusion: Both in vitro and in vivo data of GS-9770 support its unboosted, once daily oral administration. This poster will walk audience through our medicinal chemistry efforts with structure-based drug design approach towards GS-9770.

638 Discovery of MK-8527: A Long-Acting HIV-1 Nucleoside Reverse Transcriptase Translocation Inhibitor

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Background: Nucleoside reverse transcriptase translocation inhibitors (NRTTIs) such as islatravir (ISL) are potent inhibitors of HIV-1 replication. We have invented a novel NRTTI with antiviral potency and pharmacokinetics (PK) suitable for less-frequent-than-daily dosing, an attractive profile for HIV pre-exposure prophylaxis. MK-8527 is a 7-deaza-deoxyadenosine analog and is phosphorylated intracellularly to its active triphosphate (TP) form, which is a potent inhibitor of HIV-1 replication.

Methods: MK-8527 was discovered through a lead optimization campaign focused on identifying structurally and functionally novel NRTTIs with the potential for extended-duration dosing. The mechanism of MK-8527-TP was evaluated in primer extension and footprinting assays, and antiviral activity and persistence after washout were measured in cell-based assays. PK parameters were evaluated in rats and Rhesus monkeys. Off-target activity was assessed against human DNA polymerases and in a panel of 114 enzyme/receptor binding assays.

Results: Systematic evaluation of key positions around the nucleoside core confirmed steep SAR associated with this compound class, particularly at the 2', 3', and 4' positions. Nucleobase modifications were tolerated, and a thorough evaluation of this and other positions led to the discovery of MK-8527. MK-8527-TP inhibits reverse transcriptase by immediate (translocation) and delayed chain termination. MK-8527 has comparable antiviral activity (human PBMC $IC_{50} = 0.21$ µM) and persistence of antiviral effect after washout to ISL. The PK of MK-8527 in rats and monkeys was characterized by low to moderate clearance and volume of distribution, with good oral absorption . Following oral administration of MK-8527 to monkeys, the TP had an intracellular half-life ($t_{1/2}$) in PBMCs (~48 h), significantly longer than the plasma $t_{1/2}$ of the parent, MK-8527 (~7 h), as observed with other nucleos(t)ide analogs. MK-8527-TP displayed IC_{50} values of ≥95 µM against the human DNA polymerases tested. Neither MK-8527 nor MK-8527-TP exhibited off-target activities at 10 µM in the panel of enzyme/receptor binding assays tested.

Conclusion: The subnanomolar potency, absence of off-target activity, and suitable PK for at least once-weekly dosing make MK-8527 an attractive clinical candidate for prophylaxis of HIV-1 infection

639 High-Dose VH3810109 (N6LS) ± Recombinant Human Hyaluronidase PH20: Phase I SPAN Study Safety Results

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Background: Broadly neutralizing antibodies are being developed for long-acting HIV-1 therapy. VH3810109 (N6LS), a CD4-binding site antibody with broad and potent neutralization activity in vitro, demonstrated robust antiviral effect in adults with HIV-1 in the phase IIa BANNER study. Here, we report safety and tolerability for the highest subcutaneous (SC) and intravenous (IV) single N6LS doses ever administered, with and without recombinant human hyaluronidase PH20 (rHuPH20).

Methods: SPAN (NCT05291520) is a phase I, open-label, 3-part study assessing safety, tolerability, and pharmacokinetics of single-dose N6LS in healthy adults. Part 1 evaluated N6LS 20 mg/kg SC + rHuPH20 2000 U/mL, part 2 N6LS 60 mg/kg IV, and part 3 N6LS 3000 mg SC + rHuPH20 2000 U/mL. Adverse events (AEs), injection site reactions (ISRs), vital signs, electrocardiograms, and clinical laboratory values were monitored for 24 weeks.

Results: Eight participants were enrolled in each part to receive a single dose of N6LS. In the SC N6LS + rHuPH20 dose groups (parts 1 and 3), no relevant differences in overall AE incidences were observed (Table); across parts, no AEs led to withdrawal. In parts 1 and 3, among 32 ISRs reported by 15/16 (94%) participants, 17 were grade 3 (all injection site erythema based on size; mean duration: 2.9 days [part 1] and 5.7 days [part 3]; Table). All ISRs resolved without sequelae within ≤7 days except for 1 in part 3 that resolved after 27 days. Biphasic injection site erythema was reported in parts 1 (2/8 [25%]) and 3 (4/8 [50%]). Most participants rated local reactions and pain as acceptable and were in favor of injection treatment. No local secondary infections were reported with ISRs. In part 2 (IV), 1 participant experienced 2 grade 1 AEs; no ISRs were reported. A higher frequency of AEs was reported with SC administration compared with IV, mainly driven by ISRs. Across doses, no serious AEs or deaths occurred, and no clinically significant changes from baseline in vital signs, electrocardiograms, or laboratory values were observed.

Conclusion: High-dose N6LS, when given IV or SC + rHuPH20, was generally safe and well tolerated in this study. These results support the ongoing clinical development of N6LS 3000 mg SC + rHuPH20 and N6LS 60 mg/kg IV into phase IIb.

Table. AEs and Injection/Infusion Site Reactions

Participants, n (%)	Part 1 N6LS 20 mg/kg SC + rHuPH20 2000 U/mL (N=8)	Part 2 N6LS 60 mg/kg IV (N=8)	Part 3 N6LS 3000 mg SC + rHuPH20 2000 U/mL (N=8)	Total (N=24)
Any AE	8 (100)	1 (13)	8 (100)	17 (71)
Grade ≥3 AEs	6 (75)	0	8 (100)	14 (58)
Drug-related AEs	7 (88)	0	8 (100)	15 (63)
Grade ≥3 drug-related AEs	6 (75)	0	8 (100)	14 (58)
ISRs within 7 days of administration [number of ISR events]	7 (88) [14]	0 [0]	8 (100) [18]	15 (63) [32]
Grade 1-2	4 (50)	0	5 (63)	9 (38)
Grade 3[a]	6 (75)	0	8 (100)	14 (58)

Sum of AEs/ISRs may be greater than reported at each summarization level as participants were counted once if they reported 1 or more events.
[a]All grade 3 ISRs were injection site erythema based on size; no complications (eg, secondary infection, ulceration) were reported.

640 A Dose Escalation Study of Safety & PK of TMB-365 & TMB-380 in People With Suppressed HIV

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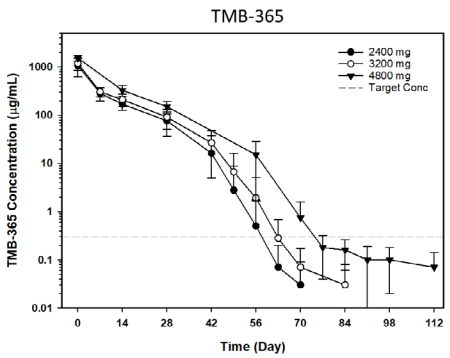
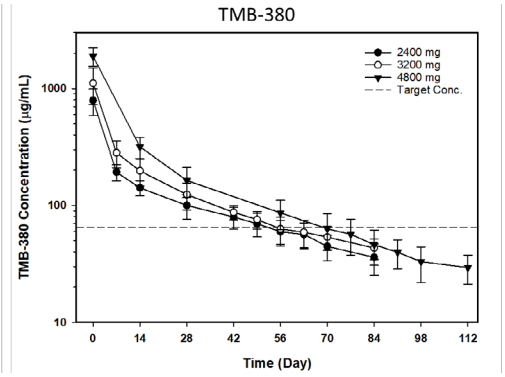
Background: TMB-365, a second generation post-attachment bNAb, binds to the second domain of CD4 and is designed to display improved PK, antiviral activity, and breadth of coverage when compared to ibalizumab. TMB-380 (aka VRC07-523LS) is a bNAb that binds to the CD4 binding site of HIV Env and has potent antiviral activity and favorable safety and PK profile. The combination is designed as a complete regimen for HIV therapy. Here we present available safety and PK results of the combination given as a single IV infusion to inform the feasibility of maintenance therapy given every 8-12 weeks in suppressed HIV-infected individuals.

Methods: Three groups of 10 subjects were infused with 2400 mg (Group 1), 3200 mg (Group 2), or 4800 mg (Group 3) of each bNAb in 250 ml NS over one hour and followed for 12 to 16 weeks. Groups were dosed sequentially with dose escalation approved by an independent Data Monitoring Committee. Participants were suppressed with continuous oral cART for at least 6 months, clinically stable, without a history of severe allergies, and had no history of virologic failure on previous treatment regimens. All infusions were performed over 60 minutes in outpatient clinics with vital sign determinations every 15 minutes during and up to 3-5 hours post-infusion. A subset of participants was pre-medicated with acetaminophen 650 mg and cetirizine 10 mg at the investigator's discretion. Trough PK targets were ≥0.3 µg/ml and 65 µg/ml for TMB-365 and TMB-380, respectively in at least 80% of participants in any treatment group.

Results: All 30 subjects completed the study. One Group 3 subject was erroneously dosed with 1600 mg of each antibody and is excluded from PK analysis. No SAEs, Grade 3 or 4 adverse events, or acute infusion events were observed. Treatment emergent AEs (N=32) were mild to moderate. 5 were attributed to infusions with bNAbs. 2 subjects experienced delayed onset of fatigue and chills interpreted as hypersensitivity. PK data is shown below. Duration of concentrations above trough targets is increased with increased dose. In Group 3 participants at week 8, mean TMB-365 and TMB-380 concentrations were 15.1 and 86.4 µg/ml, respectively, and approximately 80% of participants met pre-defined trough targets.

Conclusion: A single infusion of TMB-365 and TMB-380 in combination up to 4800 mg each is safe. Prolonged PK duration was observed for both TMB-365 and TMB-380 and results suggest that an every 8-week infusion is feasible and will be tested in a Phase 2 clinical study.





641 Switching From a Second-Line Boosted PI Regimen to B/F/TAF: Results of a Randomized Clinical Trial

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Background: Patients on second-line boosted PI-based regimens in resource-limited settings have high rates of NRTI resistance, but this information is unknown in routine clinical care. This study compared continuing boosted PI + NRTIs vs bictegravir/tenofovir alafenamide/emtricitabine (B/F/TAF) in PWH on second-line ART with no prior drug resistance testing.

Methods: This prospective, open-label trial conducted at GHESKIO in Port-au-Prince, Haiti, randomized adults (≥18 years) with viral suppression on second-line PI/r-based ART to continue their current regimen vs. switch to B/F/TAF. The primary endpoint was the proportion of participants with HIV-1 RNA ≥200 copies/mL at week 48 using the FDA snapshot algorithm, the difference between groups was assessed with a non-inferiority margin of 4%.

Results: Between October 2020 and March 2023, 290 participants were randomized and treated (B/F/TAF: 149; bPI: 141). Median age was 50 years (IQR 42, 58) and 165 (57%) were women. At enrollment, 175 (60%) were taking lopinavir/r and 115 (40%) atazanavir/r; 226 (78%) were taking tenofovir disoproxil fumarate, 51 (18%) zidovudine, and 13 (4%) abacavir; all were taking lamivudine or emtricitabine. The median time on PI/r was 3.7 years (IQR 2.2, 5.7) years. At week 48, the proportion with HIV-1 RNA ≥200 copies/mL was 0.7% (1/149) and 2.8% (4/141) in the B/F/TAF and PI/r groups, respectively: difference -2.1 (95% CI: -6.7 to 1.2), meeting non-inferiority for B/F/TAF compared to PI/r (Table 1). 140 (94.0%) and 129 (91.5%), respectively had 48-week HIV-1 RNA <200 copies/mL. Eight in each group were censored – all had HIV-1 RNA <200 copies/mL at latest test (B/F/TAF: 4 completed study with no 48-week viral load; 1 died; 3 lost or left country; PI/r: 2 completed study with no 48-week viral load; 1 stopped study due to pregnancy; 2 died; 3 were lost or left country). There were no study drug discontinuations due to adverse events in either group. Baseline archived proviral DNA (B/F/TAF group) and genotypic resistance testing for virologic failures (both groups) are pending. This study was conducted during both COVID-19 and severe civil unrest and gang-related violence in Haiti. Follow-up was enabled by community health workers and neighborhood drug distribution when travel in Port-au-Prince was not safe or not possible for participants.

Conclusion: Switching virally suppressed adults on a second-line PI/r regimen to B/F/TAF is non-inferior to continuing PI/r-based ART. Rates of viral suppression were high in both groups.

Table 1. Primary End Point – Virologic Outcomes at Week 48

Week 48 Outcome	B/F/TAF (n=149)	Boosted PI (n=141)
Primary end point: HIV-1 RNA ≥200 copies/mL	**1 (0.7%)**	**4 (2.8%)**
HIV-1 RNA ≥200 copies/mL in 48-wk window	0	3
Treatment discontinued before wk 48 owing to lack of efficacy	0	0
Died or LTFU with last available HIV-1 RNA value of ≥200 copies/mL	1	1
HIV-1 RNA <200 copies/mL in 48-wk window	**140 (94.0%)**	**129 (91.5%)**
No data for final outcome (censored)	**8 (5.4%)**	**8 (5.7%)**

642 Phase II Study of Switch to Daily BIC + LEN in Individuals on a Multitablet HIV Treatment Regimen

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Background: While single-tablet regimens (STRs) are currently the global standard for HIV treatment, some people with HIV (PWH) take multi-tablet regimens (MTR) due to treatment resistance, intolerance or drug interactions. The combination of bictegravir (BIC), an integrase strand transfer inhibitor, and lenacapavir (LEN), a first-in-class capsid inhibitor, could simplify treatment in virologically suppressed (VS) PWH for whom STRs are not indicated. We report the Phase 2, 24-Week primary outcomes for BIC + LEN versus stable baseline regimen (SBR) in VS PWH on a complex regimen.

Methods: ARTISTRY-1 (NCT05502341) is an ongoing, randomized, open-label, multicenter Phase 2/3 study. In Phase 2, 128 participants on SBR (≥6 months prior to screening) were randomized 2:2:1 to receive once-daily oral BIC 75 mg + LEN 25 mg, oral BIC 75 mg + LEN 50 mg or continue SBR. All participants receiving BIC + LEN received an oral loading dose of LEN 600 mg on Days 1 and 2 of treatment. The primary endpoint was the proportion of participants with HIV RNA ≥50 copies/mL (FDA Snapshot) at Week 24. Secondary endpoints included the proportion of participants with HIV RNA <50 copies/mL, change from baseline in CD4 cell count and the proportion of participants with treatment emergent adverse events (TEAEs) up to Week 24.

Results: 51 and 52 participants received BIC 75 mg + LEN 25 mg or BIC 75 mg + LEN 50 mg, respectively, and 25 continued SBR. At baseline, 19% of participants were female, 31% were Black and 16% were Hispanic or Latinx; median (Q1, Q3) age was 60 (56, 65) years and participants were taking a median (range) of 3 (2–9) tablets per day. Outcomes at Week 24 are shown in the Table. HIV-1 RNA was ≥50 copies/mL in 0/51 of participants in the BIC 75 mg + LEN 25 mg group, 1/52 (2%) in the BIC 75 mg + LEN 50 mg group (later suppressed to <50 copies/mL without regimen change) and 0/25 in the SBR group. CD4 counts were comparable in all groups. The most common TEAEs in the two BIC + LEN treatment groups up to Week 24 were diarrhea (7%), COVID-19 (6%) and constipation (5%). Drug-related TEAEs occurred in 18%, 6% and 0% of participants, respectively.

Conclusion: BIC + LEN was highly effective in maintaining viral suppression in participants switching from an MTR, with similar safety profiles observed in the two BIC + LEN treatment groups. These data support the use of BIC and LEN in combination to simplify treatment in VS PWH who are receiving complex regimens. A BIC/LEN STR will be tested in the Phase 3 part of the study.

Table.

Outcomes at Week 24 (Phase 2)	BIC 75 mg + LEN 25 mg N = 51	BIC 75 mg + LEN 50 mg N = 52	SBR N = 25
HIV viral load ≥50 copies/mL (FDA Snapshot analysis), n (%)	0	1 (2)	0
HIV viral load <50 copies/mL (FDA Snapshot analysis), n (%)*	49 (96)	50 (96)	25 (100)
Change from baseline in CD4 count cells/µL, mean (SD)	33[†] (155)	5[‡] (145)	43[‡] (180)
≥ 1 TEAE up to Week 24, n (%)	39 (76)	33 (63)	17 (68)
≥ 1 TEAE leading to treatment discontinuation up to Week 24, n (%)	1[¶] (2)	1[#] (2)	0
≥ 1 drug-related TEAE up to Week 24, n (%)	9 (18)	3 (6)	0
≥ 1 serious TEAE up to Week 24, n (%)	2 (4)	1 (2)	2 (8)
Death, n (%)	0	1[‖] (2)	0

*No data at Week 24: n=2 for BIC 75 mg + LEN 25 mg; n=1 for BIC 75 mg + LEN 50 mg; [†]n=49; [‡]n=51; [§]n=25; [¶]nausea; [#]vomiting; [‖]unrelated to treatment. BIC, bictegravir; LEN, lenacapavir; SBR, stable baseline regimen; TEAE, treatment emergent adverse event

643 A Randomized Trial Switching Adults ≥ 60 Years Old From First-Line ART to B/F/TAF: Week 48 Results

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Background: Age-related comorbidities and toxicities of some antiretrovirals (ART) limit treatment options for the aging population of people living with HIV.

We evaluated the efficacy and safety of switching older adults from a first-line regimen to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF).
Methods: The B/F/TAF-elderly study is an open-label, randomized, active controlled, non-inferiority trial conducted at two sites in Kenya. Participants include HIV-1 positive older adults (≥60 years) on any first line regimen with HIV RNA <50 copies/mL for at least 12 weeks prior to enrolment and randomized 1:1 to switch to B/F/TAF or continue current ARV regimen (CAR). The co-primary endpoints are proportion of participants with HIV-1 RNA ≥50 copies/mL at week 48 in the intention-to-treat-exposed population using FDA Snapshot algorithm with a non-inferiority margin of 4%, and mean percentage change in lumbar spine bone mineral density (BMD) from baseline to week 48. The trial is continuing to week 96. ClinicalTrials.govNCT0524360
Results: Between Feb and May 2022, 520 participants were randomized and received treatment (260 B/F/TAF, 260 CAR). Of these, 296 were enrolled in the BMD monitoring population (143 B/F/TAF, 153 CAR). All participants were black, median age 64 years (range 60-80), 267 (51%) were female, with baseline characteristics balanced between arms. At baseline, 495 (95%) participants were on tenofovir disoproxil fumarate (TDF) and 177 (60%) of the BMD population had osteoporosis. At week 48, 5/260 participants (1.9%) in the B/F/TAF arm and 7/260 (2.7%) in the CAR arm had HIV-1 RNA ≥50 copies/mL (difference [95% CI], -0.8% [-3.4 to 1.8]), meeting non-inferiority criteria (Figure 1A). No participant with protocol defined virologic failure met the threshold for drug resistance testing of ≥500 copies/ml. The mean percentage change in lumbar spine BMD was +2.17% (SD 5.23) in the B/F/TAF arm and +0.61% (SD 5.44) in the CAR arm (difference [95% CI], 1.56 [0.32 to 2.79], p=0.014, Figure 1B). Grade 3 or 4 adverse events (AEs) were uncommon (3.1% on B/F/TAF; 2.3% on CAR) with no treatment-related serious AEs. Participants discontinuing study drug due to any AE was 1 (0.4%) on B/F/TAF and 15 (5.8%, all due to declining kidney function) on CAR.
Conclusion: Switching to B/F/TAF may be effective and safe for virally suppressed adults ≥60 years on a TDF containing regimen and is associated with improvement in BMD and fewer requirements for regimen modification due to worsening kidney function.

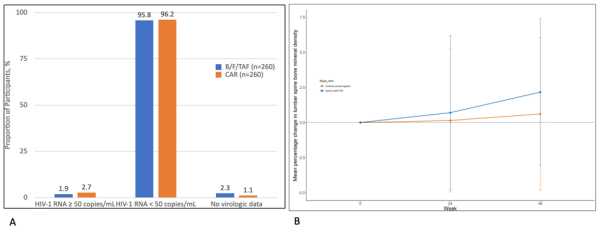

Figure 1: Co-primary outcomes at Week 48
A. Virologic outcomes in the intention-to-treat-exposed population by US FDA Snapshot algorithm. B. Mean percentage change in lumbar spine bone mineral density. Error bars represent standard deviations. Abbreviations: B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAR, current antiretroviral regimen.

644 Impact of Switching From Dual to Triple Therapy on Inflammation: INSTINCT Study

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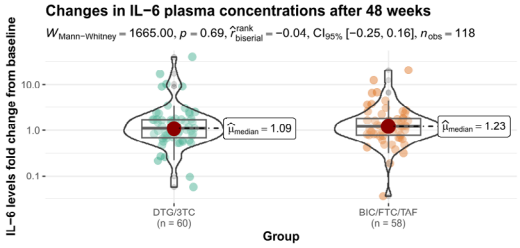
Background: Because inflammation is associated with mortality and has been linked to HIV transcription in lymphoid tissues during ART, it is necessary to address the long-term effects of switching ART regimens with different numbers of antiretrovirals on inflammation.
Methods: In this interim analysis of the randomized, open-label, multicenter INSTINCT trial (clinicaltrial.gov: NCT04076423), we evaluated the effect of switching from DTG/3TC to BIC/FTC/TAF vs. remaining on DTG/3TC on systemic inflammation up to 48 weeks. Participants were adults with confirmed, virologically suppressed HIV, on stable ART with DTG/3TC for a minimum of 48 weeks. Exclusions included previous virological failure, drug resistance, and autoimmune conditions. We focused on IL-6 changes from baseline to week 48 using high-sensitivity ELISA. IL-6 levels were analyzed using Mann-Whitney tests and linear regression adjusted for potential confounders in R studio.
Results: A total of 118 patients with available week 0 and 48 plasma samples were included; 17% women, mean age 44 ± 11 years, 79% white, 62% MSM, 9% with past AIDS diagnosis, median nadir CD4 338 cells/uL, baseline CD4 counts 776/uL, median duration of HIV suppression 5.2 years, median IL6 levels within normal range (0.96 pg/mL [0.53-1.44]). No differences were observed in the general characteristics between groups. No significant differences in IL-6 changes were observed between groups from week 0 to 48 (median fold change for DTG/3TC, 1.1 [0.7-1.7]; for BIC/FTC/TAF, 1.2 [0.8-1.8], P = 0.688)(Figure 1). Multivariate linear regression analyses corroborated these findings (Coef -0.07, P = 0.931).
Conclusion: This analysis revealed no significant impact on IL-6 levels when switching from DTG/3TC to BIC/FTC/TAF after 48 weeks. These preliminary findings suggest a neutral inflammatory effect for the ART switch, warranting further study to elucidate the longer-term influence on inflammation.



645 Switching to DTG+3TC vs 3-Drug Regimens in Routine Clinical Care: Long-Term Swedish Data

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Background: Swedish HIV treatment guidelines recommend that switching to the 2-drug regimen dolutegravir (DTG) + lamivudine (3TC) for maintaining virologic suppression should be considered in people living with HIV (PLHIV) in routine clinical care. We assessed long-term outcomes of switching to DTG+3TC (vs 3-drug regimens, 3DR) in virologically suppressed individuals in Sweden.
Methods: Retrospective data of all ART-experienced PLHIV with HIV RNA <50 copies/ml and switching to either DTG+3TC or any 3DR were obtained from the Swedish National Quality Registry for HIV (InfCareHIV). Within-group precision rates for virological failure (VF, having two consecutive HIV RNA levels ≥200 copies/mL prior to/by assessment timepoint) were determined for DTG+3TC and 3DR groups at months M6, M12, M24, M36, and M42 post-switch. A logistic generalized estimating equations (GEE) model was used to find associations between patient demographic and clinical predictors on VF.
Results: 2461 PLHIV switched regimen between July 2019 – May 2023; 1125 (46%) to DTG+3TC and 1336 (54%) to 3DR. The mean estimated time of extended exposure was 17.4 and 23.7 months for DTG+3TC and 3DR groups, respectively. 1778 PLHIV had data at M6, M12 (n=1418), M24 (n=985), M36 (n=444), and M42 (n=174). 37 on 3DR met VF – versus seven on DTG+3TC. VF rates for DTG+3TC group were 0.0013 (95% CI 0.0002, 0.009) at M6, and 0.0036 (0.0009, 0.014) at M12, 0.003 (0.0005, 0.02) at M24, 0.018 (0.005, 0.07) at M36, and 0.029 (0.004, 0.2) at M42. VF rates for 3DR group were 0.003 (0.001, 0.009) at M6, 0.014 (0.008, 0.024) at M12, 0.018 (0.01, 0.031) at M24, 0.021 (0.01, 0.044) at M36, and 0.023 (0.009, 0.061) at M42. In a GEE model (adjusting for treatment, ART adherence, time, sex, age, baseline CD4, HIV subtype, baseline drug resistance mutations, HBV, and HCV serostatus, viral blips before baseline and during the study), male sex, and CD4 count ≥500 at baseline were significantly associated with decreased risk of VF (adjusted odds ratio 0.41 [0.19–0.86], p=0.019, and 0.28 [0.14–0.59], p=0.001, respectively). Viral blips post-switch, and suboptimal adherence were significantly associated with increased risk of VF (4.84 [2.45–9.589], p<0.001, and 3.72 [1.12–12.34], p=0.032, respectively).
Conclusion: In this long-term real-world retrospective study, no significant difference in the risk of VF between DTG+3TC and 3DR were found. These

findings strengthen switching to DTG+3TC as an effective strategy for maintaining virologic suppression in clinical practice.

646 Impact of Switch to 3TC/DTG on the HIV-1 Transcriptional Reservoir in a Randomized Controlled Trial

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Background: The Rumba study is the first randomized clinical trial evaluating the impact on the viral reservoir of switch from a 2nd generation integrase inhibitor (INI)-based triple ART regimen towards 3TC/DTG vs. B/F/TAF. We observed no differences in the dynamics of the total and intact HIV-1 DNA reservoir after 48 weeks. Here, we quantified the mean change from baseline at 48 weeks of different HIV-1 RNA transcripts as a secondary objective, to ensure switching to 3TC/DTG does not increase transcriptional activity.

Methods: In this prospective controlled switch trial, participants with HIV-1 RNA<50 copies/ml plasma at least 3 months on any stable 2nd generation INI-based triple ART were randomized to switch to 3TC/DTG (N=89) or to switch or stay on B/F/TAF (N=45). HIV-1 transcripts that define distinct blocks to transcription were analyzed on CD4 T cell cDNA of subtype B participants in duplicate. An in-house 4-plex Rainbow transcriptional RNA dPCR assay for long LTR, pol, polyA and tat-rev was run on the QIAcuity system. RNA concentrations were used to normalize HIV-1 RNA transcripts. Statistical analysis was performed with an ordinary linear regression model on log-transformed data, adjusted for baseline response value, CD4 nadir and time on ART. Data analysis was performed with an in-house R script, a modified version of ddpcrquant to accommodate QIAcuity data analysis.

Results: Baseline characteristics are reported in Table 1. In this complete case analysis (3TC/DTG n=52; vs. B/F/TAF n=23), the mean baseline copy number per µg RNA was 207.7 for long LTR (elongated transcripts), 24.5 for pol (unspliced transcripts) and 77.9 for polyA (completed transcripts), suggesting a block to completion of transcription. Tat-rev (multiple-spliced transcripts, surrogate for productive infection) was undetectable in the majority of the samples at both timepoints. After 48 weeks, the relative change from baseline of elongated, unspliced and completed HIV-1 RNA transcript copies was not significantly different between 3TC/DTG and B/F/TAF, (1.11 [0.78-1.56], 0.83 [0.55-1.25] and 1.17 [0.85-1.61] respectively, point estimates and 95% CI). Also, within the treatment arms, no evidence of a significant mean difference over time was observed.

Conclusion: There is no evidence that simplification of a triple ART INI-based regimen to 3TC/DTG impacts the overall size of the reservoir, neither the fraction of intact virus nor the transcriptional activity.

Table 1: Baseline characteristics

Randomized participants	Total N=134	B/F/TAF N=45	3TC/DTG N=89
ITT-E population	n=130	n=43	n=87
Sex (M/F)	118/12	39/4	79/8
Ethnicity (European/African/other)	102/14/14	32/5/6	70/9/8
Subtype (B/non-B)	86/44	26/17	60/27
Age (y)*	47 (37;55)	46 (38;52)	48 (40;56)
CD4 nadir (cells/µl)*	302 (200;459)	256 (130;332)	309 (155;449)
Time on ART (y)*	7,2 (4,6;10,8)	6 (4,35;8,95)	8,6 (5,2;11,5)

*Median and IQR are reported.
ITT-E: Intention-to-treat-exposed

647 Impact of DTG+3TC as First-Line ART on HIV-1 Reservoir and Inflammatory Markers in Peripheral Blood

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Background: Data on the effect of dual therapy with DTG/3TC as first-line ART on the evolution of the HIV-1 reservoir and inflammatory biomarkers are lacking. Our objective was to compare the effect of first-line ART with DTG+3TC versus one standard 3-drug regimen (3DR) on the dynamics of viral persistence in lymph nodes and peripheral blood and on immune activation biomarkers during the 1st year after ART initiation. Here, we present data on the evolution of HIV persistence and immune-associated parameters in peripheral blood.

Methods: DUALITY is a 48-week, single-centre, randomized, open-label clinical trial in ART-naïve people with HIV (PWH). Participants were randomized (1:1) to receive DTG+3TC (2DR group), or with DTG+FTC/TAF (3DR group). Total and intact proviral HIV-1 DNA and cell-associated RNA (ca-RNA) in CD4+ T cells were longitudinally determined by ddPCR. The inducible reservoir was measured as the frequency of HIV-infected CD4+ T cells able to produce p24 by the VIP-SPOT assay. Soluble inflammatory markers (IL-6, sCD14, TRAIL, IP10, FABP2, CRP and D-dimer) were quantified by ELISA. Activation (HLA-DR/CD38) and exhaustion markers (PD-1/TIGIT) in CD4+ and CD8+ T cells were determined by multiparametric flow cytometry.

Results: Fourty-for participants were included (22 per study arm). At baseline, mean (SD) log_{10} pVL and CD4+ T cell count were 4.4 (0.7) copies/mL and 493 (221) cells/mm³. Two participants were lost, and one withdrew informed consent before week 48. All participants completing the study (2DR n=20; 3DR n=21) had pVL <50 copies/mL at week 48, except one in the 2DR group who was resuppressed after treatment for syphilis. Changes from baseline to week 48 in all reservoir parameters were similar between 2DR and 3DR groups (Table). At week 48, levels of total and intact proviruses were similar between both groups, and correlated with pre-ART pVL (Rho 0.50, p=0.002 for intact HIV-1 DNA). Changes in soluble inflammatory biomarkers and in levels of activated/exhausted CD4+ and CD8+ T cells were also comparable between study groups. Complementary data on anatomic distribution of antiretroviral drugs and viral expression in lymph nodes are under study.

Conclusion: First-line dual ART with DTG+3TC resulted in a similar decay in parameters of HIV-1 persistence in periphery as well as in immune-associated markers compared to 3DR with DTG+FTC/TAF. Our results further support recommendation of DTG/3TC as one preferred option for first-line ART in PWH.

Table: Median (min-max) fold change from baseline to week 48 in HIV-1 persistence parameters.

	2DR Group	3DR Group	p value
Total DNA	0.81 (0.33-0.93)	0.82 (0.50-0.94)	0.46
Intact DNA	0.82 (0.50-0.95)	0.84 (-0.32-0.97)	0.62
ca-RNA	0.93 (0.76-1.00)	0.94 (0.21-1.00)	0.90
VIP-SPOT	0.97 (0.78-1.00)	0.96 (0.49-1.00)	0.93

648 48-Week Outcomes After Programmatic Transition to Dolutegravir in South Africa

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Background: South Africa introduced tenofovir/lamivudine/dolutegravir (TLD) as the preferred first-line antiretroviral therapy (ART) regimen in 2019. Few data are available from individuals who transitioned from efavirenz (EFV)-based ART to TLD in rural public sector clinics in South Africa. Our objective was to evaluate viral suppression and regimen tolerability for individuals who were transitioned to TLD in this setting.

Methods: We conducted a prospective cohort study in rural KwaZulu-Natal. We enrolled adults ages >18 years who were transitioned from EFV-based ART to TLD by the clinic. Participants were enrolled on the date of TLD transition with follow-up visits 24 and 48 weeks later. We obtained blood specimens at each visit for retrospective viral load (VL) testing. Our primary outcome was viral suppression <50 copies/mL with retention in care at 48-weeks post-TLD transition. We fitted a multivariable logistic regression model to assess predictors of the composite outcome of viral suppression with retention in care.

Results: We enrolled 499 participants with a median age of 39 years (IQR 32–50 years), and 80% were female. The median duration of ART prior to TLD transition was 6 years (IQR 4-9 years). At the time of TLD transition, 93% had VL <50 copies/mL, 3% had VL between 50 and 1,000 copies/mL, and 3% had VL >1,000 copies/mL. By 48 weeks, 81% were suppressed and in care, 5% were unsuppressed and in care, 9% were lost from care, 0.5% were deceased,

2% were retained in care with missing VL data, and 3% had disenrolled. Only 3 participants discontinued TLD. In a multivariable logistic regression model, those with age <40 years and detectable viremia at the time of TLD transition were less likely to be virally suppressed and in care at 48 weeks (Table). Furthermore, only two-thirds of those with detectable viremia at the time of transition to TLD were virally suppressed after 48 weeks.

Conclusion: In the South African public sector, TLD was well tolerated with a <1% discontinuation rate. However, using an observational cohort approach with intensive outcome monitoring, only 81% of participants were virally suppressed and in care at 48 weeks. Over half of those who did not achieve the primary endpoint were lost from care or deceased. While high rates of viral suppression among those in care support widespread programmatic transition to TLD, further efforts are needed to optimize adherence and retention in care to attain programmatic goals of >95% viral suppression among those on ART.

Predictors	Proportion	AOR	95% CI	P value
VL <50 copies/mL at the time of switch	381/441 (86%)	Reference		
VL ≥50 copies/mL at the time of switch	21/31 (68%)	0.38	0.17-0.87	**0.022***
Age ≥40 years	218/243 (90%)	Reference		
Age <40s	186/231 (81%)	0.49	0.28-0.84	**0.009***
Female	321/377 (85%)	Reference		
Male	83/97 (86%)	0.98	0.50-1.91	0.948

*VL = viral load, AOR = adjusted odds ratio, CI = confidence interval

649 Uptake of Rapid and Early ART Initiation in Latin America and the Caribbean and Associated Factors

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Background: In 2015, the WHO recommended initiation of ART in all persons with HIV (PWH) regardless of CD4 count. Same-day ART has proven to be feasible and effective in low- and middle-income countries and has become a standard of care in Haiti for those without TB symptoms since 2017. Nevertheless, implementation of starting ART rapidly represents a challenge in diverse settings. Thus, we evaluated the proportion of PWH with rapid and early ART initiation, associated factors and survival in our region.

Methods: We included PWH ≥18 years of age, diagnosed between 2017 and 2021, and presenting for care in CCASAnet sites. We estimated the proportion of those who initiated rapid ART (≤7days; R-ART) and early ART (≤14days; E-ART) after HIV diagnosis overall and within each site. We analyzed factors associated with E-ART (age, sex at birth, education level, mode of HIV acquisition, site, calendar year, CD4 cell count) with a logistic regression (excluding Haiti where R-ART is standard of care) and the association of E-ART with overall survival with adjusted Cox models.

Results: A total of 9173 PWH were included; 8507(92.7%) initiated ART, and of those 3146(37%) initiated R-ART and 4237(49%) E-ART. Overall, most of E-ART and R-ART starters were from Haiti: 2759(88%) and 3532(83%), respectively. Among those included on each site, the proportion of E-ART were: Argentina 3%, Chile 5.4%, Peru 6.8%, Mexico 25%, Brazil 34%, Honduras 44%, and Haiti 79%. Excluding Haiti, more recent year was associated with a higher probability (aOR[95%CI]) of E-ART (1.24[1.93-2.12]) in 2018 and (2.47 [2.25-2.62]) in 2021 vs 2017. Additionally, being female (1.71[1.55-1.89]), other mode of acquisition vs heterosexual mode (1.67[1.19-2.35]), upper secondary vs primary school (1.16[1.05-1.28]), and age at diagnosis (0.93[0.90-0.96]) per each 10 additional years) were associated with E-ART. Overall, E-ART was not associated with higher survival (aHR: 0.93[95%CI:0.87-1.00], p=0.052 including Haiti; aHR: 0.90(95%CI:0.77-1.05), p=0.19 excluding Haiti).

Conclusion: Despite of the recommendation of ART initiation as soon as possible, Haiti is the only site in CCASAnet to initiate ART early after diagnosis of HIV in most patients. Women, younger and more educated people were more likely to initiate E-ART. Heterogeneity between health systems, policies and differential characteristics of participant sites including linkage to care strategies may contribute to these results . More research to explain these findings, is needed.

650 Bictegravir as Universal Initial Antiretroviral Therapy: A National Target Trial Emulation Study

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Background: Bictegravir (BIC) has been shown to be non-inferior to dolutegravir (DTG) as initial antiretroviral therapy (ART) in non-inferiority randomized controlled trials (RCTs). Mexico established in 2019 a national policy to start ART with BIC to every ART naïve person with HIV (PWH). However, BIC has not been compared to efavirenz (EFV) or raltegravir (RAL) (commonly prescribed in Mexico) and no superiority trials have been performed.

Methods: We used data from the national antiretroviral surveillance system in Mexico to perform three target trial (TT) emulations for initial ART among PWH starting ART from 2019 onwards: BIC vs DTG, BIC vs EFV, and BIC vs RAL. Our approach consists of specifying the protocol of an index TT (the RCT we would ideally conduct) and emulate it with observational data while adjusting for confounding to approach randomization. Baseline was the date of ART start. People with missing viral load (VL), VL <500 copies/mm^3, and/or missing CD4 count within the last year before ART start, those started on double-dose DTG and/or reduced-dose emtricitabine, lamivudine or tenofovir disoproxil fumarate were excluded. We performed individual logistic regressions while adjusting for treatment-outcome confounders (baseline VL and CD4, age, gender, imprisonment status, state of residence, year of ART start) to estimate risk of undetectable VL (UVL) (<50 copies/mm^3) for each person at 3 and 12 months. We performed intention-to-treat analyses. We calculated the mean risk of UVL for each group, risk ratios (RR) and 95% percentile-based confidence intervals using 500 bootstrap resamples.

Results: 26178 PWH were included: 18894 started BIC, 2530 DTG, 562 RAL, and 4192 EFV. Most PWH were cis men (85%), median age was 31 years. 57% had a baseline viral load <100k copies, and median CD4 cell count was of 213. Only 1% of PWH were in a prison. At three months, the risk of UVL was of 79.2% vs 78.4% (BIC vs DTG, RR 1.01 [0.98-1.03]), 79.7% vs 71% (BIC vs RAL, RR 1.12 [1.03-1.22]), and 79.7% vs 63.6% (BIC vs EFV, RR 1.25 [1.21-1.3]). At twelve months, the risk of UVL was of 85.9% vs 83.6% (BIC vs DTG, RR 1.02 [0.98-1.08]), 85.9% vs 79% (BIC vs RAL, RR 1.08 [1-1.23]), and 86.6% vs 83% (BIC vs EFV, RR 1.04 [1.01-1.08]).

Conclusion: BIC is superior to RAL and EFV, but not DTG, as initial ART in treatment naïve PWH for reaching UVL at 3 and 12 months. These results support existing RCTs and argue in favor of this type of country-wide strategy.

651 HIV Detectable Low-Level Viremia Suggests a Revised Threshold for Viral Suppression in Cameroon

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Background: Transitioning to dolutegravir-based therapy in Cameroon has improved viral suppression (VS) rates, known as low-level viremia (LLV) <1000copies/ml. However, there is a growing number of patients experiencing VS with detectable LLV, indicating risk of virological failure. This study aimed to characterize the distribution of LLV and associated factors in the Cameroonian context.

Methods: A laboratory-based study was conducted among treatment-experienced patients monitored for HIV plasma viral load (PVL) from January 2020 through April 2022 at the Chantal BIYA International Reference Centre (CIRCB), Yaoundé-Cameroon. PVL was measured using the Abbott m2000RT-PCR. Among patients with LLV, levels of PVL were stratified into 4 cut-points: <50, 50-200, 201-500, and 501-999 copies/ml, with p<0.05 considered statistically significant.

Results: Overall, 14970 patients were enrolled: 72.5% were female; 14219 adults, 466 adolescents, 285 children. By ART-regimens, 3411 were on NNRTI-based, 505 on PI/r-based and 11054 on DTG-based ART. Median [IQR] duration on ART was 36[27-39] months. Overall VS (<1000 copies/ml) rate was 88.8% (13291/14970) (95% CI: 88.2-89.3), and stratification in this population showed 1.5% (207/13291) with 501-999 copies/ml, 3.3% (445/13291) with 200-500 copies/ml, 10.8% (1439/13291) had 50-200 copies/ml, and 84.2%

(11200/13291) with <50 copies/ml, p<0.0001. By ART-regimens, detectable LLV (50-999copies/ml) was 13.9% (1540/11054) with DTG-containing versus 14.1% (551/3916) with other ART-regimens, p=0.81.By age, detectable LLV was 13.8% among adults versus 16.9% children/adolescents, p=0.01. Most importantly, the trend overtime of detectable LLV between 50-200 copies/ml increased significantly from 65.2% (534/819) in 2020, 70.7% (678/958) in 2021 and 72.2% (227/314) in 2022, p=0.001.

Conclusion: Even though VS rate appears encouraging, there is a significant increasing proportion of patients with detectable LLV in this DTG-era. Of note, LLV with 50-200 copies appears highly predominant, suggesting a revision of threshold for VS at a maximum of 200 copies/ml in resource-limited settings like Cameroon.

652 Increased Viral Suppression With Adherence Counseling Incorporating a Point-of-Care Urine TFV Test

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Background: Innovative approaches are needed to achieve the third UNAIDS 95-95-95 target, to increase and sustain virologic suppression (VS) in patients on ART, specifically co-formulated tenofovir (TFV)-lamivudine-dolutegravir (DTG) or TLD. Virologic failure in patients on TLD is likely due to non-adherence because of DTG's high resistance barrier. Identifying non-adherence to TLD with a point-of-care (POC) metric and tailored counseling on the test may help patients achieve viral suppression (VS). We integrated a low-cost, POC urine test to detect TFV into standard WHO-recommended enhanced adherence counseling (EAC) to improve VS in adults with non-VS on TLD in Namibia.

Methods: Patients on TLD with viral load (VL) >1000 copies/mL after completing ≥1 round of EAC were enrolled from 42 clinics across Namibia. At each monthly ART pick-up, participants completed the POC urine test and received EAC informed by test results. After 3 months (round 1), participants received a viral load (VL) test. If VS was not achieved, up to 3 additional rounds of POC urine testing with EAC was provided, with an HIV drug resistance test sent at month(M) 9. Acceptability of the urine assay was assessed via surveys administered to participants and providers.

Results: Of 211 participants enrolled (median age 33 years, interquartile range 22-46, 61% female), 195 reached M3 and received a follow-up VL, with 169 (87%) achieving VS within M3 and 182 (93%) by M9. Moreover, in those who achieved VS, positive TFV in urine increased from 81% at baseline to 96% at M9 compared to a change from 31% to 41% among unsuppressed individuals. Drug resistance testing was performed in 5 remaining participants with high VL at M9. All 5 had variable urine TFV results over visits and one had DTG resistance (N155H and R263K mutations). Overall, 84% of participants and 89% of interviewed providers agreed/strongly agreed that the urine test improved EAC.

Conclusion: Nearly 90% of patients on TLD with VL >1000 copies/mL achieved VS within 3 months (93% at M9) following EAC that incorporated a urine-based POC TFV test, compared to 33% of individuals receiving 1-3 rounds of standard WHO-recommended EAC. Encouraging results of this pre-post intervention support rigorous testing in a future randomized clinical trial. Given the cost of VL and resistance testing in lower-and middle-income countries, this POC urine test has great potential to help achieve the third 95-95-95 target in a low-cost, scalable manner.

653 Preclinical Pharmacokinetics of a Novel Long-Acting Bictegravir Solid Injectable in Rats

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Background: Bictegravir (BIC), is an integrase strand transfer inhibitor, effective for HIV treatment when combined with emtricitabine and tenofovir alafenamide. Another integrase inhibitor, cabotegravir, has been demonstrated to be effective in pre-exposure prophylaxis as a single agent and is available as a long-acting (LA) injectable medicine. This work describes preclinical pharmacology of a novel BIC LA solid injectable.

Methods: A solid drug nanoparticle (SDN) formulation of BIC was manufactured using emulsion-templated freeze-drying (ETFD) prior to formation of a solid format using vacuum compression moulding (VCM). Resulting BIC formulations were injected (16.8mg BIC per animal) subcutaneously with a 12-gauge needle into the scapular region of male Sprague Dawley rats (n = 4, 250-300g). Plasma samples were collected from the lateral tail vein for 13-weeks post injection. BIC concentrations were quantified in plasma using validated LC-MS/MS and the injection site was terminally harvested for histopathological analysis.

Results: ETFD yielded solids consisting of 70% BIC by weight, with subsequent dispersion in water yielding BIC particles with hydrodynamic diameters (Dz) between 700-850 nm, as determined by dynamic light scattering. Plasma BIC concentrations exceeded the human oral steady-state C_{trough} within 3 hours of administration and remained above this level for 42 days (T_{max} = 2 days; $AUC_{0\text{-}tlast}$ = 22427 µg.h/mL). No behavioural issues were encountered, animals gained weight throughout and no visible injection-site reactions were evident.

Conclusion: Preclinical data for a novel BIC solid injectable demonstrated sustained therapeutic concentrations in rats for 42 days. Further work is required to understand dose linearity and proportionality, assess removability, and estimate doses and durations likely to be achievable in humans.

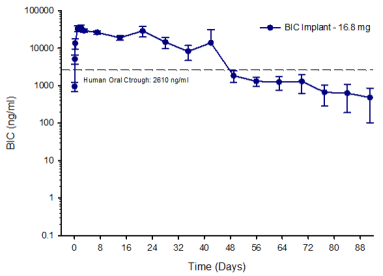

Figure 1. Plasma concentration-time curve in Sprague Dawley rats following a single administration of bictegravir as a solid injectable. Data are expressed as the mean ± SD (n = 4) and dashed horizontal line represents steady state C_{trough} concentrations in human receiving the approved oral dose.

654 Shape-Shifting Tail Decay Is the Pharmacokinetic Profile of an Ultra-Long Acting Bictegravir Prodrug

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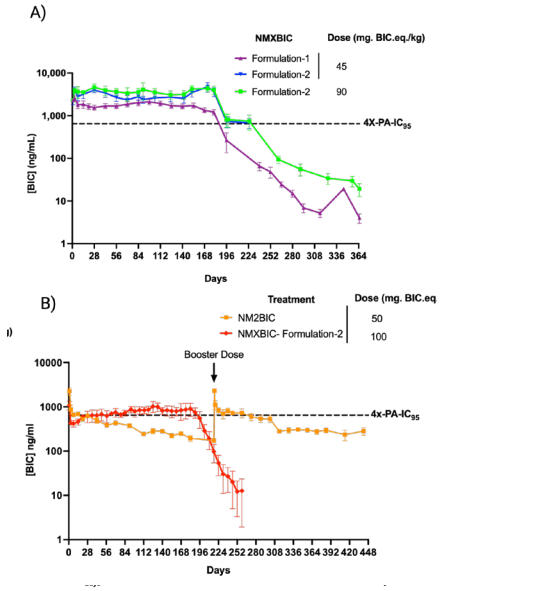
Background: The advantages of long-acting (LA) antiretroviral therapy (ART) for regimen adherence and sustained viral suppression are unquestioned. However, the requirement for bi-monthly clinic visits, injection site reactions, large dosing volumes, and long pharmacokinetic (PK) tail pose notable challenges to widespread LA ART use. Consequently, there is an immediate need for ultra-LA (ULA) ART capable of synchronizing dosing intervals with established six-month clinic visits. We report the PK and biodistribution profiles of two lead bictegravir (BIC) prodrug formulations in two animal species, in pursuit of a ULA BIC prodrug formulation with a short PK tail.

Methods: Dimeric (MXBIC) and monomeric (M2BIC) BIC prodrugs were synthesized by esterification reactions and converted into aqueous surfactant stabilized solid drug nanosuspensions by high-pressure homogenization. Formulation stability, particle size, homogeneity, and surface charge were assessed. PK profiles, biodistribution, and terminal phase PK tails were evaluated in Sprague Dawley (SD) rats and rhesus macaques (RM) after intramuscular (IM) injection dosing.

Results: Dimeric BIC prodrug formulations (NMXBIC formulations 1 and 2) demonstrated plasma BIC levels above the protein-adjusted 95% inhibitory concentration ($PA\text{-}IC_{95}$) for > 6 months in SD rats after a single 45 mg BIC.eq./kg IM injection. Increasing the formulation concentration of NMXBIC by 1.5 fold (NMXBIC formulation 2) and subsequent reduction of injection volume boosted plasma BIC levels, but doubling the dose for formulation 2 in SD rats did not lead to a proportional increase in plasma BIC levels. Specifically, BIC levels following NMXBIC formulation 2 dosing were sustained at levels ≥ 14x $PA\text{-}IC_{95}$ for 6 months. In RM, a single IM injection of NMXBIC (100mg. BIC eq./kg) sustained plasma BIC levels at ≥ 4x $PA\text{-}IC_{95}$ for more than 6 months. Notably, regardless of the dose and species, plasma BIC levels after NMXBIC treatment exhibited

rapid drug decay after 7 months, demonstrating a short PK tail (Figure A-B). In contrast, the monomeric BIC prodrug formulation (NM2BIC) exhibited a much slower BIC plasma decay curve after 7 months post-dosing in RM. An equivalent booster dose of NM2BIC (50 mg. BIC eq./kg) in RM on day 217 resulted in higher plasma BIC levels than the corresponding time points after the first injection.
Conclusion: The dimeric NMXBIC formulation exhibits high plasma BIC exposure and a shorter PK tail with the potential for dosing at 6-month intervals.



Plasma BIC levels (mean ±SEM). (A) SD rats and (B) RMs were injected intramuscularly with NMXBIC or NM2BIC. For NM2BIC, a booster dose was injected on day217 in RM.

655 WITHDRAWN

656 Cabotegravir Stearate (XVIR-110), an InSTI Prodrug, Provides Ultra-Long Acting Cabotegravir Exposure

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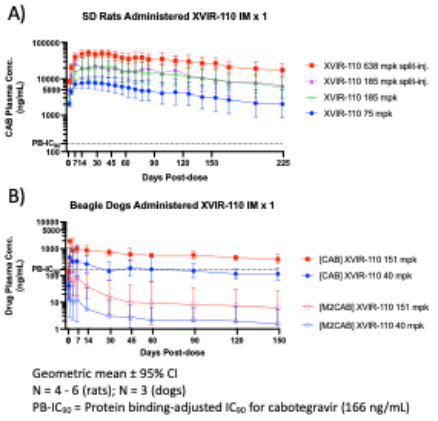
Background: Cabotegravir stearate (M2CAB) is a novel prodrug of the INSTI cabotegravir (CAB) that forms local and macrophage-distributed M2CAB depots, resulting in "flip-flop" plasma pharmacokinetics (PK) yielding a protracted apparent elimination half-life. M2CAB is formulated as an extended-release injectable suspension (XVIR-110) for intramuscular (IM) administration that may achieve ultra-long-acting therapeutic CAB exposures with infrequent administration.
Methods: We evaluated the PK profile of M2CAB and/or CAB in following a single IM (thigh muscle(s) of hind limb; 28 ga. syringe) administration of XVIR-110 to male SD rats and male beagle dogs. XVIR-110 was dosed at target M2CAB doses of 75, 185 (single and (2)-split injections) and 638 mpk (split injections) in rats and at 40 and 151 mpk in dogs. PK were assessed at multiple timepoints over up to 12 months until CAB concentrations fell to less than the protein binding-adjusted IC_{90} (PB-IC_{90}) of 166 ng/mL. Drug concentrations were measured using validated UPLC-MS/MS methods. Additionally, a separate study of injection site reactions (ISR) with histopathologic evaluation of head-to-head administration of XVIR-110 and commercial cabotegravir was conducted in rats.
Results: Concentration-time profiles are presented in Figure 1 for CAB in rats (Panel A) and for M2CAB and CAB in dogs (Panel B) below. A single IM administration XVIR-110 resulted in low exposures of the prodrug M2CAB but yielded high and persistent exposures of active CAB in both rats and dogs over the period of study to date, 7 and 5 months, respectively. The study is ongoing and based on the projected apparent terminal-elimination half-life of CAB, concentrations above the PB-IC_{90} of CAB are expected to remain for more than 12 months. Based upon modelling, these data suggest that XVIR-110 could be dosed once- or twice-yearly in humans. XVIR-110 was well tolerated without evidence for dose-limiting ISRs and demonstrated less pronounced early post-injection microscopic changes, including tissue necrosis, inflammation, and immune cell infiltration vs. commercial cabotegravir at equivalent doses.
Conclusion: XVIR-110 demonstrated sustained CAB exposures and a favorable ISR profile in nonclinical species. As such, XVIR-110 may be ideally suited where daily, self-directed, or more frequent IM or SQ may be less desirable or feasible, particularly where inconsistent and/or ad hoc adherence is a risk, such as pre-exposure prophylaxis (PrEP) or in patients with known adherence challenges.



657 Effect of Remdesivir on Post-COVID Conditions Among Individuals Hospitalized With COVID-19 by Age

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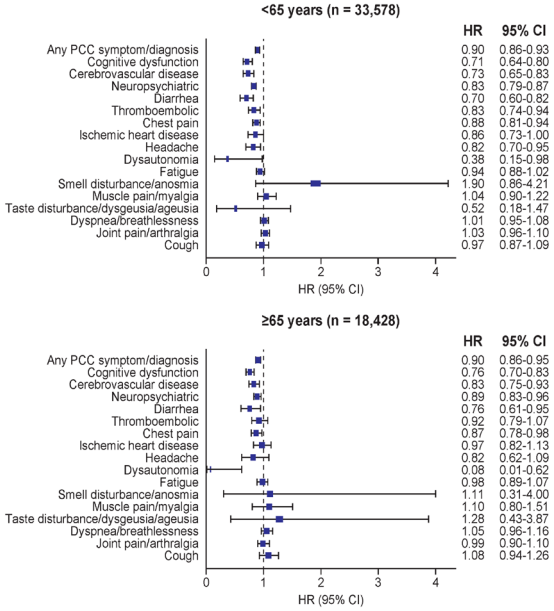
Background: Post-COVID conditions (PCC), or long COVID, are part of a persistent, multisystemic syndrome occurring after COVID-19. The effect of the antiviral remdesivir (RDV) on subsequent outcomes associated with PCC is unknown. Of particular interest are RDV's effects stratified by age, which is a predictor of outcomes in patients hospitalized with COVID-19.

Methods: The HealthVerity database of hospital chargemaster data linked to closed claims for >25 million US patients was queried for individuals aged ≥12 years hospitalized for ≥2 days with COVID-19 between 5/1/2020 and 9/30/2021. The analysis was stratified by age category (<65 vs ≥65 years of age). Cox proportional hazards models used inverse probability of treatment weighting to calculate hazard ratios (HR) for 16 individual PCC-related symptoms or diagnoses and a composite of any PCC, occurring 90-270 days posthospitalization, in patients hospitalized with COVID-19 receiving RDV versus comparators not receiving RDV. Individuals without ≥90 days of follow-up still contributed person-time up to their day of censoring.

Results: Of 3,661,303 individuals hospitalized for any reason during the study period, 52,006 had acute COVID-19 and met inclusion criteria, of which 33,578 (64.6%) were <65 years of age. In the <65 and ≥65 age groups, respectively, 36.1% and 27.2% received RDV. The most common PCC-related symptom/diagnosis was neuropsychiatric features, with an incident rate per 100 person-years of 58.0 and 52.4 in <65 and ≥65 age groups, respectively. Overall, RDV (vs no RDV) was associated with significantly lower relative hazard of any PCC in both age groups: HR 0.90 (95% confidence interval [CI]: 0.86–0.93) in those <65 years old and HR 0.90 (95% CI: 0.86–0.95) in those ≥65 years old. RDV was associated with lower risk for 6 of 16 individual symptoms/diagnoses in the ≥65 age group (cognitive dysfunction, cerebrovascular disease, neuropsychiatric features, diarrhea, chest pain, and dysautonomia) and for 8 of 16 individual symptoms/diagnoses in the <65 age group (including the same 6 symptoms, as well as thromboembolic disease and headache).

Conclusion: RDV was associated with reduced risk of PCC after COVID-19 hospitalization in patients <65 and ≥65 years of age, though more symptoms were impacted, and the effect size tended to be stronger in the younger age group. The majority of patients did not receive RDV, indicating a missed opportunity for treatment of acute COVID-19 and potential prevention of long-term sequelae of infection.



658 Extended Nirmatrelvir/Ritonavir Treatment Durations for Immunocompromised Patients With COVID-19

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Background: Nirmatrelvir/ritonavir (NMV/r) is an FDA-approved treatment for adults with mild to moderate COVID-19 who are at high risk for progression to severe disease. Limited data support dosing recommendations in immunocompromised (IC) patients. This study compared the approved 5-day regimen with 10- and 15-day regimens in IC patients.

Methods: This multinational, randomized, double-blind, phase 2 study enrolled 156 nonhospitalized IC patients ≥12 years of age with symptomatic COVID-19 who tested SARS-CoV-2–positive within 5 days of study entry. Subjects were randomized 1:1:1 to receive 300/100 mg NMV/r twice daily for 5, 10, or 15 days. Nasopharyngeal (NP) swabs for PCR and rapid antigen testing were collected at baseline and on Days 5, 10, 15, 21, 28, 35, and 44. The primary endpoint was proportion of subjects with NP SARS-CoV-2 RNA below the lower limit of quantification (LLOQ; defined as 2.0 $\log_{10}$ copies/mL) from Days 15 through 44.

Results: The primary endpoint was achieved in 62%, 71%, and 66% of subjects in the 5-, 10-, and 15-day treatment groups, respectively. No formal hypothesis testing was performed. The median time to achieving sustained NP SARS-CoV-2 RNA <LLOQ through Day 44 was numerically longer in the 5-day treatment group (15 days) compared with the 10-day (11 days) and 15-day (10 days) treatment groups. An increase in viral RNA following the end of treatment occurred in 17% of subjects treated for 5 days, compared with 2% in each of the 10- and 15-day treatment groups. Severely IC subjects (those with hematologic malignancy and/or hematopoietic stem cell transplantation, CAR T-cell therapy, or B-cell–depleting therapy) experienced better virologic control with extended treatment than with the standard 5-day treatment (Figure). Overall, RAT positivity from Days 10 through 44 occurred in 23% of subjects treated for 5 days in contrast with 4% and 6% of subjects treated for 10 and 15 days, respectively. No deaths occurred through Day 44; 2 severely IC subjects in the 5-day group were hospitalized due to COVID-19. No Mpro mutations with the potential to reduce NMV activity were identified. The safety profile of extended treatment with NMV/r was consistent with previous placebo-controlled clinical trials

Conclusion: The approved 5-day treatment course of NMV/r appears to be adequate for SARS-CoV-2 viral clearance in non-severely IC patients. Extending NMV/r treatment beyond 5 days may improve SARS-CoV-2 viral clearance in severely IC patients. NCT05438602 Funding: Pfizer.

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659 Nirmatrelvir/Ritonavir Reduces COVID-19 Symptom Duration Across Subgroups of Patients at High Risk

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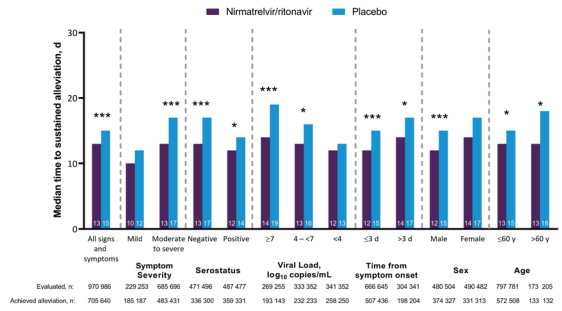
Background: Nirmatrelvir with ritonavir (nirmatrelvir/r) is an oral antiviral treatment for COVID-19. We report times to sustained alleviation and resolution of COVID-19 symptoms, overall and across subgroups of non-hospitalized adults with COVID-19 at increased risk of severe disease treated with nirmatrelvir/r compared to placebo (PBO).
Methods: EPIC-High Risk (HR) was a Ph 2/3 double-blind, randomized, PBO-controlled study to evaluate nirmatrelvir/r in symptomatic, unvaccinated, nonhospitalized patients (pts) with ≥1 risk factor for progression to severe COVID-19. Eligible adults with confirmed SARS-CoV-2 and ≤ 5 days (d) of symptoms were randomized 1:1 to nirmatrelvir/r 300 mg/100 mg or PBO every 12 hrs for 5 d. Pts logged presence and severity of prespecified COVID-19 symptoms daily Day 1 through 28. Times to sustained alleviation and resolution of all targeted symptoms within pt subgroups were assessed and compared between treatment groups using a COX proportional hazard model.
Results: Among 2113 randomized pts, 1996 (nirmatrelvir/r, n=977; PBO, n=989) were included in the analysis population (≤ 5 d of symptom onset, did not/not expected to receive an mAb). Nirmatrelvir/r significantly reduced the times to sustained alleviation (median 13 vs 15 d, Hazard Ratio [HR]=1.27, p<0.0001) and resolution (16 vs 19 d, HR=1.20, p=0.0022) of all targeted symptoms through Day 28. Reduction in median time to sustained alleviation was observed in nirmatrelvir/r treated pts in all subgroups by baseline symptom severity, serostatus, viral load (VL), time since symptom onset, sex and age; with largest reductions among pts with moderate/severe symptoms at baseline (13 vs 17 d; p=0.0001), seronegative pts (13 vs 17 d; p=0.0001), pts with baseline VL ≥7 log_{10} copies/mL (14 vs 19 d; p<0.0001), and pts >60 years of age (13 vs 18 d, p=0.0024) (Figure 1). The reduction in median time to sustained symptom resolution was more apparent in the same subgroups: pts with moderate/severe symptoms at baseline (20 vs 23 d; p=0.0101), seronegative pts (19 vs 23 d; p=0.0086), pts with baseline VL ≥7 log_{10} copies/mL (19 vs 25 d; p=0.0272), and pts >60 years of age (18 vs 22 d, p=0.0386).
Conclusion: Nirmatrelvir/r treatment reduced median times to sustained alleviation and resolution of all targeted COVID-19 symptoms vs PBO significantly overall, and consistently across pt subgroups (by baseline symptom severity, serostatus, VL, time since symptom onset, sex and age) in pts at high risk for progressing to severe disease.

Figure 1. Median time to sustained alleviation of all targeted COVID-19 symptoms through D28 by baseline status (mITT1 population)



Significant differences between treatment groups are denoted with asterisks: *p ≤0.05; ***p ≤0.0001.

660 Large Fraction of COVID-19 Hospitalizations Preventable With Oral SARS-CoV-2 Antiviral Treatment

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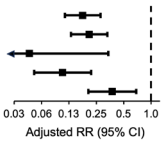
Background: Oral SARS-CoV-2 antiviral agents are an important treatment option for preventing severe COVID-19. We aimed to quantify the reduction in hospitalizations achievable through complete compliance with oral antiviral treatment guidelines in high-risk adults.
Methods: Using electronic health record data from health systems in Minnesota and Nevada, we identified oral antiviral-eligible SARS-CoV-2 patients between April 2022 and June 2023 as those ≥50 years old, unvaccinated, or with ≥1 high-risk medical condition. Modified Poisson regression was employed to estimate adjusted risk ratios (RRs) for the association between nirmatrelvir-ritonavir (NMV/r) or molnupiravir (MPV) treatment and hospitalization within ≤14 days after the positive test, stratified by immunocompromised status. Using adjusted RRs and treatment prevalence, we also calculated the preventable fraction of hospitalizations that could have been averted had all eligible patients been treated.
Results: Among 3,525 SARS-CoV-2 patients with risk factors for severe COVID-19, 2,223 (63.1%) were ≥50 years old (35.4% ≥65), 829 (23.5%) were unvaccinated, and 2,932 (83.2%) had ≥1 high-risk medical condition. Overall, 1,033 (29.3%) were prescribed an oral antiviral agent (911 NMV/r; 122 MPV) and 300 (8.5%) were hospitalized. Only 1.9% of treated patients vs. 11.2% of untreated patients were hospitalized (p<0.001). In adjusted analyses, treatment with any oral antiviral agent (RR=0.18), with NMV/r (RR=0.21), and with MPV (RR=0.05) were each significantly associated with a lower risk of hospitalization (Figure). The protective association for any antiviral was stronger in immunocompetent (RR=0.11) vs. immunocompromised (RR=0.37) patients (interaction, p<0.001). If all patients had been treated, 76.8% (95% CI: 66.6-85.9) of all hospitalizations could have been averted, including 85.7% (95% CI: 74.5-94.9) of those in immunocompetent and 54.9% (95% CI: 32.4-77.6) of those in immunocompromised patients.
Conclusion: Three-quarters of COVID-19 hospitalizations in high-risk patients could have been prevented had all patients received oral antiviral treatment prior to disease progression. This noteworthy finding is attributed to the strong observed protective effect of treatment coupled with large treatment gaps. Moreover, the diminished protection among immunocompromised patients underscores the importance of close symptom monitoring and consideration of additional therapeutic options such as remdesivir and COVID-19 convalescent plasma.

Figure. Association between oral antiviral treatment and risk of hospitalization.

Treatment comparison and subgroup	Adjusted RR (95% CI)
Any vs. no oral antiviral, overall	0.18 (0.11-0.28)
Nirmatrelvir/ritonavir vs. no oral antiviral, overall	0.21 (0.13-0.33)
Molnupiravir vs. no oral antiviral, overall	0.05 (0.01-0.34)
Any vs. no oral antiviral, immunocompetent	0.11 (0.05-0.22)
Any vs. no oral antiviral, immunocompromised	0.37 (0.21-0.69)

Adjusted for calendar date, health system, age, sex, race/ethnicity, SARS-CoV-2 vaccination status, nirmatrelvir/ritonavir contraindication, smoking, asthma, chronic lung disease, cardiovascular disease, cerebrovascular disease, dementia, diabetes, obesity, cancer, chronic kidney disease, liver disease, psychiatric disorder, primary immunodeficiency, and immunosuppressive medication use.



661 Pooled Analysis of Randomized Trials Comparing Drug Efficacy for Early COVID-19 During Omicron Waves

Valentina Mazzotta[1], Fulvia Mazzaferri[2], Simone Lanini[1], Massimo Mirandola[2], Alessandro Cozzi-Lepri[3], Alessandra Vergori[1], Alessia Savoldi[2], Francesca Bai[4], Gaia Maccarrone[2], L. Sarmati[5], Carlo Tascini[6], Enrico Girardi[1], Annamaria Cattelan[7], Andrea Antinori[1], Evelina Tacconelli[2]
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Background:Antivirals and monoclonal antibodies are largely used for early treatment of COVID-19 in high-risk people, based on data from randomized trials (RCTs) among unvaccinated people before the omicron era. No evidence from RCTs is available on the comparison of clinical efficacy of currently available treatments. We present a pooled analysis of two RCTs conducted in Italy during omicron waves.
Methods: MANTICO (EudraCT 2021-002612-31) and MONET (EudraCT 2021-004188-28) are two multicentric, open-label, phase 4 RCTs supported by the Italian Drug Agency. Non-hospitalized patients (pts) with early COVID-19 (≤5 days after symptoms onset) and >=1 risk factor were randomized 1:1:1 to receive 500 mg of intravenous sotrovimab (SOT) or 600 mg of intramuscular tixagevimab/cilgavimab (T/C) or oral 5-days course of nirmatrelvir/ritonavir (N/r) 300/100 mg BID. Primary outcome was COVID-19-related hospitalization or death within 29 days after randomization. Fisher's exact test for pooled data and incidence of failure was reported as overall and by arm with respective 95% CI. Exact logistic regression models were implemented to estimate differences between arms and to adjust for residual confounding (age, sex, and variables with imbalance >=5%). Secondary outcome analysis on the variation of

symptom prevalence over time across the arms by fitting hierarchical mixed multivariate regressions.

Results: 991 pts (SOT=332, T/C=327, N/r=332) enrolled from Mar 2022 to Feb 2023. Vaccinated people were 93%. Diabetes, lung, and cardiovascular diseases reported an imbalance between 5% and 10%. Among the 8/991 hospitalizations observed, one resulted in death. The overall estimate of failure was 0.81% (95%CI; 0.35-1.58%). Incidence across the arm varied from 0% (0.00-1.10) for N/r, to 0.60% (0.07-2.16) for SOT and 1.83% (0.68-3.95%) for T/C (p=0.015 by Fisher test for pooled data). The adjusted model showed evidence for an increased risk of failure in T/C arm compared with N/r arm (OR 8.41; 95%CI 1.21-inf. p=0.015) but not for other comparisons. No difference was detected in symptom prevalence over time between arms, with some symptoms persisting in more than 15% of pts on day 29.

Conclusion: This RCT pooled analysis in the omicron era showed that N/r was superior to T/C in reducing hospital admission or death. Given the low number of events, the study produced no evidence on the other comparisons. No significant difference in symptom prevalence over time across the arms was found.

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662 Predictors of Failure to COVID-19 Early Therapies and Drugs Efficacy Comparison by Emulation Trial

Valentina Mazzotta[1], Alessandro Cozzi-Lepri[2], Cosmo Del Borgo[3], Silvia Rosati[1], Martina Rueca[1], Enrico Girardi[1], L. Sarmati[4], Claudio Maria Mastroianni[3], Massimo Fantoni[5], Fabrizio Maggi[1], Emanuele Nicastri[1], Miriam Lichtner[3], Andrea Antinori[1], for the Early Treatment for COVID-[19] Lazio Study Group

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Background: Although widespread vaccination and lower pathogenicity of the omicron variant had drastically reduced the rate of COVID-19-related hospitalization/death (CovH/D), real-world evidence can help to identify categories still at risk of severe outcomes and inform on the efficacy of different treatments used.

Methods: Multicenter cohort of high-risk outpatients (pts) treated with monoclonal antibodies (mAbs) or antivirals for mild-to-moderate COVID-19 from March 2021 to May 2023 in the Latium Region. The outcome was CovH/D by day 30 from baseline by fitting logistic regression models, including a specific set of potential confounders, for each exposure of interest: age>75 years; vaccination; calendar period (reflecting the main circulating VoC), immunocompromised status. Among pts enrolled in 2022, the difference in risk between interventions (Sotrovimab=SOT; Molnupiravir=MLP; Remdesivr=RDV; tixagevimab/cilgavimab=T/C; nirmatrelvir/rit=N/r) was estimated in emulated parallel trials using a marginal structural model.

Results: 12,466 pts enrolled [female 50.2%, median age 70 yrs (IQR 57-80), unvaccinated 21%, immunocompromised 23.2%]. Primary endpoint occurred in 384/12,466 pts, with a day-30 incident risk of 3.08% (95% CI:2.7-3.4%). After controlling for potential confounders, a higher risk was observed for older aged (OR 2.01; 1.64-2.46), unvaccinated (2.30;1.73-3.05), and immunocompromised (1.41; 1.09-1.82). Using the "Delta period" as a reference, a decreased risk was observed in the Omicron waves. Among the 10,042 pts treated in 2022 (1,919 SOT, 3,733 MLP, 1,447 RDV, 433 T/C, 2510 N/r), failure rate according to intervention varied from 0.87% (0.55-1.32) for N/r, 1.68% (1.2-2.1) for MLP, 3.0% (1.6-5) for T/C, 3.5% (2.7-4.5) for SOT and 5.1% (4.1-6.4) for RDV. Emulation trial for comparison of different treatment options showed higher efficacy of oral antivirals in the prevention of CovH/D compared to mAbs or RDV; no significant differences were observed between the oral antivirals or between mAbs and RDV, respectively.

Conclusion: Despite the decreasing risk of CovH/D across the calendar periods, older aged, unvaccinated, and immunocompromised patients remained at the highest risk of developing severe COVID-19. Oral antivirals showed higher efficacy in reducing Cov/H, while no significant differences were observed between them or between mAbs and RDV. These data could help to tailor therapies according to different risk factors and specific contraindications.

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663 Disparities in Treatment Initiation by Race and Ethnicity Among Patients Hospitalized for COVID-19

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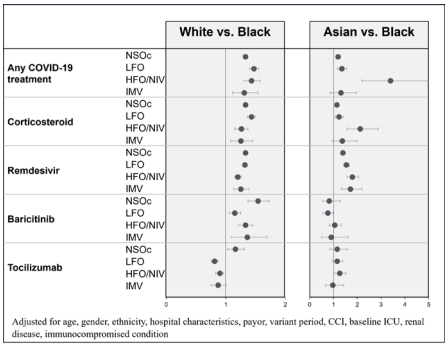
Background: The pandemic has shed light on the heightened risks of morbidity and mortality faced by minority patients hospitalized with COVID-19. However, there is a significant lack of real-world data that explores whether Black inpatients are less likely to receive appropriate pharmaceutical treatment for COVID-19 in the hospital than other racial groups. To address this evidence gap, we evaluated whether the initiation of evidence-based COVID-19 treatments upon hospital admission was related to race and ethnicity.

Methods: Adults hospitalized with a primary diagnosis of COVID-19 between 5/2020- 4/2022 in the PINC AI Healthcare Database were examined. Baseline was defined as the first 2 days of hospitalization. Multivariable logistic regression models adjusting for key demographic, hospital, and clinical characteristics, were used to assess the association between race/ethnicity and initiation of COVID-19 treatments at baseline. Patients with no supplemental oxygen charges (NSOc), low-flow oxygen (LFO), high-flow oxygen/non-invasive ventilation (HFO/NIV) and invasive mechanical ventilation (IMV) at baseline were examined.

Results: Of the 454,761 patients included in the study, 70% were White, 17% Black, 2% Asian, 11% other races, and 16% were Hispanic. Further, 86% patients received any COVID-19 treatment (84% corticosteroids, 52% remdesivir, and 4% received tocilizumab or baricitinib). Across all supplemental oxygen levels, White patients were significantly more likely to receive any COVID-19 treatment as well as corticosteroids, remdesivir, and baricitinib treatment as compared to Black patients (Figure). White patients on NSOc were more likely but those on LFO and HFO/NIV were significantly less likely to receive treatment with tocilizumab than Black patients (Figure). Treatment initiation for Non-Hispanic vs. Hispanic patients varied by baseline supplemental oxygen requirements.

Conclusion: Black patients hospitalized for COVID-19 were significantly less likely to be treated with evidence-based COVID-19 treatments compared to other races across all levels of oxygen supplementation. As we enter the endemic phase, it is crucial that we highlight persistent disparities in patient management and strive towards standardized care for all patients during hospitalization for COVID-19, regardless of racial background or ethnicity.



664 Remdesivir Reduces Mortality in Immunocompromised Patients Hospitalised for COVID-19 During Omicron

Essy Mozaffari[1], Aastha Chandak[2], Robert L. Gottlieb[3], Chidinma Chima-Melton[4], Mark Berry[1], Alpesh N. Amin[5], Tobias Welte[6], Paul E. Sax[7], Andre C. Kalil[8]

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Background: Previous research has established the effectiveness of remdesivir (RDV) in reducing mortality among immunocompromised patients hospitalized for COVID-19. In this study, we present data from the Omicron predominant era (Dec'21-Apr'23) by examining in-hospital all-cause mortality for early RDV initiation vs. not initiating RDV among immunocompromised hospitalized COVID-19 patients.

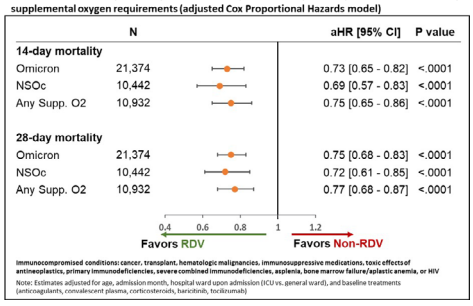
Methods: Using the PINC AI Healthcare database, adults with immunocompromised conditions (cancer, transplant, hematologic

malignancies, immunosuppressive medications, toxic effects of antineoplastics, primary immunodeficiencies, severe combined immunodeficiencies, asplenia, bone marrow failure/aplastic anaemia, or HIV) hospitalized with a primary discharge diagnosis of COVID-19 flagged as "present-on-admission" from Dec'21 to Apr'23 were identified. Analyses were stratified by no supplemental oxygen charges (NSOc) and any supplemental oxygen requirements upon admission. Patients initiating RDV in the first 2 days of admission vs. those not initiating RDV during the hospitalization were matched using 1:1 preferential within-hospital propensity matching with replacement. Time to 14- and 28-day in-hospital mortality or discharge to hospice was examined using Cox Proportional Hazards Model.

Results: In the study period, 10,687 RDV-treated patients were matched to 4,989 unique non-RDV patients. Post-matching balance was achieved with 74% being 65+ years, 49% with NSOc, and 51% with any supplemental oxygen charges. Unadjusted mortality rate for RDV patients vs. non-RDV patients was 10.3% vs. 13.7% at 14 days and 15.0% vs. 19.2% at 28 days, respectively. After adjusting for baseline and clinical covariates, RDV showed significantly lower mortality risk compared to non-RDV overall (adjusted hazard ratio [95% CI]: 0.75 [0.68-0.83]) in patients with NSOc (0.72 [0.61-0.85]) and in patients with any supplemental oxygen requirement (0.77[0.68-0.87]) at 28 days. A similar benefit for RDV vs. non-RDV was observed for 14-day mortality overall (0.73 [0.65-0.82]) in patients with NSOc (0.69 [0.57-0.83]) and in patients with any supplemental oxygen requirement (0.75 [0.65-0.86]) (Figure).

Conclusion: RDV continues demonstrating significant mortality reduction among immunocompromised patients hospitalized with a primary diagnosis of COVID-19 in the more recent Omicron period, irrespective of the supplemental oxygen requirements.

Time to 14- and 28-day mortality in immunocompromised hospitalized patients for COVID-19 by supplemental oxygen requirements (adjusted Cox Proportional Hazards model)



665 Remdesivir+Dexamethasone vs Dexamethasone for the Treatment of COVID-19: Real-World Study in the US

Essy Mozaffari[1], Aastha Chandak[2], Robert L. Gottlieb[3], Chidinma Chima-Melton[4], Mark Berry[1], Thomas Oppelt[1], Jason F. Okulicz[1], Alpesh N. Amin[5], Andre C. Kalil[6], Tobias Welte[7], Paul E. Sax[8]

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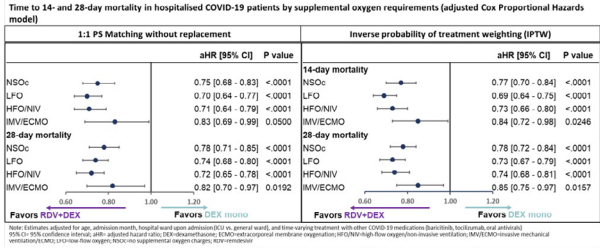
Background: Dual therapy with remdesivir (RDV) and dexamethasone (DEX) among patients with COVID-19 has demonstrated improved clinical outcomes compared to DEX monotherapy. We evaluated the effectiveness of RDV+DEX vs. DEX monotherapy by applying and comparing two established methods used to balance two inherently different groups due to confounding by indication in observational research.

Methods: Adults hospitalised during the Omicron period (Dec'21-Apr'23) with a primary discharge diagnosis of COVID-19 flagged as "present-on-admission" who initiated RDV+DEX or DEX monotherapy in the first 2 days of hospitalisation (baseline period) were identified in the PINC AI Healthcare database. Patients were categorized by baseline supplemental oxygen requirement: no supplemental oxygen charges (NSOc), low-flow oxygen (LFO), high-flow oxygen/non-invasive ventilation (HFO/NIV), or invasive mechanical ventilation (IMV)/ECMO. Balanced distribution of underlying confounders in the treatment groups was achieved through 1) 1:1 propensity score matching (PSM) without replacement, which estimates the effectiveness of RDV+DEX by matching patients in the two groups excluding unmatched patients and 2) Inverse probability of treatment weighting (IPTW), which estimates the effectiveness of RDV+DEX in the full cohort keeping all eligible patients in the analysis. Cox Proportional Hazards Model was used to assess time to 14- and 28-day mortality.

Results: Among 151,215 hospitalised patients for COVID-19, 61,236 (40%) initiated RDV+DEX and 36,489 (24%) DEX monotherapy in the first 2 days. Using PSM, 33,089 RDV+DEX patients were matched to 33,089 DEX monotherapy patients. RDV+DEX had a significantly lower mortality risk compared to DEX monotherapy across all supplemental oxygen requirements at 14 days (NSOc: adjusted hazard ratio[95% C]:0.75[0.68-0.83], LFO:0.70[0.64-0.77], HFO/NIV:0.71[0.64-0.79], IMV/ECMO:0.83[0.69-0.99]); 28 days (NSOc:0.78[0.71-0.85], LFO:0.74[0.68-0.80], HFO/NIV:0.72[0.65-0.78], and IMV/ECMO:0.82[0.70-0.97]) (Fig). Using IPTW, consistent results were obtained across all supplemental oxygen levels (Fig).

Conclusion: The effectiveness of RDV+DEX in reducing mortality compared to DEX monotherapy was confirmed through two well-established methods of addressing confounding by indication bias, thus providing confidence in the observed effectiveness of RDV+DEX therapy. Appropriate methodologies such as the ones applied in this study enables the use of real-world data to complement findings from RCTs.

Time to 14- and 28-day mortality in hospitalised COVID-19 patients by supplemental oxygen requirements (adjusted Cox Proportional Hazards model)



666 Real-Life Experience on the Use of Remdesivir: A Propensity Score Matched Analysis

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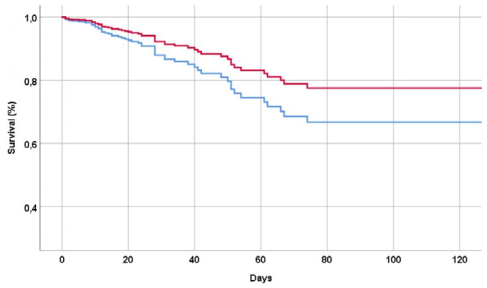
Background: Remdesivir (RDV) was the first FDA-approved medication for COVID-19, with discordant data on efficacy in reducing mortality risk and disease progression. In the context of a dynamic and rapidly changing pandemic landscape, the utilization of real-world evidence is of utmost importance. The objective of this study is to evaluate the impact of RDV on patients who have been admitted to two university referral hospitals in Italy due to COVID-19.

Methods: All patients older than 18 years and hospitalized at two different universities (Bari and Palermo) were enrolled in this study. To minimize the effect of potential confounders, we used propensity score matching with one case (remdesivir) and one control that never experienced this kind of intervention during hospitalization. Mortality was the primary outcome of our investigation, and it was recorded using death certificates and/or medical records. Severe COVID-19 was defined as admission to the intensive care unit or a qSOFAscore ≥2 or CURB65scores≥3.

Results: The initial cohort included a total of 1,883 patients hospitalized for COVID-19.The participants taking remdesivir differed for several clinical characteristics compared to the controls. Therefore, a propensity score matching was proposed for better accounting of these baseline differences. After using propensity score matching, 365 patients taking remdesivir and 365 controls were included. All the other clinical, radiological, and pharmacological parameters were balanced between the two groups. The use of remdesivir in our cohort was associated with a significantly lower risk of mortality during the follow-up period (HR = 0.63; 95% CI: 0.35-0.92; p = 0.01). Moreover, RDV was associated with a significantly lower incidence of non-invasive ventilation (OR = 0.25; 95% CI: 0.18–0.35) and severe COVID (OR = 0.42; 95% CI: 0.29–0.60). Furthermore, in the 365 patients taking Remdesivir, we observed two cases of mild renal failure and two cases in which the physicians decided to interrupt Remdesivir for QT elongation.

Conclusion: Our study suggests that the use of Remdesivir in hospitalized COVID-19 patients is a safe therapy associated with improved clinical outcomes, including halvy mortality and severe COVID, and with a reduction of around 75% of the risk of invasive ventilation. In a constantly changing COVID-19 scenario, ongoing research is necessary to tailor treatment decisions based on the latest scientific evidence and optimize patient outcomes.

Figure 1. Association between use of remdesivir and mortality during the follow-up period.



In red patients taking remdesivir, in blue controls. The analyses were made after matching using a propensity score our sample.

667 Molnupiravir vs Favipiravir: An RCT in Outpatients At-Risk for COVID-19 in Thailand

Nicolas Salvadori[1], Gonzague Jourdain[1], Rungroj Krittayaphong[2], Taweegrit Siripongboonsitti[3], Subsai Kongsaengdao[4], Parichart Sakulkonkij[5], Nasikarn Angkasekwinai[2], Sarunyou Chusri[6], Tanavit Mekavuthikul[7], Anucha Apisarnthanarak[8], Sirawat Srichatrapimuk[9], Suraphan Sangsawang[10], Piya Hanvoravongchai[11], Pra-ornsuda Sukrakanchana[1], Prasert Auewarakul[2]

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Background: In December 2021, molnupiravir was granted a US FDA's emergency use authorization for patients with mild-to-moderate COVID-19 at high risk for progression to severe COVID-19 for whom alternative approved or authorized treatment options are not accessible or clinically appropriate. The efficacy of molnupiravir in a vaccinated population predominantly infected with the SARS-CoV-2 Omicron variant is unknown.

Methods: In an open-label, parallel-group, multicenter trial in Thailand, outpatients with confirmed SARS-CoV-2 infection for ≤5 days, mild to moderate COVID-19 attributable signs/symptoms for ≤5 days (and ≥1 day before randomization) and ≥1 risk factor for severe COVID-19 were randomly assigned 1:1 to receive oral molnupiravir 800 mg BID for 5 days or oral favipiravir 1800 mg BID on Day 1 then 800 mg BID until Day 5, extended to Day 10 if clinical progression. Phone calls for remote symptom assessment were made on Days 6, 11 (if favipiravir extended), 15 and 29. Participants with worsening symptoms were instructed to return to the hospital. The primary endpoint was pulmonary involvement by Day 29, as evidenced by ≥2 of the following: dyspnea, oxygen saturation <92% or imaging. 465 evaluable participants per arm (930 overall) were needed to have 80% power to detect a difference in the percentage of participants with an endpoint event, assuming 3% in molnupiravir arm and 7% in favipiravir arm (1-sided α=0.024 for final analysis).

Results: 977 participants (487 molnupiravir, 490 favipiravir) were enrolled from 8 July 2022 to 19 January 2023. 55% were female and median age was 56 years (interquartile range, 41-64). 98% had received ≥1 dose of COVID-19 vaccine and 83% ≥3 doses. The most common risk factors known to be associated with severity were hypertension (49%) and age ≥60 years (42%). By Day 29, pulmonary involvement occurred in 0% (0/483) in molnupiravir arm versus 1% (5/482) in favipiravir arm (-1.0%; Newcombe 95.2% CI: -2.4% to -0.0%; p=0.021); all-cause death in 0% (0/483) and <1% (1/482, from COVID-19 pneumonia); COVID-19 related hospitalization in <1% (1/483) and 1% (3/482); and treatment-related adverse event in 1% (5/483) and 1% (4/486). One participant prematurely discontinued molnupiravir on Day 4 due to rash.

Conclusion: Rates of pulmonary involvement and of other adverse outcomes were much lower than anticipated in both arms in this population highly vaccinated and mostly infected with Omicron. Pulmonary involvement was less common with molnupiravir than with favipiravir.

668 AGILE CST-8 Phase I Trial of Combined Nirmatrelvir/r and Molnupiravir for Mild-Moderate COVID-19

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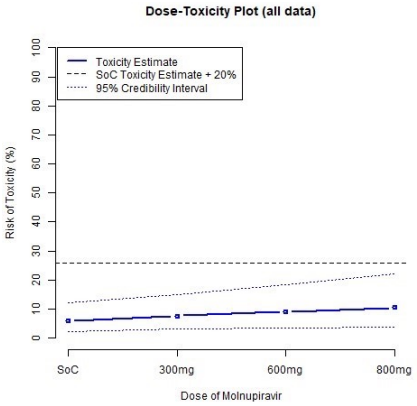
Background: AGILE (NCT04746183) is the UK platform for early-phase evaluation of COVID-19 antivirals. AGILE-CST-8 is a phase I, adaptive, dose de-escalation study of combination nirmatrelvir/ritonavir plus molnupiravir

Methods: Adults with a positive lateral flow test, within 5 days of mild-moderate symptoms were randomised (2:1, open-label) to nirmatrelvir/ritonavir plus molnupiravir versus Standard of Care (SoC). Exclusions were oxygen saturation <92%, liver or renal impairment, drug interactions and pregnancy. The primary endpoint was dose-limiting-toxicities (DLT; AEs ≥ grade 3) up to day 11; safety review after each cohort (N=6) guided stepwise dose-reduction of molnupiravir from a starting dose of 800mg bd, reducing to 600mg or 400mg bd if required, with nirmatrelvir/ritonavir maintained at standard doses throughout. A Bayesian dose de-escalation model was used to estimate DLTs. We collected a combined throat/nose swab daily for 5 days, then at day 11 for virology, and measured antiviral concentrations in plasma, saliva, tears and nasal secretions.

Results: Four cohorts totalling 24 participants (16 combination therapy, 8 SoC; 17 female) with median (range) age 35.5 years (20-70), and BMI 27 (20.2-40.2) were enrolled, at a median of 4 days (1-5) from symptom onset. No DLTs or SAEs were observed through to Day 29; all participants randomised to combination therapy received full doses of both drugs apart from one subject withdrawal on day 2 (Bayesian dose-toxicity model shown in Figure). AEs (Grade 1-2) were reported in 14/16 (87.5%, mainly gastrointestinal disorders and altered taste) of combination treatment versus 5/8 (62.5%) SoC participants. At baseline all but one (SoC arm) were SARS-CoV-2 PCR-positive. There was no evidence of differences between participants receiving combination antivirals versus SoC in baseline VL (median 5.2 vs 6.8 log_{10} copies), or at any point across the first 5 days, or at day 11. The median reduction in VL at Day 5 was 5.0 vs 5.7 log_{10} copies, with 11/16 (68.8%) of treated vs 5/8 (62.5%) of SoC participants achieving negative PCR. Nirmatrelvir concentrations in tears, nasal secretions, and saliva approximated to 86%, 70% and 18% that of plasma.

Conclusion: This first report of combination nirmatrelvir/ritonavir with molnupiravir confirms safety and tolerability at full doses used in adults. The clinical and virological benefit of this combination should be tested in larger phase II studies.



669 Viral and Symptom Rebound After COVID-19 Monoclonal Antibody Therapy in the ACTIV-2 Trial

Kara W. Chew[1], Brooke McGinley[2], Carlee Moser[3], Jonathan Z. Li[4], Teresa H. Evering[5], Justin Ritz[3], David Margolis[6], David Wohl[7], Michael D. Hughes[3], Eric Daar[8], Judith S. Currier[1], Joseph J. Eron[7], Davey M. Smith[9], for the ACTIV-2/A5401 Study Team

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Background: Risk of viral and symptom rebound after monoclonal antibody (mAb) therapy for COVID-19 is unknown.

Methods: Viral and symptom rebound in a randomized placebo-controlled trial of combination mAbs Amubarvimab/Romlusevimab (A/R), which had been shown to reduce hospitalization/death by 79%, were explored. Symptom relapse was defined as first occurrence of any moderate/severe symptom (13 symptoms recorded in a daily 29-day diary) persisting for ≥2 consecutive days, after meeting a 2-days sustained symptom improvement or resolution endpoint. End of relapse was defined as the last day with any moderate/severe symptom after improvement or any mild/moderate/severe symptom after resolution. Viral rebound was defined as anterior nasal SARS-CoV-2 RNA ≥3 $\log_{10}$ copies/mL at day 7, 14, or 28 that was ≥0.5 $\log_{10}$ copies/mL higher than day 3, or at day 14 or 28 that was ≥0.5 $\log_{10}$ copies/mL higher than day 7. Wilcoxon rank sum tests compared symptom outcomes by arm, by ranking participants in four ordered categories: 1) improved and never relapsed ordered by symptom duration; 2) improved but relapsed ordered by total time with symptoms; 3) never improved ordered by last available total symptom score (TSS, summing scores for all 13 symptoms on that day); 4) deaths. Joint modeling of time to improvement and to relapse assessed the risk of relapse among those with improvement or resolution, adjusting for day 0 TSS. Proportion of participants with viral rebound was compared between arms using Fisher's Exact test.

Results: 784 participants were included. Median age was 49 years; 52% female (>99% cisgender); 72% White and 49% Latino/Hispanic. 75% A/R and 73% placebo participants achieved symptom improvement; 5% in each arm had symptom relapse (Table). 1 placebo participant with relapse was hospitalized. Fewer participants met symptom resolution (64% A/R, 60% placebo) and relapse after resolution (3% and 2%, respectively, none subsequently hospitalized) (Table). Time to symptom relapse did not differ between arms among those who achieved improvement or resolution (Table). Viral rebound occurred in 4% in each arm (p>0.99). 3 participants with viral rebound were hospitalized, all in the placebo arm. <1% of each arm experienced both symptom and viral rebound.

Conclusion: This randomized trial found no significant differences in symptom experiences or viral rebound between mAb- vs placebo-treated participants. With or without treatment, rebound rates were low following sustained symptom improvement or resolution.

	Relapse following Improvement			Relapse following Resolution		
	A/R (n=393)	Placebo (n=391)	P-value	A/R (n=393)	Placebo (n=391)	P-value
Improved/Resolved no relapse, n (%)	273 (69)	263 (67)	0.13*	242 (62)	225 (56)	0.09*
Improved/Resolved and relapsed, n (%)	21 (5)	21 (5)		11 (3)	8 (2)	
Never improved/resolved, n (%)	99 (25)	99 (25)		140 (36)	150 (38)	
Died, n (%)	0 (0)	8 (2)		0 (0)	8 (2)	
Time to Relapse**, median (quartiles) days	9 (6, 16)	8 (5, 11)		11 (6, 18)	7 (4, 9)	
Hazard Ratio for Relapse (95%)	0.86 (0.47, 1.58)		p=0.63***	1.15 (0.45, 2.92)		p=0.77***

Table. Symptom relapse following 2 days sustained symptom improvement or 2 days sustained symptom resolution, by treatment arm. *p-value corresponds to Wilcoxon rank sum comparing ranked data across 4 categories, **time from improvement/resolution to relapse among those who relapsed, ***Wald Chi-Square

670 Risk of SARS-CoV-2 Infection in Patients With Hematologic Diseases Receiving Tixagevimab/Cilgavimab

Alessandra Vergori[1], Alessandro Cozzi-Lepri[2], Marta Chiuchiarelli[3], Valentina Mazzotta[1], Elisabetta Metafuni[3], Giulia Matusali[1], Valentina Siciliano[3], Jessica Paulicelli[1], Eleonora Alma[3], Agostina Siniscalchi[4], Elisabetta Abruzzese[5], Simona Sica[3], Massimo Fantoni[3], Andrea Antinori[1], **Antonella Cingolani**[3]

[1]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [2]University College London, London, United Kingdom, [3]Catholic University of the Sacred Heart, Rome, Italy, [4]San Filippo Neri Hospital, Rome, Italy, [5]Sant'Eugenio Hospital, Rome, Italy

Background: Despite in vitro data showing poor neutralizing activity, clinical efficacy of tixagevimab/cilgavimab (T/C) as pre-exposure prophylaxis (PrEP) in patients (pts) with hematological disease (HD) against the newest omicron sub-variants of SARS-CoV-2 was rarely investigated and long-term incidence data are lacking

Methods: Observational study of pts with HD who received 300 mg of T/C given intramuscularly as PrEP over MAR22-AUG23. Demographic and clinical characteristics were collected; BTIs were defined as a confirmed diagnosis by RT-PCR and clinical picture. The incidence of BTI (95%CI) was calculated using the Kaplan-Meier method. Factors associated with the risk of BTI were evaluated using a Cox regression model with fixed covariates after controlling for age, sex, type of HD and other comorbidities. The incidence of BTI was also calculated according to the circulating variant (VoC) as number of BTI per 100 PYFU. A Poisson regression adjusted for the same potential confounders was used to estimate relative rates of BTI by current VoC

Results: N=501pts:68% initiated T/C PrEP when BA.5 was the most prevalent, followed by XBB/EG, BA.2 and BA.1 (21%, 7% and 3%, respectively); 46% female, median age 64 years (IQR 55, 73) and a median follow-up post treatment of 162 (92-297) days. HD were non-Hodgkin Lymphoma (NHL) 66%, Multiple Myeloma (MM) 12%, Chronic Lymphocytic Leukemia (CLL) 14%, Hodgkin Lymphoma (HL) 8%; 3% received CAR-T and 9% bone marrow transplantation. 87% received 3-4 vaccine doses 60% had other comorbidities. Overall, the 1-year incidence estimate of BTIs was 21% (16.5-26.8%), with a cumulative risk which was higher the longer the time since PrEP. A greater risk of incident BTIs was observed when BA.5 and XBB/EG sub-lineages circulated as prevalent in Lazio region [aRR 5.08 (2.18, 11.83); p<.001 and 3.77 (1.48, 9.60); p=0.005, compared to BA.1, respectively]. The 6-month incidence of BTIs was higher for MM [25%; 2-47%] than that seen for other HDs. Severe COVID-19 occurred in 6 pts, 4 deaths due to COVID-19 were reported.

Conclusion: One-year incidence of BTIs after T/C PrEP was <25%, although increasing over time, possibly due to vanished neutralizing activity. The risk appears to be higher when more recent omicron sub-lineages were circulating suggesting a lack of in vitro neutralization due to viral escape.

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671 Immunogenicity of Tixagevimab/Cilgavimab for COVID-19 in Immunocompromised Children and Adolescents

Jassada Buaboonnam[1], **Supattra Rungmaitree**[1], Nuntawan Piyaphanee[1], Sirirat Charuvanij[1], Onsiri Pitisuttithum[2], Katherine Copeland[1], Chatkamol Pheerapanyawaranun[1], Suvimol Niyomnaitham[1], Kulkanya Chokephaibulkit[1]

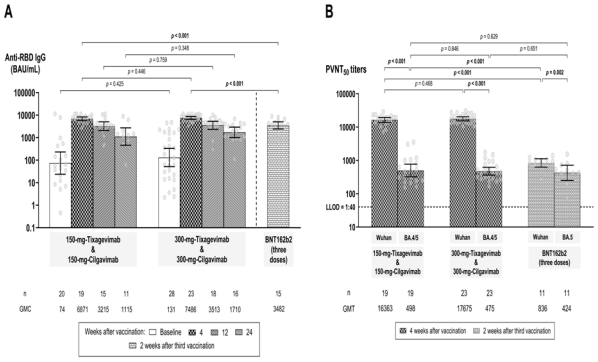
[1]Mahidol University, Bangkok, Thailand, [2]AstraZeneca, Bangkok, Thailand

Background: COVID-19 vaccination prevents severe manifestations, hospitalization, and mortality in healthy patients. Immunocompromised populations have a higher risk of complications, but poorer responses to vaccination. Long-acting monoclonal antibodies Tixagevimab/Cilgavimab effectively prevented COVID-19 and improved clinical outcomes when administered early after infection. They were approved for emergency use in ≥40 kg and ≥12 years old immunocompromised patients. Few studied its use in young children. This trial assessed the immunogenicity and safety of an alternative dose in immunocompromised 20-<40 kg children and adolescents.

Methods: 6–18-year-old immunocompromised patients were enrolled in this single-center, prospective, open-labelled, randomized clinical trial. Participants were divided into two groups by body weight: 150-mg-Tixagevimab/150-mg-Cilgavimab (20-<40 kg) and 300-mg-Tixagevimab/300-mg-Cilgavimab (≥40 kg). Anti-SARS-CoV-2 receptor binding domain IgG (anti-RBD IgG) and pseudovirus neutralizing antibody (NAb) titers were measured as primary outcomes 4, 12, and 24 weeks after administration. Immunogenicity data at 4 weeks was compared with reference data from 5-11-year-old healthy children 2 weeks after a third dose of 10-µg-BNT162b2. Adverse events were closely monitored by telephone calls up to 7 days after administration.

Results: Of 59 enrolled participants, 49.2% were female, with a median (IQR) age of 12 (9, 15) years. Fourteen children (24%) had malignancies. Four weeks after administration, similarly high levels of anti-RBD IgG geometric mean concentrations were observed for both arms (6,871 vs 7,486 BAU/mL in 20-40 kg, respectively; P = 0.446), and significantly higher levels than the reference (3,842 BAU/mL two weeks after three doses of BNT162b2; P < 0.001). NAb geometric mean titers (GMTs) for the ancestral Wuhan strain in both arms were similarly high (16,363 vs 17,675 BAU/mL in 20-40 kg, respectively; P = 0.468) and significantly higher than the reference (836 BAU/mL; P < 0.001). NAb GMTs for Omicron BA.4/5 in both arms were on par with the reference. Most adverse events were mild and well-tolerated.

Conclusion: Half dose Tixagevimab/Cilgavimab in 20-<40 kg children and adolescents generated equivalent and significantly higher antibodies than ≥40 kg and healthy children with three vaccinations, respectively. This supports further study of next generation long-acting monoclonal antibodies.



672 Sotrovimab Lacks Efficacy in Treatment of Syrian Golden Hamsters Infected With SARS-CoV-2 BQ.1.1

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Background: Monoclonal antibodies (mAbs) demonstrate diminished neutralisation of Omicron sub-lineages such that continued use of sotrovimab (SOT) is not supported by current pharmacokinetic-pharmacodynamic (PK-PD) understanding. However, SOT is still used in immunocompromised patients in some geographies. Published preclinical studies have shown virological efficacy in prophylaxis for BQ.1.1 but no data are available in treatment. This study investigated the virological efficacy of SOT in healthy and immunocompromised male hamsters infected with Delta or BQ.1.1 variants using experimental designs reflective of prophylaxis and treatment.
Methods: Intramuscular SOT (14 mg/kg) was administered 24h before or after intranasal inoculation with 10[4] PFU Delta or BQ.1.1. Control groups were dosed IM with vehicle 24h after inoculation. A subset of hamsters were immunosuppressed using 100 mg/kg IP-administered cyclophosphamide. Hamsters were sacrificed at 3-dpi and viral replication was quantified using qPCR to measure total (N-gene) viral RNA. Data were normalised to 18S for quantitation. Terminal blood samples were taken and ELISAs were used for SOT plasma quantification.
Results: Reductions in pulmonary viral RNA were observed in prophylaxis and treatment for Delta in healthy and immunocompromised animals (Table 1.). Smaller and statistically insignificant reductions were observed for BQ.1.1 for prophylaxis and treatment, in healthy and immunocompromised animals. Reduced pulmonary viral RNA was evident in untreated BQ.1.1 inoculated, compared to untreated Delta inoculated, hamsters in healthy and immunocompromised groups (log_{10} -3.38; P=0.007, log_{10} -1.85; P=<0.0001, respectively). SOT plasma concentrations were comparable across Delta (44.13 ± [SD] 5.40 µg/mL) and BQ.1.1 (47.06 ± [SD] 4.44 µg/mL) inoculated groups and consistent with values reported for prior hamster studies.
Conclusion: Consistent with PK-PD understanding from RCTs, SOT did not exert virological efficacy in the treatment of immunocompromised hamsters infected with BQ.1.1. SOT did not block infection of Delta or BQ.1.1 when given in prophylaxis. The relevance of changes in viral RNA at high SOT concentrations, early in the profile, to longer-term prophylaxis are unclear. Analysis of pulmonary viral RNA and compartmental SOT concentrations across an extended experimental design is warranted. Caution should be taken when interpreting preclinical experimental designs that may not be reflective of the clinical use case.

Table 1. Mean log_{10} fold-changes in SARS-CoV-2 N-RNA, relative to vehicle control groups, in hamster lung samples at 3-dpi following inoculation with 10^4 PFU Delta or BQ.1.1 variants. Statistical comparisons using unpaired two-tailed t-test.

	Log_{10} fold-change in pulmonary viral RNA compared to vehicle control			
SARS-CoV-2 variant	14 mg/kg SOT dosed 24h before inoculation		14 mg/kg SOT dosed 24h after inoculation	
	Healthy	Immunocompromised	Healthy	Immunocompromised
Delta	-3.65, P=0.007	-2.29, P=<0.0001	-0.38, P=0.164	-0.58, P=0.001
BQ.1.1	-1.36, P=0.306	-1.83, P=0.260	-0.52, P=0.300	-0.11, P=0.818

673 First-in-Human Phase I Trial of an Adjuvanted SARS-CoV-2 Spike Ferritin Nanoparticle Vaccine

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Background: Next-generation coronavirus (CoV) vaccines must confer broader protection against a range of SARS-CoV-2 variants as well as novel species that may cross over from zoonotic reservoirs in the future. The SARS-CoV-2 recombinant spike ferritin nanoparticle (SpFN) vaccine co-formulated with Army Liposomal Formulation (ALFQ) adjuvant containing monophosphoryl lipid A and QS-21 (SpFN/ALFQ) was previously shown to be immunogenic and protective in challenge experiments in rodents and non-human primates against SARS-CoV-2 and variants of concern (VoC). This study reports the first-in-human randomized, double-blind, placebo-controlled clinical trial of SpFN/ALFQ.
Methods: Healthy, SARS-CoV-2 seronegative and unvaccinated adults aged 18-55 years, majority male, were randomly assigned to receive either 25µg or 50µg of SpFN/ALFQ or saline placebo intramuscularly at days 1 and 29, with an optional open-label third vaccination at day 181. Local and systemic reactogenicity, adverse events and humoral immunity were quantified and analyzed by Clopper-Pearson. Binding and neutralizing antibody responses against multiple CoV were quantified. To further test breadth of cross-protection, IgG antibodies from vaccinees were infused into Syrian Golden hamsters (SGH) prior to SARS-CoV-1 Urbani challenge. Lung tissue was recovered at days 3 and 6 post challenge. Virus detected by quantitative RT-PCR was analyzed by two-way ANOVA, as well as immunohistochemistry staining.
Results: Of the 29 participants enrolled, all received 2 doses and a subset who did not receive EUA vaccines received a third vaccination. Local and systemic reactogenicity was mild to moderate, and no participants experienced any adverse events of special interest. Binding and neutralizing antibody responses peaked at day 43. Neutralizing antibody titers against Omicron subvariants and clade 1 sarbecoviruses were detectable after two immunizations and peaked after the subset of volunteers who received a third immunization and were present at day 361. Passive IgG transferred from vaccinated volunteers into hamsters-controlled replication of SARS-CoV-1 post challenge.
Conclusion: Individuals vaccinated with SpFN/ALFQ mounted neutralizing antibody responses against multiple clade 1 sarbecoviruses. The results of this first-in-human clinical trial represents a platform upon which to build future sarbecovirus vaccine development.

674 PREVENT: Phase I Clinical Trial of a Q-Griffithsin (Q-GRFT) Nasal Spray for Prevention of SARS-CoV-2

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Background: The COVID pandemic highlighted the need to develop vaccine alternatives to prevent the spread of SARS-CoV-2, especially in immunosuppressed people. Q-GRFT, a broad-spectrum viral entry inhibitor, functions by binding oligomannose glycans on viral envelopes and is highly potent, with an IC_{90} of 645 ng/mL against the SARS-CoV-2 BA.5 variant. A nasal spray formulation was designed to deliver Q-GRFT to the upper respiratory mucosa for topical prophylaxis.
Methods: PREVENT (NCT05180500) was a phase I randomized, double-blind, placebo-controlled study to determine the safety and drug persistence of 14 doses of Q-GRFT intranasal spray (two 100 µL bursts of 7.5 mg/mL Q-GRFT per nostril, 400 µL total). Healthy, SARS-CoV-2 -vaccinated participants aged 18-55 with normal nasal and pharyngeal exams were randomized 2:1 to either Q-GRFT (n=33) or placebo (n=17). Participants initially received one metered dose of the study drug; after establishing initial tolerance at 24 hours, participants self-administered the spray for 13 consecutive days. Grade 2 or higher adverse events (AEs) related to study product were compared between groups using Fisher's exact test. Drug persistence was assessed by measuring Q-GRFT concentrations in nasopharyngeal (NP) and nares swabs. Systemic exposure and immune response were measured by Q-GRFT and antidrug antibody (ADA) concentrations in plasma. Acceptability was assessed by questionnaire.

Results: There was no difference in the proportion of participants with related Grade 2 or higher AEs between groups. The most frequent AEs were mild nasal irritation and congestion; two participants in the Q-GRFT arm withdrew due to nasal congestion. After adjusting for the dilution factor, Q-GRFT was detected at 50-200X the IC_{90} in NP and nares swabs at 1 hour and at 1-2X the IC_{90} at 24 hours after use (Table); results did not differ by sex. ADA was detectable in low levels in plasma in 46% of participants; ADA's impact on antiviral activity is being assessed. No Q-GRFT was detected in plasma samples (lower limit of quantitation: 3 ng/mL). Acceptability of the nasal spray (somewhat or highly acceptable) was similar between the two groups (87% Q-GRFT vs. 100% placebo, P= 0.28).

Conclusion: The Q-GRFT nasal spray administered for a total of 14 doses was well tolerated and demonstrated persistence up to 24 hours in clinically important anatomic sites without systemic absorption. This nasal spray could address the need for an on-demand product for prevention of SARS-CoV-2.

Table. Q-GRFT Detection in Nasopharyngeal (NP) and Nares Swabs Stratified by Randomization Arm

Site/Time frame	Q-GRFT Arm (n=32) ng/ml Median (IQR)	Placebo (n=17) ng/ml Median (IQR)	P-value*
NP 1 hour post-single dose	50100 (19795, 123015)	All BLQ	<.001
NP 24 hours post-single dose, n=31	1007 (BLQ, 1740)	All BLQ	<.001
NP 24 hours post-last multi dose, n=30	974 (BLQ, 2096)	All BLQ	<.001
Nares 1 hour post-single dose	137342 (41798, 344089)	All BLQ	<.001
Nares 24 hours post-single dose, n=31	1488 (BLQ, 6333)	All BLQ	<.001
Nares 24 hours post-last multi dose, n=30	1586 (DLQ, 3214)	All DLQ	<.001

* P-value from Mann-Whitney U test

IQR= inter-quartile range

BLQ <3 ng/mL

675 ACTG 5381: Virologic and Resistance Outcomes After Switch to TLD for Failing 1st- or 2nd-Line ART

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Background: Most countries recommend tenofovir-lamivudine-dolutegravir (TLD) for individuals starting antiretroviral therapy (ART) or switching from suppressive 1st-line NNRTI- or 2nd-line PI-based ART but country guidelines have been more variable about using TLD for those with unsuppressed (plasma HIV-1 RNA>1000 c/ml) viral load (VL) on ART. We report virologic and resistance outcomes for unsuppressed individuals switching to TLD in the A5381 prospective cohort study.

Methods: Participants were adults or adolescents aged >10y with VL>1000 c/ml switching from 1st-line NNRTI-based (Cohort 1) or 2nd-line PI-based (Cohort 2) ART. Primary endpoints were proportion with VL≤1000 c/ml at 6 months (m) after switch among those still on TLD and proportion with new DTG resistance mutations (baseline and 6m samples were sequenced for those with VL>1000 c/ml at 6m). A case-control study (unsuppressed vs suppressed) evaluated tenofovir diphosphate (TFV-DP) concentrations in dried blood spots.

Results: From Dec2019 to Sep2022, 44 participants were enrolled into Cohort 1 (77% female, median age 33y) and 173 were enrolled into Cohort 2 (57% female, median age 41y) at 13 sites in Haiti and Africa. In Cohort 1, median VL was 4.0 log_{10} c/ml, CD4 count was 306 cells/mm^3, time on ART was 5.5y. In Cohort 2, median VL was 4.2 log_{10} c/ml, CD4 count was 262 cells/mm^3, time on ART was 5.4y. Of 42 participants in Cohort 1 on TLD with VL results at 6m, 88% had VL≤1000 c/ml (95% CI: 74%, 96%) and 83% had VL≤200 c/ml (CI: 69%, 93%); 0/42 (0%) had new DTG mutations (CI: 0%, 8%). Of 165 participants in Cohort 2 on TLD with VL results at 6m, 72% had VL≤1000 c/ml (CI: 64%, 78%) and 67% had VL≤200 c/ml (CI: 59%, 74%); 2/163 (1.2%, CI: 0%, 4%) had new DTG mutations (G118R and R263K). Viral suppression declined in both groups over 24m (Table). TFV-DP concentrations were lower among participants with VL >1000 vs ≤1000 at 6m: median 127 vs 663 fmol/punch in Cohort 1 (p=0.19; n=5 pairs) and 169 vs 1029 fmol/punch in Cohort 2 (p<0.001

Conclusion: Participants with unsuppressed VL who switched to TLD had improved but suboptimal virologic suppression (<90%) that did not improve over time. Viral suppression was lower in participants switching from 2nd-line PI-based regimens than from failing 1st-line NNRTI-based regimens. Infrequent emergence of DTG mutations and lower TFV-DP concentrations in unsuppressed vs suppressed suggest that incomplete adherence to TLD was the major mechanism for failure to suppress viremia.

Table: Virologic Suppression Rates Over Time (note: follow-up time achieved varied at study closure)

		Cohort 1: switched from 1st-line NNRTI-based ART (N=44)		Cohort 2: switched from 2nd-line PI-based ART (N=173)	
		n/(N on TLD with RNA results) (%)	Exact 95% CI	n/(N on TLD with RNA results) (%)	Exact 95% CI
HIV-1 RNA ≤1000 c/ml	6 months	37/42 (88%)	74%, 96%	118/165 (72%)	64%, 78%
	12 months	30/34 (88%)	73%, 97%	104/140 (74%)	66%, 81%
	24 months	16/21 (76%)	53%, 92%	45/64 (70%)	58%, 81%
HIV-1 RNA ≤200 c/ml	6 months	35/42 (83%)	69%, 93%	110/165 (67%)	59%, 74%
	12 months	30/34 (88%)	73%, 97%	91/140 (65%)	57%, 73%
	24 months	16/21 (76%)	53%, 92%	39/64 (61%)	48%, 73%

676 Viremia and Drug Resistance 2 Years After Routine Switching to Dolutegravir-Based First-Line ART

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Background: People living with HIV (PLHIV) who switch to a dolutegravir (DTG)-based regimen with HIV-1 viremia and possibly NRTI resistance may be at a higher risk of virologic failure and integrase strand transfer inhibitor (INSTI) resistance. We report viral load (VL) and drug resistance from the 2-year follow-up of the DTG SWITCH study in Malawi and Zambia. In Malawi, PLHIV were switched irrespective of their VL value whereas in Zambia, only patients with the last routine VL <1000 copies/mL were switched.

Methods: We present proportions of patients with viremia (VL >400 copies/mL) 2 years after switching (+/-90 days) to DTG-based first-line ART between Nov/2019 and Dec/2020, by country and VL at switch. We calculated relative risks (RR) of viremia at 2 years, with exact 95% confidence intervals (CI). We also report major integrase drug resistance mutations (DRM) detected in 2-year samples among participants with VL >1000 copies/mL.

Results: Of PLHIV switched during the study period, 1422/1458 (97.5%) in Malawi and 1410/1417 (99.5%) in Zambia had a viral load measurement available at switch and were eligible. Most participants were women; 1409 (91%) in Malawi and 1169 (83%) in Zambia; median time on ART was 6.1 years. Seventy-seven PLHIV were viremic at baseline in Malawi (5.4%), compared to 42 (3.0%) in Zambia. In Malawi, 1149/1422 (81%) participants had a 2-year VL available: among those viremic at switch, 27.8% were viremic at 2 years compared to 3.7% among those suppressed at switch, RR=7.8 (4.2-13.4). In Zambia, 1248/1410 (89%) participants had a 2-year VL; the corresponding percentages were 5.1% and 1.7%, RR=3.1 (0.4-12.0). Viremia at switch was strongly associated with an increased risk of viremia at 2 years in Malawi but not in Zambia (Table). Integrase sequencing was successful for 45 of 62 samples with VL ≥1000 c/mL at 2 years. Two had major INSTI DRM: G118R, E138K, T66A (Malawi); G118R, E138K (Zambia); and both were viremic at switch and/or 1 year. The sample from Malawi also contained NRTI mutations (D67N, K70R, M184V, K219Q).

Conclusion: Viremia was uncommon two years after the programmatic switch to DTG-based first-line ART, and only two cases of emergent DTG drug resistance were detected. Still, PLHIV switching to DTG with viremia had a substantially higher risk of viremia at 2 years than PLHIV with viral suppression at switch. The Zambian policy of only switching virologically suppressed patients may have reduced the risk of developing viremia and virologic failure on DTG.

Table: Virologic outcomes of PLWH at 2 years after programmatic switching to Dolutegravir (DTG)-based first-line ART, in two ART programs in Malawi and Zambia.

Viral load at switch	Viral load at 2 years (No. of participants)		
	Suppressed	Viremic	Total
Malawi			
Suppressed*	1056	39 (3.6%)	1095
Viremic	39	15 (27.8%)	54
Relative risk (95% CI)	7.8 (4.2 to 13.4)		
P	< 0.001		
Zambia			
Suppressed	1180	20 (1.7%)	1209
Viremic	37	2 (5.1%)	39
Relative risk (95% CI)	3.1 (0.36 to 12.0)		
P	0.3		

CI, confidence interval; VL, Viral load; P, P-value
* Virologic suppression was defined as VL <400 HIV-1 copies/mL

677 DTG Resistance in Patients with Previous ARV Experience and Viremia in Kenya Receiving DTG-Based ART

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Background: Kenya began rolling out DTG-based ART in late 2017 as both 1st- and 2nd-line treatment for adults and children living with HIV (PLHV). HIV drug resistance (HIVDR) data is limited in PLHIV failing DTG-based ART. We used the cyclical-acquired HIVDR (CADRE) methodology to assess the frequency of HIVDR mutations in PLHIV with detectable viremia on DTG-based ART between January and March 2023 in Kenya.
Methods: The National AIDS and STI control program(NASCOP) collected remnant plasma from HIV viral load testing between January and March 2023 from PLHIV in 15 high/moderate HIV prevalence counties receiving DTG-based ART through the Kenya HIV Care and Treatment Program. We received 191 samples from PLHIV out of the expected CADRE-calculated sample size of 622. Plasma was genotyped using Thermo-Fisher Sanger pro/RT/int sequencing on samples >200 cp/mL and mutations were identified using Stanford HIVdb v9.5. Clinical and demographic data on treatment history and duration was obtained from viral load request forms.
Results: Samples were available for 138 of 332 (42%) adults, median age 36 [IQR 26-45] years, and 52 of 290 (18%) children (median age 15 [IQR 12-16] years) with 1 of unknown age. 146 of 191 total (76%) received DTG as 2nd-line, with 141 on NNRTI-based ART and 5 on PI-based ART for a median of 5 [IQR 2-8] years before switching to DTG-based ART; the remaining PLHIV (45 of 191; 24%) received DTG as 1st-line. 56 of 191 (29%) had HIV-1 VL >200 cp/mL; 44 of 56 (79%) were successfully genotyped. 7 of 32 (22%) ART-experienced PLHIV had INSTI resistance with E138K alone or with up to three additional major INSTI mutations including T66I, G118R, G140A, S147G, Q148KNR, and/or N155H. All 7 also had multiple NNRTI and NRTI DRMs including 5 with thymidine analogue mutations. 1 of 12 (8%) PLHIV on 1st-line TLD had VL 296 c/mL after 17 months on ART and the INSTI DRM R263K with only K70Q and M184V in RT (Table).
Conclusion: The frequency of INSTI HIVDR was high (22%) in ART-experienced PLHIV on DTG-based ART used as 2nd-line ART and lower (8%) in ART-naïve adults using DTG for 1st-line ART, suggesting the risk of failing DTG may be higher in a background of pre-existing mutations to NRTIs in the regimen. Our data emphasizes the importance of HIVDR monitoring in PLHIV on DTG-based ART given the anticipated introduction of long-acting cabotegravir for HIV prevention and the potential for transmission of INSTI-resistant virus from those on failing DTG-based ART to cabotegravir PrEP recipients.

HIVDR_mutations(INSTI/NRTI) among PLHIV on DTG-based-ART.

HIV-VL(cp/mL)	Treatment_experienced	DTG-ART(months)	INSTI_DR_mutations	NRTI_DR_(*TAMs)
1030	Yes	48	E138K	M184V
5726	Yes	37	E138K,G140A,Q148KN	D67GS68G,K70R,M184V,*T215F,*K219Q
93486	Yes	40	E138K,G140A,S147G,Q148R	D67HN*,K70R,V75VM,M184V,T215FI*,K219E*
2054	Yes	40	E138K,G140A,S147G,Q148R	M41L*,M184V,T215Y*
502	Yes	27	T66I,G118R,E138K	M41L*,S68G,M184V,L210LW*,T215F*
88926	Yes	22	T66I,G118R,E138K	K65R,S68N,Y115F,M184V
2012	Yes	37	E138EK,S147G,N155H	S68G,M184V,T215F*
296	No	17	R263K	K70Q*,M184V

678 Emerging Dolutegravir Resistance in Lesotho

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Background: Since 2018, the World Health Organization has recommended dolutegravir- (DTG-) based antiretroviral therapy (ART) as the preferred regimen for most people with HIV. Most African countries have thus shifted from non-nucleoside transcriptase inhibitor- (NNRTI-) to DTG-based ART, often without requiring prior viral suppression and without access to resistance testing in case of viremia. National programs report higher rates of viral suppression since changing to DTG, including among people with unsuppressed viremia before the change. To date, few DTG resistance-associated mutations (RAMs) have been reported from African routine care cohorts.
Methods: This study aims to assess emerging DTG RAMs among participants of the Viral Load Cohort North-East Lesotho (VICONEL). Eligibility criteria were i) written informed consent, ii) having changed from NNRTI- based to DTG-based ART, and iii) subsequently having ≥2 viral loads ≥50 copies/mL (c/mL), including at least one available sample ≥500 c/mL and taken ≥18 months after changing to DTG (data closure: April 20, 2023). For each participant, the last-available sample with a viral load ≥500 c/mL, as well as previous samples if DTG RAMs were detected, were analysed near full-length HIV sequencing for genotypic resistance testing (GRT). RAMs were interpreted using the Stanford HIVdb (9.5.0).
Results: Among 14'881 VICONEL participants who had changed to DTG ≥18 months before data closure, 75 (0.5%) fulfilled the inclusion criteria (median age at change 27 years, 57% female). GRT were available for 54/75 (72%). Among these 54 participants (median age at change 24 years, 54% female), high-level and low-level resistance to DTG was detected in five and one, respectively. None of these six had a documented viral load <50 c/mL <6 months before changing to DTG (Figure). DTG RAMs detected were H51Y (participant 6 in Figure), E92Q (6), G118R (1,2,3,5), E138A (3), E138K (1,2,3,5), N155H (4), and R263K (1,4,5). GRT data from before the change to DTG were available for three of these six participants (participants 1, 3, 6 in Figure): in all cases, RAMs against the nucleoside reverse transcriptase inhibitor backbone but no RAMs in the integrase region were recorded before change.
Conclusion: Among participants who changed from NNRTI- to DTG-based ART with sustained viremia ≥18 months after change, DTG resistance was more frequent than expected, highlighting the need for national programs to ensure close follow-up with access to GRT for this specific subgroup.

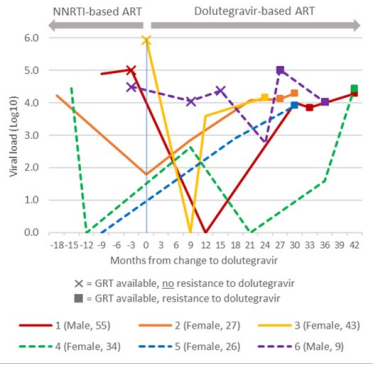

Figure: Dynamics of log10 viral loads pre- and post-change to dolutegravir in the six participants with detected dolutegravir resistance. GRT: genotypic resistance test; NNRTI: non-nucleoside transcriptase inhibitor.

679 Resistance to Second-Generation InSTIs in Mexican PLWH: Emergence of the R263K Mutant

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Background: Clinical trials and real-life experience have shown limited resistance development after use of second generation INSTIs, specially in first line. One of the mutants found in this scenario is the R263K, a nonpolymorphic mutation that alone reduces DTG, BIC, and CAB susceptibility about 2-fold. This mutation has been described in first line failure to second generation INSTIs.

Methods: We analyzed all the samples submitted for integrase resistance genotype (Abbot ViroSeq HIV 1 Genotyping System) to our reference laboratory from October 2021 to September 2023. Our lab that performs all the resistance tests from 25 states in México, centers that care for about 2/3 of the cases in the country. In all cases the test was ordered to detect integrase resistance.
Results: Ninety-four samples were submitted to integrase resistant tests to our referral laboratory; 77(72%) have RAMs to INSTIs, but only 19 (18%) had primary resistant mutants in 12 of them accompanied by secondary mutations. The most common mutants detected were the combination of Q148H plus G140S in eight cases, all failing to DTG BID after previous failure to RAL; followed by mutation R263K present in 7 cases 6 of them detected in 2023 tests. R263K was detected in 2cases failing to DTG and 3 to Bictegravir/TAF/emtricitabine (BIC/TAF/FTC) used as a first line treatment. All cases failing to BIC/TAF/FTC had R263K together with M50I, and were failing for at least one year, always with viremias lower than 5,000 copies/ml.
Conclusion: Despite the widespread use in México of second generation INSTIs, especially after 2019 were BICTAF is used as first line treatment in close to 90% of starting cases; the number of failures is limited. Only 18% of the tests submitted had primary mutations in the integrase gene, mostly in failures after RAL use. The 3 cases of resistance to BIC/TAF/FTC in first line showed a rare mutant combination associated to low viral fitness, and are probably related to bad adherence.

680 Virologic Outcomes With Tenofovir-Lamivudine-Dolutegravir for PI-Based Second-Line ART Failure

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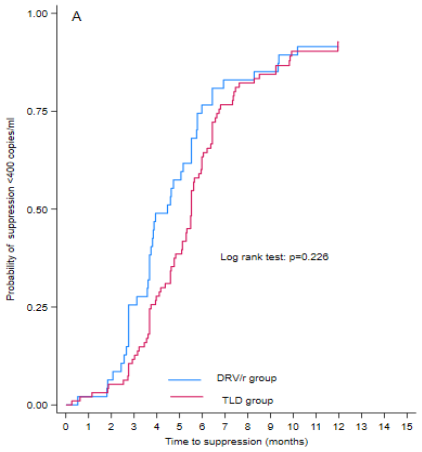
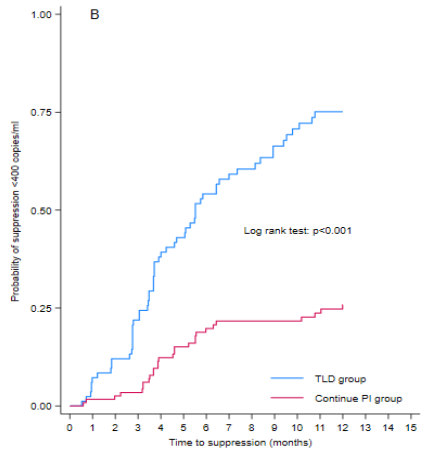
Background: Patients failing protease inhibitor (PI)-based 2nd-line antiretroviral therapy (ART) in the South African ART programme qualify for genotypic antiretroviral resistance testing (GART) – those with PI resistance receive a darunavir (DRV/r)-based 3rd-line regimen; those without PI resistance continue their regimen with adherence support. In the Western Cape Province from September 2020, an adaption to the national guideline allowed switching to tenofovir-lamivudine-dolutegravir (TLD) in such patients who had no tenofovir resistance irrespective of PI resistance.
Methods: We conducted a prospective cohort study to evaluate virologic outcomes on TLD amongst consecutive adults who had virologic failure on a PI (lopinavir or atazanavir) 2nd-line regimen in whom GART was performed. We compared outcomes in patients switched to TLD between August 2019 and March 2022, and those continuing the same PI regimens or switched to DRV/r-based regimens. Patients were followed up until the primary outcome (time to HIV-1 RNA <400 copies/mL), or censored at death, loss to follow-up, or July 2023.
Results: 355 patients were enrolled: 133 switched to TLD, 101 switched to DRV/r-based regimens (84% switched to DRV/r with dolutegravir), and 121 continued the same PI regimens. Median age was 40 years (IQR 34–46), 69% female, median duration on PI regimens was 65 months (IQR 34–91), median HIV-1 RNA was 4.7 log10 copies/mL (IQR 4.1–5.2) at the time of PI regimen failure. 36% and 38% had resistance to lopinavir and atazanavir, respectively. Baseline characteristics were similar between the 3 groups. In patients with PI resistance, 44/47 (94%) in the TLD group suppressed to HIV-1 RNA <400 copies/mL compared to 89/99 (90%) in the DRV/r group (HR 1.25, 95% CI 0.86–1.82, Figure A). In patients without PI resistance, 66/86 (77%) in the TLD group suppressed to HIV-1 RNA <400 copies/mL compared to 43/120 (36%) in the continue PI group (HR 4.35, 95% CI 2.78–7.14, Figure B). Death occurred in 1/128 (0.8%) in the TLD group, 3/95 (3.2%) in the DRV/r group, and 8/114 (7.0%) in the continue PI group at 6 months. Two (2%) patients in the TLD group were known to have developed virologic failure with dolutegravir resistance at 1-3 years.
Conclusion: Among patients with virologic failure on PI-based 2nd-line ART, switching to TLD when there was no PI resistance was associated with higher virologic suppression likely due to improved adherence. Virologic outcomes were similar in patients with PI resistance switched to DRV/r or TLD.





681 Phenotypic Characterization of Replication-Impaired Lenacapavir-Resistant HIV Clinical Isolates

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Background: Lenacapavir (LEN) is a potent, first-in-class long-acting HIV capsid (CA) inhibitor, approved by the FDA as a twice-yearly treatment option for people living with multi-drug resistant HIV. Out of 258 people with HIV (PWH) who received LEN in clinical studies, CA mutations were observed in 14 participants (M66I, Q67H/K/N, K70H/N/R/S, N74D/H, A105T/S, and T107A/C/N/S). Phenotypic analyses of these mutants were successful in a single cycle (SC) assay; however, in the majority of capsid mutants, replication was impaired and too low for phenotyping by the multicycle (MC) MT-2 cytopathic assay. These mutants also had low replication capacity (RC) in the SC PhenoSense Gag-Pro assay (Monogram Biosciences). Here, we have developed and optimized a novel MC phenotyping assay using a Rev-dependent HIV reporter-controlled cell line, Rev-CEM-Luc/GFP (RevLucGFP), to characterize CA mutants with low infectivity.
Methods: The HIV Gag-Protease fragments from plasma samples with CA resistance mutations (CAPELLA and CALIBRATE studies, n=21) and associated site-directed mutants (SDM, n=15) were cloned into pXXLAI HIV molecular clone followed by transfection into 293T cells. Replicative viral supernatants were evaluated in 2 different MC infection formats; MT-2 and RevLucGFP cell lines, with readouts of cell viability and viral replication, respectively. Patient isolates were also evaluated in the PhenoSense Gag-Pro assay. Outputs for antiviral assays included fold change (FC) in LEN susceptibility and RC (Gag-Pro assay).
Results: We successfully phenotyped 11 mutants in RevLucGFP cells that were non-infectious in MT-2 assays, including clinical isolates containing M66I in various genetic contexts and combinations of LEN resistance associated mutations (RAMs) with FC ranging from 43.5 to >1000. Antiviral activity and susceptibility in the RevLucGFP MC assay aligned with the previously observed data in the SC PhenoSense Gag-Pro assay and MT-2 cells. Additionally, we observed that SDMs generated in a clinical isolate background containing common polymorphisms have a greater ability to be phenotyped, as compared

to SDMs generated in WT lab isolate background. All CA mutants with resistance to LEN remained sensitive to other main HIV drug classes.
Conclusion: Using a sensitive HIV-dependent reporter-based system, we evaluated phenotypic susceptibility of several viruses with low RC (0.6-24% of WT) that were previously uncharacterized, expanding our understanding of LEN resistance and interactions between CA RAMs.

682 Rapid Selection of HIV-2 Capsid Mutations After Failure of a Lenacapavir-Containing Regimen

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Background: Drug resistance is a major hurdle in the treatment of people living with HIV-2 (PLWH-2). The limited number of therapeutic options combined with the rapid selection of mutations can lead to therapeutic dead ends. Lenacapavir (LEN) is the first capsid inhibitor, with in vitro activity against both HIV-1 and HIV-2. It has been approved for PLWH-1 with multi-drug resistant viruses but its genetic barrier is low and several drug-resistance associated mutations (DRAMs) have been reported.
Methods: French PLWH-2 with multi-drug resistant viruses had access to LEN through a compassionate use program. LEN was initiated along with an optimized background regimen (OBR). Plasma viral loads were measured throughout follow-up, and capsid genotyping was performed at time of virological failure using an in-house PCR assay, followed by high-throughput sequencing. Capsid sequences were compared with viral sequences obtained prior to LEN initiation to identify potential DRAMs.
Results: A total of 8 PLWH-2 (4 female) initiated a treatment with LEN and an OBR. The genotypic susceptibility score (GSS) of the OBR was equal to, or below, two for all patients. Plasma viral loads at time of initiation were detectable in 6/8 patients (median: 3,830 copies/mL, range: 665-60,450). Three additional PLWH-2 achieved virological suppression within two to three months after initiating LEN+OBR. Capsid genotyping was performed on the first positive plasma viral load (median pVL: 1,600 copies/mL, range: 260-7,210). Capsid mutations were observed in six PLWH-2: five N73D mutations and one double mutation (Q66H+R69K) (Table). In addition to the N73D mutation, an A76V mutation emerged in the viruses of two patients at 11 and 17 months after initiation of LEN. Two patients (#7 and #8) had persistently high plasma viral loads but their viruses did not select any capsid mutations. Of note, the patient with the highest GSS (#4) had adherence issues, resulting in a functional monotherapy of LEN for several weeks.
Conclusion: We report the rapid selection of capsid mutations in PLWH-2 failing a LEN-containing regimen. These mutations occurred at positions close to those previously reported in HIV-1. Additional data on the impact of these mutations on the phenotypic susceptibility to LEN are needed. This preliminary study underscores the low genetic barrier to resistance of LEN, especially when the GSS of the optimized background regimen is low, and the need to use it along with therapeutic drug monitoring and therapeutic education.

ID	Month post-LEN initiation	Plasma viral load (copies/mL)	GSS of the Optimized Background Regimen	Amino acid in the HIV-2 capsid			
				66	69	73	76
#1	M2	895	0.5	Q	R	D	A/V†
#2	M4	290	1§	Q	R	D	A
#3	M5	1,315	1§	Q	R	D	A/V†
#4	M8	2,410	2	Q	R	D	A
#5	M9	260	0.5	Q	R	D	A
#6	M3	3,175	1§	H	K	N	A

Table. First detection of capsid mutations in people living with HIV-2 treated with lenacapavir. †: An A76V mutation was selected at later time points. §: These individuals had undetectable viral loads after initiating a LEN-containing regimen, before experiencing virological failure.

Abbreviations: GSS: Genotypic Susceptibility Score; LEN: Lenacapavir; M: Month post-initiation.

683 Role of Dolutegravir in the Emergence of the S147G Integrase Resistance Mutation

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Background: Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) with high efficacy and high barrier to resistance. However some resistance mutations (RM) reduce the HIV susceptibility to this drug. While S147G RM confers high resistance to elvitegravir (EVG) in the Stanford and ANRS resistance algorithms, only STANFORD included it in the set of DTG resistance mutations. The aim of this study was to improve knowledge of S147G by specifying the context of its emergence.
Methods: The databases of the French ANRS laboratories network were consulted to collect HIV strains with emergence of S147G in integrase, whatever the therapeutic context. Ongoing antiretroviral treatment, HIV-1 subtype and viral load at the time of sequencing were collected.
Results: Eighty-eight strains harboring the S147G for the first time were included. The subtypes were B, CRF02, or other in 49 (55.7%), 19 (21.6%) and 20 (22.7%) cases, respectively. The median viral load and CD4 cell count were 5860 copies/mL (IQR 1011-24525) and 412 cells/ mm³ (228-560), respectively. The INSTI included in the ongoing treatment was DTG (n=42, 48%), EVG (n=32, 36%), raltegravir (n=9, 10%), bictegravir (n=2) and cabotegravir (n=1).Two patients were not receiving INSTI: one drug-naive patient infected with a multi-resistant virus, another had received previous INSTI regimens. The median number of other INSTI-RM associated with the S147G was 2 (1.75-3.00) for all 88 patients, 3 (2.0-3.0) for those on DTG, and 2 (1-2) on EVG. Previously, among the 42 patients with emergence of S147G during DTG regimen, 9 were INSTI naive, 6 had received another INSTI without failure, 25 had failed on INSTI but without S147G for 14/25 and without resistance data for 11/25.The INSTI-RM most frequently associated with S147G under DTG were T94A (62% of cases), N155H (59%), E138K (50%), L74I/V (38%), and Q148R (33%). Nine of these 42 strains were considered resistant to DTG QD but fully susceptible to DTG BID according to ANRS algorithm, while they harbored 4 to 6 INSTI-RMs (S147G + L74I/M, E92Q, T97A, T138K, Y143C, N155H, E157Q, or S230R). These 9 patterns were associated with intermediate resistance to DTG according to Stanford algorithm.
Conclusion: In this study, the S147G mutation is mainly identified during DTG regimen failures. In such a context it can be associated with up to 6 other INSTI-RM, including T97A and/or N155H in the majority of cases. Thus the S147G mutation needs to be added to the DTG resistance profile in the ANRS algorithm.

684 HIV-1 Resistance Mutations to Integrase Inhibitors Impair Both Integration and Reverse Transcription

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Background: Reverse transcription and integration are key steps of the Human Immunodeficiency Virus type 1 (HIV-1) replication, performed respectively by the viral enzyme's reverse transcriptase (RT) and integrase (IN). Interactions between these two enzymes are critical: IN improves both reverse transcription early steps and processivity, while the RT enhances the integrase strand transfer activity. The use of integrase strand transfer inhibitors (INSTIs) has led to emergence of resistant viral mutants, occurring mostly in the integrase gene. Most of them exhibit an impaired integration compared to wild-type (WT) viruses. However, their impacts on reverse transcription efficiency remain unclear. Our objective was to determine the impact of three of the main INSTI-associated resistance mutation profiles, R263K, N155H and G140S/Q148H on reverse transcription and kinetics of integration.
Methods: We performed in-vitro infections with wild-type and INSTI resistant viruses: R263K, N155H and G140S/Q148H, produced by site-directed mutagenesis. Early and late reverse transcription products were measured by quantitative digital-droplet PCR. Kinetics of integration were analyzed using quantitative PCR on integrated forms of HIV DNA at 24- and 72-hours post infection.

Results: R263K mutation had a major effect on reverse transcription (Figure 1A and B) and a weaker impact on integration. N155H mutation strongly affected reverse transcription (Figure 1A and B) and integration. The G140S/Q148H double mutant profile was associated with a weak impact on reverse transcription (Figure 1A and B) and a more important impact on integration compared to WT.

Conclusion: INSTI resistance mutations alter integration efficiency but also the reverse transcription step. This phenomenon is in accordance with the close interaction between these two enzymes during HIV-1 replication. These observations might contribute to explain the loss of fitness observed in INSTI resistant mutants during virological failure.

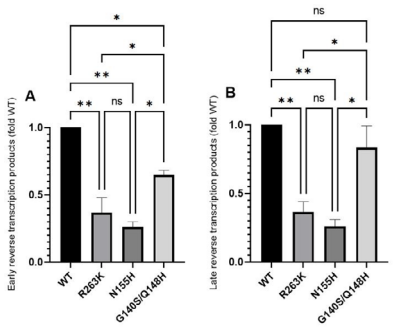

Fig 1. Effect of INSTI associated resistance on HIV reverse transcription production. A. Quantification of early reverse transcription products for WT, R263K, N155H and G140S/Q148H. B. Quantification of late reverse transcription products in WT, R263K, N155H and G140S/Q148H. Results were measured at 24 hours p.i.. *(p<0.05); **(p<0.01); ns (no significant).

685 High-Level Resistance to Integrase Inhibitors Conferred by Mutations Outside Integrase

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Background: Second-generation integrase (IN) strand transfer inhibitors (INSTIs) are highly potent antiretroviral compounds that exhibit a high genetic barrier to resistance. Recent clinical studies concluded that some INSTI-treated individuals experience virological failure in the absence of resistance mutations in IN. The aim of the study is to elucidate INSTI resistance mechanisms and pathways.

Methods: One-year passaging of HIV-1 was conducted using the SupT1 T-cell line and primary PBMCs with an escalating concentration of the INSTI dolutegravir (DTG). We evaluated the impact of the selected mutations on replication kinetics and viral infection through cell-free virion and cell-cell contact and performed an array of biochemical and structural analyses on the selected mutants.

Results: HIV-1 became resistant to DTG by sequentially acquiring mutations in Env, Gag-nucleocapsid (NC), and, occasionally, IN. By cloning env from the DTG-treated viruses selected in the SupT1 T-cell line or PBMC, we obtained heavily mutated Env clones, 7XEnv and WD-3, respectively. Both Env mutants exhibit faster-than-WT replication in spreading infection. 7XEnv exhibits resistance to multiple classes of antiretrovirals, with the fold resistance being ~2-logs higher for INSTIs than for other classes of drugs. WD-3 confers 5-fold resistance to DTG in PBMC. Viral transmission of 7XEnv through cell-cell contact is more efficient than that of WT. In contrast, WD-3 exhibits more efficient cell-free infection than WT. These results suggest that the selected Env mutations confer resistance to INSTIs by increasing infection capacity through cell-cell transmission or cell-free viral infection. Viral infection over a range of multiplicities of infection (MOI) revealed that INSTIs are more readily overwhelmed by high MOI than other classes of drugs, leading to high-level resistance to INSTIs. The NC mutations selected with DTG conferred modest (3-5-fold) resistance to INSTIs. Significantly, the NC mutations do not affect cell-free infectivity but accelerate the kinetics of early post-entry events, suggesting that they may limit the window of opportunity for INSTIs to bind intasomes and block integration.

Conclusion: These findings demonstrate that multiple regions in the HIV-1 genome – Env, NC, and IN – collectively contribute to INSTI resistance. The results provide clues to understanding high-level resistance to INSTIs and support the need for genotypic analysis outside of IN in individuals on INSTI-containing regimens.

686 Virologic Failure With Cabotegravir-Rilpivirine Injections: A Single-Site Experience

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Background: Cabotegravir-rilpivirine (CAB-RPV), the first intramuscular injectable antiretroviral therapy (ART) for people with HIV, is associated with high compliance rates and patient satisfaction. Multiple studies demonstrate low rates of virologic failure (VF) and development of resistance, confirmed by real world analyses. Here we describe our experience with a higher rate of VF at an HIV clinic in Chicago, IL.

Methods: We assessed baseline viral loads (VL) at time of switch in ART, clinic location for the injections and response after transitioning to CAB-RPV. VF was defined as two consecutive VL >200 copies/ml. Resistance mutations in patients with VF were recorded.

Results: 75 undetectable patients (UD, VL <40 copies/ml) were switched to CAB-RPV. 10 received their injections at an independent infusion center (IC) with trained injectors. 65 received injections at our clinic. Two of ten patients at IC and 1 of 65 patients at our clinic developed virologic failure (4%). One patient (pt1) had non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance (K103N), the second (pt2) had an M184V while a genotype failed for the third patient (pt3) at the time of diagnosis. Patients had lived with HIV for 23, 18 and 1 year, respectively, before switch and were lifelong nonsmokers. Pt1 was UD for 2 months and the other two were UD for >6 months prior to switch. All were on an integrase inhibitor (INI) based regimen. Body mass index (BMI) were 27, 35 and 28 respectively. The patients were UD for 6, 10 and 18 months respectively on CAB-RPV before VF. Genotypes at the time of VF revealed INI mutations in pt1: L74I, T97T/A, S147S/G, N155H, INI and NNRTI mutations in pt2: L74L/M, T97T/A, G140S, Q148H and K101E, E138K, I178L, Q207E and INI mutations in pt3: G140G/S, Q148Q/R. None had a missed or delayed dose of CAB-RPV. 1.5-inch needles were used in all three. The two IC patients raised concerns about irregular injection techniques. All three switched to a protease inhibitor-based regimen and were subsequently UD.

Conclusion: While injectable ART are revolutionary in HIV care, clinicians should be aware of possible higher real-world failure rates due to nonstandard injection practices, smoking status, high BMI or unknown pre-existing resistance mutations. Ensuring appropriate training for injecting staff, use of longer needles and obtaining HIV-1 proviral DNA resistance assays may be considered prior to switching to CAB-RPV to further decrease the risk of VF.

687 Env Conformational Flexibility Modulates HIV-1 Sensitivity to VRC01-Mediated Prevention

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Background: HIV-1 envelope glycoproteins (Envs) mediate viral entry and are the sole target of neutralizing antibodies. Envs of most primary HIV-1 strains exist in a closed conformation and occasionally sample more open Env states. Thus, current knowledge guides immunogen design to mimic the closed Env conformation as the preferred target for eliciting broadly neutralizing antibodies (bnAbs) to block HIV-1 entry.

Methods: We evaluated the conformational state of transmitted/founder (T/F) HIV-1 Envs on infectious virions by measuring HIV-1 sensitivity to: 1) antibodies that target internal epitopes, 2) bnAbs, 3) soluble CD4 (sCD4), and 4) exposure to cold. Recognition of soluble HIV-1 Envs (gp120) and surface-expressed Envs by antibodies was measured by ELISA and flow cytometry, respectively. We solved the cryo-EM structure of an unliganded T/F Envs (1059-SOSIP) at 3.6 Å resolution using a large data set and analyzed sub-class structures to estimate the heterogeneity of Env conformations.

Results: We identified T/F HIV-1 Envs that are incompletely closed and sensitive to antibodies that target internal epitopes, to sCD4, and to cold exposure. A cryo-electron microscopy structure of unliganded, incompletely closed T/F Envs (1059-SOSIP), which is resistant to VRC01, at 3.6 Å resolution exhibits an asymmetric configuration of Env protomers with increased sampling of states with incompletely closed trimer apex. We further show a correlation between efficient neutralization of multiple Env conformations and increased antiviral breadth of CD4-binding site (CD4bs) bnAbs. In particular, N6 CD4bs bnAb, which

uniquely recognizes different Env conformations, efficiently neutralizes 50% of the HIV-1 strains that were resistant to VRC01 and transmitted during the first-in-humans antibody-mediated prevention trial (HVTN 704). VRC01-resistant Envs are incompletely closed based on their sensitivity to cold and on partial sensitivity to antibodies targeting internal epitopes, which are typically occluded in tightly closed Envs. Most VRC01-resistant Envs retain the VRC01 epitope according to VRC01 binding to their gp120 subunit at concentrations that have no significant effect on virus entry, and they exhibit cross resistance to other CD4bs bnAbs that preferentially neutralize the closed Env conformation.
Conclusion: Our findings refine current knowledge of Env conformational states and provide guidance for developing new strategies for bnAb immunotherapy and Env-based immunogen design.

688 HIResist: A Database of HIV-1 Resistance to Broadly Neutralizing Antibodies

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Background: Changing the course of the human immunodeficiency virus type I (HIV-1) pandemic is a high public health priority with approximately 39 million people currently living with HIV-1 (PLWH) and about 1.5 million new infections annually worldwide. Broadly neutralizing antibodies (bnAbs) target vulnerable sites on HIV-1 envelope glycoproteins (Envs), which mediate viral entry, and block the infection of diverse HIV-1 strains. But different mechanics of HIV-1 resistance bnAbs prevent robust application of bnAbs therapeutics and preventative intervention. Here we have developed a specialized database, HIResist (HIV-1 Resistance to bnAbs), to analyze patterns of HIV-1 resistance to different bnAbs. HIResist is freely available online (at hiresist.umn.edu) and is a comprehensive online resource with analysis and visualization tools designed to support the HIV-1 research community, scientists, and the public.
Methods: HIResist is a Flask web application with Gunicorn production server and Apache reverse proxy and is written in Python (50%) and HTML/CSS/JavaScript (50%). Version control is achieved by using private GitHub repositories. The HIResist web server resides on a Linux virtual machine having eight 2.20 GHz Xeon E5-260 processors and 16 GB RAM. Data retrieved from the CATNAP database (www.hiv.lanl.gov) are stored in a periodically updated SQLite database.
Results: HIResist is a bioinformatics tool that allows identification of patterns of resistance and mechanisms of HIV-1 escape; comparison of resistant and sensitive HIV-1 strains for each bnAb; identification of resistance and sensitivity signatures associated with specific bnAbs or groups of bnAbs; and visualization of antibody pairs on cross-sensitivity plots. Additionally, several graphical interfaces are available including heatmaps to cluster selected sets of HIV-1 strains and antibodies, and alignment tools with output displayed in a standard HIResist format, and visualization of resistance/sensitivity signatures of HIV-1 Envs.
Conclusion: In addition to the tools mentioned previously, we continue to develop HIResist and plan to add several new interfaces including tools for comparison of bnAb resistance/sensitivity in HIV-1 strains from different populations of PLWH (e.g., drug users or elite controllers) and tools for assessment of emerging HIV-1 strains. HIResist is being developed to encourage engagement and exploration without the need for programming expertise of these highly relevant data by the broader scientific community.

Figure 1. bnAb Reactivity compares resistant (grouped in red) and sensitive (grouped in green) Envs to user-specified antibodied at selected threshold.

689 New HIV-1 Cell-Cell Transmission Assay Identifies Cell Type Dependency of PG9 And P16 Neutralization

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Background: HIV-1 efficiently replicates in vivo by direct transmission from infected to uninfected CD4+ T cells, which is highly resistant to broadly neutralizing antibodies (bnAbs). But an accurate and sensitive measurement of HIV-1 transmission between cells remains challenging
Methods: We developed an ultrasensitive HIV-1 cell-to-cell transmission assay that is based on a new vector, which triggers the expression nanoluciferase (nluc) reporter gene in target cells upon transmission and after reverse transcription of the HIV-1 RNA genome. The new vector is co-transfected with plasmids that express HIV-1 proteins, and the assay allows parallel measurements of free virus infection and cell-cell transmission. RT-qPCR was used to determine the efficiency of reporter RNA splicing and incorporation into HIV-1 virions
Results: Optimization of our HIV-1 cell-cell transmission assay resulted in low background, >99% splicing efficiency, high sensitivity, and wide dynamic range for detection of cell-cell transmission in different T cell lines as well as in primary CD4+ T cells. The assay efficiently detects cell-cell transmission using single-round viral vectors and HIV-1 molecular clones as sources of HIV-1 proteins in 96-well plate format. We used the new ultrasensitive assay to measure HIV-1 sensitivity to bnAbs and observed at least 10-fold less efficient neutralization of cell-cell transmission compared to free virus infection; VRC01 was the less efficient bnAb for neutralizing cell-cell transmission. Neutralization of HIV-1AD8 Env by PG9 and PG16 bnAbs, which target amino acids and glycans of the V1/V2 loop at the Env trimer apex, was depended on the type of virus producing cells. HIV-1AD8 pseudoviruses that were produced in lymphoid cell lines, and most importantly, in primary CD4+ T cells were resistant to PG9 and PG16 bnAbs, but pseudoviruses produced in 293T cells were still sensitive to these V1/V2 loop bnAbs
Conclusion: A new ultrasensitive assay can measure HIV-1 cell-cell transmission in primary CD4+ T cells and accurately detect bnAb neutralization efficiency; the type of transmission and cell origin contribute to HIV-1 sensitivity to bnAbs. This assay is a valuable tool for monitoring and understanding bnAb resistance in HIV-1 patients

690 Development of Individualized Antibody Treatment Regimens for Patients With Multidrug-Resistant HIV

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Background: People living with HIV (PLWH) who harbor multidrug-resistant (MDR) viruses have limited therapeutic options and present extensive challenges in clinical management. We examined the capacity of HIV-specific broadly neutralizing antibodies (bNAbs) and anti-CD4 antibodies to suppress infectious viral isolates derived from PLWH with MDR viruses.
Methods: We conducted immunologic and virologic analyses on 11 PLWH with MDR viruses. We measured the intact HIV proviral DNA burden and examined levels of immune activation and exhaustion markers by flow

cytometry. For comparison, we included a control group of 27 ART-naïve viremic PLWH. We determined the sensitivity of infectious viral isolates obtained from the participants against 8 bNAbs (3BNC117, 10-1074, VRC01, VRC07, N6, 10E8, PGDM1400, and PGT121) and 2 anti-CD4 antibodies (ibalizumab and anti-domain 1 CD4 antibody UB-421) using a TZM-bl-based neutralization/suppression assay.

Results: There was no significant difference in plasma viremia between the study participants with MDR HIV and the control group (P=0.2929). However, the CD4+ T cell counts of the MDR HIV group were significantly lower than those of the control group (P<0.0001). The level of intact HIV proviral DNA was comparable between the two groups (P=0.5895). Levels of activation and exhaustion markers PD-1 (P=0.0019), TIGIT (P=0.0222), 2B4 (P=0.0015), CD160 (P=0.0015), and CD38+/HLA-DR+ (P=0.0138) were significantly lower in the CD8+ T cells of the MDR HIV group. The infectious viral isolates from each study participant with MDR HIV were resistant (IC_{80} >10µg/ml or % suppression <80.7%) to at least 2 bNAbs (average 4 bNAbs per participant); however, they were sensitive to at least one of the CD4-binding and non-CD4-binding site antibodies. The majority of study participants had ibalizumab-sensitive viruses although the isolates from some participants showed reduced sensitivity to the antibody. Notably, none of the 93 infectious viral isolates obtained from the study participants were resistant to UB-421.

Conclusion: The data from our study has direct clinical implications. Our data suggest that the therapeutic options for heavily treatment-experienced PLWH with MDR viruses could be potentially expanded to include HIV-specific bNAbs and UB-421, an avenue that has not been explored until now.

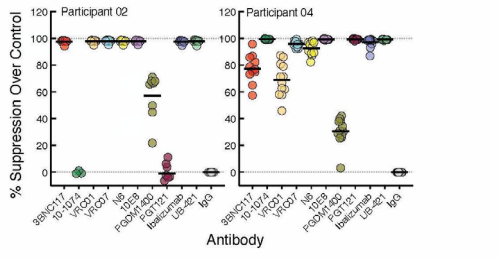

Figure 1: Neutralization/suppression capacity of bNAbs and anti-CD4 antibodies against replication-competent viral isolates derived from study participants with MDR HIV (Data shown for 2 participants out of 11 study participants)

691 Teropavimab and Zinlirvimab Sensitivity in People Living With MDR HIV-1: PRESTIGIO Registry Data

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Background: Broadly neutralizing antibodies (bNAbs) are being investigated as long-acting antiviral therapies, but sensitivity to bNAbs in persons with multidrug-resistant HIV is unknown. Here, we characterized sensitivity to teropavimab (GS-5423; 3BNC117-LS; TAB) and zinlirvimab (GS-2872; 10-1074-LS; ZAB) in people living with 4-class drug-resistant HIV (4DR-PWH).

Methods: Multicenter, observational study using plasma or peripheral blood mononuclear cells collected from 50 4DR-PWH (25 with HIV-1 RNA > 1000 copies/mL matched by age, sex, nadir CD4+ and years on ART to 25 virologically suppressed [HIV-1 RNA < 50 copies/mL]) enrolled in the PRESTIGIO Registry (NCT04098315) with a documented 4DR (NRTI, NNRTI, PI and INSTI). Phenotypic sensitivity to bNAbs was determined using the PhenoSense Monoclonal Antibody assay (Monogram), with susceptibility defined as IC_{90} ≤2 µg/mL. Descriptive statistics are used to present results. Spearman's rank test used for associations between phenotypic susceptibility and clinical variables.

Results: Characteristics of included individuals with analyzed samples were indicative of extensive treatment history (Table1). Of 46/50 (92%) participants with PhenoSense mAb assay results, 35 (76%) were phenotypically sensitive to TAB, 23 (50%) to ZAB, and 19 (41%) to both bNAbs; 7 (15%) had phenotypic resistance to both bNAbs. Of 22 viremic participants, 19 (86%) were phenotypically sensitive to TAB, 10 (45%) to ZAB, 9 (41%) to both bNAbs, and 2 (9%) to neither. Of 24 participants with virologic suppression, 67% were phenotypically sensitive to TAB, 54% to ZAB, 42% to both bNAbs, and 5 (21%) to neither. The proportion of participants with sensitivity to both bNAbs was similar (p=0.99) in viremic participants (9/22 [41%]) compared to those with virologic suppression (10/24 [42%]). Nonsignificant correlations between phenotypic sensitivity to bNAbs and age, years of ART, CD4+ cell count, HIV-RNA, type of ART regimen at the sample collection, viral tropism and HIV subtype. There were marginal correlations between phenotypic sensitivity to TAB and years since HIV diagnosis (Spearman r= 0.287, p=0.053) and phenotypic sensitivity to ZAB and CD8+cell count (Spearman r= -0.317, p=0.049).

Conclusion: A significant number of the analyzed 4DR-PWH were found to have virus susceptible to TAB and ZAB. These data provide proof-of-concept that selected multidrug-resistant PWH may be candidates for future trials investigating bNAbs-containing regimens to achieve or maintain virologic suppression.

Table 1. Characteristics of individuals with an analyzable sample at the time of sample collection (n = 46).

Characteristic	Viremic (n=22)	Virologically suppressed (n=24)	p-value*
Age, years	53.7 (32.0 - 58.1)	54.9 (49.4 - 59.1)	0.461
Male sex	18 (81.8%)	19 (79.2%)	1.000
Time since HIV diagnosis, years	25.5 (22.3 - 31.4)	26.6 (23.0 - 31.8)	0.717
Time since ART start, years	23.3 (20.8 - 26.9)	23.2 (20.7 - 25.4)	0.652
Nadir CD4+, cells/µL	43 (5 - 91)	33 (15 - 78)	0.982
Use of an ART regimen containing ≥4 drugs	13 (59%)	8 (33%)	0.138
CD4+, cells/µL	193 (111 - 289)	618 (488 - 866)	<0.0001

Descriptions by median (IQR) or frequency (%).
* Mann-Whitney or chi-square/Fisher's exact test applied

692 Studying Dual Role of Glycosylation in Resistance to Broadly Neutralizing Antibodies In Vitro

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Background: Broadly neutralizing antibodies (bNAbs) provide a useful tool for HIV cure strategies because of their ability to target conserved regions on the envelope (Env) protein in the context of both virions and infected cells. One of the most well studied bNAbs is the CD4 binding site (CD4bs) antibody, VRC01 and related antibodies. Multiple clinical trials infusing VRC01 into people living with HIV (PWH) demonstrated transient viral suppression. The major obstacle to more effective treatment with bNAbs continues to be viral escape. A deeper understanding of escape pathways from VRC01-class antibodies in genetically diverse samples is needed

Methods: We developed an in vitro viral escape assay to test bNAb and Env combinations. Ex vivo CD4+ T cells were infected with infectious molecular clone 246.F3-NL4.3 (AC) in the presence of varying concentrations of VRC01. Cultures were maintained with suboptimal concentrations of bNAbs to induce escape. Replication kinetics were monitored by p24 every 3 days. Every 14 days, target cells were replenished and cultures tested for genotypic and phenotypic measures of bNAb resistance. This was accomplished by single genome sequencing envs and by TZM-bl neutralization assay. Individual mutations were then tested for their contribution to resistance to CD4bs bNAbs by pseudovirus neutralization assay using mutated env plasmids.

Results: Using our viral escape assay, we observed both previously published and novel escape mutations. Complete resistance to VRC01 was detected in 246.F3 by day 45. A mutation at position N276 that eliminated the glycan conferred complete resistance to VRC01, despite canonically increasing sensitivity. To study the neutralization profile of this mutation in various subtypes, it was inserted into 12-virus global panel of envs and tested for sensitivity compared to wildtype against a panel of CD4bs bNAbs. This mutation was shown to both increase resistance or sensitivity depending on the envelope and bNAb in question, emphasizing a dual role of this glycan in VRC01 class neutralization.

Conclusion: Our data demonstrate that our viral escape assay can highlight novel pathways, such as the loss of glycan 276 conferring complete resistance to VRC01 in 246.F3 env. The role of this glycan in escape was demonstrated to be dependent on both the context of the env as well as the bNAb. This finding emphasizes the importance of studying viral escape with a genetically diverse library to develop a deeper understanding of various pathways.

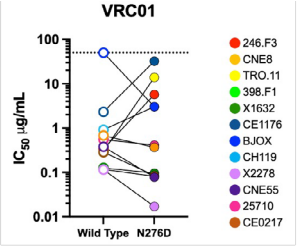

Figure 1. N276D Mutation Sensitivity to VRC01 Viral neutralization sensitivity to VRC01 is shown via change in IC50. The N276D mutation was inserted into each virus on a 12-virus global panel and tested against VRC01. The mutation may can either an increase or decrease in sensitivity depending on the envelope in question.

693 Impact of Archived Minority Populations With M184V/I on DTG/3TC for Maintenance of Viral Suppression

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Background: There is limited evidence on the utility of proviral DNA sequencing to guide treatment changes in virologically suppressed persons with HIV (PWH) and prior virologic failures. VOLVER clinical trial aimed to evaluate if proviral DNA could assist in switching to dolutegravir/lamivudine (DTG/3TC) in PWH with history of 3TC resistance.

Methods: Open-label single-arm multicentric clinical trial of virologically suppressed PWH with past 3TC resistance. Participants switched to DTG/3TC if population sequencing of proviral DNA at baseline did not detect the M184V/I mutation. Proviral DNA next-generation sequencing (NGS) was performed from baseline samples. Primary endpoint was proportion of participants with HIV-1 RNA viral load (VL) ≥50 copies/mL at 48 weeks (intention-to-treat-exposed, FDA snapshot). NCT04880785.

Results: 121 participants with a mean virological suppression of 9 years switched to DTG/3TC. 109 participants (90.1%, 95%CI: 83%-95%) had a VL <50 copies/mL at week 48, 12 premature discontinuations (4 with VL≥50 copies/mL). Baseline proviral DNA NGS (using a >5% detection threshold) data is available for 106 participants: 21 (19.8%) had M184V/I (184V: 18, 184I: 3; mean frequency 28%, range: 8-51%), 1 had K65R, 4 had thymidine analogue-associated mutations (TAMs), and 3 had other nucleoside associated mutations (NAMs) – no participant had both M184V/I and TAMs. Outcomes at 48 weeks of the 21 participants with M184V/I were: all had VL<50 copies/mL, even though 2 (9.5%) withdrew prematurely due to adverse events. Among participants who withdrew the study with VL≥50 copies/mL with baseline NGS data (3/4), none had M184V/I by NGS at baseline, including 2 who discontinued due to protocol virologic withdrawal criteria (one had NAMs 67G and 70E at baseline in NGS). At virologic withdrawal the only amplifiable sample (139 copies/mL) showed no emerging integrase resistance and the M184V with a 17% frequency by NGS in plasma RNA. After baseline, 10/103 participants with NGS data and VL<50 copies/mL at week 48 had a transient viral rebound: 1/21 with 184V/I (4.8%), 0/8 with other mutations and 9/74 without mutations (12.2%).

Conclusion: In this clinical trial of DTG/3TC for maintenance of virological suppression detecting M184V/I in proviral DNA with NGS at baseline did not predict virologic outcomes. Our results question the use of proviral DNA NGS to guide switches to DTG/3TC in PWH with a history of lamivudine resistance.

694 Switching to Doravirine/Islatravir Maintains Viral Suppression Regardless of Archived Mutations

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Background: In 2 phase 3 clinical trials, switching to the 2-drug combination doravirine/islatravir (DOR/ISL) 100/0.75mg was non-inferior to continuing the prior antiretroviral (ART) regimen. This exploratory post-hoc analysis examined the impact of pre-existing resistance-associated mutations (RAMs) on the virologic response to DOR/ISL in these trials, focusing on M184V/I and other RAMs in reverse transcriptase.

Methods: MK8591A-017 (P017; NCT04223778) was an open-label study in adults receiving any oral 2- or 3-drug ART regimen. MK8591A-018 (P018; NCT04223791) was a double-blind study in adults receiving bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF). Participants with HIV-1 RNA <50 copies/mL and no known treatment failure or DOR resistance at baseline were randomized (1:1) to switch to once-daily DOR/ISL (100/0.75mg) or to continue baseline ART (bART) in P017 or B/F/TAF in P018; at week 48, the P017 bART group switched to open-label DOR/ISL. RAMs present at baseline in HIV proviral DNA were identified by Monogram Bioscience (GenoSure Archive assay). Genotypic resistance analyses were based on IAS-USA drug resistance mutation lists for approved ART and other mutations reported in the scientific literature.

Results: Baseline resistance data were available for ~90% of study participants. Of the 889 participants who received DOR/ISL in P017 or P018 and had baseline resistance data available, 46 (5.2%) had M184M/I/V at baseline; none of these participants had confirmed viremia (CV; 2 consecutive HIV-1 RNA ≥200 copies/mL 2-4 weeks apart) or low-level viremia (LLV; 2 consecutive HIV-1 RNA ≥50 and <200 copies/mL 2-4 week apart) while receiving DOR/ISL, and 2/46 (4.3%) had ≥1 viral blips (HIV-1 RNA ≥50 copies/mL followed by <50 copies/mL at next measurement). Twenty participants (6.5%) in the bART group had M184M/I/V at baseline: 2/20 (10%) developed CV, and none had LLV or viral blips. Twelve participants (4.3%) in the B/F/TAF group had M184M/I/V at baseline: none developed CV or LLV, and 1/12 (8.3%) had ≥1 viral blips. NNRTI RAMs were present at baseline in 287 (32.3%) of 889 DOR/ISL participants, 100 (32.6%) bART participants, and 85 (30.4%) B/F/TAF participants. Among participants with NNRTI RAMs, virologic outcomes were similar in the DOR/ISL and comparator groups.

Conclusion: Switching to DOR/ISL 100/0.75mg maintains viral suppression for up to 96 weeks regardless of archived M184I/V or NNRTI RAMs in proviral DNA. The figure, table, or graphic for this abstract has been removed.

695 Longitudinal Analysis of Preexisting Resistance-Associated Mutations Prior to B/F/TAF Switch

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Background: Preexisting resistance can affect antiretroviral (ARV) efficacy. Circulating HIV-1 variants with drug resistance-associated mutations (RAMs) can be archived in viral reservoirs, where they can persist and re-emerge. Given the dynamic properties of the latent reservoir, detection of these RAMs over time has not been well defined.

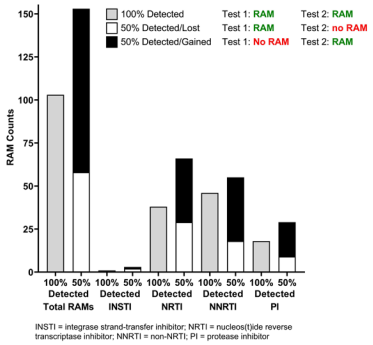
Methods: Participants from bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) switch studies (4449, 4030, 4580; virologic suppression [≥3-6 months]; no prior virologic failure) with HIV-1 RNA or proviral HIV-1 DNA genotyping (population reporting) from ≥2 pre-switch timepoints were included. For 2 timepoints only, RAMs in protease, reverse transcriptase and integrase, and other substitutions (accessory, polymorphisms) were categorized as detected 100% (2 out of 2 tests) or 50% (1 out of 2 tests; subcategorized as detection lost or gained) of the time. For >2 timepoints, RAMs were categorized as lost, gained, persistent, or fluctuating. Time between first and last tests was reported in median years (y). Nonparametric statistics were used.

Results: In all, 235 participants had evaluable data (longitudinal tracking of ≥1 RAM or other substitution). For 206 participants with 2 timepoints, 103 of 256 RAMs reported (40.2%) had 100% detection, and 153 (59.8%) had 50% detection, with 95 (62.1%) gained and 58 (37.9%) lost (Figure). 100% detection was lower for RAMs versus other substitutions (n=3329/4339 [76.7%]; p<0.0001). Time between tests was not different between RAMs with 100% and 50% detection: 7.7 y (quartile 1-3 [IQR] 3.2-11.1) vs 5.9 y (IQR 3.2-9.7), respectively (p=0.06). For 29 participants with >2 timepoints (median 3 reports, 9.3 y [IQR 5.7-13.9] between first and last tests), 66 RAMs were categorized as fluctuating (48.5%), gained (25.8%), persistent (15.2%), or, least common, lost (10.6%). K103N (n=10) and M184V/I (n=16) were predominantly fluctuating (60.0% and 43.8%, respectively) and only lost in 10.0% and 6.3% of cases, respectively.

Conclusion: Some RAMs were consistently reported, but the majority were newly detected or fluctuated and did not disappear significantly over time,

which most likely reflects both the ongoing decay and proliferation of the latent reservoir and, ARV pressure. RAMs were not always detected, and this lack of longitudinal stability enforces the need to consider an individual's treatment history and all past genotyping test results (and the detection sensitivities of reports) for treatment management.

Figure: 2-Timepoint Analysis by Drug Class



INSTI = integrase strand-transfer inhibitor; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NNRTI = non-NRTI; PI = protease inhibitor

696 A Phase II Trial of 4 Weeks of Glecaprevir/Pibrentasvir for Early Hepatitis C Virus: ACTG A5380

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Background: Shorter treatment courses have been effective in early hepatitis C (HCV) but are still longer than optimal. Shortening from 8-12 weeks to a single month simplifies treatment and may further facilitate the national plan of HCV elimination.

Methods: A5380 was a prospective, phase II, single-arm multicenter trial evaluating the efficacy and safety of once daily oral glecaprevir/pibrentasvir (G/P) 300 mg/120 mg for 4 weeks in adults with early HCV. Early HCV was defined as new ALT elevation (≥5x ULN or >250 U/L if normal ALT in prior year, or ≥10x ULN or >500 U/L if no or abnormal ALT in prior year); or detectable HCV RNA with prior negative antibody (1st infection) or HCV RNA (re-infection) within 24 weeks prior to study entry. The primary endpoint was sustained virologic response, SVR12, defined as HCV RNA <LLOQ at 12 weeks after treatment cessation. A5380 was powered to conclude that the SVR12 proportion is >80% using the 90% Wilson confidence interval (CI). Participants not achieving SVR12 were offered re-treatment.

Results: Forty-five participants (98% male, 51% White, 27% Black, 31% Hispanic/Latino, median age 36 years (range 22-65) were enrolled from the U.S. and Brazil between Nov 2019 and Jan 2023; 27% reported a history of injection drug use, 84% were 1st HCV infections. 51% were people with HIV (PWH), with CD4 / HIV RNA reported in Table 1. Median time from diagnosis to entry was 31 days (IQR: 15-49). Median baseline HCV RNA was 5.3 log IU/mL (IQR: 3.3-6.0), 71% genotype 1; median ALT was 146 U/L (range: 22-3866). SVR12 was achieved in 38 of 45 (84%) participants (CI: 74%-91%) and 86% (CI: 76%-93%) excluding 1 participant lost to follow-up (LFU). SVR12 was 83% (CI: 66%-92%) in PWH and 86% (CI: 70%-94%) in those without HIV. There were no treatment-related serious adverse events. For the 6 participants with recurrent viremia at or before SVR12, median baseline HCV RNA was 6.3 log IU/mL (IQR: 5.8-7.1) and self-reported pill counts suggested good adherence. Re-treatment with salvage regimens resulted in SVR12 for 4 of 4 participants with treatment follow-up.

Conclusion: Treatment of early HCV with 4 weeks of G/P resulted in clinically acceptable cure rates in people with or without HIV. Although SVR12 >80% could not be concluded from the CI, a planned analysis excluding LFU supports that the SVR12 proportion is >75%. As simplified treatment approaches are critical for HCV elimination, a 4-week G/P regimen should be tested in implementation programs aiming to cure early HCV.

Table: Detailed HIV and HCV Parameters

HIV present (n=23)	Median CD4 count (IQR)	545 (348-820)
	HIV < 40 copies/mL	23 (100%)
HCV genotype (n=45)	1	32 (71%)
	2	2 (4%)
	3	1 (2%)
	4	5 (11%)
	Unable to determine	5 (11%)

697 A Precision Randomized Trial of Hepatitis C Treatment Adherence Support Among 3000 PWID in India

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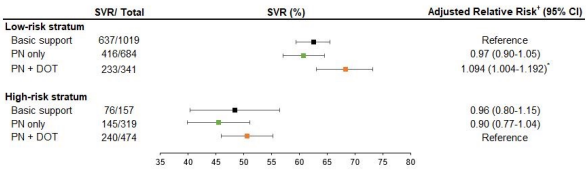
Background: HCV elimination is unlikely without curing people who inject drugs (PWID). Many PWID will need additional support to achieve HCV cure, but resources are limited, particularly in low-and-middle-income countries. A precision approach could improve the efficiency of intervention delivery. The STOP-C trial evaluated whether HCV treatment outcomes could be optimized by tailoring adherence support to PWID need across community-based centers in 7 cities across India.

Methods: We implemented a precision randomized trial where arm assignment probabilities varied by participants' estimated probability for HCV treatment failure. A prediction model generated a prognostic score that classified persons as low or high-risk for failure. Those at high-risk were randomized 3:2:1 to patient navigation + flexible directly observed therapy with ≥1 weekly dose observed (PN+DOT), PN contact ≥ every 2 weeks (PN only) or basic support. Those at low-risk were randomized 1:2:3 to PN+DOT, PN only or basic support. All had a history of drug injection and were treatment naïve; those with decompensated cirrhosis were excluded. All received sofosbuvir/velpatasvir once daily for 12 weeks. The primary outcome, sustained virologic response (SVR; HCV RNA < LLOQ 12 weeks after treatment completion) was compared by Poisson regression adjusted for site (intent to treat, missing=failure).

Results: 3000 participants were recruited from Jan 2021-Dec 2022 (2048 low-risk, 952 high-risk). Compared with participants in the low-risk stratum, those in the high-risk stratum were more likely to be younger (median 27 vs. 31), experience homelessness (26% vs 6%) and report active drug injection (89% vs. 42%). 2798 (93%) completed SVR assessment. 49% and 63% achieved SVR in high and low-risk strata, respectively. In the high-risk stratum, SVR in PN+DOT was similar to PN only and basic support. In the low-risk stratum, SVR in PN+DOT was associated with a statistically significant 9% increase in SVR vs. basic support (adjusted relative risk [aRR] 1.09; p=0.04) but did not differ in PN only vs. basic support (Figure). Within strata, SVR significantly increased with better prognostic score (aRR per 10% decrease: 1.04 low-risk, 1.10 high-risk; p<0.01 for both).

Conclusion: Greater adherence support or long-acting treatments may be required to improve cure rates among PWID at highest risk for failure. However, programs could use prognostic scores to target interventions more efficiently and proactively address barriers to treatment adherence.

Figure. Sustained virologic response (SVR) by risk stratum and intervention arm



Sample N=2994. 6 participants excluded (4 ineligibility post randomization, 2 missing lab results)
Abbreviations: PN, patient navigation; DOT, directly observed therapy
† Adjusted for site
* p<0.05

698 Prevalence and Risk Factors for Hepatitis C Viremia in People With HIV in the US During the DAA Era

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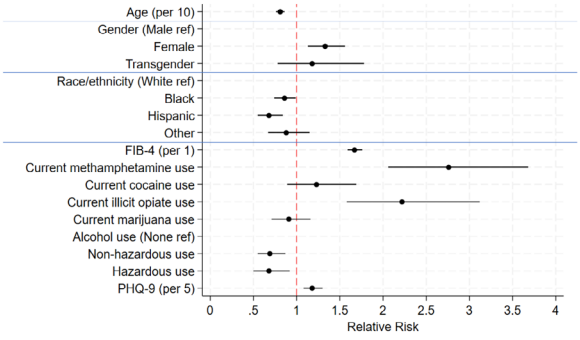
Background: Characterizing the burden and understanding the vulnerabilities and risks for active hepatitis C virus (HCV) infection in the direct-acting antiviral (DAA) era among PWH will provide key information on current progress and guide efforts toward HCV micro-elimination. We evaluated the prevalence of HCV viremia among PWH in clinical care in the US during the DAA era and examined risk factors for HCV viremia from 2018-22.

Methods: Using a serial cross-sectional design, we examined all adult PWH in clinical care at 9 sites in the CFAR Network of Integrated Clinical Systems (CNICS) cohort with ≥1 encounter in 2011-13 (pre-interferon free DAA era, number of participants=22445), 2014-17 (early DAA era, N=25161), or 2018-22 (current DAA era, N=25314). We defined HCV viremia as a positive HCV RNA or genotype. Prevalence of HCV viremia was determined for each time period, using the most recent available lab results, and by demographic group (age, gender, race/ethnicity). We administered validated survey instruments to measure current substance use (AUDIT-C, alcohol; ASSIST, other drugs) and depressive symptom severity (PHQ-9). FIB-4 score was calculated using the age and closest lab values on or before a participant's HCV lab test. We used adjusted relative risk regression (Poisson) to evaluate risk factors for HCV viremia in 2018-22.

Results: Among PWH in care, the overall prevalence of HCV viremia was 8.7% in 2011-13, 10.5% in 2014-17, and 4.8% in 2018-22. Disparities in the prevalence of HCV viremia across groups defined by age, gender, and race/ethnicity were smaller in 2018-22 than earlier time periods (overall range across all 3 demographic groups by time period: 3.0-13.0% [2011-13]; 3.5-14.4% [2014-17]; 3.2-5.6% [2018-22]). In adjusted relative risk regression, identifying as female (RR 1.33, 95% CI 1.13-1.56), FIB-4 (RR 1.67 per unit, 95% CI 1.59-1.76), depressive symptom severity (RR 1.18 per 5 units on PHQ-9, 95% CI 1.08-1.30), and current use of methamphetamine (RR 2.76, 95% CI 2.06-3.68) or illicit opioids (RR 2.22, 95% CI 1.58-3.12) (P<0.001 for each factor) were associated with higher likelihood of HCV viremia in 2018-22.

Conclusion: The prevalence of HCV viremia during the DAA era in this US-based national cohort of PWH improved over time and across demographic subgroups but remains elevated. Our findings underscore the importance of prioritizing substance use and mental health treatment in PWH to achieve HCV elimination goals.

Figure. Relative risk estimates[a] of demographic, clinical, and behavioral factors for HCV viremia in 2018-22.



[a]Model adjusted for CNICS site and listed covariates. Current substance use (AUDIT-C, alcohol; ASSIST, other drugs) and depressive symptom severity (PHQ-9) based on self-report. FIB-4 truncated at 5. Multiple imputation (m=50) used for missing data.

699 Elimination of HCV Among People With HIV in Australia

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Background: An estimated 2000-2500 people were living with HIV/HCV coinfection in Australia prior to availability of HCV direct-acting antivirals (DAAs). Rapid DAA scale-up occurred from 2016 following unrestricted DAA access for adults. The aim of this analysis was to evaluate progress towards HCV elimination among people with HIV in Australia.

Methods: The CEASE prospective cohort study enrolled people with HIV and anti-HCV antibodies, irrespective of HCV RNA status, from 11 primary and tertiary clinics. Enrolment (ENR; 2014-2016), Follow-Up 1 (FU1; 2017-2018) and Follow-Up 2 (FU2; 2021-2023) visits were undertaken. Biobehavioural data were collected at each visit and clinical data extracted from medical records. Participants with at least 2 study visits were included in analysis and proportion with HCV RNA calculated. Death and HCV reinfection incidence rates were calculated per 100 person-years (PY). Cox regression was used to assess associated factors.

Results: Of 314 participants (median age 49-years, 97% male [89% gay or bisexual], 13% cirrhosis, 80% history of injecting drug use [IDU], 42% current IDU [past month]) data were available for 295 at FU1 and 266 at FU2 (220/266 HCV RNA available). Of those with detectable HCV RNA at ENR (n=224), 210 received HCV treatment, 204 had documented cure, and 189 had post-cure visit. The proportion with detectable HCV RNA declined from 71% (ENR), to 7% (FU1), to 1% (FU2). Fourteen participants had HCV reinfection (13/14 retreated). HCV reinfection rate was 1.5/100 PY (95%CI 0.91, 2.60; median FU 5.6 years); decreasing from 2.7/100 PY (ENR-FU1) to 0.60/100 PY (FU1-FU2). Current IDU (adjusted hazard ratio [AHR] 3.72 95%CI 1.29, 10.72) increased reinfection risk. In the overall study population, 29 died. Death rate was 2.1/100 PY (95%CI 1.46, 3.01; median FU 4.7 years), stable over time. Median age at death was 56-years (range 29-68). Leading causes of death were chronic comorbidities (24%), cancer (21%), sepsis (14%), and drug overdose or suicide (7%). Older age (AHR 1.06 per year 95%CI 1.01, 1.11) and liver cirrhosis (AHR 2.46 95%CI 1.10, 5.52) increased death risk. Current IDU did not increase death risk, although younger age (<35 years) at injecting initiation did (AHR 3.56; 1.06, 12.00).

Conclusion: HCV prevalence among people with HIV in Australia has declined substantially following rapid DAA scale-up, however surveillance, for HCV (re) infection and associated morbidity and mortality, remains important.

700 Community Pop-Up Clinic: Cascade of Care and HCV Treatment of Vancouver's Inner-City PWID Population

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Background: Several strategies have been proposed to identify HCV-infected inner-city residents, engage them in care, provide them with antiviral therapy, establish conditions to maximize treatment completion and cure achievement. Elimination of HCV infection as a public health concern by the end of this decade will require a concerted effort in all target populations, including vulnerable inner-city populations, many of whom are actively using drugs and are facing other issues more challenging that HCV infection: housing and financial insecurity, untreated mental illness, and active untreated addiction.

Methods: We have evaluated a novel approach of Community Pop-Up Clinics and its ability to promote access to care, uptake of HCV therapy and its outcome, with additional analyses of HCV reinfection events and opioid-related mortality. We hypothesized that by implementing this CPC program, we will optimize engagement in care of vulnerable inner-city populations, increase successful uptake of HCV therapy and reduce reinfection events and mortality.

Results: From January 2021 – August 2023 (32 months), we conducted 112 CPCs and evaluated 1968 individuals. 620 individuals (31.5%) were found to carry HCV antibodies. Of 620 individuals we identified as carrying HCV antibodies, 474 individuals (76.5%) were found to be viremic. HCV engagement has been secured in 387 cases (81.6%). 326 (84.2%) individuals have started treatment and 60 are in the pre-treatment phase, and 1 had died of an overdose

in the pre-treatment phase. The median time from CPC attendance to HCV treatment initiation was 6 weeks. Of 326, 302 have completed treatment, 18 are currently on treatment and 1 died of an overdose during treatment. Of 302 subjects who have completed treatment, 286 are confirmed as cured (SVR 12), 16 are awaiting SVR 4, 2 documented virologic relapse and 1 documented to be reinfected, a rate of 0.31/100 person-years. 3 patients withdrew from the treatment. By mITT, the cure rate is 286/288 (99.3%). Overall, in this vulnerable population with 6-7 opioid overdose deaths/day, we only documented 2 overdose deaths over 326 PY of overall follow-up.

Conclusion: Taken together, the data we present validates the development of multidisciplinary programs such as ours aimed at treating HCV in vulnerable inner-city populations that must be engaged in care for HCV elimination to become a reality. This report also documents additional societal benefits, e.g. lower overdose death, that could be achieved from such a program.

701 Nationwide HCV Elimination Program and the Status of Microelimination in People With HIV in Taiwan

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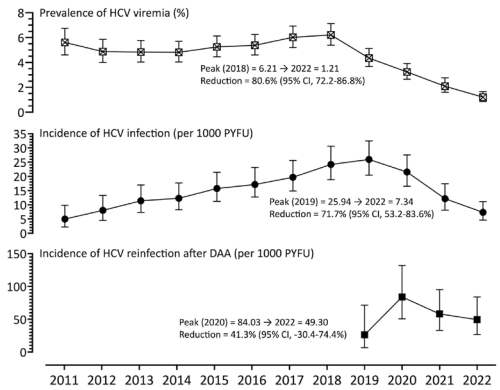
Background: Evidence from Western countries suggests that nationwide hepatitis C virus (HCV) elimination programs, typically coupled with the expansion of HCV testing and direct-acting antiviral (DAA) treatments, could mitigate new HCV infections among people with HIV (PWH). However, real-world data from Asia-Pacific region remained scarce, and the impact of HCV testing and DAA treatment program on HCV reinfection is less addressed.

Methods: Since 2018, Taiwan has initiated a nation-led HCV elimination program aiming to achieve the WHO 2030 targets by 2025. The restrictions on access to reimbursed DAA treatment were lifted and, by the end of 2021, >130,000 courses of DAA had been prescribed. In this study, PWH who were followed at a university hospital were included and the data of anti-HCV antibodies and HCV RNA and the information on DAA treatment were collected prospectively. High-risk PWH (defined as those who had had previous HCV viremia, sexually transmitted infections or unexplained elevation of liver aminotransferases within 6 months) tested for HCV viremia every 3-6 months. The prevalence, incidence and the reinfection rate after successful DAA treatment were estimated every calendar year from 2011 to 2022.

Results: In total, 4465 PWH were included, including 321 PWH who had received successful DAA treatment since 2018 and were followed for HCV reinfections. Since 2018, the prevalence of HCV viremia has started to decline significantly; as of 2022, the prevalence of HCV viremia had reduced by 80.6% (95% confidence interval [CI], 72.2-86.8) when compared to the epidemiological peak in 2018 (Figure). The rate of new HCV acquisition peaked in 2019, with an incidence rate of 25.94 per 1000 person-years of follow-up (PYFU; 95% CI, 20.44-32.47), which had declined by 71.7% (95% CI, 53.2-86.3%) by the end of 2022, to 7.34 per 1000 PYFU (95% CI, 4.61-11.13). However, the incidence of HCV reinfection peaked later in 2020 at 84.03 per 1000 PYFU (95% CI, 50.58-131.8) and remained high in 2022, with an incidence of 49.30 per 1000 PYFU (95% CI, 26.71-83.82). Compared to the 2020 peak, the rate of HCV reinfection in 2022 showed only a modest reduction by 41.3% (95% CI, -30.4% to 74.4%).

Conclusion: The ongoing HCV elimination program has resulted in significant reduction of HCV prevalence and incidence among PWH in Taiwan. However, the incidence of HCV reinfection remained high in the DAA era.



702 High Completion and Cure Rates With a Decentralized, Integrated HCV Treatment Approach in Vietnam

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Background: WHO recommends a simplified service delivery approach to the treatment of chronic hepatitis C (HCV) infection including decentralization to the primary care level and integration into existing services. In 2021, with support from the Global Fund, the Vietnam Administration for HIV/AIDS Control within the Ministry of Health scaled up HCV treatment at public HIV and methadone clinics in 36 provinces.

Methods: Patients with HCV viremic infection with and without liver fibrosis or cirrhosis were eligible for HCV treatment through the National program. Patients were treated with sofosbuvir/daclatasvir for 12 or 24 weeks following the Vietnam national guidelines. Program data were collected and stored in the Ministry of Health database. We assessed HCV treatment outcomes at national, provincial and district levels. The primary endpoints were treatment completion and sustained virologic response 12 weeks after treatment completion (SVR12). Multivariate logistic regression analysis was used to find factors associated with SVR12.

Results: Data were available for 15,196 individuals treated for HCV between May 2021 and June 2023 at HIV clinics (71.3%) or methadone sites (28.4%). The mean age was 42.3 years, 14344 (94.4%) were male, and 8696 (57.2%) had a history of injection drug use. Individuals were treated at the district [13767 (90.6%)], provincial [1167 (7.7%)], and national levels [211 (1.4%)]. Overall, only 271 (1.8%) discontinued treatment due to lost-to-follow-up [171 (63.1%)], change to private treatment [40 (14.8%)], drug stock-out [21 (7.7%)], side effects [12 (4.4%)] or death [27 (10.0%)]. Of the 7663 (51%) with an HCV RNA test 12 weeks or more after completing therapy, 7169 (93.8%) achieved an SVR12. When stratified by level of care, SVR12 rates were 98.9%, 95.9%, and 93.5% at the national, provincial, and district levels respectively. On multivariate analysis, factors independently associated with SVR12 included age > 40, identified as neither MSM or PWID, DTG-based antiretroviral regimen, and presence of liver cirrhosis (Table).

Conclusion: Decentralized treatment of HCV infection integrated into HIV and addiction care was highly effective in Vietnam with high rates of treatment completion and SVR12. Ensuring the continued availability of medications and testing reagents as well as financing mechanisms will further strengthen and sustain this program.

Table. Multivariate Analysis of Factors Associated with SVR12 Among 7663 Patients Treated for HCV Infection

Factors	OR	95% CI	p-value
Female	1.2	0.7-1.7	0.5
Age > 40 years old	1.5	1.2-1.8	0.000
Neither MSM or PWID	1.5	1.3-1.9	0.000
DTG-based regimen	1.3	1.1-1.6	0.015
Presence of liver cirrhosis	1.6	1.1-2.2	0.005

Abbreviations: SVR12, sustained virologic response 12 weeks after treatment completion; HCV, hepatitis C virus; OR, Odds ratio; CI, confidence interval; MSM, men-who-have-sex-with-men; PWID, person who injects drugs; DTG, Dolutegravir

703 High Rate of Hepatitis C Incidence in Vietnamese MSM Living With HIV

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Background: Men who have sex with men (MSM) living with HIV have higher rates of hepatitis C virus (HCV) infection than MSM without HIV infection in North America and Europe. Studies have shown similarly high rates of HCV incidence among MSM living with HIV in large Asian cities, including Bangkok, Taipei, Hong Kong, and Tokyo. There are limited data on HCV incidence among MSM in Vietnam.

Methods: MSM and transgender women (TGW) were recruited at two antiretroviral therapy clinics for people living with HIV in Ho Chi Minh City and Can Tho, Vietnam. Participants provided informed consent at the first visit and had a second visit after 12 months. At each visit, participants competed a questionnaire on risk behaviors (sexual behavior and substance use) and had

blood drawn for HCV antibody testing. The study was approved by supervising IRB in Vietnam.

Results: Enrolment included 532 participants; 521 (98%) completed two study visits and were included in the incidence analysis. The study population included 76% MSM and 24% TGW with a median age 27 (IQR 24-30). Three-quarters (75%) had high school education or above, with over half (58%) reporting at least some college education. Reported risk behaviors during the follow-up period included condomless anal/vaginal sex (47%), group sex (29%), and methamphetamine use (21%). Injection of methamphetamine appears to be a newly emerging risk in Vietnam; 3 individuals (0.6%) reported this risk at follow-up while none reported it at baseline. HCV prevalence at baseline was 3/523 (0.6%), all of whom were MSM. At 12 months, 7 new HCV infections were detected, for an incidence of 12.0 per 1,000 person years. All incident cases were among MSM participants. Restricting incidence analyses to only MSM (n=397), the incidence rate was 15.2 per 1,000 person years. In the multivariable logistic regression analysis, the only factor significantly associated with new HCV infection was participating in group sex (adjusted odds ratio (aOR) 13.8, 95% confidence interval 1.29-146.5).

Conclusion: HCV incidence is significant among MSM living with HIV in southern Vietnam. HCV infection appears to be related to sexual activity, particularly group sex, which is also often associated with use of recreational drugs such as methamphetamine. Clinics that provide HIV care to MSM clients should provide prevention counseling to at-risk MSM and regular HCV screening for those with high-risk behaviors.

704 Cost Savings Modeling of Telehealth Services for Hepatitis C Virus Infection, Cherokee Nation

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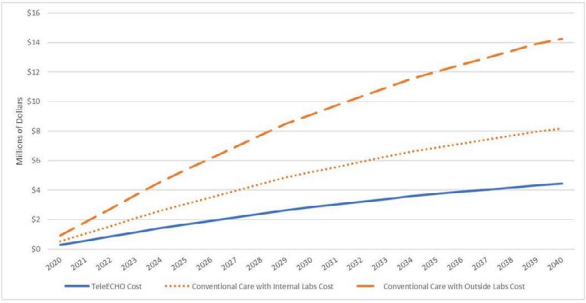
Background: American Indian and Alaska Native (AI/AN) people are disproportionately affected by hepatitis c virus (HCV) infection with the highest rate of acute HCV infection (2.7 per 100,000) and HCV-related mortality (10.17 per 100,000) compared with other races in the US. Telehealth programs using the Extension for Community Healthcare Outcomes (ECHO) Model® are effective in delivering HCV care. Cherokee Nation Health Services (CNHS) initiated ECHO to support HCV care in 2014, utilizing Indian Country ECHO's holistic, collaborative teleECHO model that emphasizes whole-person versus disease-specific care and treatment.

Methods: This study assessed cost savings of implementing CNHS' HCV ECHO compared to conventional care. The conventional care scenario modeled the costs of the HCV care program prior to adoption of ECHO, in which a patient receives in-person treatment by a specialist via referral. The ECHO scenario modeled the costs of ECHO, including laboratory tests, personnel, and other direct program components. The total cost of HCV care for both scenarios was calculated on an annual basis and compared. Costs of care via ECHO and conventional care were estimated based on CNHS financial records and publicly available data. Projections on HCV prevalence, treatment, and outcomes were based on de-identified CNHS electronic medical record data among individuals with an HCV RNA test from 2016 through 2020. Demographic estimates of population and trends were taken from US Census data to model HCV treatment and outcomes by age and sex through 2040, 10 years beyond the 2030 US national HCV elimination goal.

Results: Costs of HCV medical services per patient via ECHO were 69% lower than conventional care. ECHO was projected to have total cost savings of over $6 million in 10 years and nearly $10 million in 20 years based on $3,122 cost savings per patient. ECHO provided substantial short- and long-term cost savings for HCV services in CNHS.

Conclusion: ECHO provided substantial cost savings for HCV care provision in Cherokee Nation. Clinical sites serving communities with limited healthcare access, including rural and AI/AN communities, may consider ECHO as a model for increasing treatment and achieving cost savings for delivering HCV care.

Figure 1. Estimated cumulative costs of HCV care via ECHO and conventional care (with both outside and internal laboratory costs), Cherokee Nation Health Services, 2020-2040



705 Using County Notification Data to Characterize Recently Reported Hepatitis C Cases, Los Angeles

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Background: Hepatitis C remains a public health problem with continued incidence and a high proportion of individuals either unaware of their infection or untreated. Using the Los Angeles County hepatitis C registry of notified cases, the University of Southern California and the Los Angeles County Department of Public Health established a novel HCV case-management program. We describe the characteristics of contacted cases and the frequency and correlates of treatment.

Methods: Volunteer study case-workers contacted Los Angeles County residents with a positive HCV RNA test result reported to the Department of Public Health between January 2021 and April 2022 to assess awareness of their infection status, verify treatment, and counsel untreated cases. We evaluated bivariate associations of race/ethnicity, age, biological sex, insurance status (private, public (Medicare, Medical), and none), and symptomatic status (symptoms vs no symptoms) with treatment status (treated vs. untreated) using a Pearson's Chi-Square Test. We created a multivariable logistic regression model to assess associations between demographic and clinical characteristics and treatment status.

Results: Among 403 cases contacted, 227 (56%) had public insurance, 254 (63%) were male, 230 (57%) were 45+ years old, and 181 (45%) were Hispanic or Latino. Eighty-five percent were aware of their positive HCV result, yet 68% never received treatment. Untreated cases (N=295) were predominantly male (65%) and non-White (76%). No statistically significant differences between treatment status existed for race/ethnicity and sex. The multivariable logistic regression model showed public insurance status (vs private odds ratio [OR]: 0.56; 95% CI: 0.32, 0.98), older age group (vs young adults 18-29 years OR: 3.17, 95% CI: 1.23, 8.18), and the existence of symptoms (vs no symptoms OR: 3.70; 95% CI: 2.15, 6.64) were associated with treatment.

Conclusion: HCV case registry data can be used to inform people about their infection, assess treatment status and counsel untreated cases. Those publicly insured, younger, and asymptomatic were less likely to be treated. Local health departments should use case registry data to help accelerate HCV elimination efforts.

706 A Model to Eliminate Viral Hepatitis Infection in Migrants: A Prospective Study in Southern Italy

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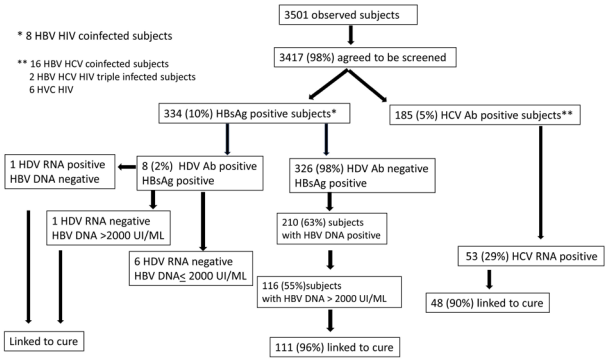
Background: Migrants born in intermediate and high HBV and HCV-prevalence countries are likely to be at an increased risk for HBV and HCV infection. Data on HCV and HBV prevalence in migrants living in Italy are scanty and there are few screening and linkage-to-care programs for this target.

Methods: A prospective, multicenter, based on the long-term active cooperation between two 3rd level units of Infectious Diseases and four 1st level clinical centers in southern Italy (Naples and Caserta) was designed. The

study started in June 2018, was stopped in February 2020, and was resumed in February 2021 until November 2021. All migrants > 18 years old consecutively evaluated for clinical consultation at one of the first-level centers were enrolled. An anonymous serological screening was offered to seek HIV, HBV and HCV. The participants who were positive for a virus hepatitis infection and or for HIV were referred for linkage to cure at one of the tertiary units.

Results: In the study period we observed 3,501 migrants; 3,417 (97.6%) agreed to be screened. Of the 3,417 subjects screened 185 (4.7%) were anti-HCV-positive, 334 (10%) were HBsAg positive, 61 (1.7%) HIV Ab positive. Of the 334 HBsAg positive subjects (figure 1), 116 (55%) had HBV DNA over than 2000 UI/ML. Of the 116 subjects with HBV DNA over than 2000 UI/ML, 111 (96%) had chronic hepatitis, 3 (2%) had cirrhosis and 2 (1.7%) had HCC; all subjects with HBV DNA over than 2000 UI/ML were linked to cure but 3 (2%) lost to follow up. Eight subjects (2%) were HDV Ab positive, but only one were HDV RNA positive, genotype 1 and was linked to cure. Of the 185 HCV ab subjects, 53 (29%) were HCV-RNA-positive. Of the 53 HCV-RNA-positive-subjects, 48 (90%) were linked to cure, 5 (10%) refused. Of these 48, 16 (33.3%) harboured HCV genotype 1b, 11 (22.9%) genotype 1a, 16 (33.3%) genotype 3, 3 (6.3%) genotype 4 and 2 (4.2%) genotype 2. All the 48 HCV-RNA-positive patients started DAA-regimen with sofosbuvir/velpatasvir and completed the 12 weeks of treatment. Of these 48 subjects, 47 (97.9%) showed a sustained virologic response (SVR) at 12 and at 24 weeks after treatment and one dropped-out in follow-up after finishing the DAA treatment.

Conclusion: After an educational phase on the route of transmission and treatment availability, nearly 98% of subjects agreed to be screened and evaluated for hepatitis virus infections, so our model seems useful in the viral hepatitis screening, linkage-to-care and treatment in a difficult to manage population.



707 Hepatitis C Screening in the Emergency Department: The Multi-Center DETECT Hep C Clinical Trial

Jason Haukoos[1], Sarah E. Rowan[1], Emily Hopkins[1], James Galbraith[2], Richard E. Rothman[3], Yu-Hsiang Hsieh[3], Stephanie Gravitz[1], Kevin Kamis[4], Carolynn Lyle[1], Michael S. Lyons[5], Douglas White[6], Alia Al-Tayyib[4], Edward Gardner[1], David L. Wyles[1], for the DETECT Hep C Screening Trial Investigators
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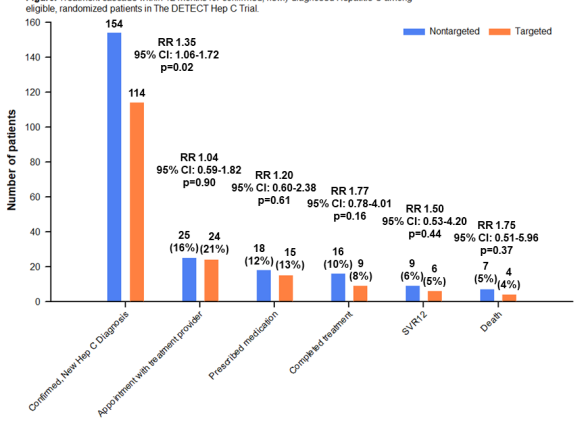
Background: Testing for hepatitis C (HCV) is the first step toward ultimately curing HCV infection and preventing transmission. Emergency departments (EDs) are key clinical settings for screening given that they serve at-risk patients who commonly do not access healthcare elsewhere. Determining the best approach to HCV screening in ED settings is imperative to maximize the benefit of this public health intervention. The goal of this study was to evaluate the effectiveness of HCV screening in EDs with the hypothesis that nontargeted screening is significantly associated with identification of new diagnoses when compared to targeted screening.

Methods: Design & Setting: Prospective multi-center randomized pragmatic trial in EDs in Denver, CO, Baltimore, MD, and Jackson, MS. Population: Patients ≥18 years of age presenting for ED care. Exclusions: critical illness, inability to consent, prior HCV diagnosis. Interventions: Eligible patients underwent concealed randomization as part of routine care to either nontargeted screening, where all were offered HCV testing, or targeted screening, where all were asked risk questions and any affirmative response led to an offer for HCV testing. Screening was fully integrated into ED care using opt-out consent; antibody positive tests were followed by reflex RNA testing. Outcomes included newly diagnosed HCV (RNA-detected) and elements of the HCV care continuum through 12 months of follow-up. Analyses: Intention-to-treat, chi-square, and risk ratios (RRs) with 95% confidence intervals (CIs).

Results: From 11/19/2019 through 8/4/2022, 147,498 eligible patients were randomized with excellent balance of characteristics. Of the 73,651 allocated to targeted screening, 23,339 (31.9%) were identified as high risk, 7,110 (30.4%) accepted testing and 4,634 (65.3%) completed testing, resulting in 114 (2.5%) new diagnoses. Of the 73,847 allocated to nontargeted screening, 16,516 (22.5%) accepted testing and 9,825 (59.5%) completed testing, resulting in 154 (1.6%) new diagnoses. Compared to targeted screening, nontargeted screening was significantly associated with new diagnoses (RR 1.35, 95% CI 1.06-1.72, p=0.02). Small proportions had treatment appointments, initiated and completed treatment, or attained SVR12 (Figure).

Conclusion: Nontargeted HCV screening was superior to targeted screening for identifying newly diagnosed HCV in the ED. The significant decay from diagnosis to SVR12 suggests innovative models of HCV treatment from the ED are needed.

Figure. Treatment cascade within 12 months for confirmed, newly diagnosed Hepatitis C among eligible, randomized patients in The DETECT Hep C Trial.



708 Navigation is Superior to Clinician Referral for Linkage to HCV Care from the Emergency Department

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Background: Emergency departments (EDs) serve as important clinical settings for hepatitis C (HCV) screening and care, yet optimal methods of linkage-to-care for HCV-diagnosed individuals remain unknown. The goal of this study was to test the effectiveness of linkage navigation (LN) and clinician referral (CR) among ED patients identified with untreated HCV with a primary hypothesis that LN plus CR is superior to CR alone.

Methods: We performed a prospective two-arm parallel-group comparative effectiveness randomized trial at Denver Health Medical Center among ED patients with untreated HCV. Participants were randomized in a concealed fashion to CR alone or CR plus LN. All participants provided informed consent. Individuals in the CR arm were educated about HCV by their primary ED clinician and given information on how to access HCV care verbally and in discharge instructions. Individuals in the LN arm met with a linkage navigator in the ED or by phone after the visit. The LN reiterated basic HCV education and helped schedule and facilitate HCV treatment appointments. Pre-specified outcomes, collected in a blinded manner, were initiation of HCV treatment (primary), appointment with an HCV clinician, completion of treatment, and sustained virologic response 12 weeks after treatment (secondary) at 6 months post-enrollment. Analyses were performed using intention-to-treat with differences, precision estimates, and bivariate hypothesis testing.

Results: From November 2019 through January 2023, 280 individuals were randomized with excellent balance in baseline characteristics, including individuals <40 years of age or with recent injection drug use (IDU). Individuals in the LN arm were significantly more likely to link to care (Δ = 18%, p=0.0004) and initiate treatment (Δ = 11%, p=0.01). More individuals in the LN arm

completed treatment though this was not statistically significant (Δ = 7%, p=0.09) (Table). Among participants <40 years or with recent IDU, treatment initiation did not differ between arms (p=0.75).

Conclusion: Among ED patients with untreated HCV, early follow-up suggests that LN in addition to CR is superior to CR-alone for initiating HCV treatment, but additional follow-up is needed to better understand the effect of a linkage navigator on the downstream elements of the HCV continuum, including treatment completion and cure, and cost effectiveness of employing a navigator. Even with a navigator, linkage rates were low suggesting new approaches to HCV treatment initiation are needed.

Table. 6-month outcomes for patients with untreated HCV enrolled in the DETECT Hep C Linkage-to-Care Trial

	Linkage Navigation + Clinician Referral N = 142		Clinical Referral N = 138				
	n	(%)	n	(%)	Δ (%)	(95% CI)	p
Linked to care for Hep C	46	(32.4)	20	(14.5)	+17.9	(+8.2 – +27.6)	0.0004
Initiated Hep C treatment	31	(21.8)	15	(10.9)	+11.0	(+2.4 – +19.5)	0.01
Completed Hep C treatment	24	(16.9)	14	(10.1)	+6.8	(-1.2 – +14.7)	0.10
Documented SVR12*	2	(1.4)	0	(0)	+1.4	(-0.5 – 3.3)	0.16

Abbreviations: CI, confidence interval; Hep C, hepatitis C; SVR12, sustained virologic response at 12 weeks
*SVR12 defined as an undetectable HCV RNA 12 weeks after completing treatment

709 Peripartum Linkage to Care in Hepatitis C: Infant Testing and Maternal Treatment

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Background: There is an increase in hepatitis C virus (HCV) infection due to injection drug use and poor access to care. Ohio had an 89% increase in HCV in women of childbearing age between 2010 and 2015 with children born to HCV-infected women increased 68%. HCV testing of infants is recommended at 18 months of age but testing and follow-up are poor. Between 2011-2013 only 16% of eligible infants in Philadelphia received appropriate testing. Maternal linkage to care and treatment are also inadequate, with rates commonly less than 20% Improvements in linkage to care as well as testing and treatment are needed.

Methods: Fifty-four pregnant women with chronic HCV infection were recruited from outpatient clinics in Ohio and West Virginia. Eligible participants were 18 or older with singleton pregnancy up to 36 weeks. Hepatitis B coinfection, active drug use and severe medical comorbidities were exclusionary. After written informed consent, participants were educated about HCV and were seen up to seven times (enrollment, 36 weeks gestation, and 12, 24, 36 and 48 weeks postpartum). All participants were offered once daily sofosbuvir-velpatasvir for 84 days at 24 weeks postpartum. Cessation of breastfeeding and negative pregnancy test were confirmed prior to treatment. Three maternal blood samples were collected (36 weeks as well as at 28- and 48-weeks postpartum) while infant blood samples were collected at 12, 24, and 48 weeks postpartum. All maternal and infant testing was performed simultaneously at co-localized appointments.

Results: Data were available for 49 mothers and 30 infants. All had a history of injection drug use; none reported use during the study. Fifty-two were White and two were Black per self-report; one participant was co-infected with HIV. Due to non-adherence, placement in foster care, and COVID19 related shutdowns, 23 of 30 (77%) of infants were tested, yielding 23 evaluable mother-infant pairs. Of these, 5 infants (22%) completed three study visits, 7 (30%) completed two visits, and 11 (48%) completed one visit. 28 of 54 subjects (52%) were successfully linked to care and completed treatment; all had undetectable HCV RNA at end of treatment. Of the 10 subjects tested 12 weeks after completion of treatment, all had undetectable HCV RNA. One infant had detectable HCV RNA (1/23 - 4%).

Conclusion: Co-localization results in increased rates of linkage to care and successful treatment while the observed 4% vertical transmission rate is within previously described rates.

710 Intracellular Sofosbuvir Concentrations in Pregnant Women With Hepatitis C Virus

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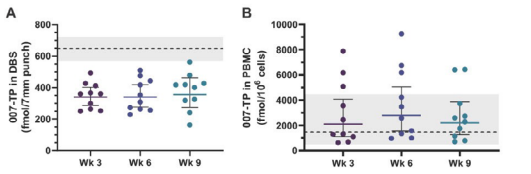
Background: Treatment of hepatitis C virus (HCV) during pregnancy could cure maternal HCV during antenatal care engagement and prevent perinatal HCV transmission. We previously showed plasma sofosbuvir (SOF) exposures were 38% higher during pregnancy, whereas as the inactive metabolite of SOF (007) was 38% lower compared to non-pregnant women. SOF is converted into its active form, 007-triphosphate (007-TP), within cells and can be used as a surrogate of activation in other tissue types and adherence markers. Our objectives were to describe 007-TP concentrations in dried blood spots (DBS) and peripheral blood mononuclear cells (PBMCs) during pregnancy.

Methods: In this open-label, phase 1 study, HIV-negative pregnant women with chronic HCV infection were enrolled between 23-25 weeks' gestation and were treated with SOF 400mg/velpatasvir (VEL) 100mg daily for 12 weeks. DBS and PBMCs were collected pre-dose at 3, 6 and 9 weeks of treatment. 007-TP in DBS (1x7mm punch) and PBMCs (normalized to 10^6 cells) were measured using validated LC/MS-MS methods. Results were summarized using descriptive statistics. Comparisons to 007-TP concentrations measured in non-pregnant persons with HCV and adherence monitoring were also performed (NCT02573376).

Results: Data were available in 10 pregnant people (9 white, 1 Black; median (range) age 31 (25-29) years and weight 75.5 (64.6-102.3) kg). Median (range) serum creatinine, glomerular filtration rate, and hematocrit were 0.5 (0.4-0.6) mg/dL, 126.1 (122.3-140.8) mL/min/1.73 m^2, and 36.1% (33.2-37.8%), respectively. Geometric mean (95% CI) 007-TP in DBS were 340 (287, 403), 340 (278, 418), and 356 (275, 461) fmol/punch at weeks 3, 6, and 9 (A). Geometric mean (95% CI) 007-TP in PBMCs were 2111 (1096, 4066), 2808 (1559, 5058), and 2212 (1267, 3864) fmol/10^6 cells at weeks 3, 6, and 9 (B). In comparison to non-pregnant adults (n=58), 007-TP concentrations in PBMCs were comparable or higher, whereas 007-TP in DBS were ~50% lower in pregnancy.

Conclusion: Though 007-TP concentrations were altered in pregnancy, the efficacy of SOF/VEL in this trial was unaffected (100% of those that attended the final maternal visit were cured [n=8]). The decreased concentrations in DBS could be due in part to physiologic hemodilution of pregnancy. Thus, if DBS samples were used to measure adherence in trials, they would need to be adjusted. An international, multicenter trial evaluating the safety and efficacy of SOF/VEL treatment in pregnancy is underway (NCT05140941).

Figure. 007-TP Concentrations in DBS (A) and PBMCs (B) during SOF/VEL treatment in pregnant women with HCV.



Data presented as geometric mean (95% CI). Dotted lines with gray shading reflect mean (95% CI) concentrations in non-pregnant persons on ledipasvir/SOF (n=58 participants).

711 Transfer of Sofosbuvir/Velpatasvir Into Breast Milk

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Background: Treatment of hepatitis C virus in the postpartum period is delayed until after the completion of breastfeeding due to lack of data on infant exposure and safety. Our objectives were to describe breast milk transfer of sofosbuvir (SOF), GS-331007 (SOF inactive metabolite) and velpatasvir (VEL) in postpartum women being treated for HCV with SOF/VEL who were not intending to breastfeed.

Methods: Women undergoing postpartum HCV treatment with SOF 400mg/VEL 100mg daily for 12 weeks and willing to provide pumped breast milk

were eligible for the study. SOF/VEL treatment was started within 36 hours of delivery. Paired maternal blood and breast milk were obtained at 2 or more pharmacokinetic (PK) visits. VEL, SOF and GS-331007 concentrations in plasma and breast milk were measured using validated UPLC-MS/MS assays (LLOQ 5 ng/mL for VEL in plasma and breast milk and SOF/007 in plasma; 1 ng/mL for SOF/007 in breast milk). The infant daily dose was calculated using drug concentrations in the milk and considering that the amount of milk ingested by an exclusively breastfed infant is 150 mL/kg/day and reported relative to the adult dose normalized to 70 kg weight and the child dose normalized to 13 kg weight. Data were summarized using descriptive statistics.

Results: Four participants were enrolled with a median (range) age of 29.5 years (27-36); 3 white, 1 multiple races; all were multiparous with median (range) weight of 69 kg (58-88) and median creatinine of 0.5mg/dL range (0.5-0.6). The participants had their first PK visit within 24 hours of initiating SOF/VEL and had 2 to 7 PK visits each yielding a total of 17 paired samples for analysis occurring a median (range) time of 1.99 days (0.19-6.13) after treatment start. VEL and GS-331007 were quantifiable in all paired samples; SOF was quantifiable in 9 breast milk and 7 plasma samples due to its short half-life (Table). SOF, GS-331007, and VEL concentrations in the breast milk were lower than maternal plasma concentrations. The estimated infant daily dose from breastmilk is less than 0.7% of the daily dose in an adult and a child adjusted to weight.

Conclusion: Based on our findings, exposure to SOF/VEL via breastmilk is minimal and reassuring for infant safety and low potential for development of HCV resistance with perinatal transmission. Clinicians should consider expedited HCV treatment in the postpartum period during breastfeeding to improve linkage to HCV care.

Table: SOF, GS-331007, and VEL concentrations in mother and breastmilk[1]

Drug	Milk concentration (ng/mL)	Plasma concentration (ng/mL)	Milk/plasma concentration ratio	Estimated infant daily dose from breastmilk (mg/kg/day)	Relative adult dose[2]	Relative child dose[3]
Sofosbuvir	11.1 (1.3, 60.1)	104.1 (22.4, 237.9)	0.13 (0.04, 0.98)	0.0017 (0.0002, 0.009)	0.029% (0.003%, 0.158%)	0.014% (0.002%, 0.078%
GS-331007[4]	5.4 (1.8, 15.0)	561.8 (183.9, 1145.5)	0.012 (0.005, 0.027)	0.0008 (0.0003, 0.0023)	0.029% (0.010%, 0.080%)	0.014% (0.005%, 0.040%
Velpatasvir	26.8 (6.6, 59.7)	90.20 (19.3, 146.7)	0.41 (0.10, 0.55)	0.0040 (0.0010, 0.0090)	0.282% (0.069%, 0.627%)	0.140% (0.034%, 0.310%)

[1]Concentrations, ratio, estimated dose, and relative dose shown as median (minimum, maximum)

[2]Adult dose of SOF 400mg/VEL 100mg normalized to 70 kilograms

[3]Child dose of SOF 150mg/VEL 37.5mg normalized to 13 kilograms

[4]SOF dose converted to 007 equivalents

712 Validation of a Point-of-Care Test Based on RT-LAMP for HCV Detection by Capillary Sampling

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Background: Every year, 1.5 million people suffer a new infection by HCV, and nearly 58 million people worldwide live with a Hepatitis C chronic infection [World Health Organization (WHO), June 2022]. To overcome the underdiagnosis of HCV among hard-to-reach population and accomplishing WHO's target of Hepatitis C virus (HCV) elimination by 2030, it is essential to develop new rapid and easy-to-use molecular diagnostic systems with similar performance values to the gold standard qRT-PCR. Loop-Mediated Isothermal Amplification (LAMP) arises as a promising tool for point-of-care (POC) molecular detection of viral diseases. In this work, we have validated a new diagnostic tool based on fluorescent reverse transcriptase (RT) LAMP technique, detecting HCV RNA directly from capillary blood samples in less than 50 minutes.

Methods: 125 samples from HCV infected patients [116 serum samples (genotypes 1 to 4) and 9 fresh blood samples], 27 individuals who tested negative for HCV but positive for HIV, and 11 healthy controls were analysed. Serum was collected from 50 µL of blood samples by 5 min centrifugation, incubated in lysis buffer for 10 min, and then mixed with RT-LAMP reagents. RT-LAMP reactions were run in parallel with two different primer sets: HCG124, a set of 9 primers designed to detect HCV genotypes 1, 2, or 4; and HCDN-G3, a set of 6 specific primers for genotype 3. Reaction mix was first incubated at 45ºC for 10 minutes for reverse transcription, and shifted to 68ºC for 40 minutes for LAMP reaction. Sybr-green fluorescence signal was recorded in real time.

Results: HCG124 and HCDN-G3 primer sets detected HCV RNA in 109/116 HCV positive serum samples and in 8/9 HCV positive blood samples in less than 40 minutes. This new RT-LAMP system has a sensitivity level of 94% and 100% specificity. The limit of detection of the present system is 550 - 1000 IU/mL, lower than WHO recommended limit for HCV POC testing (3000 IU/mL). Real time measurements could be substituted by a single end-point measurement at 40 minutes using a portable fluorescent reader at POC.

Conclusion: RT-LAMP system has showed to be highly sensitive and specific for molecular detection of HCV from less than 50 µL blood sample, easily collected by capillary punction and without a prior RNA purification step. Within less than 50 minutes, an active HCV infection can be detected at POC, implementing screening strategies among vulnerable populations as a crucial step towards HCV elimination goal.

713 Prevalence and Resistance Profiles of "Unusual" HCV Subtypes in Italy

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Background: Recent data show that "unusual" hepatitis C virus (HCV) subtypes have lower responses to direct-acting antivirals (DAAs) compared to most prevalent subtypes. We aimed to investigate the prevalence and resistance profiles of "unusual" HCV subtypes in Italy.

Methods: Clinical and virological data of "unusual" HCV genotype (GT)/subtypes (defined as GT1 non-1a/b, GT2 non-2a/b, GT3 non-3a, GT4 non-4a/d) were analyzed within the Italian VIRONET-C database. Subtype assignment was confirmed by phylogenetic analyses on NS3±NS5A±NS5B sequences. The prevalence of resistance associated substitutions (RASs) was evaluated according to Sorbo et al 2018 list.

Results: Out of 3554 individuals with an available NS3±NS5A±NS5B sequence, 282 (8%; median age [IQR], 73 [57-81]years; 58% males) were infected with "unusual" subtypes (GT1g/i/l=3/1/2; GT2c/j=247/2; GT3b/g/h/k=1/1/8/1; GT4c/i/l/m/n/o/r/v=1/1/1/1/3/5/3/1). Subtype distribution varied according to ethnicity, with GT2c and GT3h most prevalent in Italians (88-100%), other "unusual" GT3 in Asians (75%), and "unusual" GT1 and GT4 in Africans (78%). 206 individuals (73%) were DAA-naïve, while 76 were DAA-failures (27%), in particular 36 with a recommended regimen (22 glecaprevir/pibrentasvir and 14 sofosbuvir/velapatasvir±ribavirin). The patients infected with GT3 unusual subtypes were more prone to failure (91%, 10/11) followed by GT4 (44%, 7/16), GT2 (23%, 58/249) and finally GT1 (17%, 1/6). All failed patients (except one with GT4n) displayed at least one RAS in at least one protein (Figure 1). The number of RASs in each protein varied by GT, subtype and treatment exposure. Overall, NS5A-RASs were most prevalent, with complex patterns in both DAA-naïve and failures, NS3-RASs were less prevalent but present in all GT3 failures, while NS5B-RAS were rare and present across GT2-GT3-GT4, with variable patterns. NS5A-RASs at position 93 (H/F/S) were detected only at failure in GT3h/k and GT4o/v. Few patients had NS3-RASs, only at failure (3/3 GT3h:80R or 158V; 4/24 GT2c:56Y/H±168V/A).

Conclusion: In this Italian setting, GT1-GT4 unusual subtypes were frequent, predominated by GT2c in Italians, and with failure rates highest within GT3. Most DAA-failures carried complex NS5A-RAS patterns, some conferring high-level of resistance. These results advise for closer surveillance and further studies to better characterize the impact of "unusual" HCV subtypes on DAA efficacy.

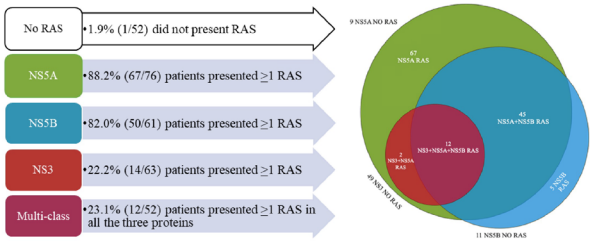

Figure 1: The arrow (left) and Venn (right) diagrams show the prevalence and frequencies of at least 1 RAS (resistance associated substitution) in NS5A, NS3, and NS5B among the 76 patients infected with unusual HCV subtypes who failed several DAA regimens.

714 Simultaneous Start Strategy With BIC/FTC/TAF in Individuals With HIV/HCV Coinfection in China

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Background: Highly Active Antiretroviral treatment (ART) with Direct-acting antiviral agents (DAAs) has demonstrated high efficacy and favorable safety profile in HIV/HCV co-infected individuals with HIV viral suppression and stable immune status. However there is great need in rapid initiation of ART and anti-HCV treatment regardless of HIV viral suppression status and CD4 T cell count as a simplified treatment strategy-To "Simultaneous Start" treatment for both HIV and HCV.
Methods: We conducted a retrospective, single-center study in Southwest China from May 2021 to August 2023. The study aimed to evaluate effectiveness and safety of immediate initiation or switch to bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) with sofosbuvir/velpatasvir (SOF/VEL) administered once daily respectively in PWH(people with HIV) with recent acquired HCV. The primary endpoints were HIV and HCV viral suppression rate, defined as HIV RNA <20 cp/mL at 12 weeks and HCV RNA <15 IU/mL at 24 weeks after the end of HCV-treatment (SVR24).
Results: Of the 128 patients enrolled, mean age of 36 years (31-39, IQR), 77% male (n=99). 52 were ART naive (TN), 76 were ART experienced (TE). The baseline characteristics were summarized in Table 1. All patients achieved HIV RNA suppression at 12 weeks and 36 weeks, 98.4% (126/128) patients achieved HCV SVR24. Among individuals with baseline CD4 T cell count < 200 cells/mm^3 (n=32, 25%) , all achieved SVR 24. And 98% (94/96) of those with baseline CD4 cell count > 200 cells/mm^3 (n=96, 75%) achieved SVR 24. The two patients who did not achieve SVR24 were PWID(people who inject drugs) infected with HCV genotype 3, had cirrhosis and poor adherence. Nine HBV/HCV/HIV co-infected patients maintained or achieved HBV DNA undetectable at 12 weeks and 36 weeks of treatment. No patient discontinued treatment due to adverse events.
Conclusion: \Immediate initiation or switch to BIC/FTC/TAF with SOF/VEL treatment provided high HIV and HCV suppression rate with a favorable safety profile. The study suggests that HCV treatment can start immediately without waiting for the CD4 T cell count to exceed 200 cells/mm^3 in HIV/HCV co-infected individuals. This simplified "Simultaneous Start" treatment may be a feasible and easy treatment strategy for HIV/HCV co-infected individuals.
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715 Similar Mortality Among Individuals With HIV/HCV-Coinfection and HCV-Monoinfection After SVR

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Background: The life expectancy of the patient with controlled HIV infection is similar to that of individuals without HIV infection. In patients with chronic HCV infection, the impact of HIV coinfection on their clinical course after SVR is not sufficiently clarified. Some studies point to a higher mortality in the setting of HIV/HCV-coinfection, while others find no difference.
Methods: Multicenter cohort study (GEHEP-011 Cohort-clinicaltrials.gov ID: NCT04460157-) including individuals with HIV/HCV coinfection or HCV-monoinfection from 18 Spanish hospitals. They met: 1) Liver stiffness measurement (LMS) ≥9.5 kPa before treatment; 2) SVR with a DAA-based regimen; 3) LSM at SVR. The main outcome was overall survival. Mortality attributable to liver disease and non-hepatic causes was also assessed. The propensity score (PS) for HIV was calculated. The association between the main variable and the various parameters analyzed was assessed by the log-rank test in the bivariate analysis and by multivariate Cox regression, including PS as a covariate.
Results: 1,119 patients (HIV/HCV: 677; HCV: 442) were included. The median follow-up from the time of SVR of individuals with HIV/HCV-coinfection and HCV-monoinfection 78 and 73 months, respectively. There was no significant difference in the proportion of pre-treatment individuals with cirrhosis (HIV/HCV: 62%, HCV: 57%, p=0.135) nor in LSM, Child category or MELD score at the time of SVR. Among people with HIV, 98% had an HIV viral load<200 c/mL at SVR and the median (Q1-Q3) CD4+ cell count was 573 (352-786) cells/mm^3. After SVR, 46 (10%) HCV-monoinfected and 74 (11%) HIV/HCV-coinfected patients died. Thirty-three patients died of liver disease, 1 of AIDS and 86 of other causes. The overall survival rate at 5 and 7 years was, respectively: HCV: 89% and 86%; HIV/HCV: 90% and 87% (p=0.707). There was no difference in hepatic and non-hepatic mortality between the two subpopulations. In multivariable analysis adjusted for age, sex, HIV infection and PS, independent predictors of all-cause death were age, MELD index and LSM at the time of SVR, but not HIV infection (HR [95% CI]: 1.01[0.67-1.53]; p=0.970].
Conclusion: In patients with HCV infection, HIV coinfection does not reduce overall survival or mortality attributable to hepatic and non-hepatic causes after SVR. Differences in the control of HIV infection or in other survival-limiting factors could explain the disparity in the data found in the different cohorts.

716 Direct-Acting Antivirals and Risk of Hepatocellular Carcinoma in People With HIV/HCV Coinfection

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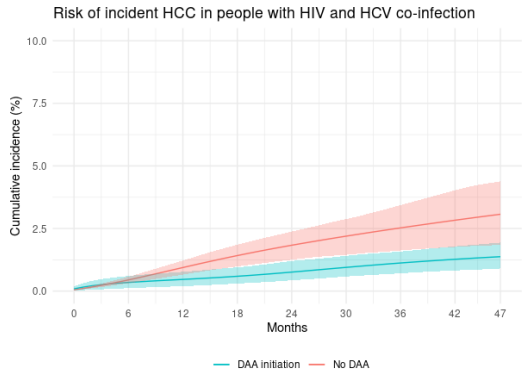
Background: Hepatitis C virus (HCV) infection is a leading cause of hepatocellular carcinoma (HCC). While direct-acting antivirals (DAA) cure ~95% of individuals with HCV, precise estimates of HCC risk and of risk trends post-DAA are urgently needed to inform HCC surveillance. We aimed to estimate the effect of DAA treatment on HCC risk in people with HIV/HCV co-infection and advanced liver fibrosis or cirrhosis.
Methods: We emulated a target trial using data on individuals with HIV/HCV from HepCAUSAL, a collaboration of 12 cohorts from Europe and North America. The eligibility criteria were: HIV infection, chronic HCV infection, advanced liver fibrosis or cirrhosis (clinical cirrhosis diagnosis, liver stiffness ≥9.5 kPa, or FIB-4 ≥3.25), DAA naïve, HIV-RNA <200 copies/mL, on antiretroviral therapy, no hepatitis B virus co-infection, and no previous HCC diagnosis or liver transplant. The treatment strategies were DAA initiation versus no DAA use during the follow-up. The outcome was incident HCC. We emulated a sequence of trials starting each month between Jan 2013 and Dec 2022 and individuals could be eligible in and contribute follow-up to multiple trials. We censored individuals in the no DAA group if/when they initiated DAA. We estimated the 4-year cumulative incidence of HCC under the two DAA strategies with adjustment for confounding and loss to follow-up via inverse probability weighting.
Results: Of 3,871 eligible individuals (87% males, median age of 56 [IQR: 50,61]), 71% initiated DAAs and 108 had an incident HCC diagnosis. These individuals contributed on average to 19 trials. The estimated 4-year HCC risk was 1.37% (95% CI: 0.90, 1.94) in the DAA group and 3.07% (95% CI: 1.84, 4.38) in the no DAA group, corresponding to a risk difference of -1.69% (95% CI: -3.16, -0.20) and a risk ratio of 0.45 (95% CI: 0.24, 0.89). In the DAA group, the risk of HCC was approximately constant over time (Figure) with a mean annual incidence of 0.35% (95% CI: 0.17, 0.59).
Conclusion: We estimated that DAA reduces the 4-year HCC risk by 2% on an absolute scale and 55% on a relative scale in people with HIV/HCV co-infection and advanced fibrosis or cirrhosis. The annual HCC risk after DAA initiation was close to the threshold (0.4%) beyond which HCC surveillance is deemed cost-effective, which suggests that continued post-cure HCC monitoring is warranted in this population.



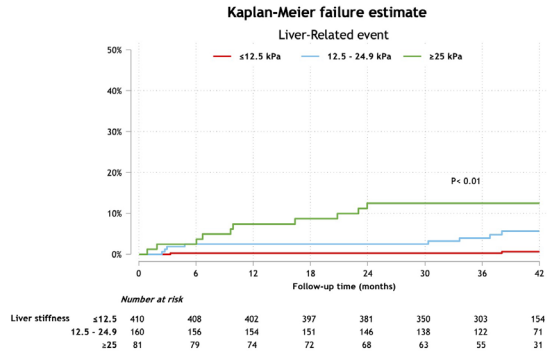


Figure. Cumulative incidence plots of liver-related events for different liver-stiffness cutoffs determined 1 year after the finalization of DAA therapy in HCV-coinfected PWH with advanced fibrosis or compensated cirrhosis

717 Predictors of Liver-Related Events Following DAA HCV Cure in PWH With Advanced Fibrosis/Cirrhosis

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Background: We assessed prognostic factors of liver-related events (LRE) among HCV-coinfected PWH with advanced fibrosis (AF) or compensated cirrhosis (CC) with SVR following all-oral direct antiviral therapy (DAA-Rx).

Methods: We leveraged 3 prospective observational studies in Spain to select coinfected PWH with AF (biopsy confirmed F3 or liver stiffness [LS] value > 9.9 and ≤ 12.5 kPa) or CC (biopsy confirmed or LS > 12.5 kPa) with SVR following DAA-Rx from 2014 to 2017. The primary outcome was an LRE: decompensation (DEC) or hepatocellular carcinoma (HCC), whichever occurred first after the finalization of DAA therapy. Independent variables (based on the underlying conceptual framework) included liver disease category, age, sex, smoking, alcohol abuse, methadone use, prior clinical AIDS, CD4+ T-cell count, albumin concentration, metabolic syndrome, TyG and HSI indexes, and values of LS and FIB4 at baseline and 1 year after finalization of DAA therapy (1-yr). Multivariable competing-risk regression analyses with multiple imputations by chained equations for missing data were used to assess the effect of the independent variables on the outcomes. We used ROC curves to determine the diagnostic capacity of LS to predict LRE with the selection of the optimum cutoff value according to Youden's J statistic.

Results: 1,145 PWH (384 AF and 761 CC) were included. After a median follow-up of 41 months, 60 patients died, 24 had DEC, and 21 developed HCC. The risk of LRE was higher among those with CC than those with AF, but no statistically significant differences in overall and cause-specific mortality were found between groups. Albumin concentration (aSHR [95% CI] 0.55 [0.35 – 0.87]) per g/L increase) and 1-yr LS values (aSHR [95% CI] 1.04 [1.01 – 1.09] per kPa increase) were the only factors independently associated with the risk of LRE. The best cutoff value of 1-yr LS to predict LRE was 12.5 kPa (NPV: 99.5% [95% CI: 98.2 – 99.9]). For each 5 kPa increase above this cutoff, the HR of LRE was 1.34 (95% CI, 1.24 – 1.45). When we took the 12.5 kPa cutoff as the reference, the HR of LRE in patients with LS values of 12.5-24.9 kPa and ≥ 25 kPa were 11.45 (95% CI, 2.48 – 52.82) and 26.49 (95% CI, 5.79 – 121-22) respectively (Figure).

Conclusion: Albumin concentration and 1-yr LS values after the finalization of a successful DAA therapy were identified as independent predictors of LRE among HCV-coinfected PWH with AF or CC. The best cutoff value of 1-yr LS to predict LRE was 12.5 kPa.

718 Immunophenotypic Profile Modifications After Spontaneous HCV Clearance or DAA Treatment in PWHIV

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Background: Acquisition of HCV is frequent among people with HIV (PWHIV), an event that profoundly modifies the natural history of both infections. Our goal was to analyze whether HCV clearance by direct-acting antivirals (DAAs) after chronic infection can partially restore both molecular and cellular immune profile to levels similar to those found in PWHIV. In addition, we explored whether changes over time in these patients were similar to those found in patients who cleared HCV spontaneously after acute infection.

Methods: We performed a longitudinal observational study in 88 PWHIV: i) 31 with active chronic HCV infection (CHC) prior to starting DAA therapy and 48 weeks after achieving sustained virological response (SVR); ii) 25 who previously cleared HCV spontaneously (AE); iii) 32 controls (HIV) never infected with HCV. Both AE and HIV also were follow-up 48 weeks after first sample. A total of 27 CD4+ and CD8+ peripheral T cell subsets were assessed by spectral flow cytometry (18 antibodies) as well as 73 plasma molecules by multiplex immunoassay (Luminex, procartaplex). Differences in cell populations and plasma molecules were assessed by generalized linear models adjusted for the most significant clinical variables and multiple comparisons (p-value corrected by Benjamin-Hochberg (q<0.15).

Results: At follow-up, lower levels of senescence markers (PD1, CD57) and central memory (CD3+CD4+or CD8+CD45RA-CCR7+CD27+CD28+) and naïve (CD3+CD4+or CD8+CD45RA+CCR7+CD27+CD28+) CD4+ and CD8+ T cells were observed in the CHC group compared to control. On the other hand, the AE group showed an increase in exhausted immune cells and immunosenescence markers over time to levels similar to those of HIV+ control patients. Also, AE group showed a higher level of effector memory CD4+ and CD8+ T cells (EM:CD45RA-CCR7-; EM_TH01: CD45RA-CCR7-CD28+CD27+; EM_TH1: CD45RA-CCR7-CD28-CD27-; EM _TH12: CD45RA-CCR7-CD28+CD27-) than HIV. The immune profile of the CHC and AE groups were very similar at follow-up. Regarding plasma molecules, 48 weeks after achieving SVR, a decrease in proinflammatory cytokines, checkpoint inhibitors and immune cell activation was observed compared to values before initiation of DAAs therapy.

Conclusion: Clearance with DAAs after chronic HCV infection improved cellular senescence profile but remained higher than controls. The slightly higher levels of circulating immunosenescence markers after 1-year follow-up in the AE group may indicate possible accelerated aging driven by acute HCV infection.

719 Influence of Markers Related to Biological Aging on Liver Regeneration in HCV Patients Achieving SVR

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Background: The achievement of sustained viral response (SVR) is associated with a reduction in HR in most patients and therefore, with a lower risk of suffering hepatic events. However, in a non-negligible percentage (10-30%) of patients who achieve SVR, liver stiffness (LS) is not reduced, and the responsible factors are not yet known. The analysis of markers related to cellular aging could offer an answer to this question.
Methods: Prospective study of parallel GEHEP and HEPAVIR cohorts at the Virgen de Valme University Hospital that met the following criteria: 1) SVR after 12 weeks with interferon-free direct-acting antivirals (DAA); 2) RH ≥ 9.5 kPa 3 months before DAA; 3) LS measurement and sample available on the SVR evaluation date. We will measure telomere length (RTL) and the levels of mitochondria, hsCRP, sCD163, sCD14, IL-6, Isoprostanate-8, CXCL10, CCL11, vWF, Vitamin D and CHI3L1, and we will analyze their association with the decrease or not of the LS at RVS.
Results: A total of 175 patients were included. In 31 (18%) patients the LS did not decrease, going from a median (Q1-Q3) of 14.4 (10.3-27.7) kPa at the beginning of treatment to 21.3 (14.4-46.4) kPa in SVR. On the other hand, the group of 144 (82%) patients in whom LS decreased went from a median of 16.8 (11.9-28.6) kPa at the beginning of treatment to 11.5 (7.6.1-18.4) kPa in SVR. In the univariate analysis, the only variables that showed an association with the absence of LS decrease in SVR were RTL [8.06 (5.83, 11.09) vs 6.41 (4.78, 8.29) (p=0.011)], hsCRP [0.8 (0.35, 1.91) vs 1.55 (0.63, 4.24) (p=0.008)], and sCD163 [49.3 (39.8, 58.4) vs 45.2 (40, 47.9) (p=0.045)]. Factors such as HIV-coinfection, baseline HR, parenteral infection, HCV-3 genotype, HCV viral load, or the MELD and Child-Pugh A indices showed no association. In the multivariate analysis adjusted for sex, age, and hsCRP and sCD163 levels, greater RTL size was the only variable independently associated with the absence of LS decrease (OR 1.173; 95% CI (1.02-1.35); p = 0.025).
Conclusion: Telomere length is independently associated with the absence of LS decrease in SVR. Greater cellular aging could be responsible, at least partially, for the absence of LS decrease in patients who achieve SVR.

720 WITHDRAWN

721 Hepatitis C Reinfection Among Men Who Have Sex With Men in an Acute HIV Cohort in Thailand

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Background: The advent of direct-acting antivirals (DAAs) revolutionized the treatment of hepatitis C (HCV). However, HCV reinfections either after spontaneous clearance or sustained virologic response (SVR) pose a challenge in HCV elimination, particularly in high-risk populations. In this study, we determined the incidence and identified risk factors of HCV reinfection in a longitudinal early-treated acute HIV cohort in Thailand.
Methods: SEARCH010/RV254 enrolls participants during acute HIV infection (Fiebig I-V) and initiates antiretroviral therapy (ART) within days of diagnosis. HCV antibody screening was performed at enrolment and then annually or if clinically indicated. HCV infection was confirmed with HCV ribonucleic acid (RNA). SVR was assessed at least 12 weeks after treatment completion. HCV RNA was monitored annually in all participants with HCV clearance (either spontaneous clearance or SVR). HCV reinfection was defined as positive HCV RNA after HCV clearance. Incidence of HCV reinfection with 95% confidence intervals (CI) per 100 person-years of follow-up (PYFU) was calculated using the exact method. Cox regression was used to identify risk factors for HCV reinfection.
Results: Between May 2009 and August 2023, 127/724 (17.5%) participants were diagnosed with HCV infection. Data analysis included 91 participants who had spontaneously cleared (n=18) or achieved SVR after HCV treatment (n=73). Among these, 14 (15.4%) developed reinfection; five after spontaneous clearance and nine after SVR. All were men who have sex with men (MSM) with median age 34.0 (IQR 29.0-37.0) years. The median time to reinfection was 1.3 years (IQR 0.8-2.8). The overall HCV reinfection incidence density rate was 6.3 per 100 PYFU (95% CI, 3.7-10.6) over 222.8 PYFU. HCV reinfection incidence was higher in the spontaneous clearance group (9.4 per 100 PYFU, [95% CI, 3.9-22.6] than the SVR group (5.3 per 100 PYFU, [95% CI, 2.8-10.2], P=0.285). Although a high proportion of participants reported current illicit drug use (50.5%), current injection drug use (33.0%), condomless sex (37.4%), or had syphilis within the previous 6 months (26.4%), no significant associations between these risk factors and HCV reinfection were found in univariable analyses.
Conclusion: In this early-treated AHI cohort of Thai MSM, there is a high incidence of HCV reinfection. Post-clearance follow-up with counseling and preventive strategies to reduce ongoing risk behavior are needed to reduce HCV reinfection.
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722 Re-Infection Following a Minimal Monitoring Approach for Treatment of Hepatitis C Virus Infection

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Background: MINMON (ACTG A5360) trial demonstrated that a minimal monitoring approach for HCV treatment with sofosbuvir-velpatasvir (SOF/VEL) was safe and efficacious (sustained viral response [SVR]: 95%) in a diverse global population. In a phylogenetic analysis, we estimated HCV re-infection rates among participants with post-treatment HCV RNA >lower limit of quantification (LLoQ).
Methods: HCV RNA evaluations were scheduled at weeks 0, 24 (SVR visit), 48 and 72 for MINMON participants. Samples with post-baseline HCV RNA >LLoQ and paired baseline samples underwent deep sequencing of NS5A and NS5B genes. Consensus sequences determined HCV genotype. FastTree generated phylogenetic trees; FigTree provided visualization. Participants

whose post-treatment HCV sequence was different from baseline were defined as re-infection. Intermingling of sequences represented treatment failure. Re-infection rates were calculated using person-time of observation starting at the final reported date of SOF/VEL and ending at the earlier of HCV RNA >LLoQ or final study visit. Re-infection rates per 100 person-years (PY) were calculated with 95% confidence intervals constructed using Poisson distribution.
Results: SVR in the primary analysis (intention to treat [ITT]) was 95% [95% CI 92.4-96.7] (379/399). Of 397 participants who had post-entry HCV RNA, 29 participants had HCV RNA >LLoQ and sequencing data available for re-infection analysis. Of these, six participants initially designated as non-SVR, and 11 participants initially classified as cured were determined to be HCV re-infections by phylogenetic analysis (total 17 re-infections). The SVR adjusting for re-infection was 96.5% [95% CI 94.2-97.9] (385/399) compared to the ITT SVR of 95%. Of all participants, 17 had re-infection during 438 person-years of follow-up (re-infection rate 3.9 per 100 PY [95% CI 2.4-6.2]). Of them, 12 were from HCV RNA collected at week 48 or 72. All 17 participants with HCV re-infection were assigned male sex at birth (13 endorsing MSM), 15 living with HIV, 14 had baseline genotype 1a, and 13 were from Thailand (of whom 11 were MSM with HIV and genotype 1a).
Conclusion: Discounting re-infections, SVR observed in MINMON was 96.5%. The high HCV reinfection rate even prior to SVR, especially among MSM living with HIV underscores the need to scale-up evidence-based interventions to reduce re-infection while simultaneously increasing screening and treatment to minimize HCV viremic burden in the population.
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723 Impact of Healthcare Expenditure on HBV and HCV in Southern Western European Countries in 2000-2019

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Background: Viral hepatitis remains a threat to public health. This Global Burden Disease study was conducted to investigate the impact of the economic crisis that began in 2008 and which severely affected the Southern Western European (SWE) countries (Greece, Italy, Portugal, Spain), on the burden of HBV and HCV disease.
Methods: Time series modelling was performed to quantify the impact of healthcare expenditure, defined as a percentage of gross domestic product, on the trend of the epidemiological estimates for HBV and HCV over the period 2000-2019. Estimates were retrieved from the Global Health Data Exchange of the Global Burden of Diseases 2019.
Results: Mortality rates due to HBV stabilised in SWE during the period 2000-2019. Declining trends in incidence and prevalence of acute HBV and chronic HBV were observed in SWE, although the pace of decline was slower in the period 2010-2019. Acute HCV metrics and chronic HCV incidence and mortality showed a stable trend in SWE, whereas the prevalence of chronic HCV showed a fluctuating trend. Liver cancer due to both hepatitis infections showed a stagnating burden over time. An inverse association was observed between healthcare expenditure and both acute HBV and HCV infections, with results close to significance for acute HBV disability-adjusted life years (DALYs) [-2.54 (-5.09 – 0.01); p=0.05)] and years of life lost to premature mortality (YLLs) [-2.53 (-5.09 – 0.03); p=0.05)] in Greece. For acute HCV, the results showed that one unit (percentage) increase in healthcare expenditure was associated with a more beneficial effect on reducing incidence cases in Italy [-8.93 (-34.31 – 16.46); p=0.49], up to 80 times higher than in the other SWE countries. A similar inverse association between healthcare expenditure and cirrhosis and other chronic liver diseases (CCLD) metrics was found for both HBV and HCV, except for CCLD-HBV prevalence in Portugal and Spain. In addition, a positive but not significant association was found between healthcare expenditure and liver cancer metrics for both HBV and HCV.
Conclusion: Epidemiological indicators for HBV and HCV showed a slower pace of decline in the period 2010-2019, with a better improvement for HBV and a stabilization of mortality and liver cancer burden due to both hepatitis. The economic crisis of 2008 had a negative impact on the burden of hepatitis B and C. Elimination of HBV and HCV by 2030 will be a major challenge in the SWE countries.

724 Epidemiologic Burden of Hepatitis D Virus in the United States

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Background: Hepatitis D affects nearly 5% of people globally who have a chronic infection with hepatitis B, according to the World Health Organization. The prevalence of hepatitis D virus (HDV) in the United States is generally considered lower than in other countries; however, HDV seroprevalence studies of the US population are limited, and reported ranges vary depending on the study population. To increase HDV detection, universal HDV testing of hepatitis B surface antigen (HBsAg)-positive specimens has been proposed. The objective of this study was to estimate the epidemiological prevalence of HDV infection within the United States in HBsAg-positive specimens.
Methods: Consecutive unique deidentified remnant HBsAg positive specimens submitted from August to September 2023 for routine clinical testing at Quest Diagnostics, representing each of the ten Health and Human Services (HHS) regions in the United States, were included in the study. A reflex algorithm using HBsAg-positive specimens for HDV total antibody testing was utilized, and further testing of anti-HDV antibody positive-specimens for HDV RNA was conducted.
Results: A total of 2,379 HBsAg-positive specimens were included in the study. The overall cohort was 46% female with a mean age of 50.1 years (50.8 years male, 49.4 years female). The overall seroprevalence of anti-HDV was 1.8%. The highest number of anti-HDV-positive specimens (n=8) were observed in HHS regions 3, 4, and 9, with prevalence (95% CI) of 0.031 (0.010-0.052), 0.017 (0.005-0.028) and 0.018 (0.006-0.030), respectively. Of the 42 anti-HDV-positive specimens, 31% were also positive for HDV RNA (viral load range: 198 - 1,070,000 IU/mL: n=10; <40 IU/mL: n=3).
Conclusion: These data suggest that HDV infection prevalence is relatively low in the United States. Further HDV seroprevalence studies are needed to determine which specific US regions would obtain the greatest benefit from future potential HDV-related interventions.

725 Incidence and Outcome of HDV Infection in People With HIV in the Era of Tenofovir-Containing Therapy

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Background: Tenofovir-containing antiretroviral therapy (ART) achieves high rates of HBV suppression and improves survival among HBV-infected people with HIV (PWH). We investigated the incidence of HDV infection among HBV-infected PWH and the impact of HDV on mortality and liver-related outcomes in the era of tenofovir-containing ART.
Methods: HBV-infected PWH seeking HIV care at the National Taiwan University Hospital between 2011 and 2022 were included and followed until September 2023. Screening for anti-HDV antibodies was performed on an annual basis on sequentially archived blood samples collected from the included PWH. The timing of incident HDV infection was estimated by the midpoint between the last time point of blood samples tested HDV-seronegative and the first time point of samples tested HDV-seropositive. Comparisons of clinical outcomes between HBV-infected PWH with and those without HDV infection were analyzed using the Kaplan-Meier method and multivariate Cox proportional hazards models.
Results: A total of 534 PWH who had chronic HBV infection were included and 36 (6.7%) tested seropositive for HDV at baseline. The median age of the included PWH was 37.8 years (IQR, 32.6-44.8) and 438 (82.0%) were men who have sex with men. Among the 498 PWH testing HDV-seronegative at baseline, 49 (9.8%) seroconverted for HDV, with 45 who were receiving tenofovir-containing ART at the time of seroconversion. After a total of 3873.54 person-years of follow-up (PYFU), the overall incidence rate of HDV superinfection was 12.65 per 1000 PYFU. After a median follow-up duration of 9.6 years (IQR 5.3-12.2), with 90.3% of the total follow-up time covered by tenofovir-containing ART, the all-cause mortality rate, liver-related mortality rate, and incidence of hepatocellular carcinoma (HCC) and cirrhosis were 4.7% (25/534), 0.9% (5/534), and 1.5% (8/534) and 2.6% (12/454), respectively (Figure). Using multivariate Cox proportional hazards models, HDV infection was associated with liver-related mortality (adjusted HR 11.632, 95% CI: 1.380-98.041, p=0.024). The risks

of all-cause mortality and development of HCC were similar for HBV-infected PWH with and those without HDV infection.
Conclusion: PWH with chronic HBV infection remain at risk for HDV superinfection, and HDV infection is associated with liver-related death in the era of tenofovir-containing ART.

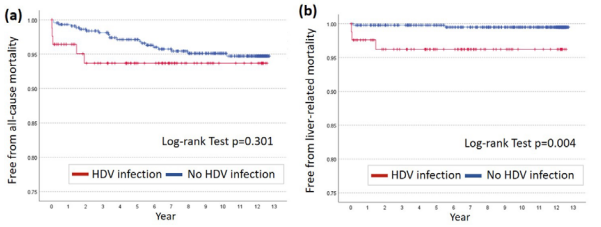

Figure. Kaplan-Meier estimates of (a) all-cause mortality and (b) liver-related mortality in HBV-infected people with HIV with and those without HDV coinfection.

726 Risk of Liver-Related Events in Individuals With HBV/HIV Coinfection With and Without HDV

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Background: Up to 10% of individuals with human immunodeficiency virus (HIV) are coinfected with hepatitis B virus (HBV). Limited data are available describing the natural history of triple infection with HBV/HIV/hepatitis delta virus (HDV). This study examines baseline liver health, HDV prevalence, and the risk of liver-related events in individuals in United States (US) administrative claims data with HBV/HIV with or without HDV.
Methods: A retrospective cohort study was conducted in the HealthVerity dataset which includes US medical and pharmacy claims, electronic medical records, and hospital data from years 2015 –2022 for > 100 million individuals. Those included were ≥ 18 years at cohort entry with one inpatient or two outpatient international classification of disease (ICD-9/10-CM) codes at least 30 days apart for each type of viral infection. Cohort entry was the date of the last infection among HBV, HIV, and HDV. All included patients had continuous insurance enrollment for 365 days prior and at least one day after cohort entry. We used Cox proportional hazard methods to estimate risk of liver-related events in individuals with vs. without HDV. Prevalence of HDV was assessed using any single HDV claim in any enrollment period.
Results: Of the 12,292 patients with HBV/HIV coinfection, we identified 608 patients with HDV and 11,177 with no evidence of HDV. At baseline, individuals with HDV were more likely to have claims for compensated (13.3 vs. 8.4%) and decompensated (10.2 vs. 6.0%) cirrhosis, HCC (1.6 vs. 1.1%), and liver transplant (1.0 vs. 0.3%). Among individuals with no evidence of these conditions at baseline, the risk of developing cirrhosis was 1.20 (0.85 – 1.69) for HDV vs. no HDV and among those with compensated cirrhosis at baseline, the risk of decompensation, HCC, or liver transplant was 1.72 (0.99 – 3.00). A sensitivity analysis excluding individuals with HCV at baseline yielded similar results. HDV prevalence was 6.8% vs. 7.4% ($p < 0.01$) and the prevalence of injection drug use among individuals with HDV was 12.8% vs. 27.7% ($p < 0.01$) in the HBV and HBV/HIV cohorts respectively.
Conclusion: HDV infection is associated with poor liver health at baseline and increased risk of liver-related events in individuals with HBV/HIV coinfection. HDV and HDV/PWID prevalence was significantly higher among patients with HBV/HIV co-infection than in the general HBV population in this dataset.
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727 Changes in Liver Fibrosis Stage Among People Living With Untreated Hepatitis B in Senegal

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Background: Hepatitis B virus (HBV) infection is the most important cause of liver cirrhosis and cancer in West Africa. Although close to 80% of persons with HBV (pwHBV) are ineligible for antiviral therapy at presentation, it is unclear how stable liver fibrosis stages measured by transient elastography remain over time, and how frequent monitoring should be performed. We assessed changes in liver fibrosis stage in pwHBV from a prospective cohort in Dakar, Senegal.
Methods: We included all HBsAg-positive individuals enrolled in SEN-B from 2019 to 2023, and who had not received antiviral treatment. Liver stiffness was evaluated 6-monthly using transient elastography and was categorized as normal (<7.0 kPa; equivalent to Metavir stage F0-1), significant fibrosis (7.1-11.0 kPa; Metavir F2-3), or cirrhosis (>11.0 kPa; Metavir F4). We evaluated fibrosis progression (F0-1 to F2-3 or F4, or F2-3 to F4) at 12 (+/– 6) months of follow-up. We used multivariable logistic regression to explore potential risk factors of fibrosis progression, including sex, age, body mass index (BMI), ALT and HBV DNA levels, HBeAg, HDV co-infection and alcohol consumption.
Results: Of 689 treatement-naïve individuals with HBV infection, 130 (18.9%) initiated antiviral treatment before the second liver stiffness measurement and were excluded. Of 556 participants analyzed, 51.1% were men, the median age was 31 years (Interquartile range [IQR] 25-39), 29.3% had a BMI ≥25 kg/m^2, 23.6% had HBV DNA>2,000 IU/mL and 5.2% had ALT>40 IU. Significant fibrosis was present in 25 (4.5%) individuals at baseline and in 36 (6.5%) at 12 months. Overall, 4.5% (25/556) of participants experienced liver fibrosis progression during follow-up, of whom 24 (96.0%) had F0-1 fibrosis stage at inclusion. In multivariable analyses, male sex (adjusted odds ratio 2.77, 95% confidence interval 1.05-7.33) was the only characteristic associated with fibrosis progression.
Conclusion: SEN-B is one of the largest prospective cohorts of people with HBV with longitudinal data on liver fibrosis in sub-Saharan Africa. Five percent of individuals ineligible for antiviral therapy experienced a progression of liver fibrosis stage during the first year of follow-up and this outcome was more likely in men than women. Long-term data is urgently needed to understand the determinants of liver fibrosis changes in Africa in order to inform monitoring strategies.

728 Prevalence and Incidence of Hepatitis B Among People Living With HIV in 4 Sub-Saharan Countries

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Background: Chronic hepatitis B is increasing despite it being a vaccine-preventable disease. Africa remains among the regions with the highest number of hepatitis B surface antigen (HBsAg) positive individuals with many studies suggesting HBV transmission occurring predominantly in childhood. To better understand the burden of hepatitis B infection in Sub-Saharan Africa, we assessed the prevalence and incidence of hepatitis B in a prospective cohort study in four African countries.
Methods: The African Cohort Study (AFRICOS) is an ongoing observational cohort that started in 2013. The study enrolls participants from PEPFAR-supported HIV clinical sites across five programs (South Rift Valley, Kenya; Kisumu West, Kenya; Kayunga, Uganda; Mbeya, Tanzania; and Abuja & Lagos, Nigeria) in four countries. People with HIV are enrolled and followed through twice-yearly visits for up to 15 years. Hepatitis B screening is performed at enrollment and annually with HBsAg test, with positive tests confirmed with HBsAg ELISA. Hepatitis B incidence rates and 95% confidence intervals (CIs) were estimated, using a Poisson distribution, as the number of new hepatitis B diagnoses per 1000 person-years (PY) of follow-up.
Results: As of June 2023, 3368 people living with HIV were enrolled, 57.9% being females, with a median age of 41.4 years. At enrollment, 216 participants (6.4%) had a reactive HBsAg result for HBV. Nigeria had the highest prevalence at 14.0% followed by Kisumu West (9.1%), with South Rift Valley having the lowest prevalence at 1.6%. There was a significant difference in prevalence between male and female participants (8.3% v 5.0%, $p<0.001$). There were 63 incident cases for an incidence rate of 4.4/1000 PY (95% CI: 3.5 – 5.7). The median age for the incident cases was 42.7 years (IQR: 36.4-48.9). Kisumu West had the highest incidence rate (9.2/1000PY, 95% CI: 6.20-14.31) followed by

Nigeria (8.60/1000PY, 95% CI: 4.76-15.53), Tanzania (5.61/1000PY, 95% CI: 3.26-9.66) and Uganda (3.41/1000PY, 95% CI: 1.78-6.58). South Rift Valley had the lowest incidence rate at 1.41/1000PY (95% CI: 0.70-2.81).

Conclusion: We observed regional variation in the prevalence of HBV infection. We also demonstrated incident cases of Hepatitis B among adults living with HIV in Sub-Saharan Africa indicating that transmission also occurs after childhood. These findings have implications for frequency of repeat HBsAg screening in PLH in Africa, particularly where HBV vaccination status may be unknown.

729 Loss of Serologic Response in Young People With HIV (PWH) Who Had Undergone HBV Revaccination

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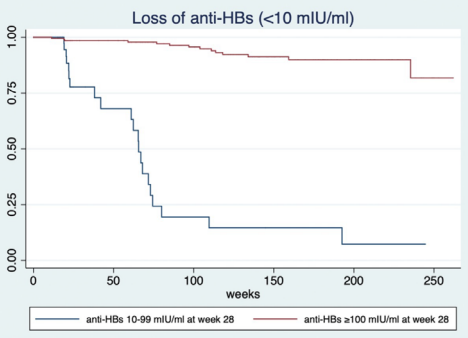
Background: We previously have shown in a clinical trial that PWH who had achieved virologic and immunologic responses with ART and were randomized to receive three double-dose (40-µg) HBV vaccine (Engerix) achieved a significantly higher seroresponse rate (anti-HBs antibody titer ≥10 mIU/ml) and high-titer (≥100 mIU/ml) seroresponse rate than PWH who received three standard-dose (20-µg) HBV vaccine. Factors associated with loss of seroprotection during follow-up were investigated.

Methods: PWH who were born after 1986 and achieved seroresponses at Wk 28 following HBV revaccination in the trial were included in the follow-up. Loss of seroresponse was defined as testing negative for HBsAg and anti-HBc with anti-HBs titer <10 mIU/ml. The clinical characteristics at revaccination and during follow-up were analyzed, including age, sex, smoking status, CD4 count, plasma HIV RNA, and pre-vaccination anti-HBs titer.

Results: 228 seroresponders (mean age, 28.5 years; median CD4, 599 cells/mm^3) after HBV revaccination were included, 112 receiving standard-dose and 116 double-dose HBV vaccine. The baseline characteristics were balanced between the two groups. The median follow-up time was 2.48 and 2.04 years for PWH receiving standard-dose and PWH receiving double-dose HBV vaccine, respectively. During the follow-up, more PWH in the standard-dose group lost seroprotection than those in the double-dose group (22.3% vs 11.2%, p=0.024). Loss of high-titer seroresponse was more common for the standard-dose group than the double-dose group (43.4% vs 19.8%, p<0.001). Factors associated with loss of seroresponse during follow-up were older age (aHR, 1.14 [95% CI, 1.03-1.27]; p=0.016), lower pre-revaccination anti-HBs titer (<2.5 mIU/ml, aHR 13.23 [95% CI, 3.15-55.47], p<0.001), and HBV vaccine dose (double-dose, aHR 0.42 [95% CI, 0.21-0.90], p=0.024). People failing to achieve high-titer responses (10-99 mIU/ml) at Wk 28 were more likely to lose seroprotection during follow-up (HR 27.9 [13.7-57.0], p<0.001) with a median time to lose anti-HBs titers being 1.26 years when compared with people achieved high-titer responses (≥100 mIU/ml) at Wk 28.

Conclusion: Three double-dose HBV revaccination leads to more sustained seroprotection than standard-dose revaccination in PWH. For PWH who fail to achieve high-titer seroresponse after revaccination, annual follow-up of anti-HBs titers is recommended to detect the loss of seroprotection for HBV revaccination to be administered timely.



730 Chronic Hepatitis B Increases Mortality Risk in COVID-19 While Vaccination Is Protective

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Background: Chronic hepatitis B virus (HBV) infection is considered a risk factor for severe SARS-CoV-2 infection (COVID-19); however, there is conflicting evidence regarding its impact on COVID-19 outcomes in dually infected individuals. Furthermore, while COVID-19 vaccination has been associated with a lower risk of death and adverse outcomes in the general population, its effect on COVID-19 outcomes in individuals with chronic HBV infection remains unexplored.

Methods: We used the TriNetX database to compare adult patients with confirmed SARS-CoV-2 infection and chronic HBV (COVID-HBV) and without chronic HBV (COVID-wo-HBV) who sought care across 77 healthcare systems in the United States from January 2020 to August 2023. We included people with HBV diagnosis codes and laboratory testing. We assessed the risk of inpatient hospitalization, intensive care unit admission, mechanical ventilation, early (30-day) and late (90-day) mortality. We further assessed the impact of COVID-19 vaccination on outcomes in subgroup analysis of COVID-HBV. We addressed potential confounders using 1:1 propensity score matching by demographics, key comorbidities, and COVID-19 vaccination. For outcomes of interest, we calculated odds ratios (OR) and 95% confidence intervals (CI), with statistical significance set at $p < 0.05$.

Results: Of 3,360,173 individuals with confirmed SARS-CoV-2, about 0.2% (7,163) were COVID-HBV, of which 13.9% (996) were vaccinated. People with COVID-HBV had higher odds of 90-day mortality (OR 1.21, 95% CI 1.02-1.44; $p = 0.032$) and ICU admission (OR 1.39, 95% CI 1.17-1.66; $p < 0.001$) compared with COVID-wo-HBV; however, there was no significant difference between groups in 30-day mortality, hospitalization, and mechanical ventilation rates. In subgroup analysis of COVID-HBV, those who received COVID-19 vaccination had lower odds of death at 30 days (OR 0.38, 95% CI 0.22-0.66; $p < 0.001$) and 90 days (OR 0.46, 95% CI 0.31-0.70; $p < 0.001$). Vaccination was not associated with decreased odds of hospitalization, ICU admission, and mechanical ventilation rates.

Conclusion: In the largest study to date, chronic HBV infection conferred higher odds of death and adverse outcomes in COVID-19. Notably, COVID-19 vaccination was associated with a significant reduction in the odds of death and the need for ICU admission, suggesting that vaccination could be an effective strategy for mitigating the impact of COVID-19 in individuals with chronic HBV infection.

Table 1. Clinical outcomes in COVID-HBV vs COVID-wo-HBV and effect of COVID-19 vaccination on outcomes

	Impact of HBV on COVID-19 Outcomes			Effect of COVID-19 Vaccination		
Outcomes	COVID-HBV	COVID-no-HBV	OR (95% CI)	HBV + Vaccinated	HBV + Unvaccinated	OR (95% CI)
Mortality (30-day)	166 (2.4%)	141 (2.0%)	1.18 (0.94-1.48)	18 (1.3%)	46 (3.3%)	**0.38 (0.22-0.66)**
Mortality (90-day)	287 (3.8%)	238 (3.2%)	**1.21 (1.02-1.44)**	34 (2.4%)	71 (5.0%)	**0.46 (0.31-0.70)**
Intensive care unit	306 (5.0%)	226 (3.6%)	**1.39 (1.17-1.66)**	74 (6.5%)	57 (4.7%)	1.40 (0.98-2.01)
Mechanical ventilation	219 (3.3%)	204 (3.0%)	1.09 (0.90-1.32)	27 (2.0%)	19 (1.4%)	1.42 (0.79-2.56)
Inpatient (non-ICU)	263 (9.7%)	296(10.5%)	0.91 (0.76-1.08)	46 (10.8%)	41 (7.9%)	1.40 (0.90-2.18)

COVID-HBV, patients with COVID and HBV; COVID-no-HBV, patients with COVID without HBV; ICU, intensive care unit; OR, odds ratio; CI, confidence interval

731 IL-21 Ameliorates Liver Inflammation by Enhancing MDSC Activity in Chronic HBV Infection

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Background: In patients with chronic HBV infection, the immune response is inadequate for HBV clearance but can cause a persistent inflammatory reaction. Alleviating hepatitis may be possible by inhibiting the function of inflammatory cells during hepatitis activity. The potential for interleukin 21 (IL-21) to suppress liver inflammation by regulating the suppressive activity of myeloid-derived suppressor cells (MDSCs) on T cell response is not well understood.

Methods: Eighty treatment-naïve patients with chronic HBV infection were recruited and classified into the immune tolerant carrier (IT; n = 37), hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB; n = 16), and inactive carrier (IC; n = 27) groups according to the American Association for the Study of Liver Diseases guidelines. Another 33 healthy controls (HCs) were also enrolled in this study. We investigated the characteristics of MDSCs and the effect of IL-21 on the phenotype and function of MDSCs by flow cytometry. The

quantity of granulocytic MDSCs (gMDSCs) in the human liver was analyzed by immunofluorescence assay. Wild-type C57BL/6 mice were used to establish a hydrodynamic injection HBV mice model.

Results: The frequency of circulating MDSCs in patients infected with chronic HBV was higher than that in the HC group. The circulating MDSCs frequency was negatively correlated with the serum levels of ALT and AST. The number of CD15 and CD66b double-positive cells indicating gMDSCs in CHB patients was higher than that in IT and IC patients. Exogenous IL-21 promoted MDSCs differentiation into M2-like macrophages while also increasing their expression of Arginase I. IL-21 also enhanced the suppressive activity of MDSCs in inhibiting the expression of IFN-γ in T cells. Hydrodynamic injection HBV mice model injected with IL-21 plasmid showed lower ALT concentration and higher production of Arginase I in MDSCs than mice injected with blank plasmid.

Conclusion: Our study highlights the robust immune-suppressive activity of MDSCs, which can be enhanced by exogenous IL-21, and their potential role in protecting against liver inflammation in chronic HBV infection. These findings provide a novel perspective on the involvement of IL-21 in the negative regulation of intrahepatic inflammation and have implications for the development of immunotherapeutic strategies to optimize the available anti-inflammatory hepatinica in chronic HBV infection.

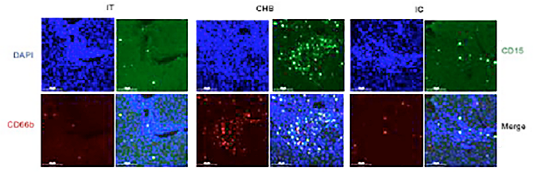

Figure. Representative immunofluorescence analysis of CD15 (in green), CD66b (in red), and DAPI (for nuclei in blue) in the livers of IT, CHB, and IC patients.

732 Factors Associated With HBV Response to B/F/TAF vs DTG + F/TDF at W96 in People With HIV-1 and HBV

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Background: The Phase 3 ALLIANCE study investigated the efficacy and safety of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) vs. dolutegravir + emtricitabine/tenofovir disoproxil fumarate (DTG+F/TDF) in people initiating therapy for HIV-1 and HBV. Over 96 weeks (W), B/F/TAF showed significantly higher rates of HBeAg loss/seroconversion, and numerically higher rates of HBsAg loss/seroconversion and ALT normalization, vs. DTG+F/TDF. Overall, rates of HBeAg and HBsAg loss/seroconversion and ALT normalization at W96 were substantially higher in ALLIANCE than in TDF or TAF studies for HBV monoinfection, especially with B/F/TAF, but the mechanism behind this difference is unclear. Here, we explore factors associated with HBV treatment response with B/F/TAF vs. DTG+F/TDF through W96.

Methods: Adults with HIV-1/HBV from 46 sites internationally (N=243) were randomized 1:1 to B/F/TAF or DTG+F/TDF plus corresponding placebos. This subgroup analysis compares the percentages of participants with HBe/sAg loss/seroconversion or ALT normalization with B/F/TAF vs. DTG+F/TDF at W96 (Year 2) according to baseline demographics, HBV genotype, and markers of HIV-1/HBV disease severity.

Results: There were significantly higher rates of HBeAg loss and seroconversion with B/F/TAF vs. DTG+F/TDF in participants who were <30 years of age, or with baseline HBV DNA <8 $\log_{10}$ IU/mL, HBV genotype B/C, or baseline ALT levels above normal (Table), and in those who were Asian, or with ≥95% study drug adherence, baseline HIV-1 RNA ≤100,000 c/mL, baseline CD4 ≥200 cells/µl, or asymptomatic HIV-1 (HBeAg loss only) at baseline. There were also significantly higher rates with B/F/TAF vs DTG+F/TDF for: HBsAg loss/seroconversion in participants with HBV genotype B/C; HBsAg loss and ALT normalization in those with baseline HBV DNA <8 $\log_{10}$ IU/mL; HBsAg loss in those who were Asian or who had ≥95% study drug adherence; ALT normalization in those who were HBeAg negative at baseline.

Conclusion: At Year 2, B/F/TAF was associated with significantly higher rates of HBeAg loss/seroconversion and numerically higher rates of HBsAg loss/seroconversion and ALT normalization compared with DTG+F/TDF in people with HIV-1/HBV. This analysis suggests that the treatment difference of TAF- vs. TDF-based therapy for some or all HBV treatment outcomes may be greater for certain subgroups, such as people <30 years of age, or with baseline HBV DNA <8 $\log_{10}$ IU/mL, HBV genotype B/C or baseline ALT levels above normal.

Table. Treatment Difference in Proportion of Participants with HBeAg Seroconversion at W96 by Subgroup

		Favors DTG+F/TDF ← → Favors B/F/TAF	n/N B/F/TAF	n/N DTG+F/TDF
Age, years	≥30		14/49	10/54
	<30		15/41	5/43
Baseline HBV DNA, IU/mL	≥8 $\log_{10}$		15/56	10/65
	<8 $\log_{10}$		14/34	5/32
HBV genotype	A/D		7/18	5/30
	B/C		20/63	7/59
Baseline ALT	>ULN*		19/43	7/36
	≤ULN*		10/47	8/61

-100 -75 -50 -25 0 25 50 75 100
Difference in percentages (95% CI)†

*Based on 2018 American Association for the Study of Liver Diseases criteria (females: 25U/L; males: 35U/L); †Based on Mantel-Haenszel proportions adjusted by baseline HBV DNA category (normal approximation without stratification was used for baseline HBV DNA)

733 Novel Biomarkers as Determinants of HBsAg Loss in Persons With HIV/HBV on Tenofovir

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Background: HBsAg loss is associated with improved clinical outcomes in persons with hepatitis B virus (HBV) infection. The association between novel biomarkers, including circulating HBV RNA and hepatitis B core-related antigen (HBcrAg), and this outcome has not been studied in persons with HIV/HBV. We aimed to evaluate rates of HBsAg loss and associated risk factors in Euro-B, a multi-cohort collaboration including participants from the Swiss HIV Cohort Study and EuroSIDA.

Methods: We included participants with a positive HBsAg and ≥6 months of follow-up on tenofovir-containing antiretroviral therapy (ART), who had quantitative HBsAg (qHBsAg), HBV DNA, HBcrAg and HBV RNA measured at tenofovir start. We evaluated rates of HBsAg loss, defined as a negative qualitative test or qHBsAg <0.05 IU/mL, after 2 years of tenofovir therapy and at the last follow-up visit. We assessed risk factors for HBsAg loss on tenofovir overall and in HBeAg-stratified analyses using multivariable logistic regression. Due to collinearity between HBcrAg and HBV RNA, we evaluated risk factors in two separate multivariable logistic regression models.

Results: Of 304 participants included, 23.0% experienced HBsAg loss during a median follow-up time of 11 years (IQR 6-15). After two years, 37/265 (14.0%) participants had experienced HBsAg loss. At tenofovir start, median age was 41 years (IQR 36-46), 61/304 (20.1%) were female at birth, 152/304 (50.0%) were ART-naïve, median CD4 count was 325 cells/mm^3 (IQR 210-482), and 109/233 (46.8%) were HBeAg positive. At tenofovir start, 72/304 (23.7%) participants had a qHBsAg <1000 IU/mL, 79/304 (26.0%) had HBV DNA <20 IU/mL, 72/304 (23.7%) had HBcrAg ≤3 $\log_{10}$ U/mL and 140/304 (46.1%) had HBV RNA <10 copies/mL. In both models, only qHBsAg <1000 IU/mL at baseline was associated with HBsAg loss (model with HBcrAg: OR 12.6, 95% CI 5.4-29.5; model with HBV RNA: OR 9.6, 95% CI 4.3-21.4). In HBeAg-positive participants, HBV RNA (OR 0.5 for 1 $\log_{10}$ increase, 95% CI 0.3-0.8) was associated with HBsAg loss. In HBeAg-negative participants, only qHBsAg <1000 IU/mL (OR 10.8, 95% CI 3.1-36.9) was associated with this outcome.

Conclusion: We found high rates of HBsAg loss among persons with HIV/HBV, with 14% of events occurring during the first two years of treatment. Baseline qHBsAg levels were strongly associated with HBsAg loss in HBeAg-negative participants, whereas HBV RNA may be an independent predictor of HBsAg loss in HBeAg-positive persons with HIV/HBV.

734 Circulating HBV RNA Helps Characterize HBV Disease in Senegal

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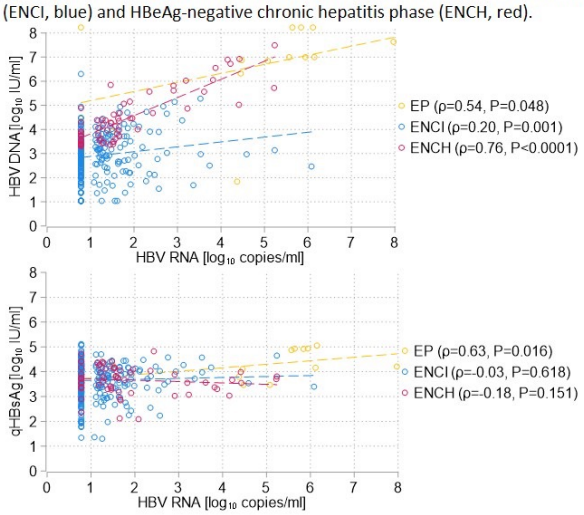
Background: Hepatitis B virus (HBV) infection affects >10% of the population in West Africa and is the most common cause of liver cirrhosis and hepatocellular carcinoma. Circulating HBV RNA may help improve the characterization of HBV disease and prognosis. We aimed to evaluate the associations between HBV RNA and conventional biomarkers of HBV replication in the Senegalese Hepatitis B Cohort study (SEN-B).

Methods: We included all treatment-naïve participants without HIV infection from SEN-B. We measured HBV RNA levels using the cobas HBV RNA investigational assay (Roche Molecular Diagnostics, Pleasanton, CA) with a lower limit of quantification of 10 copies/ml. Participants were classified into three phases of HBV infection: Hepatitis e antigen (HBeAg)-positive (EP), HBeAg-negative chronic infection (ENCI) and HBeAg-negative chronic hepatitis (ENCH). ENCH was defined by HBV DNA ≥2000 IU/ml in combination with elevated alanine aminotransferase (ALT ≥30 IU/ml for men, ≥19 IU/ml for women) and/or significant liver fibrosis (liver stiffness measurement >7.0 kPa). We compared participants with and without detectable HBV RNA using descriptive statistics and evaluated associations between HBV RNA, HBV DNA, and quantitative hepatitis B surface antigen (qHBsAg) using Spearman's rank correlation coefficient among participants with detectable HBV RNA levels.

Results: Among 713 participants, 17 (2.4%) were in the EP phase, 615 (86.3%) in the ENCI phase and 81 (11.4%) in the ENCH phase. Median age was 31 years (interquartile range 25-38) and 335 (47.0%) were female. HBV RNA was undetectable in 3/17 (17.6%) of EP individuals, 338/615 (55.0%) of ENCI individuals and 19/81 (23.5%) of ENCH individuals. The 353/713 (49.5%) participants with detectable HBV RNA were more likely to have HBV DNA >20 IU/ml (95.8% vs. 80.0%) and to have significant fibrosis (13.9% vs. 7.5%) than participants with undetectable HBV RNA levels. We did not observe significant differences in age, sex, ALT levels and qHBsAg levels between the two groups. As depicted in the Figure, HBV RNA showed strong correlation with HBV DNA in EP, moderate correlation in ENCH and poor correlation in ENCI participants. HBV RNA and qHBsAg correlated moderately in EP, but not in ENCI and ENCH participants.

Conclusion: In our cohort of treatment-naïve persons with HBV in Senegal, approximately 50% had detectable HBV RNA levels. HBV RNA correlated well with HBV DNA in the EP and ENCI groups, whereas qHBsAg levels correlated with HBV RNA only in EP individuals.

Correlation between (A) HBV RNA and HBV DNA and (B) HBV RNA and qHBsAg in the HBeAg-positive (EP, yellow), HBeAg-negative chronic infection (ENCI, blue) and HBeAg-negative chronic hepatitis phase (ENCH, red).



735 Efficacy and Safety of BLV 2 or 10 mg for 96 Weeks in CHD Including in 2 Patients With HIV/HBV/HDV

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Background: Bulevirtide (BLV) is a first-in-class, entry inhibitor, approved in the EU for the treatment of chronic hepatitis D. Limited data exists on the safety and efficacy of BLV in HIV/HBV/HDV coinfection. The aim of this Week (W) 96 analysis from the Phase 3 MYR301 (NCT03852719) study is to describe the safety and efficacy of BLV over 96 weeks including in patients with HIV/HBV/HDV.

Methods: 150 patients with CHD were randomized (1:1:1) into three arms: Arm A: no active anti-HDV treatment for 48 weeks, followed by BLV 10mg/d for 96 weeks (n=51), and Arms B or C: immediate treatment with BLV at 2 mg/d (n=49) or 10 mg/d (n=50), respectively, each for 144 weeks, with follow-up of 96 weeks after end of treatment. Efficacy was measured by combined (undetectable HDV RNA or ≥2 log_{10} IU/mL decline from BL and ALT normalization), virologic and biochemical response rates. Controlled HIV infection (defined as CD4 count >500/mL, HIV RNA <LOD) was allowed.

Results: Overall, baseline characteristics were similar between arms: mean (SD) age 41.8 (8.4) years; 57% males; 83% White; 47% compensated cirrhosis; mean (SD): HDV RNA 5.05 (1.34) log_{10} IU/mL, ALT 110.9 (69.0) U/L, and 61% on concomitant nucleos(t)ide analogue. Two patients with HIV/HBV/HDV were enrolled in the study. At baseline, Patient 1 (Arm B) was age 39 years, HCV ab neg, HIV viral load (VL) undetectable, CD4 786/mm^3 and on tenofovir/lamivudine/etravirine. Patient 2 (Arm C) was age 40 years, HCV ab pos (HCV RNA neg), HIV VL undetectable, CD4 559/mm^3 and on emtricitabine/tenofovir alafenamide/raltegravir. Overall W96 combined, virologic and biochemical responses were similar in arms B and C (Table). Key parameters from BL to W96 for Patient 1 was HDV RNA 3345358 IU/mL to <50, HBV DNA 22 IU/mL to neg, HBsAg 18000 to 6400 IU/mL and ALT 289 to 18 U/L. Key parameters from BL to week 96 for Patient 2 was HDV RNA 425354 IU/mL to <50, HBV DNA 17 IU/mL to <10, HBsAg 8100 to 5200 IU/mL and ALT 97 to 26 U/L. At W96, both HIV/HBV/HDV coinfected patients achieved combined virologic and biochemical response and neither required changes to their antiretroviral therapy. BLV was safe and well tolerated. Both HIV/HBV/HDV patients had no drug discontinuations, serious AE (SAE) or deaths attributed to BLV.

Conclusion: Virologic and biochemical responses increased with longer therapy over 96 weeks with BLV without new safety signals. Two patients with HIV/HBV/HDV achieved a combined response and tolerated BLV well. More data is needed with BLV in HIV/HBV/HDV patients.

Table: Efficacy and Safety of BLV at Weeks 48 and 96

	Week 48			Week 96		
	Arm A Delayed Treatment With BLV 10 mg (n=51)	Arm B BLV 2 mg (n=49)	Arm C BLV 10 mg (n=50)	Arm A Delayed Treatment With BLV 10 mg (n=51)	Arm B BLV 2 mg (n=49)	Arm C BLV 10 mg (n=50)
Virologic Responder n (%) 95% CI (%)	2 (4) (0, 13)	36 (73) (59, 85)	38 (76) (62, 87)	46 (90) (79, 97)	37 (76) (61, 87)	41 (82) (69, 91)
ALT Normalization n (%) 95% CI (%)	6 (12) (4, 24)	25 (51) (36, 66)	28 (56) (41, 70)	22 (43) (29, 58)	31 (63) (48, 77)	32 (64) (49, 77)
Combined Response n (%) 95% CI (%)	1 (2) (0, 10)	22 (45) (31, 60)	24 (48) (34, 63)	20 (39) (26, 54)	27 (55) (40, 69)	28 (56) (41, 70)
Adverse Events at Week 96 Number (%) of patients with:						
Any AE	39 (77)	41 (84)	44 (88)	47 (92)	47 (96)	48 (96)
Any AE related to BLV	0	24 (49)	36 (72)	22 (43)	25 (51)	36 (72)
Any SAE	1 (2)	2 (4)	1 (2)	3 (6)[a]	2 (4)	4 (8)

Combined response defined as undetectable HDV RNA or ≥2 log_{10} IU/mL decline from BL and ALT normalization.
All AEs were treatment emergent over 96 weeks.
[a]Includes 1 death due to plasma cell myeloma not related to study treatment.

736 Transaminase Elevations Among Patients With Occult HBV Infection on 2-Drug Antiretroviral Regimens

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Background: Concerns have been raised about the possibility of hepatitis reactivation among individuals with occult HBV infection (OHBVI) who discontinue antiretroviral agents with anti-HBV activity. Whether OHBVI is associated with increased risk of transaminase elevation among those switching to two-drugs regimens (2DR), discontinuing lamivudine (3TC) and/or tenofovir (TFV), merits to be investigated.

Methods: People living with HIV (PLWH) who had switched to a 2DR since 2018 were enrolled in this retrospective cohort, provided they had discontinued ≥1 anti-HBV drug and that their anti-HBV core (HBc) status was known. Rates of liver function test increase (LFTI) above the upper limit of normality were determined using Kaplan-Meier estimates and compared between those with and without OHBVI. Cox regression, adjusting for potential confounders, and random-effects linear regression with repeated measures were also used. All analyses were conducted separately according to the type of 2DR used (including 3TC or without any active HBV-agents).
Results: 162 patients switched to a 2DR containing 3TC while 105 to a regimen without 3TC and TFV. Their characteristics are shown in Fig 1. Among those on 3TC, incidence of LFTI was 13.3 and 16.8 per 100 person-years in those with and without OHBVI, respectively (IRR 0.79; 95%CI 0.36-1.64; p=0.514). Uni and multivariable Cox regression showed no significant association between OHBVI and LFTI (HR 0.8; 95%CI 0.4-1.6; p=0.583), after adjusting for possible confounders. No association between ALT levels and OHBVI was observed using a random-effects linear regression, adjusted for time and baseline ALT (coeff -0.39;95%CI -2.3-1.5). Among those with no anti-HBV agents in the regimen, LFTI rates were 13.9 and 13.9 per 100 patient-years in those with and without OHBVI, respectively (IRR 0.99; 95% CI 0.31-3; p=0.998). Using Cox regression, no significant association between OHBVI and LFTI was found (HR 1.33, p=0.568). Adjusted models for potential confounders yielded similar findings. Similarly, OHBVI was not significantly associated to ALT levels at linear regression analysis (coeff -0.87; 95%CI -3.8-2.1). No clinical HBV reactivations nor acute infections were observed.
Conclusion: Presence of OHBVI infection was not significantly associated with transaminase elevation among PLWH treated with 2DR lacking anti-HBV agents. This real-life observation provides reassurance regarding the safety of transitioning to dual therapy in patients with reactive anti-HBc.
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737 Hepatitis B Reactivation in PLWH With Anti-Core Antibody After Switch to an Anti-HBV Sparing Regimen

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Background: Anticore antibody (antiHBc) in absence of hepatitis B surface antigen (HBsAg) is defined as an isolated antiHBc status that may be associated with HBV reactivation. We decided to investigate HBV reactivation in antiHBc-PLWH (with isolated anti-HBc or with anti-HBc and anti-HBsAg) after the switch from ART including drugs active on both viruses (tenofovir disoproxil fumarate, TDF and tenofovir alafenamide, TAF) to an antiHBV sparing regimen (antiHBVsr) because in PLWH the loss of HBsAg with or without anti-HBsAg seroconversion is probably consequent to ART treatment including drugs active on both viruses (HIV/HBV) rather than past HBV infection. Additionally, HBV reactivation has been described in immunocompromised anti-HBsAg positive people.
Methods: HBV reactivation in antiHBc-PLWH was assessed by an alteration of alanine aminotransferase (ALT) above the upper limit of the normal range after the switch to antiHBVsr dolutegravir/rilpivirine (DOL/RPV) or long acting therapy cabotegravir/rilpivirine (CAB/RPVLA). Forty-one individuals with antiHBc and at least 2 ALT values available after the switch to antiHBVsr: (DOL/RPV, (number, N=15), CAB/RPVLA(N=26) were evaluated. Data were collected as part of routine clinical care and recorded into the database of the Division of Infectious Diseases of the San Raffaele Hospital (CSLHIV Cohort). Data freezing was 29 August 2023.
Results: Main characteristics of antiHBc-PLWH at antiHBVsr according to antiHBsAg status (antiHBsAg positive N=34 or negative, N=7) are described in Table 1. All variables analyzed were similarly distributed in the two groups. Overall, the median post-switch follow-up was 8.91 months (interquartile range, IQR 6.78 - 24.14): 8.96 months (IQR 6.78 - 24.14) in anti-HBsAg positive PLWH and 6.97 months (IQR 5.56 - 43.22) in anti-HBsAg negative PLWH, P=0.742. Interestingly, 1/7(14.3%) PLWH with isolated antiHBc showed an increase of ALT (about 20-fold the normal values) about 3 months after switch to CAB/RPVLA, with also appearance of HBV-DNA at high levels (4.8 x107 IU/mL) and HBsAg seroconversion. He was infected by HBV genotype A that was also identified in plasma sample obtained during HBV chronic infection phase, before any ART treatment.
Conclusion: The HBV reactivation is unlikely in antiHBc-PLWH with anti-HBsAg positivity after switch to anti-HBVsr, while close monitoring of ALT and possibly HBV-DNA in PLWH with antiHBc alone, after switch to anti-HBVsr is necessary.

Table 1. Characteristics of anti-HBc-PLWH at switch to antiHBVsr and according to anti-HBsAg positivity or negativity

Category	Overall (n 41)	AntiHBsAg neg. (n 7)	AntiHBsAg pos. (n 34)	P-value
Age	55.08 (50.19 - 62.2)	54.4 (50.19 - 61.51)	57.83 (43.19 - 70.15)	0.690
Sex, male	41 (100%)	34 (100%)	7 (100%)	0.632
Years of HIV infection	15.41 (9.45 - 20.44)	15.28 (8.94 - 19.66)	15.53 (10.12 - 26.42)	0.533
CD4 cells, number/mL	607 (460 - 772)	603 (459 - 772)	693 (485 - 867)	0.726
ALT, IU/L	27.5 (21 - 32)	28 (20 - 32)	27 (21 - 39)	0.763
HIV-RNA <50copies/mL 50-200 copies/mL	 40 (97.6%) 1 (2.4%)	 7 (100%) 0 (0%)	 33 (97.1%) 1 (2.9%)	0.661
HBV-DNA <10 IU/mL* (n=26)	26 (63.4%)	5 (71.4%)	21 (61.8%)	–

Results described by median (IQR) or frequency (%) for continuous and categorical variables
*HBV-DNA was measured at switch or within 6 months from switch to antiHBVsr

738 Circulating HBsAg-Specific B-Cells Are Partially Rescued After Achieving Functional Cure

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Background: Hepatitis B surface antigen (HBsAg) loss defines a functional cure for chronic hepatitis B infection. Herein, we aimed to characterize circulating HBsAg-specific B cells and identify B-cell epitopes directly associated with HBsAg loss.
Methods: Seventy-eight treatment-naïve patients with chronic HBV infection were classified into 4 groups according to the EASL guidelines (2017): hepatitis B e antigen (HBeAg) negative chronic infection (n=21), HBeAg-positive chronic infection (n=20), HBeAg-negative chronic hepatitis (n=17), and HBeAg-positive chronic hepatitis (n=20). Forty-six patients who achieved HBsAg loss (n=24) or seroconversion (n=22) following antiviral treatment and 16 hepatitis B vaccinees with normal alanine aminotransferase levels were enrolled. HBsAg-specific B cells phenotypes and function were analyzed by flow cytometry. ELISpot assay was used to measure the ability of B cells to secrete antibodies. HBsAg specific B-cell epitopes associated with functional cure were mapped by ELISA.
Results: The classical resting memory B cell population (RM, CD21+CD27+) in HBsAg-specific B cells was reduced while the proportion of atypical memory B cells (AtM, CD21-CD27-), a functionally exhausted subset, was expanded in chronically HBV-infected patients. An increased proportion of RM B cells and a deceased proportion of AtM B cells were observed in patients after achieving functional cure. There was no correlation between total HBsAg-specific B cells and virological parameters, but we found an inverse correlation between HBsAg levels and HBsAg-specific RM B-cell frequency. Moreover, HBsAg-specific B cells expressed lower levels of CD32 and higher levels of IL-6 upon stimulation in patients with HBsAg loss. Intriguingly, the frequency of HBsAb-secreting B cells was significantly increased after achieving functional cure. Sera from patients with HBsAg loss mainly reacted with peptides S60, S61, and S76, suggesting that they are dominant linear B-cell epitopes relevant for functional cure. Notably, an expansion of HBsAg-specific B cell was detected in S76-reactive subjects, accompanied by lower PD-1 expression.
Conclusion: HBsAg-specific B cells were partially restored in patients after achieving functional cure. Functional cure-related epitopes are promising targets of therapeutic vaccine development for chronic HBV infection to increase the functional cure rate.

739 Monthslong HBV Suppression by TFV Double Ester Prodrugs

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Background: Tenofovir (TFV) prodrugs [TFV disoproxil-/TFV alafenamide-fumarates (TDF/TAF)] are recommended daily oral treatments for chronic hepatitis B (HBV) infection. Given the growing popularity of long-acting (LA)

therapies for treatment of chronic viral infections, an ever increasing number of potent medicines will come available. One, developed in our own laboratories, is a lipophilic ProTide of TFV called M1TFV that exhibited sustained suppression of HBV DNA in mouse models of human disease [Sci. Adv.8,eade9582(2022)]. However, like other ProTide prodrugs, the reported chemical synthesis of M1TFV necessitates costly chiral catalysts and time-consuming separation of the Sp and Rp diastereomers generated at the phosphorous atom. To overcome these limitations we developed alternative amino acid free hydrophobic and lipophilic double ester crystalline TFV prodrugs. Two nanoformulated diester candidates elicited enhanced and sustained HBV DNA suppression in transgenic C57BL/6 Tg05 mice compared to limited efficacy for TAF ProTide.

Methods: Three amino acid free lipophilic double ester prodrugs of TFV were synthesized through a non-catalytic esterification of TFV monophenyl ester with either an aryl substituted lipid (M4TFV), octadecanol (M5TFV) or docosanol (M6TFV). The synthesized prodrugs were characterized and nano-formulated using biocompatible surfactants to produce stable aqueous solid drug nanosuspenisons (NM4TFV, NM5TFV and NM6TFV). Control treatment consisted of TFV alafenamide solid drug nanosuspensions (NTAF). Additional controls were infected, untreated animals. Antiviral efficacy was tested in HBV Tg05 mice. Drug formulations were administered as single intramuscular injections at 168 mg/kg TFV equivalents. HBV DNA viral load in blood was measured every other week.

Results: Three diester prodrugs of TFV were synthesized in high chemical yields and formed predominantly one of the two stereoisomers at the phosphorous chiral center. These prodrugs were crystalline and compatible with scalable formulation approaches for producing surfactant stabilized aqueos nanosuspenisons. Notably, a single IM injection of NM5TFV or NM6TFV diester prodrug nanosuspensions in Tg05 mice demonstrated enhanced and sustained efficacy compared to limited anti-HBV activity for TAF ProTide or arylated NM4TFV diester prodrug (Figure 1).

Conclusion: NM5TFV and NM6TFV diester prodrug formulations produced sustained monthslong suppression of HBV DNA in Tg05 mice without recorded adverse events.

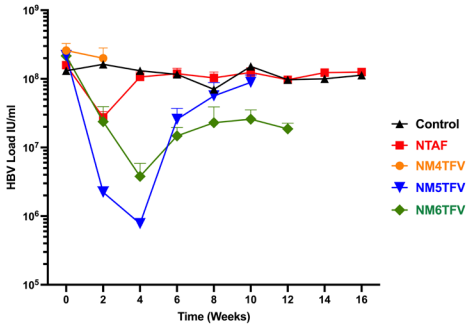

Figure 1. Suppression of HBV replication in Tg05 mice. A single intramuscular injection of NM5TFV or NM6TFV (**n=4 per group**) suppressed HBV DNA in peripheral blood by two orders of magnitude compared to untreated, NTAF or NM4TFV. Results are expressed as Mean ± SEM.

740 Evaluation of the Hepatitis B Virus Reservoir With Fine Needle Aspiration and Serum Biomarkers

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Background: Novel treatment strategies aimed at hepatitis B virus (HBV) cure must eliminate or silence the covalently closed circular (ccc)DNA reservoir, which measurement is challenging as it requires invasive sampling methods. To address this unmet medical need, we evaluated the HBV reservoir by: i) analyzing viral markers in fine needle aspirates (FNAs) as a less invasive alternative to core liver biopsy (CLB), and ii) quantifying circulating HBV RNA (cirB-RNA) as an indicator of cccDNA transcriptional activity.

Methods: We collected matched CLB/FNA/serum samples from chronic hepatitis B patients (n=9), as well as paired CLB/serum samples from untreated (n=92) and nucleos(t)ide analog (NUC)-treated (n=30) individuals. Intrahepatic viral parameters were quantified by qPCR and droplet digital (dd)PCR (LOD 3 x 10-6 copies/cell for cccDNA). cirB-RNA was quantified with the automated cobas(R) HBV RNA assay that preferentially detects viral RNAs derived from cccDNA vs. integrated sequences (LOD 5 copies/mL). Serum levels of HBV DNA, hepatitis B surface antigen (HBsAg) and hepatitis B core-related antigen (HBcrAg) were determined, as well as hepatitis B e antigen (HBeAg) status.

Results: cccDNA and 3.5-kb RNA were quantifiable in all but one CLB/FNA pair, showing the highest levels in untreated HBeAg+ patients. When comparing cccDNA and 3.5-kb RNA levels in CLB/FNA samples, no statistically significant differences were identified. The analysis of CLB/serum samples showed that all HBeAg+ chronic hepatitis (CH) patients had quantifiable cirB-RNA, compared to only 57% of HBeAg- CH and 14% of HBeAg- chronic infection (CI) untreated patients and 47% of NUC-treated patients. cirB-RNA undetectability was associated with lower intrahepatic cccDNA transcriptional activity and serum HBcrAg in both untreated and treated patients. Combined undetectability of cirB-RNA and HBcrAg in HBeAg- patients identified a subgroup with the lowest levels of transcriptionally active cccDNA.

Conclusion: In the frame of HBV cure programs, we provide a proof of concept that the less invasive FNA can be used to assess intrahepatic cccDNA using a ddPCR assay. Moreover, we show the performance and relevance of quantifying cirB-RNA as an indicator of cccDNA transcriptional activity in both untreated and NUC-treated patients. These results support the use of both approaches in clinical trials to evaluate the HBV reservoir during the development of new antivirals and immunomodulatory agents.

741 Intrahepatic cccDNA and Circulating HBV Markers in HBeAg-Negative Chronic Infection in Senegal

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Background: A better understanding of the relationship between the intrahepatic hepatitis B virus (HBV) activity and peripheral biomarkers of HBV infection is urgently needed in order to improve treatment monitoring and outcomes in high prevalence settings. We aimed to determine the relationship between intrahepatic HBV cccDNA and plasma HBV DNA, quantitative HBsAg (qHBsAg) and total HBV RNA levels in HBeAg-negative individuals from the SEN-B cohort in Senegal.

Methods: We collected paired core liver biopsies and serum/plasma samples from untreated HBeAg-negative participants enrolled in SEN-B. We measured qHBsAg and HBV DNA on site using e411 cobas® and cobas®/TaqMan® (Roche Diagnostic Systems). HBV RNA levels were measured from cryopreserved plasma samples using cobas® 8800 investigational assay (Roche Molecular Systems) with a lower limit of quantification (LLOQ) of 10 copies/mL. cccDNA was extracted from snap-frozen liver samples using modified Hirt protocol, followed by ExoV nuclease treatment, and quantified by an HBV specific digital droplet PCR. The individual correlation between levels of intrahepatic cccDNA and i) HBV DNA, ii) qHBsAg and iii) HBV RNA was assessed using Spearman correlation coefficients.

Results: Fifty SEN-B participants were included with a median age of 31 years (interquartile range 26-37) and 16/50 (32%) were female. One individual (3%) had ALT >40 IU and 13/50 (26%) had liver fibrosis defined as a Metavir stage ≥F2. HBV DNA >2,000 IU/mL was found in 19/50 (38%) participants and qHBsAg >1,000 IU/mL in 28/50 (56%). HBV RNA was detected in 26/50 (52%) participants, of whom 12/50 (24%) had >10 copies/mL. Median cccDNA (copies/cells) was similar between HBV RNA-negative and positive individuals (p=0.74). We observed no significant correlation between the intrahepatic cccDNA and plasma HBV DNA levels (r=0.21, p=0.15), as well as between the intrahepatic cccDNA and serum qHBsAg levels (r=0.02, p=0.87). There was a moderate positive correlation between cccDNA and total plasma HBV RNA among persons with detectable levels (r=0.52, p=0.006).

Conclusion: HBV RNA was the only circulating marker which correlated with intrahepatic cccDNA in our well-characterized group of persons with HBeAg-negative HBV infection in Senegal. Further research is needed to better understand the underlying mechanisms and implications of this correlation. The figure, table, or graphic for this abstract has been removed.

742 Race/Ethnicity and Risk of NAFLD and Clinically Significant Fibrosis in Persons Living With HIV

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Background: Racial and ethnic differences in non-alcoholic fatty liver disease (NAFLD) prevalence are well described in the general population, with Hispanics having the highest and African Americans having the lowest NAFLD prevalence. Whether similar disparities exist in persons with HIV (PWH) with NAFLD is largely unknown. We investigated racial and ethnic differences in the prevalence of NAFLD and clinically significant fibrosis (CSF) among PWH.

Methods: This cross-sectional analysis included participants ≥ 18years of age prospectively enrolled in two U.S. multicenter studies from 2018-2023 who had 1) a documented history of HIV on antiretroviral therapy with HIV-1 RNA <200 copies/mL 2) vibration controlled transient elastography (Fibroscan®) performed, and 3) a self-reported racial/ethnic group listed as non-Hispanic White (NHW), non-Hispanic Black (NHB), or Hispanic. NAFLD was defined by a controlled attenuation parameter (CAP) score ≥263 dB/m in the absence of excessive alcohol consumption and other causes of liver disease. CSF was defined as a liver stiffness measurement (LSM) ≥8 kPa. Multivariable logistic regression analysis was performed to examine associations between race/ethnicity and the presence of NAFLD and CSF.

Results: The study population included 1067 PWH with a mean age of 52 years and 73% with male sex at birth. 515 (48%) of participants were NHB, and 239 (22%) were Hispanic. NAFLD prevalence was highest for Hispanics (65%) and lowest for NHB (44%) compared to 57% for NHW (overall p< 0.001). The prevalence of CSF was highest for NHW (22%) compared to 15% for Hispanics and 11% for NHB (overall p<0.001). After adjusting for clinically relevant variables (Table), NHB had a lower risk of both NAFLD (adjusted OR: 0.43, 95% CI: 0.28-0.66) and CSF (adjusted OR 0.42, 95% CI: 0.26-0.68) compared to NHW. The adjusted analysis showed no differences in the risk of NAFLD or CSF between Hispanics and NHW (Table).

Conclusion: In this large, multi-ethnic cohort study of persons with well-controlled HIV, non-Hispanic Black participants had approximately 60% lower odds of having NAFLD and CSF compared to non-Hispanic Whites, after adjusting for clinically relevant risk factors. Hispanics did not have a higher risk after adjustment. Further studies are needed to determine the factors associated with racial and ethnic differences in NAFLD in PWH, including genetic variation.

Table. Independent association of NAFLD and clinically significant fibrosis (CSF) with participant's race/ethnicity, from multivariable logistic regression

	NAFLD (CAP≥263 dB/m)*		CSF (LSM≥8 kPa)*	
	OR (95% CI)	P	OR (95% CI)	P
Race/ethnicity, adjusted for age, sex at birth, BMI, T2DM, hypertension, ALT, triglycerides, platelets				
NH White	*Ref.* (1)	-	*Ref.* (1)	-
NH Black	0.43 (0.28, 0.66)	<0.001	0.42 (0.27, 0.68)	<0.001
Hispanic	1.23 (0.78, 1.96)	0.61	0.74 (0.44, 1.26)	0.26

*N=887 due to exclusion of heavy alcohol use, defined by AUDIT score ≥8, and missingness in covariates

743 De Novo Liver Steatosis Among People With HIV On Contemporary Antiretroviral Therapy

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Background: Liver steatosis affects close to 50% of people with HIV (PWH), but longitudinal data are lacking. We investigated the incidence and determinants of de novo steatosis and described the progression to steatohepatitis with significant fibrosis among individuals on antiretroviral therapy (ART) in the Swiss HIV Cohort Study.

Methods: We enrolled cohort participants at Bern University Hospital into a prospective observational study between November 2019 and April 2022. Individuals with viral hepatitis co-infection and pregnant women were excluded. We performed yearly liver assessments using vibration controlled transient elastography (VCTE) and included all patients with at least two measurements. Liver steatosis was defined as controlled attenuation parameter (CAP) ≥248dB/m. We calculated the Fibroscan-AST (FAST) score based on liver stiffness measurement (LSM), CAP and AST; A FAST score >0.67 indicated steatohepatitis with significant fibrosis. We investigated risk factors for de novo steatosis using multivariable logistic regression.

Results: Of 457 individuals enrolled, 368 (80.5%) with ≥2 valid VCTE measurements were included. Median follow-up time was 30 months (IQR 23-37), 105 participants (28.5%) were female and 261 (70.9%) Caucasian. At time of first VCTE, their median age was 52 years (interquartile range [IQR] 43-59), median CD4+ count was 728 cells/µl (IQR 547-939), and 193 (53.3%) had a BMI≥25kg/m^2. Median ART duration was 11 (IQR 6-19) years and 344 (93.5%) had a HIV viral load <50 copies/mL. At first VCTE, 190 participants (51.6%) had liver steatosis, of whom 6 (3.2%) showed steatohepatitis with significant fibrosis. Of 178 participants who did not have liver steatosis at their first assessment, 51 (28.7%) developed liver steatosis during follow-up. In multivariable analysis, BMI≥25kg/m^2 (adjusted odds ratio [aOR], 3.40; 95% confidence interval [CI], 1.66-6.96) and dyslipidemia (aOR 2.59; 95% CI 1.14-5.88) were significantly associated with the development of steatosis. Sex, age and specific ART components were not associated with de novo steatosis. Among 190 participants with steatosis at first VCTE, 6 (3.1%) developed steatohepatitis with significant fibrosis during follow-up.

Conclusion: During three years of follow-up, one in four PWH developed de novo steatosis, with obesity and dyslipidemia being the most important predictors. The progression of liver steatosis to steatohepatitis with significant fibrosis was rare.

744 A Gut Microbiome Signature for HIV and Non-Alcoholic Fatty Liver Disease

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Background: Non-alcoholic fatty liver disease (NAFLD) has emerged as an increasingly recognized problem among people living with HIV (PLWH). The gut-liver axis is considered to be strongly implicated in the pathogenesis of NAFLD. We aimed to characterize the gut microbiota composition in PLWH and NAFLD and compare it with that of two control groups: PLWH without NAFLD and individuals with NAFLD without HIV infection.

Methods: We collected clinical data and stool samples from participants. Bacterial 16S rRNA genes were amplified, sequenced, and clustered into operational taxonomic units. Alpha diversity was studied by the Shannon and Simpson indexes. To study how different the gut microbiota composition is between the different groups, beta diversity estimation was evaluated by principal coordinate analysis (PCoA) using Bray-Curtis dissimilarity. To further analyze differences in microbiome composition, we performed a linear discriminant analysis (LDA) effect size (LEfSe). We selected the genus with a LDA score >4.

Results: We included 30 HIV+NAFLD+, 30 HIV+NAFLD- and 20 HIV-NAFLD+ participants. Major butyrate producers, including Faecalibacterium, Ruminococcus, and Lachnospira dominated the microbiota in all three groups. Shannon's and Simpson's diversity metrics were higher among NAFLD+ individuals (Kruskal-Wallis p = 0.047). Beta diversity analysis showed distinct clustering in NAFLD-, with NAFLD+ participants overlapping regardless of HIV status (ADONIS significance <0.001) (Figure 1A). NAFLD was associated with increased homogeneity across individuals, in contrast to that observed in the HIV+NAFDL- group, in which the dispersion was higher (Permanova test, p value <0.001; ANOSIM, p value <0.001). NAFLD but not HIV determined a different microbiota structure (HIV+NAFLD- vs. HIV+NAFLD+, q-value = 0.002; HIV-NAFLD+ vs. HIV+NAFLD+, q-value = 0.930; and HIV-NAFLD+ vs. HIV+NAFLD-, q-value < 0.001). The most abundant genera in NAFLD- were Prevotella,

Bacteroides, Dialister, Acidaminococcos, Alloprevotella, and Catenibacterium. In contrast, the most enriched genera in NAFLD+ were Ruminococcus, Streptococcus, Holdemanella, Blautia, and Lactobacillus (Figure 1B)
Conclusion: We found a microbiome signature linked to NAFLD, which had a greater influence on the overall structure of the gut microbiota than HIV status alone. We suggest that part of the alterations in the microbiota described as associated with HIV could be confused by the presence of NAFLD, which is more prevalent in people with HIV.

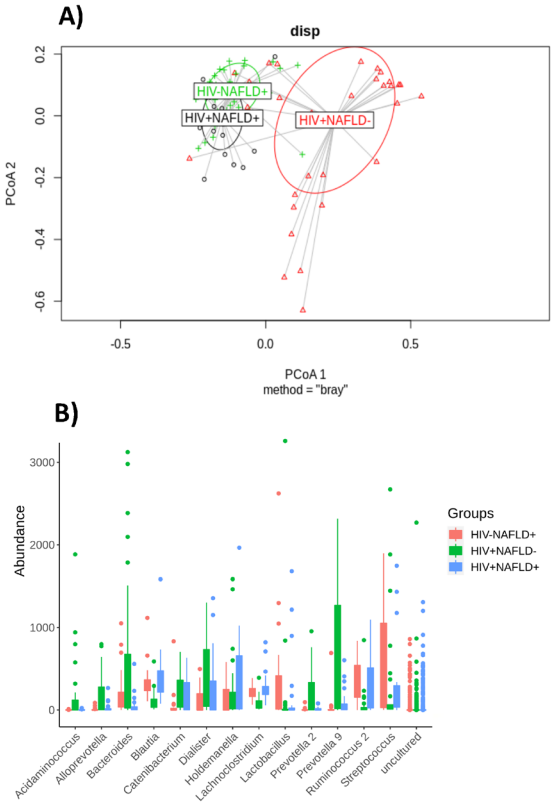

Figure 1. A) Beta-dispersion plot. **B)** Abundance of the most significant genus according to LEfSe.

745 Liver Steatosis Is Not Associated With Endothelial Function or Hormone Use in Transgender Women

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Background: Transgender women (TGW) present disproportionate chronic diseases burden. Nevertheless, very little is known about inflammation-related chronic diseases among TGW in low and middle-income countries (LMIC), especially in the context of HIV infection and gender-affirming hormone therapy (GAHT). We aimed to assess the association of liver steatosis with subclinical atherosclerosis measured by brachial artery flow-mediated dilatation (FMD) and GAHT.
Methods: Cross-sectional study among trans women aged 18+ years of the Transcendendo cohort, Rio de Janeiro, Brazil, between October/2019-May/2023. Participants answered a structured questionnaire, collected blood samples, and performed transient liver elastography by Fibroscan and FMD. Valid elastography results were considered if: had at least 10 valid measurements, the percentage of valid measurements was >60%, and Controlled Attenuation Parameter (CAP) interquartile range (IQR)/CAP <30%. Results with CAP ≥248 dM/m were classified as liver steatosis. Percentage of FMD [(peak diameter-baseline diameter)/baseline diameter] was used for analysis. Bivariate analysis compared TGW with and without liver steatosis.
Results: Among 157 TGW, 131 (83.4%) had valid liver assessments. Among these, median age was 39.0 years (IQR:31.0-44.0), 80(61.0%) were living with HIV, 65(51.0%) were currently on GAHT, and 36(27.5%) had liver steatosis. Participants with steatosis were significantly older, had a higher body mass index, LDL levels, higher proportion of metabolic syndrome, and less frequently were living with HIV. GAHT (current and exposure), hormone levels, and FMD were not associated with liver steatosis. TGW living with HIV according to liver steatosis did not differ on nadir CD4+ count and viral load. The most common antiretroviral regimen was DTG/3TC/TDF (62.5%[10/16] and 71.9%[48/64] among TGW with steatosis and without steatosis, respectively). Six participants were on dual antiretroviral therapy with 3TC/DTG (18.8%[3/16] and 4.7%[3/64] among TGW with and without steatosis, respectively).
Conclusion: Traditional factors and HIV-positive status were associated with liver steatosis among Brazilian TGW. Changes in arterial diameter and GAHT exposure were not associated with liver steatosis. Our findings reinforce the need of including traditional factors of liver steatosis for TGW's clinical assessment. This study was partially funded by ViiV Healthcare UK Ltd.
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746 Increased levels of FGF21 and GDF15 Are Associated With Severity of NAFLD in People With HIV

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Background: Non-alcoholic fatty liver disease (NAFLD) poses a significant health burden in people with HIV (PWH). Fibroblast growth factor 21 (FGF21) is an important regulator of hepatic lipid and glucose metabolism. Higher levels have been associated with hepatic steatosis and liver fibrosis in the general population. Growth differentiation factor 15 (GDF15) is upregulated in chronic inflammatory diseases and associated with cardiovascular dysfunction in PWH. We aimed to describe the trends of FGF21 and GDF15 concentrations in PWH and NAFLD.
Methods: Consenting PWH and no other known cause of liver disease underwent vibration-controlled transient elastography for controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) quantification at three US centers. NAFLD was defined as CAP ≥263 dB/m; advanced fibrosis as LSM > 12kPa. Fasting serum FGF21 and GDF15 were measured by ELISA. Relationships between biomarkers and NAFLD were analyzed using a Censored Tobit Model.
Results: Participants (n=177) had median age 52 years and were 20% cisgender women, 81% overweight/obese, 90% virally suppressed on antiretroviral therapy. Participants with NAFLD (50%) had significantly higher mean (SD) levels of FGF21 [333 (377) vs 226 (305) pg/ml, p=0.002] and GDF15 [859 (371) vs 744 (366) pg/ml, p=0.02] than participants without NAFLD. FGF21 levels increased with BMI (p=0.04). Higher FGF21 and GDF15 levels correlated modestly with higher CAP (FGF21 r=0.30, p<0.001; GDF15 r=0.21, p=0.01) and LSM scores (FGF21 r=0.25, p<0.001; GDF15 r=0.27, p=0.01). FGF-21 concentrations were 40% higher (mean Log Difference [95% confidence interval]= 0.34 (0.06,0.62), p=0.02]) and GDF15 17% higher (0.16 [0.01,0.32], p=0.04) in persons with vs. without NAFLD. Participants with the highest FGF21 levels (quartile 4) had higher NAFLD prevalence (71% vs 39%, p=0.01), higher mean CAP (301 vs 247 dB/m, p=0.001) and LSM (6.2 vs 4.5 kPA, p=0.004) values, and longer mean duration of HIV (10 vs 17 years, p<0.001) compared to persons in quartile 1. Similar trends were seen with GDF15 level quartiles.
Conclusion: PWH and NAFLD had higher levels of FGF21 and GDF15 than those without NAFLD, with higher levels correlating with greater liver steatosis and fibrosis. FGF21 and GDF15 may have a role in identifying PWH at risk of metabolic liver disease. Further research is needed to elucidate the role of these circulating factors in PWH and NAFLD and their diagnostic and prognostic value.

747 Plasma Proteomics Signature of People Living With HIV, With NAFLD, With and Without Obesity

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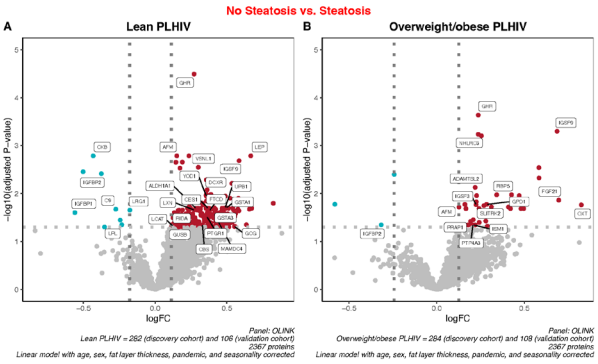
Background: Non-alcoholic fatty liver disease (NAFLD) is a leading cause of liver-related morbidity in people living with HIV (PLHIV). Obesity is an important risk factor but NAFLD also occurs in lean PLHIV, with possible different

underlying pathophysiology. Proteomics facilitate biomarker discovery and may help identify biological mechanisms.

Methods: We analyzed data from 1050 PLHIV with transient elastography measurements from the 2000HIV cohort, a Dutch multi-center study amongst virally suppressed PLHIV (NCT03994835). Proteomics was available (Olink® Explore, 2367 proteins) from 1036 individuals (98.7%). Differentially expressed proteins (DEP) were compared between PLHIV with and without liver steatosis (controlled attenuation parameter ≥ 248 dB/m) and with and without liver fibrosis (liver stiffness measurement ≥ 7.0 kPa) using a limma model. We stratified by BMI group (lean [BMI < 25 kg/m² or < 23 kg/m² in PLHIV from Asian descent] vs. overweight/obese PLHIV [other BMI]). Functional pathways from the GO biological processes, KEGG and Reactome libraries enriched with DEP were identified using Metascape. DEP were correlated to HIV-specific characteristics and antiretroviral therapy (ART).

Results: Plasma proteome of PLHIV with steatosis or fibrosis were altered from those without steatosis or fibrosis, respectively. DEP in PLHIV with steatosis were enriched in metabolic pathways, whereas DEP in PLHIV with fibrosis were enriched in interleukin-10 (IL-10) signaling, cell-adhesion, and amino acid metabolism. More DEP (n = 27) were identified in lean PLHIV with versus those without steatosis compared to overweight/obese PLHIV (n = 15), and only four DEP were shared between lean and overweight/obese PLHIV, i.e. IGFBP2, GHR, AFM, and the novel protein IGSF9. IGSF9 was also DE in PLHIV with fibrosis. Especially in lean PLHIV, multiple DEP were associated with HIV-characteristics including HIV duration and CD4 nadir and current ART (NNRTI and INSTI).

Conclusion: PLHIV with steatosis and fibrosis have an altered plasma proteome including upregulation of proteins involved in metabolism, cell-adhesion and IL-10 signaling. Steatosis signatures differed between lean and overweight/obese PLHIV. Furthermore, our findings indicate involvement of HIV-specific factors in the pathogenesis of lean NAFLD, and we discovered the potentially novel NAFLD biomarker IGSF9.



748 WT1 Upregulation by Lytic Induction of Kaposi Sarcoma Herpesvirus

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Background: Kaposi Sarcoma herpesvirus (KSHV or HHV8) is the etiologic agent of Kaposi sarcoma and is associated with Multicentric Castleman disease and Primary effusion lymphoma. KSHV demonstrates two different phases of infection in the host: latent and lytic which are both essential to KSHV pathogenesis. The viral protein regulator or transcription activator (RTA) is required for the latent to lytic switch. In previous work, we have demonstrated that de novo KSHV latent infection and in particular vFLIP upregulates Wilms' Tumor 1 (WT1) expression along with its oncogenic isoforms known to have various functions contributing to tumorigenesis. The expression and functions of WT1 have not been explored during lytic KSHV infection.

Methods: Cell culture models of latent and lytic KSHV infection were utilized, including iSLK-BAC16 cells latently infected with KSHV as well as HuARLT-1 and HUVEC E4 endothelial cells that were infected with KSHV. iSLK-BAC16 cells, which express RTA under a doxycycline-inducible promoter, were treated with sodium butyrate and doxycycline 2ug/ml for lytic reactivation. HuARLT-1 and HUVEC E4 were treated with sodium butyrate to induce the lytic program. WT1 siRNA was transfected in the iSLK-BAC16 and HUVEC E4 model systems using Lipofectamine RNAiMAX.

Results: Here we have found that upon induction of lytic reactivation of KSHV-infected iSLK-BAC16 cells, WT1 is upregulated significantly and in particular oncogenic isoforms. Significant WT1 upregulation is also noted upon treatment with sodium butyrate of de novo KSHV infected HuARLT-1 and HUVEC E4 endothelial cells. Using the iSLK-BAC16 and HUVEC E4, we also demonstrate that upon WT1 knockdown during lytic reactivation, there is noted further increase in vFLIP, LANA, and K8.1 viral gene expression.

Conclusion: These findings suggest that both latent and lytic KSHV infection upregulate WT1 expression. Furthermore, given the findings that WT1 knockdown during lytic reactivation leads to marked upregulation of viral gene expression, our data suggests that WT1 may play a complex role in regulating these two phases of infection that we are exploring further in ongoing studies.

749 Saliva Kaposi Sarcoma Herpesvirus Levels as a Diagnostic Marker of Visceral Kaposi Sarcoma

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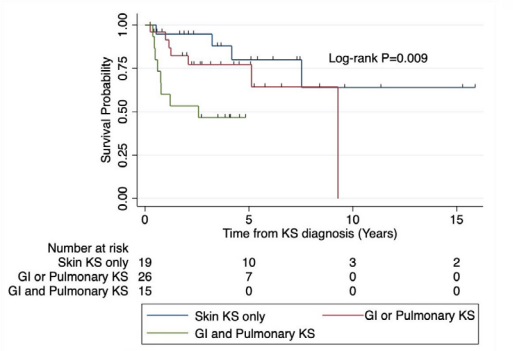
Background: Kaposi sarcoma (KS), an HIV-associated malignancy, is caused by Kaposi sarcoma herpesvirus (KSHV). KS commonly affects the skin but can also lead to symptomatic visceral manifestations in the pulmonary and gastrointestinal (GI) tracts; it requires invasive procedures such as bronchoscopy or endoscopy for diagnosis. We assessed the outcomes of patients (pts) with visceral KS and evaluated the saliva KSHV viral load (VL) as a diagnostic marker.

Methods: We conducted a retrospective study of pts with a history of KS from the HIV and AIDS Malignancy Branch who underwent bronchoscopy and/or endoscopy/colonoscopy for symptoms concerning pulmonary and GI KS between 2005-2023. Diagnosis of pulmonary KS was based on imaging and visualization of large airway lesions consistent with KS on bronchoscopy. GI KS was confirmed with a biopsy following diagnostic procedures. KSHV VL DNA was quantified in saliva and peripheral blood using primers for the KSHV K6 gene, while cell number was calculated using human endogenous retrovirus 3 primers. Receiver operator curves were created to observe sensitivity and specificity of KSHV saliva VL to diagnose visceral KS among pts with visceral KS symptoms. Overall Survival (OS) was estimated using Kaplan-Meier analysis from date of KS diagnosis to death or last follow-up.

Results: Sixty pts (57 with HIV diagnosis, 77% on antiretroviral therapy, median (med) HIV VL of 87 copies/mL and CD4 T cell count of 125 cells/μL) underwent procedures to identify visceral KS. Twenty-six had either pulmonary or GI KS (pulmonary= 8, GI= 18), 15 had both GI and pulmonary KS, and 19 had skin KS without visceral KS. Of those with any visceral KS, 51.2% had other concurrent KSHV-associated disorders. The med KSHV VL in the saliva among those with visceral KS was 1 (IQR: 1, 67566) copy/10^6 cells and was 767 (IQR: 629, 8455) copies/10^6 cells in the peripheral blood. A saliva KSHV VL level of > 190 copies/10^6 cells had a sensitivity of 46%, specificity of 76%, and a positive likelihood ratio of 2 for predicting the presence of visceral disease among symptomatic pts. Median OS in pts with skin KS only was not reached, was 9.2 years in pts with GI or pulmonary KS, and 2.6 years in pts with both GI and pulmonary KS (P=0.009, Figure 1).

Conclusion: Despite well controlled HIV among pts with KS, the presence of visceral KS impacts overall survival. Saliva KSHV VL may be a useful tool to aid in diagnosis of visceral KS in limited-resource settings.

Figure 1: OS Kaplan-Meier curve comparing different KS patient groups.



750 Baseline KSHV T-Cell Responses Are Associated With Pre-Treatment Clinical Presentation in KS

Ralph Kamel[1], Minhee Kang[2], Carlee Moser[2], Richard Ambinder[3], Dirk Dittmer[4], Lara Hosey[5], Roy Matining[2], Mina Hosseinipour[4], Margaret Borok[6], Thomas Campbell[7], Susan E. Krown[8], Bernard Macatangay[1], Charles R. Rinaldo[1], for A5263/AMC066 and A5264/AMC067

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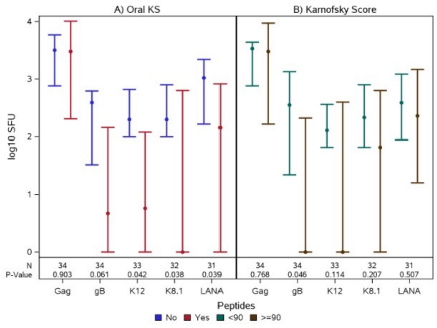
Background: T cell immunity is important in controlling KS herpesvirus (KSHV) disease progression. We evaluated T cell responses to KSHV and associations with pre-treatment clinical characteristics and outcomes in 2 ACTG/AMC studies (A5263/AMC066; A5264/AMC067) of KS treatment in resource-limited settings.

Methods: T cell ELISPOT responses (log_{10} spot-forming units [SFU]/10^6 cells) to 2 latency (LANA, K12) and 2 lytic (gB and K8.1) KSHV and to HIV Gag peptides were measured from 49 advanced KS (A5263/AMC066) and 94 mild/moderate KS (A5264/AMC067) participants with samples. In A5264/AMC067, we also measured T cell PD-1 expression by flow cytometry. Wilcoxon rank-sum and Fisher's exact tests were used.

Results: At entry, median age was 34; mostly male and black African. Median CD4 count was 250 and 190 cells/mm³, and median plasma HIV-1 RNA was 3.5 and 5.1 log_{10} cps/mL in advanced and mild/moderate KS, respectively. Advanced KS participants with oral KS had lower baseline responses to K12 (median: 0.76 vs 2.30 log_{10} SFU; p=0.042), K8.1 (0 vs 2.3 SFU; p=0.038), and LANA (2.15 vs 3.02 SFU; p=0.039) than those without. In mild/moderate KS, a higher proportion of participants without oral KS had positive response to LANA (65% vs. 19%; p=0.013). Advanced KS participants with Karnofsky scores (KPS) <90 had higher gB responses than those with KPS ≥90 (median: 2.55 vs 0 SFU; p=0.046). Similarly, in mild/moderate KS, a higher proportion of participants with KPS <90 had detectable responses to gB (63% vs. 21%; p=0.040). Despite strong responses to Gag, this response was not associated with oral KS or KPS. There was a trend for mild/moderate participants with screening T0 KS stage to respond to gB compared to those with T1 stage (54% vs 17%; p=0.056). Mild/moderate participants with oral KS had a trend for higher %PD1+CD8+ T cells (median 18.45% vs 14.40%; p=0.074) than those without. At 12 weeks, a higher proportion of mild/moderate participants without early KS disease progression had a drop in %PD-1+CD4+ (74% vs 21% with early disease progression; p=0.002) and %PD-1+CD8+ T cells (89% vs 57%; p=0.042). KSHV T cell responses were not associated with clinical outcomes in either study.

Conclusion: In advanced and mild/moderate KS, pre-treatment KSHV-specific T cell responses were associated with several pre-treatment clinical characteristics. In mild/moderate KS, decreased T cell exhaustion was associated with less early KS disease progression. This supports T cell immunity's importance in controlling KS.

Figure: T cell interferon γ responses (median;IQR) to HIV-1 and KSHV peptides according to oral KS status and screening Karnofsky score in advanced KS A5263/AMC066.



751 Description of Clonal Hematopoiesis in a Hospital-Based Cohort of People Living With HIV

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Background: In the antiretroviral therapy era, the population of people living with HIV (PLWH) is aging, with increased mortality from chronic diseases and non-AIDS defining cancers. Similarly, clonal hematopoiesis (CH) has been associated with both malignancy and cardiovascular disease in the non-HIV population. Clonal hematopoiesis has been described as infrequent in patients under 50 and becomes more prevalent in the aging population. Recent studies have demonstrated that PLWH have a higher rate of CH than people without HIV. We aimed to describe CH in a cohort of PLWH as the initial phase of an ongoing analysis to determine the prognostic implications of CH in PLWH.

Methods: We used phenotype and whole exome sequencing data from patients recruited to the Mount Sinai BioMe Biobank. We identified 487 patients in the cohort who met criteria for HIV. CH was called by excluding any patient with a myeloid malignancy and by filtering for predefined myeloid CH mutations with variant allele frequency (VAF) ≥ 2%.

Results: Out of 487 total patients with HIV, we identified 29 patients with HIV with 30 CH mutations. The median age of patients without CH was 49, while the median age of patients with CH was 57. 7 out of 29 of patients with CH were below the age of 50. In logistic regression analysis, age was significantly associated with presence of CH in the HIV population (p=0.006) while ancestry, smoking, and sex were not. The most common CH mutations in the cohort were DNMT3A (8/30) and TET2 (4/30). None of the patients had mutations in ASXL1. Median VAF was 8.4% (IQR 6.6 – 11.7%).

Conclusion:Our findings show a seemingly young age distribution of patients with CH in our cohort of PLWH, though we have not yet compared our cohort to a non-HIV population. Distinct from previously reported findings that ASXL1 was the most commonly mutated gene, we did not identify any mutations in ASXL1 in our cohort. Instead, other common CH genes such as DNMT3A and TET2 represented the majority of mutations. Interestingly, smoking, a commonly implicated risk factor for CH, was not significantly associated with presence of CH in our cohort. Multivariable analyses are ongoing with plans to investigate CH in patients with HIV as a predictor of cardiovascular disease, malignancy, and death.

752 Inflammatory Signatures Predict the Risk of Severe Non-AIDS Events, Especially Non-AIDS Cancers

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Background: While elevated levels of inflammatory biomarkers in people with HIV (PWH) have consistently been linked to a higher risk of severe non-AIDS adverse events (SNAEs), their clinical significance and the relevant inflammatory pathways are not well-established.

Methods: In this nested case-control study within the Spanish AIDS Research Cohort (CoRIS), from a pool of 18,573 PWH we selected 89 cases who experienced SNAEs after two years of ART (including cardiovascular events, non-AIDS-related cancers, or non-accidental deaths) and had available plasma at month 24 (±6) of suppressive ART. Cases were matched with 89 controls using propensity-score matching. Covariates included age, sex, risk factor for HIV transmission, AIDS history, geographical origin, year 2 CD4/CD8 ratio, baseline HIV RNA, ART regimen, total cholesterol and HDL cholesterol. We measured the expression of 368 inflammatory proteins in plasma using Olink Proteomics' Proximity Extension Assay and analyzed their functions in Metascape. We used Welch 2-sample t-tests at a confidence level of 0.95 for every protein for a given outcome and corrected for multiple testing by the Benjamini-Hochberg method.

Results: We studied 178 PWH, median age 45 years, 25% women, 49% smokers, median CD4 nadir 208 cells/uL, median CD4 counts at year 2 469 cells/uL. We found significant changes in the expression of inflammatory proteins before month 24 subsequently predicting SNAEs risk. In cases, 25 proteins were upregulated, and 8 were downregulated. The greatest size effect was found for CLIP2, SKAP2, DAPP1, MANF, with approximately two-fold increased expression in cases. A subanalysis on patients with cardiovascular events and non-accidental deaths did not show significant differences in protein expression. In contrast, cases who experienced non-AIDS cancers showed a marked (near 3-fold) upregulation of 59 plasma proteins and downregulation of 2 proteins, being SKAP2, CLIP2, DAPP1 and MANF those more discriminant between groups. Functional analyses indicated that these proteins predicting SNAEs are involved

in infection, inflammation signaling pathways, immune response activation, and cancer-related pathways, including NF-KB, PD-L1, and B-cells.
Conclusion: Our study revealed a specific inflammatory signature predicting NAEs risk, with distinct inflammatory proteins strongly associated with the onset of non-AIDS cancers. These proteins warrant further exploration as promising biomarkers for SNAEs and as potential therapeutic targets.

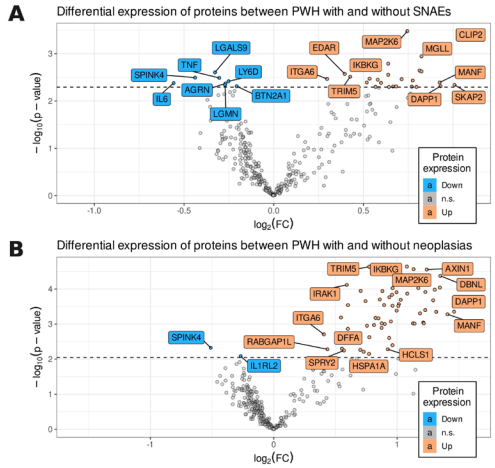

Figure 1. Observed changes in the expression of 368 inflammatory proteins measured by Proximity Extension Assay (Olink Proteomics). Proteins above the dashed lines have an adjusted p-value < 0.05. FC: fold change, n.s.: not significant.

753 Starting ART Early After HIV Acquisition Reduces Long-Term Non-AIDS-Defining Malignancy Risk

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Background: Non-AIDS Defining Malignancies (NADM) have become a prominent cause of death in people with HIV (PWH). Evidence shows that starting antiretroviral treatment (ART) at a higher CD4 count is associated with reduced NADM risk. We aimed to investigate whether starting ART early after acquiring HIV reduces NADM risk even further.
Methods: We included PWH 18 years or older from the Dutch National ATHENA cohort without a known NADM diagnosis starting ART between 1/1/2000–31/12/2022. NADM and infection-related NADM were analyzed separately. Individuals who started ART ≤365 days of a last known negative HIV test or with a documented primary infection (Fiebig stages 1-5) were categorized as "Early-ART", and all others as "Late-ART" starters. Hazard Ratios (HR) for NADM were estimated by unadjusted and adjusted Cox regression. Models were adjusted for traditional (age, sex at birth, calendar time, HIV transmission category, smoking (time-updated), and region of origin) and HIV related (time-updated CD4 count lagged by 3 months, CD4/8 ratio and time spent with HIV RNA >1000 copies/ml) factors.
Results: Early-ART compared to Late-ART starters were younger (median age 34.7 vs. 39.4 years), more often male (94.3 vs. 80.0%), with a CD4 count >500 cells/mm^3 at ART start (42.6 vs. 18.8%), less often current or former smokers (39.7 vs. 44.9%), and had shorter median follow-up (68 vs. 115 months). In the Early-ART starters (n=2,036) 28 NADM occurred during 12,454 PYFU (IR 2.2/1000 PYFU) versus 1,160 NADM during 220,237 PYFU (IR 5.3/1000 PYFU) in Late-ART starters (n=22,183). Unadjusted, Early-ART start was associated with a significantly reduced NADM hazard (HR 0.48 [95% Confidence Interval (CI) 0.33–0.69]), which was only moderately attenuated after adjustment (multivariate HR 0.63 [95% CI 0.43–0.92]). When only considering infection-related NADM, 8 events occurred in Early-ART starters (n=2,037) during 12,531 PYFU (0.6/1000 PYFU) versus 378 during 223,390 PYFU (IR 1.7/1000 PYFU) in Late-ART starters (n=22,252). Early-ART start was associated with a significantly lower infection-related NADM hazard (HR 0.38 [95% CI 0.19–0.78]) in unadjusted analysis. In our multivariable model results were similar to the all-NADM analysis, but lacked statistical significance (HR 0.64 [95% CI 0.31–1.29]).
Conclusion: Starting ART within a year of acquiring HIV or during primary infection reduces the risk of NADM compared to starting ART later after infection. Larger studies should assess the impact on individual NADM types.

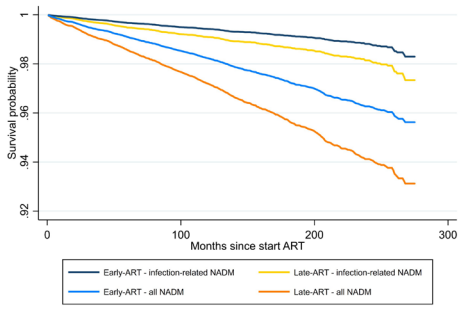

Figure1. Multivariable survival analyses in Early versus Late-ART.
Infection-related NADM: hepatocellular, base of tongue, pharyngeal, tonsillar, anal, penile, vaginal, vulvar, gastric carcinomas, and non-AIDS-defining lymphoma types.

754 Prevalence of Cancer Screening in People With HIV Utilizing a Symphony Health Data Linkage in Texas

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[1]National Cancer Institute, Rockville, MD, USA, [2]National Cancer Institute, Bethesda, MD, USA

Background: Cancer risk is elevated in people with HIV (PWH) compared to those without HIV. Screening for cancer can identify cancer at earlier stages where curative therapy can be most efficacious, or, in the case of cervical and colorectal cancers, identify precancerous lesions that can be treated, preventing progression to malignant cancer. For PWH, cancer screening is important given higher incidence of late-stage disease at diagnosis, disparities in receipt of cancer treatment, and elevated risk of cancer related mortality.
Methods: Data from the HIV/AIDS Cancer Match (HACM) Study, a population-based HIV and cancer registry linkage was linked to Symphony Health, an aggregator of health data including claims from medical, laboratory, hospital, and physician records, in Texas during 2008-2015. Among PWH, we estimated the prevalence of anal, breast, cervical, colorectal, and prostate screening using International Classification of Diseases, Ninth and Tenth Revision (ICD-9/10) diagnosis codes, Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS) codes, and revenue codes. For each screening type we limited the cohort to those who were screening eligible based on age criteria as of 2008, and then estimated ever screening during 2008-15.
Results: We included a total of 51,610 people with HIV with linked claims data. Approximately 77.6% of PWH were male, and racial/ethnic breakdown was 39.8% Non-Hispanic (NH) Black, 36.6% NH White, 21.9% Hispanic, and 1.8% Other/Unknown. For age distribution, 16.8% was aged 18-29, 24.6% aged 30-39, 35.7% aged 40-49, 18.0% aged 50-59, 4.3% aged 60-69 and 0.6% aged 70-80. For women with HIV aged 30 and older, 38.5% received cervical cancer screening and similarly, 40.0% had ever received screening for breast cancer, between the ages of 40-74 during the observation period. Approximately 31.5% of men with HIV, between the ages of 55-69 received prostate cancer screening. For PWH between the ages of 45-75, approximately 26.7% received screening for colorectal cancer. Lastly, while official guidelines do not exist for the general population, among PWH between the ages of 35-70, only 0.96% received screening for anal cancer.
Conclusion: Findings suggest utilization of screening modalities for anal, breast, cervical, colorectal, and prostate cancer are underutilized among PWH in Texas. More work is needed to determine barriers to receiving screening.

755 Racial Disparities in Cancer Incidence Among Men Who Have Sex With Men With HIV in the US, 2001-2019

Benton G. Meldrum[1], Meredith Shiels[1], Jennifer K. McGee-Avila[1], Tyler Adamson[2], Qianlai Luo[1], Tabassum Insaf[3], Ruth Pfeiffer[1], Eric Engels[1], Cameron B. Haas[1]
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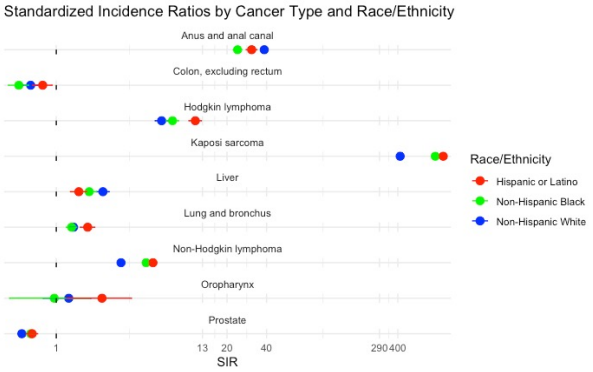
Background: Men who have sex with men (MSM) are disproportionately affected by HIV, representing 68% of new diagnoses in 2019. Racial inequities in access to HIV screening, diagnosis, and treatment result in lower prevalence of viral suppression for non-white MSM. We hypothesize that higher risk of progression to AIDS is likely to increase cancer risk among non-white MSM with HIV (MSMWH).
Methods: We investigated racial disparities in cancer risk among MSMWH from 2001-2019 using the HIV/AIDS Cancer Match Study data. We examined 9 cancer types: prostate, lung, liver, anal, non-Hodgkin lymphoma, oropharyngeal,

Kaposi sarcoma, colon, and Hodgkin lymphoma. We calculated age-adjusted incidence rates and standardized incidence ratios (SIR) by dividing observed cases by expected cases based on rates in the US population within region, age group, and year. We stratified these calculations by AIDS status.

Results: Overall, excess risk of each cancer type varied significantly by race/ethnicity. We examined 9 cancers (see figure), but these results will only discuss anal cancer because rates are particularly elevated among MSMWH. Non-Hispanic (NH) white MSM had an overall age-adjusted incidence rate of 87.4 per 100,000 person-years (95% CI = 84.8, 89.9), significantly higher than NH Black MSM (68.8; 95%CI=66.1, 71.5), and Hispanic/Latino MSM (50.3; 95%CI=47.8, 52.7). When stratified by AIDS status, those with a prior AIDS diagnosis were 3 times higher for NH white and NH Black MSM, but 4.5 times higher for Hispanic/Latino MSM, compared to those without. For SIRs, NH white MSMWH had 38.4 (95% CI = 36.3, 40.6) times the risk of anal cancer compared to all NH white men in the US population. NH Black and Hispanic/Latino MSM had 24.1 (95% CI = 22.3, 26.0) and 30.1 (95% CI = 28.0, 33.8) times the risk, respectively. These SIRs were greater among all races/ethnicities for MSM with a prior AIDS diagnosis compared to MSM without.

Conclusion: Incidence rates and relative risks compared to the general population differed significantly by race/ethnicity. When stratified by AIDS diagnosis, SIRs and SIR ratios were significantly different between races/ethnicities. Notably, risk of anal cancer was only 2.5 times higher for non-Hispanic white MSM diagnosed with AIDS compared to HIV, but 3.5 times higher for Hispanic/Latino MSM. Hispanic/Latino MSM often had the highest SIRs suggesting a significantly higher excess risk among Hispanic/Latinos or potential under-ascertainment of cancers in the general population.



756 Prevalent and Incident Cancers in a Cohort of People With HIV in Latin America

Valeria I. Fink[1], Carina Cesar[1], Shengxin Tu[2], Bryan E. Shepherd[2], Claudia P. Cortes[3], Guilherme Calvet[4], Juan Sierra-Madero[5], Eduardo Gotuzzo[6], Diana Varela[7], Jessica L. Castilho[2], for the Caribbean, Central and South America Network for HIV Epidemiology (CCASAnet)

[1]Fundación Huésped, Buenos Aires, Argentina, [2]Vanderbilt University, Nashville, TN, USA, [3]University of Chile, Santiago, Chile, [4]Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, [5]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [6]Universidad Peruana Cayetano Heredia, Lima, Peru, [7]Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras

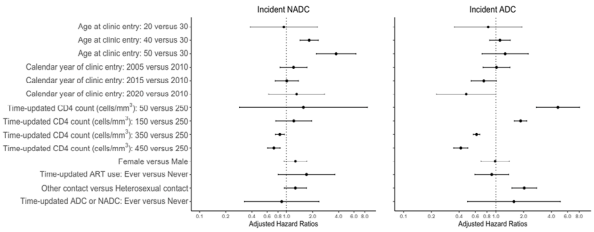
Background: Cancer is a leading cause of morbidity and mortality among people with HIV (PWH). Earlier HIV diagnosis and timely access to antiretroviral treatment (ART) have led to longer life expectancies among PWH, resulting in an increase in aging-related comorbidities, including non-AIDS-defining cancers (NADC). While the epidemiology of NADC in PWH has been described in high resource settings, less is known in low- and middle-income settings. We evaluated the prevalence and incidence of NADC and AIDS-defining cancers (ADC) within the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) and factors associated with these malignancies.

Methods: PWH ≥18 years old enrolled at CCASAnet sites in Argentina, Brazil, Chile, Honduras, Mexico and Peru from 2000-2020 were included. Prevalent (diagnosed any time before or <90 days after clinic entry) and incident (diagnosed ≥90 days after clinic entry) NADC and ADC were collected. Clinical and demographic factors associated with prevalent and incident ADC and NADC were evaluated using multivariable logistic regression and multi-state Cox proportional hazards models, respectively. Models included age, sex, HIV acquisition risk, site, year of cohort entry, and time-updated ART, CD4 cell count, and history of other respective cancer.

Results: In total, 27706 PWH were included. At clinic entry, median age was 33 years (IQR: 27-41), 78% were male, 37% had previous ART, and median CD4 cell count was 257 cells/ ml (IQR: 96- 457). Prevalent ADC was present in 795 PWH, 101 had NADC and 7 had both ADC and NADC. Risk of prevalent ADC and NADC varied by site. Older PWH, those with lower CD4 count (<250 cells/ml), and HIV acquisition risk factors other than heterosexual contact were more likely to present with prevalent ADC and NADC (p<0.05 for all). Those with male sex, earlier year of entry and prior ART were also more likely to present with ADC (p<0.05 for all). During a median of 3.9 (IQR: 1.0-9.4) years of follow up, there were 300 incident ADC and 264 NADC. Risk factors for incident ADC and NADC are shown in Figure 1.

Conclusion: Prevalent and incident ADC were more frequent than NADC among PWH in CCASAnet. Older age and lower CD4 were associated with prevalent and incident NADC and prevalent ADC. Recent years of cohort entry and higher CD4 count were associated with decreased risk of prevalent and incident ADC. These findings continue to underscore the importance of early HIV diagnosis and treatment.

Figure 1: Forest plot of adjusted hazard ratios for incident NADC and ADC estimated from the multi-state Cox proportional hazard models



757 Increased Cancer Risk With Low CD4 Counts Persists Despite Over 2 Years of Virological Suppression

Jennifer F. Hoy, for the RESPOND and D:A:D Study Groups

Alfred Hospital, Melbourne, Australia

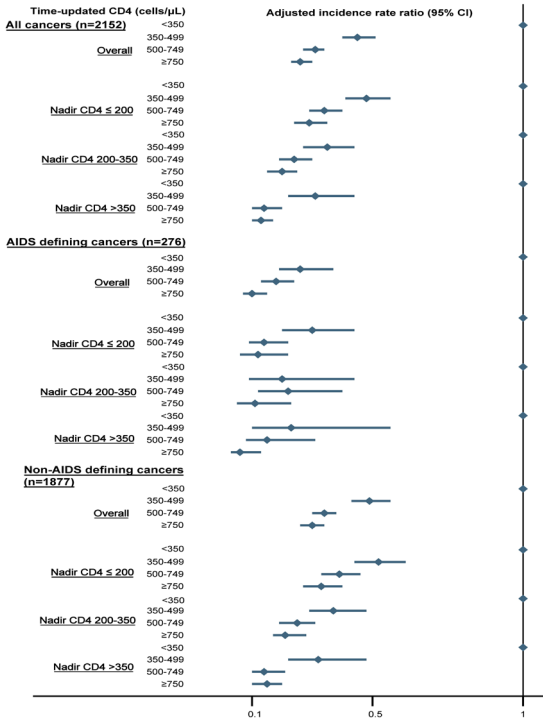
Background: Antiretroviral therapy (ART) leads to a reduction in AIDS-related events and lower CD4 counts are associated with some non-AIDS events. The impact of long term virological suppression on non-AIDS related cancers (NADC) is unclear. We determined whether the most recent CD4 count was an independent predictor of incident cancer risk in people with HIV who had virologic suppression (VS) for at least 2 years.

Methods: Individuals from the D:A:D and RESPOND cohort collaborations who achieved 2 years of VS on ART were included. Follow-up was from baseline (date of VS for 2 years) until the earliest of a first cancer event, confirmed virological failure (>200 copies/mL) or cessation of ART for >2 months, final follow-up, or administrative censoring date (D:A:D: 2/1/2016; RESPOND: 12/31/2021). Multivariable Poisson regression was used to assess associations between cancer incidence (total, AIDS-defining cancer (ADC), NADC, infection-related, smoking-related and BMI-related cancer) and time updated CD4 count (<350, 350-499, 500-749 and >750 cells/μL) stratified by pre-ART nadir CD4 count and adjusted for confounders determined a priori.

Results: Overall, 51,622 people with VS were included (median [IQR] baseline age 44 years [37, 51], CD4 count 536 cells/μL [376, 729], nadir CD4 count 238 cells/μL [112, 386], 72% male, 36% current smokers). There were 2152 incident cancers during a total of 321,126 person-years of follow-up (PYFU), median 6 years [2.9, 9.5]) (incidence rate (IR)/1000 PYFU 6.70 [95% confidence interval 6.42, 6.99]). This included 276 ADC (0.86 [0.76, 0.97]/1000 PYFU), and 1876 NADC (5.84 [5.58, 6.11]). There were 721 infection-related (2.24 [2.08, 2.41]), 927 smoking-related (2.89 [2.7, 3.08]), and 491 BMI-related (1.53 [1.4, 1.67]) cancers, which were not mutually exclusive. After adjustment, there was a significant reduction in the adjusted IR ratio (aIRR) by higher time-updated CD4 count for all cancers (overall and by type) stratified by nadir CD4 count (Figure). No significant interaction between time-updated CD4 count and time-updated age, or calendar periods was present.

Conclusion: Despite being virologically supressed on ART for >2 years, individuals with poorer immune recovery (CD4 <500 cells/μL) continue to experience a significantly higher incidence of all cancer groups. This underscores

the importance of earliest possible diagnosis of HIV and prompt initiation of ART to ensure optimal sustained risk reduction of both ADC and NADC.



758 Incidence of Diffuse Large B-Cell Lymphoma in Relation to the HIV Epidemic in South Africa 2011-2021

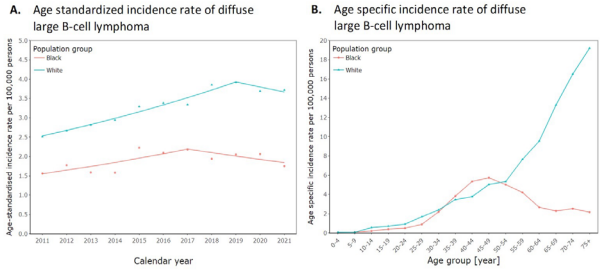
Carole Metekoua[1], Mazvita Muchengeti[2], Yann Ruffieux[1], Patricia Kellett[2], Matthias Egger[1], Eliane Rohner[1], Tracey Wiggill[3]
[1]University of Bern, Bern, Switzerland, [2]National Health Laboratory Service, Johannesburg, South Africa, [3]Stellenbosch University, Stellenbosch, South Africa

Background: Diffuse large B cell lymphoma (DLBCL) is HIV-associated and the most common type non-Hodgkin lymphoma worldwide. We examined the impact of the HIV epidemic and antiretroviral therapy (ART) roll-out on incident DLBCL in South Africa by comparing characteristics and temporal trends of incident DLBCL between the Black (high HIV prevalence) and the White (low HIV prevalence) populations

Methods: We identified DLBCL diagnosed in South Africa from 2011-2021 in the pathology-based National Cancer Registry using International Classification of Disease Oncology, 3rd Edition morphology codes. Using direct standardization, we computed age-specific incidence rates and estimated yearly age-standardized incidence rates (ASIR). We used Joinpoint regression to estimate annual percentage changes (APC) in the ASIR of DLBCL.

Results: In South Africa, 13,560 DLBCL were diagnosed from 2011-2021; 55% of them (n=7410) were among men. The median age at DLBCL diagnosis was 47 years (IQR=37-59). Two-thirds of incident DLBCL occurred in Black (65% [n=8790]) and 22% in White individuals (n=3006). The incidence of DLBCL was highest among middle-aged adults in the Black population and older White people (Figure A). The overall ASIR of DLBCL per 100,000 persons was 5.8 in the White and 1.8 in the Black population. The ASIR of DLBCL was higher in the White population across all calendar years (Figure B). In the Black population, we noted an annual increase of 5.9% (95%CI 0.02 to 37.1) from 2011-2017 with a declining trend thereafter (APC -4.2%; 95%CI -22.8 to 3.7). Similarly, in the White population, the ASIR of DLBCL showed a yearly increase of 5.6% (95%CI 4.8 to 7.9) from 2011-2019 with a declining trend thereafter (APC -3.4%; 95%CI -8.1 to 2.4).

Conclusion: Whereas incident DLBCL in the White population mostly occurs among elderly individuals, the high DLBCL incidence rates among middle-aged Black individuals in South Africa indicate that HIV primarily drives incident DLBCL in this population. However, despite the introduction of ART in 2004, the DLBCL rates continued to increase in the Black population for more than a decade and only decreased one year after introducing the universal-test-and-treat policy in 2016. This suggests that wide coverage and timely initiation of ART are needed to reduce the DLBCL incidence in the Black population in South Africa. The reduced DLBCL ASIRs in 2020-2021 might be partially attributed to the COVID-19 pandemic.



759 Clinical Predictors and Outcomes of Anal Cancer for People With HIV in an Inception Cohort

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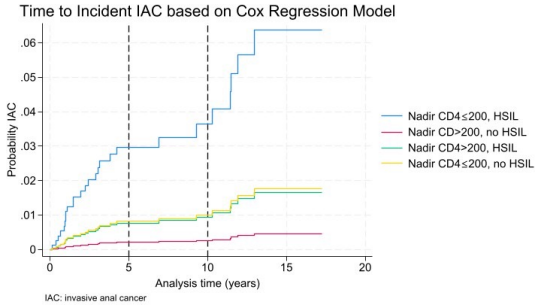
[1]University of California San Diego, San Diego, CA, USA, [2]University of California San Diego, La Jolla, CA, USA

Background: The heterogeneity of risk for invasive anal cancer (IAC) among individuals living with HIV (PWH) underscores the importance of identifying clinical predictors to inform a shared decision-making framework for screening. We investigated predictors of IAC and described outcomes among those diagnosed with IAC.

Methods: The study clinic assembled a longitudinal HIV inception cohort of anal cancer screening outcomes. Screening procedures included anal cytology, digital anorectal examination, high-resolution anoscopy (HRA), and access to ablative treatments. We computed the adjusted probabilities of developing IAC over 5 and 10 years since the initial screening anal cytology. We describe the clinical outcomes of those diagnosed with IAC. Cox proportional models with inverse probability weighting were fit to account for differential screening in the cohort and to construct a nomogram for predicting IAC risk.

Results: Between 2007 to 2020, 8139 PWH received care at UCSD Owen Clinic, of whom 4105 (49.8%) underwent at least 1 anal cytology test and were followed for a median of 5.5 years (up to 13 years). Among them, 32 individuals develop IAC (age range at diagnosis 29-76 years). Those diagnosed with IAC following their first anal cytology were more likely to be younger and exhibit anal high-grade squamous intraepithelial lesion (aHSIL) on initial or subsequent follow-up cytology. Additionally, they showed lower median and nadir CD4 cell counts and underwent anal ablative treatment less frequently. Analyses did not reveal differences in IAC development based on gender identity, race, ethnicity, HIV risk factor, or tobacco use. The highest risk of IAC was associated with PWH having nadir CD4 cell count less than 200 with a hazard ratio (HR) of 3.73 (95%CI 1.61-8.54) and cytology aHSIL (HR 3.75 1.47-9.47). PWH with a combined nadir CD4 cell count of less than 200 and cytology aHSIL will have a 5- and 10-year probability of IAC of 2.9% and 3.7%, respectively (Figure). Of 32 PWH diagnosed with IAC, 7 died due to cancer progression. All who died due to IAC had clinical stages IIIA or higher, and of them, 3 had declined to have an HRA ever, and 1 opted out of recommended HRA surveillance.

Conclusion: PWH with nadir CD4 cell count below 200 and cytology aHSIL have the highest risk of anal cancer within 5 years of follow-up. All patients who died had anal cancer clinical stages IIIA or higher at diagnosis, highlighting the importance of early diagnosis through HRA cancer surveillance.



760 Evaluation of the Performance of Different High-Resolution Anoscopy Triage Strategies in MSM LWH

Eugenio Nelson Cavallari[1], Federica Alessi[1], Chiara Eberspacher[1], Marco Ridolfi[1], Ilyass El Abboubi[2], Alessandra Latini[3], Angelina Pernazza[1], Daniela Bosco[2], Domenico Mascagni[2], Claudio Maria Mastroianni[2], Gabriella D'Ettorre[2]
[1]Azienda Ospedaliero-Universitaria Policlinico Umberto I, Rome, Italy, [2]Sapienza University of Rome, Rome, Italy, [3]San Gallicano Dermatology Institute, Rome, Italy

Background: Treatment of anal high grade squamous intraepithelial lesions (HSIL) have been proved to be effective in reducing the incidence of squamous cell carcinoma of the anus (SCCA) in men who have sex with men (MSM) living with HIV (LWH). High resolution anoscopy (HRA) is the gold standard for detection of anal HSIL. Access to HRA is still not widely available due to the small number of trained providers. Definition of triage pathways to better allocate HRA resources is crucial to implement SCCA screening programs for PLW.
Methods: To evaluate sensitivity (SE) and specificity (SP) of different HRA triage strategies, we retrospectively analyzed data from 180 MSM LWH that underwent SCCA screening with HRA directed biopsies and for whom anal cytology and anal HPV DNA collected on the same day of HRA were available. In the analysis, only HRA that led to the identification of HSIL were classified as positive. As hypothetic threshold for referral to HRA we tested: 1) cytology of atypical squamous cells of undetermined significance (ASCUS) or worse; 2) cytology of low grade squamous intraepithelial lesion (LSIL) or worse; 3) cytology of atypical squamous cells cannot exclude HSIL (ASC-H) or worse; 4) any high risk HPV genotype (HR-HPV); 5) HPV16; 6) ASCUS or worse + HR-HPV; 7) LSIL or worse + HR-HPV; 8) ASCUS or worse + HPV16.
Results: When considering cytology criteria as tirage to HRA: an ASCUS threshold would have triggered 125 HRA (SE 70.9%; SP 32.4%); an LSIL threshold would have triggered 107 HRA (SE 62%; SP 43.1%); an ASC-H threshold would have led to 10 HRA (SE 11.4%; SP 99%). When considering anal HPV infection as triage for HRA: a threshold of any HR-HPV would have triggered 105 HRA (SE 84.8%; SP 62.7%), while a threshold of anal infection with HPV16 would have led to 57 HRA (SE 50.6%%; SP 83.3%). When considering a composite triage: a threshold of ASCUS or worse + HR-HPV would have led to 81 HRA (SE 64.6%; SP 70.6%); a threshold of LSIL or worse + HR-HPV would have triggered 65 HRA (SE 54.4%%; SP 78.4%); a threshold of ASCUS or worse + HPV16 would have triggered 43 HRA (SE 38%; SP 87.3%).
Conclusion: Triage to HRA with the identification of anal HR-HPV infection offered the best balance between sensibility and specificity. The association of anal cytology (ASCUS or worse, or LSIL or worse) and HR-HPV, which present lower sensibility and higher specificity, seem feasible given the periodic nature of such screening. Official approval of assays for the diagnosis of anal HR-HPV is needed.

761 Anal Self-Sampling Is Suitable for Anal Cancer Screening Among Men Who Have Sex With Men in Togo

Valentine M. Ferré[1], Arnold Sadio[2], Romane Guilbaud[1], Meryem Zaidi[3], Mawussé K. Attiso[4], Mounerou Salou[5], Laurent Abramowitz[1], Mélanie Bertine[1], Amivi P. Amenyah-Ehlan[5], Ephram Mensah[4], Claver Anoumou Dagnra[5], Jade Ghosn[1], Diane Descamps[1], Didier Koumavi Ekouevi[2], **Charlotte Charpentier**[1]
[1]Université Paris Cité, Paris, France, [2]Centre Africain de Recherche en Épidémiologie et en Santé Publique, Lomé, Togo, [3]Assistance Publique–Hôpitaux de Paris, Paris, France, [4]NGO Espoir Vie Togo, Lomé, Togo, [5]L'Université de Lomé, Lomé, Togo

Background: Anal cancer screening guidelines exist only locally or nationally for some at-risk population like MSM living with HIV. In sub-Saharan Africa, there is no access to anal cytology analysis and proctologic consultations. There is a need to implement HPV detection strategy to screen most at-risk patients. The aim of this study was to evaluate anal self-sampling (ASS) for HPV detection compared to anal swab carried out by the practitioner (ASP).
Methods: The ANRS 12400 DepIST-H cohort included 200 MSM in Togo, half living with HIV, prospectively followed up with yearly anal sampling and proctologic exam. During the month-12 visit, ASS was proposed to MSM before clinical consultation. A flyer explaining the procedure accompanied the FloqSwab for ASS, which was discharged into eNAT. The practitioner conducted afterwards anal exam, anal sampling with a cytobrush discharged in ThinPrep. All samples were analyzed by the Virology lab of Bichat Hospital (Paris, France) with AnyplexII for detection of 14 high-risk HPV (HR-HPV). HPV16 viral load was quantified with in-house qPCR.
Results: A total of 188 MSM were included, median age of 23 years, 99% of participants found the ASS procedure was easy to carry out and 60% of them would prefer ASS to ASP at next visit while 19% had no preference. ASS was suitable for HPV detection since only 5% samples were uninterpretable compared to 7% for ASP (p=0,77). Overall, at least one HR-HPV was detected in 83% (n=148/178) and 77% (n=135/176) of ASP and ASS, respectively, and 28% and 26% were positive for HPV16. ASP and ASS showed substantial agreement (89.7%) for HR-HPV detection with Kappa's coefficient of 0.66). The agreement for HPV16 was 90.3% (Kappa's coefficient = 0.75). HPV16 median viral loads were higher in ASS than ASP (7652c/mL vs 575c/mL respectively, p=0.009). Regarding the 16 samples with discordant result for HPV16 detection, HPV16 viral load was low (160c/mL for ASS and 155c/mL for ASP in median).
Conclusion: To our knowledge, this is the first time ASS and ASP are compared for HPV detection performance at the same time. The concordance of the two sampling methods, the acceptability of ASS and the facility to implement self-sampling are in favor of using ASS for HPV detection in anal cancer screening programs. The HPV detection implementation worldwide for cervical cancer screening following the WHO's 2020 guideline will enable anal cancer screening implementation in LMIC.
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762 Long-Term ART Is Not Associated With Reduced Anogenital Cancer Risk: A Case-Cohort Study

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Background: People with HIV (PWH) are at increased risk of anogenital cancer. Malignancies of the cervix, vulva, anus, and penis have become leading causes of morbidity and death for PWH globally. HIV-related immune dysfunction may contribute to excess risk. We sought to assess whether sustained antiretroviral treatment (ART) reduces excess risk of anogenital cancer in PWH.
Methods: We conducted a case-cohort study in Botswana involving citizens aged 20 to 65. Adults with anogenital cancer were prospectively enrolled in a cancer cohort ("Thabatse") from 2012-2020 at the 4 principal cancer treatment centers in Botswana. The subcohort was drawn from the Ya Tsie trial, which included a random 20% household sample of 30 communities (2013-2015) and an 80% sample in 6 communities (2017) in Botswana. ART duration was divided into three categories: No ART, ART < 5 years, and ART ≥ 5 years. We estimated the marginal relative risk (compared to HIV-uninfected) of incident anogenital cancer by ART duration using G-computation with inverse probability of treatment weights (IPTW), accounting for common factors of HPV and HIV, ART duration, and access to cancer treatment: 5-year age strata, education, age at first intercourse, smoking status, geographic region, and time period.
Results: A total of 17,321 participants were enrolled, including 1,377 cancer cases. HIV prevalence was higher in individuals with cancer (80%) than persons without cancer (30%). PWH who received longer duration ART (≥ 5 years) were older than PWH who received shorter duration ART (< 5 years) (median age 44 and 38, respectively). Proportions of PWH on ART with CD4 nadir greater than 350 cells/μL were 55% and 58%, respectively. Greater than 95% of participants on ART had HIV virologic suppression. Following IPTW, the analytic cohort was balanced with standardized mean difference (SMD) <0.05 for included factors, and parameters of access to cancer treatment were similar across groups (SMD <0.15). In all categories of ART duration, HIV-infection was associated with a large increase in risk for each cancer studied. Compared with shorter duration, longer duration ART was associated with greater risk of anogenital cancers: anus RR 1.86 (95% CI 1.2, 2.8); vulva RR 1.83 (95% CI 1.4, 2.5); penis RR 2.58, (95% CI 1.8, 3.7); cervix RR 1.12, (95% CI 1.0, 1.3, non-significant).
Conclusion: Prolonged ART does not reduce age-standardized anogenital cancer risk. Further interventions are needed to address excess cancer risk in PWH on ART.
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763 Trial Comparing Cryotherapy to LEEP in Women With HIV: CIN2+ Recurrence After 9 Years

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Background: We aimed to determine the long-term risk of recurrent cervical intraepithelial neoplasia grade 2 or higher (CIN2+) in women living with HIV (WLWH) previously treated for cervical disease with loop electrical excision procedure (LEEP) or cryotherapy.

Methods: We conducted a long-term follow-up study of WLWH, and CIN2/3 randomized to LEEP or cryotherapy and followed 2-years post-treatment in Kenya between 2011-2016. Former participants were recontacted from January to August 2023 for Papanicolaou (PAP) screening and colposcopy-directed biopsy if indicated to determine presence of CIN2+ in the ≥9 years since initial treatment. Women with PAP results of low grade squamous intraepithelial lesions, high grade squamous intraepithelial lesions (HSIL) or Atypical Squamous Cells, HSIL cannot be excluded (ASC-H), underwent colposcopy-directed biopsy. Primary outcome was CIN2+ recurrence (CIN2/3, Carcinoma in-situ or invasive cancer) as determined by colposcopy-directed biopsy at ≥9 years after initial treatment. Log-binomial regression was used to estimate the relative risk of CIN2+ recurrence by treatment arm.

Results: Overall, 353 of 400 (88%) former participants were alive at the end of the parent trial, 14 were lost to follow-up with 33 mortalities. Of these, 288 (82%) were recontacted and 213 (74%) agreed to participate in this follow-up study. Fewer women in the LEEP arm (17%) had unsuppressed HIV viral load (≥1000 copies/ml) than the cryotherapy arm (24%). ART duration was similar between arms with a median of 11 years (IQR 10–12). Sixteen (8%) participants had a hysterectomy since the parent trial and were excluded. Of 197 screened, 5 (5%) of 107 in the cryotherapy arm and 3 (3%) of 90 in the LEEP arm had recurrent CIN2+ at ≥9 years since initial treatment. Of these eight with CIN2+, 2 (1 per arm) had a prior CIN2+ recurrence in the 2-years following initial treatment (parent trial). In addition, 48 (31 in cryotherapy and 17 in LEEP) had CIN2+ recurrence in the initial trial but not in this study. There was no difference in CIN2+ recurrence risk at ≥9 years following initial treatment between arms (RR=1.40, 95% CI, 0.34-5.71, p=0.64). In subgroup analysis, the effect of treatment on CIN2+ recurrence did not vary by viral suppression, CD4 count, and ART duration.

Conclusion: Recurrence of CIN2+ in WLWH ≥9 years after cryotherapy or LEEP was low (4%) and did not differ between the ablative and excisional therapies after initial 2-year follow-up and may be related to long-term ART use.

764 Prioritizing Anal Cancer Screening in PWH: Not All Are at the Same Risk

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Background: People with HIV (PWH) are up to 100 times more likely to develop anal cancer (AC) compared to the general population, where overall incidence is 1.6/100,000 person-years (PY). Screening programs are efficient in preventing AC but are not accessible to all PWH. Identifying individuals at higher risk is crucial to implement effective and targeted screening strategies

Methods: In this cohort study, we included all treatment naïve PWH ≥16 years from 16 hospitals in Catalonia and Balearic Islands, included in the PISCIS HIV cohort from 1998-2022. The primary outcome was the incidence rate (IR) of histologically confirmed AC. We used Poisson regression to identify AC risk factors, including age at AC, risk group, nadir CD4+ count, and period of HIV diagnosis. AC and nadir CD4+ were validated in all cases.

Results: We identified 107 AC events among 14,238 PWH, overall IR of 71.5/100,000 PY (95%CI:71.5-71.6), and median follow-up 9.5 years (IQR:4.4-15.7). Of them, 37 died, 65% AC-related deaths. The IR was highest in those with nadir CD4+ <200 cells/µL (103.0 [95%CI:102.9-103.1]), followed by those with nadir CD4+ 200-350 cells/µL (29.1, [95%CI:29.1-29.2]), and lowest in those with nadir CD4+ >350 cells/µL (2.8 [95%CI:2.8-2.9]). In the same categories, MSM had IR of 211.5 (95%CI:211.2-211.7), 37.6 (95%CI:37.5-37.7), and 4.8 (95%CI:4.8-4.9), respectively. Among PWH with <30 years, there was only 1 AC in MSM and none in the other groups. There were no cases among women or non-MSM men with nadir >350 cells. In the multivariable analysis, nadir CD4+ <200 cells/µL was associated with the highest risk compared to nadir CD4+>350 cells/µL, followed by nadir CD4+ 200-350 cells/µL (aIRR 29.1 [95%CI:4.1-206.2] and 8.8 [95%CI:1.2-66.2], respectively). Vs those with <30 years, PWH ≥60 had aIRR 27.6 [95%CI:3.7-206.8], and with 45-59 years aIRR 21.6 [95%CI:3.0-156.5]. HIV diagnosis before 1998 (32.9 [95%CI:8.0-135.1]) was also a significant risk factor. Age <45 years was a protective factor against AC with nadir CD4+ <200 cells/µL.

Conclusion: PWH with nadir CD4+ count <200 cells/µL exhibit the highest risk of AC, especially among MSM, whereas those with nadir CD4+ count >350 cells/µL had a similar risk to the general population. Tailored approaches for AC screening based on nadir CD4+ count could optimize resources by prioritizing AC screening to those with the highest risk.

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765 Contribution of HIV to the Burden of Merkel Cell Carcinoma in the US

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Background: Merkel cell carcinoma (MCC) is an aggressive form of skin cancer with a 5-year survival rate of approximately 65%. Risk factors for MCC include advanced age, immunosuppression, Merkel cell polyomavirus, lightly pigmented skin, and UV radiation. People with HIV (PWH) have elevated risk of MCC; however, prior studies had few MCC patients with HIV (ranging from 6 to 20) and did not estimate the MCC burden attributable to HIV. Using population-based cancer registry data collected in 14 US regions, we report the characteristics of MCC patients with HIV and quantify the burden of MCC among PWH during 2001–2019.

Methods: We used cancer registries in the HIV/AIDS Cancer Match (HACM) Study to identify MCC (ICD-03 8247: C44.0–C44.9) cases in the general population and the linked HIV registry data to compare cases in PWH and those without HIV. We calculated standardized incidence ratios (SIRs) to compare MCC incidence in PWH to the general population. To estimate the proportion of MCC cases in the general population due to HIV, we calculated population attributable fractions (PAFs) using the formula Pc*[(RR-1)/RR], where Pc is the prevalence of HIV among MCC patients and RR is the relative risk of MCC associated with HIV (approximated by the SIR). We also report HIV viral load and CD4 counts among PWH in the year leading up to MCC diagnosis.

Results: 13,126 MCC cases were diagnosed in HACM registries during 2001–2019, and 46 (0.4%) were among PWH (see table). Among MCC patients, the median age of diagnosis was 56 years (IQR: 50–67) in PWH, vs. 77 years (IQR: 68–84) in those without HIV. Thirty-one (67.4%) PWH and MCC had an AIDS diagnosis prior to MCC diagnosis. The risk of PWH developing MCC was almost three times higher than the general population (SIR=2.78, CI: 2.01–3.75). Only 0.2% of MCC cases were attributable to HIV; however, the PAF was higher among PWH aged 20–59 (2.0%). Among 24 individuals with a HIV viral load measure in the year before MCC diagnosis, 5 had undetectable levels (<20 copies/mL), 16 had 20-99,999 copies/mL, and 3 had >100,000 copies/mL. Among 25 individuals with a CD4 count in the year prior to MCC diagnosis, 4 had <200, 10 had 201–499, and 11 had >500.

Conclusion: PWH have a higher risk of MCC compared to the general population. While the overall contribution of HIV to the MCC burden is minor, a larger PAF was observed among younger individuals. The majority of PWH and MCC had disease markers indicating moderate to severe immunosuppression leading up to MCC diagnosis.

Burden of Merkel cell carcinoma among PWH in the US (2001-2019)

Demographic characteristics*	People with HIV n (%)	People without HIV n (%)	MCC in PWH %	SIR (95% CI)	PAF %
Overall	46	13,080	0.4	2.78 (2.01–3.75)	0.2
Sex: Male	41 (89.1)	8395 (64.2)	0.5	2.88 (2.05–3.94)	0.3
20 to 59 years old	30 (65.2)	1160 (8.9)	2.5	4.83 (3.18–7.03)	2.0
60+ years old	16 (34.8)	11,920 (91.1)	0.1	1.72 (0.99–2.80)	0.1
Hispanic or Latino	7 (15.2)	749 (5.7)	0.9	2.03 (0.75–4.42)	0.5
Non-Hispanic Black	4 (8.7)	213 (1.6)	1.8	1.87 (0.51–4.78)	0.9
Non-Hispanic White	34 (73.9)	11,909 (91.0)	0.3	3.18 (2.19–4.47)	0.2

*1 MCC case in PWH and 209 MCC cases in people without HIV have a race and ethnicity that is not listed in the table or unknown.

766 Association Between HIV Infection and Survival for Head and Neck Cancers in the US From 2008-2020

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Background: People with HIV (PWH) are at an increased risk of head and neck cancer (HNC) compared with people without HIV (PWoH). However, little is known regarding the impact of HIV on HNC survival. This study is one of the first to compare survival, by histological subtype of HNC, between PWH and PWoH.
Methods: A retrospective cohort of adults with newly diagnosed 1) oropharyngeal, 2)non-oropharyngeal (hypopharynx and larynx), 3)oral cavity cancers was identified using electronic health record data from the National Veterans Administration and Kaiser Permanente California regions from 2008 to 2020. Separate Cox regression models were used to assess the association of HIV infection with overall survival (OS) for each cancer type, adjusting for baseline sociodemographic factors, clinical characteristics, and HPV+ tumor status (oropharyngeal only). Multiple imputation was used for missing covariate data.
Results: Our analysis included 300 PWH and 30,950 PWoH HNC patients. Compared with PWoH, PWH were more likely to be younger; male; Black or Hispanic; had lower education attainment and income levels; and have co-infection with HPV, HBC, or HCV. Mortality rates for PWH vs. PWoH were 13.0 vs.9.7 per 100 person-years for oropharyngeal; 7.3 vs.13.0 for oral cavity; and 12.0 vs.14.0 for non-oropharyngeal cancers. In unadjusted analysis, HIV infection was associated with worse OS for oropharyngeal cancer (hazard ratio [HR]:1.31, 95%CI:1.02-1.66); better OS for oral cavity cancer (HR:0.57, 95%CI:0.39-0.82); and similar OS for non-oropharyngeal cancers (HR:0.83,95%CI:0.63-1.10). In adjusted analysis, similar trends were observed with worse OS in oropharyngeal cancer patients (HR:1.38, 95%CI:1.08-1.77); better OS in oral cavity cancer (HR: 0.66, 95%CI:0.46-0.96); and similar OS for non-oropharyngeal cancer (HR:0.94, 95%CI: 0.71-1.25). However, for oropharyngeal cancers, patients with HPV+ tumors had better survival compared with patients with HPV-negative tumors (HR: 0.50, 95%CI: 0.47-0.53). Other risk factors for poor OS for HNCs included older age at cancer diagnosis, early year of cancer diagnosis, higher stage of cancer, higher Charlson comorbidity index, alcohol abuse diagnosis, and ever smoking.
Conclusion: The study results suggest that PWH had poor survival for oropharyngeal cancer but better survival for oral cavity cancers compared with PWoH. Further research should focus on finding the etiological factors influencing HIV's role in outcomes related to HNCs.

Table 1. Descriptive statistics of Head and Neck cancer patients who received health care at the National Veterans Administration and Kaiser Permanente California regions from 2008-2020 stratified by HIV status.

Characteristics	Veterans Administration		Kaiser Permanente		Total		p
	PWH (N= 228), No. (%)	PWoH (N=23726), No. (%)	PWH (N= 72), No. (%)	PWoH (N= 7224), No. (%)	PWH (N= 300), No. (%)	PWoH (N= 30950), No. (%)	
Cancer histological subtype							0.28
Oropharyngeal	91 (39.9)	9781 (41.2)	36 (50.0)	3367 (46.6)	127 (42.3)	13148 (42.5)	
Non-Oropharyngeal	88 (38.6)	9276 (39.1)	8 (11.1)	1653 (22.9)	96 (32.0)	10929 (35.3)	
Oral Cavity	49 (21.5)	4669 (19.7)	28 (38.9)	2204 (30.5)	77 (25.7)	6873 (22.2)	
HPV							0.05
Negative	19 (8.3)	1598 (6.7)	1 (1.4)	228 (3.2)	20 (6.7)	1826 (5.9)	
Positive	51 (22.4)	4761 (20.1)	26 (36.1)	1880 (26.0)	77 (25.7)	6641 (21.5)	
Death within the first year	47 (20.6)	4582 (19.3)	7 (9.7)	932 (12.9)	54 (18.0)	5514 (17.8)	0.93

Abbreviations: PWH: People with HIV/AIDS, PWoH: People without HIV, HPV: Human Papillomavirus.

767 Changes in Gut Microbiota Associated With Progression of Atherosclerosis in People With HIV

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Background: Variations in gut microbiome might modulate host immune activation and inflammation, potentially linked to increased cardiovascular risk. Our objective was to longitudinally characterize the distinctive features of gut microbiota associated with progression of atherosclerosis measured through carotid artery intima-media thickness (cIMT) in people living with HIV (PLWH).
Methods: 96-week, longitudinal study in virologically suppressed (HIV-1 RNA <50 copies/mL) PLWH with no previous cardiovascular disease. cIMT was measured at baseline, 48 and 96-weeks visits using B-mode ultrasound at 6 locations. cIMT progression was defined as an increase >10% and/or detection of new carotid plaques. To profile the gut microbiome, DNA was extracted from fecal samples and quantified with the Qubit dsDNA HS Assay Kit. Amplification and sequencing of 16S ribosomal RNA (V3-V4 variable regions) were carried out following the Illumina protocol. For bioinformatic analysis of amplicons, the QIIME package was used. Biomarker analysis was performed using the LEfSe software package.
Results: 202, 190 and 169 patients had available fecal samples for microbiome analysis at the baseline, 48- and 96-week visits, respectively. At the 96w visit, 87 (43%) patients were categorized as progressors, with 54 (26.7%) of them showing a new carotid plaque. No significant differences were observed in α-diversity indices between groups at baseline. Over the 96w follow-up period, a decrease in α-diversity (Simpson's and Shannon's indices) was observed in the progressor group. Based on beta-diversity analysis at the species level, determined through principal coordinate analysis (PCoA) distances, the progressor and non-progressor groups exhibited distinct and divergent microbial profiles during each follow-up visit (p=0.001). When all sequences from the three visits were compared, the PCoA plots of Bray-Curtis distance revealed that the samples clustered in accordance with the progression of atherosclerosis (p=0.016; Permanova test) (Fig1A). LEfSe analysis revealed distinct associations between progression and specific bacterial taxa (Fig1B). *Agathobacter*, *Ruminococcus_2* and *Lachnospiraceae_UCG_003* genus were consistently observed in various consecutive visits as distinctive genus associated with progression, while *Prevotella_7* and *Allisonella* genus were linked to non-progressor patients.
Conclusion: Progression of atherosclerosis in PLWH is associated with distinctive changes in the gut microbiota.

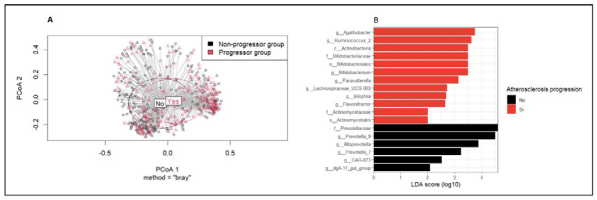

Fig1A. Principal coordinate analysis (PcoA) with Bray-Curtis distance. 1B. Taxonomic linear discriminative analysis (LDA) effect size (LEfSe) analysis by atherosclerosis progression.

768 Plasma IL-1β Predicts Incident Coronary Artery Disease and Pulmonary Embolism in PWH on ART

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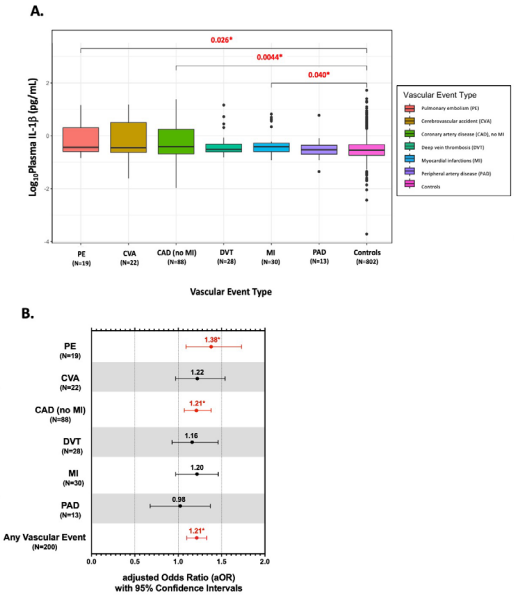
Background: Despite antiretroviral therapy (ART), people with HIV (PWH) experience higher rates of morbidity and mortality vs. age-matched HIV negative controls which may be driven by chronic inflammation due to persistent virus. Plasma interleukin 6 (IL-6) levels are amongst the strongest predictors of mortality in PWH on ART, and an upstream regulator of IL-6, interleukin-1 beta (IL-1β), may be the major driver of this risk.
Methods: We performed a case-cohort study of 1,002 PWH on ART from the U.S. Military HIV Natural History Study. Inclusion criteria were HIV-1 infection

and plasma HIV RNA <50 copies/ml. Cases were PWH on ART with incident vascular event (VE): coronary artery disease (CAD), CAD with myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolus (PE), cerebrovascular accident (CVA, stroke), and/or peripheral arterial disease (PAD). Cases were age- and gender-matched 1:4 to controls. Cryopreserved plasma (>1 year prior to censor date) were used to quantify IL-1β signaling cytokines (IL-1β, IL-6, and IL-18) using a high-sensitivity assay (MesoScale). Logistic regression models adjusted for potential vascular covariates (hypertension, hyperlipidemia, diabetes mellitus, tobacco use, alcohol use, family history of vascular disease) were fit to estimate odds ratios (ORs).

Results: A total of 200 cases and 802 controls were included. Participants were mostly male (92%), White (43%; 41% Black, 10% Hispanic), with a median age=31 years, nadir CD4+ T cell count=290 cells/mm^3, pre-ART viral load=$\log_{10}$ 4.6 copies/mL, ART suppression=6.8 years, and HIV seroconversion to ART initiation=1.8 years; overall characteristics were similar between cases vs. controls. Plasma IL-1β, but not IL-18 or IL-6, significantly predicted the composite outcome of any vascular event (OR_VE=1.21, 95% CI:1.10, 1.33) and predicted CAD, MI, and PE. The associations with PE and CAD remained significant in multivariate models adjusted for hypertension and hyperlipidemia (OR_PE=1.38, 95% CI: 1.09, 1.73 and OR_CAD=1.21, 95% CI: 1.07, 1.38).

Conclusion: Recent high sensitivity assays can now discriminate within- and across-individual plasma IL-1β levels. To our knowledge, this is the largest epidemiologic study of plasma IL-1β in PWH, as well as in the general population, in relation to vascular events. Our findings suggest that IL-1β may be a critical upstream regulator of IL-6 and have important implications for therapeutic strategies to reduce inflammation and vascular comorbidities in PWH on ART.

Figure. Plasma IL-1β levels significantly predicted vascular events in 1002 people with HIV on ART. Box plots show median (with interquartile ranges) and p-values from Wilcoxon rank sum tests (A). Odds Ratios are shown for multivariate models adjusted hypertension and hyperlipidemia (B). Red font denotes p<0.05.



769 Clonal Hematopoiesis in HIV and Atherosclerosis, Arterial Inflammation, and Hematopoietic Activity

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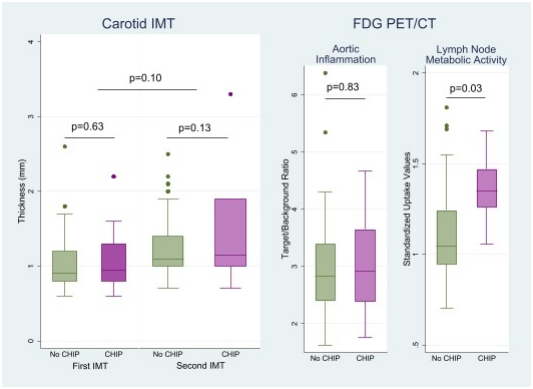
Background: Clonal hematopoiesis of indeterminate potential (CHIP) is associated with cardiovascular disease (CVD) and common in HIV, but whether CHIP contributes to atherosclerosis in HIV is unknown. We hypothesized that CHIP is associated with atherosclerosis, arterial inflammation, and hematopoietic activity among people with HIV (PWH).

Methods: In this observational study, we studied treated, suppressed PWH ages 35-70 years old with ≥1 CVD risk factor. CHIP mutations were detected from peripheral blood mononuceleic cells with a validated targeted sequencing assay. We measured carotid intima-media thickness (IMT) longitudinally with ultrasound and aortic inflammation and hematopoietic metabolic activity using cross-sectional 18F-FDG-PET. Inflammatory biomarkers were measured with a multiplex electrochemiluminescence assay. We used linear regression with adjustment for age, sex, nadir CD4 count, smoking, hypertension, diabetes, and hyperlipidemia to adjust for potential confounders.

Results: We included 231 PWH (52±9 years, 7% female). 32 (14%) had CHIP with median variant allele fraction of 3.1%. Common mutations were in DNM3TA (n=21) and TET2 (n=6). Only age was associated with CHIP (OR 2.3 per decade older, 95%CI 1.2-3.9; p=0.003. Among N=165 (CHIP=22), baseline mean IMT was 1.0 mm with and without CHIP (p=0.63), unchanged after adjustment (Figure). CHIP was not associated with prevalent (p=0.82) or incident plaque (p=0.48). Over 3.2 years, IMT progression was faster among those with CHIP (0.033 mm/year; p=0.10), attenuated after adjustment (0.022 mm/year; p=0.27). Among 80 with FDG-PET, CHIP (n=12) was associated with higher lymph node metabolic activity (p=0.03) that was attenuated in reference to background activity (p=0.69) and adjusted for risk factors (p=0.22), with a similar trend for spleen activity (p=0.14). CHIP was not strongly associated with arterial inflammation (p=0.83), bone marrow activity (p=0.50), inflammatory markers, or viral persistence markers.

Conclusion: Among PWH, CHIP mutations were not associated with subclinical atherosclerosis or arterial inflammation, proposed mechanisms of how CHIP could cause CVD. Associations with lymph node and spleen activity suggests CHIP may be induced by HIV reservoirs or induce increased reservoir activity. Clinical outcomes studies are needed to ascertain the impact of CHIP on CVD in HIV.



770 Activated and Exhausted CD8+ T-Cell Subsets Associate With Carotid Atherosclerotic Plaques in PLHIV

Marc Blaauw[1], Adriana Navas[1], Nadira Vadaq[1], Vasiliki Matzaraki[1], Elise M. Meeder[1], Wilhelm A. Vos[1], Albert L. Groenendijk[2], Louise E. van Eekeren[1], Gert Weijers[1], Marvin Berrevoets[3], Hans Koenen[1], Marien I. de Jonge[1], Andre J. van der Ven[1], Joost Rutten[1], Niels P. Riksen[1]

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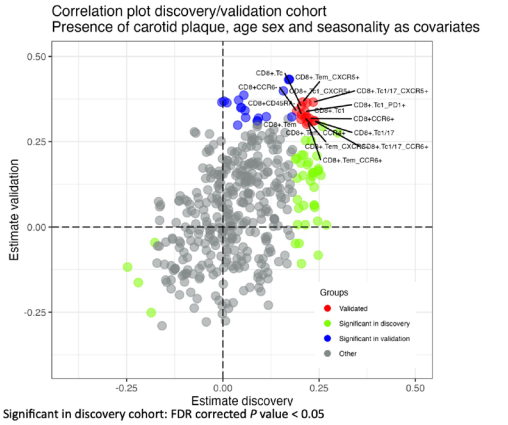
Background: Atherosclerotic cardiovascular disease (ASCVD) is one of the leading causes of morbidity and mortality in people living with HIV (PLHIV). Understanding the association between circulating immune cells and carotid plaque presence in PLHIV holds the potential to identify novel immunological mechanisms driving plaque progression in PLHIV. Flow cytometry, allows identification and quantification of immune cells within heterogeneous populations.

Methods: Our study analyzed data from the 2000HIV study (NCT03994835), comprising 1188 individuals with valid carotid ultrasound, without previous ASCVD and with valid high-dimensional flow cytometry measurements. This Dutch multi-center cross-sectional study focuses on virally suppressed PLHIV and is divided into a discovery cohort (n= 989) and validation cohort (n= 194). High dimensional flow cytometry was performed to identify the major blood immune cell subsets (403 populations) and their functional status. We performed linear regression models adjusted for age, sex and seasonality. Findings from the discovery cohort after correction for multiple testing were validated in the validation cohort.

Results: In total 584 participants (49.2%) had a carotid plaque. Our findings revealed higher numbers of different CD8+ T cell subsets in individuals with

carotid plaques (figure 1) both in the discovery and validation cohort. Among these CD8+ T cell subsets, increased proportions of T cell effector memory cells expressing CCR4, CCR6, CXCR3 and CXCR5 were observed (FDR < 0.05 for discovery and p < 0.05 in validation cohort). Furthermore, absolute numbers of CD8+ Tc1 cells expressing the exhaustion marker PD1, were increased in those with carotid plaques as compared with individuals without carotid plaques.

Conclusion: In this comprehensive study in PLHIV under suppressive ART, we identified differences within CD8+ T cell populations in individuals with carotid plaques. These alterations span activated and exhausted cell phenotypes. Our findings underscore a role of CD8+ T cells in atherogenesis. Furthermore, the concurrent elevation of CD8+ Tc1 cells expressing the exhaustion marker PD1 provides further insight into the dynamic interplay of immune responses in atherosclerosis.



Significant in discovery cohort: FDR corrected *P* value < 0.05
Significant in validation cohort: *P* value < 0.05
Validated: significant in discovery cohort (FDR < 0.05) and in validation cohort (*P* value < 0.05)

771 Co-Occurrence of MASLD and CKD Increased Cardiovascular Incidence Among Thai HIV Population

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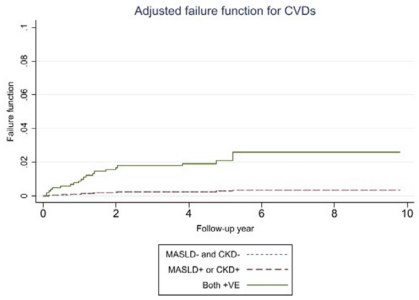
Background: Combination of Metabolic dysfunction Associated Steatotic Liver Disease (MASLD) and chronic kidney disease (CKD) are associated with cardiovascular diseases (CVDs). However, this importance finding in people living with HIV (PWH) is largely unknown. We therefore investigated the effect of combined diagnosis of MASLD and CKD on the incidence of CVDs among PWH in Thailand.

Methods: All PWH starting ART in a prospective cohort with available transient elastography /controlled attenuation parameter (CAP) and serum creatinine during June 2013 to Jul 2023were included. MASLD was defined as steatotic liver disease (CAP ≥248dB/m) plus one of five cardiometabolic criteria: body mass index (BMI) ≥25kg/m² or waist circumstance >94cm for males and >80cm for females; fasting glucose ≥100mg/dL or a diagnosis of diabetes melltius; BP ≥130/85mmHg or a diagnosis of hypertension; triglyceride ≥150mg/dL or lipid lowering agents, and HDL ≤40mg/dL in males or ≤50mg/dL for females. CKD was defined as estimated glomerular filtration rate (eGFR) ≤60ml/min/1.73m² using the CKD Epidermiology Collaboration. CVDs included coronary diseases, stroke, peripheral arterial disease and aortic disease. Follow-up started at the 1st firbroscan/ eGFR measurement and ended at the first CVDs diagnosis or most recent clinic visit in those without CVDs. Cox regression was used to evaluate factors associated with CVDs development, adjusted for potential cofounders.

Results: Totally 1940 PWH (70.8% male, median age 43 [interquartile range (IQR): 32-50] years; BMI 22.5 (IQR: 20.6-24.9); current smoker 18% (n=265); abacavir exposure 7.5% (n=143) were analysed. The prevalence of MASLD+/ CKD+ at baseline was 6.4% (n=125). During a median 4.1 years of follow-up, 20 participants developed new-onset CVDs. Multivariable Cox regression adjusting for age, sex, smoking, ART duration and protease inhibitors use showed that PWH with a combined diagnosis of MAFLD and CKD at baseline was associated with a significantly increased risk of developing CVD (adjusted hazard ratio [aHR] = 7.9 (95%CI 2.5-24.7), p<0.001)), but the presence of either comorbidity alone did not significantly increase the risk [aHR = 1.04 (95%CI 0.3 – 3.7); P=0.96] (Figure).

Conclusion: MASLD together with CKD was associated with a significantly increased risk of new-onset CVDs, but MASLD or CKD alone was not. Further studies to understand the mechanisms for the increased risk are warranted for the prevention of CVDs in this group.

Figure: Failure function for CVDs after multivariable Cox regression in the presence or absence of MASLD and CKD at baseline



772 The Association of Mild Kidney Disease With Coronary Disease Is Stronger for People With HIV

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Background: Chronic kidney disease (CKD)-a common comorbidity for people with HIV (PWH)-is also a risk factor for coronary artery disease (CAD). However, the impact of mildly impaired eGFR and microalbuminuria on CAD risk for PWH is not well defined. Using coronary computed tomography angiography (CCTA), we examined whether the association between mild kidney disease and coronary plaque might be stronger for PWH compared to people without HIV in sub-Saharan Africa.

Methods: We conducted a cross-sectional secondary analysis of data from the Ugandan sTudy of HIV effects on the Myocardium and Atherosclerosis (mUTIMA) study. mUTIMA compared 100 PWH on stable antiretroviral therapy (ART) and 100 age- and sex-matched participants without HIV, all aged over 45 with ≥1 cardiovascular disease risk factor. Participants with screening eGFR <60mL/ min/1.73m² were excluded due to risk of contrast-induced nephropathy. For 165 of these participants with available CCTA data, we performed multivariable Tobit regression stratified by HIV status to examine the association of CAD with both estimated glomerular filtration rate (eGFR) and albumin creatinine ratio (ACR). CAD was characterized using segment involvement score (SIS; total segments with plaque), segment stenosis score (SSS; segment score weighted by degree of luminal obstruction), and coronary artery calcium (CAC) score.

Results: Mean (SD) age was 57.7(6.9) years and 62.4% were female. Mean (SD) systolic blood pressure was 152.2(27.8) mmHg and 31.5% had diabetes. 96% had HIV-1 viral suppression and 47% were on tenofovir (TDF). Among PWH-but not among participants without HIV-mildly impaired eGFR (<90mL/min/1.73 m²) was associated with higher SIS (β 3.31, 95% CI: 0.41 to 6.21, p = 0.03) and SSS (β 5.95, 95% CI: 0.54 to 11.36, p = 0.03). The association with SIS remained significant after adjusting for age, gender, and 10-year ASCVD score (β 2.58, 95% CI: 0.10 to 5.06, p = 0.04). Associations of ACR with coronary plaque were not statistically significant for participants with or without HIV (all p>0.07).

Conclusion: Mild to moderately low eGFR is more strongly associated with CAD in PWH compared to those without HIV in Uganda. In addition to assessing traditional risk factors, monitoring renal function may add to cardiovascular risk assessment of PWH in sub-Saharan Africa. The observed association also highlights the need to integrate cardiovascular and renal care into HIV clinics, especially for aging PWH with higher rates of comorbid diabetes and hypertension.

Table: Relationship between eGFR, ACR, and segment involvement score (SIS) in PWH and HIV-negative controls.

Variable	HIV negative (n=87)			HIV positive (n=78)		
	β	95% CI	p-value	β	95% CI	p-value
eGFR <90 (unadj)	-0.07	-2.39; 2.25	0.95	3.31	0.41; 6.21	**0.03**
eGFR <90 (adj)	-0.22	-2.27; 1.83	0.83	2.58	0.10; 5.06	**0.04**
ACR ≥30 (unadj)	0.54	-1.70; 2.78	0.64	-1.27	-4.44;1.90	0.43
ACR ≥30 (adj)	0.40	-1.63; 2.44	0.70	-0.74	-3.55; 2.08	0.61

unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

773 Relating Pitavastatin Effects on Inflammatory Biomarkers to Plaque Changes in REPRIEVE

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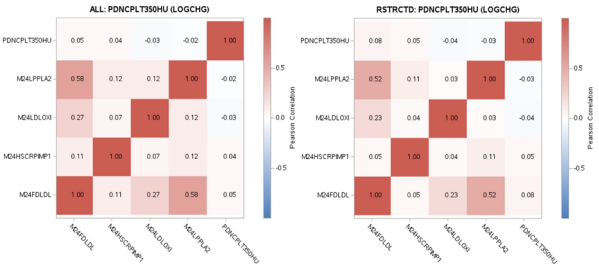
[1]Massachusetts General Hospital, Boston, MA, USA, [2]University of Cincinnati, Cincinnati, OH, USA, [3]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [4]Duke University, Durham, NC, USA, [5]The Ohio State University, Columbus, OH, USA, [6]University of California Los Angeles, Los Angeles, CA, USA, [7]Harvard TH Chan School of Public Health, Boston, MA, USA, [8]Duke University School of Medicine, Durham, NC, USA

Background: The REPRIEVE trial demonstrated that pitavastatin reduced the risk of major adverse cardiovascular events (MACE) by 35% and LDL by 30% compared to placebo over median 5.1 years of follow up. The REPRIEVE mechanistic study further demonstrated pitavastatin was associated with a significant reduction in progression of noncalcified coronary plaque volume compared to placebo as well as changes in oxLDL and LpPLA2. This analysis further interrogates these findings to examine whether pitavastatin effects on lipids and these inflammatory biomarkers relate to changes in plaque.
Methods: Coronary plaque volume was assessed at baseline and 24 months by CT angiography, using a threshold of <350 HU to define noncalcified plaque. Biomarker changes were analyzed on the log2 scale. Pearson correlation was used to assess associations between changes in LDL, biomarkers, and plaque (0 to 24 months). For this mechanistic assessment, analyses were restricted to participants who remained on randomized treatment for 24 months with biomarkers assessed.
Results: The 604 participants (304 pitavastatin, 300 placebo) included in the analysis were representative of the substudy population (mean age 51 years, sex 17% female, CVD risk median 4.6%). Over 24 months, pitavastatin was associated with a 19% [95% CI 8, 29] reduction in oxLDL and a 10% [-6, 14] reduction in LpPLA2 compared to neutral changes or increases in the placebo group. Corresponding mean fold changes in each group were 0.81 [0.71, 0.92] vs. 1.00 [0.89, 1.13] for oxLDL and 0.90 [0.87, 0.94] vs. 1.17 [1.13, 1.21] for LpPLA2, pitavastatin vs. placebo, respectively. No associations between changes in LDL, oxLDL, or LpPLA2, and either non-calcified or total plaque volume were apparent (|rho| < 0.15, Figure). Adjustment for changes in the biomarkers did not impact the effect of pitavastatin to reduce noncalcified plaque. Similar results were seen in the entire substudy population and the subset with plaque at baseline.
Conclusion: Pitavastatin significantly reduced LDL and key biomarkers of lipid oxidation and arterial inflammation in REPRIEVE, but these changes were not associated with changes in noncalcified or total plaque volumes. Further studies will assess effects of these pathways on MACE and also the effects of pitavastatin on other mechanistic pathways which might link statin effects to improvements in coronary artery disease indices and MACE in PWH.



Heat map of correlations between changes in noncalcified plaque (PDNCPLT350HU), LpPLA2, oxLDL, CRP, and LDL among all participants (left) and those with plaque at baseline (right).

774 Endothelial Microvesicles: Circulating Biomarker and Mediator of Vascular Dysfunction With HIV-1

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Background: We have previously reported that circulating endothelial cell derived extracellular microvesicles (EMVs) are elevated in adults living with HIV (ALWH) receiving antiretroviral therapy (ART) contributing to endothelial vasodilator dysfunction by negatively affecting endothelial nitric oxide synthase (eNOS) and, in turn, impairing NO production. However, whether elevations in circulating EMVs and their pathologic effects on endothelial NO production was a direct effect of HIV-1 or a consequence of ART is unknown. The experimental aims of this study were to determine: 1) whether circulating EMVs are elevated in treatment-naïve ALWH and associated with HIV-1-related endothelial vasodilator dysfunction; and 2) the effects of EMVs isolated from treatment-naïve ALWH on endothelial cell NO production, in vitro.
Methods: Twenty-four sedentary, adults were studied: 12 healthy (10M/2F; age 35±2 yr) and 12 treatment naïve ALWH (10M/2F; 35±2 yr; viral load: 7342 copies/mL). All subjects were non-obese, normotensive, normolipidemic and free of overt cardiometabolic disease. Circulating EMV (CD144-PE) number was determined by flow cytometry. Forearm blood flow (FBF: via plethysmography) was assessed by intra-arterial infusion of acetylcholine and sodium nitroprusside. Human coronary artery endothelial cells were cultured and treated with EMVs (CD144-PE) isolated from the healthy and treatment naïve ALWH.
Results: Circulating EMVs were ~75% higher (P<0.05) in the treatment naïve ALWH (234±20 EMV/μL) vs healthy (135±13 EMV/μL) adults. FBF responses to acetylcholine were significantly lower (~20%) in the treatment naïve ALWH adults (from 5.6±0.3 to 12.6±1.1 mL/100 mL tissue/min vs 4.9±0.2 to 15.8±1.1 mL/100 mL tissue/min). There were no significant differences between the groups in FBF response to sodium nitroprusside. EMVs were strongly and inversely associated with the vasodilator response to acetylcholine (r=-0.49; P=0.01). Moreover, expression of phosphorylated eNOS (78.5±6.1 vs 102.9±7.9 AU) and NO production (6.0±0.4 vs 7.3±0.4 μmol/L) was significantly lower in cells treated with EMVs from treatment naïve ALWH vs healthy adults.
Conclusion: HIV-1 is associated with elevated circulating EMVs. Moreover, circulating EMVs are not only a systemic biomarker, but appear to be a mechanistic factor underlying endothelial dysfunction with HIV-1. Circulating EMVs represent a novel causative factor underlying vascular abnormalities and the increased CVD risk associated with HIV-1.

775 Transcriptional Signatures Underlying Cardiovascular Disease in Persons Living With HIV

Laventa Obare[1], Heather Beasley[1], Xiuqi Zhang[1], Andrea G. Marshall[1], Rama D. Gangula[1], Yan Ru Su[1], Tarek Absi[1], Sara Gianella[2], Melanie R. McReynolds[3], Antentor O. Hinton[1], **Celestine Wanjalla**[1]
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Background: While statins for primary prevention reduce cardiovascular events, persons with HIV (PWH) have increased risk of cardiovascular disease, likely linked to persistent inflammation. Studies on immune drivers of atherosclerosis among PWH are needed to define additional therapeutic targets.
Methods: We obtained thoracic aorta from diseased PWH (n=3) and without HIV (n=14). Autopsies were performed within 25 hours of death. The donors with HIV included 1 female (Caucasian) and 2 males (Caucasian and Hispanic) ages 52, 65 and 72. Exclusion criteria included known autoimmune disease. We used droplet digital polymerase chain reaction (ddPCR), western blot and immunohistochemistry to detect and quantify HIV. We used spatial transcriptomics (Visium) and metabolomics to define differences in aorta by HIV status (n=4 per group). Differentially expressed genes were identified using the Loupe Browser 6 software, based on their statistical significance and fold change computed using the negative binomial test. Genes with adjusted p-values, FDR < 0.05, were considered significantly different. Global metabolomic profiling of aorta was performed using ultrasensitive Hydrophilic Interaction Liquid Chromatography-Mass Spectrometry (HILIC-MS). We detected over 320 metabolites in both (+) and (-) ionization modes. Analysis was performed using MetaboAnalyst 5.0.

Results: As expected, we detected HIV in aorta from all donors with HIV and not in those without HIV. Using spatial transcriptomics, several genes were differentially expressed by HIV status. Apolipoprotein D (APOD), a lipocalin associated with premature atherosclerosis and poor outcomes in persons with coronary artery disease was significantly higher in the aorta of all donors with HIV (n=4). Osteoglycin (OGN), a gene linked with vascular calcification, was higher in donors without HIV (Panel A). Both genes were expressed mainly by fibroblasts while APOD was also expressed in endothelial cell clusters. Metabolomic analysis of the aorta also showed differential expression of different metabolites (Panel B) with higher Linoleic acid in all three aorta samples from donors with HIV compared to donors without HIV.
Conclusion: APOD has been associated with poor outcomes in coronary artery disease, and may be a therapeutic target in persons with HIV. A comprehensive multimodal approach to investigating atherosclerotic cardiovascular disease in HIV is likely to provide new therapeutic targets.

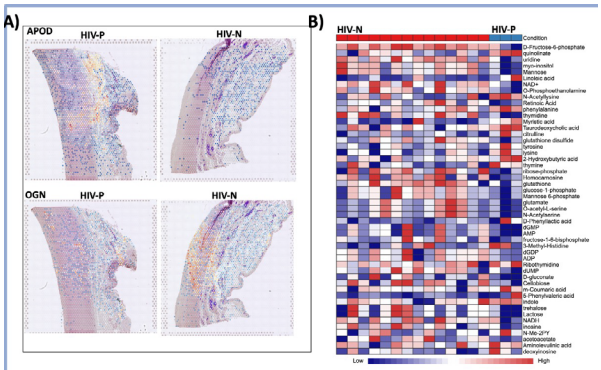

Figure. Spatial and metabolomic profiling of aorta provides insights on differences by HIV. APOD and OGN were differentially expressed by HIV status (A). Metabolic differences were also detected at the tissue level (B).

776 Endothelial Dysfunction in HIV: Exploring Cytokine and Chemokine Dynamics

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Background: In persons living with HIV (PWH), chronic inflammation promotes endothelial dysfunction, which contributes to cardiovascular disease. In this study, we sought to understand how subsets of endothelial cells (ECs) in adipose tissue modulate inflammation.
Methods: We analyzed the expression of cytokine/chemokine receptors by ECs in the subcutaneous adipose tissue of 59 PWH using single-cell RNA sequencing. We analyzed the association of EC subsets within adipose tissue with plasma cytokines and computed tomography morphometric measures. CellChat analysis was used to identify potential interactions between ECs and immune cells to further define the role of cytokines/chemokines. We also performed bulk RNA sequencing of human arterial ECs cultured in media conditioned with plasma from PWH to assess the direct effects of cytokines.
Results: The pattern of cytokine and chemokine receptor expression was different in the various subcutaneous adipose cell types identified: including capillary, venous, and arterial ECs; pericytes and vascular smooth muscle cells. Venous ECs expressed the il6r and the proportion of venous ECs was positively correlated with triglycerides (ρ=0.43, p=0.04), visceral fat volume (ρ=0.29, p=0.02), and plasma IL-6 (ρ=0.35, p<0.01), and negatively correlated with liver density (ρ=-0.32, p=0.01). Capillary ECs had relatively low levels of il6r compared to venous endothelial cells and were positively correlated with the mean liver density (ρ=0.36, p<0.01) and negatively with visceral fat volume (ρ=-0.34, p=0.01), and plasma IL-6 (ρ=-0.29, p=0.01). Analysis of intercellular communication between ECs and immune cells shows that capillary ECs have the potential to secrete chemokines that signal directly to venous endothelial cells, and this is mediated by classical and non-classical monocytes (Figure A). Arterial ECs cultured with plasma from PWH when compared to media controls differentially expressed genes that enriched for the TNF-α pathway via NFκB, and reactive oxygen species pathway (Figure B).
Conclusion: Cytokine and chemokine signaling between subcutaneous adipose tissue arterial, capillary and venous endothelial cells is potentially mediated by classical and non-classical monocytes. In PWH, this may indicate a dynamic crosstalk between vascular and immune cells that may underly, in part, the increased risk of cardiometabolic conditions linked to chronic inflammation.

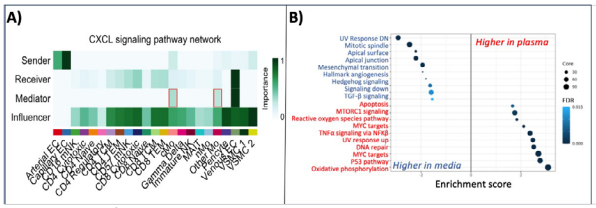

Figure. Cytokines/chemokines in EC dysfunction among PWH. (A) CXCL chemokines expressed by arterial/capillary ECs signal to venous ECs, mediated by monocytes. (B) Arterial ECs cultured in plasma activate TNF signaling.

777 Elevated Triglycerides and Endothelial Vasodilator Dysfunction in Adults Living With HIV-1

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Background: Adults living with HIV (ALWH) commonly have high triglyceride (TG) levels contributing to their increased risk of cardiovascular disease (CVD). Indeed, elevated TG levels are independently associated with an increased risk of myocardial infarction in ALWH. A major underlying mechanism for the TG-related increase in CVD is a profound worsening in vascular endothelial function. The influence of high TG levels on vascular endothelial function in ALWH is unknown. We tested the hypotheses that: 1) high TG levels are associated with worse endothelium-dependent vasodilation in antiretroviral (ART)-treated ALWH; and 2) the TG-related reduction in endothelial vasodilator function is due, in part, to diminished nitric oxide (NO) bioavailability.
Methods: Forty-two sedentary, non-obese, normotensive, non-medicated (aside from ART) middle-aged men were studied: 14 healthy adults (age: 38+3 yr; TG: 73+8 mg/dL); 14 ALWH on stable antiretroviral therapy with normal TG (42+2 yr; 98+7 mg/dL); and 14 ALWH on stable antiretroviral therapy with elevated TG (43+2 yr; 234+17 mg/dL). Aside from TGs all other lipid and lipoproteins, glucose and insulin levels were clinically normal. Forearm blood flow (FBF) responses to intra-arterial infusion of the endothelial agonist acetylcholine (Ach), in the absence and presence of the endothelial NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA), as well as the endothelium-independent vasodilator sodium nitroprusside were determined by venous occlusion plethysmography.
Results: FBF responses to Ach were significantly lower (~20%) in the ALWH with normal TG (from 4.5±0.3 to 13.1±0.7 mL/100 mL tissue/min) vs healthy adults (4.9±0.3 to 17.3±0.7 mL/100 mL tissue/min); whereas, the ALWH with high TG (4.3±0.3 to 10.2±1.0 mL/100 mL tissue/min) demonstrated FBF responses to Ach significantly lower than ALWH with normal TG and healthy adults. L-NMMA significantly reduced the FBF response to Ach in the healthy (~30%) and ALWH with normal TG (~25%) but not the ALWH with high TG (~10%). There were no significant group differences in the FBF response to sodium nitroprusside. TG levels were inversely and significantly associated with the FBF response to Ach (r=-0.51; P=0.005) in the ALWH.
Conclusion: Elevated TG levels is associated with lower endothelium-dependent vasodilation in adults living HIV-1 due, in part, to reduced NO bioavailability. Diminished NO-mediated endothelium-dependent vasodilation may underlie the increased risk of CVD in ALWH with high TG levels.

778 Spatial Profiling Reveals Immunometabolic Pathways Involved in Trained Immunity in PWH With CVD

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Background: People with HIV (PWH) are at increased risk for cardiovascular disease (CVD). Chronic exposure of innate immune cells to microbial products and pro-inflammatory lipids may drive trained immunity in these cells through transcriptomic and metabolism changes.
Methods: We measured coronary artery calcium (CAC) scores among people with and without HIV (N=25,43) to assess atherosclerosis and vascular age. Blood was collected from participants for assay of serum markers of immune

activation and differentiation of monocyte-derived macrophages (MDMs). We assessed the gene expression by RNAseq and cellular metabolism of MDMs (Seahorse) and responsiveness of these cells to bacterial products (LPS, Pam3CysSerLys4, or flagellin). We performed spatial profiling of arterial blood vessels from PWH and people without HIV (PWoH) using NanoString's GeoMx. Cells within vessels were stained for CD14 and CD163.

Results: PWH had increased CAC scores (350 vs 18; p=0.04) compared to PWoH, and among PWH vascular ages were higher than their biological ages (77y vs 55y; p<0.0001). Increasing CAC was associated with elevated inflammatory markers (osteopontin, C-reactive protein, IL6, soluble CD14; P<0.02). MDMs from PWH had altered gene expression in response to bacterial products, including higher HIF1α, mTOR, AKT1, MyD88 and NFκB, and were more dependent on glycolysis, all hallmarks of innate trained immunity. Spatial profiling confirmed increased macrophage infiltration into vessel walls in PWH. Pathway analysis of coronary arteries from PWH vs PWoH showed increased enrichment of glycolysis, TLR signaling, AKT, IGF1 and MTOR pathways. A cross-sectional comparison of regions of interest (ROI) with highest infiltration showed TLR4 and CD163 was higher in PWH. In ROI with lower infiltration, higher expression of FABP12 and CD163 was found in tissues from PWH. Analysis of pathways driving higher infiltration in both donor types identified unique pathways in PWH including innate immunity, TLR cascade, oxidative stress-induced senescence, cellular response to hypoxia, and O2-dependent proline hydroxylation of HIF1α.

Conclusion: Increased CVD risk in PWH may be driven by trained immunity as evidenced by immune functional profiling of blood-derived MDMs and spatial profiling of macrophages within blood vessel walls.

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779 IL-32 Isoforms Potentially Impact Bone and Cardiovascular Diseases in HIV Infection

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Background: We have recently demonstrated that the multi-isoform proinflammatory cytokine IL-32 is upregulated by HIV infection and is associated with subclinical CVD in people living with HIV (PLWH). However, mechanisms by which IL-32 isoforms contribute to the pathogenesis of CVD and potentially other chronic diseases like osteoporosis remain unclear. We investigated the impact of IL-32 isoforms α, β and γ on the differentiation of human mesenchymal stem cells (hMSC) and primary human monocytes into osteoblasts or osteoclasts (cells involved in calcium deposition and bone formation or bone resorption, respectively). These cells are involved in processes that are known to be dysregulated in PLWH in the bone (increased osteoporosis) and in the heart (increased non-calcified, vulnerable atherosclerotic plaque). We hypothesize that alterations in IL-32 isoforms seen in PLWH may be a common cause for bone and heart disease seen in that population.

Methods: Human CD14+CD16- monocytes or hMSC (osteoblasts precursors) were stimulated with recombinant IL-32 isoforms α, β or γ at 500 ng/ml with or without the osteoclast differentiation factor RANKL (30ng/ml) for 21 days. Immunofluorescence imaging on Spinning-Disc Zeiss AxioObserver was used to identify and analyze the differentiated cells.

Results: Both IL-32β and IL-32γ but not IL-32α induced the differentiation of hMSC as well as the primary monocytes into osteocalcin+ osteoblast cells. In contrast, IL-32α but not IL-32β or IL-32γ significantly induced the differentiation of a subset of primary CD14+CD16- monocytes into the giant multi-nucleated osteoclasts with the typical expression of the F-actin ring and TRAcP (p<0.0001). Interestingly, when either IL-32β or IL-32γ were combined with RANKL (a typical inducer of osteoclasts), these IL-32 isoforms counteracted the effect of RANKL and maintained their function by inducing osteoblast differentiation from monocytes (p<0.0001 and p=0.0001, respectively), further suggesting their dominant role in osteoblastogenesis.

Conclusion: Our data reveal a new function for IL-32 isoforms β and γ (the longest IL-32 isoforms) in inducing the differentiation of primary monocytes into osteocalcin+ osteoblasts by counteracting the osteoclast activation factor RANKL. Meanwhile, IL-32α induces the differentiation of osteoclasts. This novel demonstration of the role of IL-32 in regulation of calcium metabolism suggests that it may constitute a common, upstream cause to patterns of bone and heart disease observed in PLWH.

780 Myocardial Gene Profiling at Time of Sudden Death Demonstrates Increased Immune Responses in PWH

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Background: People with HIV (PWH) are at increased risk of sudden cardiac death (SCD). In our HIV Postmortem Systematic Investigation of Sudden Cardiac Death (POST SCD) Study we showed that PWH have higher interstitial myocardial fibrosis, a substrate for fatal cardiac arrhythmias causing SCD. However, the reason(s) for this increase are unknown. The myocardial transcriptome can reflect the acute cellular alterations for these lethal arrhythmias. We leveraged our POST SCD cohort to compare gene expression in myocardium from people with and without HIV infection.

Methods: We performed transcriptomic evaluation on left ventricular myocardium sampled at the time of SCD or traumatic death from 245 cases, 20 from PWH, using a Nanostring nCounter panel of 450 curated genes with potential association with SCD. We compared myocardial transcripts from PWH, most of whom were on ART, to 3 uninfected control groups: 1) demographic matched (N=60); 2) cause-of-sudden-death matched (N=20); 3) immediate traumatic deaths (N=11). Gene expression and ontology analyses were performed.

Results: We found a significant increase in myocardial expression of CD16 (NK and myeloid immune cell marker) in PWH compared to all 3 uninfected control sudden deaths: demographic, cause-of-death-matched, and immediate traumatic deaths. Moreover, significant increases in myocardial expression of genes related to innate immune response (CD31/PCAM), extracellular matrix homeostasis (MMP9), DNA damage/apoptosis, and leukocyte-endothelial interactions were observed in PWH compared to uninfected cause-of-death-matched controls. Myocardial CD45 expression was also significantly increased in PWH compared with demographic matched HIV- controls. Statin use did not alter myocardial gene expression in HIV+ SCD. Conversely, collagen-related genes and heart failure markers (ANP/BNP) were downregulated in myocardium from HIV+ SCD compared to that from all 3 HIV- control groups.

Conclusion: RNA profiling from myocardium sampled at time of SCD demonstrates increased immune activity but lower expression of genes associated with heart failure in PWH compared to uninfected control sudden deaths. Fibrosis-related genes were also downregulated in HIV+ myocardium, possibly because PWH already had higher levels of pre-existing fibrosis at the time of sudden death. These data suggest that increased risk of SCD in PWH may involve a multi-hit process of increased myocardial immune processes on top of previously established interstitial fibrosis.

781 Factors Affecting Risk of Major Adverse Cardiovascular Events Among People With HIV in REPRIEVE

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Background: People with HIV (PWH) have a 2-fold increased risk of major adverse cardiovascular events (MACE). REPRIEVE showed pitavastatin reduced MACE by 35% among PWH with low-to-moderate traditional risk. Enhanced understanding of the relative contributions of traditional and HIV-specific risk factors (RF) to MACE may guide concomitant individual- and population-level preventive interventions.

Methods: Analyses in the REPRIEVE population were performed for first MACE (including MI, TIA/stroke, revascularization, CV death), with median follow-up of 5.6 years through August 2023. Cox proportional hazards models stratified by randomized treatment group were used to account for treatment differences. Individual models adjusting for each entry RF were fit, and the strongest factors were then combined into a single multivariate adjusted model.

Results: Among 7,769 participants, 31.1% were natal female and 65.2% non-White. Median age was 50 years, LDL 108 mg/dL, 10-year ASCVD risk score 4.5%, diabetes prevalence <1%, and CD4 621 cell/mm³. In unadjusted models, RF associated with a higher (P<0.05) risk of first MACE were: older age, male sex, residence in a high-income region, Black/African American race (within high-income regions), family history of premature CVD, current/former smoking, hypertension (HTN), BMI ≥30 kg/m², fasting glucose ≥100 mg/dL, lower HDL, eGFR <90 mL/min/1.73 mm², lower nadir CD4, and detectable HIV-1 RNA (VL). After full adjustment, effects of natal sex, BMI, glucose, eGFR, and nadir CD4 were no longer apparent (P>0.25). Risk for first MACE was higher for older individuals (50-59 and ≥60 vs. 40-49, HR's: 1.98 and 2.11), as well as those with a family history of premature CVD (HR: 1.57), Black/African American race (vs. white race, within high-income regions HR: 1.75), current/former smoking (HR: 1.66), HTN (HR: 1.68), and detectable VL (HR 1.46), and lower for those with higher HDL-C (HR: 0.83). Individuals from a high-income region had a higher risk of first MACE vs. those from other regions, save for those from South Asia.
Conclusion: Among a global primary prevention cohort of PWH, factors associated with first MACE after accounting for statin effect included modifiable RF of cigarette smoking, HTN, and detectable VL. A protective effect of female sex was not apparent. Additional work is needed to understand the higher risk of MACE associated with residence in a high-income region, particularly among Black/African American PWH.
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782 Performance of the ACC/AHA Pooled Cohort Equations for Risk Prediction in the Global REPRIEVE Trial

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Background: People with HIV (PWH) have a higher burden of cardiovascular (CV) disease than the general population; estimating this risk is an essential component of prevention. However, it is unknown how well the 2013 ACC/AHA guideline-recommended Pooled Cohort Equation (PCE) estimates risk among PWH globally. Leveraging the international REPRIEVE Trial, which prospectively adjudicated incident CV events, we compared observed vs. predicted event rates in PWH not taking statins.
Methods: The REPRIEVE Trial used the PCE to determine eligibility of PWH at low-moderate CV risk for a statin primary prevention trial. We now assess discrimination and calibration of the PCE in those randomized to placebo (n=3869) as well as those randomized to statin but never starting treatment (n=24). To align with the median 5-year follow up in REPRIEVE, a 5-year risk score was recalculated for this analysis per established method, and follow-up beyond 5 years was censored. We limited outcomes to the specific CV events predicted by the PCE (hard MACE): CV death, myocardial infarction (MI), and stroke. We calculated the C-statistic, the observed: expected (O:E) event ratio and the Nam-D'Agostino goodness-of-fit (GND) statistic overall and in subgroups by race, natal sex, and Global Burden of Disease region. Small GND p-value indicates poor calibration.
Results: Participants were mean age 50 years, 31% female, 65% nonwhite, with a median (Q1, Q3) 10-yr PCE risk of 4.5% (2.2, 7.1). Overall, discrimination was moderate (C-statistic 0.72) and calibration was good (O:E events, 84:81, ratio 1.03, GND P=0.81). However, calibration demonstrated over-prediction of risk outside High Income regions. When restricted to High Income regions, under-prediction (O:E ratio>1.0) was suggested among females (2.56) and Black or African American participants (1.66).
Conclusion: Among a global cohort of PWH with low-to-moderate traditional CV risk, the PCE was moderately effective to predict CV death, MI or stroke over 5 years but under-predicted events in females, Blacks or African Americans and participants from high-income regions. Performance in selected subgroups should be considered when using the PCE to guide prescribing statin therapy for CV prevention among PWH.
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783 Residual HIV Viremia Doubles Cardiovascular Disease Incidence Independent of Classic Risk Factors

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Background: People living with HIV (PLHIV) have a heightened risk of atherosclerotic cardiovascular diseases (CVD) beyond that explained by traditional risk factors, potentially driven by HIV-related inflammation or other HIV-related factors. Although antiretroviral therapy (ART) should result in undetectable plasma viral loads (VL), some PLHIV show unquantifiable low yet detectable VL via PCR testing (Residual viremia, RV). We now propose a role of RV for CVD development.
Methods: The 2000HIV study enrolled 1895 virally suppressed PLHIV (2019-2021), divided in a discovery and validation cohort. VL was measured by commercial PCR assays (Roche, Abbott, Hologic or Cepheid). Only PLHIV with VL <40 c/ml (n=1815) were analyzed: compared were PLHIV with RV (unquantifiable low, yet detectable VL) with those with undetectable PCR result. Baseline blood samples were used for proteomics by Olink® Explore panel (~3000 proteins) and functional immunological testing by exposing PBMCs to various stimuli and cytokine level measurements in the supernatant. Incident CVD (stroke, transient ischemic attacks, myocardial infarction, angina pectoris or peripheral artery disease) was registered after two years follow-up. Odds ratio (OR) and p value were calculated using multivariate logistic regression accounting for age, sex, smoking, BMI, diabetes, hypertension, hypercholesterolemia and CVD family history.
Results: At baseline, 665 PLHIV had RV, 1150 had undetectable VL. Participants with RV had higher VL zenith, and shorter ART duration but did not differ in terms of statin or abacavir use, ART adherence and dual DTG based versus three-drug ART nor presence of carotid plaque on ultrasound. Participants with RV more often had a history of myocardial infarction (5.6% vs 2.7% OR 2.28 p=0.01; 7.1% vs 1.5% OR 9.6 p=0.04 in discovery and validation cohort respectively). Notably RV participants were twice as likely to develop a first cardiovascular event during follow up (3.4% vs 1.4% OR 2.58 p=0.01). Comparing PLHIV with and without RV, no differences were observed in the functional immunological assays, however plasma levels of TNF Superfamily member 10, Granzymes (A, B and H) were higher in participants with RV.
Conclusion: Our data are the first to suggest that residual viremia is a risk factor for past and future cardiovascular diseases independent from traditional CVD risk factors. The mechanism may be through upregulation of specific inflammatory biomarkers that have also been identified for CVD in non-HIV populations.

784 Temporal Trends of Cardiovascular Disease Incidence in People With HIV From 2001-2021

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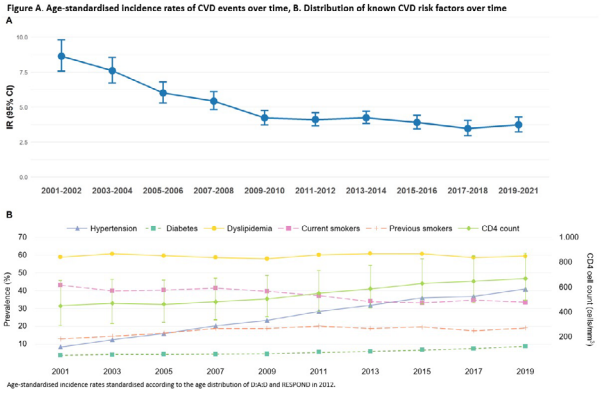
Background: With an increased focus on cardiovascular disease (CVD) as a leading cause of death in people with HIV, monitoring patterns in CVD incidence and its influencing factors in real-life settings is crucial for informed clinical decision-making.
Methods: We followed participants from the D:A:D and RESPOND cohort collaborations from baseline (D:A:D: latest of study entry or 1 Jan 2001; RESPOND: latest of local cohort enrolment or 1 Jan 2012) until the earliest of first CVD event (myocardial infarction [MI], stroke, invasive cardiovascular procedure [ICP]), final follow-up, or 1 Feb 2016 (D:A:D)/31 Dec 2021 (RESPOND). We calculated age-standardised CVD incidence rates (IRs) two-yearly from 2001–2021 and assessed temporal trends by Poisson regression, adjusting for time-updated potential confounders and cohort.
Results: Of 66,680 included individuals, 18% were age >50 (median 40, interquartile range [IQR] 33–47) at baseline, 74% were male, 38% current smokers, 45% had dyslipidemia, 8% hypertension, 3% diabetes, and 1% prior CVD. Median CD4 cell count was 437 (270–630). Over a median of 8.8 (4.5–13.1) years (586,510 person-years, PY), there were 2,811 CVD events (IR 4.79/1000 PY [95% confidence interval (CI) 4.62–4.97]; 1363 MIs, 768 strokes, 680 ICPs). While the crude CVD incidence remained relatively stable over time, age-standardised

IRs decreased from 8.65/1000 PY in 2001–2002 to 3.74/1000 PY in 2019–2021, IR ratio (IRR) 0.30 (95% CI 0.24–0.38, p<0.0001), with a steeper decline up to 2009 (Fig. A). The prevalence of most CVD risk factors was similar or decreased over time except for hypertension, which increased (Fig. B), possibly partly due to increased monitoring. Adjusting for hypertension accentuated the temporal CVD trends (IRR 0.26 [95% CI 0.20–0.32], p<0.0001) while changes in demographics (gender, ethnicity, mode of HIV acquisition), other known CVD risk factors (smoking, chronic kidney disease, body mass index, diabetes, dyslipidemia) or stage of HIV disease (CD4 nadir, prior AIDS) did not influence the decline in CVD IR.

Conclusion: Combining data from two large, international collaborations, we have shown a decline in age-standardised CVD incidence in people with HIV from 2001 to 2021, most pronounced from 2001 to 2009. While causes of the decline in CVD incidence need to be investigated further, hypertension may have contributed to a slower decline over time. The CVD decline did not appear to be affected by changes in demographics, HIV disease stage and most known CVD risk factors.

Figure A. Age-standardised incidence rates of CVD events over time, B. Distribution of known CVD risk factors over time



Age-standardised incidence rates standardised according to the age distribution of D:A:D and REGPUND in 2012.

785 The Effect of Dolutegravir on Whole-Body Glucose Disposal and Lipid Metabolism in Healthy Volunteers

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Background: Dolutegravir (DTG) is a second-generation HIV integrase inhibitor prescribed in combination with other antiretrovirals (ARVs). Although DTG has shown success in achieving and maintaining virological suppression, there is interest in the effects of DTG on glucose disposal and metabolic outcomes including diabetes mellitus. The aim of this study was to assess glucose disposal in volunteers without HIV, exposed to DTG daily for 28 days using euglycaemic clamp procedures.

Methods: An open-label, two-arm, single centre study randomised participants 1:1 to either 28 days of DTG (treatment arm, TA) or no therapy (no treatment arm, nTA). A hyperinsulinaemic euglycaemic clamp was carried out at days 1 and 28 in both arms. Statistical assessments of change in estimated glucose disposal rates were carried out using Wilcoxon signed-rank test (intra-arm) and two-sample Wilcoxon rank-sum (Mann–Whitney) test (inter-arm). The primary study outcome was change from baseline in total body glucose disposal by euglycaemic clamp method following 28 days of treatment.

Results: Fourteen volunteers in total completed the study, with 6 in the TA, and 8 in the nTA. The median glucose disposal rate for the nTA was 6.18 mg/kg/min at day 1 and 7.62 mg/kg/min at day 28 (p=0.64), with a median percentage change of +23.3% (1.44). In the TA, the median glucose disposal rate for was 6.95 mg/kg/min at day 1 and 7.93 mg/kg/min at day 28 (p=0.06), with a median percentage change of +14% (0.98). Furthermore, on day 28, no significant difference in glucose disposal rate was measured between the TA and the nTA: 7.93 mg/kg/min versus 7.62 mg/kg/min (p=0.41). In addition, there was a difference of -0.41 (-14.64%) in LDL cholesterol values between the TA (LDL 2.39 mmol/L) and the nTA (LDL 2.80 mmol/L) (p= 0.36).

Conclusion: DTG treatment for 28 days was not associated with a statistically significant change in total body glucose disposal, as measured by euglycaemic hyperinsulinaemic clamp technique, or in LDL cholesterol levels in volunteers without HIV. Long term data on DTG metabolic effects are needed.

786 Factors Associated With Smoking Cessation Among Patients in the HIV Outpatient Study, 2007-2022

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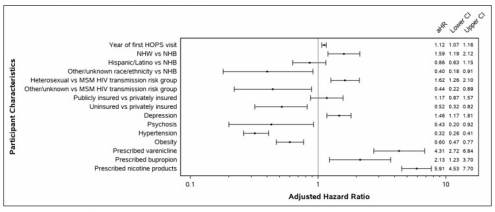
Background: The U.S. Preventive Service Task Force recommends smoking screening and cessation strategies as a part of routine care. However, people with HIV (PWH) are more likely to smoke and less likely to quit than people without HIV. We assessed factors associated with smoking cessation among cigarette smokers seen in care at outpatient clinics of the HIV Outpatient Study (HOPS).

Methods: We analyzed HOPS participants' data from clinic electronic medical records (EMR) and from an optional annual participant survey from January 1, 2007 to December 31, 2022. We included PWH with EMR or survey evidence of current cigarette use and no smoking cessation medication use at baseline (i.e., first HOPS visit) and those who began smoking cigarettes during follow-up. We identified smoking-related comorbidities based on lab results, clinical diagnoses, and treatments. Smoking quit attempts were determined via EMR and survey data during follow-up. We studied associations of first quit attempt with comorbidity diagnoses, smoking cessation medications prescriptions, sociodemographics, and clinical factors using the counting process within Cox proportional hazards analyses.

Results: Among 1,068 eligible PWH, 77% were men, 32% White persons, 48% Black persons, 18% Hispanic/Latino persons, 47% aged 40 and older. At baseline, 172 (16%) had chronic obstructive pulmonary disease (COPD)/emphysema, cardiovascular disease (CVD), and/or cancers. During a median follow-up time of 4.4 years (interquartile range: 1.9-8.6), 301 (28%) PWH were prescribed smoking cessation medications (varenicline=87, bupropion=50, nicotine products=235), and 198 (19%) quit smoking. Of these 198, 33 (17%) resumed smoking after first quit. In multivariable analysis, factors positively (p<0.05) associated with smoking cessation included: later year of HOPS enrollment, non-Hispanic/Latino (NH) white race/ethnicity versus NH Black, heterosexual HIV transmission versus men who have sex with men risk group, having a depression diagnosis, being prescribed varenicline, bupropion or nicotine products, whereas factors inversely associated included: being uninsured versus having private insurance, and having diagnoses of psychosis, hypertension, or obesity (Figure).

Conclusion: Fewer than one-third of HOPS participants who smoked cigarettes had a prescription for smoking cessation medication, and only one-in-five had a documented quit attempt, highlighting challenges for and need to strengthen prevention of smoking-related chronic diseases in PWH.

Figure: Multivariable Adjusted Hazard Ratio of Factors Associated with First Quit Smoking Attempt, the HIV Outpatient Study, 2007-2022, N=1,068.



Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; NHB, non-Hispanic/Latino Black; NHW, non-Hispanic/Latino white; MSM, men who have sex with men. The following additional factors were adjusted for in the multivariable model: CD4 cell count at baseline, alcohol use, diagnoses of cancer, COPD/emphysema, and CVD during the study period.

787 Associations Between Antiretroviral Therapy and Cardiovascular Events in People With Treated HIV

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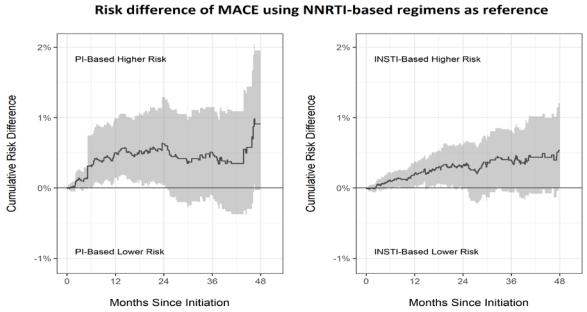
Background: Several antiretroviral therapy (ART) agents are associated with increased risk of cardiovascular disease but less is known about the safety of contemporary ART. We sought to compare the risk of major adverse cardiac events (MACE) between different ART regimens.

Methods: We used the Merative™ MarketScan® Commercial (2008-2020) and Multistate Medicaid (2011-2020) databases to identify adults between

18-64 years of age who newly initiated a stable ART regimen. We excluded people with MACE prior to and within 90 days after ART initiation. Nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens were compared to protease inhibitors (PI) and integrase inhibitors (INSTI) at class-level as well as to individual INSTI drugs. We used propensity score-weighted Kaplan-Meier functions to estimate the 6, 12, 18, 24, 36, and 48-months risks and risk differences (RD) for MACE. Secondary analyses including use of tenofovir or abacavir were performed.

Results: Among 37,935 new ART initiators, mean age was 40±11 years. The distribution of ART regimens was 45% INSTI- (14% raltegravir, 40% elvitegravir, 30% dolutegravir, and 16% bictegravir), 39% NNRTI-, and 16% PI-based regimen. INSTI initiation increased from 5% in 2008 to 97% in 2020. The median (IQR) follow-up for those starting INSTI-, NNRTI-, and PI-based regimens was 442 (224, 894), 521 (239, 1109), and 429 (212, 932) days, respectively. MACE occurred in 418 individuals (1.1%) over the study period. The highest risk of MACE occurred with PI-based regimens followed by INSTI and NNRTI. Compared to NNRTI initiators, the risk of MACE was higher at 12 months [RD 0.50, 95% CI (0.14, 0.99)], 18 months [RD 0.53, 95% CI (0.11, 1.06)] and 24 months [RD 0.62, 95% CI (0.04, 1.29)] for the PI-group, and at 12 months [RD 0.20, 95% CI (0.03, 0.37)] and 18 months [RD 0.31, 95% CI (0.06, 0.54)] for INSTI initiators; the precision of estimates was limited in later months of follow-up. Risk of MACE did not differ by individual INSTIs, tenofovir, or abacavir use.

Conclusion: In this large-scale study using U.S. claims databases, PI-based and INSTI-based regimens were associated with higher risk of MACE compared to NNRTI-based regimens after ART initiation, and the pattern of association between INSTIs and PIs with excess risk of MACE was similar.



MACE: Major adverse cardiac events; PI: protease inhibitors; INSTI: integrase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors.

Adjusted for age, sex, co-morbidities, type of insurance, preexisting cardiovascular disease, hepatitis B and C, lipid and cardiovascular medications, and calendar-year.

788 Modifiable Factors Associated With Cardiovascular Disease Risk Among Women With and Without HIV

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Background: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among women in the United States. Women living with HIV (WWH) have twice the risk of CVD events compared to women without HIV (WWoH). While increased CVD risk for WWH has been largely attributed to HIV-specific factors, interventions on modifiable factors (e.g., social support, psychological health, physical activity, diet quality, substance use, and HIV viral suppression) may decrease CVD risk among women.

Methods: We analyzed data from the Women's Interagency HIV Study (WIHS) to examine relationships between individual-level factors and CVD risk among WWH and WWoH. Women were included if they were 30-79 years of age at the time of their semiannual WIHS study visit (April – September 2019) and had data to calculate the American College of Cardiology and American Heart Association Pooled Cohort Risk Equation (PCE), a 10-year CVD risk score. Descriptive statistics and logistic regression were used to test associations between each factor and CVD risk among WWH and WWoH. CVD risk was dichotomized as low risk versus borderline or higher risk, and two-way interactions were tested by HIV status. Odds ratios [ORs] were not adjusted as age, race, and gender are included as part of the PCE.

Results: Data was available for 1,711 women (72% HIV+) with a median age of 53 years (IQR: 46-58). Approximately half (53%) were classified as having low (<5%) risk, while 13%, 24%, and 9% were classified as having borderline (5-7.4%), moderate (7.5-19.9%), or high risk (≥ 20%), respectively. 45.7% of WWH and 51.6% of WWoH were classified as having borderline or higher risk for CVD. Higher annual household income (OR: 0.57, 95% confidence interval [CI]: 0.45-0.72), greater physical activity (OR: 0.63, 95% CI: 0.54-0.73), better diet quality (OR: 1.03, 95% CI: 1.00-1.06), and <7 alcoholic drinks per week (OR: 0.63, 95% CI: 0.51-0.77) were associated with decreased odds of higher CVD risk, while current smoking (OR: 2.22, 95% CI: 1.81-2.70) was associated with increased odds of higher CVD risk. We found effect modification of smoking by HIV status, with an OR for higher risk of 2.54 (95% CI: 2.00-3.21) among WWH versus 1.53 (95% CI:1.07-2.21) among WWoH. There was a lack of modification by HIV-status for all other variables tested.

Conclusion: Interventions targeting modifiable lifestyle factors should be considered as a means to reduce CVD risk and improve outcomes among WWH and women behaviorally at risk for acquiring HIV.

789 No Increased Risk for Hypertension With CAB-LA Compared to TDF/FTC for HIV PrEP in HPTN 083

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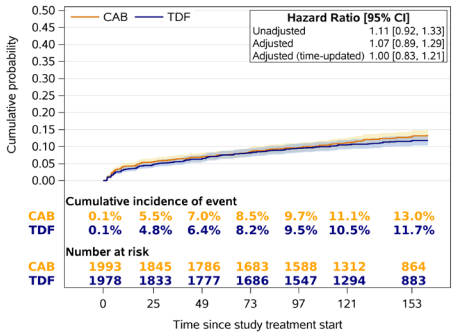
Background: Results from some trials of HIV treatment suggest an excess risk of hypertension (HTN) associated with integrase strand transfer inhibitors (INSTIs), independent of changes in weight or BMI. HPTN 083, in HIV-negative MSM and transgender women, compared injectable cabotegravir (CAB) to daily oral tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) for HIV PrEP. We performed a post-hoc analysis of HPTN 083 to compare incidence rates for HTN in the absence of HIV infection.

Methods: Of 4566 participants (ppts) enrolled, the analysis population included 3971 (1993 CAB/1978 TDF-FTC) exposed to study drug and without pre-existing HTN. Incident hypertension was defined as a new diagnosis of HTN, 2 sequential measures of SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg, or initiation of anti-HTN treatment, through 161 weeks of follow-up. Changes in blood pressure over time by study arm were estimated with mixed effect models. Cox regression models were used to estimate the hazard ratio (HR) for incident HTN between study arms, unadjusted and adjusted for race, age, baseline (BL) BMI, anti-HTN treatment, and time-updated weight change from BL (TUWC).

Results: Ppts were well matched between groups; 75% were under age 30; 4% were over age 45. 58% were normal or underweight at baseline. Over 10293 person-years of follow-up, median BMI increased +1.2 (IQR 0.1-2.3) kg/m² for CAB and 0.8 (IQR -0.2-2.1) for TDF-FTC. BMI and SBP were weakly correlated. 461 (12%) ppts had incident HTN (246 CAB, 215 TDF-FTC). Mean change per year in SBP was 0.56 mm Hg (95% CI 0.41, 0.71) and DBP was 0.73 (0.62, 0.85) in CAB and 0.30 (0.15, 0.45) and 0.66 (0.55, 0.78) in TDF-FTC. Cumulative incidence of HTN over 3 years was 13.4% for CAB and 11.8% for TDF-FTC (Figure). HTN was more common in US and African ppts and those with higher BMI, older age, and taking anti-HTN meds for non-HTN indications (MFnH). Between-arm differences were numerically largest for US ppts, older ppts, and ppts taking MFnH. HR for incident HTN was 1.11 (95% CI 0.92, 1.33, p=0.28) for CAB vs. TDF-FTC in the unadjusted analysis, and 1.00 (95% CI 0.83, 1.21) after adjustment for race, BL age, BL BMI, anti-HTN BL meds, and TUWC.

Conclusion: HTN incidence in HPTN 083 was low. Observed HTN incidence was higher in CAB vs. TDF-FTC, but was not statistically significant. Risk factors for HTN included age, BL obesity, and weight gain over time. Over 3 years there was no increase in the hazard of incident HTN in CAB vs. TDF-FTC after adjusting for relevant covariates.



790 Higher Risks of Hypertension With Use of DTG Versus PI/r in the VISEND Trial

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Background: Hypertension is a leading cause of death in sub-Saharan Africa. In the general population, risks of hypertension rise with increasing age and body weight. Many African HIV treatment programs do not include funding for treatment of hypertension. Use of tenofovir alafenamide (TAF) and dolutegravir (DTG) have been associated with higher risks of hypertension in some randomized trials and cohort studies, but other studies have not shown these associations. The VISEND study was conducted in Zambia to evaluate the safety and efficacy of second-line treatment, after NNRTI failure.

Methods: The VISEND study recruited adults previously taking NNRTI based treatment. People with HIV-1 RNA <1,000 c/mL at screening (Low VL Group) were randomized to TDF/3TC/DTG or TAF/FTC/DTG. People with HIV-1 RNA>1,000 c/mL (High VL Group) were randomized to TDF/3TC/DTG, TAF/FTC/DTG, ZDV/3TC+LPV/r or ZDV/3TC+ATV/r. Blood pressure was evaluated at study Weeks 24, 48, 96 and 144. The risk of Grade 1 hypertension (SBP/DBP >140/90 mmHg) was compared between the TDF/3TC/DTG and TAF/FTC/DTG arms, and by use of DTG vs PI/r, using Cochrane Mantel-Haenszel tests.

Results: At Week 24, there were no significant differences in Grade 1 HTN between treatment arms within either VL Group. Across the VL Groups, rises in BMI were significantly higher for people taking TAF/FTC/DTG versus TDF/3TC/DTG (p<0.001). In the high VL Group, rises in BMI were significantly greater in the TAF/FTC/DTG or TDF/3TC/DTG arms, versus the ZDV/3TC+LPV/r or ZDV/3TC/ATV/r arms (p<0.001). Systolic BP increased across TAF/FTC/DTG, TDF/3TC/DTG, and ZDV/3TC+LPV/r arms, while no changes were noted in the ZDV/3TC/ATV/r arm. The prevalence of hypertension increased over time in all treatment arms. By Week 144, the percentage with Grade 1 hypertension was significantly higher for people taking TAF/FTC/DTG, compared with TDF/FTC/DTG (p=0.02, stratified by VL Group). By Week 144 there were significantly more people in the TDF/3TC/DTG and TAF/FTC/DTG arms with Grade 1 HTN (173/343, 50%) compared with the ZDV/3TC/LPV/r or ZDV/3TC/ATV/r arms (76/258, 27%) (p<0.001).

Conclusion: In VISEND, risks of Grade 1 HTN and changes in systolic BP were higher for TAF/3TC/DTG and TDF/FTC/DTG versus ZDV/3TC/ATV/r or ZDV/3TC/LPV/r. Results were not consistent when comparing TAF/3TC/DTG and TDF/FTC/DTG, where there were no significant differences for change in systolic BP, but there were differences when comparing the risk of Grade 1 HTN.

	Low VL		High VL			
	TLD	TAFED	TLD	TAFED	ZDV/3TC+LPVr	ZDV/3TC+ATVr
Sex, female	134/207 (65%)	114/200 (57%)	110/189 (58%)	128/199 (64%)	103/148 (70%)	102/181 (56%)
Age, mean (SD)	44 (10)	44 (9)	38 (10)	39 (11)	38 (10)	38 (10)
Baseline BMI, mean (SD)	23.8 (5.5)	23.4 (5.0)	21.7 (4.9)	21.3 (4.5)	22.3 (4.6)	22.4 (4.4)
Mean BMI change to Week 144 (SD)	+1.15 (4.5)	+1.55 (2.7)	+1.80 (3.0)	+2.29 (3.1)	+1.38 (3.3)	+1.64 (2.9)
Mean Systolic change to Week 144 (SD)	+7.28 (17.9)	+11.00 (22.4)	+7.43 (18.3)	+9.61 (20.2)	+3.73 (18.3)	-0.22 (16.6)
G1 HTN Week 24	80/207 (39%)	81/199 (41%)	58/189 (31%)	61/198 (31%)	47/147 (32%)	58/181 (32%)
G1 HTN Week 144	109/188 (58%)	122/178 (69%)	83/175 (47%)	90/168 (54%)	35/113 (31%)	41/145 (28%)

791 Hypertension Treatment Gap Among People With/Without HIV in Kenya, Nigeria, Tanzania, and Uganda

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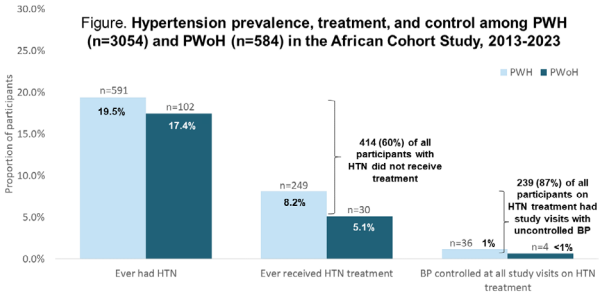
Background: Mortality associated with hypertension (HTN) in sub-Saharan Africa is among the highest globally and unlike other regions, little progress has been made in diagnosis, treatment, and control. HIV care programs have typically focused on providing HIV-related care, but as life expectancies of people with HIV (PWH) are extending, addressing noncommunicable diseases and risk factors may be increasingly important.

Methods: The prospective African Cohort Study enrolls PWH and people without HIV (PWoH), aged ≥15 years, in care at 12 PEPFAR-supported facilities in Kenya, Nigeria, Tanzania, and Uganda. Among participants with at least two 6-monthly study visits, we defined HTN as a persistently elevated systolic and/or diastolic blood pressure (BP) ≥140/90 mmHg at ≥2 consecutive visits, or receipt of any HTN medication. All subsequent study visits were classified as having HTN. Multivariable random intercept log-Poisson models with robust standard errors that included HIV status, time in the cohort, demographic and clinical characteristics, and site service delivery characteristics were used to examine associations with study visit-level rates of untreated HTN and uncontrolled BP (≥130/80 mmHg) among those on HTN treatment.

Results: From 1/2013–6/2023, 4114 participants were enrolled; 3638 with a total of 19,507 person-years of follow-up were included. Overall, 693 (19%) ever had HTN, among whom median (IQR) age was 48 (41–54) years, 591 (85%) were PWH, and 380 (55%) were female. Of those with HTN, 414 (60%) never received HTN treatment (figure). Among those on HTN treatment, 87% had one or more study visits with uncontrolled BP, with a median (IQR) proportion of study visits with uncontrolled BP of 73% (43%–100%). At their most recent study visit, 158 (57%) of those on HTN treatment received combination therapy as recommended by WHO guidelines. In multivariable models, HIV status was not significantly associated with untreated HTN (PWH vs. PWoH: adjusted rate ratio [aRR] 0.93, 95% CI: 0.84–1.03) or uncontrolled BP (PWH vs. PWoH: aRR 0.97, 95% CI: 0.81–1.17). Males had a significantly higher rate of untreated HTN (aRR 1.18, 95% CI: 1.08–1.28), but not uncontrolled BP (aRR 1.10, 95% CI: 0.96–1.26).

Conclusion: We identified a substantial burden of untreated and uncontrolled HTN, unaffected by HIV status. Strategies are needed to optimally scale up HTN diagnosis and management in the context of existing HIV treatment services for PWH and testing/prevention services for PWoH.



792 HIV-Associated Heart Failure: Phenotypes and Clinical Outcomes in a Safety Net Setting

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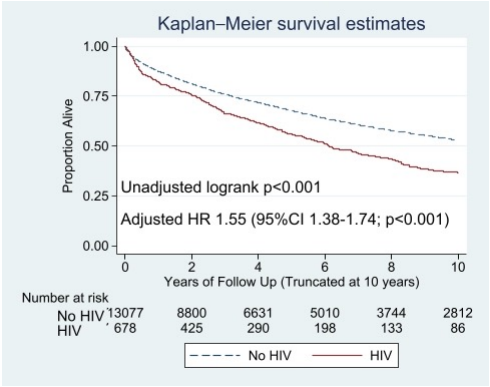
Background: HIV is associated with increased risk of heart failure and with worse outcomes after diagnosis with heart failure. However, whether cardiomyopathy phenotypes vary by HIV status and whether HIV is associated with similarly increased risk within a contemporary population who receives care within a safety-net system is unknown.

Methods: In this observational study, using an electronic health record database of all individuals with diagnosed heart failure within the San Francisco Health Network, a municipal safety-net system, from 2001-2019, we compared individuals with and without HIV (defined by ICD code and at least one CD4

count or viral load) in terms of baseline characteristics, heart failure phenotypes by ejection fraction and presumed etiology, and outcomes after heart failure diagnosis including all-cause mortality (linked to national death statistics), and hospitalization for heart failure.
Results: We included 14,829 individuals with HF, of whom 697 (4.7%) had HIV. Although 41% without HIV were female, only 19.7% with HIV were female with HIV, and the median age was 63 without HIV and 53 with HIV at time of HF diagnosis. Among those with HIV, the median nadir CD4 count was 133 (IQR 44, 275), and at HF diagnosis was 356 (IQR 173, 566). Persons with HIV had much higher proportions with documented alcohol, tobacco, opioid, cocaine and methamphetamine use (p<0.001 for each). 38% vs 33% had a reduced ejection fraction to <40% (p=0.009). There were no differences in the proportion with prior myocardial infarction or obstructive coronary artery disease on angiography. Median survival was 6.1 years (95% CI 5.4-7.1) among people with HIV compared to 11.3 years without HIV (95%CI 10.7-11.7). HIV was associated with higher risk of all-cause mortality (HR 1.55 95%CI 1.38-1.74; p<0.001; Figure) and lower odds of heart failure hospitalization (OR 0.51; 95%CI 0.39-0.66); p<0.001). Lower nadir CD4 and CD4 at the time of HF diagnosis were associated with worse survival: HR 1.37 for nadir < 200 (95%CI 1.08-1.75; p=0.009) and HR 1.69 for current <200 (95%CI 1.34-2.13; p<0.001), respectively. Viral load greater than 500 copies/ml was not associated with mortality (HR 1.02; 95%CI 0.80-1.31; p=0.87).
Conclusion: Among people with HF who receive care within a municipal safety-net system, HIV infection is associated with diagnosis with HF ten years earlier and significantly elevated risk of mortality despite lower risk of HF hospitalization.



793 Repeated Stimulant Use in the Context of Left Ventricular Dysfunction among Women Living with HIV

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Background: HIV is associated with an increased risk of heart failure (HF), which is especially pronounced in women. This is concerning because women with HIV (WWH) come predominantly from vulnerable race-ethnic minority groups that are themselves at high risk for HF. In addition, people with HIV have a disproportionately high prevalence of substance use, which is also associated with heart disease. The extent to which specific substances or substance types relate to precursors of clinical HF, such as left ventricular systolic dysfunction (LVDD) and diastolic dysfunction (LVDD), in WWH remains under-studied.
Methods: We investigated cross-sectional associations between repeated use of various substances and pre-HF phenotypes, LVSD and LVDD, in the Women's Interagency HIV Study. We defined exposures as self-reported substance use (i.e., tobacco, alcohol, cannabis, cocaine, methamphetamine/amphetamine, opioids, and sedatives) at ≥2 study visits ("repeated use") compared to no use or single-visit use. Standardized echocardiograms were performed from 2014 to 2019 in 1,162 WWH. LVSD and LVDD were defined by American Society of Echocardiography criteria.
Results: Most participants (75%) identified as non-Hispanic Black, the average age was 49 years, 58% were post-menopausal, the median nadir CD4 cell count over the study period was 478, and 55% of participants were virally suppressed at all study visits. Repeated substance use ranged from 1.3% (cocaine use) to 66.1% (alcohol). Among all participants, 5.5% had LVSD. None of the repeated substance use measures were significantly associated with LVSD. Among participants without LVSD, 6.1% had LVDD. Adjusting for socioeconomic and clinical risk factors, the odds of LVDD were 5.22 times higher among women who reported repeated methamphetamine/amphetamine use (95% CI: 1.10, 24.73) and 1.87 times higher among those who reported repeated use of tobacco (95% CI: 1.10, 3.17). HIV-specific factors and other substances did not reach levels of significance .
Conclusion: Repeated tobacco use and, to a much larger extent, repeated methamphetamine/amphetamine use had strong associations with LVDD in this population. Our findings highlight stimulant use as a potent risk factor for LVDD among WWH. Assessment and targeted interventions for WWH who use methamphetamine/amphetamine may lower cardiovascular risk in this population.

794 Proteomic Signature of HIV-Associated Myocardial Fibrosis and Incident Heart Failure

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Background: Persons living with HIV (PLWH) receiving antiretroviral therapy (ART) have greater myocardial fibrosis compared to persons without HIV (PWOH), which may contribute to risk of heart failure (HF). Mechanisms remain unclear but hypotheses include accentuated aging linked to chronic immune activation. We identified plasma proteomic signatures elevated among PLWH, cross-sectionally associated with myocardial fibrosis, and associated with incident HF among an external population of older PWOH.
Methods: We performed proteomics (Olink) on plasma obtained concurrently with cardiac magnetic resonance imaging among PLWH and PWOH in Baltimore/DC and Chicago (SMASH). Myocardial fibrosis was measured by extracellular volume fraction (ECV). Proteins were assessed individually and as clusters defined using weighted gene co-expression network analysis. We estimated associations with HIV and elevated ECV (≥30% in women, ≥28% in men) using multivariable regression and explored protein relationships using annotated enrichment analysis. We tested associations of identified signatures with incident adjudicated HF using Cox regression among older PWOH (MESA).
Results: Among 342 SMASH participants (age 55±6 years), 52% had elevated ECV and 61% were PLWH (88% on ART; 74% with undetectable plasma HIV RNA). Of 2594 proteins, 439 were associated with HIV seropositivity (SP) (414 excluding PLWH with detectable plasma HIV RNA) with a false discovery rate <0.05. We identified 39 (32) of these proteins as candidate contributors to the independent association between HIV SP and elevated ECV, including 9 proteins involved in apoptosis, 8 in cytokine signaling, 6 in T-cell activation, and 6 in the MAPK cascade. We identified one protein cluster associated with elevated ECV and HIV SP regardless of HIV viral suppression status, enriched in factors involved in TNF signaling, ephrin signaling, and extracellular matrix (ECM) organization. This protein cluster as well as 31 of 39 individual proteins were associated with incident HF among 2273 PWOH in MESA (age 68±9 years; 8.5 ±1.4 years of follow-up).
Conclusion: Proteomic signatures that may in part reflect or contribute to HIV-associated myocardial fibrosis are enriched in pathways of immune activation, cytokine signaling, and ECM organization, even among virally suppressed PLWH. These signatures also predict incident HF in a large independent cohort of older PWOH, suggesting underlying pathways that may portend risk of HF among PLWH may also drive HF pathogenesis among PWOH.
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795 Factors Linked to Reduced Myocardial Flow Reserve in HIV Using 82Rb Positron Emission Tomography

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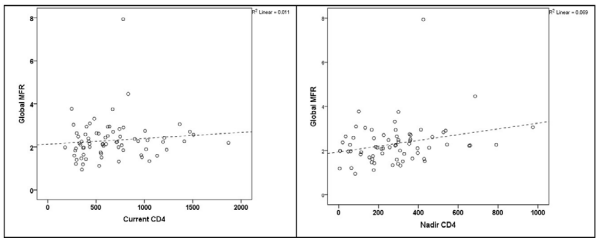
Background: Despite stable HIV suppression and substantial immune reconstitution through antiretroviral therapy, people with HIV (PWH) demonstrate an elevated risk of coronary artery disease (CAD) and elevated levels of endothelial injury markers. Myocardial flow reserve (MFR) is an indicator of coronary microvascular dysfunction and overall vascular health. This retrospective study sought to evaluate the association between HIV-related parameters and MFR, determined by the stress over rest myocardial blood flow (MBF) using 82Rubidium positron emission tomography (82Rb PET) in PWH.
Methods: Seventy-two PWH underwent dynamic rest/stress 82Rb PET using a hybrid PET 64-slice CT scanner (Discovery 690, GE Healthcare) at Yale New Haven Hospital for clinical indications between Nov 2016 and Apr 2022. Their global MFR was stratified into three categories: low (≤1.5), borderline (1.5-2.0), or normal (>2.0). Plasma HIV-1 RNA levels, nadir CD4+ T-cell and proximal CD4+ and CD8+ T-cell counts were collected from electronic records; 69/72 (95%) had proximal blood tests taken within 6 months before and 3 months after the scan date. The correlation between clinical and HIV-related factors and MFR was evaluated using Mann-Whiteny U test and Spearman correlation as appropriate.
Results: Participants included 45 (61%) males, with a median age of 59 [IQR 53,64]; 67 (91%) were virally suppressed (<50 cps/ml). Their CD4+ and CD8+ T-cell counts were 572 [IQR 371,820] and 713 [IQR 438,981] cells/mm^3, with a CD4/CD8 ratio of 0.91 [IQR 0.67,1.21]. Their nadir CD4+ T-cell count was 282 [IQR 133,361] cells/mm^3. The resting and stress MBF were 0.94 [IQR 0.71,1.16] and 2.11 [IQR 1.65,2.42] ml/min/g, respectively, while the MFR was 2.21 [IQR 1.84,2.63]. Forty-five (61%) had a normal global MFR, while 9 (12%) had a low MFR. In the entire group, a lower MFR was associated with chronic kidney disease (CKD, p=0.024) and CAD (p=0.025), but not with age, sex, body mass index, HIV suppression, hypertension, diabetes mellitus, hyperlipidemia, congestive heart disease, stroke or peripheral vascular disease. PWH with low MFR had lower CD4+ T-cell (median 364 [IQR 333,634] vs. 621 [IQR 429,866], p=0.040) and nadir CD4+ T-cell counts (median 176 [IQR 74,285] vs. 296 [IQR 192,432], p=0.017) when compared to PWH with normal MFR.
Conclusion: In addition to CKD and CAD, PWH who have lower nadir and current CD4+ T-cell counts, indicating a more compromised immune function, may be at a higher risk of coronary microvascular dysfunction.



Association between global myocardial flow reserve (MFR), current and nadir plasma CD4+ T-cell counts. Left: MFR vs. current CD4; Right: MFR vs. nadir CD4.

796 Diastolic Dysfunction With Preserved Ejection Fraction in Humanized HIV-Female Mice on cART

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Background: Early-onset diastolic dysfunction has emerged as a major threat to healthy aging in people with HIV-1 infection. Women living with HIV-1 infection (WLWH) are especially vulnerable and develop a unique pattern vascular and myocardial ischemia compared to men. Animal models that recapitulate this pathophysiology remain unreported, and this has left a void in our understanding of the molecular causes of the disease and treatment strategies to alleviate it.
Methods: Female NOD.Cg-Prkdcscidll2rgtm1Wjl/SzJ humanized mice (Hu-mice) were infected with HIV-1ADA and treated for fourteen weeks with dolutegravir (DTG)/tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) starting two weeks of infection. In vivo echocardiography was used to assess cardiac function and dimensions. Photoacoustic imaging was used to assess saturated oxygenated hemoglobin in the anterior wall of the heart, Prior to sacrifice, animals were intravenously injected with the fluorescent dye BSA-FITC and hearts were excised and evaluated for microvascular leakage/density of perfused microvessels, and fibrosis. Western blot assays and immunofluorescence and biochemical assays were also conducted.
Results: At the end of the protocol, echocardiography revealed E:A, E:e', left atria volume, global longitudinal and right ventricular diameter-systole increased by 32.1±5.1%, 28.2±5.6 %, 26.6±4.2, 32.5±4.3% and 19.6±1.3%, respectively in Hu-mice treated DTG/TDF/FTC compared to uninfected controls. Photoacoustic imaging also showed a 30.4±6.8% reduction in saturated oxygenated hemoglobin in the anterior wall of the heart. Ex vivo analyses of hearts from DTG/TDF/FTC-treated HIV mice revealed a 37.3±8.2% reduction in intact microvessels, a 30.6±6.2% reduction in the density of perfused microvessels with regions of micro-ischemia There were also 20.2±1.2 and 20.6± .3 % increases in interstitial and perivascular fibrosis, respectively. Expression of hypoxia-induced transcription factor HIF-1α was increased 2.6±0.5-fold, the cytotoxic glycolysis metabolite, methylglyoxal (MG) was increased 3.2±0.3-fold and the inflammation-induced protein, vascular adhesion protein-1 was increased 123.5±10% in hearts of HIV-infected female Hu-mice compared to uninfected controls
Conclusion: These new data show that HIV-infected Hu-mice treated with DTG/TDF/FTC can recapitulate the diastolic dysfunction, microvascular dysfunction, and hypoxia/ischemia seen in WLHV. It also provides a model to study diastolic dysfunction in HIV infection. R01HL164306
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797 Impact of Semaglutide on Weight Change Among People With HIV: A Stratified Analysis by Baseline BMI

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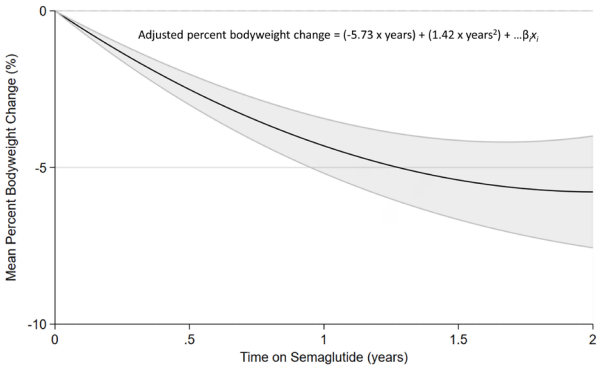
Background: Limited real-world evidence on effectiveness of semaglutide for weight loss among people with HIV (PWH) exists. We aimed to investigate weight change in a cohort of PWH initiating semaglutide use.
Methods: Adult PWH who initiated semaglutide between 2018 and 2022 and had ≥2 weight measurements from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort were assessed for within-person (1) bodyweight change in kg at 1 year and (2) percent bodyweight change using linear mixed model adjusted for age, sex, race/ethnicity, CNICS site, diabetes status, CD4 cell count, HIV viral load (VL), and time. We also investigated whether the effect of semaglutide on weight change varied by baseline BMI category, diabetes status, and semaglutide dose.
Results: During the study period 222 PWH initiated semaglutide. Mean follow up was 1.1 years. Approximately 75% were male. At baseline mean age was 53 years (standard deviation [SD]: 10), average weight was 108 kg (SD: 23), mean BMI was 35.5 kg/m^2, mean HbA1c was 7.7% and 77% had clinically recognized diabetes. At baseline, 97% were on ART and 89% were virally suppressed (VL< 50 copies/mL). The majority, 87 (69.6%) received low doses of subcutaneously injected semaglutide (0.25, 0.5, and 1 mg), while 24 (19.2%) received high doses of subcutaneously injected semaglutide (1.7, 2, and 2.4 mg). In linear mixed models, treatment with semaglutide was associated with an average weight loss of 6.5 kg at 1 year (95% CI -7.7, -5.2) and with a percent bodyweight reduction of 5.7% (-6.9 to -4.6) at 1 year. Reductions in weight among PWH were -4.1 (-7.9, -0.2) kg (p =0.04) with normal BMI, −4.6 (−6.9, −2.3) kg (p< 0.001) in overweight, −5.4 (−7.3, −3.4) kg (p< 0.001) in obesity class 1, −7.6 (−9.5, −5.7) kg (p< 0.001) in obesity class 2, and −8.8 (−10.9, −6.7) kg (p< 0.001) in obesity class 3. There was a significant difference in weight loss between PWH with obesity class 3 (reference) and PWH with normal BMI, overweight, and obesity class 1 (p for interaction <0.05). No significant differences in weight loss by diabetes status or semaglutide dose were observed.
Conclusion: Among PWH, semaglutide was associated with significant weight loss, with more substantial weight loss observed in individuals with higher BMI. These findings are highly relevant given high proportions of diabetes, overweight, and obesity among PWH.



798 Effects of Semaglutide on Inflammation and Immune Activation in HIV-Associated Lipohypertrophy

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Background: Lipohypertrophy (central adipose tissue (AT) accumulation) is a common and significant problem in people with HIV (PWH). We previously demonstrated that semaglutide, a glucagon-like peptide-1 receptor agonist, significantly decreased central AT in PWH with lipohypertrophy, primarily driven by reductions in visceral AT. Here, we assessed the effects of semaglutide on inflammation and immune activation biomarkers, known to be increased in PWH and associated with cardiovascular disease (CVD).
Methods: We conducted a single-site randomized, double-blinded, placebo-controlled trial of virologically-suppressed, non-diabetic PWH ≥18 years of age on stable antiretroviral therapy (ART) with body mass index (BMI) ≥25 kg/m^2, increased waist circumference/waist-to-hip ratio, and subjective increased abdominal girth after ART initiation. Participants were randomized 1:1 to 32 weeks semaglutide (8-week titration + 24 weeks 1.0 mg weekly subcutaneous injection) or matching placebo. Sign-rank test was used to determine changes over 32 weeks in soluble markers of inflammation/immune activation within groups; semaglutide effects were assessed using generalized estimating equations.
Results: 108 participants were enrolled (N=54 semaglutide: median age=52 years, 70% male, 61% Black, 83% integrase inhibitor). Groups were well-matched in demographics and BMI at baseline. Significant changes within semaglutide group were seen between baseline and week 32 geometric means (standard deviation) for interleukin-6 (IL-6) [2.51 (2.05), 2.13 (1.85) pg/mL; P=0.016], high-sensitivity C-reactive protein (hsCRP) [2.98 (2.69), 1.83 (2.96) µg/mL; P=0.008] (Figure 1), and sCD163 [583 (1.48), 511 (1.54) ng/mL; P=0.005] with a trend in sCD14 [1694 (1.3), 1575 (1.28) ng/mL; P=0.085]. No significant changes were observed for soluble intercellular adhesion molecule-1 (sICAM-1) or TNF-receptor-I/-II. Biomarker levels did not change significantly within the placebo group. Treatment effects of semaglutide were significant in regression analyses (β coefficient [95% confidence interval]) for log IL-6 (-0.30 [-0.54, -0.06]; P=0.015) and log hsCRP (-0.51 [-0.90, -0.12]; P=0.011) with trends in log sCD14 (-0.08 [-0.18, 0.01]; P=0.083) and log sICAM-1 (-0.11 [-0.24, 0.02]; P=0.088).
Conclusion: In non-diabetic PWH with lipohypertrophy, semaglutide had significant effects on several key biomarkers associated with CVD in HIV. Further investigation is warranted to determine the effect on co-morbidities in HIV.

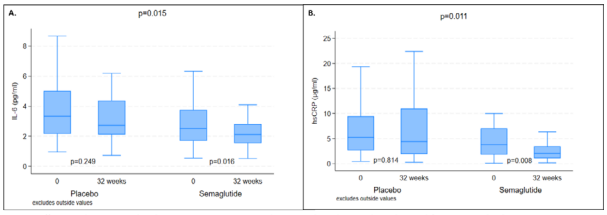

Figure. Differences between and within treatment groups over the 32-week study period are depicted for A. IL-6 and B. hsCRP.

799 Effects of Semaglutide on Muscle Structure and Function in the SLIM Liver Study

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Background: Semaglutide, a GLP-1 receptor agonist, is a highly effective medication for decreasing weight and weight complications by suppressing appetite, improving insulin signaling, and reducing intrahepatic triglycerides (IHTG). However, concomitant loss of muscle mass often accompanies weight loss, which may have consequences on muscle function. The purpose of this analysis was to examine changes in muscle quality, quantity, and function among people with HIV (PWH) treated with semaglutide for metabolic-associated steatotic liver disease (MASLD).
Methods: We leveraged data from the SLIM LIVER (ACTG A5371) study, a single-arm pilot of the effects of semaglutide on IHTG in PWH with MASLD. Participants received subcutaneous semaglutide for 24 weeks (titrated to 1 mg/week by week 4). Psoas volume/fat fraction were assessed from liver magnetic resonance imaging and physical function by 10-time chair rise test and 4m gait speed, at baseline and week 24. Mean change from baseline was estimated with linear regression modeling and associations with Spearman's correlations.
Results: 51 PWH enrolled; muscle measures were available from 46 participants. The mean age was 50 (standard deviation [SD] 11) years and BMI 35.5 (5.6) kg/m^2, 43% were women, 33% Black, and 39% Hispanic/Latino. Psoas muscle volume decreased by 9.3% (95% confidence interval [CI]: -13.4, -5.2; p<0.001) with an overall mean weight loss of -7.8 kg (CI: -9.5, -6.2) over 24 weeks. Decreases in psoas volume were greatest among PWH >60 years old (-22.8% [CI: -32.4, -13.3] vs -7.9% [CI: -12.3, -3.4]) in 40-60 and -2.4% [CI: -11.9, 7.2] in <40). No sex differences were observed. Reductions in psoas volume (%) correlated with decreases in IHTG (ρ=+0.32, p=0.028), BMI (ρ=+0.31, p=0.038), HbA1C (ρ=+0.39, p=0.007), and reduction in absolute volume was associated with reduction in fasting triglycerides (ρ=+0.33, p=0.027). Psoas muscle fat decreased by 0.42% (CI: -1.00, 0.17; absolute change), chair rise time improved by 0.73 seconds (CI: -1.4, 2.9) and gait speed improved by 0.05 m/sec (CI: -0.01, 0.10), though these changes did not reach statistical significance (p>0.078). The prevalence of slow gait speed (<1m/sec) decreased from 63% to 46% (p=0.029).
Conclusion: In PWH using low-dose semaglutide for MASLD, muscle volume decreased, similar to volume changes seen in weight-loss interventions among overweight populations. The observed average improvement in muscle function suggests a beneficial effect of semaglutide on overall muscle quality.

800 A Combination of Steatosis-Fibrosis Index Predict Mayor Cardiovascular Events in PLHIV

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Background: Metabolic dysfunction-Associated Steatosis Liver Disease (MASLD) is a high prevalent condition in people living with HIV (PLHIV) and cardiovascular events appear to depend on the presence of advanced stages of MASLD. Indeed, the underlying insulin resistance and liver fibrosis have demonstrated complex interlinked connections affecting cardiovascular damage evolution. Our objective is to analyze the usefulness of two easy-to-use surrogate biomarkers of insulin resistance and liver fibrosis in the prediction of major cardiovascular events (MACE) in PLHIV.
Methods: A retrospective cohort of PLHIV receiving ART with metabolic disorders (metabolic syndrome, DM2, arterial hypertension, and obesity) and clinically suspected MASLD was studied. We recorded all MACE occurring during follow-up, and we calculated TyG and FIB-4 indexes from the blood results performed at the initial visit in the cohort. TyG>4.68 was considered as severe insulin resistance risk. FIB-4 cut-off values considered for significant fibrosis were adjusted by hepatitis C virus (HCV) coinfection background: >1.3 for non-hepatitis C and >1.45 for HCV coinfected. TyG>4.68 plus FIB-4>1.3/1.45 was

considered as risk-combination-index. Cox models were developed to evaluate the effect of risk-combination-index in the prediction of MACE.
Results: We studied 370 subjects with a median follow-up time of 175 (131-191) months. Main baseline characteristics are shown in table 1. HCV-ab were positive in 25.9% of subjects, all of them were treated and had undetectable HCV RNA during follow-up. A total of 19 MACE (8 myocardial infarction, 6 stroke, 5 peripheral arterial disease) were registered. Along follow-up 39% developed metabolic syndrome, 37% hypertension and 17.6% DM2. TyG>4.68 was found in 56% of subjects and FiB-4>1.3/1.45 in 29.5%, these proportions being significantly higher in PLWH with MACE (74% and 55% respectively). The proportion of subjects with a risk-combination-index was 42% in MACE-population vs 14% in non-MACE-population (p<0.05). Cox regression model adjusted by age, HIV infection duration and HCV coinfection showed that risk-combination-index was associated with MACE: HR 2.6 (CI95% 1.02-6.6; p=0.04).
Conclusion: The combined interpretation of TyG and FIB-4 indexes, as surrogate markers of insulin resistance and a proxy of liver fibrosis might have a potential predictive value of major cardiovascular events in PLHIV. We recommend routine use of these indexes in the care of PLVIH with metabolic disorders.

Table: Population characteristics at the beginning of the follow-up

	Total (N= 370)	NON-MACE (N= 351)	MACE (N= 19)	p
Age[a], (year)	40.5 (34.7-45)	40 (34-45)	47 (42-57)	<0,001
Female [b]	73 (19.7)	71 (20.2)	2 (10.5)	0.39
Nadir CD4 [a]	203 (87-304)	213 (88-314)	124 (72-208)	0.04
HIV-duration[a], (year)	6.4 (0.2-14)	6 (0-14)	12 (6-19)	0.03
CDC C3 [b]	59 (18.4)	50 (16.6)	9 (47.4)	0.003
Transmission route [b]: MSM/MSW/IDU/others (%)	42/23/30/5	43/23/29/5	21/11/58/10	0.02
HCV infection*	96 (25.9)	87 (24.8)	9 (47.4)	0.05
TyG>4.68&FIB4 >1.3 / >1.45 [b]	58 (15.7)	50 (14.2)	8 (42)	0.03

a) Median (25th percentil-75th percentil) b) N (%)

801 T-Cell Subsets and Incidence of Diabetes in Persons With HIV in the ACTG Study A5001

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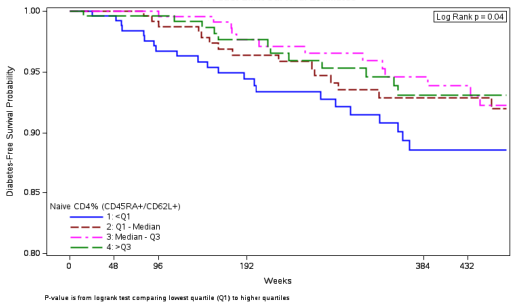
Background: Persons with HIV (PWH) have persistent changes in T cell subsets that can also be modified by aging, and may contribute to the high burden of comorbid conditions, including type 2 diabetes (DM), in older PWH. While studies in persons without HIV have found few associations between T cell subsets and DM or pre-DM, a recent study of US veterans with HIV found higher frequencies of effector memory and senescent CD4+ T cells associated with incident DM. Here, we examined associations of T cell subsets measured at a uniform time post-ART initiation with incident DM among PWH in the AIDS Clinical Trials Group study A5001.
Methods: DM was defined as: 2 consecutive non-fasting glucose >200 mg/dl or fasting glucose >126 mg/dl; DM diagnosis; or oral antiglycemic or insulin use for >30 days. We used Cox proportional hazards models to evaluate associations of T cell subsets measured 1 yr post-ART with incident DM. PWH with prevalent DM (≤ 1yr post-ART) were excluded. Multivariable models included age at ART start, sex at birth (gender not available), self-reported race/ethnicity, smoking status, time-updated BMI, triglycerides, and history of hypertension. We explored effect modification by demographic and clinical factors by including interaction terms between each T cell subset and effect modifier in multivariable models.
Results: 1015 PWH had ≥1 subset (% activated CD4 or CD8 [HLA-DR+/CD38+], % senescent CD4 or CD8 [CD28-], % memory CD4 [CD45RA-/CD45RO+], % naïve CD4 [CD45RA+/CD62L+]) measured 1yr post-ART. Most (82%) participants were male; 48% White non-Hispanic, 31% Black non-Hispanic, and 21% Hispanic/other ethnicity. Median age was 36 years (Q1,Q3=31,43). There were 62 DM events. PWH with DM were older, had higher triglycerides, higher BMI, and were more likely to have hypertension or low CD4/CD8 ratio than those without DM. PWH in the lowest quartile of % naive CD4 cells had a higher incidence of DM than those in higher quartiles (Figure). The association for lowest vs higher quartiles (combined) was observed in PWH <45 years (aHR=2.08 95% CI=1.00,4.34) but not ≥45 years (aHR=1.17, 95% CI= 0.44,3.11), though the interaction by age was not significant (p=0.32). There were no associations with other T cell subsets and DM.
Conclusion: A lower proportion of naïve CD4+ T cells, potentially reflective of reduced naïve cell replenishment or increased memory cell inflation, may be associated with increased diabetes incidence in PWH, particularly among younger persons.

Figure. Kaplan-Meier curve for incident diabetes by quartile of naïve CD4 %



P-value is from logrank test compairing lowest quartile (Q1) to higher quartiles

802 Subcutaneous Adipose Tissue Myofibroblasts Are Associated With the Lipidome

Samuel Bailin, Curtis L. Gabriel, Run Fan, Fei Ye, Mona Mashayekhi, Rama D. Gangula, LaToya Hannah, Jonathan A. Kropski, Spyros Kalams, Simon A. Mallal, Celestine Wanjalla, John Koethe
Vanderbilt University Medical Center, Nashville, Tennessee

Background: Dyslipidemia is common in persons with HIV (PWH) and mechanistically linked to the development of metabolic disease. Higher plasma triacylglycerides (TG) are associated with the diabetes, while an inverse relationship is observed for sphingomyelin (SM) and phosphatidylcholine (PC) species. Adipose tissue has a critical role in regulating lipid homeostasis, but how adipose tissue cellular composition might influence circulating lipid classes in PWH is unknown. We hypothesized that greater pro-inflammatory macrophage and pro-fibrotic stromal cells in subcutaneous adipose tissue (SAT) are associated with higher circulating TG and lower SM and PC species.
Methods: We performed single-cell RNA sequencing on SAT biopsies from PWH on contemporary antiretroviral therapy with virologic suppression and a range of metabolic fitness. We characterized SAT cell types except adipocytes, which are poorly captured with this method. We simultaneously performed untargeted lipidomic liquid chromatography-high resolution tandem mass spectrometry on plasma samples. We assessed the relationship of cell composition with normalized summed-lipid class intensities with partial Spearman's adjusted for statin use, sex, body mass index (BMI) and diabetes status.
Results: A total of 55 participants were included in this study (non-diabetic=19, prediabetic=18, diabetic=18). The median age was 49 years, BMI 31.5 kg/m^2, 73% male, 49% White, and 62% treated with an integrase strand transfer inhibitor-based regimen. A higher proportion of myofibroblasts (pro-fibrotic cells) was positively associated with TG (ρ=0.41, p=0.006) and oxidized TG (OxTG; ρ=0.39, p=0.002) levels, and inversely associated with SM (ρ=-0.27, p=0.03) and plasmenyl phosphatidylethanolamines (plasmenyl-PE) (ρ=-0.44, p=0.004) but not PC (ρ=-0.22, p=0.11) (Figure 1). Higher intermediate macrophages (IMs) were inversely associated with plasmenyl-PE (ρ=-0.36, p=0.04). The proportion of lipid-associated macrophages (LAMs) was not associated with any lipid class.
Conclusion: In PWH, higher proportion of SAT myofibroblasts was moderately associated with higher TG and OxTG, and inversely related to SM and plasmenyl-PE. IMs and LAMs were not significantly associated with these classes except IMs and plasmenyl-PE. These results suggest that a pro-fibrotic composition of non-adipocyte stromal cell types is related to circulating lipid profiles. Future studies using single nuclei RNA-sequencing will be necessary to evaluate the contribution of adipocyte populations.

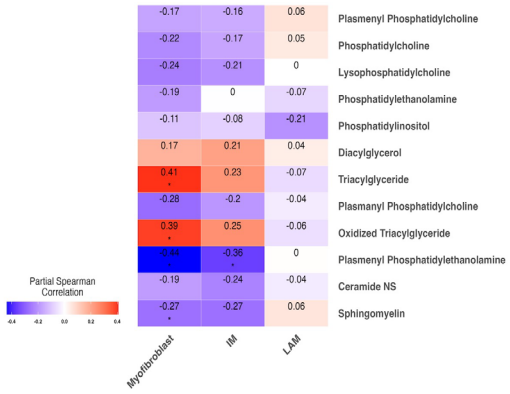


Figure 1. Heatmap of partial Spearman correlation between lipid classes and myofibroblast or macrophage proportion, adjusted for statin use, sex, body mass index, and diabetes status. For intermediate (IM) and lipid-associated macrophages (LAM), n = 50 individuals contributed.
* P < 0.05.

803 Dolutegravir Targets the Hypothalamus to Suppress Energy Expenditure via Estrogen Receptor

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Background: Antiretroviral therapy (ART) containing integrase strand transfer inhibitors (INSTI) has been associated with weight gain in both ART-initiation and switch studies, especially in women, but the underlying mechanisms are unclear. Estrogen promotes energy expenditure via suppressing AMP-dependent kinase (AMPK) in the hypothalamus and yet very few studies are available examining the central effects of INSTI on weight gain. Hence, we hypothesized that dolutegravir (DTG) may inhibit thermogenesis via estrogen receptors in the hypothalamus.
Methods: We examined the effects of DTG (10mg/kg for 5 days) on food intake, energy expenditure, oxygen consumption in female mice using the Comprehensive Laboratory Animal Monitoring System. Adipose and brain tissues were analyzed using qRT-PCR and immunoblotting for appetite and thermogenesis. Primary hypothalamic neurons and inducible human pluripotent stem cells-driven hypothalamic organoids were treated with DTG and estradiol and examined for changes in cellular signaling associated with the regulation of energy homeostasis. Computational analysis was performed to evaluate the potential interaction between DTG and estrogen receptors.
Results: We found that DTG administration to female mice reduced oxygen consumption and energy expenditure by 16% without affecting food consumption. Gene expression analyses in adipose tissues confirmed that thermogenic marker expression (UCP1, DIO2 and CIDEA) was reduced. Moreover, DTG administration activated the AMPK signaling cascade in the hypothalamus. Murine primary hypothalamic neurons treated with estrogen led to inactivation of AMPK while DTG attenuated estrogen-mediated suppression of AMPK activity. We further confirmed the DTG activates AMPK and inhibits estrogen effect on human hypothalamic organoids, which retain the heterogeneity and neural circuity of the brain. Finally, molecular docking analysis showed that DTG can physically bind to estrogen receptors.
Conclusion: DTG administration increased body weight by suppressing energy expenditure without affecting food intake. Tissue analyses revealed that DTG activates the hypothalamic AMPK pathway, which suppresses thermogenesis. In vitro study using murine primary hypothalamic neurons and human hypothalamic organoids showed that DTG inhibits estrogen-mediated hypothalamic regulation of thermogenesis. These findings suggest a novel mechanism by which INSTIs may lead to weight gain, especially in women.
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804 Weight Gain After Initiating ART Close to HIV Seroconversion: Is There a Return to Health Effect?

Nikos Pantazis[1], Sophie Grabar[2], Marc Van der Valk[3], Caroline Sabin[4], Inma Jarrin[5], Laurence Meyer[6], Christina Carlander[7], John Gill[8], Shema Tariq[4], Alain Volny Anne[9], Fiona Burns[4], Elisa Ruiz-Burga[4], Giota Touloumi[1], Kholoud Porter[4], for the CASCADE Collaboration
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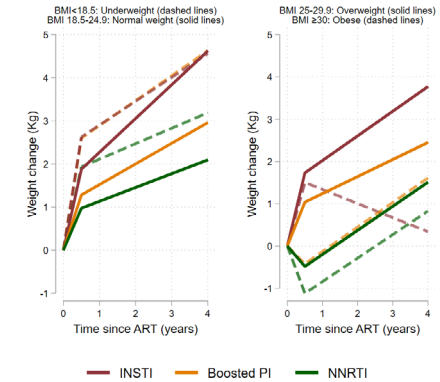
Background: Findings from seroprevalent cohorts suggest that weight gain after ART initiation is greater with regimens containing Integrase Strand Transfer Inhibitors (INSTI) than with other antiretrovirals. We investigate weight trends among individuals initiating ART within one year of seroconversion (SC).
Methods: Included individuals from the CASCADE Collaboration seroconverted 1997-2022, were ≥16 years, had HIV- to HIV+ test interval ≤1 year or other laboratory evidence of SC, and initiated ART ≤12 months from SC. Weight changes from baseline (censored after switching ART class) were analyzed with piecewise linear mixed models.
Results: 6482 (22.7%) of 28556 individuals were included (2814, 1999 and 1669 with INSTI, boosted PI or NNRTI regimens, respectively). Most acquired HIV through sex between men (79.3%), and 8.3% men and 8.9% women through heterosexual contact. Median (IQR) age at SC was 34 (27, 43) years, CD4 at ART initiation 451 (320, 620) cells/µl and follow-up time 1.4 (0.3, 3.6) years. Weight changes differed significantly (p<0.001) by ART class and baseline BMI. In the first 6 months, weight gains were generally most pronounced among those on INSTIs, regardless of baseline weight. This trend remained by 3 years for BMI categories <30, although those receiving boosted PIs also experienced weight gain. "Typical individuals" (Figure) had significant weight gains with all three ART classes after 3 years except for baseline BMI ≥30. Individuals with BMI 18.5-29.9 gained weight significantly faster with INSTIs compared to other ART classes. Overall, 16% with BMI 18.5-24.9 and 11% with BMI 25-29.9 on INSTIs gained >10% of their baseline weight after 3 years (9% and 8% for boosted PIs; 7% and 6% for NNRTIs). Significant differences in initial (0-6 months) rate of weight gain were observed between INSTI regimens (p<0.001). Bictegravir or Elvitegravir + TAF backbone were associated with the fastest rates. Dolutegravir without TAF/TDF, and Elvitegravir + TDF were associated with the slowest. Estimated (95% CI) weight gains after 3 years among "typical individuals" with BMI 18.5-24.9 were 5.6 (4.5, 6.6), 4.4 (3.5, 5.4), 3.6 (2.8, 4.4), and 3.4 (2.5, 4.2) kgs, respectively.
Conclusion: As reported in seroprevalent cohorts, Bictegravir and Elvitegravir combined with TAF were associated with the fastest increases in weight. Given that ART was initiated soon after SC, it is unlikely that this is a return to health phenomenon, although the effect of unmeasured confounders can't be disregarded.



Estimated weight changes after ART initiation by baseline BMI and ART class assuming average height and baseline CD4/VL, MSM, aged 30-39, from Europe/N. America ("typical individuals")

805 Switching to Integrase Strand Transfer Inhibitors and the Risk of Diabetes in Persons With HIV

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Background: Integrase strand transfer inhibitors (INSTIs) are commonly used antiretroviral therapy (ART) among people with HIV (PWH). INSTI use is associated with weight gain, hyperglycemia, and diabetes among ART-naïve PWH. We estimated the risk of incident diabetes associated with switching from a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or protease inhibitor (PI) to an INSTI.
Methods: We studied PWH aged ≥18 years in the Johns Hopkins HIV Clinical Cohort. PWH with no history of diabetes who had used NNRTI- or PI-based ART for ≥180 days were followed from attended HIV primary care visits between 2007 and 2022 until incident diabetes, last clinical encounter, or December 31, 2022. PWH who switched to bictegravir, dolutegravir, elvitegravir, or raltegravir were assigned to the INSTI group and PWH who were continued on an NNRTI or PI were assigned to the non-INSTI group. Incident diabetes was defined as a laboratory hemoglobin A1c value ≥6.5%, initiation of diabetes-specific drug, or initiation of non-specific diabetes drug and diabetes diagnosis with the International Classification of Diseases, Ninth or Tenth Revision codes. The association between ART exposure and incident diabetes was estimated using multivariable Cox proportional hazards models with the robust variance estimator to account for repeated observations on individuals. We adjusted for age, sex, race, year of cohort entry, body mass index, coronary artery disease, chronic kidney and liver diseases, cerebrovascular disease, dyslipidemia, heart failure, hypertension, and co-prescription of anticoagulants, antidepressants, antihypertensives, antiplatelets, antipsychotics, antilipemics, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF).
Results: Our sample included 2,354 PWH, of whom 891 PWH switched to an INSTI and contributed an encounter to the INSTI group. 2,293 PWH contributed ≥1 encounters to the non-INSTI group. The median age was 49 years and 66% were male. Switching to any INSTI was not statistically significantly associated with an increased risk of diabetes (adjusted hazard ratio [aHR], 1.05; 95% confidence intervals [CI], 0.79–1.40). The hazard ratios for specific INSTIs were similar (Table).
Conclusion: Switching from an NNRTI or PI to INSTI-based ART did not appreciably increase the risk of incident diabetes. These findings can inform antiretroviral prescribing in the common clinical scenarios, where switching to INSTI-based therapy is considered in the care of PWH.

Table. Risk of incident diabetes associated with switching to integrase strand transfer inhibitors (INSTIs) versus continuing on non-nucleoside reverse-transcriptase inhibitor (NNRTIs) or protease inhibitor (PIs).

Number of PWH contributed to each ART group	Number of events (%)	Incidence rate (per 1,000 person-years)	Adjusted hazard ratio (95% confidence intervals)
NNRTI/PI (2,293)	248 (10.8)	20.8	Reference
Any INSTI (891)	123 (13.8)	26.8	1.05 (0.79–1.40)
Bictegravir (96)	7 (7.3)	35.4	1.26 (0.53–2.98)
Dolutegravir (359)	49 (13.6)	28.9	0.94 (0.62–1.44)
Elvitegravir (206)	26 (12.6)	25.4	1.08 (0.65–1.80)
Raltegravir (230)	41 (17.8)	24.4	1.16 (0.80–1.69)

806 Effect of TDF and TAF on Duodenal Enterocytes: A Hypothesis for Different Effect on Body Weight

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Background: Tenofovir disoproxil fumarate (TDF) when compared to tenofovir alafenamide (TAF) leads to lower body weight and plasma lipid concentrations; the mechanisms of these effects are unknown. TDF as opposed to TAF is processed into free tenofovir (TFV) within enterocytes when absorbed from proximal duodenum. The effect of TFV in enterocytes is unknown, but in kidney proximal tubular cells it may cause mitochondrial damage. We hypothesize that TDF may damage enterocytes leading to reduced absorption of nutrients from this anatomical site.
Methods: People living with HIV without known gastrointestinal disease receiving stable TDF (n=12) or TAF (n=12) containing regimen underwent gastroscopy with biopsies from proximal and distal duodenum. Biopsies were scanned with Leica GT450 scanner and measurements taken in Neagen's neaLink digital pathology solution. Serum intestinal fatty acid-binding protein (I-FABP) was measured as a circulating marker of enterocyte damage. Plasma/serum concentrations of nutrients absorbed from proximal duodenum were measured.
Results: All participants were male. TDF and TAF groups were matched for third antiretroviral agent (58% integrase strand transfer inhibitor, 42% non-nucleoside reverse transcriptase inhibitor) and age (mean (SD) TDF group 55 (12) and TAF group 57 (16) years). Five patients in TDF group (celiac disease, helicobacter gastritis and 3 cases of esophagitis) and 2 patients in TAF group (2 cases of esophagitis) had a pathological macroscopic or histologic finding (p=0.178). The patient with newly diagnosed celiac disease was excluded from the rest of the analyses. Duodenal villi were flatter, crypts deeper, and villus height to crypt depth ratio was lower in TDF vs TAF group, especially in proximal duodenum (Table 1). I-FABP concentration was significantly higher in TDF vs. TAF group (3.0 (1.07) vs. 1.8 (0.53) ng/ml, p=0.003). TDF group had numerically lower plasma/serum concentrations of iron, folate, vitamins A, B1, D and E, whereas β-carotene concentration was lower in TAF group. None of these differences were statistically significant.
Conclusion: TDF group displayed signs of villous damage especially in proximal duodenum when compared to TAF group. This together with increased I-FABP suggest enterocyte damage and may contribute to the clinical effect of TDF on lowering body weight and plasma lipid concentrations when compared to TAF. Larger studies are needed to evaluate concentrations of nutrients absorbed from proximal duodenum among TDF users.

Table 1: Villus Height (VH) and Crypt Depth (CD) of Proximal and Distal Duodenal Biopsies

	TDF group (n=11)	TAF group (n=12)	p value
Proximal duodenum VH (μm)	337 (59)	397 (42)	**0.016**
Proximal duodenum CD (μm)	200 (46)	176 (27)	0.243
Proximal duodenum VH to CD ratio	1.5 (0.42)	2.5 (0.51)	**0.009**
Distal duodenum VH (μm)	343 (50)	372 (49)	0.202
Distal duodenum CD (μm)	188 (18)	171 (24)	0.09
Distal duodenum VH to CD ratio	1.8 (0.38)	2.2 (0.43)	0.08

Data are given as mean (standard deviation).

TDF = Tenofovir disoproxil fumarate

TAF = Tenofovir alafenamide

807 Weight Change After Starting Doravirine Among ART-Experienced Individuals in the US

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Background: Weight gain has been associated with the use of antiretrovirals (ARV), especially with integrase inhibitors (INSTI) and tenofovir alafenamide (TAF), but less so with non-nucleoside reverse transcriptase inhibitors (NNRTI). In 2018, doravirine (DOR) became the latest NNRTI to be approved. We assessed changes in weight over time after starting DOR among virologically suppressed individuals.
Methods:From the US-based OPERA cohort, ART-experienced adults with HIV who started a DOR-based regimen between 30AUG2018-30NOV2022 with a viral load <50 copies/mL were included (followed through 31MAY2023). Univariate linear mixed models were used to estimate rates of weight change on DOR; restricted cubic splines on time provided flexibility. Results were stratified by sex. Two sensitivity analyses were conducted to account for use of other ARVs before and after DOR start (a) restriction to those who maintained the same INSTI-TAF combination (b) stratification by efavirenz [EFV]-tenofovir disoproxil fumarate [TDF] use.
Results: Of 388 included individuals, 79% were men, 33% were Black, and 78% were overweight or obese (BMI ≥25 kg/m²) at DOR start. Most regimens prior to DOR start included an INSTI with TAF (47%) or an INSTI without TAF (31%); 16% included TAF without an INSTI and 7% included neither INSTI nor TAF. DOR was combined with both INSTI and TAF (31%), with INSTI without TAF (30%), with TAF without INSTI (11%) or with neither (28%). Overall, people starting DOR lost a statistically significant average of 0.80 kg/year (95% CI: -1.32, -0.28).

Both women and men experienced a statistically significant weight loss; women (70% Black) lost weight at a rate of -1.67 kg/year (95% CI: -3.32, -0.02), and men at a rate of -0.60 kg/year (95% CI: -1.12, -0.08). Among those who had the same INSTI-TAF combination throughout, there was a statistically non-significant trend toward weight loss. When EFV and TDF were absent both before and after DOR start, DOR was statistically significantly associated with weight loss.

Conclusion: In one of the first real-world analyses of weight changes among virologically suppressed individuals who started a DOR-based regimen in the US, DOR was associated with a modest but statistically significant weight loss overall. Weight loss in women is of particular significance given that weight gain has often been associated with female sex. These findings are clinically meaningful given that most individuals included were overweight or obese at DOR start.

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808 Predictors of Weight Gain in the ADVANCE, NAMSAL, and WRHI trials: EFV, TDF, and Baseline CD4 Count

Andrew Hill[1], Bryony Simmons[2], Francois Venter[3], Alexandra Calmy[4], Eric Delaporte[5], Tamara Tovar-Sanchez[6], Charles Kouanfack[7], Mireille Mpoudi-Etame[7], Godspower Akpomiemie[3], Bronwyn Bosch[3], Simiso Sokhela[3]

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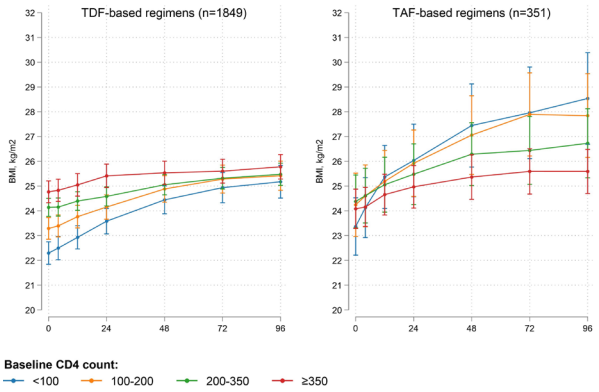
Background: Weight gain is common during first-line ARV treatment, especially among women and those of black race. Use of TDF or EFV can suppress weight gain. People with lower baseline CD4 count show greater weight gains, but this might be from regaining weight lost during advanced disease.

Methods: Data were pooled from three clinical trials: ADVANCE (n=1053), NAMSAL (n=624), and WHRI001 (n=536). These randomised trials evaluated first-line ARV regimens (TAF/XTC/DTG, TDF/XTC/DTG, and TDF/XTC/EFV) in Cameroon and South Africa. BMI over 96 weeks was analysed, stratified by baseline CD4 count as a marker for disease stage (<100, 100-200, 200-350, ≥350 cells/uL). Multivariate models at week 96 assessed factors associated with BMI and clinical obesity (BMI ≥30), adjusting for baseline CD4 category, age, sex, TDF, EFV, and clinical trial.

Results: At baseline, mean age was 34.5 (SD 8.9), 60% were female, 14% had CD4 <100 cells/uL, and 31% had CD4 ≥350. Lower baseline BMI was strongly correlated with lower baseline CD4 count (p<0.001). At week 96, mean unadjusted BMI change was highest in the <100 CD4 group (+3.2 kg/m^2; SD 3.1) and lowest in the CD4≥350 group (+1.1; SD 2.4). Individuals with advanced disease on TAF-based regimens experienced greater BMI increases compared to those on TDF-based regimens (Figure 1). For participants on TAF-based treatment (ADVANCE only), increases in BMI to Week 96 were significantly higher in people with CD4<100 (+5.0; SD 3.1) compared to the ≥350 group (1.6; SD 2.2). In the adjusted model, for people taking TAF/FTC/DTG, BMI at Week 96 was significantly higher for people with baseline CD4<100 (28.4 [95%CI 26.7-30.1]) compared to CD4≥350 (25.3 [95%CI 24.4-26.3]; p=0.001). However, on TDF or EFV-based regimens, there was no difference in BMI across the CD4 categories. Analyses using clinical obesity (BMI >30 kg/m^2) showed consistent results: people taking TAF/FTC/DTG with CD4<100 were significantly more likely to become obese after 96 weeks of first-line treatment.

Conclusion: For people taking TAF/FTC/DTG, baseline CD4<100 cells/uL at treatment initiation was associated with significantly higher BMI and clinical obesity at Week 96. Weight continued to rise over time for people with low CD4 counts taking TAF/FTC/DTG, above the levels seen with higher baseline CD4 counts. Use of TDF and EFV were associated with smaller rises in weight. Effective weight management is required with current regimens to avoid complications associated with significant weight increases.



809 The Relationship Between Plasma Oxylipins and InSTI-Associated Weight Gain in Women Living With HIV

Chin-An Yang, Cyra C. Mehta, Qian Yang, Tsungirirai Maramba, Igho Ofotokun, Kehmia Titanji, Anandi N. Sheth, Kristal M. Maner-Smith, Thomas R. Ziegler, Cecile D. Lahiri, Jessica A. Alvarez

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Background: Initiating or switching to integrase strand-transfer inhibitors (INSTIs) for HIV is associated with body weight gain, particularly in women. However, the specific mechanisms driving this effect remain unclear. Previous findings have implicated omega-6-derived poly-unsaturated fatty acids (PUFAs) as potential mediators of increased adiposity in people without HIV. This study investigated the relationship between INSTI-associated weight gain and plasma oxylipins, downstream PUFA metabolites, in women living with HIV (WLH) by utilizing a targeted lipidomics approach in a longitudinal design.

Methods: Virologically suppressed (<200 c/mL) WLH from the Atlanta Women's Interagency HIV Study (WIHS) on antiretroviral therapy were grouped based on INSTI usage and weight change during the follow-up period (weight gain defined as ≥5% change, or weight maintenance as <5% change from baseline). We leveraged stored blood samples collected at three time points: 6-12 months before switching to or adding INSTI (baseline), 1-6 months post switch/add, and 1-2 years post switch/add, with comparable time points in the non-INSTI group. Targeted lipidomics assessed 40 oxylipins via liquid chromatography-mass spectrometry, and differences between groups assessed using linear mixed models.

Results: Sixty women, aged 28-62 years, were included (n=33 INSTI, n=27 non-INSTI) with n=15 weight gainers in the INSTI group and n=9 weight gainers in the non-INSTI group. Fifty-six women identified as Black, 3 as White, and 1 as Hispanic. Within the INSTI group, nine oxylipins differed between weight gainers and maintainers over time (p-value < 0.05, Figure). Three oxylipins, linoleoyl ethanolamide (LEA), arachidonoyl ethanolamide (AEA), and 9-HpODE also differed between weight gainers and maintainers among women in the non-INSTI group. Six oxylipins were unique to those who switched to INSTI, including α-linolenoyl ethanolamide (ALEA), palmitoyl ethanolamide (PEA), oleoyl ethanolamide (OEA), 9-HODE, 9-HOTrE, and prostaglandin E2 glycerol ester (PGE2-G).

Conclusion: Employing a targeted lipidomics approach, six oxylipins were linked to INSTI-associated weight gain in WLH. Among these oxylipins, ALEA and OEA have been previously implicated in weight gain processes in healthy adults, while 9-HODE and 9-HOTrE have been linked to weight gain in mouse models. Further research is needed to identify oxylipin profiles unique to INSTI usage and to determine potential underlying biological mechanisms for INSTI-associated weight gain.

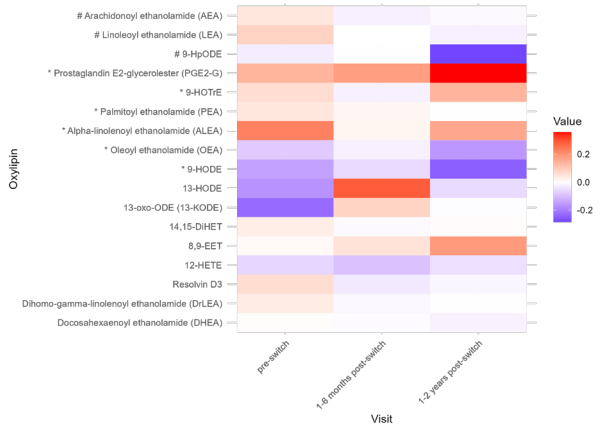

Figure: Heatmap displays Estimated Marginal Mean (EMM) differences in oxylipin temporal concentration between weight gain and weight maintain groups in women living with HIV who switched to INSTI therapy. *Significant oxylipins observed uniquely in INSTI switchers. #Significant oxylipins observed in both INSTI switchers and non-switchers.

810 Dolutegravir-Based Therapy, Diet, Activity & Weight Gain: 48-Week Prospective Cohort in South Africa

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Background: Weight gain has been reported among people with HIV (PWH) after transitioning to tenofovir, lamivudine, and dolutegravir (TLD) antiretroviral therapy (ART). However, the contribution of changes in diet and physical activity to weight gain in this population remains poorly understood. We estimated relationships between diet, physical activity, and clinically significant weight gain over 48 weeks among PWH in South Africa after transitioning to TLD.

Methods: The DISCO cohort study followed 500 PWH at four public-sector clinics in KwaZulu-Natal, South Africa. Eligible participants were >18 years of age and on efavirenz-based, first-line ART for >6 months before transitioning to TLD by clinic staff. Anthropomorphic, diet, and physical activity data were measured at enrollment, 24-week, and 48-week study visits. Our primary exposures of interest were change in four dietary and exercise behaviors over 48 weeks: (1) fruit consumption, (2) fast-food consumption, (3) sugar-sweetened beverage (SSB) consumption, and (4) physical activity (in metabolic equivalent-minutes/week). Our primary outcome was clinically significant weight gain, defined as ≥10% increase in weight from baseline to 48 weeks. We estimated differences in each exposure by presence versus absence of weight gain using multivariable logistic regression models adjusted for age, sex, education, and ART duration.

Results: We analyzed data from 367 PWH having a mean age of 43 (standard deviation = 12) years and 78% women. People with clinically significant weight gain had an increase in fruit intake while those without clinically significant weight gain had decreased intake (0.21 servings/week [95% CI: -0.9 to 1.3] v. -1.07 servings/week [95% CI: -1.5 to -0.7], respectively) (p=0.015), but there were no significant differences in frequency of fast-food intake, frequency of SSB consumption or physical activity (Figure 1). In adjusted models, change in fruit intake remained significantly associated with clinically significant weight gain over 48 weeks ([95% CI: 1.0 to 1.1], p=0.033).

Conclusion: Clinically significant weight gain was associated with increased fruit intake but not with other dietary or physical activity changes over 48 weeks after transitioning ART. Interventions to modify behavior in this population may have a limited role in mitigating clinical obesity. Pharmacological interventions to mitigate clinical obesity in this population may be needed.

811 Dolutegravir, Body Mass Index, and Metabolic Syndrome in the IeDEA Sentinel Research Network

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Background: Dolutegravir (DTG) use has been associated with increased weight compared to efavirenz in many international settings. As such, we hypothesized that DTG is also associated with greater cardiometabolic risk globally.

Methods: We performed a cross-sectional study examining associations between DTG use, body mass index (BMI), and metabolic syndrome (MetS; as defined by the International Diabetes Federation) using baseline data of the IeDEA Sentinel Research Network (SRN) cohort study. The SRN prospectively collected data from people with HIV from low-and middle-income sites worldwide, aged ≥40 years, and on ART for at least six months at time of enrollment. Using multivariable linear and logistic regression models, respectively, BMI and MetS were assessed using independent variables of DTG use vs. non-use at enrollment, age, sex, country, smoking status (ever vs. never), and HIV RNA level (<200 vs. ≥200 c/mL). CD4 cell count was not included as it was unavailable in some countries. We assessed the potential for interaction by sex by country.

Results: 1446 participants from Brazil (N=212), Côte d'Ivoire (N=298), India (N=188), Kenya (N=77), Mexico (N=193), Togo (N=244), Uganda (N=100), and Zambia (N=134) were included. Overall, 54% were female, 94% had HIV-1 RNA <200c/mL, 53% were using DTG (78% for >6 mos), and median age was 50.5 years. Median BMI was 25.3 kg/m², and 35% had MetS. DTG use and younger age were significantly associated with higher BMI (Table), with a significant interaction by sex by country. In India, females and males had similar BMI; in other countries BMI was similar among females and varied in males (higher in Brazil and Mexico and lower in in Kenya, Uganda, and Zambia). MetS was significantly associated with older age and again with significant interaction by sex by country. Compared to males, females had higher odds [adjusted OR (95% CI)] of MetS in Zambia [20.75 (2.71, 158.97)], Uganda [15.17 (4.69, 49.11)], Kenya [12.53 (2.55, 61.69)], Togo [4.31 (1.98, 9.36)], Côte d'Ivoire [3.21 (1.80, 5.74)], and Mexico [3.02 (1.18, 7.72)], but not in Brazil or India. No other interactions involving DTG use, sex, and country were associated with BMI or MetS.

Conclusion: DTG was associated with modestly higher BMI but not with MetS in the IeDEA SRN cohort. These data suggest cardiometabolic risk varies across low- and middle-income settings and is dependent on age, sex, and country.

Table. Multivariable models of body mass index and metabolic syndrome in the IeDEA SRN.

Body Mass Index (kg/m²)			Metabolic Syndrome		
Variable	Estimate (95% CI)	P-value	Variable	Odds Ratio (95% CI)	P-value
DTG use (yes vs. no)	0.773 (0.089, 1.456)	0.0267	DTG use (yes vs. no)	1.197 (0.884, 1.620)	0.2450
Age, years	-0.041 (-0.074, -0.008)	0.0163	Age <52 (vs. ≥52), years	0.620 (0.489, 0.786)	<.0001
Smoking status (ever vs. never)	-0.086 (-0.769, 0.597)	0.80	Smoking status (ever vs. never)	1.273 (0.930, 1.742)	0.1318
HIV RNA level (≥200 vs. <200 c/mL)	-0.707 (-1.814, 0.400)	0.21	HIV RNA level (≥200 vs. <200 c/mL)	0.884 (0.538, 1.451)	0.6249
Sex*country interaction	See text	<0.0001	Sex*country interaction	See text	<.0001

812 TDF and Efavirenz but Not InSTI or TAF Use Are Associated With Weight Gain During cART

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Background: Combination antiretroviral therapy (cART) containing integrase strand transfer inhibitors (INSTIs) and/or tenofovir alafenamide (TAF) has been associated with greater weight gain (WG) than cART without these drugs. Yet few studies have adjusted for multiple individual antiretrovirals (ARV) and for both anchor and backbone ARV component.

Methods: We studied WG in cART-naïve patients by analyzing body mass index (BMI) change every 3 months for 3 years after cART initiation in a large HIV Clinic in the Southern US. From 2008-2022 we studied all patients who initiated cART with either dolutegravir (DTG), bictegravir, elvitegravir, raltegravir, atazanavir, darunavir (DRV), rilpivirine (RIL), or efavirenz (EFV) as exclusive anchor drug

if used in combination with either TAF, tenofovir disoproxil fumarate (TDF), or abacavir (ABC) as backbone. We used multi-variable generalized estimating equations (GEE) to assess the association between WG and individual ARV use in the anchor and backbone category. Within each category, patients were censored if they stopped, switched, or added another ARV. We adjusted for main effects of HIV-related, demographic, substance use, and clinic utilization parameters, in addition to time, and retained only significant covariates and factors for the final model.

Results: 4,194 patients contributed 6,514 patient-years and 20,528 BMI measurements. The majority were black (55%), male (77%), and non-Hispanic (72%). Median baseline BMI was 24.4, inter-quartile range (IQR) 21.6-28.2. After 3-years, median BMI was 27.1 (IQR 23.8-31.3), and median BMI gain was 1.8 (IQR 0.2-4.1). The most used ARVs were DTG (23%), EFV (22%), and DRV (14%) in the anchor, and TDF (58%), TAF (21%), and ABC (21%) in the backbone group. In the final model, within the anchor group, we found no significant WG differences in pairwise comparisons between any of the INSTIs, RIL, or protease inhibitors; the same was true for ABC and TAF in the backbone group. In contrast, both EFV and TDF were associated with significantly lower WG in all pairwise comparisons within their respective groups and were retained for the final model shown in the table. Calendar year, annual follow-up frequency, and Hispanic ethnicity did not significantly contribute to BMI change.

Conclusion: Over a 15-year period, our demographically diverse patient population experienced substantial WG in the first 3 years after cART initiation. Among 11 examined ARVs, only EFV and TDF were independently associated with (decreased) WG.

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813 Lipidome Composition and Weight Changes at 48-week 3TC-DTG and FTC/TAF/BIC: Data of the ICONA Cohort

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Background: cART start has been associated with weight gain (WG), which entails an increased dysmetabolic risk in PLWH, the biologic correlates of which are ill defined. We assessed WG and lipidome profile in cART-naïve patients starting INSTI-based dual (DT-3TC-DTG) or triple (TT-FTC/TAF/BIC) cART.

Methods: We performed untargeted lipidomic on PLWH of the ICONA cohort both prior (T0) and 48w after DT or TT cART (T1). Raw data were aligned, normalized, and ions from both modes were merged for multivariate analysis. Supervised regression modelling was performed with Orthogonal Partial Least Squares Discriminant Analysis, and significant biomarkers are selected based on variables' significance in the model (VIP>1.5), t-test ($p<0.05$), and fold change (FC>2), followed by pathway enrichment analysis (PEA).

Results: 119 PLWH were included: 62 DT, 57 TT. At T0, DT patients were older, more frequently male, with higher CD4, lower HIV-RNA, fewer AIDS diagnoses, higher body weight and HDL, despite comparable total and LDL cholesterol, triglycerides and lipid lowering agents (Fig.1A). At T1, TT showed higher WG versus DT (5.1 ± 5.8 vs 2.2 ± 3.2Kg SD, $p<0.001$). Both TT and DT displayed a net separation in the OPLS-DA model between T0 and T1, witnessing substantial lipidomic changes (Fig.1B-C). In DT, 109 lipids were significantly different at T1, and 66 lipids in TT, with a higher proportion of up-regulated lipids in TT (83.3% vs 30.3%, $p<0.0001$) (Fig.1D-E). While both treatments resulted in glycerolipids and glycerophospholipids changes (PEA), DT mainly modified glycerolipids (diacylglycerol-DAG, monoacylglycerols-MG, monoradylglycerols-MAG), and TT glycerophospholipids (phosphatidylcholines-PC, lysophosphatidic acids-LPA). When seeking for associations between WG and lipidome, WG positively correlated with PC lipids, and negatively with DAG in TT PLWH only, with no significant correlations detected in DT.

Conclusion: First-line 48-week cART substantially and differentially shapes the plasmatic lipidome composition, with 3TC/DTG mainly affecting DAG, and FTC/TAF/BIC the PC pathways. Most interestingly, the correlation between higher WG and glycerophospholipids metabolism with potential phosphatidylcholines involvement in FTC/TAF/BIC, that is not seen in DT, suggests distinct interactions between lipidomic signature and body weight according to cART regimens, that merit consideration when treating PLWH with additional metabolic risk factors.

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814 Phase 4 DEFINE Switch Study to Manage InSTI-related Weight Gain: Metabolics and Biomarker Analysis

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Background: Integrase strand transfer inhibitor (INSTI)–based antiretroviral therapies are associated with greater weight gain than non-nucleoside reverse transcriptase inhibitor– or boosted protease inhibitor (PI)–based regimens, and these effects disproportionately impact Black and Hispanic individuals and women living with HIV-1. DEFINE is the first prospective, randomized trial to explore the impact of switching from an INSTI-based regimen to a PI-based regimen to mitigate or reverse INSTI-related weight gain. As previously reported, the primary Week 24 analysis found no significant difference in percent change in body weight from baseline when switching to darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) compared to continuing INSTI+tenofovir alafenamide (TAF)/emtricitabine (FTC).

Methods: DEFINE (NCT04442737) is a randomized (1:1), prospective, 48-week, active-controlled, open-label, multicenter phase 4 study evaluating switching to D/C/F/TAF versus continuing INSTI+TAF/FTC in virologically suppressed adults with HIV-1 who had ≥10% weight gain while on the INSTI-based regimen. The primary objective was to assess percent change in body weight from baseline to Week 24. Metabolic and biomarker data through Week 24 are reported in this analysis.

Results: Among the 103 adults who were randomized to D/C/F/TAF (n=53) or continued INSTI+TAF/FTC (n=50), 30% were female, 61% were Black/African American, and the median BMI was 32.7 kg/m². Consistent with the primary endpoint, at Week 24 most participants remained classified as obese (D/C/F/TAF, 53%; INSTI+TAF/FTC, 70%) and had experienced minimal BMI and waist circumference changes. Glucose and HbA1c values remained largely unchanged through Week 24; however, there were small decreases in insulin and HOMA-IR values in the INSTI+TAF/FTC arm (Table). No participants in either arm decreased medication dosages or entirely stopped lipid-lowering, anti-glycemic, or anti-hypertensive medications through Week 24. Changes in leptin, adiponectin, and α-melanocyte stimulating hormone were minimal in both arms, as were changes in NAFLD fibrosis score. The percent of participants at high risk of NASH by HAIR score decreased in both arms.

Conclusion: Consistent with the minimal body weight changes observed through Week 24, metabolic and biomarker data remained relatively stable. Metabolic parameters in this high-BMI population did not improve following antiretroviral switch, highlighting that weight gain should be a pretreatment consideration.

Table. Summary of key metabolic parameters and biomarkers

	D/C/F/TAF (baseline)	D/C/F/TAF (Week 24)	INSTI+TAF/FTC (baseline)	INSTI+TAF/FTC (Week 24)
Insulin, median, µIU/mL	10.9 (n=53)	11.7 (n=47)	12.7 (n=50)	9.9 (n=45)
HOMA-IR, median	2.59 (n=53)	2.78 (n=47)	3.40 (n=50)	2.33 (n=43)
Leptin, median, µg/L	16.88 (n=45)	22.09 (n=42)	22.76 (n=49)	19.72 (n=41)
Adiponectin, median, mg/L	3.69 (n=51)	3.84 (n=46)	4.01 (n=49)	3.67 (n=45)
α-melanocyte stimulating hormone, median, ng/L	18.0 (n=42)	15.0 (n=31)	13.0 (n=44)	17.0 (n=35)
NAFLD fibrosis stage F3-F4, n (%)*	3 (5.7) (n=53)	3 (5.7) (n=53)	5 (10.0) (n=50)	7 (14.0) (n=50)
HAIR score ≥2 (high risk of NASH), n (%)†	10 (18.9) (n=53)	3 (5.7) (n=53)	10 (20.0) (n=50)	7 (14.0) (n=50)

*Participants missing data: D/C/F/TAF baseline, 4 (7.5%); D/C/F/TAF Week 24, 14 (26.4%); INSTI+TAF/FTC baseline, 6 (12.0%); INSTI+TAF/FTC Week 24, 9 (18.0%).
†Participants missing data: D/C/F/TAF baseline, 2 (3.8%); D/C/F/TAF Week 24, 9 (17.0%); INSTI+TAF/FTC baseline, 2 (4.0%); INSTI+TAF/FTC Week 24, 8 (16.0%).

815 Weight Gain in People With HIV (PWH) vs People Without HIV (PWoH) Over a 3-Year Period

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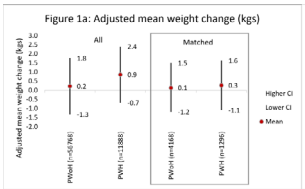
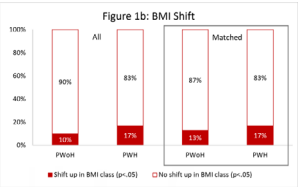
Background: The study evaluated weight (wt) change and shift in BMI class in PWH on antiretroviral therapy (ART) over 3 years (3y) vs PWoH matched on baseline (BL) characteristics.

Methods: Retrospective study using Trio Health HIV Network EMR data from federally qualified health centers in US. Eligibility: ≥18 yrs, in care between 1/1/2015-8/15/2023, with BL and 3y wt measures (all); PWH: treatment-experienced suppressed at BL and 3y or suppressed on 1st ART with BL≥ 6mo since suppression and ≥ 12mo since ART start. BL characteristics were compared (X-square, t-test). Propensity scores (PS) and odds of shifting up BMI class were calculated (logistic regression); groups were matched on site, BL year, gender, age, race, and PS to compare 3y wt and BMI changes, with additional adjustment for imbalanced covariates.

Results: Of 68856 qualified individuals, 11888 (17%) were PWH suppressed, 902 (8%) suppressed on 1st ART. PWH and PWoH differed respectively in key BL characteristics (all listed p<.05): age (median 50 vs 54 years), gender (male 77 vs 40%), race (42 vs 48% Black), eGFR <60 mL/min/1.73m^2 (11 vs 6%), obesity (BMI> 30 kg/m^2; 29 vs 47%), hyperlipidemia (14 vs 4%), hypertension (24 vs 46%), diabetes (5 vs 2%), neuropsychiatric disorders (26 vs 14%), cardiovascular disease (28 vs 49%), sexually transmitted diseases (10 vs 1%), smoking (11 vs 2%), or substance use (9 vs 6%). PWoH had statistically higher mean [median] BL BMI (all: 30.8 [29.4] vs 28 [26.9], matched: 29.6 [27.5] vs 28.6 [26.9]). In unmatched analyses, PWH gained 0.6 kg (95% CI 0.3-1.0) more at 3y vs PWoH after adjusting for BL differences. After matching, PWH and PWoH did not differ in 3y wt change (0.1 kg CI -0.5-0.7), Figure 1. Despite small differences in wt change, unmatched PWH were 1.3 (CI 1.1-1.5) times more likely to shift up a BMI class (17% vs 10% PWoH); smaller, but similar differences were observed in matched cohorts (17% vs 13%; 1.3 [CI 1.1-1.7]).

Conclusion: This is the largest study that matched and compared wt change in suppressed PWH vs PWoH, accounting for return to health, population differences, and geography. After adjusting for differences in BL characteristics, small (unmatched) and no difference (matched) in 3y mean wt change were observed in PWH vs PWoH. A greater proportion of PWH vs PWoH shifted up a BMI class after 3 y, although results may be influenced by higher prevalence of obesity at BL among PWoH. Further examination of drivers of outlier wt gain and the role of ARTs is ongoing.





816 Effect of Obesity on Response to Antiretroviral Therapy in SIV-Infected Rhesus Macaques

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Background: Modern antiretroviral therapy (ART) regimens are associated with increased risk of weight gain and overt metabolic disease. Adipokines play a role in adipose tissue dysfunction and are indicators of cardiometabolic disease risk. A reduced adiponectin:leptin ratio (ALR) is a predictive biomarker that correlates with a number of metabolic risk factors, as well as with markers of chronic inflammation. We employed the rhesus macaque model of SIV infection to determine if a modern ART regimen comprised of TDF, FTC, and DTG would elicit metabolic dysfunction with a corresponding decrease in the ALR, and if this effect was exacerbated by pre-existing obesity.

Methods: Lean, metabolically healthy (n=6) and western-style diet-induced obese (n=5) adult male macaques were infected i.v. with SIVmac239 and ART was initiated at 5 weeks post-infection and continued for 16 months. Baseline and longitudinal assessments of plasma, adipose tissue morphology, and systemic measures of metabolism were obtained.

Results: Unsurprisingly, the obese cohort exhibited a significantly lower ALR at baseline compared to the lean cohort (Obese 0.21±0.06 vs Lean 0.87±0.32, p=0.02). The lean cohort experienced a progressive decrease in ALR that was driven by a decrease in adiponectin, throughout the time course of chronic infection, ART initiation, and full suppression of viremia, that became significant at 56 weeks post-infection (PI) (Lean average 0.30±0.05). The change in ALR was inversely correlated to % change in body weight and fat mass, where animals in the lean group with the largest decrease in their ALR also had the greatest weight and fat mass gain. Additionally, the change in ALR in all animals was inversely correlated to % change in fasting insulin levels and HOMA-IR. The obese cohort also exhibited significantly elevated circulating C-reactive protein (CRP) and lipopolysaccharide (LPS)-binding protein (LBP) at baseline compared to the lean cohort. The lean cohort exhibited a drastic increase in both CRP and LBP throughout the time course. The ALR was inversely correlated to CRP levels at necropsy.

Conclusion: SIV infection and subsequent ART significantly decrease the ALR in lean animals to values similar to those seen in pre-diabetic and dysmetabolic obese animals. Thus, SIV and ART induce an obese phenotype in initially lean animals. Therefore, weight gain and/or increases in BMI in people living with HIV are not adequate measures as cardiometabolic risks may be independent of these factors.

817 Transcriptomics and Proteomics Reveal Differential Pathways in DTG/3TC vs 3DR Regimens in PLHIV

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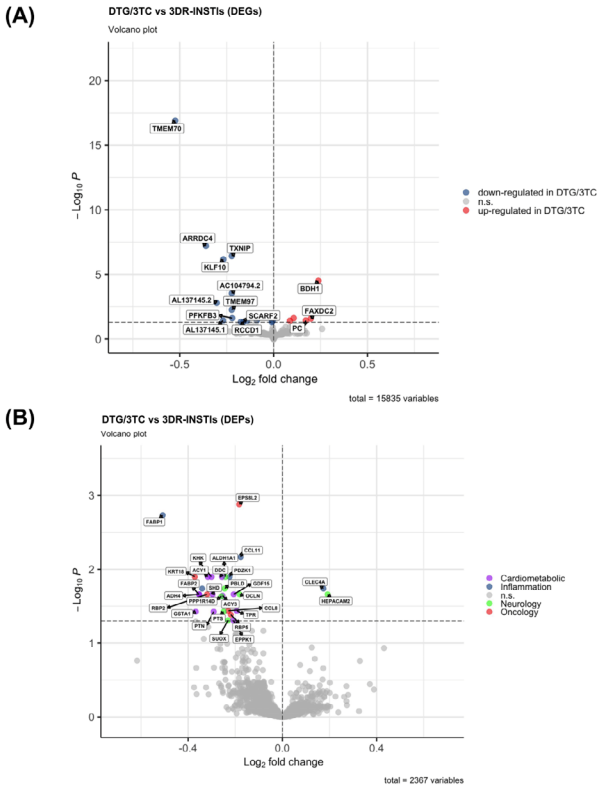
Background: Drug toxicity in people living with HIV (PLHIV) using cART is a concern. Nucleoside analogues are associated with mitochondrial damage. Two-drug regimens (2DR), such as DTG (integrase strand inhibitor) and 3TC may reduce drug toxicity, but the molecular effects remain unclear. Systemic effects of DTG/3TC and triple therapies (3DR) were studied using multi-omics.

Methods: Data are used from the 2000HIV (NTC03994835) study that includes discovery (n=1275) and validation (n=212) cohorts of PLHIV with ~11.5 years of cART stratified by treatment regimen. We measured ~2368 plasma proteins (Olink Explore), and ~58347 genes expression by PBMC Bulk RNA-seq. We compared differential gene (DEG) and protein (DEP) expression and enriched pathways between PLHIV using DTG/3TC (n=188) versus 3DR containing INSTI (3DR-INSTI, n=526) or without (3DR-non-INSTI, n=773), and compared 3DR-INSTI versus 3DR-non-INSTI, adjusting for sex, age, ethnicity, and pre-cART conditions.

Results: Discovery cohort data showed limited DEG (5 up, 15 down) and DEP (2 up, 27 down) in DTG/3TC compared to 3DR-INSTI (Figure). DTG/3TC and 3DR-non-INSTI comparison showed 21 DEG (14 down) and 131 DEP (119 down). 3DR-INSTI versus 3DR-non-INSTI revealed no DEG and limited DEP (63 up, 83 down). Gene set enrichment analysis on the total summary statistics of genes and proteins ranked by -$\log_{10}$(p-value)*sign(log2FC) revealed significant results (p<0.05). DTG/3TC genes compared to 3DR-INSTI revealed the up-regulation of the ATPase complex and down-regulation of the Oxidative stress pathway; meanwhile proteins revealed a down-regulation of the Biological oxidations with ALDH1A1, ACY1, ACY3, and ADH4 DEPs as leading markers. DTG/3TC compared to 3DR-non-INSTI genes showed an up-regulation of the TCA cycle with PC DEG as leading marker and down-regulation of the OXPHOS system with TMEM70 DEG as leading marker of the latest, while proteins revealed a down-regulation of the Biological oxidation enzymes and Oxidoreductase activity with ADH4, AKR7L, DCXR, and ADH1B DEPs leading markers. 3DR-INSTI proteins compared 3DR-non-INSTI showed a down-regulation of the Fat digestion and Metabolism with CKMT1A, RBP2, FABP2, and DDC DEPs as leading markers. The direction of our findings was confirmed in the validation cohort.

Conclusion: This study suggests that DTG/3TC reduces mitochondrial and oxidative stress in PLHIV compared to 3DR containing NRTIs. We also showed the negative effects on fat metabolism of INSTI compared to non-INSTI based regimens.



Differentially Expressed Genes and Proteins (DTG/3TC versus 3DR-INSTIs)
Panel A shows the differentially expressed genes in the discovery cohort (FDR-adjusted p-value < 0.05)
Panel B shows the differentially expressed proteins in the discovery cohort (FDR-adjusted p-value < 0.05)

818 Inflammatory Profile of B/F/TAF, DTG/ABC/3TC, and DTG+F/TAF Over 5 Years and Effects of Viral Blips

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Background: Elevated levels of inflammatory markers are linked to increased morbidity/mortality in people with HIV (PWH) and often remain elevated after suppression of HIV-1 replication below the limit of detection by antiretroviral therapy (ART). As new combinations of ART become available, an evaluation of their effects on biomarkers of inflammation are needed. Additionally, it remains unknown whether transient elevations of viral load ("blips") during ART are associated with increases in inflammatory biomarkers. This study analyzed the effect of ART on selected biomarkers of inflammation and immune activation.
Methods: We utilized cryopreserved samples from treatment-naïve PWH enrolled in two Phase 3 clinical studies investigating the efficacy and safety of B/F/TAF, DTG/ABC/3TC and DTG+F/TAF over a 5-year window (GS-US-380-1489/1490). At wk144, participants were switched to open label B/F/TAF. We measured levels of interleukin-6 (IL-6), C-reactive protein (hsCRP), D-dimer, soluble CD14 (sCD14), and tumor necrosis factor-α receptor 1 (TNFR1) by ELISA from select baseline, wk 24, 48, 144, and 240 samples (B/F/TAF, N=123; DTG/ABC/3TC, N=62; DTG+F/TAF, N=58). Samples from PWH who experienced a viral blip (n=44, defined as single VL>50c/mL) were also analyzed and paired with the most recent suppressed sample. Longitudinal biomarker changes were assessed using a constrained mixed effects linear regression model adjusting for covariates.
Results: Baseline demographics and selected laboratory characteristics were similar across studies. Significant decreases in D-dimer, sCD14, and TNFR1 were observed in all treatment arms, with no significant differences between arms at any timepoint. Similarly, biomarker levels also remained stable following ART-switch at week 144. No significant changes in hsCRP or IL-6 were observed in any arm at any timepoint. In the analysis of viral blips, a significant association was observed between sCD14 and increasing viral load (p=0.022); a similar trend was seen with D-dimer
Conclusion: Viral suppression was associated with significantly reduced inflammation in treatment-naïve PWH, with no significant differences in selected inflammatory biomarkers among the three ART regimens during the 144-week randomized period and each was sustained after the open label switch to B/F/TAF. Viral blips were associated with increases in some of the markers. The small number of available samples limited this study, thus the findings warrant additional investigation.

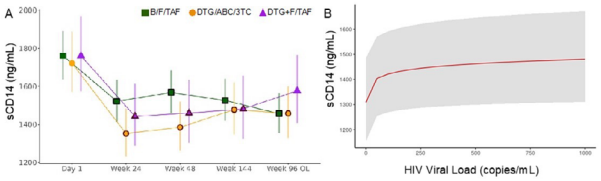

Figure 1. A) Significant reductions in sCD14 levels compared to baselines were observed in all treatment arms at most visits (bold borders). B) Significant association (p=0.022) was observed between increasing HIV viral load and elevated sCD14 level in paired viral blip and suppressed samples (n=88).

819 Impact of Raltegravir Intensification on the Gut Microbiota of People With Chronic HIV-1 Infection

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Background: Chronic human immunodeficiency virus 1 (HIV-1) infection is associated with gut microbiota alterations, including low gene richness and shifts in certain bacterial species, which have been linked to immune dysfunction. Residual HIV-1 replication might contribute to perpetuating such gut dysbiosis. We sought to explore if antiretroviral treatment (ART) intensification with raltegravir (RAL) had the ability to modify the gut microbiome composition and related immune parameters.
Methods: This was a prospective, double-blind, placebo-controlled, 2-arm randomized trial, where aviremic subjects with HIV-1 under stable NNRTI- or PIr-based ART were randomized 2:1 to add RAL (1200 mg QD) or placebo to their ongoing ART, stratified by NNRTI vs PIr ART at study entry. We evaluated the longitudinal effect of RAL intensification on the gut microbiome by shotgun metagenomics as well as on soluble markers of immune activation and gut integrity (sCD14, DDimer, IFABP, IP10, and LBP) and cellular markers of immune activation and maturation (HLA-DR, CD38), exhaustion (PD-1) and senescence (CD57) at weeks 0, 12, 24 and 48. Non-parametric paired and unpaired tests and Linear Mixed Models (LMM) were used to analyse the data as needed.
Results: Fifty-seven subjects were included, 38 received RAL and 19 placebo. Microbial gene richness did not change in subjects receiving RAL but increased in those receiving Placebo (LMM p=0.009). There were no differences in beta-diversity between groups. In subjects receiving RAL, 3 Roseburia species (R. hominis, intestinalis and unilivorans) decreased over time, whereas Bifidobacterium longum and Paraprevotella xylaniphila increased. Treatment intensification was associated with lower Streptococcus termophilus abundance than placebo from week 12 onwards. All subjects remained aviremic throughout the study. RAL intensification was not associated with changes in CD4+, CD8+, sCD14, DDimer, IFABP, IP10, or LBP. In the placebo arm, we observed longitudinal increases in HLADR+ effector memory and TEMRA CD8+ T-cells, as well as in CD38+ Naïve CD4+ and CD57+ TEMRA CD4+ T-cells. Additionally, we noted decreases in CD57+ TEMRA CD8+ T-cells. No changes in cellular markers occurred in the RAL arm.
Conclusion: RAL intensification of PI/r or NNRTI-based regimens is associated with reduced immune activation and senescence in CD8+ T-cells, coupled with minor changes in the gut microbiome composition.

820 Blood Telomere Length in ART-Naive PLWH Starting DTG+3TC vs Triple Regimen With 2 Nucleosides

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Background: People living with HIV (PLWH) show a marked shortening of blood telomere length (BTL) early after seroconversion. This is caused by uncontrolled viral replication with sustained immune activation, immunosenescence and inhibition of telomerase by HIV proteins. Antiretroviral

therapy (ART) causes an increase in naïve and central memory cells that have longer telomeres, leading to an overall BTL increase. However, tenofovir (TDF/TAF) and abacavir (ABC), which are potent inhibitors of human telomerase activity, have been shown to negatively affect the BTL increase. We investigated the effect on BTL over 96 weeks after starting a dual therapy (DT) with dolutegravir (DTG) plus lamivudine (3TC) vs a standard triple therapy (TT) with an anchor drug plus two NRTIs, one of which was TDF/TAF or ABC.

Methods: In this prospective longitudinal study we enrolled ART-naïve PLWH who started DT or TT, with no current AIDS event. We assessed BTL by monochrome multiplex qPCR (expressed as telomere to single-copy gene ratio, T/S) at the time of ART initiation (baseline, BL), virological success (VS) (achievement of HIV-RNA<50cps/mL), and at weeks 48 (W48) and 96 (W96). We used an adjusted mixed model (GLM) to evaluate the effects of both the between- and within-subject factors. Linear regressions were performed to identify the variables associated with BL BTL and BTL changes over W96.

Results: From 2018-2022 we enrolled 71 participants: 41 in the TT and 30 in the DT group (Table1). Compared to TT, participants in DT were younger and with higher CD4 count. However, the two groups showed comparable BL HIV-RNA and HIV-DNA load, they similarly reached VS within 2 months and maintained viral suppression over the follow-up. At BL, the medians (IQR) of BTL were similar in the TT and DT groups: 0.93 (0.79-1.09) and 1.06 (0.84-1.19) (p=0.103). Overall, BTL increased over time, showing a similar trend in both groups (p=0.769); specifically, we observed no variation up to W48 (+0.02, p=0.803) and a significant mean gain at W96 (+0.11, p=0.015). BL BTL was associated with younger age (-0.07 per 10 yr. increase; -0.11/-0.02; p=0.004). Higher BTL change was associated with shorter BL BTL (-0.90; -1.20/-0.60; p<0.001).

Conclusion: In this setting, ART-naïve PLWH who initiated either DT or TT showed a similar evolution of BTL over time. They did not show any significant change in BTL after 1-year follow-up,. However, a gain was observed at W96, suggesting a beneficial effect of ART, regardless of triple or dual regimen use.

Table 1. Characteristics of participants at baseline

	Entire population n=71	TT n=41	DT n=30	p
Male sex, n (%)	55 (77.5)	30 (73.2)	25 (83.3)	0.311
Age, median (IQR), years	38 (32-52)	44 (36-54)	35 (25-50)	**0.008**
BMI, median (IQR), Kg/m²	23 (22-25)	23 (22-25)	24 (23-25)	0.208
Smokers, n (%)[a]	29 (40.8)	15 (36.6)	14 (46.7)	0.393
Alcohol habit, n (%)[b]	25 (35.2)	12 (29.3)	13 (43.3)	0.220
CD4 count, median (IQR), cells/µL	290 (171-508)	225 (76-481)	382 (261-598)	**0.002**
HIV-RNA, median (IQR), Log_{10} copies/mL	4.77 (4.15-5.50)	5.27 (4.11-5.92)	4.67 (4.19-5.07)	0.110
HIV-DNA, median (IQR), Log_{10} copies/10^6CD4	4.21 (3.58-4.59)	4.30 (3.62-4.92)	4.08 (3.55-4.28)	0.130

Abbreviations: BMI: Body mass Index; [a] >10 cigarettes per day; [b] ≥2 alcoholic units/day

821 Age Modifies the Association Between Sex and the Plasma Inflammatory Proteome in Treated HIV

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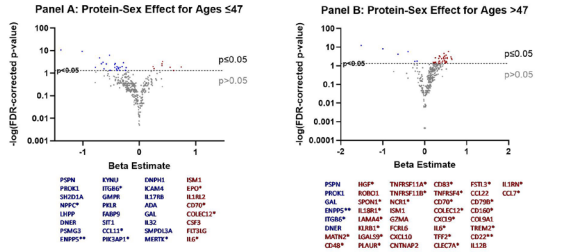
Background: Among ART-suppressed people with HIV (PWH), women have higher levels of several plasma inflammatory markers than men, but the effect of sex on the larger plasma inflammatory proteome, and whether these differences are modified by age, remains unclear.

Methods: We analyzed 363 unique plasma proteins (Olink Inflammation Explore panel) within a randomly sampled sub-cohort of ART-suppressed (<400 copies HIV RNA/mL) CNICS participants. The relationship between natal sex and plasma proteins was assessed with linear regression models adjusted for age, natal sex, nadir CD4, site, race, MSM status, and clinical factors (smoking, IDU, HCV history, ASCVD risk score). Age-sex interaction terms were also assessed, stratifying age above and below the median age of 47, which in prior studies has approximated the average age of menopause in women with HIV. Mortality was separately assessed in Cox proportional hazards models adjusted for VACS index and site. All p-values were adjusted for multiple comparisons by controlling for the false discovery rate (FDR) using the Benjamini-Hochberg method.

Results: Of the 922 ART-suppressed participants sampled, 103 died over a median follow-up of 9 years. Median age was 47; 162 (18%) were female. Median current and nadir CD4 count were 579 cells/mm³ and 245 cells/mm³, respectively, with a median ART duration of 5 years. A large number of sex differences in inflammatory markers were identified along with significant evidence for an age-by-sex interaction for 157 of all 363 proteins assessed (43%) after FDR correction. In those ≤47 years (Panel A), women had lower levels of largely immunoregulatory proteins than men, 4 of which were associated with higher mortality in the overall cohort. In contrast, in those >47 years, women had higher levels of predominantly inflammatory markers (36/42) than men, 26 of which were associated with higher mortality in the larger cohort (Panel B). Women also had lower levels of the immunoregulatory protein integrin beta 6 (which activates TGF-β1) than men regardless of age.

Conclusion: The impact of sex on the plasma inflammatory proteome is highly dependent on age among ART-suppressed PWH, with women exhibiting more inflammation than men primarily at older ages. Whether menopause is responsible for unmasking these sex differences requires further study and is of high importance as many of these pathways are associated with increased mortality.



*Associated with higher mortality. **Associated with lower mortality. Lower in women. Higher in women.

822 Consequences of Low-Level Viremia by Sex Among People With HIV in the United States

Amalia Aldredge[1], Cyra C. Mehta[1], Cecile D. Lahiri[1], Maria L. Alcaide[2], Kathryn Anastos[3], Todd T. Brown[4], Audrey L. French[5], Frank Palella[6], Michael Schneider[7], Phyllis Tien[8], Anandi N. Sheth[1], Lauren F. Collins[1]

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Background: Low-level viremia (LLV) is common in people with HIV (PWH) receiving antiretroviral therapy (ART) and has been associated with adverse outcomes including virologic failure (VF), drug resistance, and non-AIDS comorbidities (NACM). As differences in these outcomes have been observed in men versus women with HIV, we investigated the effect of LLV on these outcomes by sex.

Methods: We included men enrolled in the Multicenter AIDS Cohort Study (MACS) and women in the Women's Interagency HIV Study (WIHS) from 2003-2020 who reported ART use for ≥1 year with ≥2 consecutive HIV-1 viral loads (VL) <200 c/mL. PWH were then categorized using 4 consecutive VL results (baseline period) as: virologic suppression (VS; all VL below lower limit of assay detection), intermittent LLV (iLLV; non-consecutive detected VL <200 c/mL), persistent LLV (pLLV; ≥2 consecutive detected VL <200 c/mL), or VF (any VL ≥200 c/mL). Outcomes were assessed from after baseline period through 5 years. Those with baseline VF were excluded. At first visit after baseline period, PWH with multimorbidity (≥2 of 5 NACM: hypertension, dyslipidemia, diabetes, cardiovascular disease, kidney disease) were excluded from that analysis. Adjusted Cox proportional hazards models estimated the association of virologic category with time to incident a) VF and b) multimorbidity.

Results: Of 2,395 PWH, 67% were women, median age was 48 years, 53% were Black, 20% were Hispanic, median CD4 count was 616 cells/µL, and 89% reported ≥95% ART adherence. Over the baseline period (median 1.5 years), VS, iLLV, and pLLV occurred in 61%, 18%, and 6%, respectively. Among 1968 and 1123 PWH included in each analysis, incident VF and multimorbidity occurred in 25% and 21%, respectively. Compared to PWH with VS, the adjusted hazard ratio (aHR) for incident VF in women was 1.8 (95% CI 1.4,2.4) for iLLV and 2.4 (1.5,3.6) for pLLV, while in men was 1.4 (0.9,2.3) for iLLV and 3.1 (1.7,5.6) for pLLV (LLV*sex interaction p=0.4). Compared to PWH with VS, the aHR for incident multimorbidity in women was 0.9 (0.6,1.3) for iLLV and 1.7 (1.0,2.9) for pLLV, while in men was 1.4 (0.9,2.4) for iLLV and 0.7 (0.2,1.9) for pLLV (LLV*sex interaction p=0.1) (Table).

Conclusion: In a diverse cohort of US PWH, LLV was associated with an increased risk of developing VF, regardless of sex. There was a trend toward pLLV

being associated with increased risk of multimorbidity in women but not in men. Further research is needed to mitigate the adverse consequences of LLV in men and women.

Survival analysis comparing time to incident virologic failure and multimorbidity by virologic category, overall and by sex.

	Incident Virologic Failure Adjusted Hazard Ratio (95% Confidence Interval)*			Incident Multimorbidity Adjusted Hazard Ratio (95% Confidence Interval)**		
Virologic Category	All n=1968	Women n=1304	Men n=664	All n=1123	Women n=773	Men n=350
Virologic Suppression	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT	REFERENT
Intermittent LLV	1.6 (1.2, 2.1)	1.8 (1.4, 2.4)	1.4 (0.9, 2.3)	1.1 (0.8, 1.6)	0.9 (0.6, 1.3)	1.4 (0.9, 2.4)
Persistent LLV	2.7 (1.9, 3.9)	2.4 (1.6, 3.6)	3.1 (1.7, 5.6)	1.1 (0.6, 1.9)	1.7 (1.0, 2.9)	0.7 (0.2, 1.9)

*Adjusted for age, ±sex (overall), ±LLV*sex (overall), race, socioeconomic status (SES), CD4, adherence, antiretroviral anchor
**Adjusted for age, ±sex (overall), ±LLV*sex (overall), race, SES, obesity, smoking, CD4, adherence, integrase inhibitor use

823 Short- and Long-Term Body Weight Gain Following Switch to Integrase Inhibitors Differs by Sex

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Background: Integrase strand-transfer inhibitors (INSTIs) are associated with weight gain among persons with HIV (PWH), which may be more severe in women. We assessed differences in weight change by sex up to 6 years following switch to INSTIs.

Methods: We used data collected between 2007-2020 in virally-suppressed (<200 c/mL) INSTI-naïve PWH on antiretroviral therapy (ART) for ≥2 years and persons without HIV (HIV-) enrolled in the MACS/WIHS Combined Cohort Study. We compared PWH who switched/added an INSTI to those who remained on non-INSTI ART and to HIV- controls. Follow-up time was years since switch visit or comparable visit in controls. Weight change was the difference between post- and pre-switch visits. Linear regression mixed effect models assessed the effects of sex (assigned at birth), group, and time on absolute and percent (%) weight change, adjusted for age, race/ethnicity, socioeconomic status, and diabetes.

Results: 3466 participants contributed a mean 3.2 (±1.5) years of data, including 1940 women (411 INSTI, 711 Non-INSTI, 818 HIV-) and 1526 men (223 INSTI, 412 Non-INSTI, 891 HIV-). Compared to men, women were younger (47.2 vs 54.5 years), more likely to be non-Hispanic Black (65 vs 23%), had higher pre-switch BMI (31.5 vs 26.9 kg/m^2), and higher prevalence of diabetes (19 vs 13%), respectively. Absolute weight gain in women versus men was +3.2 (±9.8) vs +1.6 (±6.1) kg in INSTI, +0.8 (±9.4) vs +1.0 (±6.6) kg in non-INSTI, and +0.2 (±11.2) vs +0.2 (±7.2) kg in HIV- groups. In adjusted models, sex and group modified % weight change by time (sex*group*years interaction, p<0.0001). Men switching to INSTIs experienced greater % weight gain compared to non-INSTI and HIV- controls up to 1-2 years post-switch: +2.42% (95% CI 1.41-3.42) vs +0.58% (-0.17-1.34) and +0.58% (0.02-1.14), respectively, with no differences between groups beyond 3 years. In contrast, women on INSTIs experienced greater % weight gain for up to 3-4 years post-switch compared to women on non-INSTIs [+4.49% (95% CI 3.60-5.37) vs +2.08% (1.30-2.87)] and up to 5-6 years post-switch versus HIV- women [+5.16% (3.80-6.52) vs +0.02% (-1.24-1.28)], Figure.

Conclusion: Short and long-term body weight gain in PWH switching to INSTIs differed by sex, with women experiencing a greater amount and longer duration of weight gain relative to controls. Further research is needed to understand implications of weight gain on cardiometabolic disease and support sex-specific preventative and therapeutic intervention strategies.

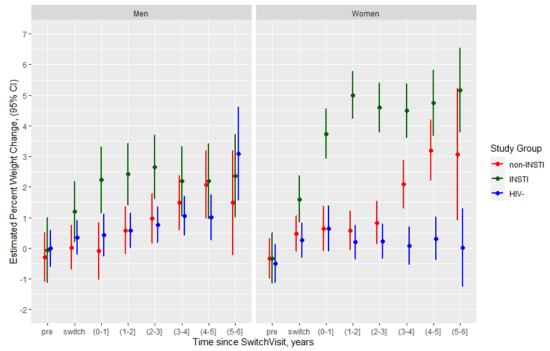

Figure. Model-estimated mean percent weight change among men and women with and without HIV in the MACS/WIHS Combined Cohort Study, stratified by study group and years since switch, adjusted for covariates (age, race/ethnicity, socioeconomic status, diabetes). Sex*group*years interaction term, p<0.0001.

824 Body Composition Changes Among DMPA and Non-Hormonal Users on TDF Based ART Switched to B/F/TAF

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Background: We previously demonstrated a higher bone mass among DMPA users on tenofovir alafenamide (TAF) compared with tenofovir disoproxil fumarate (TDF) containing ART. However, concerns about metabolic complications remain. We assessed the effect of switching women living with HIV (WLWH) from TDF/ lamivudine/ dolutegravir to Bictergravir /Emtricitabine /TAF (B/F/TAF; Biktarvy®) on body composition over a two-year period in the BONE: STAR study.

Methods: WLWH on TDF and DMPA-IM were randomized in a 1:1 ratio to either continue on a TDF based ART regimen (HIV+/DMPA+/TDF+) or switch to B/F/TAF (HIV+/DMPA+/TAF+). A third group of WLWH on TDF and using non-hormonal contraception were all offered B/F/TAF (HIV+/DMPA−/TAF+). Dual energy x-ray absorptiometry was used to measure lean mass, total, trunk, and extremity fat at enrollment and every 6 months for 2 years. Multivariable linear regression was used to assess differences in mean percent (%) change in fat and lean mass adjusting for age, and in body mass index.

Results: A total of 346 WLWH were included in the analysis, with follow-up between December 2019 and August 2023. Median age was 31 years (interquartile range, 27.9 to 34.7 years). Both non-hormonal and DMPA groups who switched to B/F/TAF had significant increases in mean lean mass, total, trunk, and extremity fat post switch, p-value <0.001. There were no significant differences were in body composition parameters between women on B/F/TAF and DMPA or non-hormonal contraception, versus and TDF users, p>0.173. Similarly, no differences were noted between women on B/F/TAF using DMPA versus non-hormonal contraception, p>0.125.

Conclusion: Significant increases were observed in fat and lean mass in both groups with no differences between DMPA users on TDF and DMPA or non-hormonal contraception switched to B/F/TAF. Longer term follow -up data beyond 2 years are needed to further understand the impact in WLWH of different ART options on fat gain and obesity-related conditions.
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825 Sleep Apnea in People With and Without HIV in Primary Care

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Background: Sleep apnea negatively impacts health and quality of life. A better understanding of potential differences in sleep apnea incidence and risk factors between people with HIV (PWH) and people without HIV (PWoH) could inform prevention and management strategies.

Methods: We conducted a study of adult (≥18-years-old) members of Kaiser Permanente Northern California, an integrated U.S. healthcare system. PWH and PWoH with membership between July 2013 and December 2021 were matched

1:20 by age, sex, and race/ethnicity. Sleep apnea diagnoses were identified by ICD codes in electronic health records. Using Poisson regression, incident sleep apnea was compared between PWH and PWoH, overall and with PWH stratified by HIV treatment status. Optimal HIV treatment was defined as being on ART (≥1 ART prescription fill), with undetectable HIV RNA (<200 copies/ml), and without immunosuppression (CD4 count ≥500 cells/µl). Next, both HIV-specific and general (non-HIV-specific) risk factors were evaluated. All models included the following covariates: age, sex, race/ethnicity, body mass index, smoking status, substance use, depression, anxiety, cardiovascular disease, diabetes, cerebrovascular disease, cognitive impairment, and number of outpatient visits in the year before baseline. HIV-specific models also included ART use, HIV RNA level, and CD4 count.

Results: The study included 11,568 PWH and 225,097 PWoH (for PWH: mean baseline age 48 years, 90% men, 48% White, 20% Hispanic, 17% Black, 7% Asian, 8% Other/unknown race/ethnicity; 93% on ART). During follow-up, 820 PWH and 19,058 of PWoH were diagnosed with sleep apnea. Sleep apnea incidence was significantly lower in PWH (vs. PWoH, adjusted incidence rate ratio [aIRR] = 0.90, 0.84-0.97). Notably, in analyses with PWH stratified by treatment status, lower incidence was observed in sub-optimally treated PWH (vs. PWoH, aIRR = 0.79, 0.70-0.89) but not in optimally treated PWH (vs. PWoH, aIRR = 0.97, 0.89-1.06). Among PWH, incidence was lower in PWH with lower CD4 (vs. PWH with CD4 ≥500 cells/µl: CD4 200-499, aIRR = 0.89, 0.75-1.05; CD4 <200, aIRR = 0.58, 0.35-0.99) or with higher viral load (vs. PWH with HIV RNA <200 copies/ml: HIV RNA ≥10,000, aIRR = 0.59, 0.29-1.19). The associations of general risk factors with sleep apnea were similar by HIV status (data not shown).

Conclusion: Sleep apnea risk is independent of HIV status. Lower overall incidence of sleep apnea among PWH may reflect under-diagnosis in PWH with untreated or uncontrolled HIV infection.

PWH		PWoH		Incidence rate ratio (95% CI)			
Cases	Incidence (per 1,000 person-years)	Cases	Incidence (per 1,000 person-years)	Unadjusted All PWH vs PWoH	Adjusted[a] All PWH vs PWoH	Adjusted[a] PWH with sub-optimally treated HIV[b] vs PWoH	Adjusted[a] PWH with optimally treated HIV[b] vs PWoH
820	17.2	19,058	19.6	0.88 (0.82-0.94)	0.90 (0.84-0.97)	0.79 (0.70-0.89)	0.97 (0.89-1.06)

[a] Adjusted for age, sex, race, body mass index, smoking, substance use disorders, depression, anxiety, cardiovascular disease, diabetes, cerebrovascular disease, cognitive impairment, and number of outpatient visits in the year before baseline.
[b] Optimal HIV treatment: on ART, with HIV RNA <200 copies/ml, and CD4 count ≥500 cells/µl.

826 Outcome of a Multidimensional Intervention for Insomnia in a Cohort of People Living With HIV

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Background: No studies specifically assessed interventions for improving sleep quality (SQ) in people with HIV (PWH). We introduced a multidimensional program for SQ in the routine management at our outpatient clinic and assessed its impact on PWH suffering from insomnia.

Methods: Interventional study in adult PWH with subthreshold (≥8), moderate (≥15), or severe (≥22) insomnia at the Insomnia Severity Index (ISI).Participants received sleep hygiene counseling and underwent tailored interventions as shown in the study flow. Based on compliance with prescribed interventions, participants were classified as fully, partial (at least 1 intervention attended when more than one prescribed), and non-adherent (FA-PA-NA). SQ, depression (PHQ9), and well-being were assessed at baseline and after 6 months from the beginning of any interventions. The impact of interventions on insomnia was assessed by mixed-effects models for repeated measures and paired tests for longitudinal data (Wilcoxon, Friedman).

Results: Among 730 PWH screened, 277 had altered ISI score, and 175 eventually participated (Fig1A). 65.7% were male, median age and CD4+ T cell count were 51 years and 650 cell/µL, 95.4% PWH had HIV-RNA<50 cp/mL. 94.8%, 91.0% and 2.8% of participants were referred to psychologist, psychiatrist, and neurologist, and 30.3% and 20.5% had indication to hypo-inducing drugs/antidepressants and psychotherapy/cognitive-behavioral therapy. Seventy-seven participants (44.0%) were NA, 16 (9.1%) PA, and 82 (46.8%) FA, with no relevant baseline differences detected in demographics and clinical parameters among them. Baseline ISI categories and their trajectory over time had an improvement in ISI score and in the distribution of insomnia categories; the highest effect size was in FA (Z=-5.8,p<0.001 vs -2.1,p=0.035 in PA, and -2.6,p=0.010 in NA). Perceived wellness and hours slept per night increased in all but more relevantly in FA (Z=4.3 and Z=4, both p<0.001). After adjusting by age, sex, and baseline ISI, PHQ9 and adherence to interventions were the only independent factors associated with ISI overtime: compared to NA, ISI decreased in FA (aβ -1.24 [-2.09; -0.38], p=0.005) and showed a trend of reduction in PA (aβ -0.71 [-2.21; 0.78], p=0.349).

Conclusion: A real-life outpatient multidimensional management of SQ based on sleep hygiene and individual-tailored interventions proved to be effective in improving SQ and overall wellness in PWH suffering from insomnia.
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827 Protease Activity in the Lung in HIV-Associated Obstructive Lung Disease (OLD)

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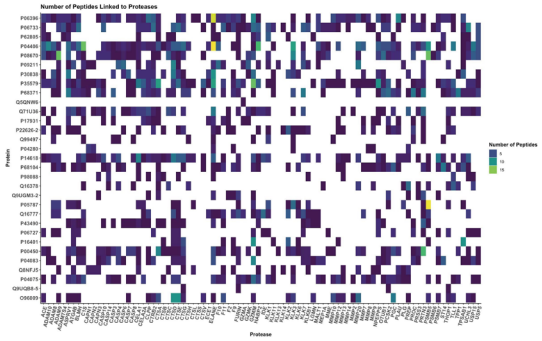
Background: Obstructive lung disease (OLD) is increasingly common among persons with HIV (PWH). The role of proteases in HIV associated OLD is unknown.

Methods: We performed mass spectrometry (MS) analysis on endogenous peptides and tandem mass tagging for protein analysis on bronchoalveolar lavage fluid (BALF) samples from PWH with OLD (n=25) and without OLD (n=26) matched on smoking status and ART. We combined untargeted MS and targeted Somascan aptamer-based proteomic approaches to quantify individual proteases and their correlation with lung function. We mapped endogenous peptides to their native proteins that were subjected to protease activity and the accompanying proteases responsible for the peptide cleavages. We used t-tests to compare average FEV1pp between samples in which each cleaved protein was detected versus absent. We accounted for multiple comparisons using a false discovery rate (FDR) adjustment. Using the MEROPS database, we identified candidate proteases for peptide generation by quantifying their affinity to binding sites via z-scores. We assigned proteases as likely responsible for cleavage by the z-scores for each peptide.

Results: We identified 27 proteases that correlated with lung function. Proteases associated with low FEV1pp included myeloblastin, kallikrein, cathepsins, metalloproteinases, caspase and neutrophil elastase. Proteases associated with high FEV1pp included carboxypeptidase M, prothrombin, urokinase and gastricin. MS analysis of endogenous peptides identified 1402 proteins that mapped to these peptides, 28 of which were observed in individuals with significantly (FDR <= 0.1) lower average FEV1pp. The top five protease targeted proteins included: alpha-enolase, gelsolin, histone H4, tubulin beta-4B chain and histone H2B type 2-F. Pathway analysis revealed these proteins were associated with gene regulation and included SUMOylation, methylate and demethylate histones, and nucleosomes. The top five proteases demonstrating activity included: neutrophil elastase, granzyme M, cathepsin D, proteinase 3, and cathepsin E (Fig. 1).

Conclusion: Like COPD unrelated to HIV, BALF protease abundance and activity is higher in individuals with HIV-associated OLD. We found that proteins involved in gene regulation are susceptible to these proteases as potential therapeutic targets.

Figure 1. Protease Activity Heatmap: The heatmap represents proteins mapped to endogenous peptides and the proteases assigned to their cleavage site.



828 Safety of Tenofovir Alafenamide in Individuals With a History of Proximal Renal Tubulopathy on TDF

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Background: Proximal renal tubulopathy (PRT, Fanconi syndrome) is an important but uncommon complication of tenofovir disoproxil fumarate (TDF). There are few long-term safety data for tenofovir alafenamide (TAF) in this population. We evaluated the safety of TAF in individuals who experienced treatment-limiting PRT while receiving TDF, and here report the five year outcomes.

Methods: Participants with HIV, a history of TDF-associated PRT, an estimated glomerular filtration rate >30 mL/min/1.73m^2, HIV RNA <200 copies/mL, and who were no longer receiving TDF and naïve to TAF were switched to a TAF-based antiretroviral therapy (ART) regimen and followed up annually for five years. The primary outcome was recurrent PRT. Secondary outcomes were changes in kidney biomarkers, alkaline phosphatase, and bone mineral density (BMD). Data were analysed using multi-level mixed effects linear regression models. The trial was registered under EudraCT 2016-003345-29.

Results: Of the 28 study participants (median age 55 [IQR 51, 60] years, 96% male, 86% white ethnicity) who agreed to continued follow up beyond week 96, 26 remained on TAF at year 5. Two participants (7%) discontinued TAF (treatment simplification, pre-emptive switch during critical care unit admission for COVID-19), 2 participants (7%) experienced transient HIV viraemia (200-1000 copies/mL) while all others remained virally suppressed; none experienced recurrent PRT during 134 person-years of follow up. Participants experienced small declines in BMD at the total hip; there were no significant changes in estimated glomerular filtration rate (eGFR-creatinine), albuminuria, proteinuria, fractional excretion of phosphate, alkaline phosphatase, or BMD at the lumbar spine.

Conclusion: In individuals with a history of PRT on TDF, cumulative exposure to TAF-based ART for five years was not associated with recurrent PRT or adverse effects on renal function or BMD. These data suggest that TAF is a safe treatment option for this vulnerable population.

Outcome	Baseline	Adjusted slope estimate (95%CI)*	P-value
eGFR-creatinine (mL/min/1.73m^2)	79 (74, 96)	-0.82 (-1.78, 0.13)	0.09
Albumin/creatinine ratio (mg/mmol)	1.3 (0.5, 2.6)	0.51 (-0.05, 1.10)	0.07
Protein/creatinine ratio (mg/mmol)	19.5 (13.2, 28.3)	-0.90 (-1.90, 0.11)	0.08
Fractional excretion of phosphate	0.79 (0.75, 0.85)	0.006 (-0.002, 0.014)	0.17
Alkaline phosphatase (IU/L)	68 (57, 87)	0.55 (-0.53, 1.63)	0.32
BMD Lumbar spine (g/cm^2)	1.129 (1.044, 1.312)	-0.002 (-0.006, 0.002)	0.20
BMD Total hip (g/cm^2)	0.984 (0.919, 1.066)	-0.003 (-0.004, -0.001)	0.02

Data are expressed as median (interquartile range); * results from multi-level mixed effects linear regression models (change per year)

eGFR=estimated glomerular filtration rate; BMD=bone mineral density

829 Urinary Exosome-Derived MicroRNAs as Biomarkers of TDF Renal Toxicity in People Living With HIV

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Background: The use of tenofovir disoproxil fumarate (TDF) may produce tubular proximal renal toxicity, but severity and outcome is controversial and specific biomarkers are still required. The aim of this study was to evaluate the expression profiles of urinary exosome-derived microRNA (miR) as biomarkers of TDF-associated renal toxicity.

Methods: In a longitudinal study, urine samples from 60 virologically suppressed people living with HIV (PWH) receiving TDF were collected. In all cases, different tubular parameters and urinary low-weight molecular proteins (LWMP, beta-2-microglobulin, retinol-binding protein) were compared according to mRNA analyzed. Tubular dysfunction was defined as the presence of at least 2 tubular abnormalities. Urine exosomes were precipitated and a pre-selected panel of miRs were isolated and quantified using miR-specific real-time qPCR.

Results: At inclusion, median time on TDF was 65 months (38-82.6), and mean eGFR was 90.9 ml/min/1.73m^2 (50.1-122; only 6% of patients with chronic kidney disease CKD diagnosis). A profile of 7 miRs were evaluated. The levels of miR-let-7d, miR-203, and miR-29a were significantly upregulated (p=0.018, and p=0.014) according to time on TDF, while miR-127 was negatively correlated (p=0.033). Moreover, miR-Let-7-d miR-107, and miR-23a positively correlated with tubular and biomarkers parameters, such as fractional excretion of phosphate, glycosuria, albumin/creatinine, β2-microglobuline/creatinine, RBP/creatinine, and protein/creatinine ratios. Thus, miR-let-7d, miR-107, and miR-423 were found to have increased expression in patients with tubular dysfunction and miR-15b was upregulated in urinary exosomes of patients with decreased eGFR (p=0.028). An increased expression of miR-let-7d predict tubular dysfunction (AUC 0.733), and miR-23a identified those with subsequent eGFR decrease (AUC 0.633), respectively, after a median follow up of 9 months (IQR, 4-13).

Conclusion: This is the first study showing the usefulness of micro-RNA as biomarkers of antiretroviral drug-associated toxicity. Specifically, the expression profile of miRs was significantly altered in urinary exosomes according to time on TDF, changes in tubular parameters and presence of tubular dysfunction, and were associated with further tubular dysfunction and eGFR decrease. Thus, this study confirms that exosome-derived miRs in urine could be used as non-invasive biomarkers for the detection of renal toxicity associated with TDF.

830 Biomarkers Influence Kidney Function Estimates More So Than Race Among Persons With HIV

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Background: Kidney function estimation equations were revised in 2021 to exclude race, refuting earlier assumptions that creatinine (Cr), a by-product of muscle metabolism, consistently differs by race. Cystatin C (CysC) is a biomarker produced by nucleated cells and can be used in conjunction with creatinine to estimate kidney function. We sought to understand the effects of different estimating equations and biomarkers on Chronic Kidney Disease (CKD) stage estimates among persons with HIV (PWH), for whom CKD is an important comorbidity.

Methods: CysC and Cr was measured in this cross-sectional single site U.S. clinic-based study from 2014-2016. The 2009 CKD-EPI-Cr and 2012 CKD-EPI-Cr-CysC (which include race), and 2021 CKD-EPI-Cr and 2021 CKD-EPI-Cr-CysC (which exclude race) estimating equations were applied to categorize CKD stage, and agreement was assessed using differences of proportions. Regression analyses evaluated factors associated with CKD stage, and the Breslow-Day test evaluated whether race served as an effect modifier.

Results: Among 306 PWH, the median age was 48.2 years, 86 (28.1%) were female,185 (60.5%) were Black,91 (29.7%) Caucasian,13 (4.3%) Latinx, and 46 (15%) had HCV co-infection. The median CD4+ count was 659/mm^3, 97.7% were on ART, and 74.5% had HIV VL < 20 c/mL. Using the 2009 and 2012 equations (including race), more individuals were categorized as having normal kidney function (Stage I) with inclusion of CysC than Cr alone (73.2% vs 54.6%, p<0.00001); fewer individuals were classified in CKD stages III-V using CysC than Cr alone, but this did not meet statistical significance (8.2% vs 11.8%, p=0.14). Using 2021 equations (excluding race) a larger proportion were classified as normal kidney function with inclusion of CysC than Cr alone (73.8% vs 49.3%, p=0. 0.00001); fewer were categorized as CKD III-V with inclusion of CysC than Cr alone (8.1% vs 13.1%, p=0.026). Multivariate linear regression identified age, the interaction between tobacco use and absolute CD4+ count, and the interaction between HCV co-infection and nadir CD4+ count as factors associated with kidney function. Race was not an effect modifier based on our analyses.

Conclusion: Among PWH, CysC shifted estimates of kidney function towards normal and resulted in shifts in kidney function categorization much more so than the small race effect. As some antiretrovirals raise creatinine without affecting renal function, CysC remains an important but under-utilized biomarker to confirm diminished kidney function.

Table 1. Distribution of kidney function estimates based on estimating equations

Stage	Kidney Function Classification	2009 CKD-EPI Creatinine	2012 CKD-EPI Creatinine-Cystatin C	2021 CKD-EPI Creatinine	2021 CKD-EPI Creatinine-Cystatin C
1	Normal/High	167	224	151	226
2	Mild	103	56	113	55
3a	Moderate	19	11	24	10
3b	Moderate	9	7	8	7
4	Severe	0	1	2	1
5	End-Stage	8	7	8	7

Note: The 2021 CKD-EPI creatinine equation is the current clinical standard

831 Markers of Macrophage Activation and Kidney Function in People With and Without HIV

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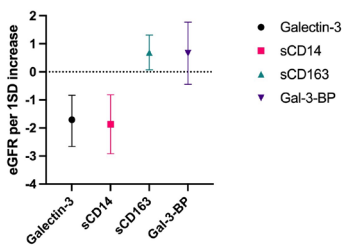
Background: HIV infects and activates macrophages, which produce important mediators of inflammation that drive age-related comorbidities. Soluble macrophage activation markers are higher in people with HIV (PWH), even with viral suppression, and have been associated with subclinical cardiovascular disease. Given the close relationship between cardiovascular and kidney disease, we hypothesized these markers would be associated with lower kidney function among PWH.

Methods: We performed a cross-sectional study nested within two prospective U.S. multicenter cohorts each of persons with and without HIV; the Women's Interagency HIV Study (WIHS) and for men the Multicenter AIDS Cohort Study (MACS). Serum levels of the macrophage activation markers soluble (s)CD163, sCD14, galectin-3 (Gal-3) and Gal-3 binding protein (Gal-3BP) were measured in 786 (73% PWH) women and 498 (65% PWH) men. Markers were log and Z-score transformed. Multivariable linear regression determined associations of these markers with estimated glomerular filtration rate (eGFR), adjusting for potential confounders including study site, sociodemographics, diabetes, hypertension, hepatitis C, HIV serostatus and tenofovir disoproxil fumarate use.

Results: Among 1284 participants, 786 (61%) were women, 902 (70%) were PWH, of whom 486 (54%) were virally suppressed (<50 cp/mL). Median age was lower among women compared to men (40 vs 49 years). sCD14, sCD163 and Gal-3BP levels were significantly higher among PWH versus without HIV ($p<0.05$). Median eGFR was higher among PWH versus without HIV (95.3 vs 93.6 mL/min in women and 92.7 vs 85.8 mL/min in men). After confounder adjustment, Gal-3 and sCD14 levels were negatively associated with eGFR. Each standard deviation (SD) increase in Gal-3 was associated with a 1.71 mL/min lower GFR (95% confidence interval -2.66, -0.84; $p=0.0004$) and each SD increase in sCD14 was associated with a 1.87 mL/min lower GFR (-2.92, -0.82; $p=0.0005$). These associations were more pronounced among PWH (p for interaction 0.08 and 0.06, respectively). A weak positive association existed between sCD163, and eGFR and no association was observed between Gal-3BP and eGFR.

Conclusion: The macrophage markers Gal-3 and sCD14 may have a role in subclinical kidney injury among PWH. Future work will examine macrophage associations with longitudinal kidney outcomes to identify whether they may play a causative role and/or have predictive value for kidney disease risk.



832 Anti-α4β7 Antibody Facilitates Improved Renal Function During SIV Infection in Macaques

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Background: Combination antiretroviral therapy (cART) reduces the incidence of HIV-associated nephropathy (HIVAN), but people living with HIV (PLWH) remain at high risk for later developing chronic kidney disease (CKD), with a poorly defined etiology. HIV acquisition is associated with reduced plasma all-trans-retinoic acid (atRA) and increased pro-fibrotic galectin (Gal)-3. Clinical trials investigating atRA receptor agonists and Gal-3 antagonists to ameliorate HIVAN/CKD were completed but discontinued after phase 2, necessitating new strategies to restore kidney function. FDA-approved vedolizumab (anti-α4β7) is well-tolerated for inflammatory bowel diseases. Here, we query whether anti-α4β7 can improve renal function in a rhesus macaque (RM) infection model.

Methods: Nine RMs were CD8-depleted and inoculated with SIVmac251. Daily cART was begun at week two, along with infusions (anti-α4β7 mAb: n=5; IgG controls: n=4) every three weeks until week 23. cART was discontinued (ATI) at week 14. Longitudinal plasma measurements were performed for serum chemistry, retinoids determined by HPLC-UV, and Gal-3 by Luminex. atRA metabolism and podocyte differentiation gene expression were determined by qPCR in kidney samples collected at necropsy and compared to uninfected RMs (n=4).

Results: Anti-α4β7 treated RMs had lower measures of urea nitrogen (BUN) and BUN:Creatinine ratio than IgG RMs following therapy and ATI ($P=0.0159$; $P=0.0250$), despite comparable measures at baseline. Acute infection was associated with reduced (~35% less) atRA in both groups ($P=0.0046$; $P=0.0014$). While atRA remained low in IgG RMs, it increased in anti-α4β7 RMs during cART ($P=0.0012$) and ATI ($P=0.0004$), resulting in differences between groups ($P=0.0101$; $P=0.037$). atRA precursor retinyl ester (RE) was higher in IgG RMs ($P=0.0139$) than anti-α4β7 RMs after ATI. RE was positively correlated with BUN:Creatinine ($P=0.0152$). Anti-α4β7 RMs had greater atRA synthesis (ALDH1A1, ALDH1A3) while IgG RMs had higher atRA catabolism (CYP26A1) gene expression than uninfected RMs. IgG (but not anti-α4β7) RMs also had lower SYNPO and RARRES expression. IgG RMs had lower Gal-3 than anti-α4β7 RMs ($P=0.004$) after ATI. Gal-3 levels associated negatively with SYNPO expression ($P=0.0299$) and positively with RE ($P=0.0275$) and BUN:Creatinine ($P=0.044$).

Conclusion: Our data provide a rationale for repurposing vedolizumab for HIVAN/CKD to restore retinoid signaling, podocyte differentiation, and glomerular filtration thereby improving quality of life in PLWH.

833 Depressive Symptom Burden Predicts Diabetes Mellitus Control Among People Living With HIV

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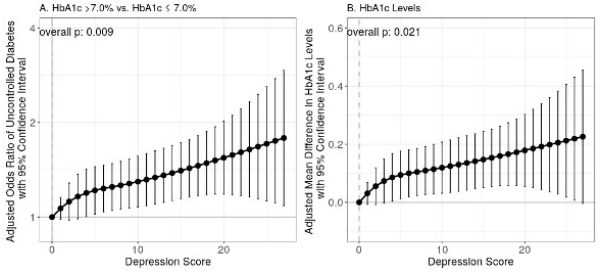
Background: Depression is common among people with HIV (PWH) and increases the risk of non-communicable diseases such as diabetes mellitus (DM). Depressive symptoms are associated with poorer medication adherence and adverse HIV outcomes, but less is known about how depression affects DM outcomes. We evaluated the association between depressive symptoms and DM control among PWH and DM.

Methods: We examined PWH and DM (defined by HbA1c ≥6.5% or receipt of DM specific medication, or DM related medication and DM diagnosis) cared for at 8 US clinical sites in the CFAR Network of Integrated Clinical Systems (CNICS) cohort from 2005-2023 and who had repeated measures of patient-reported depressive symptoms using the Patient Health Questionnaire (PHQ9),. We observed PWH from the date of first HbA1c with a PHQ9 score within 15 months prior and assessed diabetes outcomes using categorical (≤/>7.0%) and continuous HbA1c values. We examined the association between HbA1c and recent depressive symptoms (PHQ9 measured within the 15 months prior to or at the date of HbA1c) using multilevel longitudinal models whereby PWH could

contribute ≥1 HbA1c value. Continuous PHQ9 score was included in models using natural splines. Analyses were adjusted for sex at birth, race/ethnicity, HIV risk factor, CNICS site, and time-updated age, time since DM diagnosis, CD4 count, HIV RNA, year of HbA1c measurement, BMI, substance use, high-risk alcohol use, and DM medication use.

Results: Among 2040 PWH with DM, baseline median age was 54 years (IQR:47-59), 75% were male, 50% Black, 44% white, 14% Hispanic, and 22% had a PHQ9 ≥10 (severe depressive symptoms). Median baseline HbA1c was 6.5 (IQR:5.9-7.7), median time living with DM was 1.25 years, and 57% were on diabetes medication at baseline. Median follow-up time was 2.9 years (IQR:0.9-5.9) during which PWH contributed a median of 5 HbA1c measurements (IQR:3-10). Median time between HbA1c and PHQ9 measurements was 105 days (IQR:10-213). In multivariable analysis, we found a dose-dependent relationship between the PHQ9 score and an increased odds of HbA1c >7.0% (Figure A, p=0.009). Similarly, a higher burden of depressive symptoms was associated with higher HbA1c measures when assessed as a continuous outcome (Figure B, p=0.021).

Conclusion: Higher depression symptom burden was associated with poor DM control among PWH in this multisite, US cohort. Diagnosis and management of depression remains critical for long-term HIV and DM outcomes.



834 Effectiveness of Electronic Screening for Substance Use, Depression, and Anxiety in HIV Primary Care

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Background: Substance use (SU), depression and anxiety are common in persons with HIV (PWH) yet are often not diagnosed or treated.

Methods: The Promoting Access to Care Engagement (PACE) study is a stepped wedge trial to evaluate the effectiveness of electronic SU and mental health (MH) screening to increase treatment among PWH. PACE was conducted from October 2018-July 2020 in 3 large HIV primary care clinics in Kaiser Permanente Northern California, serving 5115 PWH. The intervention involved an electronic survey (via patient portal or clinic tablets) consisting of: Tobacco, Alcohol, Prescription medication and other Substance use (TAPS); Patient Health Questionnaire-9 (PHQ-9); and Generalized Anxiety Disorder-2 (GAD-2), with results visible in the electronic health record. Each clinic had a 2-year pre-interventional comparison period. The study included PWH with incident SU (first of: SU clinical diagnoses or TAPS >1) or incident MH (first of: depression/anxiety clinical diagnosis, PHQ-9 ≥10, or GAD-2 ≥3) during the pre-/post-interventional periods. The post-interventional period was stratified by how SU or MH first identified (clinically or study survey). The outcome was % treated by 6 months, defined by: medications (antidepressant, antianxiety, SU), specialty care, or behavioral health specialist visits. We compared % treated in 3 groups: (1) pre-intervention (ref), or post-intervention with SU or MH first identified (2) clinically or (3) by study survey. Adjusted hazard ratios (HR) from Cox models (variables in Table footnote).

Results: 1,988 PWH had evidence of SU problems: N=1285 pre-intervention; N=703 post-intervention (49% by survey). As shown in the Table, % treated was similar comparing PWH in pre- and post-intervention periods identified clinically (33% vs. 35%), but lower in PWH identified by survey in post-intervention period (26%). 2119 PWH had evidence of MH problems: N=1099 pre-intervention; N=1020 post-intervention (73% by survey). % treated was lower, compared with pre-intervention (83%), for PWH in post-intervention period identified clinically (73%), and by survey (65%). Results were similar in adjusted model (Table). Excluding follow-up during COVID-19 (after Mar 2020) did not impact findings (data not shown).

Conclusion: Systematic screening using validated survey tools in HIV primary care identified 49% SU and 73% MH concerns previously unrecognized by providers. The reduced % treated for these PWH suggest systematic screening may identify lower-severity groups overall.

Table. Treatment for PWH with evidence of substance use or mental health problems, pre- and post-intervention

	Evidence of substance use problems			Evidence of mental health problems		
	N	% treated*	HR (95% CI)**	N	% treated*	HR (95% CI)**
Pre-intervention	1285	33%	reference	1099	83%	reference
Post-intervention (Clinically identified)	356	35%	1.19 (0.93, 1.52)	274	73%	0.79 (0.68, 0.92)
Post-intervention (Study survey)	347	26%	0.79 (0.68, 0.92)	746	65%	0.59 (0.51, 0.69)

* % treated by 6 months (Kaplan Meier)
** Cox models adjusted for age, sex, race/ethnicity, insurance type, neighborhood deprivation index, smoking, Charlson score, HIV RNA, CD4. Models stratified by clinic, summarized by meta-analysis.

835 Group Therapy Reduces Depression Among People Newly-Enrolled in HIV Care in Kampala, Uganda

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Background: Depression in people living with HIV (PWH) is associated with reduced medication adherence, viral suppression, and retention-in-care. In low-resourced settings, depression interventions are needed for PWH to improve HIV outcomes.

Methods: This study was conducted at a large, public HIV clinic. We enrolled PWH who started HIV medications within the last 3 months and had depression. They were randomized 1:1 into an 8-week group therapy intervention or enhanced usual care. The group therapy was held once a week, facilitated by adherence counselors at the subjects' HIV clinic in groups of 6-10 individuals divided by biological sex. Depression was measured with the Patient Health Questionnaire, PHQ, with mild and moderate depression cutoffs at 5 and 10. Basic statistics were calculated. Groups were compared using the t-test and chi-square.

Results: Between February 2021 and March 2023, we enrolled 135 PWH into our study. The average age was 32 years; The group was 64% female. Of 46 PWH with data on chart review, the average CD4 cells/uL count was 369. Baseline PHQ-9 were similar between the intervention and control groups at median (IQR) 8(7-12) and 8(7-11), (p=0.36). Overall, 37% of those in the group therapy intervention group and 38% in the control group had a PHQ-9 score of >10 signifying moderate to severe depression. Of those enrolled in group therapy, 98% completed all 8 sessions. Of the 40 completing a satisfaction survey, 93% felt group therapy was acceptable. At three months, fewer subjects in group therapy had depression (PHQ-9 score median (IQR) 1.5 (1-3) versus 4 (3-5), p <0.001; PHQ-9 score of >5, 11% versus 34%, p= 0.005). By three months, only 1 of the 109 subjects overall had a PHQ-9 score of >10. By six months, the PHQ-9 had normalized in most with median (IQR) 1(0-2) from intervention group versus 2 (0-3) from control group, (p= 0.09). Only 2% of those in the group therapy group and 7% in the control had mild depression (p=0.35). No subjects had a PHQ-9 score of >10. There were two Covid-19 lockdowns during this study, which impacted follow-up rates as people moved to the countryside and back to different parts of the city.

Conclusion: An 8-week group therapy depression intervention was successful in relieving depression in PWH newly enrolled in clinic by three months compared to control. By 6-month follow-up, depression had resolved in nearly all subjects. Group therapy can be adapted to different settings and is effective in improving mood in PWH.

Figure 1. Depression Outcomes between People with HIV and Depression in a Group Therapy Intervention Group and a Control Group with Enhanced Usual Care.

	N	Intervention Group	N	Depressed Controls	P value
Baseline PHQ-9 Median (Interquartile Range)	70	8 (7-12)	65	8 (7-11)	0.36*
Mild Depression or More PHQ-9 5+ (N, %)	70	67 (96%)	65	64 (98%)	0.35**
Moderate to Severe Depression PHQ-9 10+ (N, %)	70	26 (37%)	65	25 (38%)	0.87**
PHQ-9 at Three Months Median (Interquartile Range)	47	1.5 (1-3)	62	4 (3-5)	***<0.001****
Mild Depression or More PHQ-9 5+ (N, %)	47	5 (11%)	62	21 (34%)	***0.005****
PHQ-9 Six Months Median (Interquartile Range)	42	1 (0-2)	60	2 (0-3)	0.09*
Mild Depression or More PHQ-9 5+ (N, %)	42	1 (2%)	60	4 (7%)	0.35**

*Calculated with T test and comparing the depressed groups, ** Chi Square

836 Biomarkers of Microbial Translocation and Inflammation Associated With Frailty Among People With HIV

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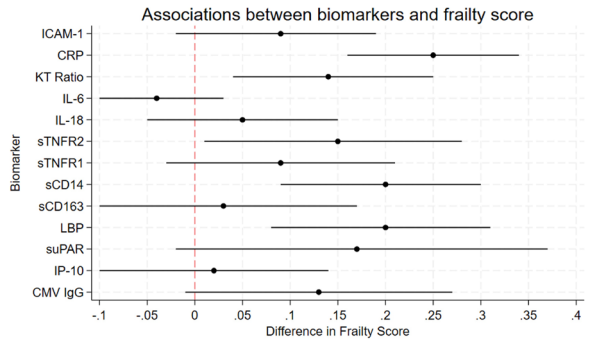
Background: Frailty is observed at high rates among people with HIV (PWH) and occurs at younger ages compared to the general population. This higher burden of frailty is often attributed to chronic inflammation and subsequent immune exhaustion, which is increasingly being targeted as a means for mitigating frailty progression and impacts. We assessed how a panel of biomarkers of inflammation, measured in a case cohort sub-study of PWH in clinical care, is associated with frailty among PWH.

Methods: A panel of 13 plasma inflammatory biomarkers was collected at a single timepoint from a subset of virally suppressed PWH in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort between 2010-2018. CNICS also collects and harmonizes data on demographic information, laboratory values, diagnoses, medications, and patient reported outcomes (PROs). Frailty over time was measured with a validated phenotype of 4 components (inactivity, immobility, fatigue, and unintentional weight loss) from the PRO assessment from biomarker date through July 2022. We considered frailty scores ranging from 0-4, with one point per endorsed component. We used linear mixed models to estimate longitudinal associations between standard deviation-scaled biomarkers and frailty score, with adjustment for demographic characteristics, clinical factors and comorbidities, and coinfections.

Results: Among 273 PWH, most were male (91%), average age at baseline was 45 years, 45% were non-Hispanic White while 35% were non-Hispanic Black, and average follow-up time was 6.2 years. Several inflammatory biomarkers were associated with higher frailty scores, including those linked to microbial translocation (soluble CD14 [sCD14], lipopolysaccharide binding protein [LBP], kynurenine-to-tryptophan [KT] ratio) and systemic inflammation (C-reactive protein [CRP] and soluble tumor necrosis factor receptor 2 [sTNFR2]) (Figure 1). For example, a standard deviation higher KT ratio was associated with a 0.14-point higher frailty score (95%CI: 0.04-0.25), CRP was associated with a 0.25-point higher frailty score (95%CI: 0.16-0.34) and sCD14 was associated with a 0.20-point higher frailty score (95%CI: 0.09-0.30) over follow-up.

Conclusion: Higher levels of biomarkers linked to microbial translocation and systemic inflammation are associated with higher frailty scores over time in a cohort of virally suppressed PWH, highlighting these pathways as potential interventional targets for preventing or reducing frailty in treated PWH.

Figure 1. Forest plot for associations between a standard deviation difference in biomarker level and frailty score adjusted for demographic characteristics, clinical factors, and coinfections. Higher CRP, KT ratio, sTNFR2, sCD14, and LBP levels were associated with higher frailty scores over follow-up.



837 Excess Inflammation Associated With AIDS and Non-AIDS Complications in Adults on ART

Kanal Singh[1], Shweta Sharma[2], Birgit Grund[2], Alejandro Arenas-Pinto[3], Nnakelu Eriobu[4], Edward Gardner[5], Win Min Han[6], Jose Hidalgo[7], Jennifer Hoy[8], Jakob Malin[9], Daniel Murray[10], Siegfried Schwarze[11], Alan Winston[12], Jason Baker[13], for the INSIGHT START Study Group

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Background: In START, immediate ART initiation lowered inflammation and risk for clinical events. It is unclear to what degree prolonged inflammation contributes to clinical risk after ART is initiated. We quantified the excess inflammation associated with ART deferral in START, and investigated its influence on clinical event risk during viral suppression.

Methods: The START trial (2009-2021) randomized participants (pts) with CD4>500 cells/μL 1:1 to immediate or deferred (when CD4 <350 cells/μL) ART. In 2015, trial results were unblinded and all pts were advised to initiate ART. In a substudy, plasma IL-6 and D-dimer (biomarkers) levels were measured at baseline, month 8 and annually. Longitudinal averages of biomarker levels from study entry through 2015 were compared between treatment arms using rank-sum tests. Kaplan-Meier curves for time to a composite outcome (AIDS, serious non-AIDS [SNA], or death) that occurred between 2016-2021 were estimated for the upper quartile (Q4) versus the lower 3 quartiles (Q1-Q3) of average longitudinal biomarkers through 2015. Associations between average biomarker levels through 2015 and the composite were estimated using Cox models adjusted for treatment arm.

Results: The analysis included 2114 pts. Through 2015 (median of 3.2 yrs), the deferred compared to the immediate arm had higher longitudinal biomarker levels: median IL-6 1.7 vs 1.5 pg/mL; D-dimer, 0.33 vs 0.27 mg/mL (both p<0.001). By 01Jan2016, 87% of pts in the deferred and 99% in the immediate arm started ART; median time to ART start in the deferred arm was 2.5 years. There were 124 AIDS, SNA, or death events from 2016-2021; 0.92 and 1.27 per 100PY in immediate and deferred arms, respectively; HR(imm/def)=0.7 (95% CI 0.5-1.0; p=0.07). Higher longitudinal IL-6 & D-dimer levels through 2015 were associated with higher risk of the composite during 2016-2021 in both arms (Figure); HR(Q4 vs Q1-Q3)=2.3(95% CI 1.6-3.2) for IL-6 and 2.1(95% CI 1.5-3.0) for D-dimer (both p<0.001), adjusting for treatment arm.

Conclusion: In START, higher average levels of inflammation over several years were associated with subsequent higher risk of AIDS, SNA or death during 6 years on continuous ART. ART deferral resulted in higher levels of inflammation, which may have contributed to higher clinical event rates after pts were switched to continuous ART. Results should be interpreted with caution, but emphasize the need to diagnose HIV early to facilitate early ART initiation.

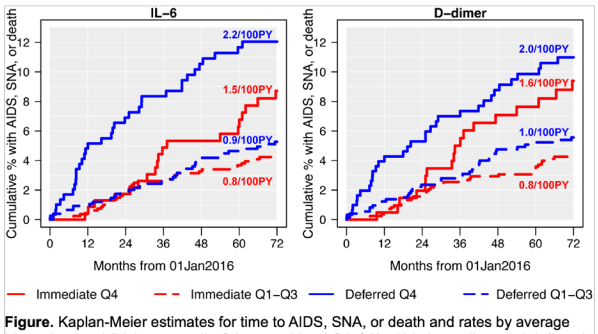

Figure. Kaplan-Meier estimates for time to AIDS, SNA, or death and rates by average biomarker level (highest quartile Q4 vs combined Q1-Q3) within immediate and deferred ART groups.

838 Optimizing Long-Term Exercise Benefits for Older Adults With HIV: The MOVING Study

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Background: We have previously demonstrated the efficiency of a 12-week multicomponent exercise program (MEP) in reversing frailty, improving physical performance, and preserving muscle mass in older adults with HIV (OAWH). The objective of this study was to analyze the efficacy of this MEP in the long term, after 1 year.
Methods: Sedentary adults 50 or over with and without HIV were included in a prospective longitudinal study with 12-, and 48-week follow-up. The intervention was a MEP performed in real-life conditions. Dependent variables were frailty (frailty phenotype), physical function (gait speed, SPPB), physical performance, and anxiety and depression (HADS and Geriatric Depression Scale Short-Form). Pre- and postintervention measurements were analyzed using McNemar's test for categorical variables and the Wilcoxon signed-rank test for quantitative variables.
Results: Sixty participants were included: 40 OAWH and 20 older adults without HIV. Median age was 56.5 years. 23.3% were women. The prevalence of frailty was 6.6% with no frail HIV-negative participants. At week 48, 32 participants continued, 21 OAWH and 11 older adults without HIV. The percentage of robustness increased after the MEP from 25.81% to 77.42% (RR 3 [95% CI, 1.7 – 5.2]), the percentage of prefrailty decreased from 64.52% to 22.58% and there were no frail patients at week 48. All participants improved [48-week vs basal] their SPPB score [12 (11-12) vs 11 (10.5-12), p =0.0001], and upper extremity strength [17 (15-20) vs 13 (12-15), p = 0.0001]. Anxiety [6.5 (4.5-11.5) vs 6 (3-10), p = 0.001] was improved only in the OAWH. In participants with an adherence ≥ 50%, the following were significantly improved [48-week vs basal]: gait speed (m/s) [1.29 (1.51-1.12) vs (1.33-1.02), p =0.02] without differences by HIV status, and aerobic endurance [74 (55-94) vs 61 (52-71), p =0.001] only in the OAWH. In participants with an adherence ≥ 50%, a significant improvement 48-week vs 12-week was found in gait speed [1.29 (1.51-1.12) vs 1.21 (1.39-1.07), p =0.03], upper limb strength [18 (16-21) vs 16.5 (15-19), p =0.003], aerobic endurance [74 (55-94) vs 64 (59-83), p =0.04], and agility [5.77 (5.2-6.7) vs 6.38 (5.7-6.8), p =0.04].
Conclusion: A 48-week MEP improves robustness, physical function, physical performance in older adults independently of HIV status, and anxiety only in OAWH. Continuing the MEP after the first 12 weeks for up to one year produces an even greater improvement in physical function and physical performance.

839 Clonal Hematopoiesis and HIV Infection Are Associated With Geriatric Outcomes: The ARCHIVE Study

Win Min Han[1], Mark Bloch[2], David A. Baker[3], Norman Roth[4], Jennifer F. Hoy[5], Ian Woolley[6], Robert Finlayson[7], Jane Costello[1], Mark Dawson[8], Sarah-Jane Dawson[8], Mark Polizzotto[9], Kathy Petoumenos[1], Paul Yeh[6], Nila J. Dharan[1], for the ARCHIVE Study Group
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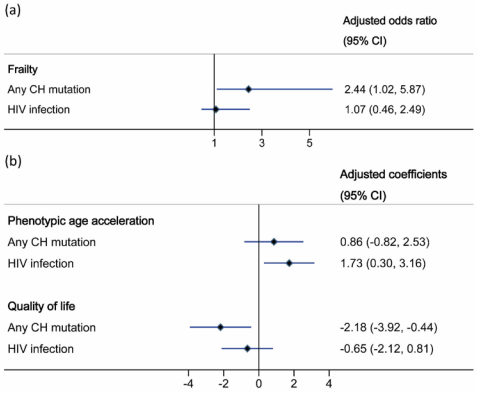
Background: People living with HIV have accelerated biological aging and a higher prevalence of aging-related comorbidities and geriatric outcomes. Clonal hematopoiesis (CH), an aging-related cellular phenomenon that is linked to adverse clinical outcomes, is increased in people living with HIV. Here we evaluated geriatric outcomes in older adults with and without HIV to determine whether HIV or CH is associated with geriatric outcomes.
Methods: Participants were enrolled from the ARCHIVE study, a prospective observational cohort of adults with and without HIV >55 years, and evaluated for CH and geriatric outcomes. Frailty was measured by the FRAIL questionnaire, which categorizes individuals as frail, pre-frail and robust. Phenotypic age acceleration (PAA) was defined as the difference between phenotypic age, measured by nine biochemical and blood cell characteristics, and chronological age. Quality of life (QoL) was measured by the CASP-19 scale. Descriptive statistics compared baseline characteristics across HIV status. Multivariable logistic and linear regression was used to evaluate for associations between HIV and CH, and geriatric outcomes.
Results: Of 344 participants, 175 had HIV and 169 did not. The median (interquartile range; IQR) age was 67 (62,72) years, 97% identified as male, 61% had a body mass index>25, 41% reported ever smoking, and 54% reported being diagnosed with cardiovascular disease. Overall, 23% had at least one CH mutation (27% of those with HIV and 18% of those without HIV; p=0.045), 7% were frail, the median (IQR) PAA was 0.6 years (-2.5,5.0), and the median (IQR) QoL score was 36 (29,39) out of 57. Participants with HIV had a median (IQR) duration of HIV of 27 (18,33) years and a median (IQR) CD4 nadir of 246 (143,372) cells/mm^3; all but one participant had a suppressed viral load. In adjusted regression analyses (Figure), HIV infection was independently associated with PAA (coefficients 1.73, 95% confidence interval [CI] 0.3-3.16, p=0.02) and CH was independently associated with reduced QoL (coefficients -2.18, CI -3.92, -0.44, p=0.01) and being frail (vs. pre-frail/robust; odds ratio 2.36, CI 1.01-5.63, p=0.049).
Conclusion: In the ARCHIVE cohort, HIV was associated with PAA and CH, and CH was associated with frailty and reduced QoL. While our results warrant further exploration, they suggest that CH may be used as a biomarker for geriatric outcomes that may prioritize individuals for interventions designed to reduce geriatric outcomes and promote healthy aging.



840 Frailty and Health-Related Quality of Life in an Aging Cohort of People With HIV, 2012-2022

Lydia N. Drumright[1], Bridget Whitney[1], Crystal Chapman Lambert[2], Amanda Willig[2], Robin M. Nance[1], Stephanie A. Ruderman[1], Sonia Napravnik[3], Katerina Christopoulos[4], Edward Cachay[5], Lara Haidar[6], Jimmy Ma[1], Mari Kitahata[1], Allison R. Webel[1], Heidi M. Crane[1]
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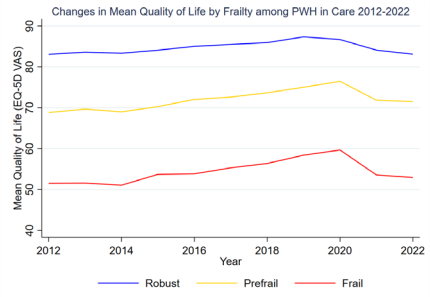
Background: Due to advancements in antiretroviral therapy, people with HIV (PWH) are living near normal lifespans, however PWH age more rapidly and experience frailty at an earlier age than the general population. We examined the impact of frailty on quality of life (QoL) over time among PWH.
Methods: We assessed changes in QoL and frailty from 2012-2022 among PWH in care at 6 CFAR Network of Integrated Clinical Systems (CNICS) sites. Assessments of QoL, using the EQ-5D visual analog scale, and frailty, using a validated, modified frailty phenotype based on 4 Fried frailty components, were collected at routine clinical visits every ~3-6 months. Linear mixed models were used to assess individual level associations between frailty and QoL over time. Linear regression of mean QoL by frailty category and year was used to assess population level changes.
Results: 12,397 PWH with 38,830 frailty assessments were included. At initial frailty assessment, mean age was 45 years, 13% were female, 52% reported non-White race/ethnicity, 41% were robust (i.e., were not frail/prefrail), 45% prefrail, 14% frail, and mean QoL was 73. PWH who were prefrail and frail reported a 10% (95% CI: -10.4, -9.6, p<0.001) and 24% (95% CI: -24.4, -23.0, p<0.001) lower QoL respectively than those who were robust after controlling for age, sex, race/ethnicity, and COVID-era (i.e., March 2020 onward). Overall, we observed an annual increase in QoL of 0.4% until 2020, then a 2% decline during the COVID-era. Similar trends were observed for population level changes in QoL, with prefrail and frail PWH having a lower mean QoL, 13% (95%CI: -14.0,-11.5; p<0.001) and 31% (95% CI: -32.0,-29.0; p<0.001) respectively compared with robust PWH (Figure).
Conclusion: In our study, PWH who were frail and prefrail reported ~30% and ~10% lower QoL respectively than those who were not frail. While QoL among PWH in care in the United States appears to be slowly increasing over time, frailty can have a significant impact on QoL. Minimizing and preventing frailty and addressing comorbidities that contribute to frailty could increase QoL among PWH.



841 Dasatinib + Quercetin Drugs Reduced Senescent-Associated Secretory Phenotype (SASP) in PLWH PBMCs

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Hospital Clinic of Barcelona, Barcelona, Spain

Background: Despite ART virological suppression, PLWH have increased inflammation and age-linked diseases. Research in cellular aging has identified key biomarkers that define senescent cells (SC) which can be eliminated by senolytic drugs. These biomarkers include SA-βGal and mediators such as MCP-1, IL-8 or IL-6 that are principal components of the Senescent Associated Secretory Phenotype (SASP). We previously found that HIV-1 infection increased SC biomarkers such as SA-βGal, Bcl-II and IL-6 in CD4+ T cells. The role of HIV-1 in promoting cellular senescence by SASP and soluble immune checkpoints is not fully understood and could be key to develop new treatments for HIV-associated aging comorbidities. We aim to determine SASP mediators, SC linked soluble immune checkpoints (IC) and to know whether Dasatinib plus Quercetin (D+Q) senolytic drugs can influence SASP levels.
Methods: PLWH from acute, chronic and advanced infection cohorts before and after a year on ART and a HIV-negative control group (NC) matched by sex and age were included (n=12). D+Q senolytic drugs were added to an ex vivo 3-day culture of PBMC with IL-2 from those cohorts. A set of 34-top SASP and 6 IC mediators were quantified by a customized Luminex in plasma and cell culture supernatants. Unpaired or paired non-parametric T-test and Pearson correlation were performed.
Results: SASP (IL-6, IL-8, IL-10, RANTES, GRO-α, TNF-RI/RII, CD30, CD30L, VEGF-A) and IC (PD-1, PD-L1, PD-L2, LAG-3, CTLA-4) mediator levels were higher in advanced and chronic patients than in NC ($p<0.05$). These mediators were only reduced to NC levels by a year of ART in the acute cohort. IL-6 and SA-βGal in CD4+ T cells levels positively correlated with SASP mediators and IC such as IL-10, MIP-1α, PD-L1, CTLA-4 and LAG-3 ($p<0.05$). D+Q ex vivo treatment decreased SASP mediators such as MCP-1, IL-8 (Figure), IL-6, IL-10, MIP-1α, IL1-RA, IL-1β, IL-1α, suPAR, PAI-I, tPA, MMP-1, MMP-12, HGF, Leptin, PIGF-1, MCP-4, GM-CSF, TNF-RI, Mip-3α, IL-7 or IL-15 ($p<0.05$) in non-ART treated PLWH. D+Q drugs in ART PLWH also decreased the above mentioned SASP mediators including MCP-1 and IL-8 (Figure
Conclusion: Advanced and chronic PLWH with or without ART showed higher levels of SASP and immune checkpoint mediators. *Ex vivo* D+Q senolytic treatment decreased the majority of SASP factors analysed, normalizing these levels. These drugs could be useful to reverse cellular senescence, chronic inflammation and aging comorbidities from PLWH.

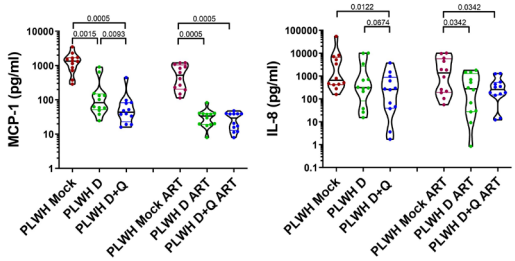

Figure 1. *D+Q senolytic drugs reduced the expression of SASP factors by Luminex quantification.*

842 Neighborhood Vulnerability Predicts Non-Communicable Disease Risk Among People With HIV

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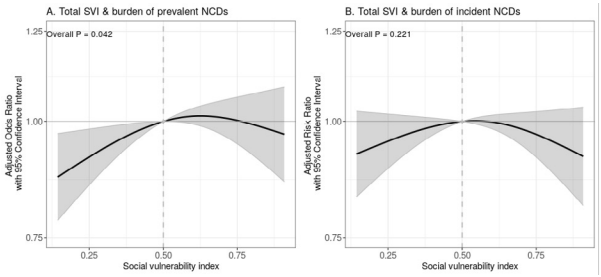
Background: Social determinants of health underly persistent disparities in the rates of non-communicable diseases (NCDs) across communities but have been understudied in people with HIV (PWH).
Methods: We assessed associations between the CDC's Social Vulnerability Index (SVI) and NCD burden and risk in PWH in care at the Vanderbilt HIV Clinic from Jan 2009-Dec 2019. The SVI is a census-tract-level measure of deprivation based on 16 factors, grouped into a total score and four themes (socioeconomic status, household composition/disability, minority status/language, and housing/transportation); higher SVI indicates greater neighborhood vulnerability. SVI was assigned using residence at enrollment or first visit after Jan 2009. NCDs included cardiovascular, liver, metabolic, and chronic kidney disease (stage ≥3), as well as non-AIDS defining cancers. Multivariable proportional odds logistic and Poisson regression models were used to assess the relationship between baseline SVI (total and themes) and both baseline and longitudinal NCDs (respectively), accounting for clustering and adjusting for age, substance use, gender/HIV risk factor, race/ethnicity, prevalent NCDs, antiretroviral therapy, depression, HIV RNA, hepatitis C, year, CD4 count, time since HIV diagnosis, and body mass index. Continuous variables including SVI were modeled using restricted cubic splines with 3 knots.
Results: Among 4440 PWH, median age was 41 years, 59% were men who have sex with men, 21% were cis-gender women, 41% were non-Hispanic Black, and 50% were non-Hispanic white. Median total SVI was 0.6 (IQR: 0.3-0.8) and median follow-up was 2.6 years (IQR: 1.1-5.4). At baseline, 44% had ≥1 NCD and 19% had ≥2 prevalent NCDs. Of 2442 PWH without prevalent NCDs, 32% developed NCDs during follow-up. Of 1916 patients with prevalent NCDs, 41% developed additional NCDs. Lower SVI was associated with lower number of prevalent NCDs (Figure 1a). In separate analyses, SVI socioeconomic status and household composition/disability themes were also associated with prevalent NCD burden (all $p<0.05$). In longitudinal analyses, there was no significant association between SVI and the risk of incident NCDs (Figure 1b).
Conclusion: Neighborhood vulnerability was associated with NCD burden among PWH, even after adjusting for individual characteristics, though confidence intervals included the null for incident NCDs. Relationships between neighborhood-level social determinants of health and NCD comorbidity among PWH warrant further study.



843 Application of STOPP Criteria in an Urban Cohort of People Aging With HIV

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Background: The validated Screening Tool of Older People's Prescriptions (STOPP), which identifies potentially inappropriate prescribing (PIP), i.e., treatment for which the potential risk outweighs the potential benefit, may be particularly important for aging people with HIV (PWH) and comorbidities. PIP may exacerbate symptoms and worsen adherence, which is particularly relevant among PWH. Our objectives were to: (1) Apply STOPP to identify PIP among an urban cohort of PWH aged >50 years with >1 comorbidity; (2) Describe

correlates of PIP; (3) Evaluate the relationship between PIP, symptom burden and quality of life (QOL.).
Methods: We analyzed data from the DC Cohort, a multicenter longitudinal study of 12,000 PWH receiving care in Washington, DC. Participants who completed a survey on symptom burden, social determinants of health (SDOH), and QOL were included. Symptom burden was measured with a continuous global distress index. We used STOPP to identify PIP and evaluated unadjusted/adjusted logistic regression models to determine demographics, comorbidities, HIV clinical factors, and SDOH associated with PIP. We then used structural equation modeling to evaluate whether symptom burden mediates the relationship between PIP and QOL.
Results: Of the eligible DC Cohort participants (n=), 902 (%) completed surveys and 511 (56.6%) had STOPP-designated PIP. The most common PIP were related to the musculoskeletal (n=349 (38.7%)), central nervous (n=335 (37.1%)), and urogenital (n=259 (28.7%)) systems. The strongest predictor of PIP was hypertension (aOR (95% CI): 5.17 (3.15, 8.51)). Non-Hispanic White participants were significantly more likely to have PIP than Non-Hispanic Black participants (aOR: 2.45 (95% CI: 1.42, 4.23)). Older age, having a housing or utility need, or receiving HIV care at a hospital versus a community site were all significantly associated with increased odds of PIP. In mediation models, symptom burden was a statistically significant mediator, but the direct effect (non-mediated) of PIP on QOL was not significant.
Conclusion: We found that over half of our participants had a PIP and hypertension is a strong predictor of PIP. Future interventions should use STOPP as a means of alerting clinical teams to clinically relevant PIP, especially among the high-risk groups identified here.
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844 Effects of HIV Status on Incidence of Post-COVID Conditions in Patients With SARS-CoV-2 (COVID-19)

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Background: SARS-CoV-2 (COVID) has been linked to long-term effects known as Post-COVID Conditions (PCC), that present post-acute COVID infection. While many studies have estimated PCC incidence, few have focused on immunocompromised patients, such as people with HIV (PWH). We estimated PCC incidence among PWH compared with people without HIV (PWoH) within Kaiser Permanente Mid-Atlantic States (KPMAS), an integrated closed healthcare system with high ascertainment of COVID-19 testing, vaccinations, and diagnoses among our patient membership.
Methods: Using KPMAS electronic health records, we identified adult patients (≥18 years) with a positive polymerase chain reaction (PCR) test for COVID between 1/1/2020-1/31/2022. PWH, identified from the KPMAS HIV registry, were matched to PWoH by month of first PCR-positive test, age group (deciles), race, sex, vaccination status prior to test, and service area (to account for physician diagnostic variation), using 1:3 variable ratio matching. Patients were considered to have PCC if diagnosed with one of 17 previously identified PCC-related conditions incident in the 30-180 days post first positive test date. From our earlier work, PCC-related conditions included anosmia, cardiac dysrhythmia, diabetes, gastrointestinal, neurologic, and genitourinary disorders, malaise, and non-specific chest pain. Relative risk with 95% confidence intervals were calculated and the association between HIV and PCC was evaluated with Rao-Scott Chi-Square (significance at $p<0.05$), weighted to account for disproportionate matching.
Results: We matched 749 PWH to 2,236 PWoH with >98% having 1:3 matching (1:3 = 740; 1:2 = 7; 1:1 = 2; [table]). The matched cohort was predominately black (80%) and male (64%) with a median age of 47 years. Overall, 22% of PWH and 19% of PWoH developed PCC. Risk of incident PCC among PWH (vs PWoH) was 19% higher (RR=1.19, 95% CI: 1.01-1.40; p=0.035). While PCC incidence was higher among PWH with CD4 ≤200/µL (37%, among 27) compared to those with CD4 >200/µL (22% among 633, p=0.07); PCC incidence did not vary by viral suppression status (> or <200 copies/mL; 22%, p=0.95).
Conclusion: We found PWH are at greater risk for PCC compared to PWoH, contributing evidence for enhanced care of immunocompromised populations who are infected with COVID. Assessment for PCC 30-180 days post-COVID, especially among PWH, should be a best practice. Further research into specific PCC conditions, effects of vaccination, and COVID disease severity among PWH is needed.

Table

Variables		PWH n(%); N=749	PWOH n(%); N=2,236
Matching Ratio	1:3; 1:2; 1:1 (n only)	740; 7; 2	2,220; 14; 2
Sex	Female; Male	270 (36.1%); 479 (64.0%)	804 (36.0%); 1,432 (64.0%)
Vaccine Status at Index Date	Vaccinated	296 (39.5%)	882 (39.4%)
Race/Ethnicity	Non-Hispanic Black	600 (80.11%)	1,794 (80.23%)
	Hispanic	67 (8.95%)	201 (8.99%)
Age at Index [Median years (IQR)]		47.7 (27.4, 68.0)	47.4 (27.4, 67.4)
Variant Time Period	Alpha	262 (35.0%)	782 (35.0%)
	Delta	170 (22.7%)	505 (22.6%)
	Omicron	317 (42.3%)	949 (42.4%)
Outcome	Met Incident PCC Criteria	166 (22.2%)	416 (18.6%)
Relative Risk PWH to PWoH	1.19 [1.01,1.40]		
Rao-Scott Chi-Square	0.035		

845 Evaluating the Effect of Vaccination on Post-COVID Conditions Among Patients With and Without HIV

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Background: Previous studies have described conditions presenting post-acute SARS-CoV-2 (COVID) infection, known as Post-COVID Conditions (PCC) or as Long COVID; but the effect of vaccination, especially among immunocompromised patients, is unclear. We evaluated the effect of COVID-19 vaccination on PCC within an integrated health system (Kaiser Permanente Mid-Atlantic States; KPMAS), for patients with HIV (PWH) and without HIV (PWoH). KPMAS is a closed healthcare system with high ascertainment of COVID-19 diagnostic and vaccination records.
Methods: Using KPMAS electronic health records, we identified adult patients (≥18 years) with a positive SARS-CoV-2 PCR test result between 1/1/2021-1/31/2022. The first positive result in this period defined the index date. Vaccination was defined as having ≥2 doses of mRNA or 1 for J&J COVID-19 vaccine ≥14 days prior to the index date. AHRQ Clinical Classification Software was used to group ICD-10 codes for 17 previously-identified PCC-related conditions, including anosmia, cardiac dysrhythmia, diabetes, gastrointestinal, neurologic and genitourinary disorders, malaise, and non-specific chest pain. PCC was defined as having an incident diagnosis of any of these conditions, 30-180 days after index. Poisson regression models with robust variance determined if the relative risk of PCC by COVID-19 vaccination status was the same among PWH (from KPMAS HIV registry) and PWoH, accounting for sex, race/ethnicity, age at index, service area within KPMAS (to account for diagnostic variation), and COVID-19 variant calendar periods. We tested for effect modification of HIV by vaccination status.
Results: Overall, 72,376 patients were identified, including 429 PWH and 71,884 PWoH, of whom 39% and 44% were unvaccinated, respectively (table). No interaction was found between HIV and vaccination (p value=0.81). After removing the interaction term, PWH showed significant increased risk versus PWoH (RR 1.25; p=0.01), while unvaccinated patients versus vaccinated did not (RR 1.02; p=0.27). Sex, age, service area, and race all showed significant risk ratios. Men showed lower risk (RR=0.78) compared to women, while greater age (RR=1.52 85+; Ref =18-29), non-white race and Hispanic ethnicity (RR=1.14 Hispanic; Ref =NH White) showed increased risk.
Conclusion: After adjusting for demographic characteristics, risk of PCC did not differ by vaccination status among PWH or PWoH. These findings may suggest COVID-19 vaccination is not protective against PCC after breakthrough infection.
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846 Post-Acute Sequelae of COVID-19 in an Early-Treated HIV Cohort in Thailand

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Background: People with HIV (PWH) may be at elevated risk of post-acute sequelae of COVID-19 (PASC), but PASC frequency and risk factors in PWH

who initiated antiretroviral therapy (ART) during acute HIV (AHI) is unknown. We assessed pre-COVID-19 characteristics and compared immunologic and neuropsychiatric outcomes of participants with and without PASC in the RV254 AHI study in Thailand.

Methods: Participants enrolled and initiated ART during AHI, with standardized longitudinal assessment of blood T cell counts and viral load (VL), cognition (Color Trails 1 & 2, Grooved Pegboard, Trail Making A), and mood (Hospital Anxiety & Depression Scale, Patient Health Questionnaire-9). By 7/2023, those ≥1 year after confirmed COVID were stratified as no PASC or PASC by persistence or occurrence of >1 PASC symptom (on a PASC symptom questionnaire) ≥3 months after acute COVID, lasting for >2 months. Demographic characteristics, COVID-19 course (time period/variant, number of infections, and hospitalization), and immunologic, cognitive, and mood parameters pre- and post-COVID-19 were compared in PASC vs no PASC using nonparametric methods.

Results: 216 RV254 participants were assessed a median 15[IQR 13-17] months after acute COVID; 55(25%) had experienced PASC and 15(7%) had ongoing symptoms. Common symptoms were fatigue (55%), exercise intolerance (25%), sleep disturbance (15%), cough (13%), and memory impairment (13%). PASC vs no PASC had similar pre-COVID parameters including median age 30 vs 31 years; 95% vs 98% male; CD4+ count 706 vs 701 cells/ul; pre-COVID VL >50 cps/ml 0% vs 1%; duration from AHI to acute COVID 6.0 vs 5.4 years (all p>.05). Those with PASC had a higher pre-COVID frequency of moderate-to-severe anxiety (HADS-A>11), fewer COVID vaccinations, and higher hospitalization rates with longer median hospital stay (Table 1). No differences were detected in variant type, number of infections, or immunologic and neuropsychiatric measures pre- to post-COVID between PASC and no PASC participants.

Conclusion: In this cohort of young mostly male PWH on suppressive ART initiated during AHI, 25% experienced PASC and 7% had ongoing symptoms >1year after documented COVID-19. Immunologic and neuropsychiatric changes pre- and post-COVID did not differ in participants with and without PASC. Higher pre-COVID anxiety severity, frequency of COVID hospitalization, and fewer COVID vaccinations associated with PASC, suggesting opportunities to prevent PASC in PWH including mental health interventions and vaccination

Table 1. Characteristics differentiating RV254 participants with and without post-acute sequelae of COVID-19 (PASC) based on non-parametric statistical tests

Characteristics	With PASC (*n*=55)	Without PASC (*n*=161)	*p*-value
PHQ-9 (depression) assessment pre-COVID-19 5-9 (mild-moderate) vs. 10-14 (mod) vs. ≥ 15 (mod-severe)	21(43%) vs. 5(10%) vs. 1(2%)	39 (29%) vs. 13(10%) vs. 3(2%)	0.357
HADS-A ≥ 11 (moderate-to-severe anxiety) pre-COVID-19	8 (15%)	6 (4%)	**0.010**
HADS-D ≥ 11 (moderate-to-severe depression) pre-COVID-19	4 (7%)	3 (2%)	0.073
COVID-19 vaccines prior to COVID-19, *n (%)* 0 – 1 vs. 2 vs. 3	17(31%) vs. 31(56%) vs. 7(13%)	37 (23%) vs. 72(45%) vs. 52 (32%)	**0.019**
Hospitalization during acute COVID, *n (%)*	34 (62%)	61 (38%)	**0.002**
Hospital length of stay, days, *median (IQR)*	12 (10-15)	10 (8-14)	**0.023**

847 Post-COVID Conditions Following COVID-19 Vaccination: A Matched Analysis of Patients With SARS-CoV-2

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Background: COVID-19 vaccinations protect against severe illness and death, but associations with post-COVID conditions (PCC) are less clear. We aimed to evaluate the association between prior vaccination and new-onset PCC among individuals with SARS-CoV-2 infection across eight large healthcare systems in the United States.

Methods: This study was a retrospective matched cohort study using electronic health records (EHR) from patients of all ages with SARS-CoV-2 positive tests (PCR or antigen) during March 2021-February 2022. Vaccinated and unvaccinated COVID-19 cases were matched on location, test date, severity of acute infection, age, and sex. Vaccination status was ascertained using EHR and integrated data on externally administered vaccines. Adjusted relative risks (RRs) were obtained from Poisson regression. PCC was defined as a new diagnosis in one of 13 PCC categories from 30 days to 6 months following a SARS-CoV-2 positive test.

Results: The primary analysis included 161,531 COVID-19 cases among vaccinated patients and 161,531 matched unvaccinated cases. Compared to unvaccinated cases, vaccinated cases had a similar or lower risk of all PCC categories except mental health disorders (RR: 1.06, 95% CI:1.02-1.10). Vaccination was associated with ≥10% lower risk of sensory (RR 0.90,95% CI 0.86-0.95), circulatory (RR 0.88, 95% CI 0.83-0.94), blood and hematologic (RR 0.79, 95% CI 0.71-0.89), skin and subcutaneous (RR 0.69, 95% CI 0.66-0.72), and non-specific COVID-19 related disorders (RR: 0.53, 95% CI: 0.51-0.56). In general, associations were slightly stronger at younger ages but persisted regardless of SARS-CoV-2 variant period, number of vaccine doses received, or time since vaccination.

Conclusion: Pre-infection vaccination was associated with reduced risk of several PCC outcomes and hence may decrease the long-term consequences of COVID-19.

848 Long COVID Between People With and Without HIV: A Statewide Cohort Analysis

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Background: Evidence on stratification of long COVID symptoms by immunocompromise status is lacking. People with HIV (PWH) have been documented to have an elevated risk of severe COVID-19 outcomes, yet the data on long COVID among PWH are limited. Using a large, statewide sampled dataset, this study aims to characterize and compare the risks of a panel of post-acute sequelae of COVID-19 between PWH and non-PWH comparison group.

Methods: Using an integrated statewide electronic health record data from HIV cohort and COVID-19 tester cohort, we were able to identify COVID-19 positive individuals by HIV status between March 02, 2020 and April 14, 2022 in South Carolina. Using the COVID-19 diagnosis date as the index date, a total of 132 individual long COVID sequelae were ascertained through ICD-10 codes until the end of the cohort. Risks of individual sequelae were compared between PWH and non-PWH groups. For each long COVID condition, we examined diagnnoses as outcomes separately and only excluded the specific diagnosis one year before the index date for models examining that same outcome in both PWH and non-PWH. We employed logistic regression models to estimate the odds ratio of the risks of individual sequelae between case and control groups, adjusting for socio-demographics and comorbidities.

Results: Among a total of 1,351,489 COVID-19 positive individuals, 3,485 were PWH and 1,348,004 were PWoH. PWH were generally older than PWoH (47 vs 36 years old), had a higher proportion of male (64% vs 45%) and Black population (73% vs 26%). The prevalence of any long COVID condition was 58.68% and 33.80% for PWH and non-PWH, respectively. After adjusting covariates, PWH were associated with a higher risk of 118 individual long COVID sequelae in nearly every organ system, such as Circulatory Disease (Encephalis: adjusted odds ratio [aOR]:5.86, 95%CI: 2.37-14.48), Mental, Behavioral and Neurodevelopmental Disorders (Stimulant-related disorders: aOR:4.61, 95%CI: 3.31-6.43; Sedative-related disorders: aOR:3.20, 95%CI: 1.31-7.78; Miscellaneous Mental and Behavioral Disorders/conditions: aOR:3.03, 95%CI: 1.56-5.90), and Diseases of the Genitourinary System (Nephritis: aOR:3.98, 95%CI: 1.75-9.06).

Conclusion: In this large observational study, PWH appears to have a higher risk of a variety of long COVID outcomes. These findings warrant further investigation in understanding how PWH leads to worse long COVID outcomes with more observational studies in persons with or without HIV.

849 COVID-19 Vaccine Protection Against Long COVID: A Population-Based Cohort Study

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Background: Vaccination before SARS-CoV-2 infection might confer partial protection against the development of post-COVID conditions ("long COVID") compared to unvaccinated individuals. However, evidence is limited in this regard. This study aims to systematically investigate the association between different vaccination status on a series of long COVID conditions by organ system.

Methods: We identified COVID-19 positive adults between March 17, 2021 and January 15, 2022 from the statewide COVID-19 tester cohort. Setting the date of first positive SARS-CoV-2 as the index time (T0), we selected the individuals who were alive at least 30 days after T0. A total of 132 individual long COVID conditions were ascertained through ICD-10 codes from day 30 after T0 until a maximum of 180 days of follow-up. Individuals were classified as: partially vaccinated if they receive one dose of Pfizer-BioNTech or Moderna vaccines; fully vaccinated if they received either two doses of Pfizer-BioNTech or Moderna vaccines or a single dose of Janssen; and boosted vaccination if they receive the booster dose before T0. We employed Cox regression models to estimate the

hazard ratio of the risks of individual sequelae by vaccination status, adjusting for relevant covariates. The incident symptoms or conditions that were significantly associated with vaccination status were grouped by organ systems.
Results: Among a total of 246,508 subjects, the prevalence of any long COVID conditions was 26.03%, with no major differences across the pandemic waves (e.g., Omicron). With a reference group of unvaccinated individuals, individuals with any dose of vaccination were associated with lower odds of 68 individual sequalae conditions, which involves 11 organ systems. Such protective effect was even higher among individuals who received booster dose. For example, a decreased risk of the disease of the Respiratory System was observed for individuals with fully (adjusted hazard ratio [aHR]: 0.75, 95%CI: 0.68, 0.84) and booster vaccination (aHR: 0.60, 95%CI: 0.53-0.68). Likewise, a reduced risk was also observed for the diseases of the Circulatory System (fully: aHR: 0.88, 95%CI: 0.83-0.93; booster: aHR:0.72, 95%CI: 0.64-0.81), Skin and Subcutaneous Tissue (fully: aHR:0.75, 95%CI: 0.68, 0.84; booster: aHR: 0.52, 95%CI: 0.40-0.69).
Conclusion: In this statewide longitudinal observational study, we observed that fully or boosted vaccination appears to have some extent of protection against the development of multiple long COVID outcomes.

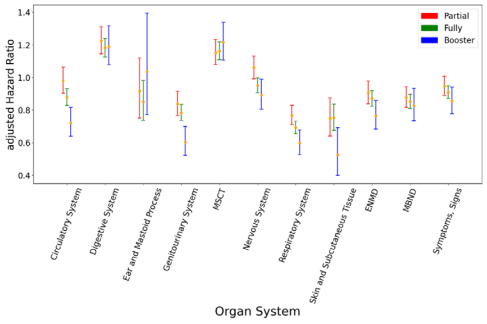

Figure 1. The association between vaccination status and long COVID conditions by organ system
Note: "MSCT": Musculoskeletal System and Connective Tissue, "ENMD": Endocrine, Nutritional and Metabolic Diseases, "MBND": Mental, Behavioral and Neurodevelopmental Disorders, "Symptoms, Signs": Symptoms, Signs and Abnormal Clinical and Laboratory Findings, Not Elsewhere Classified

850 Sexual Minority Adults Experienced More Severe and Longer COVID-19 Symptoms Than Heterosexual Adults

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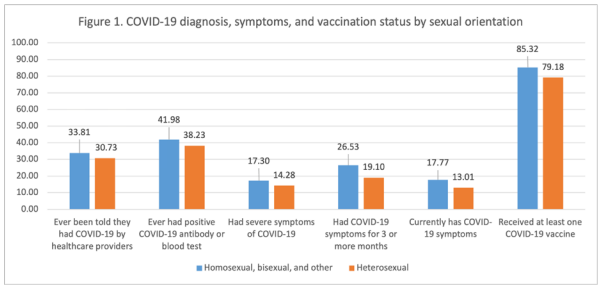
Background: Lacking access to COVID-19-related care could prolong symptoms and accentuate adverse health outcomes among vulnerable populations, including sexual minority populations. We investigated the relationships between sexual orientation and COVID-19 diagnosis, symptoms, and vaccination status.
Methods: Data for this analysis were from the 2022 National Health Interview Survey. Sexual orientation was self-reported, categorized as sexual minority (self-identified as gay, lesbian, bisexual, or other) and heterosexual. Weighted percentages of self-reported COVID-19 diagnosis, symptoms, and vaccination status were tabulated by sexual orientation, with p-values computed using Rao-Scott Chi-squared tests. Separate weighted logistic regression models were fit to compare these outcomes by sexual orientation and to calculate adjusted odds ratios (aOR) and 95% confidence intervals (95% CI), controlling for age, race/ethnicity, education level, health insurance coverage, and general health status. All analyses accounted for complex sample design.
Results: The unweighted sample was 26,057 (weighted n=239,527,538); of whom 94.5% identified as heterosexual and 5.5% as sexual minority. Compared with heterosexual adults, higher proportions of sexual minority adults reported ever been told they had COVID-19 by healthcare providers (33.8% vs. 30.7%, p=0.05), tested positive for COVID-19 by an antibody or blood test (42.0% vs. 38.2%, p=0.02), experienced severe symptoms (17.3%vs. 14.3%, p=0.10), had symptoms for ≥3 months (26.5% vs. 19.2%, p<0.001), received at least one COVID vaccine (85.3% vs. 79.2%, p<0.001), and are currently experiencing symptoms (17.8% vs. 13.0%, p<0.001). After covariate adjustment, sexual minority adults had greater odds of having had severe COVID-19 symptoms (aOR: 1.36, 95% CI: 1.01-1.83), symptoms for ≥3 months (aOR: 1.56, 95% CI: 1.21-2.02), and currently experiencing symptoms (aOR: 1.63, 95% CI: 1.23-2.15) than heterosexual adults. Sexual minority adults also had greater odds of having received the vaccine (aOR: 2.19, 95%CI: 1.77-2.71).
Conclusion: In this national U.S. sample, sexual minority populations experienced more severe and prolonged COVID-19 symptoms than their heterosexual counterparts, despite being more likely to be vaccinated. Future research is needed to explore factors contributed to severe COVID-19 symptoms or long COVID in sexual minority populations.



851 Persistence of Anxiety and Depression in US Adults by COVID-19 Vaccination Status, 2020-2023

Yanhan Shen[1], Kate Penrose[1], McKaylee Robertson[1], Rachael Piltch-Loeb[1], Sasha Fleary[1], Sarah Kulkarni[1], Chloe Teasdale[1], William You[1], Subha Balasubramanian[1], Surabhi Yadav[1], Bai Xi Jasmine Chan[1], Milton L. Wainberg[2], Scott Ratzan[1], Denis Nash[1], Angela Parcesepe[3]
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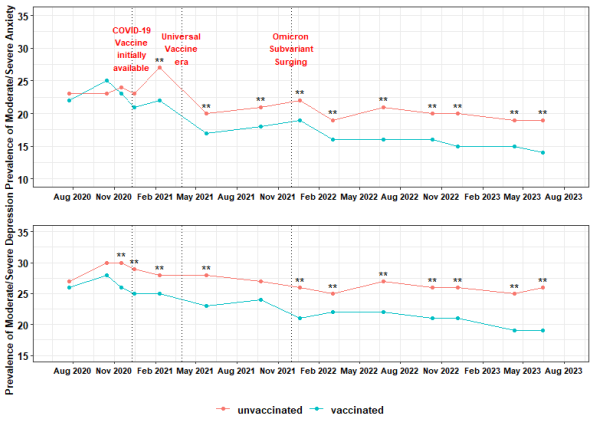
Background: The COVID-19 pandemic has impacted mental health among adults in the US. However, little is known about the persistence of symptoms of anxiety and depression, over the three years since the emergence of SARS-CoV-2 or the relationship between such symptoms and COVID-19 vaccination. We described the persistence of anxiety and depression among a large cohort of US adults.
Methods: Participants from the CHASING COVID Cohort completed the Generalized Anxiety Disorder (GAD-7) and Patient Health Questionnaire (PHQ-8) at least one of 14 assessments, approximately every 3 months between July 2020 and June 2023. Persistent symptoms of anxiety or depression was defined as reported moderate/severe symptoms of anxiety (GAD-7>9) or depression (PHQ-8 >9) for >=7 assessments. Participants were classified as vaccinated (or unvaccinated) if they reported any (or never) COVID-19 vaccine between December 2020 and June 2023. We conducted multiple imputations for 18.3% missing GAD-7 or PHQ-8 scores. We used latent class growth analysis (LCGA) to identify groups of participants with shared GAD-7 or PHQ-8 trajectories over 36 months of follow-up. Chi-square tests were used to compare sociodemographic factors among those with and without persistent symptoms of anxiety/depression and by LCGA groups. At each time point, log-binomial models were used to estimate the age- and gender-adjusted prevalence of moderate/severe anxiety or depression stratified by vaccination status.
Results: Among 5652 participants, prevalence of persistent symptoms of anxiety or depression was 19.0% (N=1074) and 22.8% (N=1288) over 36 months, respectively. Using LCGA model, 26.7% (N=1509) and 26.8% (N=1516) of participants had persistently high trajectory of GAD-7 or PHQ-8 over 36 months. Participants who were young, female, non-White, socioeconomically disadvantaged, and unvaccinated were more likely to have persistent symptoms of anxiety/depression or persistent high trajectory of GAD-7/PHQ-8. After COVID-19 vaccines became universally available, the adjusted prevalence of moderate/severe anxiety or depression symptoms decreased among vaccinated individuals compared with unvaccinated (Figure). These differences were sustained over the duration of follow-up.
Conclusion: Further investigations are warranted to elucidate bidirectional relationships between COVID-19 vaccination and mental health symptoms, including the extent to which moderate/severe mental health symptoms may be a barrier to staying up to date on COVID-19 vaccination.

Figure. Age- and Gender-Adjusted Prevalence of Moderate/Severe Anxiety and Depression by COVID-19 Vaccination Status
**Difference p<0.05 between vaccinated and unvaccinated individuals.



852 Predictors of Long COVID in Adults With Untreated Mild-To-Moderate COVID-19

Teresa H. Evering[1], Pooja T. Saha[2], Carlee Moser[2], Nikolaus Jilg[3], Rachel A. Bender Ignacio[4], Prasanna Jagannathan[5], Katya Corado[6], Kevin Wongsodirdjo[2], Justin Ritz[2], Jonathan Z. Li[7], Davey M. Smith[8], Michael D. Hughes[2], Judith S. Currier[9], Kara W. Chew[9], for the ACTIV-2/A5401 Study Team

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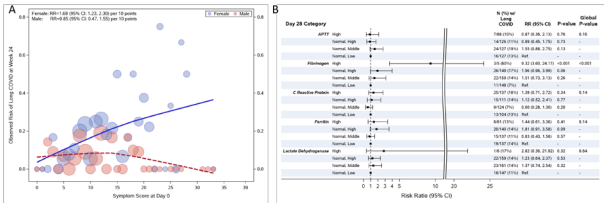
Background: Identifying Long COVID predictors is crucial. We studied associations with Long COVID in untreated adults in the ACTIV-2/A5401 trial.

Methods: Non-hospitalized adults with COVID-19 randomized to placebo within 10 days of symptom onset were analyzed. Long COVID was defined as self-reporting overall COVID-19 symptoms as present in the 4 weeks preceding study week 24 (W24) in a long-term (LT) diary, which also assessed 27 individual symptoms. Demographics, clinical and biomarker variables at day 0 (body mass index, smoking, COVID-19 vaccination, comorbidities, symptom score summed across 13 acute symptoms each graded as absent[0]/mild[1]/moderate[2]/severe[3], anterior nasal viral RNA levels, serostatus by anti-Spike and anti-nucleocapsid antibody), and inflammatory/coagulation markers (classified as above normal or tertiles of normal values) at days 0 and 28 were evaluated as predictors of Long COVID using regression models.

Results: 546/702 (78%) of participants who received placebo January-August 2021 completed LT diary at W24: median age 44 years, 53% female, 99% cis-gender, 13% Black, 53% Hispanic/Latino, 15% previously vaccinated, 49% seropositive. At W24, 74/546 (14%) had Long COVID, including 55/287 (19%) women and 19/259 (7%) men. Symptoms reported by ≥40% with Long COVID were fatigue (70%), musculoskeletal pain (51%), difficulty concentrating/thinking (42%), muscle weakness (42%), cough (41%), breathing difficulties (40%); most were mild. Of demographic/clinical variables, only female sex and higher symptom score at day 0 were significant predictors of Long COVID in univariable and multivariable analyses: female sex adjusted risk ratio (aRR) 2.40 (95% CI: 1.43, 4.04; p<0.001), symptom score aRR 1.45 per 10 point higher score (1.10, 1.90; p<0.009). The association of symptom score with Long COVID appeared different in women (aRR 1.68 per 10 point higher score) than men (aRR 0.85), p=0.050 (Figure 1A). Viral RNA measures and serostatus were not significant in multivariable analysis. Of other biomarkers, higher fibrinogen at day 28 was associated with increased risk of Long COVID (Figure 1B).

Conclusion: In untreated adults with mild-to-moderate COVID-19, female sex, higher fibrinogen levels at day 28, and symptom burden at day 0 among women but not men were associated with increased risk of Long COVID. This supports sex-stratified investigations into mechanisms of Long COVID and a potential role of clotting as a risk factor.

Figure 1: (A) Risk of Long COVID at Week 24 by Symptom Score (SS) at Day 0 and Sex (bubble size proportional to number participants with each SS, smoothed curves fit with LOESS), (B) Adjusted Risk Ratios of Long COVID for each Biomarker Category



853 Long COVID in Children Is Associated With Lower Anti-RBD IgG/IgA and Neutralizing Antibody Levels

Jon Izquierdo-Pujol[1], Sara Morón-López[1], Núria Pedreño[1], Tetyana Pidkova[1], Victor Urrea[1], Judith Dalmau[1], Alba Gonzalez-Aumatell[2], Clara Carreras-Abad[2], Maria Mendez[2], Carlos Rodrigo[2], Julià Blanco[1], Jorge Carrillo[1], Benjamin Trinité[1], Javier Martinez-Picado[1]

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Background: Most people recover quickly after SARS-CoV-2 acute infection; however, a significant percentage can develop long-term persistent symptoms, a condition known as long COVID, post-acute sequelae of SARS-CoV-2 (PASC) or Post-COVID-19 Condition (PCC). One of the main hypotheses on the underlying mechanism is the dysregulation of immune and inflammatory responses that persists after the acute infection. Most studies are focused on adults, neglecting cases in children and young people (CYP), where mechanisms may differ. Here, we analyzed the humoral and neutralizing antibody response in pediatric population with and without long COVID.

Methods: We analyzed 131 blood samples from the pediaCOVID cohort (Hospital Germans Trias i Pujol), which includes 108 children/adolescents diagnosed with long COVID and 23 control CYP. An in-house ELISA was used to measure SARS-CoV-2 specific IgG and IgA antibody plasma levels (Anti-S2, Anti-RBD and Anti-N). In addition, neutralizing antibody levels were measured using a luciferase-reporter lentiviral pseudovirus assay, expressing SARS-CoV-2 S protein.

Results: The long COVID cohort had a median age of 14.3 (IQR, 12.5-15.2) and 69.1% of female participants (no differences with control cohort). Patients had a median of 10 symptoms associated with long COVID (IQR, 7-16). The most common symptoms were asthenia/fatigue, (98%), neurocognitive disorders (84%) and brain fog (82%). CYP with long COVID had significant lower levels of both anti-RBD IgG and IgA antibodies compared to the control cohort (p-value < 0.0001 and 0.0332, respectively). Consistently, children and adolescents with long COVID had significant lower levels of neutralizing antibodies against the D614G variant compared to the control cohort (p-value: 0.0064). However, plasma levels of both anti-S2 and anti-N antibodies remained similar to the control group.

Conclusion: Our study is the first to report antibody levels in CYP with long COVID. These results indicate that, in our cohort, CYP with long COVID had lower antibody response against the RBD of SARS-CoV-2, along with less neutralizing activity. Further experiments are needed to assess the reason and how this could impact the development of long COVID and its associated symptoms. Importantly, the lower anti-RBD antibody response could provide a potential biomarker for the diagnosis of long COVID in the pediatric population.

854 Characterization of Circulating Biomarkers Levels in Participants With Long COVID

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Background: Post-acute sequelae of COVID19 or 'Long COVID' is a common but heterogenous condition associated with significant morbidity. Its pathogenesis remains poorly understood, with a number of different clinical phenotypes reported. We aimed to characterize host inflammatory responses by identifying inflammatory patterns and their association with demographic factors, comorbidities, and symptoms.

Methods: In plasma from individuals with PCR-confirmed COVID-19 diagnosed with Long COVID (symptoms ≥4 weeks post-acute COVID-19), part of the All-Ireland Infectious Diseases Cohort study, we measured 57 biomarkers mapped

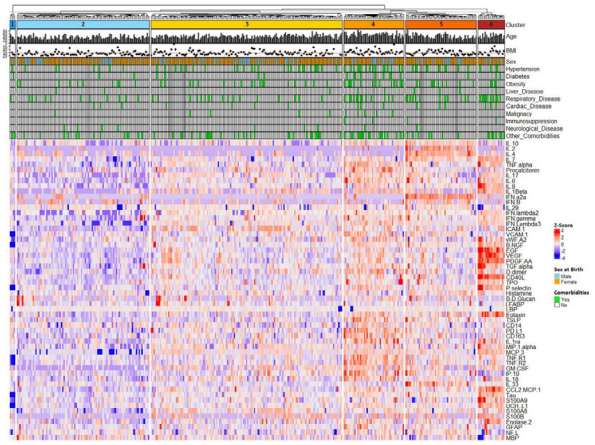
to systemic inflammation, antiviral cytokine responses, endothelial dysfunction, tissue damage, coagulation, microbial translocation, innate immune activation, immune regulation and axonal injury using quantitative immunoassays. We used principal component analysis and unsupervised hierarchical clustering to identify distinctive biological clusters. We used Kruskal-Wallis and Chi-Square tests to explore demographic and clinical parameter differences between clusters.

Results: We included 364 individuals (median (IQR) age 44 (35-53) years, BMI 27 (22-32), 74% female, 85% Caucasian) in the analysis. We identified 6 distinct biological clusters (Figure 1 A). Clusters 1,2 and 3 (68,9%) exhibited low inflammatory biomarkers, lower BMI, younger age, and fewer comorbidities. In contrast, clusters 4,5 and 6 were characterized by higher inflammatory profiles. Cluster 4 characterized by higher innate immune activation markers, had the highest BMI, oldest age, and more prevalent comorbidities like hypertension and obesity, suggesting metabolic syndrome. In contrast, cluster 5 had higher anti-inflammatory (IL2, IL4, IL10) and antiviral biomarkers (IFN-α2a, IFN-B) and was relatively younger, suggesting a persistent immune response to infection. Cluster 6, mainly cardiorespiratory (60%) (Fig-1 B), and higher expression levels of tissue damage biomarkers (VEGF, EGF, PDGF, TGF-α, β-NGF), coagulation (CD40L, P-selectin, TPO, vWF), and axonal injury (S100A9, S100B, Tau, ENO2, UCH-L1) and had higher reported respiratory illness.

Conclusion: From 6 distinct biological clusters, we identified three inflammatory clusters in individuals with long COVID with specific clinical and biological characteristics, including patterns suggesting tissue damage/coagulation and persistent antiviral immune responses. The data suggest a number of distinct underlying pathogenesis in individuals with long COVID.

Figure 1 – (A) Heatmap of the six distinct clusters. (B) Clinical table.

(A)



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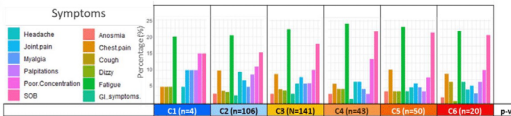

	C1 (n=4)	C2 (n=106)	C3 (N=141)	C4 (n=43)	C5 (n=50)	C6 (n=20)	p-value
Age	40.5 (35 - 45)	38.5 (29 - 46)	44 (37 - 52)	57 (48.5 - 64.5)	46 (31 - 55)	48 (38.5 - 49)	**<0.0001**
Sex (F)	2 (50)	79 (75)	106 (75)	30 (70)	39 (78)	15 (75)	0.8313
BMI	23 (16 - 25)	25 (22 - 29)	25 (21 - 31)	30 (27 - 34)	27 (24 - 34)	29 (23 - 34)	**0.0006**
Hypertension	1 (25)	8 (8)	24 (17)	16 (37)	11 (22)	4 (20)	**0.0014**
Diabetes	1 (25)	2 (2)	4 (3)	9 (21)	1 (2)	2 (10)	**<0.0001**
Obesity	0	12 (11)	18 (13)	14 (33)	8 (16)	4 (20)	**0.0243**
Respiratory disease	1 (25)	11 (10)	17 (12)	13 (30)	12 (24)	10(50)	**<0.0001**

Legend: (A) Heatmap demonstrating individual demographics and hierarchical clustering of biomarkers for each individual. (B) Comparisons of clinical demographics between clusters.

855 Relationship Between Serum Cortisol Level and Long COVID Symptoms in Post-Acute COVID-19

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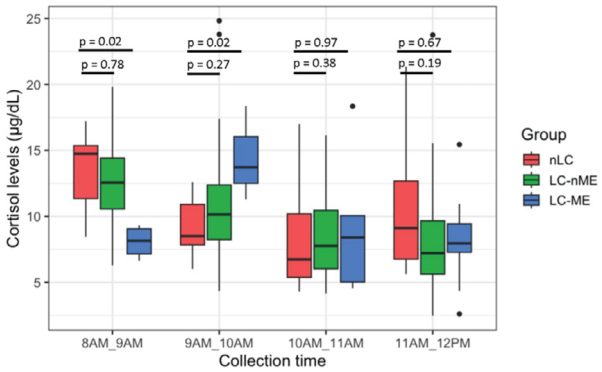
Background: Low cortisol levels have been reported in some people with Long COVID (LC), but this observation has yet to be confirmed. Some people with LC meet the definition of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), an illness that has also been associated with cortisol dysregulation. Further evaluation of cortisol post-COVID could better define LC biology.

Methods: We evaluated 200 individuals in the UCSF LIINC post-COVID study cross-sectionally, 3-6 months after SARS-CoV-2 infection. We defined LC as ≥1 COVID-attributed symptom (n=144), and non-LC (nLC) as no symptoms (n=56). We further defined those with LC who met Institute of Medicine ME/CFS criteria at 3 months as LC-ME (n=28) and those with LC but without LC-ME as LC-nME (n= 116). We measured cortisol on serum collected 8AM-12PM on day of assessment and performed analyses stratified by collection time.

Results: The cohort was 55% female; median age was 43. Cortisol levels (μg/dL) did not differ between LC and nLC groups (median 8.9 vs 8.8) when aggregated across collection time. Proportions with subnormal cortisol levels (<5) were similar (9.7% vs 8.9%). When stratified by collection time, 8-9AM cortisol levels tended to be lower in those with LC compared to nLC (12.4 vs 14.9, p=0.36), and 9-10AM cortisol levels tended to be higher comparing LC to nLC (10.3 vs 8.5, p=0.15), albeit neither difference was statistically significant. No differences were observed between 10-11AM and 11AM-12PM. When stratified by post-COVID ME status, cortisol levels between 8-9AM were significantly lower in the LC-ME group compared to the nLC group (8.2 vs 14.8, p=0.02), even after adjusting for age, sex and BMI (Fig 1). Conversely, cortisol levels between 9-10AM were significantly higher in the LC-ME group compared to the nLC group (13.7 vs 8.5, p=0.02), also after adjusting for age, sex, and BMI (Fig 1). No differences were observed comparing LC-nME to nLC.

Conclusion: We found that cortisol levels tended to be lower between 8-9AM and to be higher between 9-10AM in those with LC, and that this difference appears to be driven by those with LC-ME, consistent with prior observations of a delayed cortisol peak in ME/CFS. These findings significantly add to our understanding of cortisol in LC and highlight the importance of considering collection time. Longitudinal measures of cortisol in individuals with LC will be critical to further inform the biology of the condition.



856 Association of Long COVID With Health-Related Quality-of-Life Outcomes

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Background: Long COVID is a significant and growing public health burden. The association of long COVID with health-related quality-of-life (HrQOL) has not been well-characterized.

Methods: Participants (N=546) who received blinded placebo in the ACTIV-2/A5401 outpatient COVID-19 treatment trial with symptom diary data at week 24 were assessed for long COVID, defined as presence of self-assessed COVID-19 symptoms within the last 4 weeks at the week 24 visit. HrQOL at week 24 was evaluated by the EQ-5D-5L (EQ-5D) and SF-36v2 (SF-36) questionnaires. Modified Poisson regression and Wilcoxon rank-sum tests compared EQ-5D and SF-36 measures between participants with vs without long COVID.

Results: This cohort enrolled between January and August, 2021; median age was 44 years, median time from symptom onset was 5 days; 53% female, 99% cisgender, 80% White, 13% Black, 53% Hispanic, 58% high-risk for severe COVID-19, 36% with Delta and 64% pre-Delta variant infection, 16% vaccinated, and 52% anti-nucleocapsid or anti-spike antibody positive. Long COVID was present in 13.6% (74/546) of participants. EQ-5D was completed by 80% and

SF-36 by 81%. A higher frequency of participants with vs without long COVID reported problems in each of the five EQ-5D dimensions; mobility (24% vs 6%, p<0.001), self-care (8% vs 2%, p=0.007), usual activities (38% vs 6%, p<0.001), pain/discomfort (57% vs 14%, p<0.001), and anxiety/depression (41% vs 15%, p<0.001), with risk ratios of 2.75 to 6.18 (Figure 1A). Participants with vs without long COVID had lower scores on EQ-5D visual analogue scale, in which current health was self-rated from 0 (worst) to 100 (best) (median 85 vs 95, p<0.001). Participants with long COVID also had lower scores in each of the eight SF-36 domains (general health, physical functioning, physical role, bodily pain, vitality, social functioning, emotional role, and mental health; all p<0.001) (Figure 1B) and composite physical and mental component scores (both p<0.001).

Conclusion: Long COVID is associated with worse HrQOL outcomes across multiple domains, highlighting the need to develop preventative and therapeutic interventions for this condition.

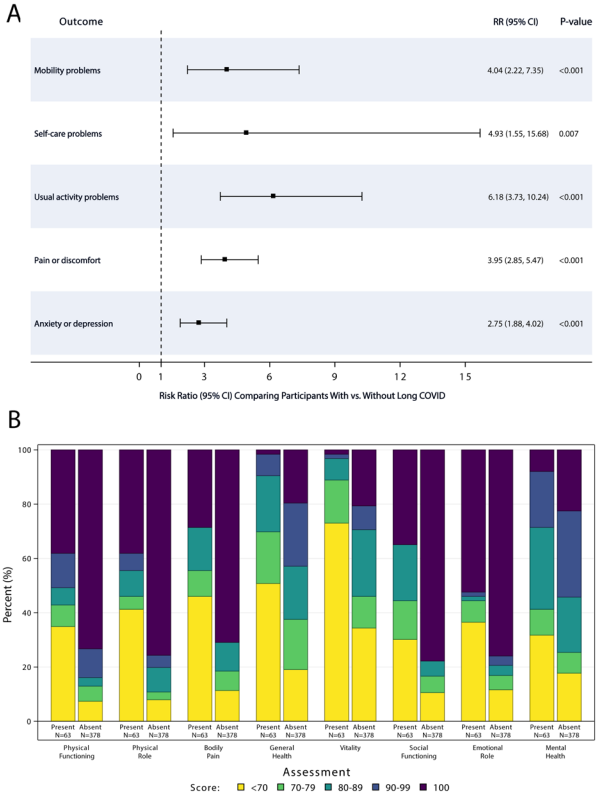

Figure 1. (A) Risk ratios comparing participants with versus without long COVID for each EQ-5D dimension and (B) distribution of scores for each SF-36 domain by long COVID status (Present or Absent)

857 Predictors of Breakthrough COVID-19 Infection From the STOPCoV Cohort

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Background: Our current understanding of the human immune response to SARS-CoV-2 does not enable us to quantify the degree of protection COVID-19 vaccines confer against infection and transmission especially with emerging variants.

Methods: The STOPCoV (Safety and effectiveness of Preventative COVID Vaccines) study is an ongoing prospective decentralized study with the primary aim of comparison of the antibody responses to COVID vaccines in those aged > 70 years relative to a younger cohort aged 30-50 years. In this analysis, we assessed predictors of breakthrough COVID-19 infection during the Omicron BA5/EG5/XBB waves in Ontario, Canada. Antibodies were eluted from self-collected dried blood spots (DBS) tested by Enyzme linked Immunosorbent Assay for antibodies (IgG) against the receptor binding domain (RBD) and nucleocapsid proteins (NP). Values were converted to WHO BAU/ml International Standards. Monthly data captured vaccine boosters and breakthrough infections. The extended Cox proportional hazards models was used to investigate the association between the risk of breakthrough infection and predictor variables. RBD antibody levels were treated as a time-dependent covariate.

Results: 983/1286 participants submitted at least one DBS after the primary two dose vaccine series (Spring 2021). 538 participants submitted a DBS following the availability of bivalent BA.4/BA.5 vaccines (September 2022). Of this 175 (32%) developed their first breakthrough infection. In multivariable analysis of these 538 participants, breakthrough infection was not associated with the brand of the primary vaccine series (two mRNA1273- Moderna vs other brands or combinations) nor with underlying comorbidity (diabetes, cardiovascular disease, respiratory disease, cancer or transplant), current smoking, gender or non-white race. Those who were > 70 years of age were less likely to have breakthrough infection compared to those aged 30-50 years; HR 0.652 [0.434, 0.979]. Those with lower RBD antibody levels were not more likely to have breakthrough infection. The strongest correlation of protection was receipt of a bivalent vaccine booster, HR 0.363 [0.265, 0.496].

Conclusion: Bivalent booster vaccines matching the circulating COVID strains had the greatest association with protection against first breakthrough infection. We could not identify a threshold RBD antibody level for protection. The elderly were less likely to have breakthrough infection possibly related to behavioral differences.

858 Immunosuppressive Conditions Are Associated With Poor Outcomes in Patients Hospitalized for COVID-19

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Background: Immunosuppressed adults (primary immunodeficiency (PI), HIV (unsuppressed and poor immune recovery), and solid organ transplant) are more likely to have severe COVID-19 and poor outcomes. Less is known about outcomes of severe COVID-19 for adults with specific immunosuppressive conditions compared to immunocompetent adults. We hypothesized that outcomes for adults with certain immunosuppressive conditions hospitalized for COVID-19 would be significantly worse.

Methods: We identified adults hospitalized for COVID-19 from 03/2020 to 05/2022 in EHR data from Northwestern Medicine (NM). Based on extracted diagnosis, lab, and procedure codes, we identified and categorized those with PI (antibody deficiency, combined immunodeficiency, common variable immunodeficiency, ataxia-telangiectasia, phagocyte deficiency, or complement deficiency), history of organ transplant (kidney, liver, heart, or lung), and HIV (defined above). Assessed COVID-19 outcomes included a seven-point ordinal severity scale based on maximum oxygen requirements during care (1 = Death), hospitalization length, and one-year cumulative incidence of death (all-cause). Regression and relative risk analyses were performed in R 4.2.0.

Results: We included 10,713 adults hospitalized for COVID-19 at NM of which 214 had PI, 669 had history of organ transplant, and 183 had HIV (defined above). Patients with PI had a significantly higher mean hospitalization length of 11.8 days and a significantly lower mean maximum severity of 3.3 compared to 7.8 days and 3.9 in immunocompetent patients when controlling for obesity and T2DM. These effects were not significant when controlling for age. Patients with organ transplant had a significantly higher mean hospitalization length of 15.8 days when controlling for obesity, T2DM, and age, and a significantly lower mean maximum severity of 3.2 when controlling for obesity. Significantly higher mortalities were observed in PI and transplant (RR = 1.5, 95% CI 1.2 to 2.0; RR = 1.5, 95% CI 1.3 to 1.7), but these effects were not significant when controlling for age. There were no significant differences in any outcomes for patients with HIV.

Conclusion: Our results suggest patients with PI or organ transplant hospitalized for COVID-19 may have worse clinical outcomes compared to immunocompetent patients. This contrasts with patients with HIV, who had similar outcomes to immunocompetent patients, suggesting that people with different immunosuppressive phenotypes may respond variably to severe COVID-19.

Table 1. Demographics and outcomes of patients with and without immunosuppressive conditions hospitalized for COVID-19

	No immunosuppression N = 9647	Primary immunodeficiency N = 214	Solid organ transplant N = 669	Active HIV infection N = 183
Baseline characteristics				
Mean age at admission (SD), years	61.0 (19.5)	63.2 (16.3)	56.5 (14.6)	50.9 (13.3)
Men, n (%)	4368 (45%)	103 (48%)	410 (61%)	110 (60%)
Non-white, n (%)	3053 (32%)	60 (28%)	268 (40%)	87 (44%)
Uninsured, n (%)	535 (6%)	3 (1%)	17 (3%)	8 (4%)
Outcomes				
Mean maximum COVID-19 severity (SD)	3.9 (1.6)	3.3 (1.5)	3.2 (1.6)	4 (1.6)
Mean hospitalization length (SD), days	7.8 (10.5)	11.8 (13.0)	15.8 (25.7)	7.3 (8.7)
One-year all-cause mortality, n (%)	1354 (14%)	45 (21%)	138 (21%)	19 (10%)

Data are expressed as means or counts (percentages)
Abbreviations: SD denotes standard deviation

859 Characteristics and Outcomes of Patients with Kidney Transplant Hospitalized for COVID-19 in the US

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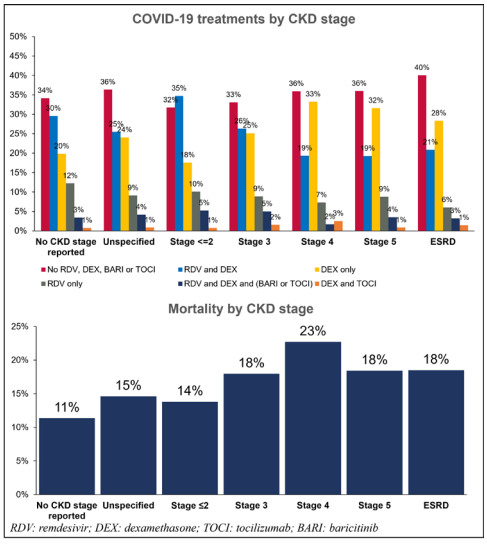
Background: Immunocompromising conditions and advanced renal dysfunction are individually risk factors for adverse outcomes from COVID-19. We explored the intersection of these risk factors by examining variations in treatment patterns and mortality among hospitalized COVID-19 patients with a history of kidney transplant.
Methods: Patients with a history of kidney transplant (ICD-10-CM: Z94.0) hospitalized in the US for COVID-19 (ICD-10-CM: U07.1) between May 2020-Jan 2023 were identified using the Premier Healthcare Database. Baseline was considered as first two days of hospitalization. We characterized patient demographics, treatment patterns and in-hospital all-cause mortality by chronic kidney disease (CKD) stage as a surrogate for renal allograft dysfunction.
Results: Of the 8,785 patients included in this study from 831 hospitals, 55% were White, 27% Black, 40% female with a median age of 62 years [IQR: 52-70]. Key comorbidities included hypertension (90%) and diabetes (60%). Baseline COVID-19 severity included 68% patients with no supplemental oxygen charges, 17% low-flow supplemental oxygen, 10% high-flow/non-invasive ventilation, and 5% invasive mechanical ventilation/ECMO. Patients were hospitalized for a median of 5 days [IQR: 3-10] with 29% admitted to the ICU and 16% mortality rate. Over the variant periods, patient characteristics remained similar except higher supplemental oxygen requirements, ICU stay and mortality rate in the Delta period as compared to Pre-Delta and Omicron. Despite risk of progression, use of COVID-19 treatments was lower with higher CKD stage, and use of triple therapy with remdesivir+dexamethasone with baricitinib/tocilizumab increased with higher supplemental oxygen requirement (Figure). Mortality increased from 14% for CKD Stage ≤2 to 23% for Stage 4 and 18% for Stage 5 (Figure).
Conclusion: In this study of kidney transplant recipients hospitalized with COVID-19, the lack of any COVID-19 treatment was seen more often as renal function diminished despite a notable increase in overall mortality observed in tandem with compromised renal function. This study sheds light on a persistent therapeutic gap that has affected these patients historically, attributed to factors such as potential drug interactions, past uncertainties regarding the renal clearance of therapeutics, and existing gaps in medical education and awareness.



860 COVID-19 Omicron Infection and Severe Outcomes in HIV and Matched Non-HIV Cohorts in Ontario, Canada

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Background: There is concern that people living with HIV may be at greater risk for COVID-19 infection or severe outcomes, and that vaccination may offer less protection, compared to those not living with HIV. Our aim was to quantify rates of SARS-CoV-2 testing and COVID-19 infection and hospitalization/death in the Omicron period and compare this by HIV and vaccination status.
Methods: We identified community-dwelling people living with HIV aged ≥19 years in health administrative databases using a validated algorithm and followed them from January 2, 2022, to March 31, 2023, along with an HIV-negative cohort matched on age, sex, census tract, and immigrant status. Vaccination status was ascertained from the provincial COVID-19 vaccine registry. Most distributed vaccines during this period were monovalent mRNA vaccines. We report rates per 1000 person-years (PY) for time to first PCR testing for SARS-CoV-2, PCR-confirmed infection, and COVID-19-related hospitalization/death among HIV and non-HIV matched cohorts, with 95% confidence intervals (CI).
Results: A total of 20,978 people living with HIV and 20,978 matched HIV-negative individuals were included. Cohorts were comparable by matching factors age (mean 50.5 years), sex (21.9% female), region, and immigrant status (72.3% non-immigrant), and had a similar number of comorbidities. However, people living with HIV were more likely than HIV-negative individuals to have received 3+ doses of SARS-CoV-2 vaccine (31.5% cf 23.9%), recent influenza vaccination (42.9% cf 29.1%), and certain comorbidities: chronic kidney disease (5.9% cf 2.6%), frailty/dementia (5.3% cf 2.7%) or advanced liver disease (3.5% cf 1.2%). Rates of SARS-CoV-2 PCR testing and COVID-19 outcomes were consistently higher among people living with HIV, even when compared within vaccine dose strata (Table). Compared with HIV-negative hospitalized cases (n=100), hospitalized cases who were living with HIV (n=215) were more likely to be vaccinated (88.4% cf 79.0%); they were also younger, more likely to be female or an immigrant, and differed in comorbidities.
Conclusion: Timely booster doses and efforts to reduce SARS-CoV-2 exposure remain important for people living with HIV given higher rates of infection and severe outcomes. Limitations include incomplete confounding control and imprecision for severe events which were rare. Ongoing monitoring is needed for more recent vaccine formulations and against newer variants.
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861 SARS-CoV-2 Infection and Hospitalization in Immunocompromised Children: A Population-Based Study

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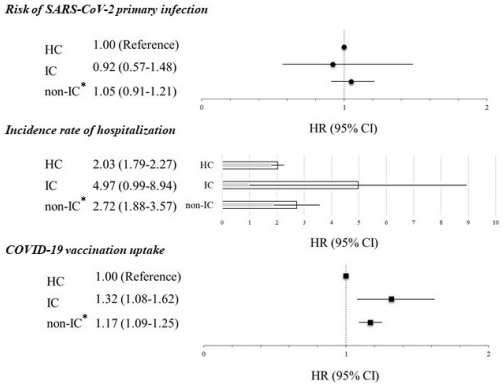
Background: The burden of SARS-CoV-2 infection in immunocompromised children remains unclear due to limited population-based studies. We aimed to assess the incidence of SARS-CoV-2 infection and hospitalization in children with and without immunocompromising conditions.
Methods: We conducted a population-based cohort study of children aged 0-14 years in the Veneto region, Italy, from February 2020-May 2023. Data were obtained from an Italian pediatric primary-care database (Pedianet) linked to the Veneto region's hospitalization and COVID-19 nasopharyngeal swab (NPS) registries. Three groups of children were included in this cohort: children with an immunocompromising condition and/or on immunosuppressive treatments (IC), non-immunocompromised children with at least one specific comorbidity other than immunocompromising diseases (non-IC), and healthy children (HC). Adjusted hazard ratios (aHR) and 95% confidence interval (CI) for the risk of SARS-CoV-2 primary infection and COVID-19 vaccine uptake among IC, non-IC, and HC were estimated using Cox proportional hazard models. Models were adjusted for several potential confounders (age, gender, deprivation index, number of visits and antibiotic prescriptions). Hospitalisations' incidence rate

(IR) and 95% CI was condidered within ten days after a positive NPS per 10,000 person days.

Results: In total, 26,606 children with active follow-up and at least one COVID-19 NPS within the study period were included in the study analysis. Overall, 23,858 were HC, 2,527 non-IC, and 221 IC. Compared to HC, we observed the same risk of SARS-CoV-2 primary infection in IC (aHR = 0.92 [95% CI: 0.57-1.48]) and non-IC (aHR = 1.05 [95% CI: 0.91-1.21]) (Figure). Among 14,968 children with a positive NPS, IC had a higher IR of being hospitalized (IR = 4.97 [95% CI:0.99-8.94]) compared to non-IC (IR = 2.72 [95% CI:1.88-3.57]) and to HC (IR = 2.03 [95% CI:1.79-2.27]) (Figure). IC (aHR = 1.32 [95% CI:1.08-1.62]) and non-IC (aHR = 1.17 [95% CI:1.09-1.25]) were more likely to be vaccinated against COVID-19 than HC (Figure).

Conclusion: Similar SARS-CoV-2 infection likelihood and higher incidence of hospitalization were observed in IC compared to HC. Greater hospitalization rates in IC may be partly due to lower thresholds for hospital admission for these patients. Hospital-setting surveillance studies evaluating additional outcomes of severity, including intensive care admission and death, are needed to confirm our findings.



*non-IC included children with at least one comorbidity which was recognized as a risk factor for severe COVID-19 other than immunocompromising diseases (i.e., type 1 diabetes, chronic pneumopathies, cardiac and circulatory congenital anomalies, and obesity).

862 Epidemiology, Clinical Features, and Severity of COVID-19 in Immunocompromised Children in Canada

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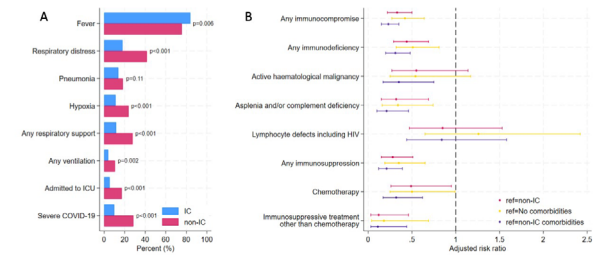
Background: The impact of immunocompromised states on pediatric COVID-19 and outcomes remains unclear. We aimed to evaluate clinical features and severity of SARS-CoV-2 infection in hospitalized children with and without immunocompromising conditions.

Methods: We conducted a national surveillance study of children <17 years hospitalized for COVID-19 from April 2020–May 2022. Data were captured through two surveillance programs The Canadian Pediatric Surveillance Program and the Canadian Immunization Monitoring Program, ACTive which covers ~90% of all Canadian tertiary-care pediatric beds. Incidental SARS-CoV-2 positive cases were excluded. Immunocompromised children (IC) were defined as those with an immunocompromising condition and/or on immunosuppressive treatment(s). Severe COVID-19 was defined as a requirement for intensive care unit (ICU) admission, ventilator or hemodynamic support, organ system complications (neurologic, cardiac, and respiratory), or death. Adjusted risk ratios (aRR) for severe COVID-19 among IC versus non-IC were calculated using robust Poisson regression, adjusted for age, sex, non-IC comorbidities, lineage, and vaccination status.

Results: Overall, 1874 children were hospitalized with COVID-19, of which 224 (12%) were IC. IC were older (median age 7 years [interquartile range (IQR) 3.6–12.0] than non-IC (1.3 years [IQR 0.3–2.9] years; p<.001) and had fewer comorbidities other than immunocompromise (31.7% vs 39.6%; p=.02). A lower frequency of respiratory distress was observed in IC compared to non-IC (17.9% vs 41.6%; p<.001). Severe COVID-19 (9.8% vs 28.4%; p<.001), as well as the need for any respiratory support (11.6% vs 27.7%; p<.001) and ICU admission (5.4% vs 17.1%; p<.001) were less frequent among IC (Panel-A). In multivariable analyses, IC were less likely to have severe COVID-19 compared to non-IC (aRR=0.33 [95%CI:0.20-0.50]). Subcategories of immunocompromise, such as immunodeficiency (aRR=0.44 [95%CI:0.29-0.69]) and immunosuppression (aRR=0.28 [95%CI:0.15-0.51]) were individually also associated with a reduced likelihood of severe COVID-19. Compared to children with comorbidities other than immunocompromise, IC were also less likely to have severe COVID-19 (aRR=0.23 [95%CI:0.15-0.35]) (Panel-B).

Conclusion: Lower risk of severe COVID-19 was observed in hospitalized IC compared to non-IC and to those with other comorbidities, potentially in part due to lower thresholds for hospital admission for IC. Population-based studies are needed to confirm these findings.

Figure. Characteristics and severity outcomes of COVID-19 among immunocompromised (IC) and non-immunocompromised (non-IC) children.



Panel-A shows COVID-19 clinical features and severity in our study population. Panel-B shows severe COVID-19 risk among IC subcategories 1) immunodeficiency (hematological malignancy, asplenia, complement deficiency, lymphocyte defects), and 2) immunosuppression (chemotherapy, other treatments) compared to non-IC children.

863 In-Hospital Mortality During Different SARS-CoV-2 Variant Waves in the EuCARE Multinational Cohort

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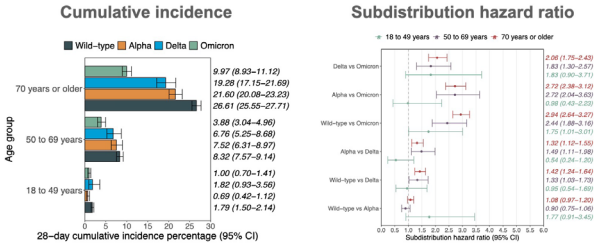
Background: Investigating outcomes of patients hospitalized with COVID-19 throughout the pandemic is crucial to understand the effects of SARS-CoV-2 variants, previous immunity, and healthcare interventions. We compared 28-day in-hospital mortality in adults hospitalized with COVID-19 caused by Wild-type, Alpha, Delta, or Omicron variants. Whether the difference in risk by variant might vary by age was also evaluated.

Methods: We conducted a multinational cohort study including patients hospitalized with COVID-19 from 9 countries (EuCARE hospitalized study). Patients >18 years, hospitalized any time from 2020-02-01 to 2022-10-15 with a SARS-CoV-2 positive test were included. Variant was classified based on sequenced viruses (if available) or from national public metadata. In-hospital mortality was compared using the cumulative incidence (CI) function and Fine-Gray sub-distribution hazard models adjusted for age, sex, and comorbidities which are risk factors for severe COVID-19. Results were shown age-stratified since there was evidence that age was an effect measure modifier.

Results: We included 38,585 SARS CoV-2 infected hospitalized patients (16,754 females and 21,831 males): 19,763 Wild-type, 6,387 Alpha, 3,640 Delta, and 8,795 Omicron. For in-hospital mortality, an interaction between age group and variant was observed (P=0.03), driven by the youngest group for whom smaller differences in mortality risk by variant were seen (Figure). In the older groups, the largest differences were observed between Omicron and the other variants. Among patients aged >70 years, the aSHR for Delta vs. Omicron was 2.06 (95% confidence interval 1.75-2.43). This estimate was 2.72 (2.38-3.12) for Alpha vs. Omicron, and 2.94 (2.64-3.27) for Wild-type vs. Omicron. Among unvaccinated patients, the aSHR was 1.33 (1.03-1.74) for Delta vs. Omicron, 1.61 (1.32-1.98) for Alpha vs. Omicron, and 1.69 (1.42-2.02) for Wild-type vs. Omicron. When comparing Omicron sublineages, the aSHR for the BA.1 sublineage was 2.04 (154-2.70) compared to the BA.2 sublineage and 1.71 (1.26-2.31) compared to the BA.5 sublineage.

Conclusion: Overall, the cumulative incidence and hazard of in-hospital mortality rates decreased throughout the study period, particularly during the Omicron period. However, contrasts varied by age, especially for those relative to the Alpha variant. BA.1 carried a higher risk of death than that seen with the more recently circulating BA.2 and BA.5 sublineages.

Age-stratified cumulative incidences and subdistribution hazard ratios for 28-day in-hospital mortality



Note: The cumulative incidence was at 28 days except for Wild-type 18-49 years (day 27), Alpha 18-49 years (day 16), and Omicron 18-49 years (day 19). The Fine-Gray subdistribution hazard models were adjusted for age, sex, and comorbidities leading to an increased risk of severe COVID-19.
Abbreviations: CI=Confidence interval

864 Effects of Pitavastatin on COVID-19 Incidence and Seriousness Among People With HIV

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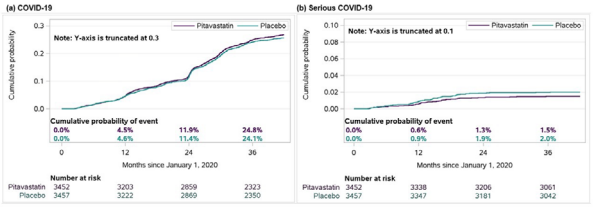
Background: Among people with HIV (PWH), COVID-19 is common and potentially severe. We leveraged data from the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) to assess effects of pitavastatin on COVID-19 outcomes (incidence and serious cases) among a global cohort of PWH. Statin therapy was a priori hypothesized to reduce serious COVID-19 by 35%, with 200 anticipated serious COVID-19 events.
Methods: COVID-19 data collection was implemented in REPRIEVE in April 2020 to capture all events from the start of 2020. COVID-19 was defined by positive test or clinical diagnosis; serious COVID-19 according to ICH definition, including life-threatening events or those resulting in hospitalization or death. Among participants in follow-up on January 1, 2020, Cox proportional hazards modeling was used to estimate the hazard ratio (HR) of COVID-19 (pitavastatin/placebo), stratified by global burden of disease region. Modification of statin effect following COVID-19 vaccination was evaluated via interaction with time-updated vaccination status.
Results: Among 6909 PWH, 32% were natal females and 41% were Black or African-American. Median age was 53 years and median 10-year ASCVD risk score 4.5%. HIV-1 viremia was suppressed in 87%, 30% had CD4 <500 cells/mm^3, 23% BMI ≥30 kg/m^2, 45% hypertension, and 3% diabetes. Treatment groups were balanced on baseline characteristics. COVID-19 was reported in 1689 participants, including 117 serious cases (Figure 1). Statin therapy did not reduce COVID-19 incidence (HR 1.05, 95% CI: 0.95-1.15) but appeared to reduce incidence of serious COVID-19 (0.75, 0.52-1.09). Among the 1689 with COVID-19, the relative risk (pitavastatin/placebo) for serious COVID-19 was 0.73 (0.52-1.03). Treatment effect size for serious COVID-19 fell within the hypothesized range, but CI crossed 1 given fewer-than-anticipated cases (117 vs. 200). 83% reported COVID-19 vaccination by end-of-study, with a strong protective effect on serious COVID-19 (HR 0.28, p<0.0001). Protective statin effect was observed prior to vaccination (0.74, 0.50-1.10; 42/58 cases), with only 17 cases observed following vaccination (0.87, 0.33-2.24; 8/9).
Conclusion: In a global cohort of PWH, statin therapy had no effect on COVID-19 incidence but showed potential to reduce the risk of serious COVID-19 prior to COVID-19 vaccination. Vaccination was protective for serious COVID-19. Additional research is needed to understand and harness potential mechanisms of protective statin effects on serious COVID-19.

Figure 1: Cumulative Probability of COVID-19 Over Time



865 The Effect of COVID-19 Infection on Fat, Lean Mass, and Bone Mineral Density

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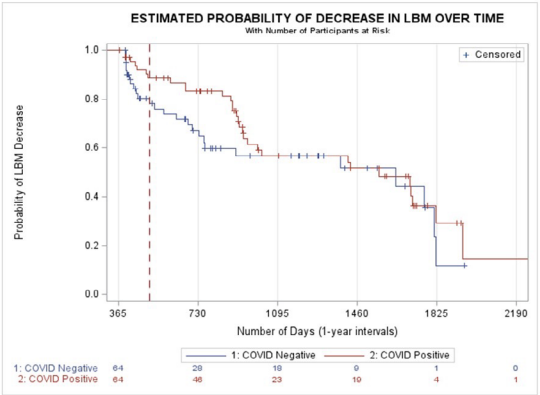
Background: The effect of COVID-19 infection, versus the indirect effect of the COVID pandemic, on changes in body composition remains unclear. This study aims to investigate long-term changes in lean body mass (LBM), total bone mineral density (BMD), and total and trunk fat in COVID – 19 survivors compared to a control group.
Methods: This is a prospective study involving adult individuals who had a pre-pandemic whole body DXA scan (DXA#1) performed between 2017-2019 as part of involvement in ongoing metabolic studies. Participants were asked to return for a repeat whole body DXA scan (DXA #2) on the same machine as DXA #1. Detailed data were collected including demographics, lifestyle factors, medications, and detailed COVID history (by diagnoses and testing). In addition, all participants underwent SARS-Co-V2 antibody testing at the time of DEXA scan. For those participants who had a COVID infection between the 2 DXA scanning, their DXA#2 was acquired at least one year after the COVID-19 infection.
Results: Overall, 128 adults were enrolled; mean age 41.7 ± 14.6 years, 55.5% non-white race, and 28% female, without differences at baseline between those who ended up COVID+ and those who did not. Half (n=64) of the participants had documented COVID infection between their 2 DXA scans (COVID+ group), and the other 50% never had COVID infection or symptoms suggestive of COVID, their SARS-Co-V2 nucleocapsid antibodies were negative and spike antibodies negative in those unimmunized (COVID-negative group). Between DXA#1 and DEXA#2, the COVID+ group had 1.3 kg gain in total fat (0.0002), 1 kg gain in trunk fat (p = 0.002) and 2 Kg weight gain (p = 0.01) without change in BMD (p = 0.45). Similar changes were found within the COVID- group without difference in the annualized rate of change between the two groups. However, the annualized change in LBM was different between COVID+ and COVID- groups (p=0.04). COVID+ adults have more than three times the risk [HR: 3.3 (95% Cis: 1.7, 6.5)] of decreasing LBM following COVID infection (log-rank, p=0.01) when compared to COVID- adults.
Conclusion: COVID – 19 infected individuals had similar changes in weight, total and trunk fat, total bone BMD compared to the COVID-negative group. Despite the lack of differences in weight and fat depots, participants who had COVID during the study experienced sarcopenia when compared to those who never had COVID. Longer term studies are needed to understand the impact of the loss of lean mass.



866 ICU-Acquired Infections More Common in Patients With COVID-19 Than in Patients With Influenza

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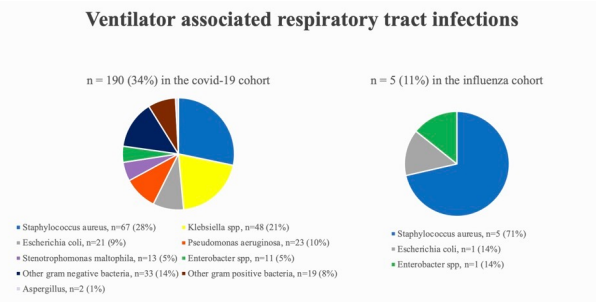
Background: During the covid-19 pandemic, intensive care unit-acquired infections (ICU-AI) were frequently diagnosed in critically ill patients. The primary aim of the study was to determine the impact of ICU-AI on mortality and ICU-stay in patients with covid-19 and influenza. The secondary aim was to compare the microbial pattern in patients with covid-19 vs influenza.
Methods: This is an observational study including (1) all patients 18 years and older treated with invasive mechanical ventilation (IMV) due to covid-19 at Sahlgrenska University Hospital (SU) January 2020–March 2022, and (2) all patients 18 years and older treated with IMV due to influenza at SU January 2015–May 2023. Data was collected from medical charts and the microbiology laboratory at SU. The definition of ICU-AI required both clinical criteria and a positive culture of a significant pathogen, according to ECDC's standards. Frequencies were compared by Fisher's exact test and continuous variables by t-test and Mann Whitney U test.
Results: A total of 480 participants were included in the final analysis, of whom 436 had covid-19. ICU-AI was confirmed in 190 patients (44%) with covid-19 and 7 patients (16%) with influenza. Ventilator associated lower respiratory tract infection (VA-LRTI) was most common, being present in 149 patients (34%) with covid-19 and in 5 patients (11%) with influenza. The most common pathogens associated with VA-LRTI are presented in the figure below. Blood stream infections were relatively common in patients with covid-19 (n = 77, 18%) but were rare in influenza patients (n = 3, 7%). Gram-positive bacteria and candida were the most frequent findings in blood cultures in both groups. Corticosteroid treatment was associated with an increased risk of ICU-AI in patients with covid-19 (adjusted OR 2.095, 95% CI 1.263–3.475). Median (range) number of days in ICU for patients with an ICU-AI was 27 (4–103) and 12 (2–69) for patients without ICU-AI ($p < 0.001$). Having an ICU-AI was also associated with an increased risk of 90-day mortality (adjusted OR 1.794, 95% CI 1.134–2.838).
Conclusion: Secondary infections were more common in critically ill patients with covid-19 than with influenza and were associated with an increased time in ICU and mortality. Gram-negative bacteria caused a majority of VA-LRTI in patients with covid-19, while S. aureus was the singular most common pathogen in VA-LRTI in patients with influenza and covid-19.



867 Plasma Thrombomodulin Predicts Thrombotic Events & Mortality in Patients Hospitalized With COVID-19

Sergio Padilla[1], Pascual Marco[2], Ana Marco-Rico[2], Christian Ledesma[1], Carolina Ding[1], Marta Fernández-González[1], Alba de la Rica[1], Javier García-Abellán[1], Paula Mascarell[1], Angela Botella[1], Nuria Ena[1], Lidia García[1], Jose Carlos Asenjo[1], Mar Masiá[1], Félix Gutiérrez[1]
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Background: Plasma concentration of soluble thrombomodulin (sTM) is a marker of endothelial damage, and its elevation has been linked to cardiovascular diseases. The study aims to evaluate the predictive potential of sTM for thrombotic events, one of the most serious complications of COVID-19.
Methods: Nested case-control study within a large cohort of hospitalized COVID-19 patients throughout the pandemic. Cases involved serious venous and arterial thrombotic events (TE) up to 28 days following hospital admission and they were compared with controls matched by sex, age, Charlson comorbidity index, and WHO-COVID-19 severity scale by propensity scores (PS) in a 1:3 ratio. We determined the plasma concentration of sTM in all available frozen samples collected prior to the TE using an automated immunoassay technique.
Results: Between March 1st, 2020 and July 31st, 2022, a total of 2524 patients were hospitalized due to SARS-CoV-2 infection (22% Omicron variant). Forty-three percent of them were female and the median (Q1, Q3) age at admission was 67 (54, 80) years. There were 75 TE (58 venous-TE: 48 pulmonary embolism (PE) and 10 deep vein thrombosis (DVT); 17 arterial-TE (AT)) accounting for an incidence rate [95% CI] of 1.17 [0.92-1.47] per 1000 patient-days of follow-up. Frozen plasma samples were available in 43 cases (29 PE, 6 DVT, 8 AT) and in 176 PS-matched controls. There was no significant correlation between sTM and D-dimer (DD) (R-Pearson [p-value] +0.01 [0.85]). Elevated plasma concentration of sTM was significantly associated with both mortality (median [Q1, Q3], 3.32 [2.16, 4.65] vs. 1.58 [1.11, 2.73] ng/mL; p=0.001) and TE (2.77 [1.67, 4.01] vs. 1.52 [1.1, 2.65] ng/mL; p=0.001), while DD showed a specific association with TE (2.1 [0.83, 5.6] vs. 0.66 [0.4, 1.12] mcg/mL; p-value=0.001). The association with thrombotic events remained in adjusted models (OR [95%CI] per unit increase, 1.31 [1.03-1.68] for sTM; 1.11 [1.02-1.28] for DD). The adjusted regression model that included both variables (sTM and DD) improved significatively the predictive capacity of the same model without sTM (p-value=0.011; sensitivity 84% and specificity 32% for TE diagnosis).
Conclusion: Elevated soluble thrombomodulin levels were significantly associated with both thrombotic events and mortality in hospitalized COVID-19 patients. The measurements of thrombomodulin, along with D-dimer plasma levels, could enhance thrombotic risk assessment in this population.

868 Decline in Time to Recovery From Mild-Moderate COVID-19 in a Large Platform Placebo-Controlled Trial

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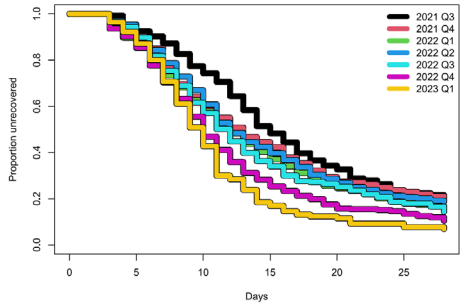
Background: Epidemiological data suggest that the duration of symptoms in patients with COVID-19 has decreased over the course of the pandemic. Robust estimates of the magnitude of change are not yet available. We estimated the change in time to recovery from COVID-19 among participants enrolled in the placebo arms of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 platform, the largest ongoing randomized clinical trial evaluating treatment of outpatients with COVID-19.
Methods: Outpatients with mild to moderate COVID-19 were randomized to one of five placebo-controlled intervention groups between June 2021 and January 2023. Participants completed daily symptom reporting for at least 14 days or until symptom resolution. We estimated time to sustained recovery, defined as the third day of 3 consecutive days without symptoms, for participants receiving placebo only. A cox proportional hazards model was used to assess differences in time to sustained recovery over yearly quartiles during the study period.
Results: Among 6,708 total participants randomized, 2,435 received a matched placebo to one of the active drugs. Overall, the median age was 48 (IQR 39-58) years, and 61% were female. The median time to sustained recovery decreased from 15 (95% CI 14-17) days in Q3 of 2021 to 10 (95% CI 9-11) days in Q1 of 2023. Among 135 participants recruited in the 3rd quarter (Q3) of 2021, only 20 (14.8%) reported any vaccination for SARS-CoV-2. This increased to 429/486 (88.3%) by Q2 of 2022. Participants recruited later in the trial had quicker time to sustained recovery ($p<0.001$) (Figure 1). The most important predictors of recovery were baseline symptom severity, the duration of symptoms, sex, and calendar time of enrollment.
Conclusion: Time to recovery in outpatients with mild to moderate COVID-19 enrolled in the placebo arms of ACTIV-6 decreased over the duration of the trial. This trend is likely multifactorial including increased vaccination, prior infection, as well as evolving SARS-CoV-2 variants and subvariants. Future trials should take this into consideration when selecting endpoints and developing statistical analysis plans.



869 Estimating Optimal Anti-TB Drug Concentrations in a Prospective, Observational Cohort in Brazil

Gustavo Amorim[1], David W. Haas[1], Marina C. Figueiredo[1], Cody Staats[1], Marcelo Cordeiro-Santos[2], Afrânio L. Kritski[3], Brian C. Hachey[1], Bruno B. Andrade[1], Timothy R. Sterling[1], Valeria C. Rolla[4], for the RePORT-Brazil Consortia

[1]Vanderbilt University, Nashville, TN, USA, [2]Fundação de Medicina Tropical Doutor Heitor Vieira Dourado, Manaus, Brazil, [3]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [4]Oswaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil

Background: Tuberculosis (TB) treatment is highly effective, but in real-world settings, >10% of TB patients experience drug toxicity or treatment failure. Current target drug levels of standard anti-TB medications (isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB)) are based on expected levels two hours after dosing. We assessed a large Brazilian cohort of pulmonary TB patients undergoing anti-TB therapy for concomitant optimal drug levels associated with minimal toxicity and maximum effectiveness.

Methods: Plasma drug levels from participants enrolled in Regional Prospective Observational Research in Tuberculosis (RePORT)-Brazil were used to estimate therapeutic drug range for all four anti-TB drugs. Pharmacokinetic (PK) analyses using drug concentrations and time since last anti-TB dose were performed using Extreme Gradient Boosting. The PK model was built using 10-fold cross-validation, adjusting for sex, BMI, HIV positivity, smoking and alcohol use, substance use, HbA1c, ancestry informative genetic markers, directly observed therapy assigned at baseline, and NAT2 acetylator status. Maximum drug concentrations (C_{max}) computed from individual PK profiles were tested for correlation with TB treatment outcomes: toxicity (Grade ≥ 3 adverse events) and treatment failure or recurrence. Safety and effectiveness bounds were defined as drug concentrations that would lead to probabilities of toxicity or treatment failure/recurrence of no more than 5%, respectively. Confidence intervals were computed after 999 bootstrap resamples. Therapeutic drug range was defined as concentrations that were both safe and effective.

Results: There were 966 plasma samples from 459 participants. Overall, 11 (2.4%) experienced toxicity after month 1, and 13 (2.8%) had treatment failure or TB recurrence. Log-transformed C_{max} for RIF was associated with greater odds of toxicity: Odds Ratio (OR) = 12.9 [95% CI=3.5-47.1]. Log-transformed C_{max} for INH, EMB, and PZA were associated with decreased odds of failure/recurrence: OR = 0.5 [0.2-0.9], OR = 0.6 [0.4-1.0], and OR = 0.4 [0.2-0.8], respectively. Therapeutic drug ranges for all four anti-TB drugs are shown in the Table.

Conclusion: Our findings suggest target Cm_ax values, particularly for INH and RIF, that differ somewhat from currently recommended targets. Further studies with less variation in PK profiles are still needed to compute optimal targets for concentration ranges.

Table: Associations of isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA) C_{max} with TB treatment in the RePORT-Brazil cohort. Estimated therapeutic drug ranges are also shown.

	Associations of C_{max} (µg/mL) with TB treatment outcomes		Therapeutic drug range (µg/mL) at two hours since last anti-TB drug		
	Effectiveness (TB treatment failure or TB recurrence) OR (95%CI)	Toxicity (Grade 3 or higher adverse drug reaction) OR (95%CI)	Estimated effectiveness bound (95% CI)	Estimated safety bound (95% CI)	Current recommend therapeutic drug range*
INH	0.5 [0.2; 0.9]	8.2 [0.9; 74.8]	2.2 [0; 3.7]	9.7 [7.9; 14.5]	3-6
RIF	0.8 [0.3, 1.9]	12.9 [3.5; 47.1]	0.8 [0; 21.6]	8.8 [7.4; 16.2]	8-24
EMB	0.6 [0.4; 1.0]	3.5 [0.5, 23.8]	0.3 [0; 0.7]	3.5 [2.6; 5.6]	2-6
PZA	0.4 [0.2; 0.8]	1.9 [0.3 12.0]	11.7 [0; 17.6]	61.6 [38.9; 64.2]	20-60

*Verbeeck et al. Optimizing treatment outcome of first-line anti-tuberculosis drugs: the role of therapeutic drug monitoring. *European J Clin Pharmacol* 72:905-916;2016.

870 Pharmacogenetic Associations With HIV-1 Virologic Suppression Among Patients with TB/HIV in Brazil

Felipe Ridolfi[1], Gustavo Amorim[1], David W. Haas[1], Maria B. Arriaga[1], Cody Staats[1], Marcelo Cordeiro-Santos[2], Afrânio L. Kritski[3], Marina C. Figueiredo[1], Bruno B. Andrade[1], Timothy R. Sterling[1], Valeria C. Rolla[4]

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Background: Human genetic variants can affect TB and HIV drug pharmacokinetics (PK), which may affect risk for toxicity or treatment failure. Here we evaluated associations between pre-specified genetic variants and HIV virologic suppression (VS) among patients treated for TB and HIV.

Methods: We included TB/HIV RePORT-Brazil participants who initiated standard TB treatment [2 months of isoniazid/rifampicin (or rifabutin)/ pyrazinamide/ethambutol, then 4 months or more of isoniazid/rifampicin (or rifabutin)], and who also received antiretroviral therapy (ART) during this period. The outcome was HIV-1 VS (for this study we considered as <50 HIV-1 RNA c/mL) after at least 2 weeks of ART. Regimens were categorized as containing an integrase strand transfer inhibitor (INSTI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). We genotyped *UGT1A1* rs887829 that affects dolutegravir (DTG) and raltegravir (RAL) PK, and *CYP2B6* rs3745274, rs28399499, rs4803419 that affect efavirenz (EFV) PK; all have defined normal, intermediate, and poor metabolizer groups. Genotyping was by MassARRAY iPLEX Gold. We compared outcome proportions (Fisher's test) and time-to-VS (survival analysis, Wilcoxon-Gehan test).

Results: Among 194 TB/HIV participants included, 88 (45%) achieved VS. RAL was the most frequent INSTI (n=88, 88%), and EFV the most frequent NNRTI (n=76, 99%; and one participant used etravirine). In the INSTI group, similar proportions of VS were achieved for *UGT1A1* normal (n=16, 39%) and intermediate (n=17, 41%) genotypes. Among participants receiving EFV, those who achieved VS were more likely to be *CYP2B6* intermediate metabolizers (n=23, 70%). There were inconclusive associations comparing the proportions of VS among INSTI- and EFV-based ART, and based on *CYP2B6* and *UGT1A1* genotypes (Table 1). Furthermore, no consistent associations were found comparing the time-to-VS among ART regimens and genotypes.

Conclusion: In this cohort of patients treated for TB/HIV, genetic variants that affect ART PK were not significantly associated with likelihood of VS.

Table 1. ART and genotype groups stratified by HIV-1 virologic suppression

ART groups[1]		HIV-1 viral load: Non-suppressed (≥50 c/mL) [n(%)]	HIV-1 viral load: Suppressed[2] (<50 c/mL) [n(%)]	*p*-value
INSTI-based ART, n=90	*UGT1A1*			
	Normal	22 (45%)	16 (39%)	*
	Intermediate	21 (43%)	17 (41%)	*
	Poor	6 (12%)	8 (20%)	*
	Total	49 (100)	41 (100)	0.66
EFV-based ART, n=64	*CYP2B6*			
	Normal	11 (36)	5 (15)	*
	Intermediate	15 (48)	23 (70)	*
	Poor	5 (16)	5 (15)	*
	Total	31 (100)	33 (100)	0.15

Footnotes: * Columns proportions do not differ significantly from each other at the .05 level
[1] Of 100 participants on INSTI-based ART, 90 (90%) had genotype data. Of 76 participants on EFV-based ART, 64 (84%) had genotype data. [2] threshold of 50 c/mL defined for this study.

871 Pharmacokinetics of Isoniazid Metabolites During Pregnancy and Postpartum

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Background: IMPAACT P1078 evaluated the safety of isoniazid (INH) preventative therapy initiated antepartum (AP) or postpartum (PP) in women with HIV (WWH). Hepatotoxicity occurred at high rates (~6-7%) across both arms during the PP period and a higher risk of adverse pregnancy outcomes was also identified among N-acetyltransferase type 2 (NAT2) slow acetylators. These adverse outcomes may be due in part to toxic INH metabolites, such as hydrazine (Hz), which have not been previously evaluated in pregnancy. INH can either be converted to acetylisoniazid (AcINH) via NAT2 and then acetylhydrazine (AcHz), or to isonicotinic acid (INA) via amidases, with both pathways contributing to Hz

formation. Here we describe the PK of INH, INA, AcINH, AcHz, and Hz in AP and PP WWH receiving IPT.

Methods: Samples and data from intensive PK assessments among WWH enrolled in P1078 were included in the analysis. WWH received INH 300 mg once daily for at least 2 weeks prior to the intensive PK assessment. Samples were collected at 0, 1, 2, 4, 6, 8 and 12 h post-dose. Intensive PK during AP occurred ≥28 weeks of gestation and 16 (±2) weeks PP. INH, INA, AcINH, AcHz, and Hz were quantified using a validated LC-MS/MS method (lower limit of quantification 10 ng/mL for all analytes). PK data were analyzed using noncompartmental methods. Data were summarized descriptively by pregnancy stage and NAT2 acetylation status (fast, intermediate, slow). Linear mixed models were used to compare percent differences (95% confidence intervals [CI]) between AP vs. PP for each analyte.

Results: Data from 31 WWH were analyzed (10 AP and PP, 4 AP only, 17 PP only). The median (range) gestational age at entry was 26 (14-34) weeks. Maternal median (range) age was 29 (18-41) years with 81% Black and 19% Asian. Observed AcINH exposures were higher among intermediate and fast acetylators, whereas INH, INA, and AcHz exposures were higher in intermediate and/or slow acetylators (Table). INA and AcHz were lower AP versus PP after controlling for NAT2 status. Hz was quantifiable in 5/14 AP and 23/27 PP WWH, with numerically higher AUCs observed PP.

Conclusion: These data demonstrate relationships between NAT2 and the formation of INH metabolites in pregnant and postpartum WWH. INA and AcHz AUCs were higher and Hz was detectable in more women during PP. Analyses to examine the influence of pregnancy and other factors affecting INH metabolite PK in the overall study population and potential associations with hepatotoxicity in P1078 are ongoing.

Table. Influence of Pregnancy and NAT2 Status on INH and Metabolite AUCs

Analyte	AP AUC (uM*hr)			PP AUC (uM*hr)			AP vs. PP[a]
	NAT2 Fast (n=2)[b]	NAT2 Intermediate (n=6)	NAT2 Slow (n=6)	NAT2 Fast (n=7)	NAT2 Intermediate (n=13)	NAT2 Slow (n=7)	Percent Difference (95% CI)
INH	31.9	57.7 (29.0)	142 (20.8)	82.3 (145)	80.5 (25.8)[c]	155 (18.9)	-9.2% (-21.6%, 5.0%)
AcINH	127	83.1 (45.8)	31.3 (34.5)	87.6 (60.9)	100 (53.3)[c]	33.9 (33.3)	-11.3% (-27.1%, 7.9%)
INA	16.8	34.3 (83.1)	26.3 (39.3)	29.6 (40.2)	47.4 (59.6)	43.3 (27.6)	-36.4% (-52.3%, -15.2%)
AcHz	20.2	46.4 (55.7)	39.4 (25.4)	41.0 (47.5)	61.1 (48.3)	66.3 (31.0)	-37.0% (-50.6%, -19.8%)
Hz[d]	--	2.75[b]	2.47 (75.1)	6.05 (36.6)	3.90 (28.1)	7.71 (34.4)	--

Data presented as geometric mean (geometric %CV). [a]AP vs. PP after controlling for NAT2 status
[c]CV not reported [b]n=12 [d]AP: n=1 intermediate, 4 slow; PP: 5 fast, 11 intermediate, 7 slow

872 Testicular Safety of a Pretomanid Regimen (BPaMZ) in Men With Pulmonary Drug-Resistant Tuberculosis

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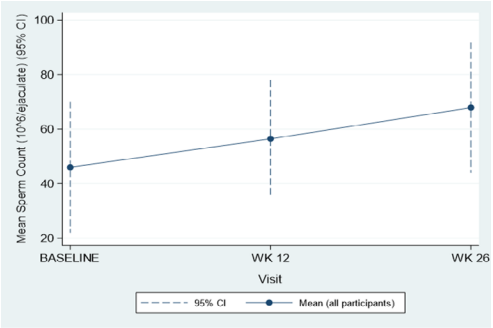
Background: Testicular toxicity was observed in rodents exposed to high doses of pretomanid. Pretomanid is approved for use in treatment regimens for drug-resistant tuberculosis (DR-TB). This study evaluated the testicular safety of 26 weeks of pretomanid in adult males with DR-TB as part of a BPaMZ (bedaquiline, pretomanid, moxifloxacin, pyrazinamide) regimen.

Methods: Twenty-six men with DR-TB were enrolled at 4 sites in South Africa and Georgia. They received BPaMZ at recommended doses for 26 weeks, with a 52-week safety follow-up. The primary outcome was the change from baseline in total sperm count at Week 26. Secondary outcomes included change from baseline in total sperm count at Week 12 and 44; change from baseline over time in sperm concentration, sperm volume, and male reproductive hormones (testosterone, inhibin B, FSH, LH).

Results: Of 26 men enrolled, 22 completed treatment and were assessed for study endpoints. Among completers, mean age was 36 years, 68% were Black and 36% living with HIV. At the Week 26 timepoint (primary outcome), mean total sperm count increased from baseline by 20.0x106 sperm/ejaculate. Mean sperm concentration increased from baseline at Week 26 by 25.8x106 sperm/mL. For both total sperm count and sperm concentration, 13/22 (59%) participants had a >50% increase by Week 26. At Week 26, 2 participants had a >50% decrease in total sperm count, maybe due to low semen volume, while none had a >50% decrease in sperm concentration. There was large variability in sperm parameters among participants. Mean semen volume was unchanged at both Week 12 and 26. Reproductive hormone changes showed improved gonadal status, consistent with improved spermatogenesis. Body weight increased, indicating improved health status. Sputum cultures were negative in all participants from Week 8 onwards. Of 26 enrolled participants, 2 discontinued treatment due to elevated liver enzymes, one due to pyrazinamide resistance and one withdrew consent. Two participants experienced serious adverse events (infectious exacerbation of bronchiectasis and increased liver enzymes).

Conclusion: This is the first study designed to investigate severe testicular toxicity in adult males with DR-TB. Results show that pretomanid, as part of the BPaMZ regimen, does not appear to have negative effects on reproductive function in adult males with DR-TB.



873 Cardiac Involvement in Tuberculosis Patients at the Start and End of Treatment in Southern Africa

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Background: Tuberculosis (TB) primarily affects the lungs but can also involve cardiovascular structures such as the pericardium. Little is known about the type, frequency, and clinical significance of cardiovascular involvement in people with TB. We established two cohorts in Zambia and South Africa to measure pulmonary and cardiovascular complications in HIV-positive and HIV-negative TB patients before and after TB treatment.

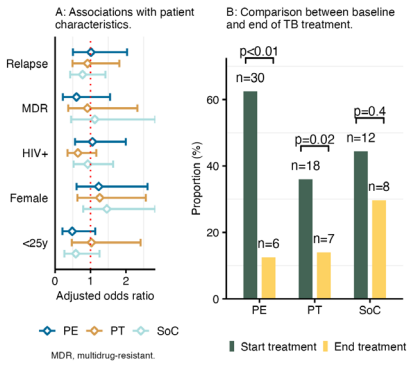
Methods: As part of the ongoing TB cohort, we consecutively recruited clinically or microbiologically confirmed TB patients (>15 years old) between October 2022 and July 2023 in Lusaka/Zambia and Johannesburg/South Africa. Clinical and laboratory data were collected electronically from all participants. We performed standardized transthoracic echocardiography at the start (baseline) and at the end of TB treatment (6-month follow-up). We estimated associations of pericardial changes with baseline characteristics using linear regression models.

Results: We included 240 TB patients; 50 had follow-up images. The median age was 34 years (Interquartile range: 28-42 years); 187 (78%) were men, and 92 (38%) were HIV-positive. At baseline, most frequent echocardiographic abnormalities were pericardial effusion (PE; 116 persons, 48%) and pericardial thickening (PT; 82, 34%), followed by left atrial (LA) dilatation (39/225, 17%) and pericardial calcifications (7, 3%); 4/49 (8%) had diastolic dysfunction. Signs of constriction (SoC) were observed in 94/201 (47%) patients and a definitive diagnosis of constriction was made in 15/70 (21%) patients at baseline. Abnormal LV geometry was found in 111/228 (49%) patients, most commonly concentric remodeling (97, 87%). LV dilatation was seen in 2/225 (1%) patients and RV dilation in 14/208 (7%). Left ventricular (LV) systolic function was preserved in almost all patients (235/237, 99%), and right ventricular (RV) systolic dysfunction was observed in 11/224 (5%) patients. PT tended to be negatively associated with HIV infection, PE with younger age (Figure A). In 50 patients with follow-up imaging, pericardial changes tended to improve during TB treatment (Figure B).

Conclusion: Cardiac involvement of TB patients at the time of treatment start were relatively frequent, particularly signs of constrictive pericarditis. Pericardial thickening tended to be less frequent in TB patients with HIV. Outcomes tended to improve during treatment, but long-term outcomes

such as heart failure and constriction need to be studied beyond the end of TB treatment.

Figure. Pericardial effusion (PE), pericardial thickness (PT), and signs of constrictions (SoC) in tuberculosis patients in South Africa and Zambia.



874 Efficacy and Safety of endTB Regimens for Fluoroquinolone-Susceptible RR-TB in People With HIV

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Background: endTB (NCT02754765) was an open-label Phase 3 randomized, controlled clinical trial to evaluate the efficacy and safety of five 9-month, all-oral regimens for fluoroquinolone-susceptible rifampin-resistant TB, compared to the WHO-recommended standard of care, in people 15 years of age or older. In the primary analysis, three experimental regimens (9BLMZ, 9BCLLfxZ, and 9BDLLfxZ) had noninferior efficacy compared to the control and were safe. Here, we present efficacy and safety results among people with HIV (PWH).

Methods: endTB inclusion was irrespective of HIV status or CD4 count. The safety population included all randomized participants who started study treatment, and the modified intention-to-treat (mITT) population included those in the safety population who had a positive pre-randomization TB culture and no resistance to study drugs. The primary efficacy endpoint was favorable outcome at Week 73 post-randomization, defined as either [1] two consecutive, negative cultures (one between Weeks 65 and 73); or [2] favorable evolution. Unfavorable outcomes included death, treatment failure, drug addition/replacement, and retreatment. Safety outcomes were Grade 3-4 adverse events (AEs); serious AEs (SAEs); deaths; AEs of special interest (AESIs) defined as Grade 3-4 hepatotoxicity, myelosuppression, optic neuritis, peripheral neuropathy, or prolonged QTcF; and AEs leading to permanent discontinuation of at least one drug.

Results: From 2017-2021, we randomized 754 participants in 7 countries; 104 (13.8%) were PWH. The safety population included 103 (99.0%) and the mITT 98 (94.2%). Median age was 39 years (range 19-70 years); 46 (46.9%) were female; median CD4 count was 296 (range 5-1294); and 61 (62.2%) were on antiretrovirals at baseline. Two of the noninferior experimental arms from the endTB trial demonstrated high efficacy in PWH, with favorable outcomes in 93.3% (9BLMZ) and 100.0% (9BCLLfxZ). The remaining three experimental arms and the control also performed well but showed relatively lower efficacy: 70.6% (9BDLLfxZ), 83.3% (9DCLLfxZ), 73.3% (9DCMZ), and 89.5% (control). Grade 3-4 AEs, SAEs, AESIs, and AEs leading to drug discontinuation were more common in the control than in experimental arms.

Conclusion: Among regimens that were noninferior to the WHO control in the primary analysis, 9BLMZ and 9BCLLfxZ appeared to be particularly efficacious and safe for PWH. Additional research is needed to establish optimal all-oral shorter regimens in PWH.

Table 1. Efficacy and safety of endTB regimens for fluoroquinolone-susceptible RR-TB in people with HIV at Week 73.

Efficacy outcome (mITT population)	endTB1 (9BLMZ) (n = 15)	endTB2 (9BCLLfxZ) (n = 14)	endTB3 (9BDLLfxZ) (n = 17)	endTB4 (9DCLLfxZ) (n = 18)	endTB5 (9DCMZ) (n = 15)	endTB6 (Control) (n = 19)	Total (N = 98)
Favorable outcomes at Week 73, 95% CI	14 (93.3%) [68.1%;99.8%]	14 (100.0%) [76.8%;100.0%]	12 (70.6%) [44.0%;89.7%]	15 (83.3%) [58.6%;96.4%]	11 (73.3%) [44.9%;92.2%]	17 (89.5%) [66.9%;98.7%]	83 (84.7%) [76.0%;91.2%]
Safety outcome (safety population)	(n = 17)	(n = 15)	(n = 18)	(n = 18)	(n = 16)	(n = 19)	(N = 103)
At least one grade 3 or higher AE or SAE of any grade	11 (64.7%)	8 (53.3%)	12 (66.7%)	12 (66.7%)	8 (50.0%)	16 (84.2%)	67 (65.1%)
At least one SAE	7 (41.2%)	4 (26.7%)	6 (33.3%)	7 (38.9%)	3 (18.8%)	9 (47.4%)	36 (35.0%)
Death	1 (5.9%)	0 (0%)	2 (11.1%)	1 (5.6%)	0 (0%)	0 (0%)	4 (3.9%)
At least one AESI	9 (52.9%)	6 (40.0%)	4 (22.2%)	7 (38.9%)	4 (25.0%)	11 (57.9%)	41 (39.8%)
At least one AE leading to permanent discontinuation of ≥1 drug	6 (35.3%)	4 (26.7%)	8 (44.4%)	3 (16.7%)	1 (6.3%)	13 (68.4%)	35 (34.0%)

B=bedaquiline; C, clofazimine; D, delamanid; L, linezolid; Lfx, levofloxacin; M, moxifloxacin; Z, pyrazinamide.
* Calculated as the percent of participants with favorable outcome in the experimental minus control arms.

875 Changes in Physical and Mental Health Among TB Patients During Treatment in Southern Africa

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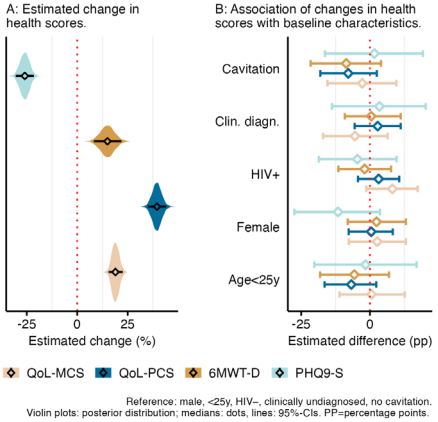
Background: Tuberculosis (TB) contributes to high morbidity and mortality worldwide. TB may also impair people's quality of life (QoL) and physical fitness. We studied the change in health-related QoL and functional exercise capacity (cardio-pulmonary function) in TB patients living with and without HIV between treatment start and end.

Methods: We recruited people with TB aged ≥15 years between October 2022 and July 2023 in five ongoing cohorts in Zambia, South Africa, Malawi, Mozambique, and Zimbabwe. At the start (baseline) and end of TB treatment, we measured physical and mental health outcomes using the standardized QoL Short Form Health Survey (SF-12), depression using the Patient Health Questionnaire (PHQ-9), and physical fitness using the 6-min walk test (6MWT). We also collected age, sex, HIV status, type of diagnosis (clinical vs microbiologically confirmed), chest X-ray findings, and TB multidrug resistance. We estimated changes in the QoL physical (QoL-PCS) and mental (QoL-MCS) t-score component, the depression score (PHQ9-S), and 6MWT distance (6MWT-D) between the start and end of TB treatment. We estimated the association of these changes with baseline characteristics using Bayesian multivariable log-linear regression models and cohort-specific random effects.

Results: We included 200 TB patients with at least one outcome at the start and end of treatment. Overall, the median age was 36 years (Interquartile Range [IQR]: 28-43 years), 55 (27%) female, 79 (40%) living with HIV, 101 (51%) were clinically diagnosed, 34 (17%) had lung cavitations, and 3 (1%) presented with TB drug resistance. At treatment start, overall median QoL-PCS was 37 (IQR 29-43), QoL-MCS was 44 (IQR 39-50), PHQ9-CS was 6 (IQR 3-10), and 6MWT-D was 400m (IQR 332-464). QoL-PCS increased by 39% (95%-Credible Interval [CI] 35-44%), QoL-MCS by 19% (95%-CI 16-22%), 6-MWT-D by 15% (95%-CI 8-22%), and PHQ9-S decreased by 26% (95%-CI 22-31%) (Figure A). Lung cavitations tended to be negatively associated with improvements in QoL and physical fitness, and female gender was negatively associated with QoL-MCS (Figure B). Recruitment and study visits six months after completion of TB treatment are ongoing.

Conclusion: QoL and physical fitness were reduced at the start of treatment in South African TB patients but improved by the end of treatment. More emphasis should be placed on improving clinical management with respect to QoL and mental health aspects during and after TB treatment.

Figure.



876 Cryptococcal Meningitis as an Indicator for Monitoring HIV Treatment Program Success in Botswana

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Background: Cryptococcal meningitis (CM) remains a frequent opportunistic infection among individuals living with advanced HIV disease (AHD) in much of Africa. Despite widespread expansion of ART programmes, modelled estimates indicate that the incidence of CM has not substantially decreased between 2014 and 2020, suggesting that the prevalence of AHD remains high in the region. CM incidence could provide a useful indicator for monitoring AHD rates and HIV program success, especially in the context of declining access to CD4 testing; most patients present to healthcare facilities with a well-defined clinical syndrome, and diagnosis can be made using low-cost and highly accurate rapid diagnostic tests. Very few countries collect reliable statistics on CM incidence, and the impact of WHO universal HIV treatment guidelines on the incidence of AHD is not known.

Methods: We analyzed 8 years of national meningitis surveillance data (2015-2022) captured from electronic health records in Botswana. All laboratory records from cerebrospinal fluid samples analysed within government healthcare facilities in Botswana were extracted from a central online repository. Adjustments for missing data were made based on triangulation for underestimates using comprehensive prospective datasets. CM case frequency was enumerated using a case definition and incidence was calculated using national census data.

Results: A total of 1,744 episodes of CM were identified. The estimated national incidence of CM in Botswana approximately halved between 2015 and 2022, from 15.0 cases/100,000 person years (PYO) (95% CI 13.5-16.7 cases/100,00) to 7.43 cases/100,000 PYO (95% CI 6.4-8.6 cases/100,000). Among all people living with HIV, the incidence of CM decreased from 92.0 cases/100,000 PYO (95% CI 82.2-102.6 cases/100,000 PYO) to 49.1 cases/100,000 PYO (95% CI 42.2-57.0 cases/100,000 PYO) between 2015 and 2022. There was no clear increase in the rate of decline following the introduction of universal treatment in 2016. The highest incidence was observed in men and individuals aged 40-44. The proportion of cases diagnosed through rapid cryptococcal antigen (CrAg) testing increased during the study period from 35.5% to 86.3%.

Conclusion: CM incidence has decreased with expanded ART treatment but persists at a relatively high rate despite excellent reported ART coverage. Most cases are now diagnosed through the rapid CrAg lateral flow assay highlighting the potential of using CM as key indicator for programme success in the Treat All era.

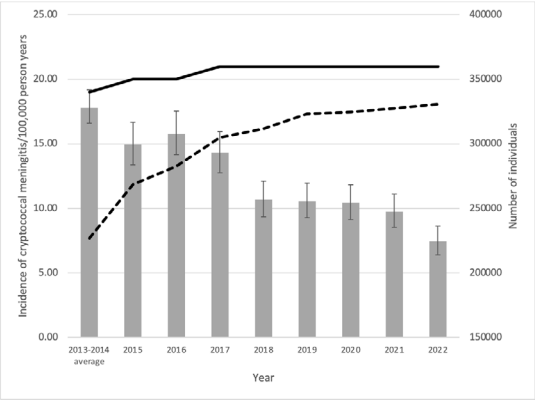

Figure 1 *Incidence of cryptococcal meningitis in Botswana/100,000 person years of observation from 2013-2022 (bar chart), overall incidence and 95% confidence intervals. UNAIDS estimate of total numbers of people living with HIV (black line) and number of people receiving ART (dotted line).*

877 Effect of Smoking on Longitudinal Interferon-ϒ Release Assay Results Among Tuberculosis Contacts

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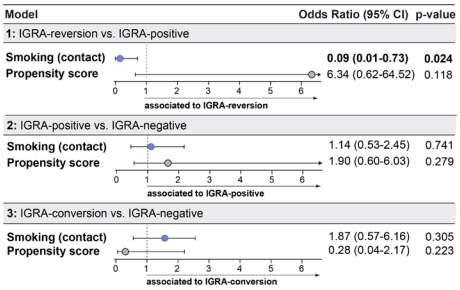
Background: Diagnosis of M. tuberculosis (Mtb) infection in close tuberculosis (TB) contacts is critical for TB control. Interferon-gamma release assays (IGRAs) diagnose Mtb infection, but the test is limited by assay variability, including the conversion (negative to positive) and reversion (positive to negative) of IGRA responses that may not always reflect changes in Mtb infection status. Several studies have revealed that smoking is a risk factor for Mtb infection and TB disease but its effect on longitudinal IGRA results remains unknown.

Methods: We conducted a multi-site prospective study in RePORT-Brazil between 2015-2019 among close contacts of adults with culture-confirmed pulmonary TB. IGRA testing was performed at baseline, month 6 and month 24-30 after enrollment. IGRA results were categorized as IGRA-positive (maintained from baseline to last visit), IGRA-conversion (from negative to positive at any time), IGRA-reversion (from positive to negative at any time), and IGRA-negative (maintained from baseline to last visit). Associations between IGRA results and smoking status at baseline (current/former vs never) in contacts were evaluated using propensity score-adjusted logistic regression models to avoid overfitting. More specifically, we first estimated the propensity of smoking using Lasso. Next, this estimated propensity score was used as a covariate in the main outcome model, which regressed the outcome (IGRA-positive, IGRA-conversion, IGRA-reversion) on smoking status.

Results: There were 430 close contacts of 139 TB cases. Of the contacts, 89 (21%) were IGRA-positive, 30 (7%) were converters, and 30 (7%) were reverters; 22 (5.1%) had an indeterminate result. The frequency of smoking among contacts was 26 (29.2%), 7 (23.3%) and 3 (10%) in IGRA-positive, IGRA-conversion and IGRA-reversion groups, correspondingly. Smoking in contacts was associated with lower odds for IGRA-reversion (adjusted odds ratio=0.09; 95% confidence interval=[0.01;0.73]). We did not detect associations between smoking and IGRA-positive or IGRA-conversion at the 5% level.

Conclusion: Contacts who reported smoking (past/former) had lower odds of reverting from an IGRA-positive to an IGRA-negative result. Our findings highlight the importance of smoking on longitudinal IGRA results. This has implications for clinical care and clinical trials in which IGRA status is monitored or used as an outcome, such as TB vaccine trials.



878 Viral Suppression Among Adults Receiving Dolutegravir-Based ART and 3-Months Isoniazid-Rifapentine

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Background: Prior studies have reported conflicting results regarding the safety and/or effectiveness of rifapentine-based tuberculosis (TB) preventive therapy with dolutegravir (DTG)-based ART. In an interim analysis, we previously found that co-administration of 3HP (3 months weekly isoniazid+rifapentine) with TDF/3TC/DTG (TLD) was safe for adults initiating routine ART, but that those who received 3HP+TLD were less likely to achieve 6-month viral suppression compared to those who received TLD alone. Here, we present an updated analysis of 1) safety of 3HP+TLD and 2) viral suppression among those initiating 3HP+TLD vs TLD alone.

Methods: In an ongoing phase 3 randomized trial comparing two TB screening strategies among adults with HIV initiating routine ART in Uganda (NCT04557176), participants who screened negative for TB were assessed for

3HP eligibility using a standardized questionnaire and liver enzyme testing; those eligible initiated self-administered 3HP two weeks after ART initiation. HIV viral load (VL) was measured as part of routine care at 6 and 12 months. We evaluated 3HP discontinuation due to drug toxicity among participants receiving 3HP+TLD, and compared viral suppression (VL≤50 copies/mL) among adults who initiated 3HP+TLD vs TLD alone using chi-square tests and log-binomial regression.

Results: From November 2020 to January 2023, 1,379 participants without TB initiated TLD, including 539 (39.1%) who initiated 3HP (163 participants receiving 3HP+TLD were previously reported). Those who initiated 3HP+TLD were more likely to be male (35% vs 31%, p=0.06) and had higher pre-ART CD4 counts (median 296 vs 238 cells/μL, p<0.01) than those who initiated TLD alone. Overall, 509 of 539 (94%) participants completed 3HP; reasons for discontinuation included adverse events (n=2), TB diagnosis (n=3), pregnancy (n=3), and self-discontinuation (n=22). Of 974 (71%) participants with 6-month VL results and 536 (39%) participants with 12-month VL results, there was no difference in viral suppression (VL≤50 copies/mL) between those who received 3HP+TLD vs TLD alone (6-months: 72.7% vs 72.8%; adjusted risk ratio [aRR] 1.00, 95%CI 0.93-1.08; 12-months: 76.3% vs 77.3%; aRR 0.97, 95%CI 0.89-1.07).

Conclusion: Co-administration of 3HP+TLD was well-tolerated, with high completion. Now with data from 1,379 participants, and contrary to our interim findings, there was no difference in viral suppression between those receiving TLD+3HP versus TLD alone.

A. Baseline characteristics	Total N=1,379	3HP+TLD N=539	TLD N=840	p-value
Female sex	931 (67.5%)	348 (64.6%)	583 (69.4%)	0.06
Median pre-ART CD4 count, cells/μL (IQR)	257 (136-403)	296 (172-477)	238 (120-365)	<0.01
Median BMI, kg/m^2 (IQR)	22.9 (20.5-25.8)	22.8 (20.7-25.7)	23.0 (20.4-25.9)	0.89
B. 6-month follow-up	**Total N=974**	**3HP+TLD N=418**	**TLD N=556**	**p-value**
Median $\log_{10}$ viral load (IQR)	1.70 (1.70-1.76)	1.70 (1.70-1.75)	1.70 (1.70-1.76)	0.97
VL ≤50 copies/mL	709 (72.8%)	304 (72.7%)	405 (72.8%)	0.97
VL ≤200 copies/mL	865 (88.8%)	378 (90.4%)	487 (87.6%)	0.16

879 Outcomes of Adults With HIV Receiving TB Preventive Therapy in Kampala, Uganda

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Background: After decades of underuse, tuberculosis preventive therapy (TPT) underwent rapid scale-up in Uganda in 2020 as part of a national campaign. This campaign overlapped with a pragmatic trial comparing the impact of TB screening strategies on TPT uptake among antiretroviral therapy (ART)-naïve adults that also included standardized protocols for assessing TPT eligibility and TPT-specific follow-up. We compared clinical outcomes among trial participants who received study- vs clinic-initiated TPT.

Methods: In an ongoing randomized controlled trial (NCT04557176), participants who screened negative for TB were assessed for 3HP (3-months weekly isoniazid+rifapentine) eligibility using a standardized questionnaire and liver enzyme testing. Eligible participants started self-administered 3HP two weeks after ART initiation; participants were assessed monthly for adverse events (AEs) using standardized checklists and adherence by pill count. Those ineligible for study-initiated 3HP were reassessed through routine care after three months and were offered clinic-initiated, self-administered TPT (isoniazid or 3HP) based on clinical assessment. Completion of clinic-initiated TPT was assessed by recall at the end of treatment. We compared personal characteristics, TPT completion and TB incidence among participants initiating study- vs clinic-initiated TPT.

Results: Of 1,719 total participants, 541 (31%) received study-initiated 3HP and 235 (14%) received clinic-initiated TPT (94% isoniazid, 6% 3HP). Median follow-up was 584 days (IQR 422-727). Study-initiated participants were younger (median 29 vs 32 years, p=0.01), more often female (65% vs 59%, p<0.01), and had higher pre-ART CD4 counts (median 295 vs 138 cells/μL, p<0.01) than clinic-initiated participants. Permanent TPT discontinuations due to suspected AEs were uncommon for both groups (≤1.5%), but completion was higher for study- than clinic-initiated TPT (94.5% vs 76.6%, p<0.01; Table). TB incidence was lower among participants initiating TPT through the study than through the clinic (0.2% vs 2.1%, p=0.01).

Conclusion: Participants initiating 3HP through a randomized trial had higher CD4 counts, were more likely to complete TPT and had lower TB incidence than those who received TPT through routine clinic procedures. Standardized protocols to assess TPT eligibility, monitor AEs and ensure completion will be critical to optimizing the impact of TPT among people initiating ART in high TB/HIV burden settings.

Table. Outcomes among participants with HIV receiving study- vs clinic-initiated TPT

	Study-initiated TPT N=541	Clinic-initiated TPT N=235	p-value
Median time to TPT start, days (IQR)	14 (14-15)	91 (90-153)	<0.01
TPT discontinued due to AE	2 (0.4%)	3 (1.5%)	0.12
Completed TPT†	511 (94.5%)	180 (76.6%)	<0.01
Incident TB*	1 (0.2%)	5 (2.1%)	0.01

Abbreviations: TPT (tuberculosis preventive therapy); IQR (interquartile range); AE (adverse event); TB (tuberculosis).
Legend: †TPT completion was assessed through recall; data on completion were missing for 42 clinic-initiated participants. *Incident TB among study-initiated participants diagnosed by Xpert MTB/RIF (1) and clinic-initiated participants by Xpert Ultra MTB/RIF (4) and culture only (1); all participants with incident TB reported completing TPT.

880 Long-Acting Injectable Rifapentine With Activity in a Mouse Model of Tuberculosis Preventive Therapy

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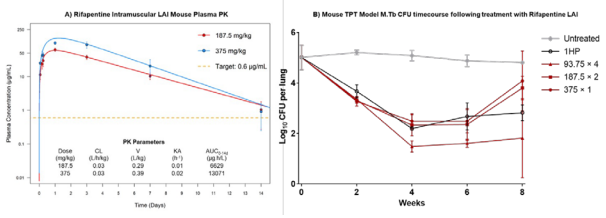
Background: Use of long-acting injectables (LAIs) has the potential to simplify tuberculosis preventive therapy (TPT) addressing issues such as pill burden and adherence. Rifapentine (RPT) is a key component of shorter TPT regimens and has physicochemical and pharmacokinetic (PK) properties amenable to LAI formulation. The aim of this work was to characterize preclinical performance of a new RPT single phase spray dried nanosuspension LAI for use in TPT.

Methods: Single intramuscular dose PK profiles were first characterized in mice and rats. Based on mouse PK, 8 RPT-LAI regimens were used to evaluate bactericidal activity in a validated mouse model of TPT. RPT (93.75, 187.5, and 375 mg/kg) was administered via 1, 2 or 4 injections over 4 weeks in expectation of clearing a 0.6 μg/mL plasma target. With 3 control groups [untreated negative control; positive control daily oral isoniazid and RPT (1HP); 4 weeks of oral RPT], a total of 186 adult female BALB/c mice were used. Lung bacterial colony-forming units (CFU) counts and plasma RPT exposures were measured 2-8 weeks after the start of treatment. Group mean CFU counts were analyzed using 1-way ANOVA and plasma exposure with compartmental PK analysis.

Results: LAI-RPT demonstrated dose-linear PK for single injection doses of 187.5 and 375 mg/kg (AUC0-14d 6629 and 13071 μg·h/mL, respectively) in mice, with PK disposition parameter estimates in keeping with reported mouse RPT values and a release-dependent, "flip-flop" terminal phase (Fig.1A). As for other successful LAI which demonstrate longer half-lives in larger species, longer exposure durations were observed in rats. All RPT-LAI regimens had bactericidal activity in mice, which was dose-dependent and greatest when divided into 4 weekly injections. Several regimens had bactericidal activity equal to or greater than the 1HP control regimen: 375 mg/kg x 1, 93.75 mg/kg x 2, 187.5 mg/kg x 2, 93.75 mg/kg x 4, and 46.9 mg/kg x 4 injections (Fig.1B). PK after 2nd, 3rd or 4th dose in multiple injection regimens were inconsistent with single injection PK, with plasma exposures falling below 0.6 μg/mL target by 1 week post dose.

Conclusion: These data provide proof-of-concept for RPT-LAI to achieve efficacy comparable to 1HP in a validated mouse TPT model. Cross-species PK data suggest that efficacious RPT exposures should be achievable in humans. Further work to characterize the impact of repeat dosing on PK and conduct GLP toxicology studies to support first in human evaluation are underway.



881 One-Dose Efficacy of Long-Acting Injectable Diarylquinoline in Mouse Model of TB Preventive Therapy

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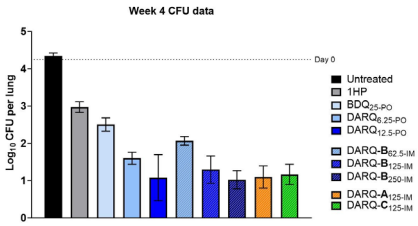
Background: Use of long-acting injectables (LAIs) has the potential to simplify tuberculosis (TB) preventive therapy (TPT) addressing issues such as pill burden and adherence. Bedaquiline (BDQ) is a key drug in new short-course regimens for treatment of rifampin-resistant TB and could provide a short-course "pan"-TPT option for drug-susceptible and rifampin-resistant infections. BDQ and other diarylquinolines (DARQ) have physicochemical and pharmacokinetic (PK) properties amenable to LAI formulation. The aim of this work was to preclinically characterize a new more potent DARQ as a single phase spray dried nanosuspension LAI formulations for use in TPT.
Methods: Single intramuscular dose PK profiles for 3 DARQ LAI formulations (formulations A-C) were characterized in mice. Based on mouse PK, formulation B was tested for bactericidal activity in a validated BALB/c mouse model of TPT at single intramuscular (IM) doses of 62.5, 125 and 250 mg/kg, with the goal of maintaining a ≥36 ng/mL plasma target for 4-8 weeks. Formulations A and C were tested only at 125 mg/kg. Negative controls were untreated. Positive controls received daily (5 days/week) oral isoniazid-rifapentine (1HP), oral BDQ or oral DARQ for 4 weeks. Lung bacterial colony-forming units (CFU) counts and plasma DARQ exposures were measured 4-12 weeks after the start of treatment. Group mean CFU counts were analyzed using 1-way ANOVA and plasma exposure with non-compartmental PK analysis.
Results: All DARQ LAI regimens had bactericidal activity over the first 4 weeks of treatment that was superior to 1HP ($p<0.0001$) and oral BDQ ($p<0.0001$ except $p=0.05$ for 62.5 mg/kg) and similar in magnitude to the same total DARQ dose given orally over 4weeks (Fig). Activity was dose-dependent for formulation B and similar for the 3 formulations at 125 mg/kg. Median DARQ C_{max} was <1 µg/ml. Median AUC0-4w values were 137, 186 and 349 µg-h/ml and plasma concentrations were ≥36 ng/ml for 4, 6 and >6 weeks after the 62.5, 125 and 250 mg/kg doses of formulation B, respectively. Lung CFU and PK data at 8 and 12 weeks post-dose are pending.
Conclusion: These data provide proof-of-concept for a highly efficacious pan-TPT regimen comprised of a single IM dose of an LAI DARQ formulation. Further preclinical development including studies to define the PK target, human dose estimates and GLP toxicology evaluation is highly warranted.



882 Single Cell Transcriptomics Reveals Depletion of TB-Specific Th1 and Th17 Cells After HIV Infection

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Background: HIV substantially increases the risk of progression of Mycobacterium tuberculosis (Mtb) infection to active tuberculosis (TB) disease. This heightened risk of developing TB persists even in people with suppressed viral loads on long-term antiretroviral therapy (ART). The mechanisms underlying the loss of immune control of Mtb in people with HIV (PWH) remains unclear. We hypothesized that HIV dysregulates Mtb-specific CD4 T cells and that initiation of ART early following HIV infection will better preserve their functional capacity.
Methods: PBMCs were collected from a longitudinal cohort of women who engage in sex work in Mombasa, Kenya. PBMCs were evaluated from women within one year before and after HIV acquisition (n=5), and from women with HIV before and after ART initiation (n=8). PBMCs were incubated overnight with Mtb whole-cell lysate, followed by FACS sorting to purify CD40L+CD69+ Mtb-specific CD4 T cells for single-cell RNA-sequencing (scRNA-seq) using the 10X Genomics platform.
Results: Unsupervised clustering of scRNA-seq data revealed that distinct populations of Mtb-specific Th1 and Th17 cells are depleted after HIV infection. Differential gene expression analysis indicated decreased expression of genes encoding multiple effector molecules, including *IFNG*, *IL22*, *TNF*, *IL17F*, *GZMB*, *GZMA*, and *GNLY*, in Mtb-specific CD4 T cells in the first year after HIV infection, compared with Mtb-specific CD4 T cells from the same individuals before HIV infection. Moreover, PWH who initiated ART within 6 months of HIV infection exhibited increased proportions of Th1 and Th17 cells following ART compared with before ART, whereas recovery of Mtb-specific Th1 and Th17 cells was not observed in PWH who initiated ART >1 year after HIV acquisition. Additionally, multiple cytokine genes, including *IFNG*, *IL2*, *IL22*, and *TNF*, were downregulated in Mtb-specific CD4 T cells from PWH who started ART later (>1 year), compared with those who initiated ART earlier (<6 months) after HIV acquisition.
Conclusion: These novel single-cell transcriptomic studies indicate that HIV acquisition is associated with dysregulation of the Mtb-specific CD4 T cell transcriptome and depletion of crucial Th1 and Th17 cell populations within the first year after HIV infection, which may contribute to compromised Mtb control in PWH. Moreover, these results suggest that ART initiation within 6 months of HIV acquisition may be beneficial in preserving Mtb-specific Th1 and Th17 cells in PWH.

883 Monocyte Activation in Persons With HIV and Latent TB Co-Infection in the ACTG A5279/BRIEF TB Trial

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Background: Latent Tuberculosis infection (LTBI) has been linked to increased immune activation and cardiovascular risk. We investigated the activation profile of monocytes from persons with HIV (PWH) who participated in the ACTG A5279 trial, a phase III trial of 4 weeks of daily rifapentine (RFP)/isoniazid (INH) versus 9 months of daily INH as TB prevention therapy (TPT).
Methods: We analyzed available cryopreserved PBMCs obtained at baseline (pre-TPT) and at week 48 (post-TPT) from A5279 participants on antiretroviral therapy, with HIV viral load ≤200 copies/mL, and a tuberculin skin test (TST) or interferon-γ release assay (IGRA) result at entry. Unstimulated, thawed PBMCs were stained with markers of monocyte subsets (CD14, CD16), activation (HLA-DR, CD64, CD80, CD86), chemotaxis (CX3CR1, CCR2), and lipid uptake (CD36, CD163). In vitro stimulation with lipopolysaccharide (LPS) was performed to evaluate monocyte markers, and IL-6 and TNF-α expression. Samples were examined with multiparameter flow cytometry. Primary comparisons were between TST/IGRA-positive (evidence of LTBI) and TST/IGRA-negative groups. Linear regression of $\log_{10}$-transformed markers adjusted comparisons for age, sex at birth, country, and CD4 count.
Results: 58 participants from 4 countries were included. Median age was 38 years (IQR, 34 – 47). 33 (57%) men and 25 (43%) women. At baseline, compared to TST/IGRA-negative participants (n=27), those with LTBI (n=31) exhibited higher percentage and/or median fluorescence intensity (MFI) of CD64 and CCR2 on their total and classical monocytes. At week 48, compared to TST/IGRA-negative group, participants with LTBI had higher percentage and/or MFI of CD64 on total and all monocyte subsets, as well as differential expression of CD80, CD163, and CX3CR1 across some monocyte subsets. Upon LPS stimulation, there were no differences in IL-6 or TNF-α production by TST/IGRA status; however, LTBI was associated with higher MFI of CD36 and CCR2, and lower MFI of CX3CR1 on total monocytes and subsets. In adjusted analyses, LTBI was consistently associated with increased MFI of CD64 (unstimulated) and CCR2 (post-LPS) at baseline and week 48 across monocyte subsets (Table).
Conclusion: Compared to PWH with negative TST/IGRA, PWH with evidence of LTBI exhibited monocyte alterations indicative of persistent activation and tissue migration at baseline and week 48. Longitudinal changes will be evaluated in future studies.

Table. Fold change comparisons of MFI of monocyte markers (using multivariate linear models) between TST/IGRA-positive (evidence of LTBI) and TST/IGRA-negative groups.

Assay	Marker	Visit	Total Monocytes	Classical monocytes	Intermediate monocytes	Non-classical monocytes
Unstimulated assay	CD64	Baseline	1.90 (1.37, 2.63)***	2.38 (1.38, 4.10)**	1.80 (1.26, 2.58)**	2.42 (1.54, 3.82)***
		Week 48	2.02 (1.29, 3.15)**	2.22 (1.69, 2.92)***	1.67 (1.18, 2.38)**	2.59 (1.49, 4.50)**
	CCR2	Baseline	1.39 (1.10, 1.75)**	1.90 (1.07, 3.37)*	0.95 (0.65, 1.38)	0.78 (0.32, 1.92)
6-hour LPS stimulation assay	CCR2	Baseline	2.02 (1.47, 2.76)***	1.98 (1.43, 2.74)***	2.38 (1.51, 3.76)***	3.18 (1.57, 6.44)**
		Week 48	2.21 (1.71, 2.87)***	2.30 (1.75, 3.03)***	2.66 (1.86, 3.80)***	2.81 (1.65, 4.80)***
	CX3CR1	Baseline	0.88 (0.70, 1.10)	0.84 (0.67, 1.06)	0.75 (0.57, 0.97)*	0.90 (0.72, 1.12)
		Week 48	0.82 (0.66, 1.03)	0.76 (0.61, 0.96)*	0.65 (0.51, 0.82)***	0.85 (0.66, 1.09)

Anti-logged regression results adjusted for age, sex at birth, country (Brazil, Kenya, Thailand, USA), and CD4 count presented with 95% confidence intervals in parentheses; *p<0.05; **p<0.01; ***p<0.001

884 Persistence of PD-1+ Mtb-Specific CD4+ T Cells Is Associated With CAD During and After TB Treatment

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Background: Individuals who recovered from tuberculosis disease (post-TB) remain at increased risk of cardiovascular events and mortality. However, the underlying mechanisms of cardiovascular disease in post-TB remain unknown. Here, we aimed to characterize the immune profile of Mtb-specific CD4+ T cells in post-TB and explore their relationship with coronary artery disease (CAD).

Methods: We conducted a cross-sectional study of individuals 40 to 70 years of age with latent TB infection (LTBI), TB patients on isoniazid/rifampin consolidation treatment (TB-on-treatment); and clinically-cured individuals within one year of TB treatment completion (post-TB) between March 2018 and October 2019. Participants completed a coronary tomography angiography to assess CAD and provided blood for immune profiling of Mtb-specific CD4+ T cells using flow cytometry. Mtb-specific T cells were defined based on IFN-γ, IL-2, or TNF-α intracellular cytokine production upon in vitro PBMC stimulation with CFP-10/ESAT-6 or Mtb-whole-cell-lysate.

Results: 41 LTBI, 24 TB-on-treatment, and 11 post-TB participants without HIV were included in this analysis. After PBMC stimulation with Mtb-lysate, TB-on-treatment and post-TB patients exhibited higher percentage of Mtb-specific CD4+ T cells compared to LTBI (1.35 vs. 1.55 vs. 0.69; p=0.006). The percentage and MFI of activation markers HLA-DR, CD38, and delta HLA-DR (CD4minusMtb) were higher on Mtb-specific CD4+ T cells from TB-on-treatment and post-TB patients upon CFP-10/ESAT-6 and Mtb-lysate stimulation. Compared to LTBI, percentage of KI-67 and PD1 expression on Mtb-specific CD4+ T cells were increased in TB-on-treatment and post-TB upon Mtb-lysate stimulation (Figure 1). Polyfunctionality analyses revealed that TB-on-treatment participants exhibited a higher percentage of Mtb-specific CD4+ T cells positive to ≥2 cytokines upon Mtb-lysate stimulation, compared LTBI and post-TB participants. TB-on-treatment and post-TB individuals with CAD had higher MFI of PD1 on Mtb-specific CD4+ T cells, compared to those without CAD (181.5 vs. 123; p=0.022). Similarly, MFI of PD1 on Mtb-specific CD4+ T cells from TB-on-treatment and post-TB individuals positively correlated with CAD-RADS score (Spearman rho=+0.502; p=0.017).

Conclusion: Despite clinical TB cure, individuals post-TB exhibited signs of persistent immune activation and exhaustion of their Mtb-specific CD4+ T cell population. PD1 expression on Mtb-specific CD4+ T cells was associated with CAD during TB treatment and post-TB.

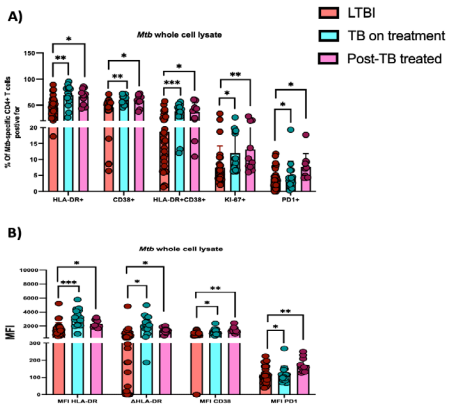

Figure 1. Immune markers expression on *Mtb*-specific CD4+ T cells. Percentage **(A)** and **(B)** MFI of immune markers on *Mtb*-specific CD4+ T cells in response to *Mtb* lysate. Significant differences are indicated at the top of the figure (*p <0.05) (**p<0.01) (***p<0.0001).

885 Suppression of Immunoglobulin Production and Mortality in HIV-Associated Cryptococcal Meningitis

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Background: Cryptococcal meningitis (CM) primarily affects those with advanced HIV disease. Regardless of antiretroviral therapy status, roughly 15-20% of those diagnosed with CM die within 2 weeks even with the best available antifungal treatment. Despite advances in the management of CM with combination antifungals, there is still a poor understanding of the possible compromised immune responses contributing to this high mortality. There have been very few studies in humans, and these have tended to focus on a handful of biomarkers. In this study, for the first time, we use whole transcriptome RNA sequencing to identify the gene expression signature in blood and CSF from those who died from CM compared to those who survived.

Methods: We performed bulk RNA-sequencing on whole blood and CSF collected from the first 200 consecutively recruited participants with HIV and CM into the AMBITION-cm trial in Botswana, Zimbabwe and Malawi. After sequencing we analysed differential gene expression and Gene Ontology pathway analysis from 99 CSF and 162 blood samples comparing those who died within 2 weeks (CSF; n = 10, Blood; n = 18) to those that survived at 2 weeks (CSF; n = 89, Blood; n = 144).

Results: We identified a robust transcriptional signature in the CSF where 1010 genes were significantly differentially expressed when comparing survivors to the deceased (Fig 1a). The majority of these differentially expressed genes (DEGs) were downregulated in participants who died within 2 weeks. Gene ontology analysis of these downregulated genes indicated that it was suppression of pathways associated with immunoglobulin production as well as complement and B cell activation that were all significantly associated with mortality (Fig 1b). From these pathways we identified 21 DEGs responsible for immunoglobulin production and structure expressed in participants that survived and absent in those that died. Analysis of whole blood did not reveal any significant transcriptional responses.

Conclusion: This study is the first of its kind to identify a unique CSF transcriptional signature that differentiates CM survivors from deceased. This was unique to CSF and was not seen in blood. We found an impaired adaptive immune response and diminished B cell response that is common in advanced HIV disease and that may lead to an inability to clear the fungus. This work can now be applied to develop better prognostic tests and improve targeted treatments for severe CM and other neurological infections.

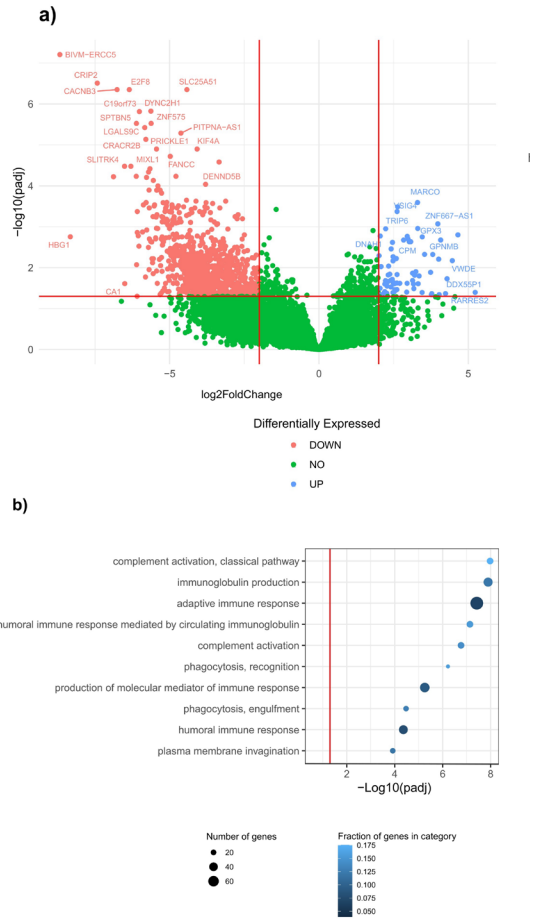

Fig 1. Bulk RNA sequencing data from 200 CSF samples. (a) Volcano plot illustrating differentially expressed genes, either downregulated or upregulated, for 2-week mortality compared to those that survived. (b) Enriched biological Gene Ontology pathways associated with downregulated genes at 2-week mortality.

886 Recent ART Initiation and Mortality Risk in HIV-Associated Cryptococcal Meningitis

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Background: Over half of patients diagnosed with cryptococcal meningitis are ART-experienced. The impact of recent ART initiation on outcomes in PLHIV who present with cryptococcal meningitis, and how to optimally manage ART, are unknown. We hypothesised that patients presenting with cryptococcal meningitis following very recent ART initiation (within 14 days) were at higher risk of mortality than ART-naïve individuals or those on ART for longer periods, and that ART interruption reduces this excess mortality.

Methods: We analysed data from the ACTA and AMBITION trials to assess whether patients diagnosed with cryptococcal meningitis within 14 days of ART initiation were at higher risk of mortality, and to evaluate the impact of ART interruption on mortality. ART interruption was only performed at clinicians' discretion in the AMBITION trial. Participants were grouped according to ART status and duration of ART. A generalized linear model was used to assess differences in mortality rates between groups.

Results: 1484 individuals were included, 707 (48%) not on ART and 777 on ART. ART timing data were available for 649 ART-experienced participants; 18% (120/649) initiated ART 14 days or less prior to diagnosis of CM. Patients who had initiated ART within 14 days had higher CD4 counts, and higher fungal burden than those on ART for over 14 days. 2-week mortality risk was 21.7% (95% CI 14.3-29.0%) in those on ART for 14 days or less, 13.8% (95% CI 7.9-19.8%) on ART for 15-60 days, and 7.6% (95% CI 2.2-13.0%) on ART for 61 days-6 months, increasing to 16% (95% CI 12.2-20.4%) in those on ART for more than 6 months (compared to 16% in those not on ART). Similar mortality trends were seen at 10 weeks. There was a significant interaction between the clinical decision to interrupt ART at enrolment and ART timing on mortality risk (p= 0.01); Among individuals on ART for less than 14 days in the AMBITION trial, 2-week mortality was 35% (8/23) with continued ART versus 14% (7/42) in those who discontinued ART (p=0.05).

Conclusion: Our findings show an increased risk of early mortality in cryptococcal meningitis patients who started ART in the past 2 weeks in keeping with prior preliminary data. ART interruption at CM diagnosis in recent ART initiators does not lead to increased mortality and may be associated with improved outcomes. Intervention studies are needed to definitively determine whether ART interruption in patients presenting with cryptococcal meningitis having recently started ART is beneficial.

887 CSF HIV Viral Escape Is Associated With Improved Survival in Adults With HIV-Associated Meningitis

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Background: Cryptococcal meningitis and tuberculous meningitis (TBM) remain the most common causes of HIV-associated meningitis, accounting for >20% of AIDS-related deaths globally. Acute mortality associated with these infectious meningitides remains devastatingly high (25-50%), even in the context of clinical trials. We hypothesised that cerebrospinal fluid (CSF) HIV viral escape may contribute to central nervous system (CNS) damage and be associated with increased mortality.

Methods: We conducted a cohort study of HIV-positive Uganda adults with suspected meningitis in Kampala, Uganda. We performed baseline paired plasma/CSF HIV viral load (VL) testing (Xpert; Cepheid, Sunnyvale, CA, USA). We determined the prevalence of CSF HIV viral escape, defined as per the consensus definition of presence of quantifiable HIV in the CSF at a concentration above that in plasma, and investigated for associations with mortality using Cox regression. Participants were followed through to hospital discharge, or until week-18 if recruited into a subsequent randomised controlled trial.

Results: We recruited 152 adults, 47% were male, median CD4 was 59 (IQR 14-132) cells/mcL, 41% were receiving antiretroviral therapy (ART) at time of presentation. The majority (48%, 73/152) had cryptococcal meningitis, 32% (49/152) had definite/probable TBM, 20% (30/152) suspected "other" meningitis. CSF HIV viral escape was present in 30% (46/152) overall; it was strongly associated (p<0.001) with higher CSF white cell count (102 vs. <5 cells/mcL); and shorter duration of ART (16 vs. 144 days). Amongst those on ART <100 days, CSF HIV viral escape prevalence was 60%. CSF HIV viral escape was associated with improved 18-week survival with an unadjusted Hazard Ratio 0.41 (95%CI, 0.18 – 0.92, p=0.031). CSF viraemia alone was not associated with survival (unadjusted Hazard Ratio 1.04, 95%CI 0.52 – 2.09, p=0.9).

Conclusion: In our HIV-associated meningitis cohort, CSF HIV viral escape was common, especially amongst participants recently initiated on ART. As HIV viral replication suppresses more slowly in CSF than plasma, in such cases it is possible that with longer ART duration the CSF would also suppress. Given the observed associations with CSF pleocytosis and improved survival, in the context of HIV-associated meningitis, CSF HIV viral escape is likely a by-stander phenomenon and an indicator of effective host immune response with trafficking of monocytes and CD4 lymphocytes containing HIV RNA into the CNS.

Table 1: Baseline characteristics and survival outcomes of 152 adults with HIV-associated meningitis with stratification by CSF HIV viral escape status

	N	CSF HIV viral escape n=46 N (%) or median (IQR)	No CSF HIV viral escape n=106 N (%) or median (IQR)	P
Diagnosis	152			0.2
Cryptococcal meningitis		24 (52)	49 (46)	
TBM		17 (37)	32 (30)	
"Other" meningitis		5 (11)	25 (24)	
ART status	148			0.11
ART naïve		21 (47)	42 (41)	
Currently on ART		21 (47)	40 (39)	
ART defaulter		3 (6.7)	21 (20)	
ART Days	59			<0.001
< 100 (days)		15 (71)	10 (26)	
>= 100 (days)		6 (29)	28 (74)	
CD4 cell count (cells/μL)	129	55 (16 – 102)	61 (13 - 162)	0.5
CSF white cell count (cells/μL)	148	104 (<5 – 230)	<5 (<5 – 69)	< 0.001
Log10(CSF viral load) (copies/ml)	152	4.7 (2.8 – 5.5)	2.6 (0.0-4.8)	< 0.001
18-week mortality	152	7 (15%)	33 (31%)	0.041

For categorical variables, the P value is from Chi squared. For non-categorical variables P-values are from Wilcoxon rank sum test.

888 Quantitative Antifungal Activity of Daily Liposomal Amphotericin With 5FC in Cryptococcal Meningitis

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Background: Daily liposomal amphotericin B (AMB) with flucytosine (5FC) is recommended as first line therapy in US cryptoococcal meningitis treatment guidelines. Liposomal AMB monotherapy at 3mg/kg/d in its FDA registrational trial did not meet the prespecified non-inferiority criteria of <10% difference in 10-week survival or 10-week culture conversion rate compared to AMB dexoxycholate. Daily liposomal AMB combination therapy with 5FC, although recommended, has not been studied in a clincial trial. We sought to assess the quantitative antifungal activity of this first-line recommended regimen.

Methods: We enrolled Ugandans with HIV-related cryptococcal meningitis into prospective cohorts and clinical trials from 2018-2023. We assessed the early fungicidal activity (EFA) of the cerebrospinal fluid (CSF) Cryptococcus clearance rate between those receiving AMB deoxycholate 1mg/kg + 5FC 100 mg/kg/d versus those receiving daily liposomal AMB 3 mg/kg/d + 5FC 100 mg/kg/d. Induction AMB + 5FC was given for 7 days, followed by fluconazole 1200 mg/d. We calculated EFA by linear regression from longitudinal quantitative CSF fungal cultures collected over 2 weeks of therapy.

Results: Among 199 participants with longitudinal quantitative CSF culture data, 156 received AMB deoxycholate, and 43 received liposomal AMB. For AMB deoxycholate, the mean EFA was 0.403 (95%CI, 0.36-0.44) log_{10}CFU/mL/day. For daily liposomal AMB, the mean EFA was 0.493 (95%CI, 0.35-0.64) log_{10} CFU/mL/day. The absolute EFA difference was 0.09 (95%CI, -0.02 to 0.20) log_{10}CFU/mL/day favoring liposomal AMB. Grade ≥3 adverse events were less frequent among those receiving liposomal AMB.

Conclusion: Despite never being quantified in a randomized clinical trial, the combination of liposomal AMB with 5FC had good antifungal activity in humans with cryptococcosis which did not statistically differ from that of AMB deoxycholate.

889 IgG Responses Are Associated With Severe Disease and Mortality in AIDS-Associated Talaromycosis

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Background: There is dearth of data on antibody responses to AIDS-associated talaromycosis and how they impact disease phenotype and patient outcomes. Data from our talaromycosis Itraconazole versus Amphotericin B for Penicilliosis (IVAP) trial (N=440) showed that patients presenting with an acute pulmonary syndrome had higher mortality. Here, we tested the hypothesis that acute pulmonary syndrome is associated with a serological pattern of acute infection, and an acute serological pattern is associated with severe disease and mortality.

Methods: Longitudinal IgG antibody responses to talaromycosis were measured in available plasma samples of IVAP patients using a direct anti-Mp1p IgG enzyme immunoassay. Patients were classified into three IgG response types: Negative IgG, Increasing IgG, and Positive Unchanged IgG through analysis of the IgG trend over 24-weeks. Univariate and multivariate logistic regression were used to assess association of IgG type and disease severity (defined as a respiratory rate >22, dyspnea requiring oxygen, and/or respiratory failure diagnosis at presentation) and 24-week mortality.

Results: Plasma samples and complete data were available for 409 of 440 IVAP patients. Mean age was 34.7 years (SD:7.4). Mean CD4 count was 23.3cell/mm³ (SD:49.1). Serial samples for classification of IgG response into 3 types were available for 312 patients: 88 (28.2%) Negative IgG, 114 (36.5%) Increasing IgG, 110 (35.3%) Positive Unchanged IgG. In the multivariate models of the 312 sub-population (N=312) adjusting for age, history of injection drug use, CD4 count, and antifungal treatment arm, Negative IgG was associated with higher risk of death (OR=3.20,95% CI:1.18-8.96,P=0.023) while Increasing IgG was protective of death (OR=0.14,95% CI:0.02-0.56,P=0.013). In the multivariate models of the full population (N=409) where IgG type could only be classified as Negative or Positive at baseline, Negative IgG was associated with disease severity (OR=1.62,95% CI:1.02-2.55,P=0.039) and had a non-statistically significant association with mortality. Disease severity was an independent predictor of death (OR=2.44,95% CI:1.38 – 4.34,P=0.002).

Conclusion: Although these results were unexpected, the findings that 28% of talaromycosis patients do not mount an IgG response, and these patients have more severe disease and higher mortality suggest a central role of humoral immune response in talaromycosis pathogenicity, which has so far been overlooked. These findings have important clinical implications.

Table 1. Independent association of Negative IgG response and 24-week mortality in 312 AIDS-associated talaromycosis patients

Characteristics	All patients (*N* = 312)	Dead (*N* = 18)	Alive (N = 294)	Univariate effect: OR (95% CI)	Adjusted effect from multiple logistic regression: OR (95% CI)
Age (+10years), [SD]	34.3 [7.37]	38.1 [7.18]	34.1 [7.18]	1.85 (1.05 – 3.17), *P* = 0.035	1.70 (0.94 – 3.02), *P* = 0.080
IVDU (yes), (%)	91 [29.2%]	5 [27.8%]	86 [29.3%]	0.93 (0.29 – 2.55), *P* = 0.893	1.38 (0.41 – 4.15), *P* = 0.581
CD4 (+10cells/dL), [SD]	20.0 [31.5]	14.3 [25.9]	20.3 [31.8]	0.90 (0.63 – 1.08), *P* = 0.345	0.91 (0.63 – 1.09), *P* = 0.398
IgG Response Type (Negative IgG), (%)	88 [28.2%]	10 [55.6%]	78 [26.5%]	3.46 (1.32 – 9.37), *P* = 0.012	3.20 (1.18 – 8.96), *P* = 0.023
Treatment (Itraconazole), (%)	164 [52.6%]	12 [66.7%]	152 [51.7%]	1.87 (0.71 – 5.49), *P* = 0.212	2.12 (0.78 – 6.40), *P* = 0.1447

890 Triple Screening for Invasive Mycoses in Patients With Advanced HIV Disease in Vietnam

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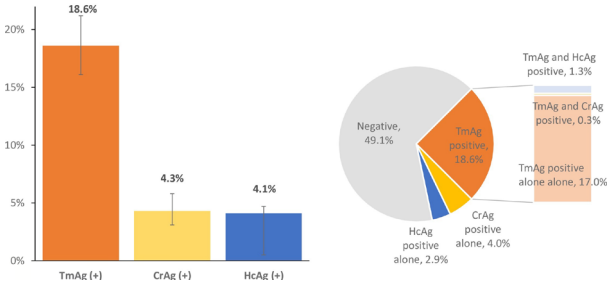
Background: Invasive mycoses are second to TB as a leading cause of death in advanced HIV diseases (AHD). The WHO recommends screening for TB and cryptococcosis in a package of care for AHD; however, invasive mycoses endemic in Asia Pacific - talaromycosis and histoplasmosis - are not included due to the lack of diagnostics and data on burden of diseases to inform policy. We present the results of a triple fungal screening program for in patients with AHD in Vietnam.

Methods: This is an ongoing multi-center prospective fungal screening cohort study of patients with AHD who presented for hospitalisation (cohort 1, n=900) or for ART initiation in outpatient clinics (cohort 2, n=600) in three hospitals in Hanoi and Ho Chi Minh city, Vietnam. We enrolled patients aged ≥18 years, with CD4 count ≤100 cells/mm³ or WHO stage 3 or 4, not on ART OR recent ART ≤3 months OR suspected or confirmed treatment failure on ART ≥12 months. We excluded patients currently on effective systemic antifungal treatment. All patients received antigen screening for cryptococcosis using the IMMY Cryptococcal antigen lateral flow assay (CrAg LFA) in blood, histoplasmosis using the IMMY Clarus Histoplasma GM enzyme immunoassay (HAg EIA) in urine, and talaromycosis using a novel in-house Mp1p EIA (TmAg EIA) in blood and urine, alongside conventional diagnostics including BACTEC and MycoF/Lytic blood cultures. Patients were followed up monthly over 6 months (cohort 1) and 12 months (cohort 2) to assess outcomes.

Results: 1366 patients were enrolled, including 900 hospitalised patients (100% target for cohort 1) and 466 outpatients (77.7% target for cohort 2) between February 2021 and August 2023. In cohort 1, the median age was 36 years (IQR: 30–44). 746 (82.9%) were men. The positivity for fungal antigens was 18.6% (95% CI: 16.1-21.2%) for TmAg, 4.3% (95% CI: 3.1-5.8%) for CrAg, and 4.1% (95% CI: 3.0-5.6%) for HcAg. Among TmAg-positive patients, 6.6% (95%CI 3.5-11.1%) were HAg-positive and 1.8% (95%CI 0.5-4.7%) were CrAg-positive. In cohort 2, the positivity for fungal antigens was 8.4% (95% CI: 6.1-11.1%) for TmAg, 3.9% (95% CI: 2.4-5.9%) for CrAg, and 2.1% (95% CI: 1.1-3.8%) for HcAg. The analysis of clinical outcome is ongoing.

Conclusion: Invasive mycoses were detected in 25% of hospitalised and 14% of outpatients with AHD in Vietnam. Talaromycosis is the leading mycosis and together with histoplasmosis should be added to the WHO package of care for AHD in the Asia Pacific region.

Figure 1. Prevalence of *Talaromyces marneffei*, *Cryptococcus*, and *Histoplasma* antigens in 900 hospitalized patients with advanced HIV disease in Hanoi and Ho Chi Minh City, Vietnam



891 Enhancing Advanced HIV Screening: Innovating With the "Hub and Spoke" Testing Model in Tanzania

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Background: Despite the global adoption of the World Health Organization's 'test and treat' policy, the proportion of people living with HIV (PLHIV) presenting with advanced HIV disease (AHD) remains high at around 30% in Tanzania. Due to gaps in identification, recipients of care (RoC) with AHD face an elevated risk of mortality primarily because of opportunistic infections (OIs) such as tuberculosis and cryptococcal meningitis (CM). We demonstrated the implementation of AHD screening through CD4 testing to detect and manage OIs, particularly cryptococcal infection.

Methods: In collaboration with the Kigoma, Pwani, and Shinyanga Regional and Council Health Management Teams, we revived CD4 testing for all newly diagnosed PLHIV along with reflex Cryptococcal antigen (CrAg) testing. We extracted data from the HIV Care and Treatment Clinic database, comparing the identification of AHD after the intervention through CD4 and Crag testing. In 2019, we integrated CD4 testing within the established viral load sample transportation system using a 'hub and spoke' model and point of care (PoC). Healthcare providers received training on AHD screening and management, including CD4 testing for all newly enrolled to care and laboratory-reflex CrAg testing at the laboratory for all samples with CD4 counts of <200 cells/µL. We used the client's recorded cards and care and treatment database as the main data source. The analysis focused only on newly enrolled RoC.

Results: Enhancing sample transportation led to 167 (68%) supported facilities without CD4 machines to access CD4 testing and cryptococcal screening through CrAg tests at the hub sites. The number and proportion of newly enrolled RoC tested for CD4 at 245 supported facilities rose from 1,931 (7%) in 2020 to 9,900 (95%) in 2023. Simultaneously, the proportion of samples with CD4 counts <200 undergoing laboratory-reflex CrAg testing increased from 173 (36%) in 2020 to 1,474 (96%) in 2023, resulting in CrAg positive identification of 35 (20%) individuals in 2020, 89 (16%) in 2021, 102 (10%) in 2022, and 90 (6%) as of June 2023. CM cases identified increased from 5 in 2020 to 39 in 2023.

Conclusion: The CD4 testing for newly diagnosed HIV-positive clients has substantially increased the identification of individuals with asymptomatic cryptococcal infection. The successful implementation of early AHD screening among newly diagnosed PLHIV in resource-constrained settings is feasible through sample transportation integration and expanding point of care CD4 testing

892 Clinical Relevance of the CRAG Semiquantitative Scores in CRAG-Positive People with AIDS

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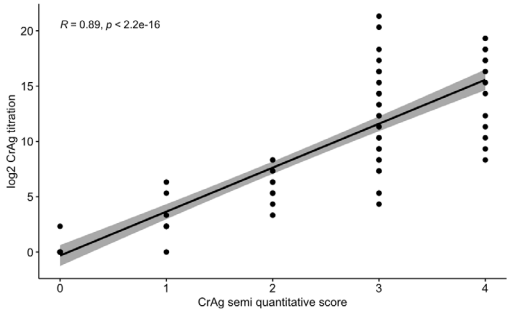
Background: High cryptococcal antigen (CrAg) titer is associated with higher mortality in patients with cryptococcal meningitis and in asymptomatic CrAg-positive people in Africa. CrAg titer testing may improve patient management; however, titer testing is cumbersome and expensive. Here, we evaluate the diagnostic performance of IMMY CrAg semiquantitative (CrAg SQ) LFA and determine the association of CrAG SQ scores with CrAg titers and mortality in CrAg positive patients with advanced HIV disease (AHD) in Vietnam.

Methods: This is a nested case control study using serum samples from 2 multi-center cryptococcal screening cohorts enrolling patients with AHD (CD4 count <100 cells/µL or WHO stage III/IV disease). Cohort 1 enrolled 1177 asymptomatic patients from 22 clinics across Vietnam between 2015 and 2019. Cohort 2 enrolled 900 hospitalized patients from 3 hospitals between 2021 and 2023. Cases (N=86) were all patients who were CrAg positive by CrAg LFA. Controls (N=30) were randomly selected CrAg negative patients. CrAg titer was tested for all CrAg-positive samples. We evaluated the sensitivity and specificity of the CrAg SQ LFA using CrAg LFA as the reference standard and the correlation between CrAg SQ score & CrAg LFA titer. We determined the association between CrAg SQ score and 12-month mortality using Cox regression modeling. The results of the CrAg SQ were interpreted by 2 double-blinded readers, and interrater reliability (IRR) was determined by intra-class correlation.

Results: CrAg SQ demonstrated a sensitivity of 97.6% (95% CI: 90.9-99.6) and specificity of 94.8% (95% CI: 77.8-98.9). CrAg SQ scores were highly associated with CrAg titers, Pearson's correlation coefficient r = 0.89 (95% CI: 0.88 to 0.92; P < 0.001). The median CrAg titers that correspond to the CrAg SQ scores were 1:5 (IQR, 1:5-1:7) for 1+ score, 1:60 (IQR, 1:40-1:140) for 2+ score, 1:5120 (IQR, 1:320-1: 40960) for 3+ score, and 1:122880 (IQR, 1: 8960-1:327680) for 4+ score. Multivariate analysis revealed an average 29% increase in the odds of 12-month mortality for every one unit increase in the CrAg SQ score (OR 1.29 [0.77 – 2.28], P = 0.34). The IRR was excellent at 0.98 (95% CI: 0.96 - 0.99; P < 0.001).

Conclusion: The CrAg SQ demonstrated excellent sensitivity and specificity compared to the CrAg LFA. There is excellent correlation between CrAg SQ score and CrAg titers, and a non-significant but positive association between CrAg SQ scores and 12-month mortality.



893 Semi-Quantitative Cryptococcal Antigen Testing and Mortality in HIV-Related Cryptococcal Meningitis

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Background: Cryptococcal meningitis (CM) causes 19% of HIV-related deaths, and 10-week mortality rates with current treatments are high (25-45%). Risk stratification at disease presentation with tailoring of treatment could reduce

mortality. Higher fungal loads are strongly associated with mortality; but obtaining fungal loads requires serial CrAg LFA dilutions or quantitative fungal cultures (QFC), both are time and resource consuming, need expertise, and are difficult to implement in resource limited settings (RLS). The IMMY CrAgSQ is an improvement on the widely used IMMY CrAg LFA with comparable diagnostic performance, yielding a semi-quantitative (SQ) score. Previous studies involved fewer HIV-CM patients and did not definitively evaluate the utility of CrAgSQ in predicting mortality. We conducted a study on stored plasma and CSF samples from the AMBITION trial to evaluate whether CrAgSQ can predict outcomes.

Methods: 810 patients with HIV-CM were enrolled onto the Ambition Phase 3 randomised clinical trial evaluating CM therapy in Botswana, Zimbabwe, Malawi, Uganda and South Africa. Stored plasma and CSF samples collected at disease diagnosis before treatment were tested using CrAgSQ, yielding a score of 1-5. Clinical outcomes and laboratory data were documented during 10 weeks of follow-up. Associations between CrAg SQ scores in plasma and CSF and 2- and 10-week mortality were examined.

Results: 756 CSF and 745 plasma collected from 796 Ambition Trial patients were assessed; 61% of the patients were male, median age was 37 (IQR 32-43 years), and median CD4 count was 27 (IQR 10-58 cells/uL). Overall mortality was 13% and 23% by 2 and 10 weeks. In plasma, 0.13% (1/745) were negative, 4.03% (30/745) had an SQ score of 1, 3.49% (26/745) 2, 83.62% (623/745) 3, and 8.72% (65/745) 4. In CSF, 1.32% (10/756) were negative, 7.01% (53/756) had an SQ score of 1, 5.69% (43/756) 2, 63.76% (482/756) 3, and 22.22% (168/756) 4. CrAg SQ scores in plasma (Figure) and CSF positively correlated with QFCs. Increasing CrAg SQ scores in plasma were strongly associated with increasing mortality risk at 2- and 10-weeks. Mortality was 0% (0/22) in those with plasma SQ score of 1, 4.4% (1/23) 2, 13.9% (75/540) 3, and 34.55% (19/55) 4 (p for trend <0.001).

Conclusion: Plasma CrAgSQ is a promising prognostic tool for 2-week mortality in patients with HIV-CM, making it a viable option for RLS. Further research is warranted to establish how it could be used to stratify management in individuals presenting with HIV-CM.

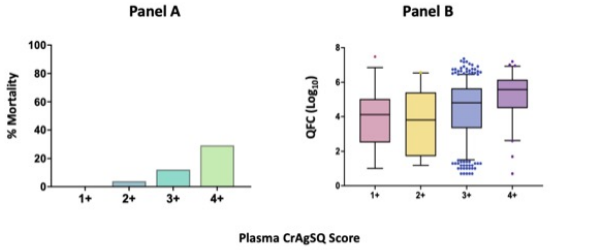

Figure1: Panel A: Mortality increased with increasing plasma CrAgSQ scores (left), and PANEL B: box and whisker plot showing relationship between plasma CrAg scores and baseline QFC log_{10} in all patients

894 NSE and UCHL1 as Prognostic Biomarkers for Mortality From Cryptococcal Meningitis

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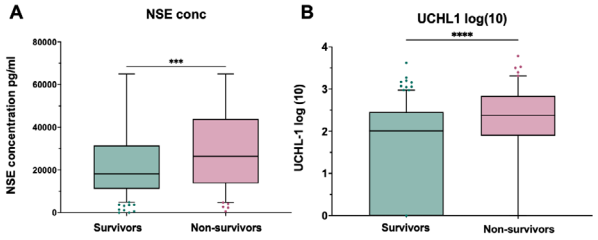
Background: Despite new, more effective treatments, mortality due to HIV-associated cryptococcal meningitis remains high. Markers that are associated with mortality may be helpful to identify individuals who would benefit from intensive management and monitoring, and also improve understanding of underlying disease pathology. The neurological biomarkers Neuron specific enolase (NSE), Ubiquitin C-terminal hydrolase-L1 (UCHL1), and Glial fibrillary acidic protein (GFAP) have been associated with traumatic brain injury but have never been studied in the context of cryptococcal meningitis. This exploratory study examined cerebrospinal fluid levels of these biomarkers in patients from the AMBITION-cm trial. It was hypothesized that UCHL1, NSE, and GFAP would be elevated in participants who died from cryptococcal meningitis.

Methods: One hundred participants who died of cryptococcal meningitis within the first two-weeks (non-survivors) and a random selection of 200 participants who survived (survivors) were selected using the R software for statistical computing. Levels of UCHL1, NSE, and GFAP in day 1 cerebrospinal fluid (CSF) were measured using Luminex analysis, and associations between these biomarkers and clinical and laboratory variables determined. Data was analyzed using Graphpad Prism software.

Results: Non-survivors were more likely to have Glasgow Coma Score <15 and had significantly higher median CSF cryptococcal quantitative culture, and lower median CD4-cell counts and CSF white blood cell counts. The mean concentration of NSE in the survivors was 23463 pg/mL, and 30984 pg/mL in the non-survivors (p<0.001). Mean concentration of UCHL1 was also significantly higher in the non-survivors at 548.9 pg/mL compared to 243 pg/mL in the survivors (p<0.0001). Mean concentration of GFAP did not differ significantly, at 561.8 pg/mL in the non-survivors, and 369.9 pg/mL in the survivors (p=0.2635).

Conclusion: The neurological markers UCHL1 and NSE were significantly elevated on day 1 CSF in cryptococcal meningitis patients who died by 2 weeks compared to those who survived. Further study of these markers may be used to identify patients who require more intensive management, monitoring and follow-up and generate novel insights into cryptococcal disease pathology.



NSE and UCHL1 are significantly elevated in day 1 cerebrospinal fluid of cryptococcal meningitis non-survivors. Median concentration of Neuron specific enolase (NSE) (A), and Log(10) median concentration of Ubiquitin C-terminal hydrolase-L1 (UCHL1) (B) are shown. *p<0.05 using unpaired t-test.

895 Histoplasmosis in Advanced HIV Disease: A Multi-Center Prospective Diagnostic Validation Study

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Background: Histoplasmosis burden in advanced HIV disease (AHD) in Southeast Asia is unknown due to the lack of diagnostics. We report results of an ongoing multi-center prospective histoplasmosis diagnostic validation study in patients with AHD in Vietnam.

Methods: We recruited hospitalized HIV-infected adults, CD4 count ≤ 100 cells/μL or WHO stage 3 or 4 disease, ART-naive or on ART for ≤ 3 months or >12 months from 3 hospitals in Vietnam. All patients were screened for Histoplasma antigen using the IMMY Clarus Histoplasma GM enzyme immunoassay (HAg EIA) in urine and Myco/F Lytic blood culture (over 6 weeks), alongside conventional microscopy and cultures of other specimens as clinically indicated. Proven histoplasmosis was defined as culture-positive disease. Probable histoplasmosis was defined as a compatible clinical syndrome and resolution of HAg levels on antifungal therapy. Patients were followed up monthly for over 6 months.

Results: 900 patients were recruited between 02/2021 and 08/2023. Overall prevalence of HAg positivity was 37/900 (4.1%) and was higher in southern vs. northern Vietnam, 30/581(5.2%) vs. 7/319 (2.2%), P= 0.035, Fisher Exact. Among the 37 HAg-positive patients, 15 (40.5%) had proven histoplasmosis; 13 (35.1%) had probable histoplasmosis; and 9 (24.3%) did not develop disease over 6 months. The median HAg EIA unit of proven and probable histoplasmosis patients was 35.84 (IQR 4.31 to 40.96) compared to -0.04 (IQR -0.08 to 0.03) of non-histoplasmosis patients, P<0.001, Mann-Whitney. At a cut-off EIA unit of 1.2, HAg EIA had 100% sensitivity (95% CI: 87.7% - 100%), 99% specificity (95% CI 98.1% - 99.5%), 75.7% positive predictive value (95% CI 61.9% - 85.6%), 100% negative predictive value (95% CI 99.6% - 100%), and an accuracy of 99.8% (95% CI: 99.7% – 100%). Among 28 histoplasmosis patients, the median CD4 count was 17 (IQR, 7 - 31) cells/μL. H. capsulatum was isolated from blood in 12 (42.9%), bone marrow in 11 (39.3%), skin lesions in 1 (3.6%) patients. Median

time to culture positivity in bone marrow and blood was: 10.5 (IQR, 7 – 16.5) days and 17 (IQR, 11.5 – 19) days, P=0.160, Wilcoxon. 7/28 (25%) patients died by month 6 despite antifungal therapy.

Conclusion: Our study demonstrates an excellent diagnostic performance of the HAg EIA and unveils a substantial burden of histoplasmosis in AHD in Vietnam. The mortality remains high (25%) despite antifungal therapy, highlighting the need to screen for Histoplasma antigen, preferably before patients become symptomatic.

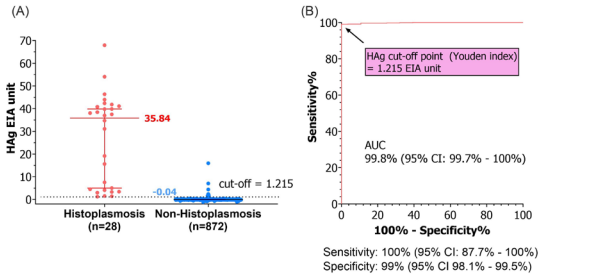

Figure: Diagnostic performance of the IMMY Clarus Histoplasma GM EIA
(A) Scatter plot of the Histoplasma EIA unit in proven or probable histoplasmosis vs non-histoplasmosis patients.
(B) The Receiver Operating Characteristic (ROC) curve

896 Ultra Xpert in Blood and Urine and Myco/F Lytic Blood Culture in Patients With Advanced HIV Disease

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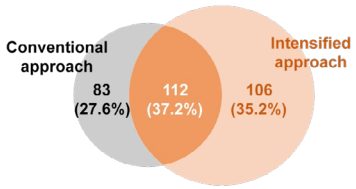
Background: TB is a leading cause of death in patients with advanced HIV disease (AHD). Current TB screening in AHD relies mainly on Xpert in sputum and urine LAM; both have low yield. We report results of an ongoing multi-center prospective study testing an intensified screening approach using Ultra Xpert (UXpert) directly from blood and urine and Myco/F lytic (MFL) blood culture compared to a conventional symptom-based diagnostic approach for detecting mycobacterial infections in AHD in Vietnam.

Methods: This sub-study was part of a triple fungal screening program in AHD (N=900 patients). Eligible patients included all hospitalized adults aged ≥18 with CD4 count ≤ 100 cells/μL or WHO stage 3 or 4 disease, not on ART or were on ART for ≤ 3 months or >12 months from two major hospitals for tropical diseases in Hanoi and Ho Chi Minh City. Intensified screening approach included blood UXpert and MFL blood culture in all patients. Urine UXpert was an add on for the last 174 patients. Conventional approach included acid-fast stain, UXpert and MGIT culture of sputum and other specimens as clinically indicated. Patients were followed up monthly over 6 months. Diagnostic yield was compared between two approaches.

Results: The 900 patients were recruited between February 2021 and July 2023. 82.9% were men. Median age was 36 (IQR: 29-44) years. A total of 301 (33.4%) patients had microbiological-confirmed mycobacterial infections: 243 (80.7%) had TB; 30 (10.0%) had non-TB mycobacteria (NTM) - 27/30 (90.9%) were due to M. avium complex. The number of cases diagnosed by conventional, intensified, and both approaches were 83, 106, and 112 respectively. The intensified screening approach increased the number of mycobacterial diagnoses from 195 to 301 (54.4% increase) compared to conventional approach alone. In the 106 cases diagnosed by intensified approach only, 55 (52%) were diagnosed from blood and/or urine UXpert, enabling TB therapy earlier than would otherwise. 75 of 301 (24.9%) mycobacteria-infected patients died before completing TB/NTM treatment by month 6 of follow up.

Conclusion: The intensified screening approach using UXpert in blood and urine and MFL blood culture increases the number of mycobacterial diagnoses by 54% compared to conventional method alone in hospitalized patients with AHD. Implementation of UXpert in blood and urine in routine care is feasible, reduces time to diagnosis and treatment, and has the potential to reduce HIV mortality.

Figure 1. Venn diagram showing overlap and non-overlap numbers of mycobacterial infections diagnosed by the conventional and intensified approaches in the screening for mycobacterial infections in 900 hospitalized patients with advanced HIV disease in Vietnam



897 Tuberculosis Drug Resistance Profiling by Targeted Next-Generation Sequencing in Sub-Saharan Africa

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Background: Drug-resistant tuberculosis (DR-TB) remains a global health threat. Drug susceptibility testing (DST) is essential for diagnosing and treating DR-TB effectively, but culture-based methods are time and resource-intensive. Culture-free targeted next-generation sequencing (tNGS) can comprehensively detect drug resistance mutations but its practicality in routine settings requires further exploration. We tested Oxford Nanopore Technologies' tNGS assay for TB in two laboratories in sub-Saharan Africa.

Methods: The study was conducted at two sites, Johannesburg/South Africa and Lusaka/Zambia, as part of an ongoing prospective cohort study. On-site lab procedures included automated DNA extraction, amplification of 25 gene regions linked to drug resistance across 18 TB drugs, and real-time Nanopore sequencing and analysis with compact MinION sequencers. Native sputa and decontaminated sediments of 70 TB-positive patients with a GeneXpert MTB/RIF Ultra result of "low" to "high", were sequenced. Sequencing results were compared to local routine DST (phenotypic MGIT DST to first-line drugs and GeneXpert MTB/XDR).

Results: Predicted DR results were available 24 hours after initiating DNA extraction. We obtained sequencing results for 51/82 (62%) native sputum and 59/82 (72%) sediment samples (p=0.25, Fig. A). Complete sequencing results, covering all 25 targets, were obtained for 25/51 (49%) sputum and 46/59 (78%) sediment samples (p<0.01, Fig. B). For incomplete samples the median number of targets missed in sputum and sediment samples was similar (9 vs. 11). Among five samples with rifampicin resistance detected by GeneXpert MTB/RIF Ultra and confirmed by phenotypic DST, sequencing predicted resistance in 3 of these samples, was indeterminate in one sample, and missed resistance in one. Sequencing also predicted resistance to isoniazid and ethionamide in four and one samples, respectively, all confirmed by local DST. Xpert MTB/XDR results were available for a subset of 40 samples, for which predicted DR profiles were all concordant. Recruitment, sequencing, and reference testing, using local routine DST are ongoing.

Conclusion: Nanopore tNGS was implemented successfully at both sites. Sequencing from sputum and sediment samples was comparable and detected TB and DR-associated mutations. Nanopore tNGS promises a feasible and rapid sequencing approach for comprehensive genotypic DR profiling in TB high-burden countries but technical and logistic challenges complicate its routine implementation.

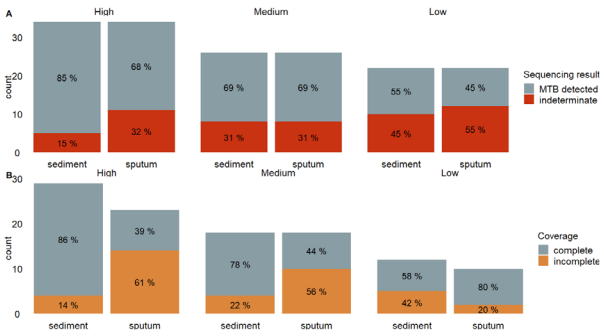

Figure: Sequencing performance (A) of sputum and sediment samples, grouped by GeneXpert MTB/RIF Ultra category. Sequencing coverage (B) in MTB-positive sputum and sediment samples, grouped by GeneXpert MTB/RIF Ultra.

898 High Genetic Diversity of Rifampicin-Resistant *Mycobacterium tuberculosis* Strains in Botswana

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Background: The emergence of drug-resistant Mycobacterium tuberculosis (M.tb) strains remains a threat to tuberculosis(TB) control. For effective TB control, it is important to obtain genetic information on lineages of M.tb and to understand the drug resistance profiles of the circulating strains. This study aimed to describe the genetic diversity and drug resistance profiles of rifampicin-resistant M.tb strains circulating in Botswana using whole genome sequencing (WGS).

Methods: This retrospective study utilized 100 M.tb isolates from people diagnosed with Rifampicin-resistant TB (RR-TB) between January 2016-December 2021. Genomic DNA was extracted using the cetyltrimethylammonium bromide (CTAB) method. Library preparation was performed with Rapid Barcoding Kit (SQK-BK110.96), following the manufacturer's instructions. Sequencing was performed on an Oxford Nanopore Technology GridION X5 sequencer using an R9.4 flow cell. TB-profiler was used to identify known M.tb lineages and drug resistance profiles. Univariate and multivariate logistic regression models were used to identify factors associated with unsuccessful TB treatment outcomes.

Results: WGS analysis revealed the following drug resistance profiles; MDR (57%: 95% CI; 46.7%-66.9), Pre-XDR (21%, 95% CI:13.5-30.3), RR-TB (21%: 95% CI; 13.5-30.3), and HR-TB (1%:95% CI; 0.2-5.5). Additionally, we identified a high genetic diversity with 3 predominant M.tb lineages: Lineage 4 (62%:95%CI;51.7-71.5), Lineage 1(19%: 95%CI; 11.8-28.1), Lineage 2(18%: 95%CI;11.0-26.9) and Lineage 3(2%:95%CI;2.4-7.0) which was the least common. The most frequently observed mutations for rifampicin, isoniazid, ethambutol, pyrazinamide, and fluoroquinolones were: rpoB Ser450Leu (52%), katG Ser315Thr (60.8%), embA_c.-29_-28delCT, embB Gln497Arg (31%), rrs_n.517C>T (59%), and gyrA Asp90Val(71%), respectively. Bedaquiline and Delamanid resistance-associated mutations were not detected among RR-TB isolates. Residing in rural areas was associated with unsuccessful TB treatment outcomes (adjusted odds ratios: 9.1, 95% CI: 3.0-27.9, p-value<0.001). No specific lineage was associated with any TB treatment outcome.

Conclusion: A high genetic diversity and predominance of M.tb lineage four among individuals with RR-TB was observed in Botswana. Data generated from this study provides insights into the genetic diversity and drug resistance mutations present in RR M.tb strains circulating in Botswana.

899 Exposure to PrEP and Safety Monitoring in Pregnancy: Importance of Objective Exposure Measurement

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Background: To date, TDF/FTC for pre-exposure prophylaxis (PrEP) safety in pregnancy has been based on self-reported adherence or study allocation with no safety studies using objective exposure measures.

Methods: The PrEP in pregnancy and postpartum (PrEP-PP) study in Cape Town enrolled pregnant women =>16 years without HIV at their first antenatal care visit followed-up through 12-months postpartum; all women were counselled on HIV risk including oral PrEP (TDF/FTC). In women who reported taking PrEP in the last month, we quantified tenofovir diphosphate (TFV-DP) levels in dried blood spots (DBS). Here we compare pregnancy outcomes in those: (1) self-reporting PrEP use in pregnancy, (2) with objective levels of PrEP use (any TFV-DP detected), (3) missing PrEP exposure data (received prescription but never confirmed PrEP use) using multivariable logistic regression adjusting for maternal age and gestational age at baseline.

Results: In 826 women who reported PrEP use during pregnancy with pregnancy outcome data, the median age was 27 years (IQR:23-31), baseline gestation age (GA) was 22 weeks (IQR:14:30); 32% were primigravid. In pregnant women reporting PrEP use in the last 30 days, 181 of 471 (39%) pregnant women had objective levels of PrEP use (any TFV-DP in DBS). Women with TFV-DP present were older age, >20 weeks GA (vs <20 weeks) at PrEP start, had a partner living with HIV (or unknown serostatus), had higher sex frequency in past month (>5 times vs <5 times or no sex) (p<0.05). Women with missing PrEP exposures had the highest rates of adverse pregnancy outcomes during the study period at 32.6% (18.4% pregnancy loss, 10.4% preterm delivery, 8.7% infant born SGA). In women with TFV-DP in their DBS (n=181), adverse outcomes were significantly lower at overall composite outcome at 17%, including 3.9% had pregnancy loss, 6.6% had preterm delivery, 6.6% had an infant born SGA (Table 1). Correlation between self-reported PrEP use and TFV-DP was −0.07 in pregnancy.

Conclusion: The proportion of "PrEP-exposed" pregnant women with adverse pregnancy outcomes differed significantly based on how PrEP exposure was defined in the study, highlighting the importance of objective monitoring in pregnancy safety studies as self-reported PrEP use did not correlate with objective levels. Pregnant women who discontinued PrEP had poorest pregnancy outcomes and may require additional interventions for PrEP and pregnancy health. Rapid, cost-effective methods for measuring objective PrEP use are urgently needed.

Table 1. Comparison of pregnancy outcomes by PrEP exposure: (1) self-report, (2) objective measures of TFV-DP in DBS, (3) missing PrEP exposure (received prescription but did not return to confirm PrEP use) in PrEP-PP study, Cape Town, South Africa, August 2019-February 2023

	1. Self-reported PrEP use in pregnancy	2. Objective levels of TFV-DP in pregnancy (subset of #1)	3. Missing PrEP exposure (never returned for follow-up)
Total	**826**	**181**	**141**
Pregnancy loss (miscarriage or stillbirth)	27 (3.3)	7 (3.9)	26 (18.4)
Preterm delivery	68 (8.5)	12 (6.6)	12 (10.4)
SGA	74 (9.3)	12 (6.6)	10 (8.7)
Composite adverse outcome	**169 (20.5)**	**31 (17.1)**	**46 (32.6)**

*Composite outcome includes pregnancy loss, neonatal death, infant born SGA, preterm birth or low birthweight infant

900 Pharmacokinetic Study Comparing TAF and TDF as PrEP in Pregnant and Postpartum Women in South Africa

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Background: ARVs for PrEP are effective at preventing HIV. However, among pregnant women receiving tenofovir disoproxil fumarate and emtricitabine (TDF/FTC), lower tenofovir (TFV) and intracellular tenofovir-diphosphate (TFV-DP) concentrations in red blood cells have been found compared to postpartum periods. No studies have been conducted to establish concentrations of TFV-DP after administration of tenofovir alafenamide (TAF) in pregnant and postpartum individuals.

Methods: Between June 2022 and March 2023, we recruited eligible and consenting pregnant women from a cohort study in Cape Town, South Africa. We randomized participants in the 2nd trimester 1:1 to daily dosing of tenofovir alafenamide-emtricitabine (TAF/FTC) or TDF/FTC. Participants had 8 weekly study visits and bloods drawn (plasma, dried blood spots [DBS]) during pregnancy and again postpartum. Adherence was monitored using video directly observed therapy. We compared TFV-DP concentrations between TDF and TAF for pregnancy vs. postpartum in both DBS and PBMCs including geometric mean ratios (GMR) for log concentrations and 95% CIs (STATA v18).

Results: We evaluated 37 paired pregnancy and postpartum individuals; 19 in the TAF arm and 18 in the TDF arm. Two participants did not adhere to the protocol and were excluded. Median age was 28.2 years (IQR=23-32); median gestation age at PrEP start/study baseline was 24 weeks (IQR=21-24 weeks). In TAF, median concentrations of TFV-DP in DBS were 51% higher in postpartum and 1% higher in PBMCs when compared to pregnancy. In TDF, median concentrations of TFV-DP in DBS were 12% higher in postpartum and 35% higher in PBMCs samples vs. pregnancy (Table 1). GMR for postpartum vs. pregnancy for TFV-DP was 1.68 (1.61-1.76) for TAF DBS, and 1.01 (0.94-1.07) for TAF PBMCs. GMR for TFV-DP in TDF samples was 1.62 (1.53-1.71) for DBS and 1.39 (1.34-1.45) in PBMCs. In TAF samples, median FTC-TP was 9.42 (IQR:6.47-14.0) in pregnancy and 10.45 (6.6-14.45) in postpartum (GMR=1.15; 1.11-1.99). Comparing TAF vs. TDF PBMCs, GMR was 30.1 (25.0-36.2), similar in pregnant and postpartum samples. No safety related adverse events were found.

Conclusion: Our findings demonstrate high concentrations of TFV-DP in PBMC in pregnancy and postpartum among women receiving TAF suggesting PrEP efficacy is retained. DBS adherence benchmarks for daily dosing were established for TAF in pregnant and postpartum in African women. Efficacy

and safety studies are warranted to evaluate TAF for PrEP in pregnant and postpartum women.

Table 1: Median levels of tenofovir diphosphate (TFV-DP) and FTC-TP in TAF and TDF arms, comparing pregnant vs. postpartum periods with log transformed geometric mean ratios (GMR) in Cape Town, South Africa (PrEP-PP PK Study, June 2022 – June 2023)

	Pregnancy (8 weeks); Median (IQR)	Postpartum (16 weeks); Median (IQR)	GMR (95% CI) comparing log transformed pregnant vs. postpartum concentrations
TAF/FTC (n=19)			
TFV-DP DBS (fmol/3 mm punch)	837 (675-964)	1268 (982-1635)	1.68 (1.61, 1.76)
TFV-DP PBMC (fmol/10^6 cell)	876 (336-1305)	889 (553-1256)	1.01 (0.94, 1.07)
FTC-TP in PBMC (pmol/10^6 cell)	9.42 (6.47-14)	10.45 (6.6-14.45)	1.15 (1.11, 1.99)
TDF/FTC (n=18)			
TFV-DP DBS (fmol/3 mm punch)	554 (348-743)	618 (348-743)	1.62 (1.53, 1.71)
TFV-DP PBMC (ng/mL)	66.55 (49.3-117)	90 (48.6-134)	1.39 (1.34, 1.45)
FTC-TP in PBMC (pmol/10^6 cell)	15 (8.6-21.4)	11 (5.36-13.3)	0.97 (0.91, 1.04)

901 Video Observed Therapy for Preexposure Prophylaxis Use in South African Pregnant/Postpartum Women

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Background: Daily use of oral PrEP is essential for effectiveness. Video observed therapy (VOT) is an adherence technique involving daily observation of participant dosing via digital means. VOT is an alternative to directly observed therapy and may be useful for resource-scarce settings and pharmacokinetic (PK) studies. This study aims to evaluate the feasibility and acceptability of VOT in a PK study (PrEP PK) of oral PrEP in pregnant and postpartum South African women.

Methods: We analyzed data from adult pregnant and postpartum women collected over a year in the PrEP PK study. Each participant was observed for 16 weeks: 8 weeks in pregnancy, 8 weeks postpartum. Feasibility was defined as participant adherence to VOTs, reported as fraction of expected doses observed (FEDO). A median FEDO of ≥85% indicated VOT feasibility while <85% indicated lack of feasibility. Logistic regression analysis was used to determine the impact of baseline characteristics on FEDO score. Linear mixed effect models (LME) were used to examine the effect of observation time and pregnancy state on FEDO score. Acceptability was assessed through semi-structured questionnaires and interviews.

Results: Among n=53 women in the study, 39(73.6%) completed all 16 weeks of observation, median(IQR) observation time: 15(14-16) weeks. Mean(SD) age was 28(6) years. Of the 4571 videos expected 4112(90.0%) were received. Reasons for missed videos are in Table 1. Median(IQR) FEDO exceeded the feasibility threshold and was 91.4(82.9-97.1)%. There was no significant impact of baseline characteristics on FEDO score. FEDO increased over weeks of observation: FEDO at week 1(81%); week 7(92%) and week 15(97%). On LME modelling, every additional week of observation time was associated with a 0.5%(95% CI: 0.20%, 0.89%) increase in median FEDO score (p value=0.002). During pregnancy, 94% of expected videos were received; 98% were received postpartum. There was no significant association between pregnancy state and FEDO score in LME modelling (P value= 0.523). When participants were asked about their experiences with VOT, 100% of respondents said that they would do VOTs again and 98% felt that it helped them adhere to PrEP.

Conclusion: VOT is feasible and acceptable in pregnant and postpartum women for monitoring and supporting daily PrEP adherence. A high proportion of women successfully completed the observation period. VOT was also a useful technique for assuring daily dosing; and can be applied to future PK studies that require strict adherence.

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902 PrEP Discontinuation and High HIV Incidence in South African Pregnant and Postpartum Women

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Background: High HIV incidence is a major concern for pregnant and breastfeeding women (PBFW) in South Africa (SA) due to increased risk of HIV acquisition doubling during these periods. In 2019, the SA Department of Health guidelines were updated to include oral pre-exposure prophylaxis (PrEP) for PBFW, but availability of PrEP for PBFW is still limited in SA health facilities and PrEP discontinuation remains a challenge to effective use in this population.

Methods: In an antenatal clinic based in Cape Town, SA, the observational study recruited pregnant women without HIV between Aug 2019–Oct 2021. The study provided HIV testing, counseling and offer of oral PrEP (TDF/FTC) to all pregnant women at their first visit, with follow-up through 12 months postpartum. At quarterly study visits study counselors conducted HIV testing and counselling to monitor serostatus of PBFW. In addition, HIV results, CD4 counts, and viral loads were reviewed for all study participants at the end of follow-up to confirm final serostatuses in electronic patient and laboratory files. We calculated HIV incidence rate using study follow-up person-time of Aug 2019 – Feb 2023. The numerator included seroconversions in study and lab results (incl. lost to follow-up [LTFU]). HIV incidence was stratified by pregnancy and postpartum time, using estimated delivery dates for those who were LTFU.

Results: Of the 1195 women enrolled, 1009 (84%) received a PrEP prescription and 82% confirmed PrEP initiation through self-report. After 12 months follow-up, 283 (26%) women continued PrEP use. Overall, 16 women (0.5%) seroconverted over 1684.8 woman-years of follow-up with an HIV incidence rate of 0.95/100 woman-years [95% confidence interval (CI) 0.58–1.55]. Of 16 seroconversions, 1 woman (6%) reported taking PrEP in the past 3 months, 1 (6%) seroconverted during pregnancy, and HIV incidence was higher among women who had stopped or never started PrEP (1.89/100 woman-years vs 0.11/100 woman-years who continued PrEP). In the first 6 months postpartum, HIV incidence was 1.07/100 woman-years [95% CI 0.43–2.22] and 60% of the women seroconverted later in postpartum (>6 months) in 1.12/100 woman-years.

Conclusion: Despite the high PrEP initiation at enrolment, we observed a high HIV incidence rate in postpartum in women who had started PrEP and discontinued, highlighting the importance of appropriate interventions targeting postdelivery PrEP continuation through integration of PrEP delivery with services such as family planning and baby visits.

Table 1. Rates of HIV incidence in PrEP-PP Cohort Study (2019-2022), Cape Town, South Africa

	Time in study (years)	Seroconversions (n)	Rate per 100 years	[95% Confidence interval]	
By PrEP use					
Continued PrEP	889.3151	1	0.1124	0.01584	0.7982
Discontinued PrEP	795.4521	15	1.886	1.137	3.128
By pregnancy status					
Pregnant	357.9836	1	0.2793	0.03935	1.983
≤6 months pp	563.2576	6	1.065	0.4318	2.216
>6 months pp	763.526	9	1.179	0.6133	2.265
Total	**1684.767**	**16**	**0.9497**	**0.5818**	**1.55**

* Continued PrEP: Self-reported PrEP use in last 3 months at final study visit

903 The Role of Maternal Broadly Neutralizing Antibody Activity in Perinatal Transmission of HIV-1

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Background: Despite increased availability to antiretroviral therapy (ART), up to 5% of women living with HIV (WLH) still transmit the virus to their infants. While broadly neutralizing antibodies (bNAbs) are the immunologic goal of HIV-1 vaccine candidates, we have demonstrated escape of infant HIV variants in the presence of bNAbs targeting a single, dominant epitope in postnatal transmitters. We hypothesize that WLH with bNAb responses against single epitopes of the HIV envelope are at higher risk of perinatal transmission due to viral escape, and this impacts the development of a bNAb response in infants.

Methods: Plasma was acquired around delivery from 15 perinatal transmitters and 47 non-transmitters with HIV from the US-based, pre-ART era Mother-Infant Cohort Study (MICS), matched 1:3 on CD4+ T-cell counts, maternal age, delivery type. Plasma from paired infants with HIV was acquired at 1- 3 years of age. Maternal and infant plasma was screened for neutralization against a global HIV-1 panel, with breadth defined as neutralizing ≥ 5 out of 10 viruses with an ID_{50}≥40. For transmitters with breadth, plasma was screened against HIV-1 pseudoviruses with epitope mutations, and a two-fold reduction in neutralization compared to wild-type was considered as mapping to an epitope. Antibody dependent cellular cytotoxicity (ADCC), was assessed against cells infected with a transmitted/founder subtype B virus (WITO).

Results: A greater proportion of perinatal transmitters (7 out of 15, 47%) had neutralization breadth compared to non-transmitters (15 out of 47, 32%); these responses mapped to the V2/V3 glycan region for 4 out of 6 (67%) transmitters with neutralization breadth tested so far. Maternal transmitters also trended towards higher ADCC against WITO compared to non-transmitters. Finally, infants seemed to frequently a develop a bNAb response between ages 1 - 3 irrespective of maternal bNAb status, as infants of both transmitters with bNAb activity (4 of 5, 80%), and without (7out of 7, 100%), exhibited bNAb activity.
Conclusion: Our findings support the existence of increased bNAb activity in transmitters that is frequently specific to a single epitope, which could lead to emergence of bNAb-resistant viral variants that can be transmitted perinatally to the infant, which in turn may contribute to endogenous bNAb responses. Thus, bNAb-based pediatric HIV prevention and treatments that are synergistic with ART will likely need to be multi-specific to effectively eliminate and cure pediatric HIV.

904 Long-term Outcomes After Loss to Follow-Up From PMTCT Services for Women and Children in Kenya

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Background: Many prevention of mother-to-child HIV transmission (PMTCT) studies assess outcomes within a year post-delivery and exclude patients who became lost to follow-up (LTFU) or transferred out, biasing outcomes toward those retained in care at the facility where they first enrolled in PMTCT services.
Methods: We recruited women living with HIV (WLH) ≥18 years that enrolled in antenatal clinic (ANC) at five public facilities in western Kenya. WLH retained in care (RW) were recruited during the 3rd trimester of pregnancy and followed with their children through 6 months post-delivery; WLH who became LTFU (LW, last visit >90 days) after ANC enrollment and before 6 months postpartum were recruited through community tracing. Re-contact at 3 years post-delivery was attempted for all WLH, using community tracing for WLH LTFU (>60 days since last missed scheduled visit before 36 months) and transferred. Primary outcomes of retention in care and child HIV-free survival were determined at 6 months and 3 years post-delivery.
Results: 333 WLH were recruited from 2018-2019. At 6 months postpartum, 222 WLH were classified as RW and 111 as LW (79 disengaged from care, 32 silently transferred/retained elsewhere). More LW compared to RW were newly diagnosed with HIV at ANC enrollment (50% vs. 24%), not virally suppressed at study enrollment (40% vs. 8%), and miscarried (12% vs. 1%) ($p<0.01$ for all). HIV-free survival at 6 months was lower for children of LW vs. RW (88% vs. 99%, $p<0.01$). At 3 years, 230 WLH were retained at the study facility (81% of RW, 46% of LW), 30 officially transferred out (28 retained at a new facility, 2 unknown), 70 LTFU (8 silently transferred/retained elsewhere, 19 disengaged, 43 unknown), and 3 deceased. Child HIV-free survival at 3 years was 82% (59% for children of LW, 92% for RW), 3.7% were living with HIV (11% LW, 0.4% RW), 3.7% were deceased (7% LW, 2% RW), and 11% had unknown HIV/vital status (23% LW, 5% RW).
Conclusion: HIV-free survival was lower for children of LW compared to RW at 6 months and 3 years post-delivery, emphasizing the need for interventions targeting early loss to follow-up from PMTCT services. Although most LW had re-engaged in care by 3 years, many remained LTFU and tracing-ascertained engagement in care was lower for WLH silently vs. officially transferred. Community tracing of patients who become LTFU can inform PMTCT outcome estimates and service delivery priorities for this population.

905 ART Adherence And Elevated Viral Load in Pregnant & Postpartum Women Initiating DTG Versus EFV

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Background: There is extensive evidence of non-adherence in pregnant and postpartum women living with HIV (PHIV). But despite the expansion of dolutegravir (DTG) replacing efavirenz (EFV) in first-line ART, there are few data on objective adherence to DTG vs EFV and how non-adherence is associated with elevated viral load (VL) in this population.
Methods: The DolPHIN-2 trial (NCT03249181) randomised pregnant women initiating ART from 28w gestation to DTG vs EFV with tenofovir (TDF) and lamivudine/emtricitabine. Within the trial cohort we conducted a nested case-control study to examine adherence to DTG vs EFV using random plasma tenofovir (TFV) levels as an objective adherence measure in both arms (≥35.5ng/mL indicating effective adherence [EA]). Eligible participants had an initial VL>1000 at enrolment and achieved viral suppression (VS <20) during follow-up through 18m postpartum. Case specimens had ≥1 VL>20 after initial VS; control specimens were incidence density sampled from PHIV with persistent VS, matched on ART duration and trial arm (DTG vs EFV). Additional specimens were included from the suppressed visit preceding the first VL>20 (cases) or a time-matched visit (controls) and all visits after viraemia for cases (subsequent visits). Logistic regression, with conditional models for matched data, was used to examine associations between EA and elevated VL.
Results: Overall 172 case and 338 control specimens were included from 88 PHIV (mean age, 28y). At preceding visits with VS, EA was higher in DTG compared to EFV (58% vs 42%). Self-reported missed doses (4%) and ARV-related side effects (2%) were low and similar by regimen. At the time of VL>20, cases had a mean VL2.95 $\log_{10}$ copies/mL; EA was observed in 37% of cases compared with 74% of controls with VL<20 at a matched ART duration. Differences were consistent between DTG (OR=6.3; 95% CI=2.3–17.2) and EFV (OR=3.8; 95% CI=1.3-10.8). Among cases, at the preceding visit 46% had EA compared with 37% at viraemic visit (conditional OR=1.4 95% CI 0.7-2.6) with no difference by regimen. At subsequent visits, 86% with detectable TFV achieved VS again with no differences by regimen.
Conclusion: The association between objectively measured adherence and viraemia was similar with DTG versus EFV. EA was higher in DTG at visits with VL<20. Taken together, these data suggest that DTG may be associated with better ART adherence compared to EFV but is not more forgiving of the short-term non-adherence that occurs commonly during the postpartum period.

906 A Novel Risk Calculator to Predict Sub-Optimal Outcomes Among Pregnant and Postpartum Women With HV

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Background: Pregnant and postpartum women living with HIV (PPWH) experience differential treatment success. No tool currently exists to assess a PPWH's cumulative risk of disengagement from care or treatment failure with a quantifiable score during the peripartum period. To identify PPWH at risk and intervene before negative outcomes occur, this study sought to develop and validate a parsimonious risk calculator capable of predicting disengagement from care and treatment failure.
Methods: We used a derivation dataset with data from 1331 PPWH enrolled in the Mother-Infant Visit Adherence and Treatment Engagement trial in southwestern Kenya. Least absolute shrinkage and selection operator (LASSO) logistic regression procedures selected the most predictive variables from a list of 16 candidate factors based on prior research, including psychosocial, demographic, and clinical factors. We applied the Minimum Extended Bayes information criterion (EBIC) and 10-fold cross validation methods to find the regularization parameter lambda to give the minimum mean cross-validated

concordance index. Multiple imputation with chained equations was used to address missing values. Predictors with nonzero coefficients in the LASSO regression model were selected for calculating predicted risk of a missed visit (>30 days) or elevated viral load ≥400 copies/ml). Backward selection with the imputed dataset was used to identify a final concise calibrated model. Model calibration and discrimination were assessed.

Results: The final model resulted in 5 risk predictors of a future missed visit or elevated viral load, including baseline viral load> 1000 copies/ml, prior history of a missed visit, anticipated HIV stigma, low male partner support, and fair/poor self-reported baseline ART adherence. The predicted risk scores ranged from 3.6% to 81.6%. The mean predicted probability of the outcome in the low-risk group, moderate-risk group, and high-risk group were 4.9%, 55.6%, and 68.0%, respectively. Model calibration was fair and intercept adjustment was done. The C-statistic by bootstrap cross validation indicated a strong model discrimination, 0.89 (95%CI 0.87, 0.91). The overall model performance was good (brier score = 0.14).

Conclusion: The risk calculator will be validated in a separate sample. The risk calculator has the potential to be used in research and clinical care to identify PPWH at greatest need of interventions and enhanced support to achieve treatment success.

907 Mentor Mothers! Community Model to Attain Elimination of Mother-to-Child HIV Transmission, Tanzania

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Background: Despite the remarkable progress in Tanzania on ART provision to pregnant women living with HIV there are still significant number of new HIV infections among children. Data shows that progress in preventing HIV transmission from mother to child has almost stagnated. These can be linked with poor uptake of HIV testing, gaps in ART initiation, low retention rates and poor adherence to treatment. Social cultural factors associated with early pregnancy stages can also be linked to the above challenges. We aim to address these gaps through the use of a community peer model accepted and trusted by the community members.

Methods: From January to June 2023 Amref implemented a community model using mentor mothers(MM) who are women living with HIV pregnant or breastfeeding champions identified from PMTCT clinics. Selection criteria included good adherence, willingness to disclose or have disclosed status and influential who can perform the task. We implemented it in 330 health facilities within 10 regions and 58 councils. A total of 947 MM who were trained, paired with Antenatal care supervisors in a health facility within their catchment areas to ensure early identification and linkage, throughout the cascade of care. Sites positivity rates of more than 5% in 2020 with HIV pregnant or breastfeeding attending PMTCT were identified. Each facility selected a total of 4 MM and one facility supervisor who were trained using MM National curriculum.

Results: The implementation has increased early ANC bookings, couple counselling and HIV testing as well as increased number of women returned to care. From January to June 2023, we reached a total of 59,582 (93%) of pregnant women who were tested for HIV out of our target and 398 the positivity rate was 0.7%. We reached 51,818 women who tested for HIV. 540 were HIV+ which is 1.1%, their male partners reached were 36,888 and 395 were HIV positive which is 1.3% yield. Mother mentors were able to trace back a total of 219 out of 254 clients who were lost to follow up and linked back to services. To ensure retention a total of 1,839 beneficiaries from 289 groups are continuously supported and linked to psychosocial support groups and income-generating activities (PSAG). MM also identified 287 adolescents who are attending

Conclusion: Mentor mothers model has improved follow up and retention to care for BFPW through out the continum of care, it is a community peer model accepted by the community and hence scale up will contribute to reaching eMTCT.

908 Comparison of Models of Care to Promote Postpartum Viral Suppression in South African Women

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Background: Maintaining viral suppression (VS) in postpartum women on antiretroviral therapy (ART) is a major concern. There is significant interest in both integrated models of service delivery for maternal and child health (MCH), and in differentiated service delivery models (DSD) postpartum, but there are few rigorous data comparing these intervention strategies.

Methods: We conducted a secondary analysis of individual patient trial data from Cape Town to compare head-to-head (i) an integrated MCH model with maternal and child care co-located and co-scheduled (MCHART; NCT01933477) versus (ii) a DSD model with mothers referred to community based "adherence clubs" for maternal ART dispensing (PACART; NCT03200054). Data for both interventions came from RCTs conducted in the same primary care community health service comparing each intervention to the local standard of care (SOC, referral to general adult ART services). Both trials measured demographic and behavioural covariates using the same tools; study viral load testing was conducted by trial personnel separate to routine antenatal ART (tenofovir+lamivudine+efavirenz). Analyses used frequentist network methods via generalised linear mixed models to compare VS (<50 copies/ml) under each model of care at 6m and 12m postpartum using the SOC as the reference; results are reported as odds ratios (OR) with 95% CI.

Results: A total of 882 women (mean age: 29y; median time postpartum at enrolment, 1w [IQR, 0.6-1.9]) were included: 471 in MCHART and 411 in PACART. Follow-up through 12m was >85% in both trials; in women retained, VS was achieved by 299/375(80%) and 289/349(83%) women at 6m, and by 229/336(68%) and 231/329(70%) women at 12m, postpartum in MCHART and PACART, respectively. VS in integrated MCH at 6m and 12m was higher than in the DSD model (6m: 88% vs 87%; 12m: 80% vs 74%); VS under the SOC was higher in PACART than MCHART (6m: 79% vs 71%; 12m: 67% vs 55%, both p<0.05). In network comparisons, integrated MCH in MCHART was associated with significantly higher levels of VS compared to the DSD model in PACART at 12m postpartum (aOR 2.48; 95%CI 1.25-4.95; Table); results were consistent at VL<1000 copies/mL and robust across a range of sensitivity analyses.

Conclusion: These novel data comparing two postpartum interventions in the same community suggest that integration of ART and postpartum MCH services achieved higher levels of VS compared to referral of mothers to DSD models of care in this setting.

Table 1 – Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) for viral suppression <50 copies/mL at 6 and 12 months postpartum comparing models of ART care using generalized linear mixed effect models

Model	Comparison	6 months (n = 720)	12 months (n = 657)
		OR (95% CI)	OR (95% CI)
Unadjusted	MCH vs SOC (direct)	3.27 (1.90 – 5.62)	3.30 (2.03 – 5.35)
	DSD vs SOC (direct)	1.73 (1.00 – 3.01)	1.43 (0.89 – 2.29)
	MCH vs DSD (indirect)	1.90 (0.88 – 4.07)	2.31 (1.18 – 4.55)
Adjusted*	MCH vs SOC (direct)	3.17 (1.85 – 5.45)	3.33 (2.02 – 5.49)
	DSD vs SOC (direct)	1.83 (1.01 – 3.31)	1.33 (0.81 – 2.19)
	MCH vs DSD (indirect)	1.73 (0.78 – 3.84)	2.48 (1.25 – 4.95)

OR: Odds Ratio; MCH: Integrated Maternal and Child Health ART model; DSD: Differentiated Service Delivery model (Adherence Club); SOC: Standard of Care
* Adjusted for age, parity, education, employment, socioeconomic score, marital status, HIV diagnosis status, TB history, and duration on ART

909 Budget Impact Analysis of an Enhanced Retention Strategy for PMTCT Programs in Uganda

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Background: Novel retention strategies have the potential to reduce mother-to-child transmission and improve patient outcomes for people living with HIV. The enhanced retention strategy (ERS) of the DoIPHIN-2 trial in Uganda achieved a retention rate of 92% among women receiving PMTCT services and reduced perinatal transmission (PT) from 2.8% (national rate) to 1.5% (DoIPHIN cohort). This analysis built on the DoIPHIN findings by estimating the budget impact of the ERS compared to the standard of care (SOC) approach for preventing PT among women initiating antiretroviral therapy (ART) in late pregnancy in Uganda.

Methods: A budget impact analysis (BIA) was conducted from the payer (Uganda Ministry of Health) perspective with a 5-year time horizon. A

Microsoft Excel-based BIA model was populated with HIV epidemiological data and expenditures from the literature and the DolPHIN trial. These cost projections accounted for a variety of programmatic inputs, disease progression, differences in mortality based on treatment status, subsequent pregnancies, and other factors. The eligible population matched the DolPHIN inclusion criteria, including pregnant women with an adjustment for pre-pregnancy and ART- data. We conservatively assumed a 50-50% market share for the ERS and SOC and an annual discount rate of 3%. Main outcomes of the analysis were incremental budget costs and infections averted over 5 years.

Results: Adopting the ERS would lead to a net cost increase of $64 million over the next 5 years, or a net cost increase of $13.8 million per year compared to the SOC. Newly enrolled patients account for $40 million of these marginal costs, while in-system patients account for $24 million. Direct programmatic costs of the ERS only account for 3% of this additional cost, with 97% of the marginal increase coming from the cost of providing ART for women who would otherwise be lost to follow-up. The ERS would avert an additional 6,933 infant infections compared to the SOC, and more than double the probability that women would be retained on ART at the start of subsequent pregnancies (24.94% for ERS vs 10.87% for SOC).

Conclusion: Implementing the ERS is likely to produce a significant budget impact to Uganda's Ministry of Health while potentially offering substantial health benefits to people living with HIV. Though costly, the ERS gives an alternative to reducing loss-to-follow-up among marginalized groups.

Parameter	Input
Fertility rate	4.7
Median birth interval	31.9 months
PT rates (ERS and SOC)	1.5% and 2.8%
Mortality rate with ART	0.30%
Mortality rate without ART	15%
HIV-positive pregnant women	90256
Coverage of HIV prevention services	100%

910 Hypertension in Pregnant Persons by HIV Status and by DTG vs EFV Use in Botswana

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Background: In non-pregnant adults, some studies suggest dolutegravir (DTG) is associated with increased risk of hypertension (HTN). Given the serious implications of HTN for pregnancy outcomes, we compared the risk of hypertensive disorders of pregnancy (HDP) among pregnant people on DTG-based antiretroviral treatment (ART) to those on efavirenz (EFV)-based ART and to pregnant people without HIV (w/o HIV).

Methods: Methods: Among deliveries captured by the Tsepamo Birth Outcomes Surveillance Study (8/2014-8/2022), we included people who presented to antenatal care prior to 20 weeks gestational age (GA) and were either w/o HIV or with HIV and conceived 0.5-5 years after starting DTG- or EFV-based ART. Blood pressures (BP) and medical history of HTN were abstracted from antenatal medical records. Chronic HTN was defined as a pre-pregnancy history of HTN or HTN (systolic BP >140 or diastolic BP >90 mm Hg) before 20 weeks GA. HDP was onset of any HTN (including mild and severe) >20 weeks and predelivery among women without chronic HTN. We determined proportions with chronic HTN and HDP by exposure group, and fit multivariable log-binomial regression models to estimate the adjusted risk ratio (aRR) of HDP in the EFV and w/o HIV groups each compared to the DTG group, adjusted for maternal age, marital status, education, and tertiary delivery site.

Results: Of 265,410 deliveries in the study period, we included 127,946; 5,866 conceiving on DTG, 4,771 conceiving on EFV, and 117,309 w/o HIV. Median maternal age was 25 yrs in those w/o HIV and 31 yrs in the DTG and EFV groups (Table 1). The prevalence of chronic HTN was 4.4%, 4.4% and 4.6% and the risk of HDP was 10.2%, 8.1% and 11.7% in the DTG, EFV and w/o HIV groups, respectively. The risk of HDP was 20% lower (aRR=0.80, 95% CI 0.71,0.91) in the EFV group and 20% higher (aRR=1.20, 95% CI 1.10,1.30) in the w/o HIV group, compared to the DTG group.

Conclusion: The prevalence of chronic HTN was similar across exposure groups. While pregnant people who conceived on DTG-based ART had a higher risk of HDP than those on an EFV-based regimen, both groups had a lower risk than those without HIV. In future analyses it will be important to elucidate the mechanisms responsible for these differences, including the impact of weight and weight gain.

Table 1. Characteristics and hypertensive outcomes among women on DTG at conception, EFV at conception, and women without HIV from the Tsepamo study in Botswana (2014-2022)

	DTG at conception (N=5866)	EFV at conception (N=4771)	Women without HIV (N=117,309)
Median age in yrs (IQR)	31 (26, 36)	31 (27, 35)	25 (21, 30)
Married	8.9%	10.4%	11.6%
Primary education or higher	91.2%	88.8%	55.4%
Chronic Hypertension	261/5866 (4.4%)	209/4771 (4.4%)	5426/117309 (4.6%)
Gestational Hypertension	573/5605 (10.2%)	369/4562 (8.1%)	13060/111887 (11.7%)
Unadjusted relative risk	Ref.	0.79 (0.70, 0.90)	1.14 (1.05, 1.24)
Adjusted relative risk*	Ref.	0.80 (0.71, 0.91)	1.20 (1.10, 1.30)

*Model adjusted for maternal age, marital status, education, parity, tertiary delivery site

911 Gestational Diabetes in South African Women With HIV on Dolutegravir: Results From the ORCHID Study

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Background: Few data exist on gestational diabetes (GDM) in Africa, particularly in women with HIV (WWH) receiving dolutegravir-based antiretroviral therapy (ART). This study aimed to assess the association of HIV infection and duration on tenofovir/lamivudine/dolutegravir (TLD) with GDM.

Methods: The ORCHID study enrolls WWH initiating/receiving TLD and HIV-seronegative (HIV-) women >16 years and <18 weeks gestational age (GA) in South Africa. Pregnant women with diabetes or hypertension are excluded. Participants undergo air displacement plethysmography assessment of body composition and a 75g oral glucose tolerance test at enrollment and 32-34 wks GA. GDM is defined as meeting WHO 2013 criteria or clinician diagnosed GDM. Duration of TLD was categorized as initiating <14 (TLD14) vs 15-90 (TLD15-90) vs >90 (TLD>90) days prior to enrollment. Logistic regression models were fit to assess the association of 1) HIV status and 2) duration of TLD with GDM, adjusting for confounders.

Results: 1574 women were included (627 WWH, 947 HIV-); among WWH there were 166 TLD14, 92 TLD15-90, and 369 TLD>90. WWH were older (median 30 vs 26 years) with a lower proportion primigravid (21 vs 40%). At enrollment, median (interquartile range) GA was 13 (10-16) wks, BMI 30 (25-35) kg/m², and fat mass index (FMI) 12.3 (8.8-16.3) kg/m², with no differences between WWH and HIV- women. Among WWH, 93% had CD4 >200 cells/mm³ and 79% had viral load (VL) <50 copies/mL. Overall, 8.0% of WWH and 8.1% of HIV- women had GDM; adjusted analyses confirmed similar rates of GDM by HIV status. (Table) Of the 127 participants with GDM, 69% were diagnosed at enrollment, 24% at 32-34 wks, and 7.1% by clinician between enrollment and 32-34 wks. Among WWH, the TLD15-90 group had the highest rates of GDM compared to TLD14 and TLD>90 (14 vs 4.8 vs 7.9%, respectively). After adjusting for age, GA at enrollment, education, gravidity, FMI, CD4, and VL, WWH receiving TLD15-90 had higher odds of GDM vs those on TLD14 [adjusted odds ratio (95% confidence interval) = 2.83 (1.01-8.30)]. No differences in GDM risk were observed comparing TLD>90 vs TLD14.

Conclusion: WWH and HIV- women have similar rates of GDM in South Africa, consistent with the reported prevalence in sub-Saharan Africa. WWH on TLD for 15-90 days who initiated TLD periconception or in the 1st trimester may be at higher risk for GDM. Future studies are warranted to confirm this finding and assess the potential benefits of screening for GDM at this earlier timepoint in this population.

Table. Unadjusted and adjusted odds ratios assessing the associations of HIV status and duration of TLD with gestational diabetes

	Unadjusted OR	95% Confidence Interval	*p* value	Adjusted OR	95% Confidence Interval	*p* value
Model (Entire Cohort)[a]						
HIV status						
Women with HIV	0.98	0.67, 1.41	>0.90	0.83	0.56, 1.22	0.30
HIV-seronegative	Ref	Ref	Ref	Ref	Ref	Ref
Model (Women with HIV)[b]						
TLD_{14}	Ref	Ref	Ref	Ref	Ref	Ref
TLD_{15-90}	3.25	1.31, 8.52	0.012	2.83	1.01, 8.30	0.050
$TLD_{>90}$	1.68	0.79, 4.03	0.20	1.36	0.57, 3.61	0.50

[a] Adjusted for age, gestational age at enrollment, education, gravidity, and fat mass index. [b] Additionally adjusted for CD4, HIV viral load and same covariates as in entire cohort model.

912 Pregnancy History Affects Age-Related Comorbidity Burden in US Women With and Without HIV

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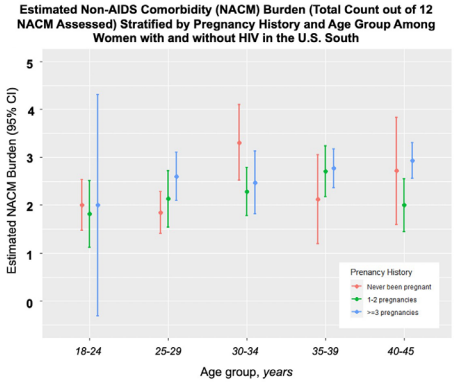
Background: Despite non-AIDS comorbidities (NACM) being more common and occurring earlier in life among women versus men with HIV, evidence is lacking to understand potential drivers of sex differences. We evaluated the effect of reproductive history on NACM development in women.

Methods: We performed a cross-sectional analysis of the Study of Treatment And Reproductive outcomes (STAR), a longitudinal cohort of women with and without HIV (WWH; WwoH) aged 18-45 years enrolled in 6 Southern U.S. sites. NACM prevalence and burden (total NACM count of 12 assessed) was determined at STAR enrollment. Pregnancy history was categorized as zero, 1-2, or ≥3 prior pregnancies. Linear regression models evaluated the association of NACM burden with HIV serostatus, age, and pregnancy history.

Results: Among 519 women (354 WWH; 165 WwoH), median age was 36 (Q1-Q3 30-41) years, 75% reported Black race, 45% ever smoked; 22%, 32%, and 46% had zero, 1-2, and ≥3 pregnancies, respectively. Among WWH, median CD4 count was 666 (Q1-Q3 448-938) cells/mm^3 and 77% had HIV-1 RNA <200 c/ml. NACM prevalence was (WWH/WwoH): obesity (59%/55%), psychiatric illness (54%/46%), anemia (38%/30%), lung disease (30%/29%), hypertension (25%/26%), bone disease (25%/28%), diabetes (8%/6%), cardiovascular disease (7%/4%), liver disease (7%/1%), dyslipidemia (4%/3%), kidney disease (3%/1%), non-AIDS cancer (1%/1%). Among women with available data for all NACM assessed (n=332), WWH vs WwoH had a mean NACM burden of 2.5 vs 2.4, p=0.24. Among women overall, mean NACM burden increased with age group: 1.9 (18-24y), 2.2 (25-29y), 2.5 (30-34y), 2.7 (35-39y), 2.7 (40-45y) (p-trend=0.002). Among women with zero, 1-2, ≥3 pregnancies, age-adjusted mean NACM burden was 2.4, 2.2, and 2.6 (p-trend=0.20). HIV serostatus did not modify the effect of age and pregnancy history on NACM burden (HIV*age*pregnancy interaction p=0.76). Among women across HIV status, pregnancy history was associated with estimated NACM burden in certain age groups: 18-24y (p-trend>0.99), 25-29y (p-trend=0.03), 30-34y (p-trend=0.11), 35-39y (p-trend=0.21), 40-45y (p-trend=0.71) (Figure).

Conclusion: Among reproductive age women in the U.S. South, the burden of 12 NACM was high overall, increased with age, and was associated with pregnancy history in some age groups; further, the distribution of NACM prevalence differed by HIV serostatus. These data may inform the development and timing of NACM screening and prevention strategies to be deployed across the reproductive life course.



913 Maternal HIV Is Associated With Lower Risk of Preeclampsia Among Zambian Women

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Background: Preeclampsia (PEC) – an important cause of maternal and fetal morbidity – may be caused by an abnormal maternal immune response to the fetal allograft. We examined the association between HIV infection and PEC in a well-characterized urban population of pregnant women in Zambia.

Methods: We combined three contemporaneous studies conducted at two facilities in Lusaka between 2015-2022: the IPOP trial (n=800), VP trial (n=140), and ZAPPS cohort (n=3,239). Each study drew from the same population and shared most protocol elements, including antenatal assessments, visit timing, and a standardized procedure for phenotyping adverse birth outcomes. We defined PEC as new-onset (≥20wks) hypertension (≥140 systolic or ≥90 diastolic) with concurrent proteinuria (≥1+). We defined severe PEC as (a) new-onset severe-range BP (≥160 systolic or ≥110 diastolic, (b) eclamptic seizure, or (c) provider-initiated preterm delivery (<37wks) for PEC. Using marginal probabilities from logistic regression, we estimated the crude and adjusted risk of PEC associated with HIV infection.

Results: The 4,176 women included in the combined cohort had an average age of 28yr (±6) and average BMI of 26kg/m^2 (±5), with 46% completing ≥12yrs of education and 82% living with a partner or husband. In the cohort, 293 (7.0%) were diagnosed with PEC, including 74 (4.6%) of 1,597 women with HIV and 219 (8.5%) of 2,579 women without HIV. Of women with HIV, 74% were on preconception antiretroviral therapy (ART) and 57% had an undetectable viral load (VL) at study enrollment. In both univariate (RR 0.55; 95%CI 0.42-0.70) and multivariate analyses adjusting for maternal age, BMI, chronic hypertension, nulliparity, and twin gestation (ARR 0.53; 95%CI 0.41-0.69), HIV infection was associated with decreased risk of preeclampsia. This reduced risk persisted when the cohort was stratified by preconception ART exposure, detectable VL at study enrollment, and CD4 count at enrollment. Findings were similar when the more stringent definition of severe PEC was applied (Table).

Conclusion: In this large, well-phenotyped pregnancy cohort from Zambia, women with HIV are less likely to have preeclampsia compared to those without infection. Although the association does not appear to be mitigated by maternal disease status, further investigation into whether the relative immune suppression of maternal HIV is protective against preeclampsia is warranted.

Table: Multivariate logistic regression analyses of the association between preeclampsia (PEC) and severe PEC and three stratified HIV positive populations with HIV negative as the referent group

Exposure		Total, N	PEC, n (%)	ARR (95%CI)	Severe PEC, n (%)	ARR (95%)
HIV negative		2,579	219 (8.5%)	1.00 (Referent)	186 (7.2%)	1.00 (Referent)
1	HIV positive on preconception ART	1,147	53 (4.6%)	0.53 (0.39-0.72)	48 (4.2%)	0.57 (0.41-0.78)
	HIV positive on postconception ART	405	20 (4.9%)	0.55 (0.35-0.87)	19 (4.7%)	0.65 (0.41-1.03)
2	HIV positive with detectable VL	604	32 (5.3%)	0.61 (0.42-0.88)	29 (4.8%)	0.67 (0.46-0.99)
	HIV positive with undetectable VL	789	38 (4.8%)	0.54 (0.38-0.77)	35 (4.4%)	0.59 (0.41-0.86)
3	HIV positive with CD4>500 cells/mm3	701	38 (5.4%)	0.55 (0.37-0.84)	36 (5.1%)	0.58 (0.37-0.90)
	HIV positive CD4≤500 cells/mm3	510	24 (4.7%)	0.62 (0.44-0.87)	21 (4.1%)	0.67 (0.49-0.99)

ARR from marginal probabilities adjusted for maternal age, BMI, chronic HTN, nulliparity, and twin gestation

914 Pregnancy Inflammatory Markers Predict Postpartum Weight in South African People Living With HIV

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Background: Postpartum weight (PPW) contributes to long-term obesity, a growing concern in women living with HIV (WLH) characterised by low-grade inflammation. We hypothesised that inflammatory markers in pregnancy may be an early indicator of postpartum (PP) obesity risk in WLH.

Methods: The Prematurity Immunology in Mothers and their Infants Study (PIMS) enrolled pregnant PWH in Cape Town. All women were either already on tenofovir+emtricitabine/lamivudine+efavirenz (TEE) pre-conception or initiated at enrolment. We included 57 pregnant PWH who were enrolled at ≤14 weeks (wks) gestational age (GA) as assessed by ultrasonography, with viral load (VL) <200 copies/mL, stored plasma collected at ≤14 wks GA (T1) and 29-36 wks GA (T3), and ≥3 PPW measurements (<2, 10, 24, and 48 wks). Soluble (s) CD14, sCD163, leptin, tumour necrosis factor receptor 1 (TNFR-1), resistin, adiponectin, and interleukin-6 (IL-6) were assayed in duplicate using

the Luminex platform. We considered each inflammatory marker at T1 and T3 as a separate exposure of interest. Linear mixed effects models were fit to examine whether each exposure was associated with average PPW and PPW trajectories; linear regression was used for associations with PPW change between T1 and 48 weeks.

Results: Median age was 32y (IQR, 29-35), 98% were multigravida, and 49% had a BMI≥30 kg/m². The median weight change between T1 and 48 wks PP was 0.10 kg (IQR -3.50 to 4.50). Sixty-one percent initiated TEE pre-conception; all but three participants had VL <100 copies/mL; 86% had a CD4 count >200 cells/µL at T1. TNFR-1 (0.60 vs 0.73 ng/mL, p=0.018) and IL-6 (1.09 vs 1.53 pg/mL, p=0.054) significantly increased between T1 and T3. Levels of other inflammatory markers did not change significantly between T1 and T3. In models adjusted for age, T1 weight, CD4 count, and weight at 2 wks PP, higher T1 sCD14 levels were associated with higher average weight through 48 wks PP (ß = 0.002, p=0.047), and T3 sCD14 with higher PPW gain (ß = 0.006, p=0.048) (Table). Resistin (ß = 0.644, p=0.024), leptin (ß = 0.329, p=0.036) and TNFR-1 (ß = 9.224, p=0.028) at T3 were associated with higher average PPW, and IL-6 (ß = 2.627, p=0.009) with PPW gain.

Conclusion: In this sample of pregnant WLH, we found that sCD14 in early and late pregnancy, as well as resistin, leptin, TNFR-1 and IL-6 in late pregnancy were associated with increased PPW, pointing to potential causal mechanisms with implications for long-term cardiometabolic health in WLH.

Linear and log-binomial regression for the association of inflammatory markers at T1 and T3 with postpartum weight-related outcomes

	Average PPW β (p-value)		PPW trajectory β (p-value		PPW change (48 weeks PP – T1) β (p-value)	
Inflammatory marker	T1	T3	T1	T3	T1	T3
sCD14 (ng/mL)	0.002 (0.047)	0.003 (0.181)	0.001 (0.762)	0.001 (0.112)	0.002 (0.117)	0.006 (0.048)
sCD163 (ng/mL)	0.006 (0.225)	0.005 (0.233)	0.001 (0.427)	0.001 (0.099)	0.008 (0.205)	0.009 (0.071)
Leptin (ng/mL)	0.028 (0.662)	0.329 (0.036)	0.001 (0.799)	0.001 (0.488)	0.011 (0.883)	0.221 (0.281)
TNFR-1 (ng/mL)	2.692 (0.320)	9.224 (0.028)	-0.001 (0.869)	-0.002 (0.861)	1.352 (0.650)	12.296 (0.070)
Resistin (ng/mL)	0.231 (0.372)	0.644 (0.024)	0.001 (0.182)	0.001 (0.025)	0.488 (0.091)	0.790 (0.040)
Adiponectin (µg/mL)	0.729 (0.111)	-0.531 (0.273)	-0.001 (0.631)	-0.001 (0.734)	0.644 (0.217)	-0.582 (0.379)
IL-6 (pg/mL)	0.512 (0.236)	1.192 (0.112)	0.001 (0.506)	0.005 (0.003)	0.420 (0.385)	2.627 (0.009)

PPW: postpartum weight; PP: postpartum; T1: ≤14 weeks gestation; T3: 29 36 weeks gestation.

915 Changes in Body Composition During Pregnancy in South African Women Living With HIV on ART

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Background: Despite widespread interest in how HIV and antiretroviral therapy (ART) affects weight and body composition there are few data from women living with HIV (WLH), and none from pregnant populations, in sub-Saharan Africa.

Methods: In the Obesogenic oRigins of maternal and Child metabolic Health Involving Dolutegravir (ORCHID) study, we explored the relationship between HIV and ART duration and changes in body composition [weight, fat mass (FM), fat free mass (FFM)] between ≤18w (T1) and 32-34w (T3) of pregnancy. We enrolled WLH receiving tenofovir/lamivudine/dolutegravir (TLD) and HIV-seronegative (HIV-) women [enrolment age ≥16y and ≤18w gestational age (GA)]. Weight, FM and FFM were measured using air displacement plethysmography adjusted for the increase in hydration constant of FFM at T3; resting energy exposure (REE) was measured using indirect calorimetry; GA was confirmed via ultrasound; physical activity was estimated using the Pregnancy Physical Activity Questionnaire. Linear regression was used to explore the relationship between HIV status and TLD duration (<28d, 28-182d and >182d) with changes in body composition parameters between T1 and T3 after adjusting for potential confounders.

Results: Overall 970 women were followed: 376 WLH (80% VL <50 copies/mL; 92% CD4 >200 cells/µL; median duration TLD 126d [IQR, 12-465]) and 594 HIV-. Median age was higher in WLH (30y vs 26y, p<0.01) but WLH and HIV- women were similar with respect to median GA (13w), BMI (29 kg/m²), REE (1543 kcal/d) and total physical activity (189 MET hours/w). At T1, women on TLD>182d were most similar to HIV- women in weight, FM and FFM. Between T1 and T3, WLH experienced significantly smaller increases in weight, FM and FFM compared to HIV- women; for weight and FM these reductions were greatest in WLH on TLD<28d (Table). There were no differences in changes during gestation in REE or physical activity between WLH and HIV- women. Findings persisted in sensitivity analyses restricted to women assessed <14w gestation.

Conclusion: South African WLH on TLD had lower weight gain during gestation compared to HIV- women despite similar REE and physical activity. Reductions in FFM accrual are similar by duration of TLD exposure but FM accrual appears most restricted in women recently initiated on ART. The long-term consequences of these differences for maternal and child metabolic health require urgent attention.

Association between changes in body composition between T1 and T3 and (a) HIV status or (b) duration of TLD use

	Weight (kg) * Adjusted β (95% CI)	p-value	Fat mass (kg) ** Adjusted β (95% CI)	p-value	Fat free mass (kg) *** Adjusted β (95% CI)	p-value
(a) HIV Status						
HIV-	Ref	-	Ref	-	Ref	-
WLH	-0.97 (-1.55, -0.39)	0.001	-0.43 (-0.93, 0.08)	0.097	-0.74 (-1.11, -0.38)	<0.001
(b) Duration of TLD use						
HIV-	Ref	-	Ref	-	Ref	-
<28 days	-1.34 (-2.20, -0.48)	0.002	-0.99 (-1.74, -0.24)	0.009	-0.60 (-1.14, -0.06)	0.031
28 - 182 days	-1.00 (-1.99, -0.01)	0.048	-0.59 (-1.45, 0.27)	0.179	-0.67 (-1.30, -0.05)	0.035
>182 days	-0.68 (-1.44, 0.06)	0.073	0.07 (-0.59, 0.72)	0.844	-0.89 (-1.37, -0.41)	<0.001

* Adjusted for: REE, T1 body mass, maternal age, gestational age, smoking, alcohol, physical activity.
** Adjusted for fat mass instead of body mass
*** Adjusted for fat free mass instead of body mass

916 Association of HIV and Dolutegravir With Changes in Blood Pressure During Pregnancy and Postpartum

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Background: There is growing interest in whether dolutegravir (DTG) use may be associated with changes in blood pressure (BP) in women living with HIV (WLH) but there are few data from pregnant and postpartum women, in particular with BP measures from early pregnancy, and few comparisons with women testing HIV-.

Methods: Within the Obesogenic Origins of Maternal and Child Metabolic Health with Dolutegravir (ORCHID) cohort, we enrolled 1601 women at <18 wks gestational age (GA) in Cape Town, South Africa. Women with prevalent diabetes or hypertension were excluded. All WLH were on tenofovir+lamivudine+DTG (TLD). Women were followed through 6 weeks postpartum with serial, standardised BP measures (three measures of the left arm using an automated, calibrated BP cuff sized to participant BMI) conducted separate from routine care. Analyses examined changes in mean systolic and diastolic BP (sBP and dBP) as well as incident hypertension (BP>140/>90mmHg or initiation of antihypertensive agents), comparing (i) WLH to HIV- controls and (ii) varying durations of TLD use among WLH.

Results: Between September 2021 and September 2023, 1601 women were enrolled (633 WLH, 968 HIV-; median (IQR) age 28 years [24-32]; BMI 30 kg/m² [25-35]; GA at enrolment 13 weeks [10-16]; 32% primigravida; 6% current smokers). In WLH median duration of TLD use was 190 days (IQR 11-532) and 30% of women initiated TLD in the preceding month. Mean sBP and dBP in pregnancy were similar throughout pregnancy until 6 weeks postpartum between WLH and HIV- controls (Figure). This absence of any association was not altered by adjustment for maternal age, GA, BMI, smoking or family history (sBP coefficient, -0.39mmHg; 95%CI: -1.35, 0.58; dBP coefficient, 0.13mmHg; 95%CI: -0.59, 0.84). In separate analyses increasing duration of TLD was not associated with changes in sBP or dBP (not shown). Through 6 weeks postpartum 9% of women experienced incident hypertension, with no variation by HIV status (adjusted hazard ratio, 1.27; 95% CI, 0.80, 1.94) or duration of DTG use among WLH. The absence of any association was not altered in subgroups of women with BMI<30kg/m² nor in women with their first BP measures <13 weeks' GA. In adjusted models, higher sBP/dBP was associated with increasing age and BMI.

Conclusion: While longer durations of follow-up are required to understand the cardiovascular health of WLH on TLD, these reassuring data suggest no association during pregnancy of HIV status or TLD duration with BP or incident hypertension.

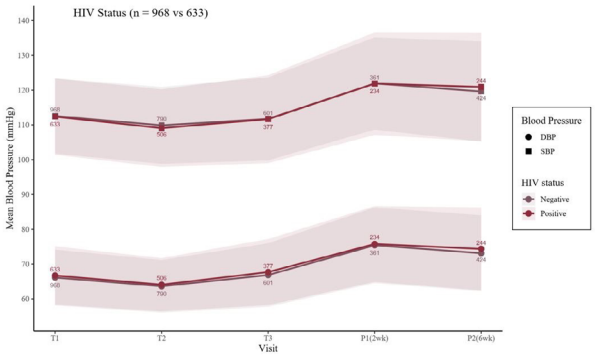

Figure. Plot of Mean Systolic (SBP) and Diastolic Blood Pressure (DBP) in the ORCHID cohort, among WLH and HIV- controls, from enrolment in 1st trimester (T1) through 6 weeks postpartum. Shaded regions represent 1 standard deviation around the means at each time point; numbers of observations for each group at each time point are shown on the plot.

917 High Proportions of Adverse Births in Women With HIV and Non-Communicable Disease Comorbidities

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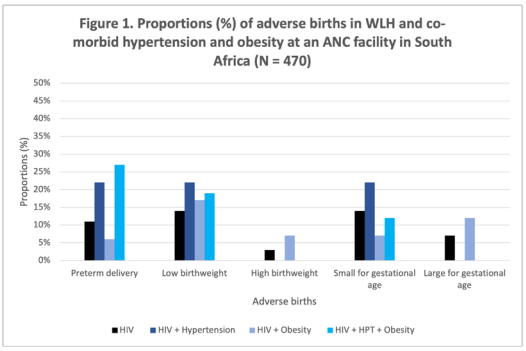
Background: HIV/antiretroviral therapy (ART) and non-communicable diseases (NCDs) like hypertension, diabetes and obesity are independently implicated in poor pregnancy outcomes. However, there is limited data on the interplay of HIV/ART and these NCDs, and associations with adverse birth outcomes in South African women.
Methods: In a retrospective study in an urban primary care antenatal care facility (ANC) in Cape Town, South Africa, 470 women living with HIV (WLH) and 505 without HIV (HIV-) (≥18 years) were enrolled from the first ANC visit between 2017 and 2019 and followed through to delivery. We examined HIV, hypertension (HPT), diabetes mellitus (DM) alone and HIV with obesity, hypertension, and diabetes comorbidity (irrespective of chronicity) and the following outcomes: preterm delivery (PTD <37 gestational weeks), low birthweight (LBW <2500g), high birthweight (HBW ≥4000g) (abstracted from medical records) and small for gestational age (SGA <10 percentile), large for gestational age (LGA >90th percentile) (generated using the INTERGROWTH tool). Differences in proportions of adverse birth outcomes between exposure groups were tested with Chi-squared tests among live singleton births.
Results: In this study, median age was 29y (IQR,25-33) and 21% of women were primigravid. Additionally, 47% were obese (BMI≥30 kg/m^2), 8% hypertensive and 2% diabetic. Overall, 10% of infants were PTD, 11% LBW, 4% HBW, 10% SGA and 10% LGA. Women with HPT only had 41% PTD, 35% LBW and 29% SGA. Those with obesity only had 4% PTD, 5% LBW, 6% HBW, 5% SGA and 17% LGA. Excluding all NCDs, WLV had 11% PTD, 14% LBW, 3% HBW, 14% SGA and 7% LGA. WLH with obesity had higher LGA (12 vs 7%, p <0.01) and HBW (7 vs 3%, p <0.01) but lower PTD (6 vs 11%, p <0.01), LBW (7 vs 14%, p <0.01) and SGA (5 vs 14%, p <0.01) compared to WLH only. WLH with hypertension co-morbidity had higher PTD (22 vs 11%, p = 0.01), LBW (22 vs 14%, p = 0.03) and SGA (22 vs 14%, p = 0.03) compared to WLH only. Further, WLH with both obesity and HPT had higher LBW (27 vs 11%, p = 0.04) and LBW (19 vs 14%, p = 0.03) compared to WLH only. DM only coexisted with other co-morbidities and not HIV.
Conclusion: WLH and an NCD co-morbidity had a higher proportion of some adverse birth outcomes compared to WLH only. Integration of NCD management interventions with ANC services is essential to avert excess adverse outcomes in high HIV burden settings.



918 DTG Versus EFV Initiation in Pregnancy Is Not Associated With Postpartum Blood Pressure

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Background: Several studies in non-pregnant adults have suggested increases in blood pressure (BP) associated with dolutegravir (DTG) use, however findings are mixed. There are notably few data from (i) sub-Saharan Africa and (ii) pregnant and postpartum women living with HIV (PLH).
Methods: We compared BP in PLH initiating DTG- versus Efavirenz-(EFV-) containing regimens initiated during pregnancy in a secondary analysis of the DolPHIN-2 trial (NCT03249181). At sites in Uganda and South Africa, PLH initiating ART ≥28w gestation were randomly assigned tenofovir+lamivudine/emtricitabine and either DTG or Efavirenz (EFV) as first-line therapy. PLH were followed with 8 study visits through 72 weeks postpartum including standardised anthropometric and BP assessments including sized cuffs. Given physiologic changes in BP during the perinatal period, analyses focused on systolic (sBP) and diastolic BP (dBP) at 24, 48 and 72 weeks postpartum in PLH assigned to DTG vs EFV using mixed effects linear models adjusted for age, BMI, site, and enrolment BP; temporal changes were evaluated using time interactions in separate models. In addition, we examined the risk of incident hypertension (BP>140/>90) among those with BP<140/<90 at enrolment and 6 weeks postpartum.
Results: Overall 268 women were enrolled (median age 28 years; median gestation 31 weeks; median BMI 28kg/m^2). Participants in South Africa had consistently higher BMI, sBP and dBP compared to those in Uganda at enrolment and throughout follow-up. However after accounting for site and baseline values there were no associations observed between DTG use and sBP (beta=2.2mmHg; 95% CI -0.6 to 5.0), dBP (beta=1.54mmHg; 95% CI: -0.9 to 4.0) or weight (beta=0.7kg; 95% CI -0.9 to 2.3) through 72w postpartum. Four participants had hypertension detected at enrolment; during follow-up 8 participants switched treatment assignment, none related to blood pressure or weight gain. There was no association between DTG versus EFV and incident hypertension at any time point.
Conclusion: These reassuring RCT data suggest that after adjustment for important pre-treatment covariates there was no association between DTG vs EFV initiated late in pregnancy and BP through 18 months postpartum. There is ongoing need for attention to the long-term cardiometabolic effects of DTG use in PLH.

919 The Impact of HIV and the Postpartum Period on the Gut Microbiota in South African Women

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Background: The perinatal and post-partum (PP) period is a window to future metabolic health, including type 2 diabetes (T2D). Between the 1st and 3rd trimester (T3), the gut microbiota (GM) is altered and associated with increased inflammation and reduced insulin sensitivity (IS) at T3. Similarly, among persons with HIV (PWH), there is emerging evidence for GM alterations, including reduced microbial diversity and altered functional features. Approximately 30% of pregnant South African (SA) women are PWH. We hypothesized that the composition of the GM differed by HIV status and PP period among SA women.

Methods: We performed a cross-sectional analysis of GM composition, using 16S rRNA amplicon sequencing, on early morning stool samples collected from 65 PP women originally enrolled in the Cardiometabolic Health in Pregnancy study (2019-2022). Body composition was measured using dual x-ray absorptiometry and IS measured using an oral glucose tolerance test to derive the Matsuda Index.

Results: Of 65 PP women, 46 were PWH, with no differences in the length of the PP period by HIV status. PWH had lower BMIs (28.1 [24.1-33.8] vs. 31.2 [27.8-40.2] kg/m², p=0.046), and fat (31.9 [25.1-43.3] vs. 40.3 [27.1-54.5] kg) and fat free mass (37.7 (34.6-43.6) vs. 42.6 [36.9-49.0] kg), but similar fasted glucose, insulin, and Matsuda Index. After demultiplexing, 2,162,496 sequence reads were obtained from the stool samples, with a median of 32,990 sequence reads. Overall, 1,569 amplicon sequence variants (ASVs) including 19 phyla and 370 genera were identified, with the most abundant phyla across all the two groups being Firmicutes, Bacteroidetes, Firmicutes C and D and Proteobacteria. At the genus level, most ASVs belonged to Prevotella, Faecalibacterium, Agathobacter_164117, Dialister and Blautia_A_141781. Thirteen microbial taxa differential abundance differed by HIV status, with 11 being over-represented in PWH, including Fusobacterium, Bilophila, Sneathia and Clostridium. These genera have previously been associated with persistent immune dysfunction. The PP period also differed by microbial taxa, whereby those >12 months had a greater proportion of Ellagibacter, associated with anti-inflammatory activity, irrespective of HIV status.

Conclusion: We confirm that the GM differs by HIV status and the length of PP period. Future research should explore the persistent effects of the PP period and HIV status on the composition of the gut microbiota, given the syndemic of HIV and T2D in SA.

Participant characteristics by HIV status, *adjusted for age and PP period.

	HIV negative (N=19)	PWH (N=46)	P-value
Age (yr)	30 (26-35)	31 (26-34)	0.774
Days post-partum	369 (291-469)	277 (225-507)	0.519
Weight (kg)*	86.1(65.4-105.9)	72.2 (65.3-86.7)	0.052
BMI (kg/m²)*	31.2 (27.8-40.2)	28.1 (24.1-33.8)	0.046
FM (kg)*	40.3 (27.1-54.5)	31.9 (25.1-43.3)	0.050
FFM (kg)*	42.6 (36.9-49.0)	37.7 (34.6-43.6)	0.044
Matsuda Index*	5.23 (3.27-6.32)	6.69 (1.01-1.47)	0.113

920 A Multicomponent Intervention Improves Disclosure and ART Adherence for Pregnant/Postpartum Women

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Background: Disclosure of HIV status to anyone and adherence to ART among pregnant and postpartum women are critical for sustained HIV care engagement and elimination of vertical transmission in Sub-Saharan Africa. We evaluated the effect of a multi-component intervention, including Enhanced viral load (VL) counseling and Standardized Peer-mother Support (ENHANCED-SPS), on disclosure and ART adherence among pregnant and postpartum women with HIV in rural Uganda.

Methods: We developed an ENHANCED-SPS intervention informed by the empirically-validated PRECEDE framework. Intervention components included: 1) Provider training and mentorship on enhanced VL counselling (predisposing), 2) standardized peer mother support and bi-weekly phone calls to mothers to provide VL and adherence counselling (enabling) and, 3) point of care VL monitoring and feedback meetings with providers and peer mothers (reinforcing). At routine clinic visits, mothers also received an assessment of barriers to disclosure and adherence as well as discussion on plans to address those barriers. We evaluated the effect of the intervention on disclosure and adherence after 12-month of follow-up

Results: We enrolled 505 pregnant and post-partum women at the 7 public health clinics from September 2019 to October 2020. Participants' median age was 28 years [Q1:24, Q3:24], 157/505 (31%) were newly diagnosed with HIV, 318/455 (70%) were virally suppressed (HIV RNA<1000 c/mL) and 79% (95%CI:69-90%) had disclosed their HIV status to anyone at baseline. After 12 months of the intervention, disclosure increased to 88% (95%CI:83-94%), corresponding to a 9% (95%CI:1-18%; p=0.02) absolute increase from baseline. The intervention increased disclosure within subgroups of age and enrollment group, especially among younger women (15-24years) with 17% increase (95%CI:5-29%; p=0.008) and the newly diagnosed pregnant women with 39% increase (95%CI:18-61%; p=0.003). Similar effects were observed when examining disclosure to a partner or spouse. Additionally, the intervention increased adherence to ART to 93% (95%CI:83-100%), corresponding to a 25% (95%CI:12-39%; p=0.002) absolute increase from the baseline measurement of 68% (95%CI:62-73%).

Conclusion: The multi-component, peer-led, enhanced VL counselling intervention significantly increased disclosure of HIV status and ART adherence among pregnant and postpartum women within 1 year of implementation. Young women and 1st time presenters with new HIV diagnosis had increased benefit.

Table 1: Enhanced Counselling and Standardized peer mother support intervention (Peer-led Model)

Intervention	Target audience and frequency of delivery	Purpose
Development of the enhanced viral load counselling protocol (Viral load as a risk factor to MTCT and role of adherence in Viral suppression) Midwives and peer mothers received the initial training on how to deliver the intervention Education, case studies and discussion on concept of viral load and adherence counselling	1.Training to midwives and peer mentors at the start of the study and continued mentorship throughout the study by the study staff. 2. Midwives and peer mothers provided the initial and ongoing viral load counselling at every visit 3. Assessment of individual barriers on adherence to ART and clinic visit schedule by the midwives at every clinic visit and peer mothers every 2 weeks via a phone call	Predisposing
Enhanced-SPS intervention package (viral load counselling, assessment of adherence barriers, point of care viral load monitoring and appointment scheduling discussions). Mothers also received bi-weekly phone calls on adherence counseling and assessment of adherence. Client information cards (translated in local; languages) on importance of adherence in MTCT and reminders of the next visit appointments.	All mothers attending ANC and enrolled in the study were offered counselling based on their viral load results by the peer mothers every two weeks through phone calls; Peer mothers and midwives discussed adherence barriers based on the VL results .i.e if viral load is high, likely poor adherence and if VL is low likely good adherence.	Enabling
Provider phone check-in to participant every two weeks to provide VL counselling and supportive adherence counselling. Feedback meetings between the peer mothers and midwives from all the intervention facilities	Mothers were provided with a phone contact of the peer mentor to consult and ask any questions during the study. In addition, the peer mothers contacted all mothers to provide VL counselling and assess adherence barriers and any other concerns every 2weeks throughout the 12 moths follow up. Feedback meetings between peer mothers and midwives from all intervention facilities were held quarterly in a central place for best lessons and best practices sharing. POC VL monitoring at baseline and 12 months	Reinforcing

921 High Prevalence of Depression and Anxiety in Women Without HIV and Women With HIV on DTG-ART

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Background: Common mental disorders are a leading global cause of disability. Little is known about the prevalence and nature of depression and anxiety symptoms among women living with HIV taking dolutegravir (DTG)-based antiretroviral treatment (ART), particularly in southern Africa.

Methods: From March 2021 to May 2023 (a period affected by COVID-19), we enrolled women living with HIV (most on DTG-based ART at enrollment) and without HIV in the "Motheo" study of child neurodevelopment and maternal mental health, in one city and one village in Botswana. At enrollment, trained staff administered the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7) in Setswana or English. PHQ-9 score >8 was defined as probable depression (per prior Botswana data) and GAD-7 >8 as probable anxiety. For 3-category ordinal endpoints, we used PHQ-9 score 1-4 (minimal), 5-9 (moderate), and >9 (moderate/severe) for depression; and GAD-7 score 0-4

(minimal), 5-9 (moderate), and >9 (moderate/severe) for anxiety. Unadjusted and adjusted analyses were performed using GEE regression.

Results: We evaluated 385 women living with HIV on DTG-based ART and 160 without HIV. Women living with HIV were older than women without HIV (mean 35 vs. 30 years) and were less likely to be from a village (31% vs. 44%) or to have completed senior secondary school or higher education (40% vs. 62%). Overall, 13% of women had scores consistent with moderate/severe depression and 8% with moderate/severe anxiety. Test scores and prevalence of probable depression or anxiety were numerically higher in (but did not differ significantly between) women living with HIV compared with without HIV: probable depression (17% vs. 15%), suicidal ideation (16% vs. 14%), probable anxiety (15% vs. 14%), and referral for mental health services (23% vs. 20%), respectively (Table). After adjustment, differences between women living with and without HIV remained non-statistically significant (Table); severity of depression and anxiety (mild/moderate/severe) also did not differ by HIV status.

Conclusion: We observed relatively high overall prevalence of probable depression, anxiety and suicidal ideation. Compared to women without HIV, women living with HIV on DTG-based ART had numerically higher prevalence of depression, anxiety, and suicide ideation, but differences were not statistically significant We referred more than 20% of women for mental health services. Additional mental health services are urgently needed to meet the high demand.

	Women with HIV, on DTG-ART (N=385)	Women without HIV (N=160)	Unadjusted Estimated mean difference (95% CI)	p-value	Adjusted* Estimated mean difference (95% CI)	p-value
GAD-7 total, mean (SD) †	3.7 (4.2)	3.3 (3.9)	0.33 (-0.42, 1.09)	0.39	0.44 (-0.37, 1.25)	0.28
PHQ-9 total, mean (SD) †	4.2 (5.0)	4.0 (4.4)	0.20 (-0.69, 1.08)	0.67	0.42 (-0.51, 1.35)	0.38
	N (%) with outcome	N (%) with outcome	Relative Risk	p-value	Adjusted* Relative Risk	p-value
Probable depression ‡	65 (17%)	24 (15%)	1.13 (0.70, 1.80)	0.62	1.19 (0.70, 2.01)	0.53
Suicidal ideation ‡	61 (16%)	23 (14%)	1.10 (0.68, 1.78)	0.69	1.13 (0.65, 1.95)	0.66
Probable anxiety ‡	57 (15%)	23 (14%)	1.03 (0.63, 1.67)	0.91	1.04 (0.60, 1.79)	0.90
Referred for mental health ‡	87 (23%)	32 (20%)	1.13 (0.75, 1.69)	0.56	1.21 (0.77, 1.91)	0.41

* Adjusted for site of enrollment; maternal age, education, marital status, income, occupation; and whether participant had to skip meal in the last four weeks.
† Continuous outcomes assessed with linear GEE regression.
‡ Binary outcomes assessed with modified Poisson GEE regression.

922 Dolutegravir Versus Efavirenz: Depression, Anxiety, and Sleep Disorders in Pregnancy and Postpartum

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Background: Both integrase strand transferase-inhibitors and non-nucleoside reverse transcriptase-inhibitors such as dolutegravir and efavirenz, respectively, are known to be effective in pregnancy and post-partum to prevent vertical transmission of HIV and to maintain maternal health. Both drugs have also been associated with neuropsychiatric symptoms such as depression, anxiety and sleep disorders. To what extent these symptoms occur in pregnant and post-partum women, however, is not yet known.

Methods: This was a secondary analysis of the DolPHIN2 study, a multicentre randomized trial among women presenting late in pregnancy with untreated HIV- who received either a dolutegravir- or an efavirenz- containing regimen. Longitudinal measures of depression, anxiety and sleep quality (Edinburgh Postnatal Depression scale (EPDS)), Hospital Anxiety and Depression Scale (HADS) and Pittsburgh Sleeping Quality Index (PSQI)) were analysed during pregnancy and up to 48 weeks post-partum.

Results: Among 268 women median (IQR) EPDS scores were 8 (3-11) and highest at enrolment at the time of initial HIV diagnosis. In the dolutegravir -and efavirenz arm, respectively, 23.7% and 25.6% had an EPDS score above 9, indicating possible or probable depression. HADS scores were also highest at enrolment and decreased over time. An abnormal HADS score (above 11) was seen at least once during follow up in 42 of patients (15.7%), although no differences were seen between treatment arms. For the anxiety-component 1.9% and 1.5% of the dolutegravir and efavirenz arms, respectively, had a score of 11 or higher. No association was found between EPDS, suicidality (question 10 of EPDS) and HADS scores and the assigned regimen (p = 0.93, 0.97 and 0.18 respectively). Abnormal scores for the depression-component were seen in 3.4% of participants in both treatment arms. Median (IQR) PSQI scores for dolutegravir- and efavirenz were 6 (5-7) and 5 (5-6.5) respectively, p=0.70.

Conclusion: No statistically significant differences were observed across these measures between pregnant and post-partum women treated with efavirenz- or dolutegravir containing regimens. Rates of depression on the EPDS were high, but decreased over the course of time and confirm the need for psychological support after initial HIV diagnosis in pregnancy.

923 Maternal Mental Health and Referral Outcomes Among Women Living With and Without HIV in Botswana

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Background: Poor mental health among women living with HIV can impact care engagement, treatment adherence, and parenting. We sought to quantify prevalence of depression and anxiety among mothers participating in the Botswana-based FLOURISH study, an ongoing longitudinal observational study following maternal-child pairs, including mothers living with and without HIV and their children, ranging in age from birth to 17 years.

Methods: Maternal participants are administered the PHQ-9 and GAD-7 standardized instruments at enrollment to screen for depression and anxiety, respectively. Prevalence of screening positive was compared by HIV status. Unadjusted and adjusted logistic regression models were fit to identify risk factors associated with screening positive.

Results: 1087 mothers, including 819 (75.3%) mothers living with HIV (MLHIV), were screened at FLOURISH study entry. Compared to mothers without HIV, MLHIV were older (38.9 years versus 30.9 years; p<0.0001), had lower academic attainment (p<0.0001), lower income (p<0.0001) and reported higher prevalence of severe food insecurity (p=0.001). A total of 104 (9.6%) mothers screened positive for depression including 90 (11.0%) MLHIV and 14 (5.1%) without HIV (p=0.06). Screening positive for moderate to severe depression occurred in 52 (6.3%) MLHIV and 10 (3.7%) without HIV compared to the remainder who screen positive for mild depression.. Prevalence of screening positive for anxiety was 4.8% among MLHIV compared to 6.6% among mothers without HIV (p=0.20). In unadjusted analyses, living with HIV [Odds Ratio (OR) 1.8 (95% Confidence Interval (CI) 1.1, 3.1) p=0.02] and severe household food insecurity [OR 2.3 (95% CI 1.4, 3.9) p=0.002) were significantly associated with screening positive, but no association was noted between maternal age, education level, or household income. In adjusted analysis, severe household food insecurity remained significantly associated with screening positive of depression or anxiety [OR 2.4 (95% CI 1.4, 4.2) p=0.001] but the association between living with HIV and a positive screen was no longer significant after adjusting for age.

Conclusion: In this large cohort, mothers living with HIV were more likely to screen positive for depression, but not anxiety. Food insecurity was significantly associated with a positive screening score, highlighting the need for a comprehensive psychosocial support package of care in high burden HIV settings.

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924 Metabolomic Perturbations of Tryptophan & Arginine Metabolites in the Breast Milk of Women With HIV

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Background: Infants born to women with HIV (WWH), but not infected (HIV-exposed uninfected, HEU) have two to three times the mortality rate of infants born to women without HIV (WWoH). Tryptophan is an essential amino acid critical for immune development, neurocognitive development, and growth. We investigated the milk metabolome from WWH and WWoH in the pre-ART era to determine if metabolic perturbations may contribute to the impaired immune development of infants born to WWH.

Methods: Untargeted metabolomics was performed on 1599 breast milk samples collected longitudinally up to 24 months post-partum from 38 WWoH and 288 WWH with known infant outcomes from a randomized clinical trial conducted in Lusaka, Zambia 2001-2008. The milks of WWH were further separated by infant outcome into 4 groups: HEU infants who survived (n=76) or died (n=78) and infants who became infected either via early mucosal transmission (n=53) or through breast milk (n=81). Linear mixed effects

models were used to identify differentially abundant compounds in breast milk between the infant outgroups among WWH and WWoH. All p-values were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate method.
Results: 1597/1599 samples were successfully analyzed with identification of 765 known biochemicals and 74 unknown biochemicals. Tryptophan levels were significantly lower in the milk samples of WWH compared to WWoH at all timepoints. Log-transformed kynurenine:tryptophan (KT) ratios were elevated in the milk of WWH at all timepoints ($p < 0.001$). The KT-ratio at 1 month was correlated with baseline maternal plasma and 1 month breast milk HIV RNA (r2 of 0.28 and 0.20, respectively), and inversely with baseline CD4 count (r2 = -0.32); all $p<0.001$. Dimethylarginine was elevated in the milk of WWH during the first 9 months of lactation. A novel metabolite, X-12127, was significantly elevated in the milk of WWH at all timepoints following the first week of life ($p<0.001$ through 12 mos, then $p<0.1$ at 15 and 18 mos).
Conclusion: Tryptophan is significantly lower in the milk of WWH throughout early infancy. As breast milk serves as the only source of this essential amino acid, this depletion likely contributes to the impaired immune development of children born to WWH. Elevations of dimethylarginines may alter nitric oxide levels. Identifying key alterations and novel therapeutics is of critical importance for the one million children born to WWH each year.

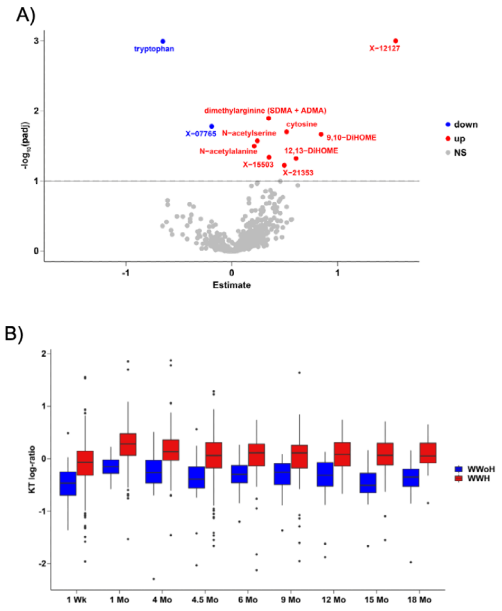

Figure: Tryptophan levels are decreased and KT ratios are increased in the breast milk of WWH. A) Volcano plot from 1 month of lactation showing metabolites either decreased (blue) or increased (red) in milks of WWH. B) Boxplots of the milk KT ratio over the course of lactation.

925 Breast Milk Transfer and Infant Exposures to DTG, TAF, and TFV: Results From IMPAACT 2010/VESTED

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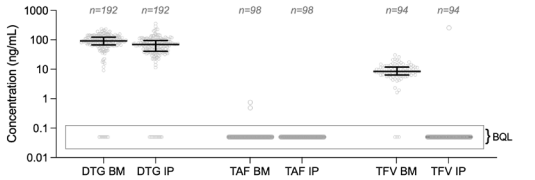
Background: Limited information is available on breast milk transfer and subsequent infant systemic exposure to dolutegravir (DTG), tenofovir alafenamide (TAF), and tenofovir (TFV). We evaluated concentrations of these antiretroviral (ARV) drugs in time-matched samples (maternal plasma, breast milk, and infant plasma) in a post hoc analysis of IMPAACT 2010, a randomized trial that evaluated three ARV treatment regimens in pregnancy.
Methods: Pregnant women with HIV in 9 countries were randomized 1:1:1 to start open-label ART with DTG+emtricitabine (FTC)/TAF, DTG+FTC/tenofovir disoproxil fumarate (TDF), or efavirenz (EFV)/FTC/TDF at 14-28 weeks of gestation. Matched maternal and infant samples were prospectively collected at random at Week 6 postpartum. Validated liquid chromatography-tandem mass spectrometry assays quantitated plasma and breastmilk concentrations of DTG, TAF, and TFV. The lower limit of quantitation for DTG, TAF, and TFV in breast milk and plasma was 7.8, 0.195, and 0.0977 ng/mL and 9.8, 3.9, and 0.977 ng/mL, respectively. Samples below the quantitation limit (BQL) were imputed to 0. The relative infant dose for each ARV was estimated by assuming an average milk intake of 150 mL/kg/day and each ARV's observed breast milk concentrations.
Results: Data were available from 192 postpartum lactating women and their 192 predominantly breastfed infants. The average (SD) age of mothers at enrollment was 26 (6) years old, and most participants (85%) lived in Zimbabwe, Uganda, or Tanzania. Overall, 55% of infants were female with a mean (SD) gestational age of 40 (2) weeks, weight of 3089 (490) grams, and length of 50 (3) cm at birth. Median (range) maternal plasma concentrations of DTG, TAF, and TFV were 2810 (0.0-7460), 0.0 (0.0-158), and 96.1 (0.0-353) ng/mL, respectively. Breast milk (BM) and infant plasma (IP) concentrations are displayed in the Figure. The estimated median (range) relative infant dose of DTG, TAF, and TFV from breastfeeding was 1.92% (0.00-4.89), 0.00% (0.00-0.03), and 0.03% (0.00-0.11), respectively.
Conclusion: Breast milk transfer of DTG, TAF, and TFV is low and results in minimal systemic exposure in predominantly breastfed infants. The clinical relevance of subtherapeutic concentrations of these ARVs in breast milk is unknown but should be considered in the context of risk of drug resistance in infants who acquire HIV.

Figure: DTG, TAF, and TFV Concentrations in Breast Milk and Infant Plasma



Lines show median and interquartile range. The number of BQL samples (shown in the box) for DTG, TAF, and TFV in breastmilk were 9, 96, and 3 and in infant plasma were 11, 98, and 93, respectively.

926 1077BF: Breast Milk Reservoir, Tenofovir Levels, and HIV Transmission Among Breastfeeding Mothers

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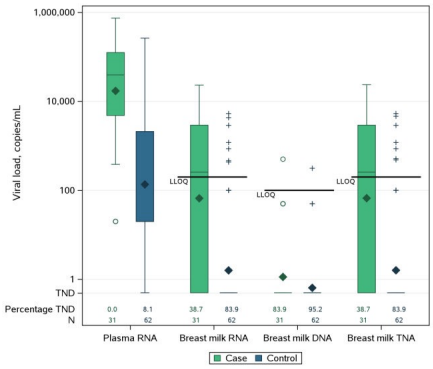
Background: Recent studies observed detectable HIV-1 virus levels in breastmilk (BM) despite undetectable HIV-1 RNA viral load (VL) in plasma. This discordance between HIV VL in plasma and BM could account for residual vertical HIV-1 transmission during lactation. We assessed the association of vertical HIV-1 transmission with HIV VL in plasma and BM, and with tenofovir (TFV) drug levels.
Methods: This case-control study was nested within the IMPAACT PROMISE 1077BF perinatal HIV trial which evaluated maternal ARV strategies to prevent BM HIV transmission. Cases were mother-infant pairs with infants who had a positive HIV nucleic acid test (NAT) during the breastfeeding period; control pairs had infants who were HIV NAT negative. Two controls were matched for each case by infant sex, study site, maternal age at delivery, and 1077BF component at infection. Maternal plasma and BM collected near an infant's infection date were assayed for HIV total nucleic acid (TNA; DNA + RNA) VL, DNA VL, RNA VL, and TFV concentration. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).
Results: 93 mother-infant pairs (31 cases; 62 controls) were enrolled from Malawi, Uganda, South Africa, Zimbabwe and India. Median maternal age at delivery was 25 years, 39 (42%) were male infants, 57 (61%) were randomized in the postpartum component. Median (Q1, Q3) age of infection was 6 (3, 14) months. Over 70% (22/31) of samples were taken on the same day or within one month of infection. Median (Q1, Q3) maternal plasma VL was 39,228 (4822, 124,886) copies/ml for cases vs 20 (20, 2,104) for controls. BM RNA VL was above lower limit of quantification for 17 (55%) cases and 7 (11%) controls. The odds

of infant HIV infection were 2.6 times higher for each log_{10} increase in maternal plasma RNA VL (95% CI: 1.6-4.5) and 1.8 times higher for each log_{10} increase in BM RNA VL (95% CI: 1.3-2.6). BM DNA VL was not detected in 26 (84%) cases and 59 (95%) controls. Only 3/14 (21%) case mothers on a TFV-containing regimen had detectable TFV levels in their plasma or BM vs 31/37 (84%) control mothers with detectable TFV in plasma and 29/37 (78%) in BM. In case mothers, plasma TFV levels were 10-fold lower (geometric mean ratio (95% CI): 0.11 (0.04-0.26) compared with controls, and BM TFV levels were 5-fold lower 0.18 (0.08-0.43) in case mothers compared with controls.

Conclusion: Odds of breastmilk HIV-1 transmission is associated with higher maternal plasma and BM VL and lower TFV levels.

Figure 1: Box plot of Maternal Viral loads



LLOQ was 20-400 copies/ml for plasma RNA, 200 copies/mL for breastmilk RNA, 100 copies/mL for breastmilk DNA, and 200 copies/mL for breastmilk TNA. Target not detected (TND) was imputed as 0.5 copies/mL. Diamond represents mean; thin horizontal line represents median.

927 Could This Be Cell-Associated Perinatal HIV Transmission?

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Background: Recent French Perinatal Cohort data demonstrated no vertical transmissions among 5482 women living with HIV fulfilling the following criteria: effective ART from conception; undetectable plasma HIV RNA viral load (VL) near delivery; infant post-exposure prophylaxis (PEP); no breastfeeding. Despite fulfilling these criteria, we present two cases of vertical transmission from one UK centre and review the literature.

Methods: Retrospective case series of two infant HIV infections, without known vertical transmission risks. Review of maternal and infant notes. Literature review for cases of HIV transmission despite undetectable maternal plasma HIV RNA.

Results: Cases series. Both mothers conceived on triple ART. Excellent adherence reported. With an exception of 380 HIV RNA copies/ml (cpm) at gestational age (GA) 8 weeks in case A, both had multiple VL measures <50 cpm during pregnancy and around delivery (38 weeks GA for mother A; 36 weeks GA for mother B). Mother A had 6 weeks of enoxaparin from 11 weeks GA; mother B an iron infusion at 33 weeks GA. Both deliveries were term, one vaginal with induction of labour for pre-eclampsia at 38 weeks with <1 hour ruptured membranes, and one a planned pre-labour, pre-rupture of membranes Caesarean section at 39 weeks. Both infants had negative HIV VL at birth, had standard of care zidovudine PEP for 2–4 weeks as per contemporary guidelines and were exclusively formula-fed. HIV RNA was first detected in Infant A at 12 weeks (17.6 x 106 cpm) and in infant B at 6 weeks (1.4 x 106 cpm). Literature review. One late transmission reported in Dolphin-2: Efavirenz-based ART commenced week 28 GA with HIV VL undetectable at delivery, weeks 6, 12, 24, 48 and 72 post-partum. Exclusive breastfeeding to 24 weeks, breastmilk and solids to 48 weeks when breastfeeding stopped. The infant was HIV negative on VL testing until week 72. HIV sequencing and phylogenetic analyses linked all infant and maternal viruses.

Conclusion: Without detectable maternal viraemia, vertical HIV transmission is rare. Residual transmission may be from cell-associated virus, the dominant mode of transmission for other human retroviruses. ART may limit cell-associated HIV transmission. Exposure to maternal ART in utero may act as foetal pre-exposure prophylaxis and infant PEP protects for a limited period postnatally. Maternal lymphocyte persistence in the infant circulation, whether transplacental or gut-absorption, with cell-associated transmission, is likely implicated in these rare cases.

928 Arteriolar Dysfunction in Placentas of HIV-Exposed, Small-for-Gestational-Age Neonates

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Background: Birthing individuals with HIV (BIHIV) are more likely to deliver small-for-gestational-age (SGA) neonates. Fetal growth restriction largely results from limited delivery of nutrients and O2 during development. We hypothesized that placental microvascular dysfunction may contribute to SGA among BIHIV.

Methods: Immediately after delivery, we biopsied placentas with/without HIV-exposure and with/without SGA birthweight between 36-41weeks gestation. We assessed fetoplacental arteriolar function by myograph; we measured dose-dependent contraction to U-46,619 (a thromboxane-prostanoid receptor agonist), endothelin (ET1), norepinephrine (NE), and phenylephrine (PE), as well as relaxation to acetylcholine (ACh), sodium nitroprusside (SNP), and AdipoRon (ApR, an adiponectin [ApN] agonist). ET1-induced reactive oxygen species (ROS) were measured by DHE fluorescence and apR-induced nitric oxide (NO) activity by DAF-FM fluorescence using a RatioMasterTM system. Umbilical cord and maternal plasma ApN and malondialdehyde (MDA, a marker of oxidative stress) were measured by ELISA. Dose response curves across groups were compared using two-way mixed ANOVA.

Results: We collected 33 placental biopsies; we excluded 3 due to poor quality from excessive time in transit. We analyzed specimens from 9 placentas of HIV-unexposed normal birthweight (NBW) neonates, 6 HIV-unexposed SGA neonates, 11 HIV-exposed NBW neonates, and 4 HIV-exposed SGA neonates. Both U46,619 (103±4% of KClmax) and ET1 (109±5%) induced robust contractions, while vessels were unresponsive to NE (7±3%) or PE (5±2%). Contractions to ET-1 and U-46,619 were greater in placentas with HIV-exposure (p=.003; p=.03) or of SGA neonates (p=.01; p<.0001) compared to controls, and greatest in the setting of both HIV-exposure and SGA (p<.0001; p<.0001). U46,619 pre-constricted arterioles relaxed to ApR (93±4%), but only minimally to Ach (7±2%) or SNP (10±2%). Impaired arteriolar relaxation to ApR was associated with HIV-exposure (p=.01), SGA (p=.001), and combined HIV-exposure with SGA (p<.0001). Likewise, ApR-induced NO was decreased and ET1-induced ROS was increased with HIV-exposure and SGA. Birthweight was correlated directly with ApR-induced relaxation (r =.48) and inversely with MDA (r=-.68).

Conclusion: Fetoplacental arteriolar relaxation was impaired and contraction was enhanced among placentas of HIV-exposed and SGA neonates.
These findings contribute to the limited body of research elucidating the pathophysiology of SGA among BIHIV.
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929 A Target Trial of Preconception Switch From Nevirapine- to Dolutegravir-Based ART on Birth Outcomes

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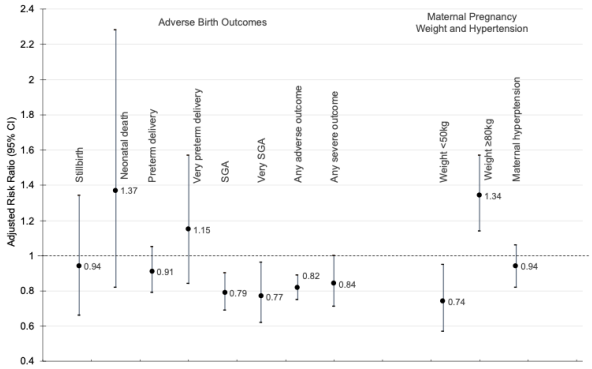
Background: Antiretroviral regimens have differential effects on adverse birth outcomes. Nevirapine (NVP) has been associated with particularly high risk of adverse birth outcomes compared with newer ART like dolutegravir (DTG). We emulated a target trial of pre-conception switch from NVP to DTG to evaluate whether switch from high-risk to low-risk regimens prior to pregnancy can favorably impact outcomes.

Methods: The Tsepamo Study has performed birth outcomes surveillance at government delivery sites in Botswana since 2014. Among individuals who initiated NVP from 2002-2014 and remained on NVP in 2016, we compared those who switched to DTG (usually for programmatic reasons, after DTG became first-line ART) with those who did not switch from NVP prior to pregnancy. We estimated adjusted risk ratios (RRs) and 95% CIs for stillbirth, in hospital neonatal death (<28 days), preterm delivery (<37 weeks), very preterm delivery (<32 weeks), small-for-gestational-age (SGA) (<10%tile), very SGA (<3%tile),

and combined endpoints of any adverse or severe adverse outcome. We also evaluated low (<50kg) and high (≥80kg) early pregnancy weight (before 24 weeks) and hypertension in pregnancy (SBP≥140 or DBP≥90 mm/Hg).
Results: Of 4,265 eligible individuals (median [IQR] age in pregnancy: 36 [32, 39] years), 1,102 (26%) switched from NVP to DTG and 3,163 (74%) did not switch from NVP prior to pregnancy. The most common backbones during pregnancy were TDF/3TC (90%) and TDF/FTC (8%) for switchers and ZDV/3TC (60%) and TDF/FTC (39%) for non-switchers. Comparing switchers with non-switchers, RRs (95% CIs) were 0.82 (0.75, 0.89) for any adverse and 0.84 (0.71, 1.00) for any severe adverse outcome. These differences were driven by SGA and very SGA (Figure, Left Panel). Switchers were less likely to have low and more likely to have high early pregnancy weight (Figure, Right Panel); the adjusted mean difference (95% CI) in early pregnancy weight was 2.9 (1.8, 4.1) kg. While switchers became pregnant in later years, sensitivity analyses indicated little evidence for time-trends in birth outcomes over the study period. Results were similar when excluding ZDV backbones.
Conclusion: Switching from legacy NVP-based regimens to DTG/TDF/XTC prior to pregnancy may reduce the risk of low maternal weight in early pregnancy and fetal growth restriction. This study provides further evidence that specific regimens impact birth outcomes, and that switching from legacy regimens prior to conception can improve birth outcomes.

Figure. Adverse birth outcomes (Left) and maternal pregnancy weight and hypertension (Right), pre-conception switchers (NVP to DTG) versus non-switchers.



930 HIV and Syphilis Coinfection in Pregnancy and Adverse Birth Outcomes in Uganda

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Background: The incidence of syphilis is increasing worldwide. Little is known about the combined impact of maternal HIV and syphilis coinfection on birth outcomes, especially in sub-Saharan Africa (sSA), where HIV prevalence is high.
Methods: We analyzed data from two prospective birth cohorts enrolled in southwestern Uganda from 2017 – 2023. All PHIV reported taking antiretroviral therapy (ART). Participants were tested for syphilis using a Treponema pallidum particle agglutination (TP-PA) rapid test on peripheral blood (positive test indicates treponemal exposure but cannot distinguish current vs prior infection). In one cohort, we also tested umbilical cord blood for and performed rapid plasma reagin (RPR) testing for TP-PA positive blood samples. Our primary outcome was a composite adverse birth outcome, including low birthweight (<2.5kg), stillbirth, neonatal death within 14 days of birth, or 5-minute APGAR<7. We compared outcomes by HIV and TP-PA seropositivity using chi-square tests and fitted multivariable logistic regression models to determine adjusted associations between maternal HIV and syphilis infection and birth outcomes.
Results: Of 944 women, 93 were TP-PA positive PHIV, 385 were TP-PA negative PHIV, 24 were TP-PA positive people without HIV and 442 were TP-PA negative people without HIV. Mean age of TP-PA positive PHIV was 28±6 years, 60/93 (65%) initiated ART before conception, and 13% had detectable HIV viremia. Of 117 (12%) TP-PA positive people, 93 (79%) were PHIV (P<0.001). There were 52/944 (6%) adverse birth outcomes, occurring in 9/93 (10%) TP-PA positive PHIV (including 5/93 [5%] stillbirths), 20/385 (5%) of TP-PA negative PHIV, 2/24 (8%) of TP-PA positive people without HIV, and 21/442 (5%) of TP-PA and HIV negative people (P=0.26). Of 54 PHIV with RPR titers available, 8 (15%) were non-reactive, 38 (70%) were <1:32 and 8 (15%) were ≥1:32. In multivariable analysis, gestational age and attending ≥4 antenatal care visits were independently associated with the composite adverse birth outcome, but maternal TP-PA seropositivity and HIV infection were not (Table). An HIV × TP-PA product term was not statistically significant.
Conclusion: Maternal HIV or TP-PA seropositivity did not increase the risk of adverse birth outcomes, though stillbirth incidence among TP-PA positive PHIV was higher than prior studies from sSA. High TP-PA seroprevalence and RPR positivity among PHIV emphasize the need to improve prenatal care for PHIV with enhanced syphilis screening and treatment.

Table. Predictors of adverse birth outcomes among pregnant women in Uganda.

Characteristic	Unadjusted Odds Ratio	*P*-value	Adjusted Odds Ratio	*P*-value
Maternal HIV infection	0.80 (0.46 – 1.41)	0.45	0.87 (0.47 - 1.59)	0.64
Maternal TP-PA seropositivity	1.96 (0.98 – 3.93)	0.06	1.75 (0.82 - 3.73)	0.15
Maternal age	0.98 (0.93 – 1.03)	0.40	0.98 (0.93 – 1.03)	0.51
Hypertensive disorder during pregnancy	0.76 (0.50 – 1.14)	0.18	0.68 (0.44 - 1.04)	0.08
Gestational age at birth	**0.75 (0.66 – 0.84)**	**<0.001**	**0.91 (0.86 – 0.97)**	**0.005**
≥4 antenatal care visits this pregnancy	**0.55 (0.31 – 0.98)**	**0.04**	**0.50 (0.27 – 0.91)**	**0.02**

931 Maternal and Pregnancy Outcomes in Women Initiating and Declining PrEP in Pregnancy: IMPAACT 2009

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Background: FTC-TDF-based PrEP is recommended for pregnant people in settings of high HIV transmission. However, few have evaluated uptake, maternal safety, and pregnancy outcomes in the context of a clinical trial.
Methods: The PrEP Comparison Component of IMPAACT 2009 enrolled pregnant participants aged 16-24 years at <32 weeks gestation in Malawi, South Africa, Uganda, and Zimbabwe. Participants were enrolled in parallel cohorts based on choice to initiate or decline daily oral FTC-TDF for PrEP at entry. All were followed in pregnancy to 6 months postpartum and could start or stop PrEP at any time. While on PrEP, they received Integrated Next Step Counseling, regular drug level feedback via TFV-DP from dried blood spots, and weekly two-way text messaging. Adverse events (AEs) were graded per DAIDS toxicity tables and assessed for relatedness to PrEP. Proportions (with Clopper-Pearson 95% confidence intervals) were calculated for highest-grade AEs through pregnancy outcome by PrEP use. Adverse pregnancy outcomes included fetal loss, preterm birth, and small-for-gestational-age by INTERGROWTH-21st standards.
Results: From March to December 2022, 350 eligible participants enrolled (mean age: 21 years; median gestational age: 24 weeks). Among 335 participants with pregnancy outcome information, 233 initiated PrEP in pregnancy (229 at enrollment, 4 later). Another 117 declined at entry and never initiated PrEP during pregnancy. Median duration of antenatal PrEP use was 11 weeks (IQR: 7.7-15). A total of 31 (9%) participants experienced at least one grade ≥3 AE through delivery, with a greater proportion among PrEP initiators (11.2%, 95%CI: 7.4-15.9%) vs. decliners (4.3%, 95%CI:1.4-9.7%). Most frequent grade ≥3 AEs were complications of pregnancy or delivery (9% for initiators vs. 3% for decliners). None were considered related to PrEP use. No participants acquired HIV infections during follow-up. Among those with delivery information, median gestational age was 39.4 weeks (IQR: 38.4-40.4) and median infant birthweight 3095g (IQR: 2800-3350). 79 (24%) participants reported adverse pregnancy outcomes, with no differences between the two groups (table).
Conclusion: Our findings further support the safety of FTC-TDF in pregnancy. Despite the high occurrence of AEs, none appeared related to PrEP use. While other PrEP modalities undergo evaluation for antenatal populations, daily oral FTC-TDF remains a safe and essential component of HIV prevention in pregnancy.

Adverse pregnancy outcomes among participants in IMPAACT 2009

	Initiated PrEP (n=233)	Declined PrEP (n=117)	P-value (Fisher's exact)
Total with pregnancy outcome	223	112	
Any adverse outcome	51 (24%)	28 (26%)	0.68
Fetal loss (stillbirth or spontaneous abortion)	2 (1%)	4 (4%)	0.10
Total Live Births	221	108	
Preterm birth <37 weeks	19 (9%)	7 (6%)	0.66
Small for gestational age	34 (16%)	19 (18%)	0.63

932 Outcomes Following Prenatal Exposure to Raltegravir: A Multi-Cohort European Study

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Background: Real world data on safety of antiretroviral drugs (ARVs) in pregnancy informs decision-making, but accumulating sufficiently large samples with specific periconception ARV exposure to rule out increased risk of rare birth defects, such as neural tube defects (NTDs), can take many years.

Methods: We assessed risk of birth defects and other adverse outcomes following prenatal exposure to raltegravir (RAL) using pooled prospectively collected individual patient data from studies in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC). Pregnancies with any documented prenatal exposure to RAL and with outcomes in 2008-2020 were included. Earliest prenatal RAL exposure timing was classified as periconception (PC) (exposure at ≤6 completed gestational weeks [GWs]), later first trimester (later T1) (exposure in T1 at >6 completed GWs), and second/third trimester (T2/T3) (exposure at >12 completed GWs).

Results: A total of 1499 pregnancies across 9 cohorts were included (1194, 79.7% from the UK). Most pregnancies were in women of Black (898/1480, 60.7%) or white (466/1480, 31.5%) ethnicity. Median age at conception was 32 years (IQR: 27-36). Half (763/1487, 51.3%) of RAL-exposed pregnancies were conceived on ARVs. There were 1429 live births (1466 live-born infants), 10 stillbirths, 41 spontaneous abortions, and 19 terminations. Among stillbirths, earliest RAL exposure was PC in 3, later T1 in 1, and T2/T3 in 6, with no defects reported. Birth outcomes of live-born singleton infants (1393) by timing of earliest RAL exposure are in the Table. Among all live-born infants (1466), earliest RAL exposure was PC in 466 (31.8%), later T1 in 62 (4.2%), T2/T3 in 892 (60.9%), and unknown in 46 (3.1%). Where data were available (1443/1466), 56 (3.9%, 95% CI 2.9, 5.0) live-born infants had a reported birth defect (9 had 2 defects), including 23/461 (5.0%, 95% CI 3.2, 7.4) of those with PC exposure; 38 (2.6%, 95% CI 1.9, 3.6) infants had defects per EUROCAT classification. Defects were in the following systems: heart (20), limb (16), CNS (5), genitourinary (4), gastrointestinal (2), oral facial cleft (2), ear, face and neck (1), respiratory (1), musculoskeletal (1), and other (13). One NTD was observed (spina bifida with PC exposure). Of the 5 neonatal deaths (2 with PC, 3 with T2/T3 exposure), 2 had defects.

Conclusion: The birth defect rate in EPPICC is consistent with and contributes to the current evidence-base on safety of periconception RAL use.

Table. Birth outcomes of live-born singleton infants by timing of earliest RAL exposure

	Timing of earliest RAL exposure*		
	Periconception	Later T1	T2/T3
Preterm delivery (<37 weeks) (n=1346)	57/435 (13.1%)	5/60 (8.3%)	98/851 (11.5%)
Very PTD (<34 weeks)	*15/435 (3.5%)*	*1/60 (1.7%)*	*37/851 (4.4%)*
Low birth weight (<2500g) (n=1307)	38/426 (8.9%)	7/59 (11.9%)	103/822 (12.5%)
Very LBW (<1500g)	*6/426 (1.4%)*	*1/59 (1.7%)*	*20/822 (2.4%)*
Small for gestational age† (n=1291)	27/414 (6.5%)	4/59 (6.8%)	80/818 (9.8%)

* Timing of exposure unavailable for 44 pregnancies
† Classified using INTERGROWTH-21ST standards

933 Birth Outcomes Following Bictegravir Use During Pregnancy

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Background: Bictegravir (BIC), co-formulated in a tablet with tenofovir alafenamide and emtricitabine, is being increasingly prescribed to pregnant persons with HIV (PWH), yet limited birth outcome data have been reported.

Methods: We conducted a descriptive analysis of PWH 18-45 years of age enrolled in at least one Pediatric HIV/AIDS Cohort Study (PHACS)-affiliated protocol who received BIC for at least 7 days during pregnancy and completed follow-up through delivery. The outcomes of interest were gestational age at birth, preterm birth (<37 weeks' gestation), gestational-age adjusted birth weight (BWZ) and length (BLZ) z-scores (CDC 2000 growth standards), small for gestational age (SGA, birthweight <10th percentile), congenital anomalies, neonatal deaths in the first 28 days of life, and infant HIV status. The prevalence [with Clopper-Pearson 95% Confidence Intervals (CIs)] of each outcome was calculated among infants exposed to BIC during gestation and, for the outcome of anomalies, in infants exposed during the first trimester. Maternal CD4 count and HIV viral load (VL) nearest and prior to delivery were reported if available.

Results: A total of 144 infants were born to 134 unique PWH (including 2 twin sets) who received BIC for at least 7 days during pregnancy. Infants were born between September 2018 and October 2023. Median maternal age at delivery was 29.7 years (interquartile range (IQR): 26.1, 33.9), 71% reported their race/ethnicity as Black or African American, and 52% had an annual household income ≤$20,000; all US census regions were represented. Fifty-three percent initiated BIC prior to conception. The mean gestational age was 38.2 weeks [standard deviation (SD)=1.5], the prevalence of preterm birth was 14.0% (95% CI: 8.8%, 20.8%) and SGA was 10.6% (95% CI 6.0%, 16.8%). Mean BWZ and BLZ were -0.49 (SD 0.93) and 0.08 (SD 1.13), respectively (Table). No neonatal deaths or perinatal HIV transmissions were reported. Among 99 infants exposed to BIC in the first trimester, 5 (5.1%, 95% CI 1.7%, 11.4%) had at least one congenital anomaly reported (Table). Maternal VL was <50 copies/mL in 82.0% and median CD4 count was 466.5 (IQR: 309.0, 744.0) cells/mm^3 nearest to delivery of exposed infants.

Conclusion: In this US cohort, BIC use during pregnancy was frequent. These findings provide initial reassuring observations about the potential safety of BIC use during pregnancy, although comparative data and continued surveillance of outcomes of antiretroviral therapy among PWH is warranted.

Table. Birth Outcomes of Infants Exposed to ≥7 days of Bictegravir during Gestation

Infant Outcome	Pre-Conception Initiation (N=76)	Post-Conception Initiation (N=68)	Total (N=144)
Gestational age	N=76 37.9 (1.5)	N=67* 38.4 (1.4)	N=143* 38.2 (1.5)
Preterm birth	15/76, 19.7% (11.5%, 30.5%)	5/67*, 7.5% (2.5%, 16.6%)	20/143*, 14.0% (8.8%, 20.8%)
Small for gestational age	3/76, 3.9% (0.8%, 11.1%)	12/66*, 18.2% (9.8%, 29.6%)	15/142*, 10.6% (6.0%, 16.8%)
Congenital anomalies (among pregnancies with 1st trimester bictegravir exposure)**	4/76, 5.3% (1.5%, 12.9%)	1/23, 4.3% (0.1%, 21.9%)	5/99, 5.1% (1.7%, 11.4%)
Birth weight Z-Score (adjusted for gestational age)	N=76 -0.50 (0.84)	N=66* -0.47 (1.03)	N=142* -0.49 (0.93)
Birth length Z-Score (adjusted for gestational age)	N=53* 0.04 (1.08)	N=50* 0.12 (1.19)	N=103* 0.08 (1.13)

Data shown as % (with 95% CI) or mean (SD).
*Differences between N in top row and column are due to incomplete data
**Anomalies included ventricular septal defect, Turner syndrome, Dandy-Walker malformation, polydactyly, and Jacob's syndrome

934 First Trimester Exposure to Newer Antiretroviral Agents and Congenital Anomalies in a US Cohort

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Background: The teratogenicity of antiretroviral medications (ARVs) is a key consideration in clinical recommendations and prescribing decisions for HIV regimens used during pregnancy. However, in the U.S., data on the association between ARV exposures and major congenital anomalies are generally limited to older ARV agents, many of which are now rarely used. Given the timing of organogenesis, it is critical to assess the safety of first-trimester fetal exposure to newer ARVs.

Methods: We evaluated the association between first trimester exposure to newer ARVs and major congenital anomalies among infants born between 2012-2022 to pregnant persons with HIV enrolled in the U.S.-based prospective Surveillance Monitoring for ART Toxicities (SMARTT) study conducted by the PHACS network. First trimester exposures to newer ARVs were abstracted from maternal medical records. Trained study site staff conducted physical exams and abstracted congenital anomalies from infant medical records, and investigators classified the anomalies using the Metropolitan Atlanta Congenital Defects Program classification system. The prevalence of major congenital anomalies identified by age 1 year was estimated for infants exposed and unexposed to each ARV. Generalized estimating equation (GEE) models were used to estimate the odds ratio (OR) and confidence interval (CI) of major congenital anomalies for each ARV exposure compared to those unexposed to that ARV, adjusting for infant birth year, maternal age at delivery, pre-pregnancy BMI, pregestational diabetes, and first trimester alcohol use, and accounting for correlation among siblings and/or multifetal births.

Results: Of 2034 eligible infants, major congenital anomalies occurred in 135 (6.6%; 95%CI: 5.6%-7.8%). Cardiovascular (n=43) and musculoskeletal (n=37) anomalies were most common. The adjusted odds ratios (95% CI) of congenital anomalies were 1.07 (0.64-1.78) for darunavir, 0.93 (0.47-1.85) for raltegravir, 1.04 (0.58-1.85) for rilpivirine, 1.25 (0.67-2.33) for elvitegravir, 0.75 (0.36-1.57) for dolutegravir, and 0.34 (0.05-2.55) for bictegravir (see Table). Findings were similar after adjustment for nucleoside backbones in the ARV regimen.

Conclusion: The odds of congenital anomalies among infants with first trimester exposure to newer ARVs did not differ substantially from that among infants unexposed to these specific ARVs. However, modest effects cannot be ruled out, highlighting the need for continued evaluation of these associations in larger populations.

Table. Association between 1st Trimester ARV Exposure and Occurrence of at Least One Major Congenital Anomaly in SMARTT Study (2012-2022)

1st Trimester ARV Exposure	# Infants Exposed in 1st Trimester n=2034	Congenital Anomaly Prevalence in Exposed % (95% CI)	Congenital Anomaly Prevalence in Unexposed % (95% CI)	Unadjusted Model OR (95% CI) n=2034	Simple Adjusted Model[1] OR (95% CI) n=2034	Fully Adjusted Model[2] OR (95% CI) n=2034
Rilpivirine (RPV)-exposed vs RPV-unexposed	291	19/291 6.5% (4.0%-10.0%)	116/1743 6.7% (5.5%-8.0%)	0.97 (0.56, 1.71)	1.04 (0.59, 1.85)	1.04 (0.58, 1.85)
Darunavir (DRV)-exposed vs DRV unexposed	268	18/268 6.7% (4.0%-10.4%)	117/1766 6.6% (5.5%-7.9%)	1.01 (0.61, 1.68)	1.03 (0.62, 1.72)	1.07 (0.64, 1.78)
Elvitegravir (EVG)-exposed vs EVG-unexposed	193	13/193 6.7% (3.6%-11.2%)	122/1841 6.6% (5.5%-7.8%)	1.02 (0.57, 1.85)	1.31 (0.71, 2.41)	1.25 (0.67, 2.33)
Dolutegravir (DTG)-exposed vs DTG-unexposed	186	8/186 4.3% (1.9%-8.3%)	127/1848 6.9% (5.8%-8.1%)	0.61 (0.30, 1.26)	0.76 (0.37, 1.57)	0.75 (0.36, 1.57)
Raltegravir (RAL)-exposed vs RAL-unexposed	152	9/152 5.9% (2.7%-10.9%)	126/1882 6.7% (5.6%-7.9%)	0.88 (0.44, 1.75)	0.91 (0.46, 1.81)	0.93 (0.47, 1.85)
Bictegravir (BIC)-exposed vs BIC-unexposed	52	1/52 1.9% (0.05%-10.3%)	134/1982 6.8% (5.7%-8.0%)	0.27 (0.04, 2.01)	0.34 (0.05, 2.51)	0.34 (0.05, 2.55)

[1]Adjusted for infant birth year, maternal age at delivery, pre-pregnancy body mass index (BMI) category, pregestational diabetes, and 1st trimester alcohol use; [2]Adjusted for above covariates, as well as concurrent use of other antiretroviral (ARV) medications in the analysis

935 Cancer Incidence in Children Who Are HIV-Exposed and Uninfected in England: Data Linkage Study

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Background: Children born to women living with HIV develop in an in utero environment that includes exposure to HIV and antiretroviral therapy (ART). However, the long-term health implications of these exposures for children who are HIV-exposed and uninfected (CHEU) are largely unknown.

Methods: Population-based surveillance data from children born to women living with HIV in England (ISOSS) between1995 and 2022 were linked to national cancer registration and mortality data. Date of last cancer registration was used where >1 cancer event occurred. Age-and-sex standardised incidence ratios (SIR) were used to compare cancer incidence in CHEU with the general child population in England. Cancer incidence and associations with maternal, HIV/ART and child characteristics were estimated using Cox-proportional hazards models.

Results: There were 19 cancer events (13 in females, 6 in males) in 17 children among 14047 CHEU records with 159,241 person-years follow-up. The cancer incidence rate was 1.07 (95% CI: 0.62-1.71). All cancer events occurred before 17 years of age and median age at last cancer event was 4 years (IQR: 7, Q1:2–Q3:9). Cancers affecting the central nervous system were most common (n=6), followed by lymphoid, haematopoietic, and related tissue cancers (n=4). There were ≤3 cancer registrations affecting the eye, kidney, thorax, bones, bronchus & lungs. Cancer events observed for males aged 0-4 years were lower than expected based on the general population (SIR: 0.14, 0.02-0.99 per 10,000 person-years) with no statistically significant differences at all other ages or among females. Univariable analyses showed weakly positive associations with cancer rate for children with a congenital anomaly (HR: 4.5, 95% CI: 1.0-20.4) and for children born small-for-gestational-age (HR: 3.2, 95% CI: 0.9-12.0) compared to children adequate for gestational age, whilst for children born to women of Black African ethnicity there was a weakly negative association with rate of cancer (HR: 0.43, 95% CI: 0.17-1.08) compared to children born to women of White ethnicity. There were no statistically significant associations between cancer rate and ART drug class used in pregnancy.

Conclusion: Cancer type and incidence among CHEU in England does not differ from that in the general population, with known risk factors in the latter such as congenital anomalies also identified in the CHEU population. Further work is ongoing on mortality risk.

936 Maternal Imprinted Immune Perturbations in HIV-Exposed Uninfected (HEU) Infants Persist for 6 Months

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Background: HEU infants exhibit higher mortality/morbidity including adverse growth, developmental, infectious, and metabolic outcomes, and perturbed immune responses. How their immune profiles are altered and influenced by maternal immunity is unknown.

Methods: The study group included 46 pregnant women with HIV (PWH)/HEU infant pairs enrolled in PACTG 316, with 23 PWH virally suppressed (VS) during pregnancy by antiretroviral therapy (ART) and 23 PWH virally non-suppressed (VNS) on similar ART. Pregnant women without HIV (PWOH)/HIV unexposed uninfected (HUU) neonates (n=18) served as a reference. HEU infants were evaluated at birth and 6 months along with a longitudinal cohort of 32 HUU infants. Maternal plasma samples were obtained at or near delivery. Twenty-one plasma biomarkers associated with germinal center (GC) development, immune activation, inflammation, and immune regulation were measured using Mesoscale. Results of two or multiple groups were compared by Mann-Whitney or Kruskal-Wallis tests, respectively, while mother/newborn biomarker correlations were assessed by Spearman's test.

Results: Compared to PWOH, biomarkers related to GC development (sCD40L, IL21), immune activation (sCD163, sCD27, IL22) and inflammation (CXCL9, CXCL10, CCL5, TNFα, IL1β) were significantly elevated in all PWH, independent of viral status. At birth, HEU compared to HUU infants had significantly higher concentrations of GC (APRIL, BAFF, sCD40L, IL21), immune activation (sCD14, IL22, IL2), inflammation (CXCL9, CCL4, CCL5, TNFα, IL1β), and immune regulation (IL1RA) that persisted for 6 months. Elevated birth levels of IL6 and IL10 normalized, while sCD27, IFNγ, and CXCL10 increased at 6 months. Correlations at birth between PWOH/HUU newborn biomarkers showed minimal relationships. In contrast, PWH/HEU pairs displayed multiple positive correlations; for example, elevation of IL6 levels in PWH correlated with increased levels of anti-

inflammatory cytokines IL10 (p=0.003, r=0.59) and IL1RA (p=0.02, r=0.48) in their newborns.

Conclusion: Biomarkers in PWH are reflected at birth in their HEU infants and persist up to 6 months. Perturbed biomarkers include chemokines and cytokines involved in early germinal center development and macrophage activation markers known to play a critical role in neonatal immune responses. Maternal immune perturbations appear to be imprinted on their HEU infants, which may alter immune ontogeny and contribute to their increased morbidity.

937 Brain Structure of South African HEU Children Exposed to Dolutegravir Versus Efavirenz

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Background: Current research suggests that children who are HIV-exposed and uninfected (CHEU) may be at risk for neurodevelopmental delay and altered structural brain development compared to children who are HIV-unexposed (CHU), however the specific factors driving this association and the potential role of specific antiretroviral regimens are poorly understood. In particular volumes of specific regions of the brain may be reduced in CHEU compared to CHU, however, there is no research published on the structural brain outcomes of children born to mothers on DTG-based ART.

Methods: We collected high resolution magnetic resonance (T1-weighted) scans were from DolPHIN-2 Plus, an open-label follow-up to the DolPHIN-2 trial (NCT03249181). In this analysis, total grey matter and total subcortical volumes were compared between CHEU and CHU groups using multivariate analysis of variance (MANOVA) adjusting for age, sex and total intracranial volume. Within the CHEU group, brain volumes were compared between children who were born to mothers who received DTG and EFV-based ART.

Results: Between 2021 and 2023, 24 CHEU (12 DTG, 12 EFV; mean age 45 months; 54% male) born in the DolPHIN-2 trial were enrolled and scanned at 2-4 years along with 64 CHU (mean age 43 months; 56% male). Demographic characteristics were similar for both CHEU vs CHU and DTG vs EFV groups. In unadjusted and adjusted analyses, there was no evidence for an effect of HIV exposure on total grey matter (adjusted p=0.642) or subcortical grey matter (p=0.549). Similarly, ART exposure showed no significant association with total grey matter (p=0.869), or subcortical grey matter (p=0.097), although there was a trend towards smaller subcortical volumes in the EFV compared to DTG groups (F = 3.05, partial Eta squared =0.138).

Conclusion: Total grey matter brain volumes were similar in CHEU and CHU at 3-4 years of age in this sample. These are the first data comparing brain volumes in HEU children born to mothers receiving DTG- versus EFV-based ART in pregnancy. While there were no significant differences by ART regimen, the trend for larger subcortical volumes in DTG-exposed children in this small sample requires further investigation.

938 Neurodevelopment in Children Exposed In Utero to Dolutegravir- or Efavirenz-Based ART in Botswana

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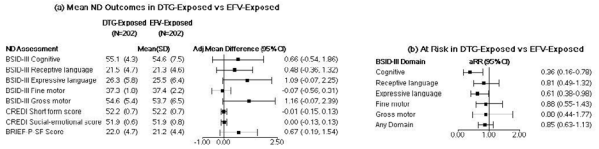
Background: Dolutegravir (DTG)- and, to a lesser extent, efavirenz (EFV)-based antiretroviral treatment (ART) regimens are commonly used by pregnant persons living with HIV in high burden HIV settings, increasingly with initiation prior to conception. Little is known about the impact of in utero exposure to DTG- or EFV-based ART on child neurodevelopmental (ND) outcomes, although some prior data have raised concerns for EFV exposure.

Methods: We prospectively enrolled 3 cohorts of 2-year-old children: HIV-exposed/uninfected (HEU)/DTG-exposed, HEU/EFV-exposed, and HIV-unexposed/uninfected (HUU), from March 2021-May 2023. DTG or EFV were taken in combination with TDF/FTC or 3TC. Child ND status was assessed using the Bayley (BSID-III), BRIEF-P-SF, and CREDI (Short; Social-Emotional). ND outcomes were compared between DTG- and EFV-exposed groups, and between HEU and HUU groups, using GEE models to account for twins, and adjusting for enrollment site, child sex/age at testing, maternal age/education/marital status/income, food insecurity (and for DTG vs EFV comparisons, breastfeeding and timing of first in utero ART exposure). Children were classified "at risk" if they scored ≥1SD below the mean or were unable to complete the BSID-III.

Results: A total of 564 children (202 HEU/EFV, 202 HEU/DTG, 160 HUU; Mage=25.7 months; 49% female) participated. Means were similar across ART-exposure groups in unadjusted and adjusted models (Figure). Adjusted relative risk (aRR) of "at risk" classification was lower in children who were DTG-exposed than EFV-exposed on BSID-III Cognitive (4.5% vs. 8.4% aRR=0.36 (95%CI:0.16, 0.78)) and Expressive Language (10.9% vs 17.3%, 0.61 (0.38, 0.98)) domains. Children HEU (EFV+DTG) were more likely than children HUU to be classified "at risk" on BSID-III Expressive Language (14.1% vs 7.5%, aRR=1.89 (1.00, 3.60)). Children HEU were rated as having slightly better executive function skills on the BRIEF-P-SF. Inferences were similar in sensitivity analyses controlling for preterm birth status.

Conclusion: Two-year ND outcomes among HEU and HUU children in Botswana were mostly comparable. However, consistent with prior studies, HEU status was associated with higher risk of adverse language outcomes. Among children HEU, those exposed in utero to EFV-ART were at higher risk of adverse cognitive and expressive language outcomes than DTG-ART-exposed. Longer-term ND follow-up is needed to examine the possibility of increased ND burden as HEU-/ART-exposed children enter school-age.



939 Prenatal PrEP Exposure and Neurodevelopment Among Children at 48 months

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Background: Data on neurodevelopmental outcomes following in utero ART exposure remains scarce and most studies to date are among women living with HIV and their infants who have both ART and HIV exposure. We assessed the relationship between prenatal PrEP exposure and child neurodevelopment through 48 months among mother-child pairs without HIV.

Methods: Data from women enrolled in a cluster RCT (NCT03070600) evaluating PrEP delivery strategies at 20 antenatal clinics in Western Kenya were analyzed. HIV-negative women were enrolled and offered oral tenofovir disoproxil fumarate (TDF)-based PrEP during pregnancy and followed through 9 months postpartum regardless of PrEP status. A subset were enrolled into an extension cohort at 4 sites to be followed until their children reached 5 years. Neurodevelopment was assessed by trained nurses at 36 and 48 months using the Malawi Developmental Assessment Tool (MDAT), a validated instrument that evaluates social, language, fine motor, and gross motor domains. The association between prenatal PrEP exposure and MDAT domain scores at 36-48 months was evaluated using linear regression models clustered by facility and adjusted for gestational age at birth, maternal age and education, infant sex, and partner HIV status.

Results: As of September 2023, 648 mother-child pairs had children aged 36-48 months and were included in the analysis, 21% had any PrEP exposure for a median duration of 3.3 months (IQR: 2.4-4.3) during pregnancy. Compared to mothers who did not take PrEP, mothers who took PrEP in pregnancy were more likely to only have primary school education (70% vs. 56% p=0.004) and to have a partner known to be living with HIV or of unknown status (67% vs 37% p<0.001). There was no difference in mean MDAT score for any domain at 36 months (adjusted mean differences: social 0.07, 95% CI: -1.61, 1.76, p=0.92; language 0.54, 95% CI: -1.57, 2.66, p=0.58; fine motor -0.50, 95% CI: -1.49, 0.49, p=0.29; gross motor -0.17, 95% CI: -1.19, 0.85, p=0.72). Results were similar at 48-months with no differences between exposure groups.

Conclusion: No differences in neurodevelopment from 36-48 months were observed between children with and without prenatal PrEP exposure. Our results support a growing body of evidence demonstrating the safety of prenatal PrEP use and add to the limited data on neurodevelopmental outcomes in PrEP exposed children.

Table 1. Univariable and multivariable linear regression models assessing mean difference in neurodevelopmental domain scores by PrEP exposure status

PrEP exposed vs Unexposed	Social, Coeff (95% CI)	*P*	Language, Coeff (95% CI)	*P*	Fine Motor, Coeff (95% CI)	*P*	Gross Motor, Coeff (95% CI)	*P*
36-month								
PrEP-exposed (ref: Unexposed) – Unadjusted[1]	0.25 (-1.20, 1.71)	0.70	0.22 (-1.76, 2.21)	0.81	-0.52 (-1.65, 0.60)	0.32	-0.33 (-1.34, 0.68)	0.48
PrEP-exposed (ref: Unexposed) – Adjusted[1,2]	0.07 (-1.61, 1.76)	0.92	0.54 (-1.57, 2.66)	0.58	-0.50 (-1.49, 0.49)	0.29	-0.17 (-1.19, 0.85)	0.72
48-months								
PrEP-exposed (ref: Unexposed) – Unadjusted[1]	-0.03 (-0.86, 0.81)	0.94	-0.48 (-1.32, 0.35)	0.47	-0.51 (-1.27, 0.25)	0.16	-0.04 (-0.58, 0.50)	0.87
PrEP-exposed (ref: Unexposed) – Adjusted[1,2]	0.17 (-0.67, 1.01)	0.67	-0.45 (-1.23, 0.33)	0.23	-0.59 (-1.39, 0.21)	0.13	-0.12 (-0.67, 0.43)	0.64

[1]*clustered by site*
[2]*Adjusted for maternal education, maternal age, infant sex, partner HIV status and gestational age at birth*

940 Simplifying Dosing by Harmonizing Weight-Band-Based Dosing Across Therapeutic Areas in Children

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Background: Pediatric WHO dosing guidance recommends using dosing weight bands, but these are not standardized across therapeutic areas. This adds to the complexity of drug prescribing and administration when treating individual children for multiple diseases and comorbidities, increasing the risk of dosing errors. Harmonized weight bands across therapeutic areas are expected to simplify dosing, relieve the burden on practitioners and caregivers, reduce dosing errors, and provide clear dosing guidance for future pediatric drug development programs. However, this cannot come at the expense of drug efficacy or safety. We investigated the impact of harmonizing weight bands for HIV, tuberculosis (TB), malaria, and Hepatitis C (HCV) treatment, based on simulated drug exposures, with the goal of providing evidence for future harmonization of pediatric weight bands.

Methods: Weight bands recommended in the Pocket Book for Hospital Care in Children, WHO Antibiotic Book, and guidance documents for HIV, TB, malaria, and HCV were selected to assess the potential for harmonization. Using available population pharmacokinetic models for individual drugs, the impact of harmonizing weight bands on drug exposures were simulated and the corresponding changes discussed with panels of clinical and pharmacological experts.

Results: The proposed weight bands align with those recommended in the WHO antibiotic book and the pocket book, Table 1. For drugs used in HIV, HCV, and for treatment and prevention of drug-susceptible TB, harmonization had minimal impact on drug exposures and are not expected to affect drug efficacy or safety. For children weighing <10 kg treated for drug-resistant TB, harmonization had a pronounced impact; nevertheless, safe, and effective exposures are expected after optimizing drug doses based on age to account for maturation of elimination pathways. Safe and effective exposures are expected with harmonized dosing for 7/9 priority malaria drugs and for all 3 drugs currently used for seasonal malaria chemoprevention.

Conclusion: This work demonstrates that harmonized pediatric weight bands, with additional age-based dosing for infants, provides sufficient flexibility for safe and effective pediatric dosing for treatment of HIV, HCV, TB, and seasonal malaria chemoprevention. For malaria treatment, additional safety, and efficacy studies are recommended due to expected exposures in 2/9 priority drugs. This analysis is expected to inform future revision of WHO guidelines.

Table 1. Differences between the proposed harmonized weight bands and weight bands currently recommended in WHO dosing guidance for general hospital care, antibiotics, HIV, TB, malaria, and HCV. Red: weight bands affected by harmonization. DS-TB: drug susceptible tuberculosis; RR/MDR-TB: rifampicin resistant/multidrug resistant tuberculosis.

Harmonized Weight bands (kg)	3 - 5.9	6 - 9.9	10 - 14.9	15 - 19.9	20 - 24.9	25 - 29.9
Hosp. care & Antibiotics	3 - 5.9	6 - 9.9	10 - 14.9	15 - 19.9	20 - 29.9	
HIV	3 - 5.9	6 - 9.9	10 - 13.9	14 - 19.9	20 - 24.9	25 - 34.5
DS-TB		4 - 7.9	8 - 11.9	12 - 15.9	16 - 24.9	>25
RR/MDR-TB	3 - 4.9	5 - 6.9	7 - 9.9	10 - 15.9	16 - 23.9	24 - 29.9
Malaria	3/6 preferred treatment combinations aligned with harmonized weight bands					
HCV	1/4 preferred treatment combinations aligned with harmonized weight bands					

941 Single-Dose PK/Safety of DTG-Dispersible Tablets in Neonates Supports Multi-Dosing: Petite-DTG Study

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Background: Dolutegravir dispersible tablets (DTG-DT) are approved for infants ≥3 kg and aged >4 weeks but their suitability for neonates remains unknown. We evaluated the pharmacokinetics (PK) and safety of pediatric DTG-DT in neonates born to women on DTG-based therapy.

Methods: PETITE-DTG is an ongoing phase I/II, open-label, single center, two-stage trial in South Africa evaluating the PK and safety of DTG-DT (10 mg, scored) in term neonates (birth weights ≥2kg). Stage 1 was designed to assess single doses of DTG on top of standard ARV prophylaxis to inform a multi-dose strategy in Stage 2. In Stage 1, a single 5 mg DTG-DT dose was administered to 8 neonates between ≥14 & <28 days of life (Cohort 1A) followed by intensive PK and safety assessments. After no safety signal was observed, 8 additional neonates received a single 5 mg DTG-DT dose at <14 days of life (Cohort 1B) followed by identical PK and safety assessments. A population PK model was developed using Stage 1 data, and different dosing scenarios were simulated to select the optimal 5 mg DTG multi-dose strategy through 28 days of life [target DTG criteria: geometric mean (GM) C_{tau} >0.67 µg/mL and individual C_{max} <17.0 µg/mL]

Results: 16 neonates, 8 per Cohort, completed Stage 1. Median (range) birth weight was 3.1 (2.6-4.2) kg and PK sampling performed between 3 to 22 days of life (Figure a). Single dose DTG C_{max} ranged from 2.0-6.6 µg/mL. No grade ≥3 adverse events (AEs) were reported, and no AEs were related to DTG. One neonate required hospitalization for a skin rash (grade 2). A one-compartment PK model described DTG plasma concentrations, with clearance (CL/F) influenced by weight and postnatal age. DTG CL/F rapidly increased after birth with ~6-fold change between day 1 and 14 of life. Simulations predicted >10% of neonates had a C_{max}>17.0 µg/mL with 5 mg DTG-DT once daily (q24) during the first 2 weeks of life. Administration of 5 mg DTG-DT every 48 hrs (q48) from Day 1 to 14 of life, followed by 5 mg DTG q24 though day 28 day would be an optimal dosing strategy (Figure b) with the predicted C_{tau} between 0.86-4.35 µg/mL and 98% of neonates with a C_{max} <17.0 µg/mL.

Conclusion: Single doses of 5 mg DTG-DT were safe in neonates. Due to slow DTG CL/F in early life, 5 mg DTG q24 was not optimal from birth. In Stage 2, the safety and PK of 5 mg DTG q48 for the first 2 weeks of life, followed by q24 through 28 days of life, will be assessed. Both the DTG-DT and the recently approved 5 mg DTG oral dispersible film will be investigated.

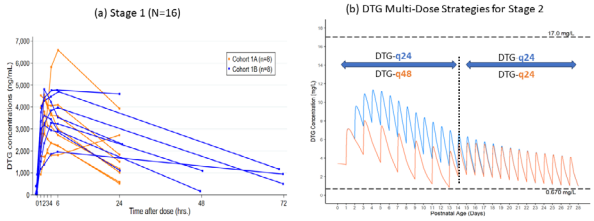

Figure. (a) Individual DTG concentration vs time curves; (b) Model-Based predictions: 5 mg DTG every 24 (q24) and 48 hours (q48) from Day 1 to 14 of life, followed by 5 mg DTG q24 until 28 days of life.

942 Lamivudine (3TC) Dosing for Preterm Neonates Exposed to HIV

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Background: Current oral lamivudine (3TC) dosing guidance for preterm neonates exposed to HIV is based on limited evidence and no pharmacokinetic (PK) studies in neonates <36 weeks gestational age (GA). As 3TC is one of only three antiretrovirals available for preterm neonates, our aim was to develop a pragmatic 3TC twice daily preterm dosing strategy stratified by GA bands: ≥27 to <30 weeks; and ≥30 to <36 weeks

Methods: 3TC plasma concentration data were pooled from 8 neonatal and infant PK studies receiving 3TC liquid formulation (10 mg/mL); 3 for HIV prevention (PACTG 353, 358, and 386), and 5 for HIV treatment (PACTG 300, 356, IMPAACT P1069, P1106, and the Early Infant HIV Treatment in Botswana study). A population PK model was developed using non-linear mixed effects regression. Different dosing simulations were assessed in a virtual population of preterm neonates (0-6 months of life) to achieve 3TC (AUC_{0-12}) exposures ranging from 3.15 to 13.24 µg·hr/mL. The model incorporated standard WHO weight-band 3TC dosing of 30 mg twice daily for weights ≥3 to <6 kg and ≥4 weeks of life.

Results: One-hundred fifty-four infants contributed 858 3TC concentrations; 34 (22%) were born preterm. At first PK sampling, median and range postnatal age (PNA) was 6.3 (0.52-26.6) weeks, body weight 3.8 (1.9-7.8) kg, and plasma serum creatinine 0.4 (0.1-1.2) mg/dL, respectively. 3TC concentrations were best described by a 1 compartment PK model. 3TC clearance (CL/F) and volume of distribution (Vd/F) were allometrically scaled to body weight. Maturation of CL/F was described using an Emax model based on PNA, which also influenced Vd/F. Simulations included GA as a covariate on birth CL/F to account for the impact of developmental changes in renal function expected in preterm neonates. The simulations predict that the optimal 3TC dosing regimen for preterm neonates for GA ≥27 to <30 weeks is 2 mg/kg twice daily from birth, and for GA ≥30 to <36 weeks is 2 mg/kg twice daily for the first 4 weeks of life, followed by 4 mg/kg twice daily. Dosing is adjusted to 30 mg twice daily per WHO weight-band dosing once infants reach ≥ 3kg and aged ≥4 weeks (Figure 1).

Conclusion: This analysis provides the first pragmatic and evidence based 3TC dosing for preterm neonates where immature renal function undergoes rapid maturation. This proposed preterm 3TC dosing guidance has been endorsed by the WHO-Pediatric Antiretroviral Working Group but should be clinically validated to provide reassurance of model predictions.

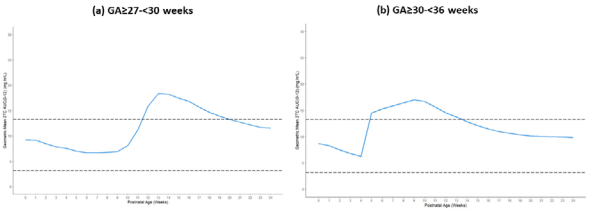

Figure: Predicted 3TC GM AUC_{0-12} through 24-weeks of life: (a) 2 mg/kg BID from birth; (b) 2 mg/kg BID, first 4-weeks of life, then 4 mg/kg BID. Infants ≥3kg and aged ≥4 weeks switch to 30mg BID (per WHO). Dotted-lines AUC_{0-12} target: 3.15-13.24 µg.hr/mL

943 High Drug Exposures in Neonates Using ABC/3TC Dispersible Tablets During the First Week of Life

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Background: Pediatric fixed dose combination (FDC) formulations are preferred for infants and young children but rapid maturation of metabolic and elimination pathways complicate their use in neonates. We previously reported the pharmacokinetics (PK) and safety of abacavir/lamivudine (ABC/3TC) FDC dispersible tablet in neonates but no PK data were available prior to 6 days of life. Our objective was to develop population PK models to estimate ABC/3TC exposures in neonates using ABC/3TC dispersible tablets from birth.

Methods: The 'PETITE' study was a phase I/II, open-label, single arm, two-stage pharmacokinetic and safety trial. HIV-exposed neonates received 30/15 mg of ABC/3TC (¼ dispersible tablet) once daily and 80/20 mg of LPV/r (2 sachets) twice daily through 28 days of life. Each neonate had intensive PK sampling on two occasions between 6 and 24 days of life. Safety visits were performed 1-2 week(s) after each PK visit. PK models of ABC and 3TC were developed using nonlinear mixed-effects modeling. Monte Carlo simulations (n=5,600 virtual neonates) were performed to predict ABC and 3TC exposures from birth through 28 days of life. Geometric mean (GM) ABC and 3TC target exposures (AUC0-24) reported in children were 6.3 to 50.4 and 6.3 to 26.5 mg.hr/L for ABC and 3TC, respectively.

Results: 16 term neonates (8 females) with a median birth weight of 3,140 g were included. One compartment PK models with first-order absorption and elimination best described both ABC and 3TC plasma concentrations, incorporating body weight and postnatal age on clearance as surrogates of hepatic and renal maturation. Simulations predicted that maximum ABC and 3TC exposures occurred at 2 days of life. The predicted GM ABC AUC0-24 decreased by 28% between 2 and 7 days of life and remained above the target during the first week of life (Figure 1(a)). The GM 3TC AUC0-24 decreased by 26% between 2 and 4 days of life and remained above the target during the first 4 days of life (Figure 1(b)).

Conclusion: Administrating 30/15 mg of ABC/3TC (¼ dispersible tablet) once daily to neonates from birth leads to plasma exposures during the first week of life above those observed in young children. While no safety issues were reported in the PETITE study, continued safety surveillance of the ABC/3TC dispersible tablets in neonates is warranted, particularly when stared in the first week of life.

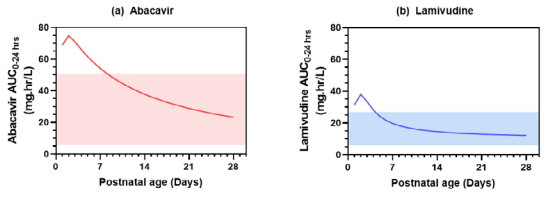

Figure: Simulated Geometric Mean (GM) (a) ABC and (b) 3TC $AUC_{0-24hrs}$ versus postnatal age. Shaded areas represent the GM target ranges, 6.3-50.4, and 6.3 to 26.5 mg.hr/L for ABC and 3TC, respectively.

944 A Single Once Daily ABC/DTG/3TC Tablet Predicts Safe and Effective Exposures in Children 3 to <6kg

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Background: Abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) is a fixed-dose combination (FDC) tablet approved for adults and children with HIV weighing ≥6kg and aged ≥3 months. We evaluated whether ABC/DTG/3TC (60mg/5mg/30mg) dispersible tablet (DT) once daily would achieve therapeutic targets in children weighing 3-<6kg (aged ≥4 weeks).
Methods: We used a population pharmacokinetic (PopPK) model-based approach leveraging existing data with single entities and FDC formulations from adults, infants, and children with HIV. Drug-specific PopPK models incorporating expected enzyme and renal maturation functions were developed for ABC, DTG and 3TC and used to predict pediatric drug exposures. Simulations were performed with 1000 replicate trials of 200 participants. Exposure metrics ($AUC_{0\text{-}24}$, C_{max}, and C24) were calculated for each drug and compared with pre-defined exposure target range (DTG C24 geometric mean [GM] 0.697-2.26 µg/mL, ABC AUC0-24 GM 6.3-50.4 µg*h/mL, and 3TC AUC0-24 GM 6.3-26.5 µg*h/mL). We reviewed safety findings for ABC, DTG and 3TC in the lowest weight bands (WBs) of three pediatric trials (P1093, ODYSSEY and IMPAACT 2019), alongside available literature describing PK and safety of ABC and 3TC in neonates and infants under 3 months (including PETITE Study).
Results: Predicted GM steady-state plasma exposures of ABC, DTG and 3TC in children 3-<6kg receiving a single FDC of ABC/DTG/3TC DT (Table 1) were within the target ranges for each component. $AUC_{0\text{-}24}$, C_{max} and C24h of ABC, DTG and 3TC were also comparable to prior pediatric and adult studies. Review of pediatric safety data showed similar safety profiles across WBs and were consistent with the known safety profile of the individual drugs. Most children in these studies were on the higher WHO doses of 3TC 60mg and ABC 120mg for this WB.
Conclusion: Predicted drug exposures support the potential use of a single FDC of ABC/DTG/3TC DT in infants weighing 3-<6kg (aged ≥4 weeks), with efficacy and safety expected to be comparable to prior pediatric studies in children ≥6kg. The once daily single tablet treatment option may be a practical solution for infants with early HIV diagnosis.

Table 1. Predicted ABC/DTG/3TC Exposures

Entity	Dispersible Tablet Dose	AUC0-24h (µg*h/mL)	C24h (µg/mL)	Cmax (µg/mL)
ABC	60 mg	17.84 (16.54, 19.24)	0.11 (0.09, 0.13)	4.73 (4.44, 5.03)
DTG	5 mg	57.79 (54.07, 61.56)	1.32 (1.18, 1.46)	4.59 (4.36, 4.83)
3TC	30 mg	11.36 (10.77, 11.97)	0.03 (0.02, 0.04)	1.80 (1.72, 1.89)

Note: AUC0-24, Cmax and C24h presented as a GM (95% CI).

945 Population Pharmacokinetics of ABC/DTG/3TC FDC to Support Dosing in Peds With HIV-1: IMPAACT 2019

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Background: Once-daily fixed-dose combinations (FDC) containing abacavir (ABC), dolutegravir (DTG), and lamivudine (3TC) have been approved in the US for adults and children with HIV weighing ≥6 kg (Dispersible tablet (DT) and Tablets). This analysis assessed the ability of previously developed ABC, DTG, and 3TC pediatric population pharmacokinetic (PopPK) models using multiple formulations to describe and predict PK data in young children using DT and Tablet formulations of ABC/DTG/3TC FDC in the IMPAACT 2019 study.
Methods: IMPAACT 2019 was a Phase I/II, multi-center, open-label study assessing the PK, safety, tolerability, and efficacy of ABC/DTG/3TC FDC (Tablets and DT) in children with HIV-1 aged <12 years and weighing ≥6 to <40 kg. Intensive and sparse PK samples were collected through 48 weeks (N=55 participants with 590 ABC, 598 DTG, and 597 3TC observations). Existing drug specific pediatric PopPK models for ABC (2-compartment), DTG (1-compartment), and 3TC (1-compartment) were applied to the IMPAACT 2019 plasma drug concentrations data without re-estimation (external validation) of PopPK parameters. Exposures were then simulated across weight bands for each drug and compared with pre-defined exposure target ranges.
Results: Goodness-of-fit and visual predictive check plots demonstrated good agreement between observed concentrations for ABC, DTG, and 3TC from IMPAACT 2019 and the respective PopPK models. The post-hoc PK parameter estimates were comparable to the NCA PK parameter estimates from IMPAACT 2019. Thus, new PopPK models to specifically describe the IMPAACT 2019 data were not necessary. Simulated geometric mean (GM) C24h DTG exposures were consistent across the weight bands (0.74 - 0.95 µg/mL) for both formulations. The predicted ABC GM AUC0-24 ranged from 14.89 to 18.50 µg*h/mL for both formulations. Similarly, predicted GM $AUC_{0\text{-}24}$ ranges for 3TC were consistent across the weight bands (10.50 - 13.20 µg*h/mL). The predicted GM exposures were within the pre-defined GM target range set for each drug (Table 1) and comparable to the previously observed PK with adults and pediatric participants with individual drugs.
Conclusion: This model-based approach leveraged existing pediatric data and models to confirm FDC ABC/DTG/3TC dosing for DT and Tablet using PK data collected in IMPAACT 2019. This analysis supports ABC/DTG/3TC FDC dosing in children weighing ≥6 kg.

Table 1 Predicted DTG/ABC/3TC Exposures with DT and Tablet Dosing

Weight Bands	Total Daily Dose (DTG/ABC/3TC)	DTG C24 (µg/mL)	ABC AUC0-24 (µg*h/mL)	3TC AUC0-24 (µg*h/mL)
≥6 to <10 kg	15 mg/180 mg/90 mg DT	0.94 (0.13 - 4.60)	17.36 (6.66 - 43.70)	11.57 (5.82 - 22.36)
≥10 to <14 kg	20 mg/240 mg/120 mg DT	0.74 (0.10 - 3.54)	16.66 (6.43 - 41.62)	11.40 (5.79 - 21.66)
≥14 to <20 kg	25 mg/300 mg/150 mg DT	0.81 (0.11 - 3.78)	15.47 (5.94 - 39.12)	10.78 (5.49 - 20.6)
≥20 to <25 kg	30 mg/360 mg/180 mg DT	0.88 (0.13 - 4.03)	14.89 (5.72 - 37.49)	10.50 (5.34 - 19.96)
≥25 kg	50 mg/600 mg/300 mg Tablet	0.95 (0.15 - 4.11)	18.50 (7.00 - 47.70)	13.20 (6.59 - 25.65)
Target GM Range		0.697 - 2.26	6.3 - 50.4	6.3 - 26.5

Note: AUC0-24 and C24 presented as a GM (90% prediction interval).

946 Pharmacokinetics of Once-Daily DTG/3TC FDC in Children Living With HIV: D3/PENTA21 Sub-Study

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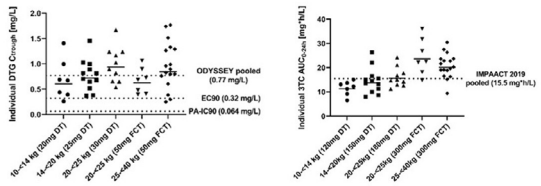
Background: There is an increasing emphasis on reducing toxicity and improving acceptability of HIV-treatment. Two-drug regimens, consisting of two different antiretroviral drug classes, are recommended as an alternative to standard three-drug regimens, with dolutegravir and lamivudine (DTG/3TC) included in a number of adult treatment guidelines. This nested pharmacokinetics (PK) sub-study within the D3/Penta21 randomized controlled trial (#NCT04337450) is evaluating DTG and 3TC concentrations in children and adolescents, previously suppressed on a three-drug first-line regimen, who switched to once-daily DTG/3TC fixed dose combinations (FDC).
Methods: Eligible children aged 2 to <15 years weighing 6-<40kg received either 5/30mg DTG/3TC dispersible tablets (DT) or 50/300mg film-coated tablets (FCT). Children in weightband (WB) 10-<14kg took 20/120mg; WB 14-<20kg 25/150mg DT; WB 20-<25kg took either 30/180mg DT or 50/300mg FCT; WB 25-<40kg took 50/300mg FCT, respectively. We aimed for ≥8 evaluable PK curves per WB/formulation. Seven blood samples were taken at steady-state after an overnight fast at t=0, and 1, 2, 3, 4, 6 and 24 h post dosing. PK parameters for DTG and 3TC and the number of children with DTG Ctrough below EC_{90} (0.32 mg/L) and PA-IC_{90} (0.064 mg/L) were summarised.
Results: 53 participants were included in this preliminary PK analysis (~70% of sub-study participants with successful PK sampling). Median(range) age was 7.1(2.8-13.8) years and weight 21.5(12.6-39.5) kg. DTG Ctrough, $AUC_{0\text{-}24h}$ and C_{max} geometric mean(GM) (%CV) were 0.77(52) mg/L, 64(35) h*mg/L and 6.38(31) mg/L. 3TC C_{trough}, $AUC_{0\text{-}24h}$ and C_{max} GM(%CV) were 0.06(35) mg/L, 17(38) h*mg/L and 3.25(37) mg/L. Figure shows PK parameters by WB. Only 3 children had DTG

C_{trough}<0.32mg/L (1 in WB 10-<14kg; 2 in WB 25-<40kg). All children had C_{trough} ≥0.064mg/L. In the 20-<25kg WB, 3TC AUC_{0-24h} GM was 1.5 times higher in children receiving 50/300mg FCT versus 30/180mg DT; however, the AUC_{0-24h} GM was not much higher than the AUC_{0-24h}GM in participants weighing ≥25kg.
Conclusion: Preliminary PK results demonstrate that DTG and 3TC concentrations after administration of a DTG/3TC FDC in virologically suppressed children living with HIV are comparable with previous paediatric PK studies of DTG (ODYSSEY) and 3TC (IMPAACT2019). As expected, because of a higher dose/kg in the 20-25kg WB in the FCT group in D3/Penta 21 compared to IMPAACT2019, (300mg v180mg), increased 3TC exposures were observed. Further PK data and safety data are awaited.

Figure: Preliminary DTG C_{trough} and 3TC AUC_{0-24h} in children on dual DTG/3TC



Individual data and geometric means (solid horizontal lines) per WB. ODYSSEY data (pooled across WBs) served as reference for DTG. IMPAACT2019 data (pooled across WBs) were reference for 3TC. Data from 70% of the participants in D3/Penta21 sub-study.

947 Pediatric PBPK Scaling Model for a New Long-Acting, 3 HIV Drug Combination in a Single Injection

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Background: The TLC-ART program successfully engineered lopinavir (LPV), ritonavir (RTV), and tenofovir (TFV) in a single 3-drug long-acting (LA) injectable suspension (TLC-ART 101) that has undergone scale-up, stability and preclinical safety studies. A First-in-Human study (NCT06850728) is ongoing. Leveraging juvenile and adult non-human primate (NHP) data, we developed and validated physiologically based pharmacokinetic models (PBPK) scalable to inform pediatric dosing of TLC-ART 101.
Methods: PBPK models have been validated with DcNP and the combined free drugs in adult and juvenile NHPs. We scaled the proposed pediatric doses iteratively and simulated time-courses in each age band to predict safe, detectable, and likely effective drug levels in plasma based on combinatory EC_{50}. AUC, terminal half-life, and concentration at 4 weeks after injection were computed. To scale to children, PBPK accounted for liver CYP3A ontogeny, organ volumes and blood flows, GFR maturation, and drug-drug interactions (DDI).
Results: The projected dose is presented for each pediatric age-weight band according to the dose- equivalent needed to provide target drug exposure (AUCs) for each of the 3 antiretrovirals (LPV/RTV/TFV) in monthly dosing. The apparent half-life for each drug in TLC-ART 101 ranged from 50-300 hours and was consistent among age groups. The equivalent-dose estimates, based on the weight and metabolic scaling among age groups, were 0.65 to 15.6 mg for LPV, 0.34 to 4.1 mg RTV, and 0.57 to 9.2 mg TFV (~12-24 fold across age bands). Furthermore, possible DDI effects on LPV pharmacokinetics by RTV, which had been observed in NHPs during chronic dosing of TLC-ART 101, were not predicted by the models with the current dosages in humans.
Conclusion: We developed a novel PBPK modeling approach that accounts for anatomical, physiological and enzymatic differences between species and age bands, including DDI assessments due to LPV- RTV. This integrated PBPK model may inform dose selection for clinical evaluation of long-acting HIV drug combinations such as TLC-ART 101, thereby accelerating pediatric access to long-acting treatments. To our knowledge, this drug-combination PBPK model is the first to demonstrate adaptability for multiple drugs as synchronized injections, integrating age-specific physiologic parameters.
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948 Bone Mineral Density in Children With HIV-1 Receiving TAF-Based Antiretroviral Therapy

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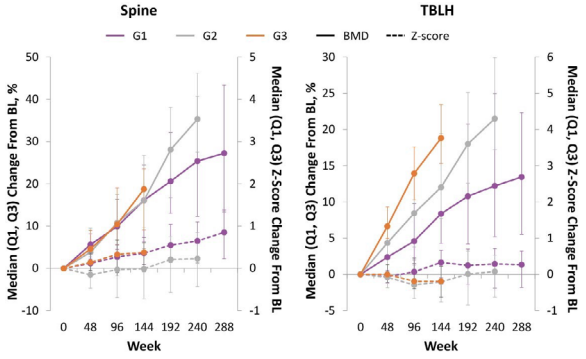
Background: Some antiretroviral agents, including tenofovir (TFV), may negatively impact bone health. Tenofovir alafenamide (TAF) results in lower TFV plasma levels than tenofovir disoproxil fumarate, and thus has a better bone safety profile. We examined the medium/long-term treatment effects of TAF-based antiretroviral therapies (ARTs) on bone safety in children and adolescents with HIV aged ≥2 y and weighing ≥14 kg.
Methods: Data from two open-label, multicohort studies including ART-naïve or -experienced pediatric participants with HIV, treated with emtricitabine/TAF-containing ARTs, were pooled by age–weight band: Group (G)1: 12–<18 y, ≥35 kg; G2: 6–<12 y, 25–<35 kg; G3: ≥2 y, 14–<25 kg. Bone mineral density (BMD) was assessed using dual-energy X-ray absorptiometry of the spine and total body less head (TBLH) and compared with measurements from individuals without HIV using height–age (HA)–adjusted BMD Z-scores.
Results: Overall, 169 participants were treated (G1=78; G2=61; G3=30). For G1, G2 and G3, median ages were 14, 10 and 7 y; 51%, 57% and 63% were female; 72%, 67% and 87% were Black; and 18%, 8% and 3% were Hispanic, respectively. At baseline (BL), the percentage of participants with HIV RNA <50 copies/mL were 35% (G1) and 100% (G2 and G3). Spine and TBLH BMD increased over time (Figure). Spine and TBLH HA-adjusted BMD z-scores also increased from BL, except for a decrease in TBLH HA z-score in female participants in G3. A >4% decrease from BL in spine BMD was observed in 0/44 children in G1 at Week (W) 288, 1/33 in G2 at W240 and 0/25 in G3 at W144. At those timepoints, no participant in any group had a decrease >4% from BL in TBLH BMD. We did not observe any significant correlations between change in HA-adjusted z-score of spine or TBLH BMD at W48 versus TFV maximum plasma concentration or area under the concentration–time curve derived from a noncompartmental analysis over the dosing interval for any of the groups.
Conclusion: These medium/long-term BMD data are reassuring regarding bone safety of TAF-containing ARTs in pediatric participants weighing ≥14 kg. Increases in spine and TBLH BMD were consistent with those observed in children and adolescents without HIV, suggesting that TAF-containing ARTs do not compromise the expected bone accrual in pediatric populations.



Spine and TBLH BMD and HA-Adjusted Z-Scores
G1: 12–<18 y, ≥35 kg; **G2:** 6–<12 y, 25–<35 kg; **G3:** ≥2 y, 14–<25 kg
BL, baseline; BMD, bone mineral density; G, group; HA, height–age; Q, quartile; TBLH, total body less head

949 IMPAACT 2017 Adolescent/Parent Experiences With LA Cabotegravir Plus Rilpivirine for HIV Treatment

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Background: The ongoing More Options for Children and Adolescents Study (MOCHA; IMPAACT 2017; Clinicaltrials.gov NCT03497676) is the first to examine use of long-acting injectable (LAI) cabotegravir (CAB) plus rilpivirine (RPV) in virologically suppressed adolescents, 12 to <18 years of age, with HIV-1. Little is known about the acceptability of this treatment approach for adolescents, including whether it changes over time.

Methods: Participants switched from pre-study antiretrovirals to adolescent/adult dosing of CAB-LAI plus RPV-LAI after oral lead-in MOCHA Cohort 2. They were queried about their preferred choice of treatment (every 8-week LAI versus daily oral) and the reasons for this preference at 8- (n=142), 24- (n=141), and 48-weeks (n=115). Reasons for the preferred regimen were recorded verbatim and coded thematically by the study team. In-depth interviews (IDIs) were conducted by phone with 8 U.S.-based adolescents and separately with 4 parents after at least 24 weeks on study to provide insight into participants' experiences. Interview transcripts were coded and analyzed using the Consolidated Framework for Implementation Research.

Results: Overall, 144 adolescents enrolled in Cohort 2 at 18 sites in 5 countries. All but 4/142 (3%) participants at week 8 and 2/141 (1%) at week 24 stated that they preferred injectable LA medicines over daily orals. The primary themes for preferring LAI were: convenience and burden reduction. The most prominent components of burden reduction were the decrease in adherence-related stress and increased privacy. IDI participants expanded on these themes. All interviewees (adolescents and parents) favored LAI and reported convenience as a driving factor for them/their child to continue the LAI regimen. Having their medical team's support and monitoring for adherence to each LAI dose was repeatedly raised as a key reducer of perceived treatment burden, as was freedom from the daily reminder of HIV diagnosis seen as inherent to oral treatment. A surprising element of the IDI data was feedback that several adolescents had not understood vital elements of the LAI process such as the location of the injections needing to be in the buttocks, despite having completed informed consent/assent counseling.

Conclusion: Feedback from adolescents receiving LAI antiretrovirals for up to 48 weeks in the MOCHA study has been favorable thus far. IDIs data suggest that structured and developmentally tailored counseling may be essential to LAI implementation for adolescents.

950 Cabotegravir PopPK Analysis of Adults & Adolescents Living With/At Risk for HIV Receiving PrEP

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Background: Cabotegravir (CAB) is an integrase strand transfer inhibitor approved in adults and adolescents (12 to <18 years) weighing >35kg as long-acting injectable (LAI) HIV-1 prevention, and for treatment in combination with rilpivirine. An existing CAB population pharmacokinetic (PopPK) model was limited to adult PK (Han 2023). We set out to extend and optimize that existing PopPK model for adolescents (12 to <18 years) by incorporating available adolescent PK data from the IMPAACT 2017/MOCHA (NCT03497676) and HPTN 083/084-01(NCT04824131/ NCT02720094) clinical trials.

Methods: PK data following oral lead-in (30mg once daily, QD for at least 4 weeks) and LAI treatment (an initial 600mg 4-week loading dose followed by 400mg Q4W or 600mg Q8W) from 147 adolescents with HIV (IMPAACT 2017) and 62 HIV-negative adolescents (HPTN 083/084-01) with weight of 35.2-168 kg, body mass index (BMI) of 15.8-51.6 kg/m² and 12 to 17 years were added to adult data (n=1647). The PopPK model parameters were re-estimated based on this pooled dataset using NONMEM 7.3. The updated PopPK model was used to simulate PK profiles for CAB for Q4W and Q8W regimens in adolescents and adults. Individual exposure metrics (e.g. C_{tau},ss) were derived and compared between adolescents and adults.

Results: A 2-compartment model with 1st-order absorption adequately described CAB PK in adolescents and adults. No new covariates were identified as compared to the adult PopPK model. Weight and smoking status were significant determinants of CL/F, and only weight was a determinant of Vc/F, Vp/F, and Q/F. Needle length, female sex, splitting of the injection, and BMI were significant determinants of KA IM (absorption rate for LAI). Adolescents had CAB LA exposure at steady state (C_{tau},ss median, 5th-95th: 2.36, 0.849-4.13 µg/mL for 600mg Q8W) comparable to that of adults (C_{tau},ss : 1.91, 0.786-3.33 µg/mL for Q8W), with their exposure levels falling within the same range across all dosing phases, and contained within the established efficacy and safety thresholds of 0.45 and 22.5µg/mL.

Conclusion: The addition of adolescent data to the adult PopPK dataset allowed expansion of the prior PopPK model down to 35 kg and optimization of predictions in adolescents. Given the similarity of CAB PK across adolescents and adults, same dosing regimens apply for adults and adolescents.

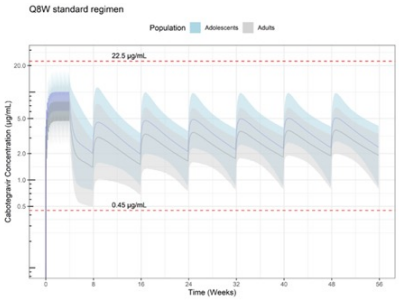

Figure. Simulated CAB concentration versus time following Q8W dosing regimen with oral lead-in by population. Red dashed lines: the efficacy (0.45 µg/mL) and safety thresholds (22.5 µg/mL). Shaded areas: the 90% PI. Solid lines: the simulated median CAB concentrations.

951 Expanded Cytotoxic T-Lymphocytes and NK Cell Subsets in Infants With Perinatal HIV

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Background: The nature of immune mechanisms that are important for HIV reservoir establishment or limiting reservoir size are poorly understood and may differ in infants compared to adults. However, immunological studies in pediatric cohorts are hindered by limited blood volume for sampling.

Methods: We investigated the immune landscape in infants with perinatal HIV from Maputo, Mozambique using multi-omic single cell analyses and 1 million PBMC. 4 HEI (HIV Exposed Infected), ART-naïve infants with plasma virus load (VL) between 5.2 and 7 logs were evaluated along with 3 HEU (HIV Exposed Uninfected) infants. Cryopreserved PBMC from blood samples collected at 1 mo of age were thawed and cultured with or without anti-CD3 and anti-CD28 Abs for 16-18 hr across 3 independent experiments. After culture, cells were labeled with TotalSeq-C universal cocktail Abs (Biolegend) for feature barcoding, followed by single cell capture using Chromium (10X Genomics). Libraries were generated for sequencing of 5' mRNA, surface protein, and V(D)J genes. Sequencing data was mapped and aligned to human reference genome via Cell Ranger (v3.1.2). Quality control, normalization, integration, clustering, and annotation were performed in R using dsb, Seurat, and Fastmnn. V(D)J was analyzed with scRepertoire.

Results: mRNA data generated 30 cell clusters which were manually annotated using a combination of gene and protein expression. Two distinct clusters were identified only in HEI infants: an NK and CD8+ T cell populations. The unique NK subset was characterized with low expression of both CD56 and CD16 by gene and protein expression compared to 3 other NK cell clusters. Relative gene expression analysis revealed downregulation of NK receptors (KLRC2, KLRC4, KLRD1) and cytokines and cytolytic transcripts (IFNG, GNLY,

GZMA, PFN1) compared to other NK cells, suggesting reduced functional capacity. The enriched CD8+ T cell population in HEI constituted 8% of cells analyzed per donor (median, IQR 1.4-17.4) compared to 0.1% of cells from HEU and V(D)J analysis showed clonal hyperexpansion in this cluster only. These cells were characterized as cytotoxic T lymphocytes (CTL) effectors based on NK-like transcriptomes and high expression of CD57, a marker of terminal differentiation. CTL also expressed FCG3RA/CD16 suggesting potential for ADCC function.

Conclusion: Perinatal HIV infection is associated with expanded CTL and NK cells in early life that may play an important role in establishment or shaping of the HIV reservoir.

952 Distinct Populations of HIV-Infected Naive and Memory CD4+ T-Cell Clones in Children on ART

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Background: Pediatric HIV remains a major public health issue with 1.7 million children living with HIV (CLWH) worldwide. The key obstacle to cure HIV infection is a reservoir of latently infected CD4+ T cells that persist despite long-term antiretroviral therapy (ART). Although HIV primarily infects memory CD4+ T cells, recent studies suggest that naïve CD4+ T cells are a significant contributor to the reservoir. Here, we characterized HIV persistence in naïve CD4+ T cells from CLWH on long-term ART.

Methods: The cohort consisted of 8 children aged 5-11 years who initiated ART at a median of 4 weeks of age (range 0-39) with suppressed viremia for a median of 8.5 years. PBMC were sorted into naïve (CD45RO-CD28+CD27+CD95-CCR7+CD45RA+) and memory (CD45RO+ CD95+) CD4+ T cells. Multiple displacement amplification (MDA) was used to amplify single proviruses in a background of genomic DNA from the sorted cell populations. MDA products were screened for HIV-1 LTR, Psi (ψ) and the Rev response element (RRE) to identify proviruses that may be intact. Intactness was verified in one donor by full length sequencing. All HIV LTR+ MDA products were also used for HIV integration site analyses.

Results: HIV infected naïve CD4+ T cells were detected in all 8 children at a median frequency of 38 infected cells/million (range 6-231), a mean of 12-fold lower than the infected memory CD4+ T cells (median 464 cells/million, range 178-506). Of the 200 total proviruses detected in the naïve cells, 8 were predicted intact by amplification of Psi and RRE. HIV integration site analyses identified 8 clones of infected naïve T cells, but none of these harbored the predicted intact proviruses. In the child with the greatest depth of sampling (85 integration sites from naïve cells and 174 from memory cells), no matching integration sites were found across subsets, including from the largest infected clones ($p<10-4$).

Conclusion: Infected naïve CD4+ T cells in children can proliferate into cell clones, contain proviruses with integration sites distinct from those of infected memory CD4+ T cells, and contain intact proviruses. Our findings suggest that naïve and memory T cells may be distinct reservoirs for HIV infection and therefore may require different approaches for targeting and eradication.

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953 Persistent Viremia With vpr/tat-Deleted HIV and No T-Cell Responses to HLA-Predicted HIV Peptides

Alyssa R. Oldroyd[1], Mariam Aziz[2], Sheila Styrchak[1], Lennie Chen[3], Wenjie Deng[3], Melanie Gasper[1], Marley Bishop[1], Cooper James[1], Madelyn Shapiro[1], Ewelina Kosmider[4], Judith A. Guzman-Cottrill[5], Farah Cassis-Ghavami[6], James Mullins[3], Lisa Frenkel[1], Ana Gervassi[1]

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Background: Two children, P1 and P2, living with HIV have persistent low-level viremia (LLV) despite adherence to ART documented by directly-observed-therapy and/or therapeutic drug monitoring. We hypothesized that their persistent viremia was due to clones of HIV-infected cells harboring HIV epitopes that escaped immune surveillance.

Methods: Plasma HIV RNA was monitored. Blood RNA and DNA from P1 over 7 years and P2 over 6 years was used to generate HIV sequences (env, pol, HIV 5' and 3'-half and 3Kb central region genomes), to determine HIV integration sites (HIVIS), and to evaluate immunologic biomarkers and HIV-specific immune responses.

Results: Plasma HIV RNA levels ranged from 79-9176c/mL in P1 and 440-15600c/mL in P2; with levels decreasing over time although neither had specimens with undetectable viral loads. No drug resistance was detected in P1, and no novel mutations were detected in 73 single-genome-sequences (SGS) from P2 after immigration to the USA. C2V5 env SGS from P1 and P2 revealed no evidence of HIV evolution over time. P1's 448 sequences and P2's 816 sequences revealed 69 and 175 unique indels in the vpr and/or tat1 sequences, with 447/448 (99.8%) and 809/816 (99.1%) genomes having defects in one or both genes. In contrast, 0% of vpr and 0.5% of tat1 genes were defective in 394 DNA sequences from 4 individuals matched for ART-suppression. Elevated immune biomarkers included C-reactive protein and myeloid-derived-suppressor-cells in P1. The largest HIV cell clones comprised 5% of P1's 235 and 3% of P2's 287 HIVIS. Interferon-gamma ELISpots with (1) non-escaped predicted HIV HLA-binding peptides (76 for P1 and 25 for P2), (2) HIV Gag, Pol, and Nef potential T-cell epitope peptide pools from the NIH and (3) control antigens, detected reactive T cells to control antigens, but no reactive T cells to HIV (1) or (2) in P1 or P2 across multiple timepoints.

Conclusion: Our data suggest that the persistent LLV in these two individuals is unlikely to have originated from proliferating HIV-infected clones or from ongoing HIV replication. Rather, their lack of HIV-specific T cell responses suggests that immune tolerance to HIV causes a failure to eliminate infected cells expressing HIV proteins. Furthermore, the near absence of intact vpr or tat1 and the high frequency of unique inactivating mutations in these genes suggests that ongoing selection maintains the cells with vpr- and tat1-deleted viruses, possibly by conferring resistance to apoptosis.

954 Proviral Landscape in Neonates With In Utero HIV-1 on Very Early ART in IMPAACT P1115

Soumia Bekka[1], Priya R. Khetan[2], Yufeng Liu[3], Adit Dhummakupt[3], Bryan S. Nelson[4], Camlin Tierney[4], Ellen G. Chadwick[5], Jennifer Jao[5], Yvonne Bryson[6], Anne Coletti[7], Nicol Nicodimus[8], Lynda Stranix-Chibanda[8], Guinevere Q. Lee[9], Stuart Ray[3], Deborah Persaud[3]

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Background: We studied the proviral landscape of neonates with in utero HIV-1 who initiated antiretroviral treatment (ART) within 48 hours of birth in the IMPAACT P1115 study.

Methods: 21 neonates with in utero HIV-1 in IMPAACT P1115 met criteria for near full-length single genome sequencing (nFLSGS) at either Step 1 (within 48 hours post-birth; N=16), Step 2 (7-18 days post-birth when infection was confirmed; N=17) or both (N=12). Of the 13 neonates excluded at either timepoint, 11 had low proviral DNA loads (<20 copies/10^6 PBMCs) and 2 had low sample volumes (<5 uL) insufficient for nFLSGS amplification. nFLSGS was performed using a standard input of HIV-1 DNA per neonate to ensure single proviral genome amplification. nFLSGS data were classified with HIVSeqinR as intact, defective, or hypermutated, and copy numbers were standardized and efficiency adjusted to c/10^6 PBMCs. The limit of detection was set to 0.5 copies per number of cells assayed. ART drug resistance was evaluated using the Stanford HIV Drug Resistance Database.

Results: In the 21 neonates analyzed, median $\log_{10}$ HIV-1 DNA load was 2.8 at Step 1 and 2.9 at Step 2 (median 15 days). nFLSGS examined 93 genomes at Step 1 and 111 genomes at Step 2 (median 6 genomes per neonate in median 50000 cells). At our sampling depth, we detected intact proviruses in 13/16 (81%) neonates at Step 1 and 14/17 (82%) at Step 2. Intact proviruses comprised a median of 50% of each neonate's observed genomes at Step 1 and 33% at Step 2. Median $\log_{10}$ intact proviral load was 2.0 at Step 1. Among the 12 neonates with data at both timepoints (median 14 days apart), intact proviruses shared >99.8% sequence identity. Defective and hypermutated proviruses were detected at either timepoint in 20/21 and 9/21 neonates. The K103N resistance mutation was detected in all intact proviruses at both timepoints for one neonate, confirmed with maternal genotyping. No other major resistance mutations were identified in the 21 neonates.

Conclusion: The proviral landscape at birth of neonates with in utero HIV-1 and quantifiable HIV-1 DNA includes a mix of intact, defective, and hypermutated proviruses, indicating in utero HIV-1 replication. Intact proviruses share >99.8% sequence identity through Step 2. These findings suggest early formation of abundant intact HIV-1 DNA populations, which could establish reservoirs that pose challenges to HIV-1 remission.

955 CMV Coinfection Drives T-Cell Differentiation but Not Reservoir Size Among Children With HIV

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Background: CMV co-infection is common among children living with HIV (CLWH), though its impact on HIV disease control is not clear. The objective of this study was to determine the impact of CMV co-infection on HIV reservoir size and T cell subset distribution among CLWH.

Methods: CLWH followed in the prospective, multicenter Canadian EPIC4 cohort from 2014-2018 were included if they were on cART for ≥ 1 year with sustained viral suppression (SVS)). CMV serostatus (IgG) was determined using ArchitectTM CMIA assay. HIV-1 reservoir size was estimated by measuring total HIV-1 DNA by PCR in unsorted peripheral blood mononuclear cells and inducible cell-free HIV-1 RNA in CD4+T cells using a prostration analog stimulation assay. For 65 participants, CD4+ and CD8+ naïve-memory-effector T cell subsets were examined using flow cytometry.

Results: Of 226 CLWH enrolled in EPIC4, 108 met sub-study inclusion criteria; of these, 82.4% were CMV+ at baseline. There were no significant differences in total HIV-1 DNA (median = 1.70 vs 1.71 $\log_{10}$ HIV DNA copies per 106 cells) or inducible cell-free HIV-1 RNA (median = 0.79 vs 0.60 $\log_{10}$ HIV RNA copies per 106 cells) between CMV+ and CMV- participants, both on univariate and multivariate analysis adjusting for age, age at treatment initiation, duration of SVS, and peak lifetime HIV viral load. However, while frequencies of total CD8+ T cells and CD8+ T central memory (TCM) cells were similar among CMV+ and CMV- children (39.7vs 31.8%, and 2.5 vs 2.9%, respectively), CMV+ children exhibited significantly lower frequencies of CD8+ T naïve (TN) cells (54.6 vs 70.9%, p = 0.003), and significantly higher frequencies of CD8+ T effector memory (TEM) cells (6.8 vs 4.6%, p = 0.047) and CD8+ T terminally differentiated effector (TEMRA) cells (19.5 vs 9.6%, p = 0.003). No differences in total, TN or TCM cell frequencies were observed in CD4+ T cells between CMV+ and CMV- participants, but CMV+ participants had a significantly higher frequency of CD4+ TEM cells (5.7 vs 3.7%, p = 0.005). This difference remained significant after adjustment for age, age at HIV treatment initiation, and age at HIV viral suppression.

Conclusion: CMV co-infection was not significantly associated with HIV reservoir size in CLWH, but significantly affected the naïve-memory-effector profile of CD4+ and CD8+ T cells. These results suggest that CMV co-infection may alter the differentiation and maturation of CD4+ and CD8+ T cells in CLWH independent of achievement of SVS.

956 Reservoir Size and Dynamics by Age at Virologic Suppression and Sex in Youth With Perinatal HIV-1

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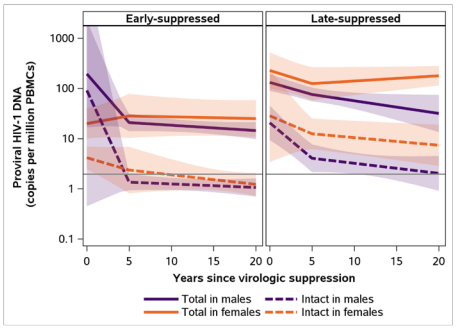
Background: Studies on HIV-1 reservoir size and dynamics in youth with perinatal HIV-1 with long-term viral suppression (VS) are limited.

Methods: We identified longitudinal peripheral blood mononuclear cells (PBMC) specimens among youth with perinatal HIV-1 in the PHACS AMP study who were early-suppressed (ES) at <1 year of age or late-suppressed (LS) at 1-5 years of age and maintained VS. LS were matched to ES by age at last specimen, percent without viral blips, and sex. HIV-1 reservoir size was assessed with the Intact Proviral DNA assay (IPDA). Data were summarized by age at VS, sex, and duration of VS. HIV-1 DNA slopes over follow-up were estimated using linear mixed-effects models.

Results: We included 11 ES (6 females, 5 males) and 15 LS (7 females, 8 males) with a median of 8 specimens per participant over a median of 17.3 years of VS. Median age at VS and duration of VS were 0.6 and 17.6 years for ES, and 2.7 and 16.5 years for LS. PBMCs were primarily collected from 5 to <15 years of VS. The median limit of detection for the IPDA with a median of 500,000 cells analyzed was 2 copies/million PBMCs. Total and intact proviruses were lower in ES compared to LS (Figure1). From 5 to <10 and 10 to <15 years of VS, median total HIV-1 DNA was 20.0 and 28.0 copies/million PBMCs in ES compared to 113.2 and 103.3 copies/million PBMCs in LS. Median intact HIV-1 DNA from 5 to <15 years of VS was undetectable in ES, and detectable at 6.3-6.4 copies/million PBMCs in LS. Median total HIV-1 DNA among ES females was lower from 5 to <10 years and higher from 10 to <15 years of VS compared to ES males. LS females had higher median total HIV-1 DNA from 5 to <15 years of VS compared to LS males. Median intact HIV-1 DNA was undetectable for both ES females and males. However, LS females had higher median intact HIV-1 DNA from 5 to <15 years of VS compared to LS males. Estimated mean slopes of total HIV-1 DNA from 5 to <15 years were similar by sex among ES but differed among LS: total HIV-1 DNA increased by 2.4% per year for females and decreased by 5.6% per year for males. Mean slopes of intact HIV-1 DNA for ES females, ES males, and LS males were uncertain due to a high percent of undetectable values, complicating comparisons by sex. Intact HIV-1 DNA decreased over VS for LS females.

Conclusion: We observed HIV-1 reservoir size to be smaller by age 5 years with early VS maintained through young adulthood. Among LS youth, we identified sex differences in the reservoir size with relevance to ART-free remission.

Figure1: Estimated total and intact HIV-1 DNA trajectories by age at virologic suppression and sex.



Note: Estimated means with 95% CI. Grey line=median limit of detection.
Abbreviations: PBMC=peripheral blood mononuclear cells

957 Latency Reversal Effects of TLR7 Agonist and HDACi in Long-Standing Perinatal HIV-1 Infection

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Background: Latency reversing agents (LRAs) such as TLR agonists and histone deacetylase inhibitors (HDACi) reactivate proviral latency in adults. We examined the LRA effects of the TLR7 agonist, GS-9670 singly and in combination with the HDACi, SAHA, in a cohort of children and young adults living with perinatal HIV-1 (CYALPH) to inform latency reversal strategies for this population.

Methods: Peripheral blood mononuclear cells (PBMCs) and purified CD4 T cells from a cohort of 8 CYALPH, median age 17.0[IQR, 16.7-20.3] yrs, with median virologic suppression of 13.3[8.2-16.3] yrs were stimulated ex-vivo with GS-9620 singly and in combination with SAHA for 96 hrs. Concomitant stimulation with PHA/PMA/Ionomycin (PPI) and DMSO were performed to assess proviral reactivation under maximal T cell stimulation and vehicle control. Proviral reactivation was determined by multiply spliced HIV-1 RNA (msRUPM) with the Tat/Rev Limiting Dilution Assay. Total, intact and defective proviral HIV-1 DNA was quantified by multiplex ddPCR, cell-surface marker and histone acetylation expression by flow cytometry, culture supernatant for 9 cytokines with the MSD platform and p24 by SIMOA.

Results: The median total HIV-1 DNA load was 262[IQR, 52-485.2] copies per million(cpm) CD4s; the 5 subtype B participants had 13[0-26.1] intact cpm, 4.96% of total HIV-1 DNA. PBMCs stimulated with GS-9620 plus SAHA showed reactivation in only 2 of 6 participants. In CD4 T cells, PPI stimulation increased msRUPM in 6[75%] participants to 13.2[7.7-20.4]; with DMSO, msRUPM was

6.04[3.4-10.6]. With GS-9620 and SAHA singly, 5[63%] and 4[50%] participants exhibited reactivation, respectively. With dual stimulation, reactivation was detected in 5 participants. Median msRUPM fold change to DMSO was 1.5[0.97-2.34] for PPI, 1.53[0.78-1.93] for GS-9620, 0.76[0-1.52] for SAHA, and 1.22[0.76-1.56] for GS-9620 plus SAHA. One participant, durably suppressed since infancy, had no reactivation, and one participant displayed inhibition of ms-transcripts under all conditions. PPI stimulation was associated with upregulation of CD69, CD25, and HLA-DR whereas only CD69 was upregulated in SAHA conditions. Secreted IL-6 was higher after GS-9620 stimulation compared to DMSO. Histone acetylation effects were seen in 5 participants after SAHA treatment.
Conclusion: These findings suggest that pediatric reservoirs can be reactivated with innate immune enhancers, such as TLR7 agonist and HDACi, with implications for use as therapeutics to purge HIV-1 reservoirs.

958 Predictive Markers for Sustained Viral Suppression on Dual bNAbs During ART Interruption in Children

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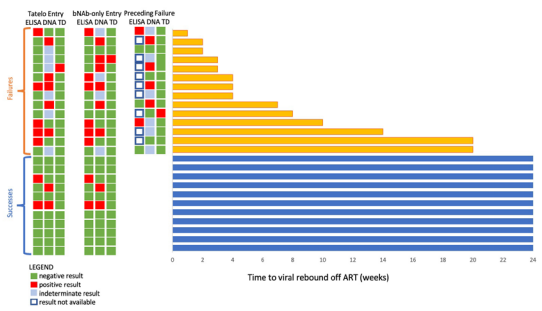
Background: Phenotyping to identify susceptibility to broadly neutralizing antibodies (bNAbs) is costly and logistically challenging, and simple clinical markers to predict bNAb treatment success for children are needed. The combination of a negative qualitative HIV DNA and negative enzyme immunosorbent assay (EIA) at study entry was previously reported to correlate with success in the Tatelo Study in Botswana. We now report findings for additional biomarker combinations, at entry to and during the bNAb-only step of the study.
Methods: Twenty-five children received up to 24 weeks of bNAb-only treatment (VRC01LS+10-1074) following ART interruption. HIV qualitative DNA and HIV RNA were performed every 1-2 weeks and EIA every 4-8 weeks. Using Fisher's exact test we compared the proportion of infants who remained virally suppressed to < 400 copies/mL (successes) to those with detectable virus by assay type.
Results: During the bNAb-only step of Tatelo there were a median of 8 qualitative HIV DNA measurements, 12 HIV-1 RNA "target detection" measurements, and 4 EIA measurements per participant available for analysis. At bNAb-only step entry, 13/25 (52%) had negative qualitative DNA and 17/25 (68%) had negative EIA, and 10/25 (40%) were negative for both. Nine of the 13 (69%) with negative qualitative DNA succeeded compared with 2/12 (17%) with positive or indeterminate qualitative DNA (p=0.02). Nine of the 17 (53%) with negative EIA succeeded compared with 2/8 (25%) with positive EIA (p=0.23). Combining biomarkers, 8/10 (80%) who were negative/negative at bNAb-only entry succeeded, compared with 3/15 (20%) with any other pattern (p=0.005); all 8 successes (and no failures) were also negative/negative at study entry (the bNAb+ART overlap step), as previously reported. HIV-1 RNA "target detection" was below the assay limit in all but one participant at the start of the bNAb-only step. In the visit immediately prior to any viral rebound, target detection occurred in only 1/14 (7%) participants (Figure 1). No marker or combination of markers reliably changed in the 3 visits prior to rebound.
Conclusion: Negative qualitative DNA, and especially negative/negative DNA and EIA, at start of bNAb-only treatment predicted maintenance of viral suppression among children on dual bNAbs. HIV-1 RNA target detection below the assay limit did not prove to be a predictive biomarker, and no biomarker combination was clinically useful in the visits preceding failure.

Figure 1: bNAb treatment success and biomarker patterns at study entry (ART+ bNAbs) and start of bNAb-only step in the Tatelo Study, Botswana



959 High Proportion of False-Positive HIV Results With Point-of-Care Birth Testing in Botswana

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Background: As countries in Sub-Saharan Africa move toward rollout of point-of-care testing (POCT), risk for false positive testing and pathways to make accurate HIV diagnoses need to be understood.
Methods: The Moso Study identified newborns at high risk of HIV acquisition at 35 delivery facilities in Botswana. High-risk status was defined primarily (but not exclusively) as limited maternal ART duration in pregnancy. HIV testing was performed using the Cepheid Xpert® HIV-1 qualitative POCT platform, with Roche CAP/CTM HIV-1 qualitative confirmation for those testing positive. Further testing with HIV-1 RNA quantification and droplet digital polymerase chain reaction (ddPCR) was conducted for discordant results. Subsequent 6-week HIV test results for infants with negative birth POCT were abstracted from national electronic laboratory/medical records.
Results: From July 2022–August 2023, using 6 Xpert® machines housed in close proximity to the 35 delivery sites, 1479 high-risk newborns were tested for HIV with POCT at a median of 21 hours of life (range 0, 158 hours). Thirty-one newborns (2%) had initial positive results, but only 11 (39%) were confirmed positive by Roche CAP/CTM testing, for an overall vertical transmission rate of 0.7% in high-risk neonates. The 20 (1.4%) false positives were further evaluated by HIV-1 RNA testing (all undetectable < 40 copies/mL); ddPCR testing was performed on 18 (90%) false positive samples with no target detected in any. Follow-up testing of false positives to date has remained negative. Of the 20 initial false positive samples, 18 (90%) were tested on just 1 of the 6 Xpert® machines; this machine was removed from service and is under evaluation, without an identifiable cause for the false positive results (operator error deemed unlikely). Excluding all 453 samples tested on this machine yields a false positivity rate of 0.2% (2/1026), or 15% (2/13) of all positive results. The median cycle threshold (CT) value for false positive results on the Xpert® platform was 39.2 (range 34.5, 43.9) compared with a median of 32.9 (range 24.2, 41.0) for true positives, indicating some overlap between groups (Figure 1).
Conclusion: The Xpert® POCT platform offers affordable and easily implementable birth testing for HIV, but false positive testing may occur. High CT values provide an initial indication of a possible false positive result, but all positive testing must be confirmed by either HIV-1 RNA testing, HIV-1 DNA testing, or both.

Figure 1: Cycle threshold values at birth using Cepheid Xpert® HIV-1 qualitative assay

960 Rapid Antiretroviral Therapy Initiation Following Point-of-Care Early Infant Diagnosis in Uganda

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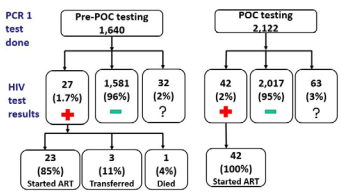
Background: Uganda Ministry of Health recommends a first HIV DNA-PCR test at 4-6 weeks for early infant diagnosis (EID) of HIV-exposed infants (HEIs), immediate results return and initiation of antiretroviral therapy (ART) for infants with HIV infection. In 2019, MOH introduced point-of-care (POC) whole-blood EID testing in 33 health facilities and scaled up to 133 in 2020. We assessed turnaround time for test results and ART linkage before and after implementation of POC testing.
Methods: We evaluated EID register data for HEI at 10 health facilities with POC and minimum EID testing volume of 12 infants per month from 2018-2021. At each facility, we abstracted data for 12 months before and after POC rollout. We compared time to sample collection, results receipt, and ART initiation between periods using medians, Wilcoxon rank-sum, and log-rank tests.
Results: Data for 4,004 HEI were extracted, including 1,688 (42%) pre-POC and 2,316 (58%) during POC. Ninety-four percent of infants (3,762/4,004) had a first EID test. Median age at sample collection was 44 (IQR 38-52) days pre-POC and 42 (IQR 38-52) days during POC (p<0.001). Of 3,762 HEIs tested, 3,667 (97%) had test results. For infants with HIV infection (n=69), median age at sample collection was 92 (IQR 45-120) days pre-POC and 127 (IQR 74-206) days during POC (p=0.03). For all infants, median days from sample collection to results receipt by infants' caregivers were 29 (IQR 16-54) pre-POC and 1 (IQR 0-28) during POC (p<0.001); among infants with HIV infection, median days were 22 (IQR 4-30) pre-POC and 0 (0-3) during POC (p<0.001). Pre-POC, 0% (0/23) infants with HIV infection started ART on the sample collection day compared to 40% (17/42) during POC; ART linkage by 7 days after HIV diagnosis was 78% (21/27) pre-POC and 95% (40/42) during POC (p<0.001).
Conclusion: POC testing improved EID results turnaround time and ART initiation for infants with HIV infection. Later age at testing among infants diagnosed with HIV suggests missed opportunities in identifying HIV-exposed infants. While POC expansion could further improve ART linkage and loss to follow-up, there's need to examine barriers surrounding the POC target of initiating ART on the sample collection day.



961 Resistance in Young Children Newly-Diagnosed With HIV in Western Cape, South Africa

Kim Anderson[1], Gert U. van Zyl[2], Nei-Yuan Hsiao[1], Vanessa Mudaly[3], Jacqueline Voget[3], Alexa Heekes[1], Emma Kalk[1], Florence Phelanyane[3], Andrew Boulle[1], Gayathri Sridhar[4], Leigh Ragone[4], Vani Vannappagari[4], Mary-Ann Davies[1]
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Background: Pretreatment drug resistance among children living with HIV (CLHIV) can potentially compromise antiretroviral therapy (ART) effectiveness. Drug resistant HIV may be directly transmitted during vertical acquisition or resistance may be acquired in infants with HIV following exposure to antiretrovirals consumed through breastfeeding or administered as prophylaxis.
Methods: We performed resistance testing in young CLHIV (age <3 years) newly diagnosed with HIV in Western Cape, South Africa (July 2021 to October 2022) who either (1) acquired HIV via possible breastfeeding transmission from mothers who received ART (any regimen) during pregnancy/postpartum and/or (2) were exposed to protease inhibitors (PIs) or integrase strand transfer inhibitors (INSTIs) in utero. Possible breastfeeding transmission was defined as a positive HIV-PCR test at age >28 days, which occurred after a previous negative HIV-PCR test. We limited mutations included to those recommended for surveillance of transmitted drug resistance.
Results: We included 135 newly diagnosed CLHIV for resistance testing, of whom 91% (123) had possible breastfeeding transmission. Most mothers started ART before pregnancy (77%) and were exposed to ≥3 classes of ART prior to infant diagnosis (66%). Overall, 58% of CLHIV (78/135) had resistance mutations detected and 15% of those with mutations (12/78) had mutations to more than one class. Non-nucleoside reverse transcriptase inhibitor (NNRTI)-associated mutations were common (73/78; 94%). Nucleoside reverse transcriptase inhibitor-, INSTI- and PI-associated mutations were found in 18% (14/78), 3% (2/78) and 1% (1/78) of CLHIV with mutations, respectively. One child with breastfeeding transmission of HIV, had high-level INSTI and NNRTI resistance detected at age 18 months at HIV diagnosis (E138K, G118R and K103N mutations). The mother had changed from efavirenz- to dolutegravir-based ART 13 months after delivery.
Conclusion: NNRTI-associated mutations are common and may be transmitted or arise from exposure to NNRTIs as prophylaxis or in breastmilk. Dolutegravir is the preferred first-line treatment for both adults and CLHIV older than 4 weeks and very low INSTI resistance levels have been observed in adults, but limited data exist on genotyping the integrase region in CLHIV. The prevalence of pretreatment INSTI resistance in CLHIV is likely to be very small but future surveillance is necessary. There is a need for further, longitudinal studies with paired mother-infant resistance results.

Table: Mutations detected in children at the time of HIV diagnosis (frequencies in parentheses)

NNRTI-associated mutations (n=135 NNRTI sequences)
K101E (6), K103N (54), K103S (3), V106A (1), V106M (8), Y181C (2), Y188H (1), Y188L (3), G190A (8), G190E (1), P225H (14)
NRTI-associated mutations (n=135 NRTI sequences)
D67N (2), T69D (1), K70E (2), M184V (7), L210W (1), T215D (1), K219Q (2)
PI-associated mutations (n=135 protease sequences)
L90M (1)
INSTI-associated mutations (n=122 INSTI sequences)
T97A (1), G118R (1), E138K (1)

Abbreviations: NNRTI non-nucleoside reverse transcriptase inhibitor, NRTI nucleoside reverse transcriptase inhibitor, PI protease inhibitor, INSTI integrase strand transfer inhibitor

962 CMV Viraemia Is Associated With Mortality Among Children With HIV Starting ART in Sub-Saharan Africa

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Background: Cytomegalovirus (CMV) co-infection is associated with mortality in adults with HIV, but the association between CMV viraemia and mortality in children with HIV is uncertain.
Methods: In 497 children enrolled in the ARROW trial (registry number ISRCTN24791884) in Uganda and Zimbabwe, CMV was quantified using real-

time polymerase chain reaction (PCR) at antiretroviral therapy (ART) initiation, and after 12 and 84 weeks post-initiation in a case-cohort design. Associations between CMV viraemia and mortality were evaluated using multivariable models, adjusting for HIV viral load, CD4 percentage and inflammatory biomarkers.

Results: CMV viraemia was associated with mortality, but the relationship differed by country and assay type. In Zimbabwe, where a more sensitive assay led to a high prevalence of detectable CMV (73%), each log rise in CMV viral load was associated with 2-fold higher mortality (adjusted hazard ratio (aHR) 2.35; 95% confidence interval (CI) 1.34, 4.12). In Uganda, where the assay sensitivity was lower, children with detectable CMV viraemia (26%) had almost 3-fold higher mortality than children without detectable CMV (aHR 2.86; 95%CI 1.02, 8.33).

Conclusion: CMV viraemia at the time of ART initiation is associated with mortality in children with HIV in sub-Saharan Africa, independent of HIV viral load, immunosuppression and immune activation. Future studies should evaluate whether suppressing CMV viraemia reduces mortality in children with HIV.

963 Sex Differences in Growth Trajectories Between Early-Treated Infants With HIV and Controls

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Background: Perinatally-acquired HIV infection is associated with increased risk of postnatal growth deficits which are only partially corrected with antiretroviral therapy (ART). Studies of sex differences in immune recovery and virologic response to ART among infants with perinatally acquired HIV (IHIV) have reported conflicting results. Here we investigate the role of sex in modifying the growth trajectories of IHIV who started ART at an early age.

Methods: As part of an early ART trial conducted in Johannesburg, South Africa (2015-2018), 116 IVHIV diagnosed within 48 hours of birth initiated ART as early as possible, consisting of nevirapine (switched to lopinavir-ritonavir >= 42 weeks postmenstrual age) lamivudine, and zidovudine (switched to abacavir at 3 months). Eighty infants born to mothers living with HIV but found to be uninfected (IHEU) were enrolled as controls, receiving daily nevirapine for 6 weeks, and twice-daily zidovudine added if high risk. Both groups were followed prospectively through 48 weeks and anthropometric parameters collected. Age and sex adjusted Z-scores for weight (WAZ) and length (LAZ) were compared between IHIV and IHEU, as well as stratified by sex. Generalized linear models were used to describe growth trajectories and main and interactive effects.

Results: Just under half the infants were male (48.5%), similar proportions in IHIV and IHEU. The deficits in growth through 48 weeks associated with HIV status were most marked in female infants (Figure). Mean WAZ (β= -0.51 [standard error,0.22], p=0.02) and LAZ (β= -0.50 [0.21], p=0.02) were lower in female IHIV than in female IHEU overall (Figure). In contrast, trajectories of WAZ (β= -0.21 [0.30], p=0.48) and LAZ (β= 0.03 [0.32], p=0.92) between male IHIV and male IHEU were similar. Combining the two groups, males had lower WAZ than females over the 48 week period. Males also had lower LAZ than females, with significant differences at 12 and 24 weeks (-1.84 [0.22] vs -1.34[0.12], p=0.04 and -1.53 [0.19] vs -1.01 [0.12], p=0.02). The mean WAZ and LAZ in neither group attained WHO standards by 48 weeks.

Conclusion: Deficits in WAZ and LAZ in IHIV with early ART compared to IHEU were greater in girls. This pattern was observed despite boys having consistently lower anthropometric parameters than girls in both groups. Factors responsible for this sex difference are not clear, but early ART initiation and/or perinatal infection appears have a differential impact on growth according to sex.

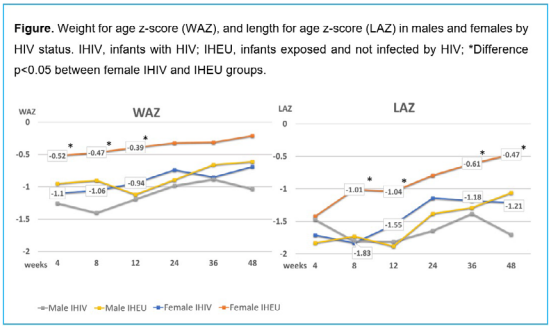

Figure. Weight for age z-score (WAZ), and length for age z-score (LAZ) in males and females by HIV status. IHIV, infants with HIV; IHEU, infants exposed and not infected by HIV; *Difference p<0.05 between female IHIV and IHEU groups.

964 1 in 5 Sub-Saharan Infants Switches From Undetectable to Detectable HIV Viral Load During Follow-Up

Sheila Fernández-Luis[1], Sara Dominguez-Rodriguez[1], Louise Kuhn[2], Mark F. Cotton[3], Carlo Giaquinto[4], Paolo Rossi[5], Anita Janse van Rensburg[3], Avy Violari[6], Maria Grazia Lain[7], Elisa López-Varela[8], Mariam Sylla[9], Pauline Amugue[10], Pablo Rojo[1], **Alfredo Tagarro**[1], for epiical

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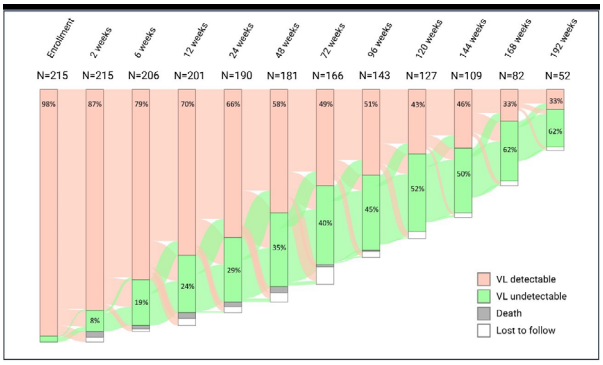
Background: The initiation of antiretroviral therapy (ART) early in HIV infection results in a rapid decline in viral load (VL) and a small HIV reservoir. However, children treated early face long-term challenges to maintaining viral suppression. We studied the longer-term VL dynamics of a cohort of early treated children.

Methods: From May 2018 to May 2021, we enrolled infants initiating ART within 6 months of birth and within 3 months of diagnosis in six sites from 3 African countries. We represented VL status transitions with Sankey plot.

Results: Of 215 infants enrolled, the median age at HIV diagnosis was 31 days [0; 48]. The median age at ART initiation was 34 days [26;73]. The most common starting ART regimen was Lamivudine + Abacavir + Lopinavir/ritonavir in 140/215 (65%), 10% switched to DTG in 2021. Median VL at ART initiation was 4.9 log_{10} copies/mL [3.6;5.8]. Median follow-up duration at analysis was 34.0 months [IQR, 16.3;44.1]. Twenty-five children (11.6%) died, 51/215 (23.7%) completed 4 years of follow-up, 76/215 (35.3%) remained in care and 63/215 (29.3%) were lost to follow-up. A total of 58.0% and 51.1% of children had detectable VL at 1 year and 2 years year of follow-up, respectively. Ninety-eight of 193 infants (50.7%) achieved virologic suppression at some point during the study. Among these, the median time to suppression (ART initiation to two consecutives undetectable VLs) was 5.5 months [IQR, 2.1-15.6]. Over time, the proportion of children with undetectable VLs increased, but a median of 19.1% switched from undetectable to undetectable VLs during follow-up visits. Notably, most patients who died or were lost to follow-up had detectable VLs in previous visits.

Conclusion: Undetectable VL increased across time, but oscillations between undetectable and detectable VL in the long term were frequent. This underscores the need for further investigations to assess the potential clinical implications of these fluctuations on patient outcomes and the size of the viral reservoir.



965 Causes of Death After Early ART in Infants Living With HIV From 3 Sub-Saharan African Countries

Alfredo Tagarro[1], Sheila Fernández-Luis[1], Sara Dominguez-Rodriguez[1], Alvaro Ballesteros[1], Louise Kuhn[2], Mark F. Cotton[3], Carlo Giaquinto[4], Paolo Rossi[5], Moira Spyer[6], Kennedy Otwombe[7], Osee Behuhuma[8], Paula Vaz[9], Caroline Foster[10], Pablo Rojo[1], for EPIICAL

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Background: Despite comprising only 4% of all positive people, children account for 15% of all HIV/AIDS-related deaths. Mortality unrelated to AIDS is also high in LMIC. We investigated causes of death, potential relationship with HIV infection, and associated factors in a cohort of early treated children.

Methods: From May 2018 to May 2021, we recruited infants who initiated ART within the first 6 months of life and within 3 months of diagnosis. Follow-up was 4 years. There were 6 study sites in South Africa, Mozambique and Mali. HIV/AIDS-related mortality was determined by an independent Endpoint Review Committee comprising three HIV Pediatric infectious disease specialists not directly involved in participant care. The experts assessed the relationship of each death to HIV advanced disease using available epidemiological, clinical, and laboratory data from the study database. Mortality risk factors were analyzed using a competing risk Cox multivariable regression model.

Results: Of 215 infants enrolled, the median age at HIV diagnosis was 31 days with ART initiation at a median age of 34 days [IQR 26.0;73.0]. Follow-up was 34.0 months [IQR 16.3;44.1]. Median VL at ART initiation was log 4.95 [IQR 3.58;5.82] copies/mL. Twenty-five infants (11.6%) died at a median age of 5.3 months [IQR 3.0;9.6]. The probability of death within the first year of ART initiation was 12% (95%CI 6-14), and after 2 and 3 years, 12% (95% CI, 8-17). The primary causes of death were pneumonia (36%), unknown (24%), tuberculosis (12%), malnutrition (8%), diarrhea (8%), sepsis (8%) and malaria (4%). Cause of death was assigned as likely HIV/AIDS-related in 8/25 (32%) of deaths. VL at ART initiation was significantly associated with all deaths (HIV/AIDS-related cause HR:3.0 (95%CI 1.3-7.1), p=0.014; unclear relation, HR:1.7 (95%CI 1.1-2.8), p=0.019). The more positive the CD4 slope, the lower the probability of death in HIV/AIDS-related (HR:0.7 (95%CI 0.5-1.0, p=0.067) or unrelated (HR:0.7 (95%CI 0.5-0.9), p=0.007). Patients from Mali had a higher probability of death from HIV/AIDS-unrelated causes , compared to those enrolled in South Africa (HR:13.8 [95%CI 1.92-98.8], p=0.009).

Conclusion: Mortality, both related with HIV/AIDS or probably unrelated, were associated with baseline VL and poor CD4 restoration. However, the 3-fold risk for high baseline VL and HIV/AIDS-related causes supports a strong biological effect of baseline VL along with a challenging social environment.

966 Usefulness of Clinical Signs for Tuberculosis Diagnosis in Infants Living With HIV With Pneumonia

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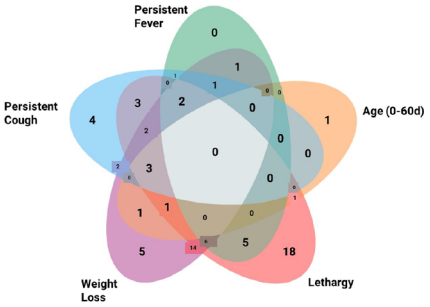
Background: Children living with HIV are at increased risk of tuberculosis (TB) morbidity and mortality. However, TB diagnosis remains challenging, particularly in infants who have paucibacillary disease and are more likely to have atypical clinical presentations. Consensus case definitions based on microbiological confirmation, signs/symptoms, chest radiograph features, TB exposure/immunological evidence of infection, and response to treatment have been proposed by Graham et al. to standardize the reporting of cases of intrathoracic tuberculosis. We evaluated the prevalence of the Graham clinical criteria (persistent cough, weight loss/failure to thrive, persistent unexplained fever or lethargy, neonatal pneumonia or hepatosplenomegaly) in relation to confirmed TB diagnosis in infants living with HIV hospitalized with severe pneumonia.

Methods: EMPIRICAL is a randomized clinical trial (#NCT03915366) funded by EDCTP (RIA2017MC-2013) investigating the impact of empirical treatment of cytomegalovirus and/or TB treatment on mortality in infants living with HIV hospitalized with severe pneumonia in six African countries. Infants with clinical or confirmed TB diagnoses are excluded from entry, as are infants with close TB contacts. At enrollment, stool and nasopharyngeal aspirates are collected for Xpert Ultra testing, and urine for lipoarabinomannan (LAM). TB culture was not performed. Infants enrolled between March 2020-July 2023 were included in this interim analysis.

Results: Laboratory-confirmed TB was present in 23% (114/496) infants; 96% (109/114) presented with >1 Graham clinical criteria and 71% (81/114) with >2. The distribution of patients with specific clinical criteria is shown in Figure 1. Persistent cough was the only criteria with a significant relative risk for laboratory-confirmed TB (1.51 [1.12;2.05], p=0.008). The presence of >1 clinical criteria had a sensitivity of 96%, specificity of 8.1%, positive predictive value (PPV) of 32.3%, and negative predictive value (NPV) of 80% for laboratory-confirmed TB. The presence of >2 criteria had sensitivity of 71.1%, specificity of 42.7%, PPV of 36.3% and NPV of 76.3%.

Conclusion: Despite excluding the patients most likely to have TB, almost one quarter of infants living with HIV hospitalized with severe pneumonia had Xpert or LAM-confirmed TB after study enrollment, and almost all of them had at least one of the signs/symptoms in the Graham clinical criteria, suggesting that these criteria are valid for this specific patient population.

Figure 1: Distribution of Graham clinical criteria in 114 infants living with HIV hospitalized with severe pneumonia having Xpert and/or LAM-confirmed TB



967 Influence of Childhood Adversity on Cardiovascular Health in HIV Youth in Uganda

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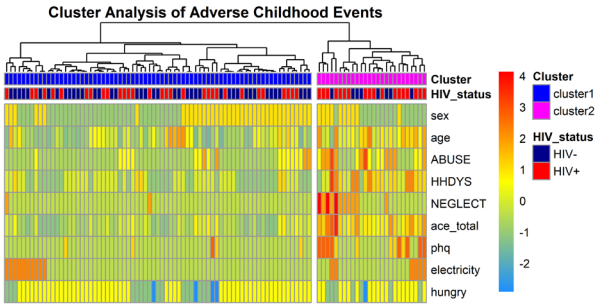
Background: Data suggest that adverse childhood experiences (ACEs) are associated with an increased risk of cardiovascular disease (CVD). However, little data exist on the effect of ACEs and health in children. We examined the relationship between ACEs and CVD risk factors in youth living with perinatally acquired HIV (YPHIV) in Uganda.

Methods: A prospective observational cohort study was performed in 49 YPHIV and 51 HIV- from 2017-2021 at the JCRC in Uganda at baseline and 96 weeks later. All participants were between 10-18 years of age. YPHIVs were on ART with HIV-1 RNA level ≤400 copies/mL. Mean common carotid artery intima-media thickness (IMT), pulse wave velocity (PWV), plasma and cellular markers of systemic inflammation and immune activation were evaluated at baseline and 96 weeks. The Adverse Childhood Experiences-International Questionnaire (ACEs), Patient Health Questionnaire-9 (PHQ-9) and socioeconomic questionnaires were administered, and ACEs sub scored of abuse, neglect and household dysfunction (HHDYS) were calculated. Hierarchical cluster analysis was performed to identify natural clusters of ACEs and socioeconomics.

Results: At baseline, median age was 12 years (IQR: 11-14), 52% were female. YPHIV were more likely to have a history of abuse, and higher ACE total scores (p=0.015). Two optimal clusters were derived from ACEs, PHQ-9 mean scores, and socioeconomic variables (figure 1). Compared to cluster 1, participants in cluster 2 had higher ACEs (p≤0.001 for all), and were more likely to have: HIV (69% vs 42%, p=0.019), higher levels of monocytes and T cell activation

(CD14+CD6- and CD14+CD16+% monocytes; CD8 expressing CD38 and HLA DR, p≤0.037); higher systolic blood pressure (p=0.040), and higher increases in PWV over 96 weeks (p=0.047). In mixed linear regression models adjusting for HIV status, age, gender, physical activity (met-kcal/hour), mean PHQ-9 score, monocytes, activated CD8 T cells, total ACE score (β=0.10) and HHDYS (β=-0.09) remained associated with a higher change in PWV over 96 weeks.

Conclusion: Findings suggest that ACEs may contribute to CVD risk in YPHIV in Uganda, even after adjusting for factors known to influence cardiovascular health. Early life stress may play an important role on inflammation and cardiovascular health in this setting. Further research is warranted to determine the impact of emotional events on physical outcomes in HIV, whether this is a potentially modifiable risk factor, and how to mitigate long-term consequences.



968 Changes in the Lipidome Are Associated With Immune Activation in Ugandan PHIV

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Background: Lipidomics, the analysis of the composition and concentrations of lipid classes and species, may provide greater mechanistic insight into the basis of cardiovascular disease (CVD). This study examined the changes in the lipidome and associations with immune activation in youth living with perinatally acquired HIV (PHIV).

Methods: The serum lipidome, including 850 different lipid species across 13 lipid classes, as well as the fatty acid composition of these molecules, was measured by direct infusion-tandem mass spectrometry from 100 ART-treated PHIV and 98 age- and sex-matched HIV- Ugandan children at baseline and 96 weeks. All participants were between 10-18 yrs of age. PHIVs had HIV-1 RNA level ≤50 c/mL. In addition, plasma markers of systemic inflammation (hsCRP, IL6), monocyte activation (sCD14 and sCD163), gut integrity and translocation (I-FABP and BDG) were measured by ELISA. T cell activation (expression of CD38 and HLA-DR on CD4+ and CD8+ T cells) was measured by flow cytometry. Comparisons of lipid concentrations between groups were evaluated using 2-sample t-test. Spearman correlations were used to assess correlations between changes in lipid concentration and immune activation.

Results: Overall, median age [IQR] was 12 years [11-14]; 52% were females. In PHIV, median CD4+ cell counts were 988 cells/μL, and 85% had viral load <50 copies/mL throughout the study. Total cholesterol, LDL, and HDL were similar between the groups, however, the concentrations of ceramides, diacylglycerols, free fatty acids, lysophysophatidylcholines and phosphatidylcholines, were significantly higher in PHIV (P≤0.03). A network figure highlights the associations between changes in lipid species concentrations and inflammatory biomarkers over 96 weeks with a correlation >|0.4|. Notable trends included the predominant association with increases in unsaturated triacylglycerols with increase in activated CD4+ and CD8+ T cells and in fungal translocation, and with decreases in sCD14 and IFAB.

Conclusion: Despite similar basic lipid panels as HIV-, virologically suppressed PHIV on ART have elevated lipid species that are known to be associated with CVD. Our network analysis identified that triacylglycerols with long and unsaturated acyl chains, previously shown to be associated with an increased risk of plaques in adults living with HIV, are associated with immune activation and fungal translocation. Further studies are warranted to determine whether these lipid species may serve as novel biomarkers.

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969 Activated Proinflammatory NK Cells Promote Atherogenesis in Adolescents w/ Perinatally Acquired HIV

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Background: Perinatally acquired HIV (PHIV) and lifelong antiretroviral therapy (ART) may alter the development and function of the immune system. Published literature and our preliminary data suggest reprogramming of innate immune cells may accelerate aging and increase the risk for future end-organ complications, including cardiovascular disease (CVD). Natural killer (NK) cells are a heterogeneous group of innate immune cells with divergent functions; little is known about the role of NK cells in HIV-associated atherogenesis.

Methods: In this cross-sectional study, using high dimensional flow cytometry, plasma biomarker profiling, and transcriptomics, we compared immune signatures in cryopreserved peripheral blood mononuclear cells and cardiovascular biomarkers in Ugandan adolescents with PHIV on ART (n=18), and age/sex-matched HIV-unexposed and uninfected adolescents (n=20). Statistical comparisons employed the Mann-Whitney U test, with significance at p< 0.05. We explored the connection between immune signatures and plasma biomarkers using the Pearson correlation coefficient.

Results: The median age was 14 years, and 50% were females and all PHIVs were virally suppressed (HIV1 RNA< 50c/mL). Among PHIVs, markers of activation (CD69, HLA-DR, NKp44), maturation and memory (CD57), and migration to inflamed tissue (CXCR3) were elevated in most NK subsets (based on CD56 and CD16 expression) compared to levels in HIV- (p<0.05 for all). Oxidized LDL (ox-LDL) levels were significantly lower in the plasma of PHIVs (p<0.05). Further, negative correlations were found between most of the activated NK subsets expressing chemokine receptor CCR5 and plasma ox-LDL among PHIVs (p<0.05 for all). Our in vitro studies confirmed increased uptake of ox-LDL by macrophages in the presence of activated NK cells (p<0.05). Bulk-RNA sequencing data revealed differential expression of genes associated with immune cell migration, cholesterol uptake into tissue, vascular remodeling, and enrichment of pathways associated with NK activation and epigenetic regulation in the PHIV group (p<0.05).

Conclusion: Our data demonstrate, for the first time, increased expression of several activated, mature NK subsets with the potential to home to vascular tissue and influence increased uptake of plasma ox-LDL into vessel wall macrophages and initiate atherogenesis in adolescents with PHIV. We are currently performing mechanistic and longitudinal studies to confirm these findings.

970 DNA Methylation Signatures of Inflammation in Youth Living With Perinatally-Acquired HIV

Stephanie Shiau[1], Sean Brummel[2], Jasmine Douglas[1], Francesca Zumpano[1], Michael J. Corley[3], Jennifer Jao[4], Murli Purswani[5], Kunjal Patel[2], Carmen Marsit[6], for the Pediatric HIV/AIDS Cohort Study (PHACS)
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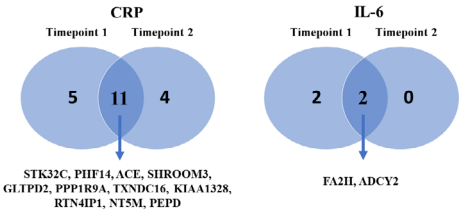
Background: Epigenetic modifications may highlight mechanisms through which HIV and antiretroviral therapy (ART) exposure during critical developmental periods affect biological pathways and disease risk. We examined if perinatally-acquired HIV is associated with genome-wide alterations in the DNA methylome by comparing youth living with perinatal HIV (YPHIV) and youth who are perinatally HIV-exposed uninfected (YPHEU) at two timepoints. Among YPHIV, we examined associations between viral load (VL), CD4 count, and markers of inflammation with genome-wide alterations in the DNA methylome.

Methods: 32 YPHIV and 7 YPHEU with peripheral blood mononuclear cell samples collected at two timepoints ≥3 years apart were selected from the US-based PHACS Adolescent Master Protocol. DNA methylation was assayed using the Illumina MethylationEPIC (850K) array. Using the limma package, we tested for differentially methylated (DM) CpG sites (FDR p-value <0.05 and ≥5% difference in methylation) between groups at each timepoint. 15 targeted genes identified from prior work (PMID: 31324826) were also assessed for DM CpG sites. Among YPHIV, genome-wide associations of cumulative VL,

cumulative CD4, C-reactive protein [CRP], and Interleukin-6 [IL-6] with DNA methylation were adjusted for ART type and age at ART initiation.
Results: Overall, median age was 11 and 17 years at timepoints 1 and 2, respectively. Groups were balanced by sex (51% male) and race/ethnicity (64% non-Hispanic Black). Genome-wide, there were no DM sites comparing YPHIV to YPHEU at either timepoint. For targeted genes, 1 CpG site on SPERT and 6 CpG sites on PSMB9 were DM at timepoint 1 comparing YPHIV to YPHEU. At timepoint 2, 10 CpG sites on PSMB9 and 4 CpG sites on EBF4 were DM comparing YPHIV to YPHEU. Among YPHIV, cumulative VL or CD4 count were not associated with any CpG sites. CRP was associated with 27 CpG sites (16 genes) at timepoint 1 and 19 CpG sites (15 genes) at timepoint 2, with 11 genes overlapping timepoints (Fig 1). IL-6 was associated with 6 CpG sites (4 genes) at timepoint 1 and 2 CpG sites (2 genes) at timepoint 2, with 2 genes overlapping timepoints (Fig 1).
Conclusion: Associations between markers of inflammation and epigenetic signatures among genes involved in blood pressure regulation, chronic kidney disease, and fatty acid processing were detected in YPHIV at two timepoints in childhood/adolescence. These genes may provide insight into inflammatory pathways contributing to HIV-associated chronic comorbidities among YPHIV.

Fig 1. Unique genes from CpG sites significantly associated with C-reactive protein [CRP] and Interleukin-6 [IL-6] identified from genome-wide analyses at two timepoints in youth living with perinatally-acquired HIV (YPHIV)



971 Young CPHIV Have Low Proinsulin to C-Peptide Ratios That Inversely Correlate With T-Cell Exhaustion

Wei Li[1], Emily Sims Emily Sims[1], Mussa Mwamzuka[32], Fatma Marshed[2], Aabid Ahmed[2], Alka Khaitan[1]
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Background: Persons with HIV have an increased risk of developing diabetes mellitus. The ratio of immature (Pro-insulin) relative to mature (C-peptide) insulin products (PI:C) in circulation serves as a biomarker of pancreatic β cell stress and predicts progression to type 1 or type 2 diabetes. In adults with HIV lower PI:C was observed in untreated persons compared to those on treatment or without HIV, suggesting immune dysregulation may preserve β cell function. Children with perinatal HIV (CPHIV) have higher rates of insulin resistance compared with healthy children, but whether β cell dysfunction contributes is unknown. We investigated PI:C ratios in CPHIV and their correlations with clinical and immune activation and exhaustion markers.
Methods: We quantified plasma levels of proinsulin (TECO intact proinsulin ELISA) and C-peptide (TOSOH immunoassay) in 200 Kenyan children who were HIV unexposed (HU) and CPHIV who were treatment naïve (ART-) or virally suppressed on treatment (ART+) aged 0-5 years ("0-5y" n=28 ART-, 21 ART+, 36 HU) and 5-20 years ("5-20y" n=41 ART-, 28 ART+, 46 HU). We calculated PI:C and assessed correlations with HIV viral load, CD4%, CD4:CD8, monocyte (sCD14, sCD163), T cell (CD38+HLA-DR+), and systemic (CRP, IL-6) activation markers and immune checkpoints (ICPs: PD-1, CD160, TIM3) on memory T cells. Mann-Whitney and Spearman's correlations were performed on GraphPad Prism.
Results: Compared to HU, 0-5y ART- had lower proinsulin levels (p=0.005) and PI:C (p=0.004), whereas ART+ trended toward lower PI:C (p=0.06). In 5-20y, both ART- and ART+ had a higher C-peptide level (p=0.006 and p=0.04), and ART+ had lower PI:C (p=0.04). In both age groups in CPHIV, PI:C did not correlate with age, viral load, CD4 levels, or activation markers. However, in 0-5y CPHIV PI:C inversely correlated with PD-1 (p=0.05, r=-0.46) and TIM3 (p=0.01, r=-0.40) on memory CD4 T cells as well as PD-1 (p=0.03, r=-0.51) and CD160 (p=0.04, r=-0.32) on memory CD8 T cells. There were no significant correlations between PI:C with ICPs in older CPHIV.
Conclusion: CPHIV had a lower PI:C compared with HU, stemming from lower proinsulin in younger CPHIV and higher C-peptide in older CPHIV. Clinical markers of HIV disease progression and inflammation were not associated with β cell stress in CPHIV. T cell exhaustion correlated with PI:C in younger CPHIV. Overall, our data show no evidence of β cell dysfunction in CPHIV and suggest ICPs may play a protective role against β cell stress in young CPHIV.
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972 Metabolomic Signature in Youth With Perinatally Acquired HIV and Non-Alcoholic Fatty Liver Disease

Silvia Chafino[1], Laura Tarancón-Diez[2], Jara Hurtado-Gallego[3], Sonia Alcolea[3], Antonio Olveira[3], María Luisa Navarro[2], Salvador Fernández-Arroyo[4], Consuelo Viladés[1], María Luisa Montes[5], Francesc Vidal[4], Joaquim Peraire[1], Anna Rull[1], Talia Sainz[5]
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Background: Non-alcoholic fatty liver disease (NAFLD) is characterized by accumulated fat producing hepatocellular inflammation and injury. Persistent immune activation and chronic inflammation in response to HIV infection may be factors underlying the development of NAFLD which is recognized as a cause of liver disease although currently diagnosis and management are a challenge. Specifically, metabolomic changes and biomarkers associated with this pathology are poorly studied in perinatally acquired HIV people (PHIV).
Methods: Plasmatic lipidomic and bile acids were analysed by LC-QTOF and HPLC-MS/MS in the study cohort consisted of 29 youth living with HIV under viral suppression by ART, of whom 10 presented NAFLD and 19 did not (control). Shear wave ultrasound and/or controlled attenuation parameter (CAP) ≥248 dB/m were used to determine NAFLD condition
Results: The PHIV study cohort was composed mainly of women with a median age of 18 (13.5-24) years. Body mass index was higher in NAFLD group (23.25 Kg/m²) than control (19 Kg/m²) (P=0.051). Interestingly, 30% of NAFLD patients was overweight and 10% presented obesity, whereas only 5.3% was overweight in the control. The hepatic steatosis index (HSI) was significantly increased in the NAFLD group (33.95 (28.475-39.72)) compared to control (27.95 (26.84-32.05)) (P=0.017). Circulating concentrations of ursodeoxycholic acid (UDCA) and eight different lipid species (diglyceride (DG) 36:3 and triglycerides (TG) 53:4, TG54:4, TG54:5, TG52:4, TG52:5, TG52:3, and TG56:7) were significantly increased in PHIV presenting NAFLD. Random forest analyses identified UDCA, TG56:7, and TG54:5 as the plasmatic metabolites that better differentiate both groups although the TG56:7 obtained the best discriminatory power to identify NAFLD with an AUC of 0.898. Additionally, regression model combining UDCA, TG56:7, and TG54:5 with the clinical HSI parameter increased the discriminatory power of the model up to an AUC of 0.920. Of interest, principal compound analysis based on bile acid levels identified two possible subpopulations within the control group. One subpopulation was differentiated from the NAFLD group (n=6) and the other one (n=13) showed an intermediate profile, suggesting that the biomarker panel could identify patients at risk for progression to NAFLD
Conclusion: A panel containing UDCA, TG56:7 and TG54:5 in combination with HSI could be a good predictive biomarker to identify individuals at risk of NAFLD among PHIV

973 Low Bone Density Accrual and Increased Inflammation in Zimbabwean Adolescents With Perinatal HIV

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Background: Living with HIV is associated bone density deficits, increasing fracture risk. We investigated the effect of HIV on bone density accrual over one year and inflammatory biomarkers relevant to osteoclast formation in peripubertal children and adolescents with and without perinatal HIV.
Methods: From 2018 to 2020, clinically healthy children with HIV (CWH) on antiretroviral treatment (ART) for at least 2 years, aged 8-16 years, were recruited from HIV clinics as were children of similar ages without HIV (CWOH) from nearby schools in Harare, Zimbabwe. Dual X-ray absorptiometry was performed at baseline and at 12months quantifying height-adjusted total-body less-head bone mineral content for lean mass (TBLH-BMC) and size-adjusted lumbar spine bone mineral apparent density (LS-BMAD) Z-scores. Change in Z-scores accounted for follow-up time. Baseline plasma levels for CRP, sCD14, TNFα, IL-6, IL-17α, IL-18, IL-10 and IFNλ were measured using Luminex. Bone outcome measurements were univariately plotted with age, with linear regression used to compare longitudinal changes in bone density by HIV status, adjusting for age, pubertal stage and baseline bone density. Principal components analysis was used to group inflammatory biomarkers. Linear

regression models were used to compare these components by HIV status adjusting for age and pubertal stage.

Results: There were 275 CWH (mean±SD 12.6±2.5 years old, 134[49.6%] girls) and 283 CWOH (12.7±2.5 years old, 149[50.4%] girls) at baseline. No deaths were reported, but 19% were lost to follow-up. ART regimens included either a non-nucleoside reverse-transcriptase or protease inhibitor; 211 (70%) and 89 (29%) respectively. HIV was associated with impaired gains in bone density, particularly among males (Figure 1). While females with and without HIV had similar bone density gains, males living with HIV gained less LS-BMAD (adjusted mean difference[95%CI] -0.14[-0.25 to -0.02], p=0.02) and TBLH-BMC (-0.19[-0.33 to -0.04], p<0.015) compared to males without HIV. Living with HIV was associated with higher levels of a component representing IL-18, CRP, sCD14 and TNFα for females (βcoefficient[95% CI] 0.63[0.27 to 0.98], p=0.001) and males (0.80[0.45 to 1.15], p<0.001).

Conclusion: Children living with HIV on ART have impaired bone density accrual and increased inflammation. Further investigation is ongoing into the effect of higher inflammation on peak bone mass among this population.

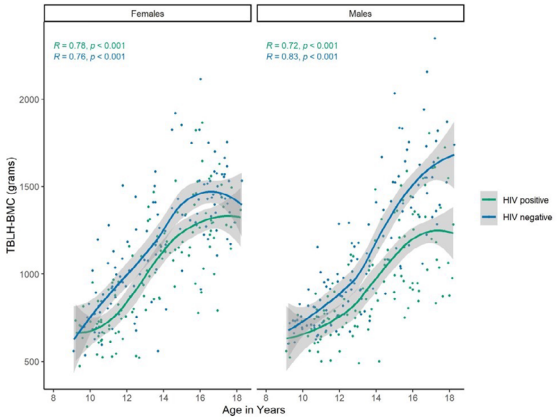

Figure 1: Best fit plot for the association between age and TBLH-BMC (grams) at follow-up stratified by sex and HIV status

974 WITHDRAWN

975 Association Between HIV and Cytomegalovirus and Neuropsychological Outcomes Among Children With HIV

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Background: Children with HIV may experience adverse neuropsychological outcomes despite antiretroviral treatment (ART). Uncontrolled cytomegalovirus (CMV) is common in children with HIV. Among children on ART, we examined the influences of early CMV DNA, HIV DNA, and viral load (VL) on neurocognition.

Methods: Children who initiated ART before 12 months of age were enrolled from 2007-2010 in Nairobi, Kenya. Blood was collected at enrollment and every 6 months thereafter. Neuropsychological assessments were conducted when children were a median age of 7 years. Primary outcomes included cognitive ability measured by the Kaufman Assessment Battery for Children 2nd Edition (KABC), executive function measured by Behavior Rating Inventory of Executive Functioning (BRIEF), motor measured by Bruinick's-Oseretsky Test of Motor Proficiency 2nd Edition Brief Form (BOT), and attention measured by Visual Test of Variables of Attention (TOVA). Secondary outcomes included short-term memory, visual-spatial, learning, non-verbal, and delayed memory from the KABC; behavior regulation and metacognition from the BRIEF; and processing speed from the TOVA. Generalized linear models were used to determine associations between HIV VL (pre-ART and cumulative), peak total and intact HIV DNA (by 12 months of age), peak CMV DNA (by 24 months of age) and neuropsychological outcomes.

Results: Overall, 39 children completed neuropsychological assessments. Median age at ART initiation was 4.6 months. In adjusted models, higher peak CMV viremia by 24 months of age was associated with lower cognitive ability and motor z-scores. Higher pre-ART HIV VL, total HIV DNA, and intact HIV DNA were associated with lower executive function z-scores. Higher HIV DNA levels also were associated with higher motor z-scores and higher intact HIV DNA with higher attention z-scores. Among secondary outcomes, higher intact HIV DNA levels were associated with lower behavior regulation z-scores and higher pre-ART VL was associated with lower nonverbal and metacognition z-scores.

Conclusion: Pre-ART VL, early post-ART total and intact HIV DNA, and CMV DNA in infancy predicted neuropsychological scores in childhood. These findings suggest long-term benefits of early HIV viral suppression, reservoir containment, and CMV control on neurocognition.

976 Regional Brain Volume as Predictor of Cognitive and Mental Health Outcomes in Youth Living With HIV

Sedthapong Chunamchai[1], Anantaporn Sena[2], Akarin Hiransuthikul[2], Phillip Chan[3], Robert Paul[4], Somchai Sriplienchan[5], Thanyawee Puthanakit[1], Serena Spudich[3], Chaipat Chunharas[1]

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Background: Youth living with HIV face a risk of developing cognitive, mental health, and behavioral challenges as they progress into adulthood. However, the specific contributions of biological, neurological, and social factors to these

adverse outcomes remain poorly understood. This study seeks to examine factors that can predict resilience at both baseline and after a 2-year period.
Methods: The RESILIENCE study is a 2-year cohort investigation that enrolled youth with perinatal HIV infection and controls. We collected data on various factors, including biological (age, HIV serostatus, viral load), neurological (regional brain volumes), and social (family and financial status). Resilient outcomes were assessed through cognitive function (intelligence, executive function, visuomotor, and memory), mental health (the symptom checklist SCL-90), risk-taking behavior (the behavioral health outcome questionnaire ACASI), and behavioral issues (the child behavior checklist). Multivariable logistic regression analysis with nested model comparisons was employed to identify predictors for each outcome.
Results: The study comprised 30 youth living with HIV and 62 controls, with a median (IQR) age of 15 (13-16) years. At baseline, regional brain volumes emerged as the primary predictor of resilience for cognitive (AUC = 0.65, p<0.001) and mental health outcomes (AUC = 0.74, p<0.001). For resilience in risk-taking behavior, a combination of all biological and social factors proved to be the most effective predictor (AUC = 0.70, p<0.001), while resilience in behavioral issues was best predicted by a combination of regional brain volumes and social factors (AUC = 0.64, p<0.001). At week 96, regional brain volumes alone were the strongest predictors of cognitive problems (AUC = 0.71, p<0.001), mental health problems (AUC = 0.74, p<0.001), and risk-taking behavior (AUC = 0.66, p<0.001). In contrast, resilience in behavioral issues was predicted by a combination of regional brain volumes and biological factors (AUC = 0.75, p<0.001).
Conclusion: Our findings reveal distinct predictors associated with resilience to various adverse outcomes in youth living with HIV. Cognitive and mental health outcomes are closely linked to regional brain volume, while behavioral issues and risk-taking behaviors are more strongly associated with a combination of biological and social factors. Recognizing these distinctions could enable targeted identification, monitoring, and intervention strategies for populations at special risk.

977 Neurocognitive Performance in Adolescents Living With HIV in Zimbabwe

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Background: Neurocognitive impairment in children and adolescents is complex and multifactorial. This study aimed to characterise the extent and nature of cognitive impairment in adolescents living with HIV (ALWH) in Harare, Zimbabwe and describe interactions between HIV, cognition and stunting.
Methods: In this cross-sectional study, ALWH aged 11-19 years, who established on ART for at least 6 months, were recruited from a public sector HIV clinic. An age-matched HIV negative (HIV-) comparison group was recruited from the same catchment area. Neurocognitive function was evaluated using the Kaufman Assessment Battery for Children 2nd Edition (KABC-II). Anthropometry measurements alongside questionnaires assessing socioeconomic status (SES), school performance and food security were completed. SES was assessed using household asset ownership questions.
Results: 503 participants (251 ALWH, 252 HIV-) were recruited from September 2022 to June 2023 and completed a KABC-II. ALWH median age 16 years, 45% male. HIV negative group median age 15 years, 50.4% male. Most participants aged 11-16 years were in education (95.3% ALWH, 91.2% HIV-). Among those in school, 38.0% of ALWH vs 17.9% of HIV negative participants were below expected school grade for age (p=0.001). 32% (n = 80) of ALWH were stunted compared to 10.8% (n = 27) of HIV-. More ALWH than the HIV-negative group were in the poorest SES group (29.1% vs 11.1%, p< 0.001) and experienced food insecurity (23.6 % vs 13.1 %, p=0.017). Adjusting for age, sex and SES, ALWH scored lower than HIV negative peers on KABC Mental Processing Index (MPI) -3.42 [95%CI -5.33, -1.51] and across all KABC subdomains (Sequential -2.49 [95%CI -4.68, -0.31], Simultaneous -3.83 [95%CI -6.15, 1.5], Learning -1.37 [95%CI -3.96, 1.21] and Planning -5.74 [95%CI -7.93, -3.55]). There was evidence of interaction of lower KABC MPI with stunting in ALWH (-4.71 [95%CI -9.62, 0.20]). There was no association between stunting and KABC MPI score in HIV negative adolescents.
Conclusion: Cognitive function in ALWH was impaired across all domains, the effect was magnified in stunted individuals. ALWH faced a multitude of adverse childhood experiences including food insecurity and poverty which may have impacted on their cognitive and physical development. Future longitudinal studies are required to evaluate the impact of nutritional interventions on growth and cognition in ALWH.

978 Development of Domain-General Cognition in Adolescents With HIV Is Slower Than Healthy Individuals

Anantaporn Sena[1], Sedthapong Chunamchai[2], Akarin Hiransuthikul[1], Phillip Chan[3], Robert Paul[4], Somchai Sriplienchan[5], Thanyawee Puthanakit[2], Serena Spudich[3], Chaipat Chunharas[2]
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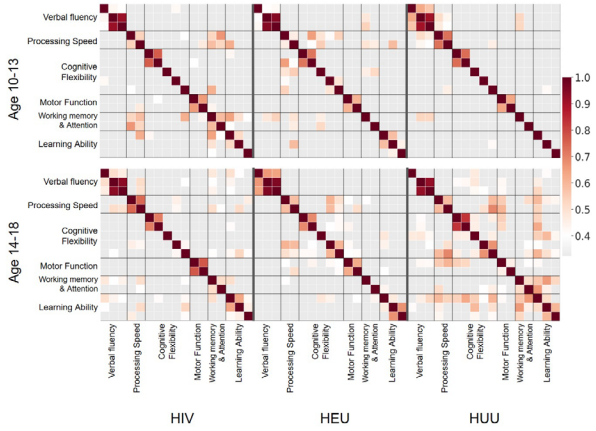
Background: While neuropsychological tests are designed to test specific cognitive abilities, a person who performs well in one task tends to perform well in others ("general cognitive ability" or g-factor). Previous studies showed that g-factor is associated with higher functional connectivity measuring by resting state fMRI. If perinatal HIV exposure can negatively affect white matter integrity, it's possible that the development of g-factor in these individuals might differ from individuals with no exposure. Here, we studied domain-general cognitive ability and how it differed between older and younger adolescents with different HIV statuses.
Methods: Data from the RESILIENCE study, a cohort conducted from 2015-2019, were analyzed to assess the correlation among 17 neuropsychological tests subscores across 6 cognitive domains. Participants were grouped by perinatal HIV status: HIV-exposed infected children group (HIV), HIV-exposed uninfected children group (HEU), and HIV-unexposed uninfected children group (HUU); and age: early adolescents (10-13 years) and middle adolescents (14-18) years. The number of moderate-to-strong correlations (Spearman's correlation coefficient ≥ 0.4) between cognitive tests were used as a marker of domain-general cognitive ability. We used permutation methods for the test statistic. Connection strength within and between domains was also explored.
Results: There were 96 HIV, 80 HEU, and 98 HUU in the early adolescent group and 105 HIV, 51 HEU, and 46 HUU in the middle adolescent group with matched genders. At the baseline, we found no difference in the number of connections. However, the HUU group showed a significantly greater increase in connections across age ranges (difference = 34) compared to the HIV (difference = 9, p<0.05) and HEU (difference = 5, p<0.001) groups. There was no difference in the increase of connections between the HIV and HEU groups. Additionally, only the HUU group had a significant decrease within-domain connection strength across age groups (average coefficient difference = 0.17, p<0.001).
Conclusion: Our study reveals a slower progression of general cognitive ability among individuals exposed to HIV. This observation aligns with the well-documented impact of HIV on white matter integrity and extends our comprehension of cognitive development within the HIV-exposed population. Our future research will involve a direct exploration of functional connectivity and its relationship with the g-factor.



979 Adult Outcomes Among Young People With Perinatal HIV Infection and Exposure in the United States

Elaine J. Abrams[1], Reuben Robbins[1], Afifa Ahmed[1], Curtis Dolezal[1], Luke Kluisza[1], Ohemaa Poku[1], Michael T. Yin[1], Andrew Wiznia[2], Claude Mellins[1]
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Background: Most young people with perinatal HIV infection (YPPHIV) and with perinatal HIV exposure but who are uninfected (YPPHEU) born in the United States are from vulnerable, under-resourced, marginalized communities and are now entering adulthood. Yet, little is known about their adult outcomes (i.e., medical, behavioral, psychiatric, substance use [SU], neurocognitive, and milestone achievement [e.g., employment, school, offspring]).
Methods: CASAH is a New York City-based longitudinal behavioral health cohort study of YPPHIV and YPPHEU that began in 2003; data are presented from visits in 2019-23. Psychiatric and SU disorders were assessed using the young adult version of the Diagnostic Interview Schedule for Children, and cognitive functioning with NeuroScreen.
Results: Among 187 participants (124 YPPHIV; 63 YPPHEU), mean age was 27.8 years; 60% female; 64% Black, 47% Latino. Among YPPHIV: median CD4+ =450 cells/mm^3; 64% had viral load <200 cps/ml; 57% received 2NRTI+INSTI or bPI; 24% 2NRTI+INSTI+bPI or NNRTI. Most participants were never married (94%) and currently sexually active (73%); over half in both groups reported condomless sex in past 3 months. Over 50% of females and 42% of males reported pregnancy in self or partner, with no group differences. Overall, 27% met criteria for a non-SU psychiatric disorder (14% depression; 16% anxiety); 32% met criteria for a SU disorder (primarily alcohol and/or marijuana). YPPHIV performed worse on cognitive tests with 20% (vs 4% YPPHEU, p =.01) having global test performance 2 SDs below the sample mean. Overall, 78% completed high school or GED; 50% were in school or currently employed with higher rates in YPPHEU vs YPPHIV (65% vs 43%, p=.004). YPPHIV were more likely than YPPHEU to receive housing assistance (73% vs 53% p=.007), public assistance (29% vs 8%, p=.001) and food stamps (68% vs 29%, p>.001). Homelessness history was higher in YPPHIV (46% vs 26% YPPHEU, p=.009); 18% of participants reported incarceration history with no HIV-status differences.
Conclusion: Despite early challenges, many YPPHIV and YPPHEU had positive behavioral health outcomes. Yet psychiatric and SU disorders, neurocognitive deficits, and challenges with education and employment were also observed and can be associated with poor health and adult functioning problems, especially in the context of HIV infection. These findings underscore an urgent need to identify those at risk for poor outcomes and develop and escalate interventions.

980 High Burden of HIV-Related Disease Among Adults With Perinatally-Acquired HIV in Argentina

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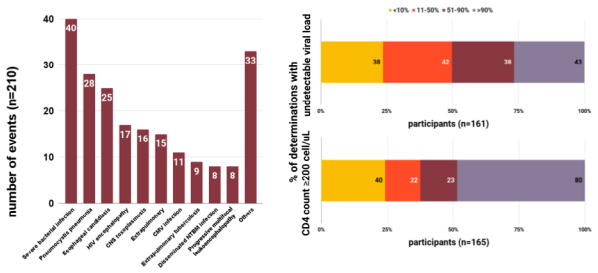
Background: Limited data is available regarding population size and burden of HIV-related disease among adults living with perinatally-acquired HIV (paHIV) in Latin America. This study is aimed at describing HIV-related burden of disease in a cohort of adults living with paHIV from Buenos Aires, Argentina.
Methods: This is a retrospective cohort study. People living with paHIV aged >16 and linked to care in an HIV referral clinic in Buenos Aires, Argentina between Oct-2008 and Sep-2023 were included. Data was collected from clinical records and epidemiological surveillance systems. Clinical status was classified as per WHO HIV staging system, and advanced HIV disease was defined as WHO stages 3-4. Ethics approval was obtained as appropriate.
Results: A total of 170 adults (60% females) with paHIV were included in the analyses. Median age at baseline was 19 years and median individual follow-up was 5.7 years (Q1-Q3 3.6-9.5). Prevalence of clinically advanced HIV disease was 47% (79/170); 34/79 participants presented 1, 36/79 presented 2-5 and 9/79 presented >5 WHO stage 3-4 events. Graphic 1 shows frequency of incident WHO stage 3-4 events (1a) and proportion of undetectable viral loads and CD4 counts ≥200 cells/uL per participant (1b)(data available for 161 and 165 individuals, respectively). There were 133 HIV-related hospital admissions in 49 participants. Global mortality was 11% (18/170) and median age at the time of death was 23.5 years (Q1-Q3 21.2-27). The majority (11/18) of the deaths were HIV-related and one third (6/18) occurred within the first year after transition to adult care.
Conclusion: Adults living with paHIV have high HIV-related morbimortality and HIV-related complications are the leading cause of death in our cohort. To our knowledge, this is the largest description of a cohort of adults living with paHIV in Latin America. Further research is needed to complete the characterization of this population in order to design and implement differentiated service delivery models that contemplate their singularity.

Graphic 1 - Frequency of WHO stage 3-4 events (1a) and proportion of undetectable viral loads and CD4 counts ≥200 cells/uL per participant (1b)



981 No Early Signal That DTG Improves 24-Week Viral Suppression in Infants in Botswana

Maureen Sakoi-Mosetlhi[1], Gbolahan Ajibola[1], Oganne Batlang[1], Kenneth Maswabi[1], Molly Pretorius Holme[2], Kathleen M. Powis[3], Shahin Lockman[4], Michael D. Hughes[1], Joseph M. Makhema[1], Daniel R. Kuritzkes[4], Mathias Lichterfeld[5], Roger Shapiro[2]
[1]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Brigham and Women's Hospital, Boston, MA, USA, [5]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: The World Health Organization recommends dolutegravir (DTG)-based 3-drug antiretroviral therapy (ART) in children >4 weeks weighing >3kg. DTG-based ART achieves rapid viral load decline in adults and low rates of treatment failure in older children, but outcomes for children treated from birth, a time when adherence challenges are of particular concern, are limited.
Methods: We compared prevalence of 24-week HIV-1 RNA suppression in early-treated children on lopinavir-ritonavir (LPV/r)–based ART in the EIT cohort (2015-2018) to DTG-based ART in the Moso cohort (2022-2023) in Botswana. All children started nevirapine (NVP)+lamivudine (3TC)+zidovudine (ZDV) in the first week of life and switched to LPV/r+3TC+ZDV at 2-5 weeks (in EIT) or DTG+abacavir (ABC)+3TC at 4-6 weeks (in Moso). The proportion of children with HIV-1 RNA<40 copies/ml at 24 weeks of age was compared between both cohorts and logistic regression models were fit to evaluate risk factors for non-suppression.
Results: Thirty-eight of 40 EIT participants and 7 of 11 Moso participants had 24-week results (2 EIT deaths <24 weeks; 1 Moso death <24 weeks and 3 Moso participants <24 weeks follow-up). HIV-1 RNA was <40 copies/mL at the 24-week visit in 27/38 (71%) EIT participants on LPV/r and in 4/7 (57%) Moso participants on DTG. Figure 1 summarizes viremia over time in both cohorts. Median $\log_{10}$ infant HIV-1 RNA at birth was 4.1 copies/mL and 3.8 copies/mL for EIT and Moso, respectively. Median time on LPV/r and DTG prior to 24 weeks was 154 days (range 130, 168) and 140 days (range 126, 148), respectively. No maternal or infant factors significantly predicted viral suppression at 24 weeks in either cohort, but caregiver-reported adherence challenges were common in most children with detectable viremia at 24 weeks.
Conclusion: Despite its proven benefit for achieving rapid and durable viral suppression in adults and older children, data from a small number of early-treated infants in Botswana indicate no improvement in viral suppression with the use of DTG-based ART through 24 weeks.

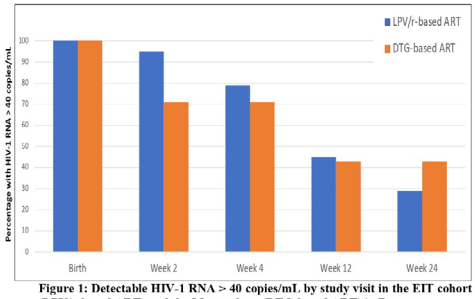


Figure 1: Detectable HIV-1 RNA > 40 copies/mL by study visit in the EIT cohort (LPV/r-based ART) and the Moso cohort (DTG-based ART) in Botswana

982 HIV Viral Suppression Among Children and Adolescents 2 Years After Transition to Dolutegravir

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Background: Children and adolescents with HIV experience high rates of treatment failure. Antiretroviral therapy (ART) containing dolutegravir has recently been rolled out across much of Africa and has several potential benefits over previously preferred ART regimens, though long-term real-world data in pediatric populations are lacking. Here, we report treatment outcomes among children and adolescents in Lesotho, southern Africa, who transitioned from non-nucleoside reverse transcriptase inhibitor- (NNRTI-) to dolutegravir-based ART through two years' follow-up.

Methods: Data were derived from two open cohort studies in Lesotho (Baylor College of Medicine Children's Foundation Lesotho and Viral Load Cohort North-East Lesotho). Children and adolescents aged <18 years who transitioned from NNRTI- (efavirenz or nevirapine) to dolutegravir-based ART ≥18 months before data closure were included. We report viral load (VL) results <12 months before, 12 (window: 6-17) months after, and 24 (window: 18-29) months after transition to dolutegravir. Associations of demographic and clinical factors with 24-month viremia were assessed through multivariable logistic regression.

Results: Among 2121 children and adolescents included, 1099 (51.8%) were female. At transition to dolutegravir, median age was 14.0 years (interquartile range [IQR] 11.5-15.8), median time taking ART was 7.6 years (IQR 4.4-10.6), and most participants had been taking an efavirenz-based regimen (1433/2121 (67.6%)). Participants were followed up over a median of 2.6 years (IQR 2.3-2.9). A VL was available for 1971/2121 (92.8%) <12 months before, 2006/2121 (94.6%) 12 months after, and 1887/2121 (89.0%) 24 months after transition to dolutegravir. Among those with a VL result at the respective time points, viral suppression to <50 copies/mL was achieved by 1633/1971 (82.9%) <12 months before, 1840/2006 (91.7%) 12 months after, and 1708/1887 (90.5%) 24 months after transition to dolutegravir. The Figure shows VL dynamics for participants with VL data at all time points. Pre-transition viremia was associated with viremia at 24 months, though 227/272 (83.5%) and 232/272 (85.3%) participants with pre-transition viremia had achieved resuppression to <50 copies/mL at 12- and 24 months after transition to dolutegravir, respectively.

Conclusion: Rates of viremia dropped after transition to dolutegravir. However, further progress is needed to reach global targets in children and adolescents.

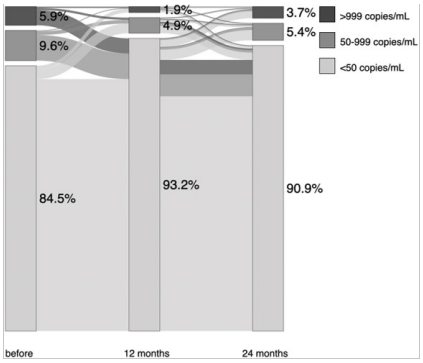

Figure: Viral load (VL) dynamics among participants with an available VL <12 months before, 12 months after, and 24 months after transition to dolutegravir (n=1718). Node shade: VL category at respective time point; flow shade: VL category before transition.

983 Longitudinal Viral Outcomes in Kenyan Youth With HIV Switching to Dolutegravir-Based Therapy

Vlad Novitsky[1], Winstone Nyandiko[2], Allison DeLong[1], Edwin Sang[3], Joel Hague[1], Ashley Chory[4], Josephine Aluoch[3], Eslyne Jepkemboi[3], Millicent Orido[3], Joseph Hogan[1], Rachel Vreeman[4], Rami Kantor[1]

[1]Brown University, Providence, RI, USA, [2]Moi University, Eldoret, Kenya, [3]Academic Model Providing Access to Healthcare, Eldoret, Kenya, [4]Icahn School of Medicine at Mt Sinai, New York, NY, USA

Background: Dolutegravir (DTG)-based antiretroviral therapy (ART) is now recommended in all treatment lines in resource limited settings. Data on global implementation and longitudinal impact of DTG rollout for children and adolescents living with HIV (CAWH) are currently needed to inform care and policy.

Methods: In a well characterized longitudinal cohort (since 2010) of perinatally infected CAWH cared for at the Academic Model Providing Access to Health care (AMPATH) in western Kenya, we determined viral outcomes, and compared outcomes between CAWH with and without provider-initiated switch to DTG-based regimens. During the 18-month follow up, viral load (VL) was tested at 6-month intervals and drug resistance genotyping was performed for VL>1,000 copies/mL, and interpreted with Stanford HIV Drug Resistance Database tools. Differences in proportions were estimated using Fisher's exact test.

Results: Of 390 CAWH followed for 18 months between July 2020-February 2023 (median age 19 years; 48% female; median 13 years on ART), 83% switched to DTG-based regimens and 17% remained on older regimens (2% NNRTI- and 98% PI-based). Among 324 CAWH on DTG-based regimens at 18 months, 293 (90%) were suppressed at that timepoint, 103 (32%) had VL>40 copies/mL, and 64 (20%) had VL>1,000 copies/mL at any follow up time point. Among 66 CAWH on non-DTG-based regimens, 47 (71%) were suppressed at 18 months ($p<0.005$), 37 (56%) had VL>40 copies/mL, and 30 (45%) had VL>1,000 copies/mL at any follow up time point. Of 186 patient-visits with VL>1,000 copies/mL in at least one timepoint during follow up, 141 sequences were available, including 69 from 52/324 (16%) CAWH on DTG-based regimens and 72 from 37/66 (56%) CAWH on non-DTG-based regimens. Any drug resistance was present in 58% of those on DTG-based, and in 86% of those on non-DTG-based regimens ($p<0.01$), including major PI drug resistance mutations (DRMs) in 2% vs. 16% ($p<0.02$), NRTI DRMs in 27% vs. 68% ($p<0.001$) and NNRTI DRMs in 46% vs. 78% ($p<0.01$), respectively. No major INSTI DRMs were detected, with accessory INSTI DRMs identified in 12% vs. 11% (p-value not significant).

Conclusion: Longitudinal data in Kenyan CAWH support switching to DTG-based ART to improve viral suppression and prevent resistance accumulation. Lack of major INSTI DRMs during this short follow up is encouraging, yet cumulative viral failures, including low level viremia, mandate close monitoring of adherence, VL and resistance in this vulnerable population.

984 Global Transition to Dolutegravir-Based ART in Children and Adolescents 0-19 Years Living With HIV

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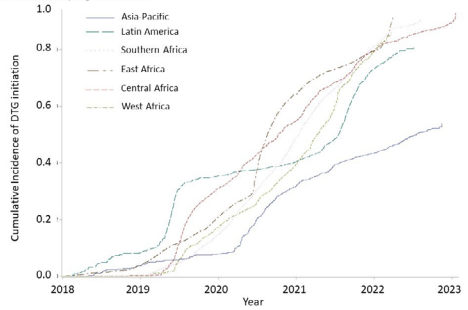
Background: Dolutegravir (DTG)-based regimens are recommended as first-line antiretroviral therapy (ART) for all children and adolescents living with HIV (CALHIV). We describe transition to DTG in the multiregional IeDEA cohort.
Methods: We included all CALHIV enrolled in IeDEA sites where DTG was available from 6 regions (Asia-Pacific, Latin America, Central Africa, West Africa, East Africa, Southern Africa). The observation period of the study was from January 2018 through March 2023. Follow-up (FU) for individual patients began on the date at which their site began to use DTG or at ART initiation, whichever occurred later (i.e., baseline); FU ended at DTG initiation or database closure/death/loss to FU (LTFU; no visit >7 months), whichever came first. We computed regional cumulative incidence functions (CIF) for DTG initiation. Associated factors were explored in a Cox proportional hazard model adjusted for sex, age, ART regimen and viral load (VL), and stratified by region, using a calendar time scale.
Results: Overall, 80% of sites had access to DTG and 61,324 CALHIV were included in our study; 55% were female and 60% were from Southern Africa. At baseline, median age was 12.2 years (IQR: 7.3-16.3), and 37% had VL assessments, of whom 51% were suppressed (<50 copies/mL). Median follow-up was 16.6 months (IQR: 6.0-27.8) during which 711 (1%) CALHIV died and 14,514 (24%) were LTFU. The overall CIF for DTG initiation reached 92% (95%CI: 91-93) and was significantly lower in the Asia-Pacific (44%; 95%CI:41-47) compared to other regions (Figure). In adjusted models, CALHIV <5 years (compared with older CALHIV), those with detectable VL (compared to those with undetectable VL), and those on protease inhibitor-based regimens (compared with non-nucleoside-based regimens) were less likely to initiate or transition to DTG. Additionally, we found in all 4 African regions that female CALHIV were significantly less likely to access DTG than their male counterparts. In other regions, sex was not associated with initiation or transition to DTG.
Conclusion: We report an unequal transition to DTG in sites where it has been available. Access to pediatric DTG should be scaled up for younger CALHIV. Moreover, our results highlight the need to promote equitable use of DTG regardless of sex and VL. Continued documentation of treatment practices is required to ensure universal and equal access to DTG for all CALHIV.

Figure – Estimated cumulative Incidence (CIF) of DTG initiation among CALHIV aged 0-19 years in sites where DTG has been available, by region, in IeDEA



985 Treatment Interruption Patterns Among Young People in USAID-Supported PEPFAR Programs

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Background: Continuity of treatment for people living with HIV is paramount in order to achieve the UNAIDS 95-95-95 targets and reach epidemic control. Treatment disengagement is linked to increases in viral load and onward HIV transmission. To better understand continuity of treatment, we analyzed treatment interruption patterns among children, adolescents, and young adults in USAID-supported PEPFAR countries.
Methods: Routinely collected programmatic data from 42 USAID-supported PEPFAR country and regional programs were analyzed for U.S. fiscal year (FY) 2022 Quarter(Q) 3 through FY2023 Q2 (April 2022 - March 2023). We compared trends in the percent and volume of interruptions in treatment (IIT; overall, <3 months on treatment, 3-5 months on treatment, and 6+ months on treatment) among children (0-9 years), adolescents (10-19 years), and young adults (20-29 years). Interruption in treatment is defined as no clinical contact for 28 days after the last expected clinical appointment or medication pick-up date.
Results: Comparing FY22Q3 to FY23Q2, the overall %IIT as well as absolute number of IIT decreased for all age groups: children (2.8% vs 2.6%; 3,613 vs 3,303), adolescents (2.8% vs 2.6%; 8,141 vs 7,853), and young adults (3.5% vs 3.4%; 44,721 vs 37,435); however, a peak in %IIT was observed for all ages in FY23Q1 (3.2%, 3.1% and 4.1%, respectively). Though overall %IIT is highest for young adults in all quarters, in FY22Q4 through FY23Q2 the highest rates of %IIT occurred in adolescents who have been on treatment for <3 months (12.1%, 14.9% and 11.9%) followed by adolescents who have been on treatment for 3-5 months (11.2%, 12,7% and 8.0%). %IIT among those who have been on treatment for 6+ months is greatest for young adults across all four quarters. For all age groups between FY22Q4 and FY23Q2, the absolute number of IIT is largest at 6+ months, however, compared to overall %IIT, higher rates of % IIT are observed within the first three months on treatment (ranging from 2.7 - 4.8 times more often) followed by 3-5 months (ranging from 2.1 - 4.8 times more often).
Conclusion: Overall rates of IIT among children, adolescents, and young adults in USAID-supported PEPFAR programs between FY22Q3 and FY23Q2 remain high. The pattern of markedly high rates of IIT in individuals, particularly adolescents, on treatment <3 months and 3-5 months, highlights the need for targeted interventions and support for new initiators to ensure continuity of treatment.

986 Dolutegravir and Growth in Pediatric Populations With HIV-1: IMPAACT P1093 and IMPAACT 2019

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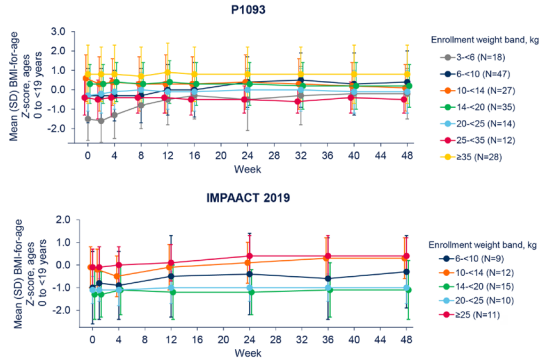
Background: Weight gain has been associated with dolutegravir (DTG)-based regimens in clinical studies of adults with HIV-1 and in observational studies of children and adolescents using DTG. Data from DTG randomized clinical trials did not show excessive weight gain in children and adolescents living with HIV, but knowledge is limited. We report body mass index (BMI)-based growth parameter changes in pediatric participants from 2 single-arm studies of DTG in IMPAACT 1093 (P1093) and DTG/abacavir/lamivudine in IMPAACT 2019, through 48 weeks of treatment.
Methods: Separate descriptive post hoc analyses were performed for each study. Age- and sex-specific BMI-for-age Z-scores (BAZ; standard deviation scores) were calculated per 2006 and 2007 World Health Organization references. BAZ was summarized at each visit from baseline to Week 48 by enrollment weight and age bands, baseline BMI, and sex at birth. Proportions of participants aged ≥2 years who started with BAZ ≤1 (normal BAZ and low BAZ) and became overweight (BAZ >2 but ≤3 for age 2-≤5 years and >1 but ≤2 for age >5 years) or exhibited obesity (BAZ >3 for age 2-≤5 years and >2 for age >5 years) were evaluated. Growth-related adverse events were assessed.
Results: Data from P1093 (N=181; aged 4 weeks to <18 years) and IMPAACT 2019 (N=57; aged 6 months to <12 years) were analyzed. Overall mean (SD) BAZ increased from 0.0 (1.4) at baseline to 0.2 (1.3) at Week 48 in P1093 and from −0.7 (1.1) to −0.4 (1.2) in IMPAACT 2019. Similar patterns were seen in subgroups by sex at birth and enrollment weight or age bands (Figure). In a descriptive analysis, mean (SD) BAZ across visits ranged from −0.1 (1.4) to 0.3 (1.3) in P1093 and from −0.7 (1.1) to 0.3 (0.8) in IMPAACT 2019. Mean (SD) BAZ for those with baseline BAZ <−3 and −3 to <−2 improved from baseline to Week 48 in P1093 from −3.6 (0.6) and −2.3 (0.2) to −0.4 (1.1) and −0.6 (1.6), respectively, and in IMPAACT 2019 from −3.1 (0.0) and −2.2 (0.3) to −2.7 (0.7) and −0.8 (0.8), respectively. At Week 48, 6 (6%) P1093 and 2 (4%) IMPAACT

2019 participants aged ≥2 years had a change from baseline BAZ ≤1 to newly overweight or obesity-level BAZ. No AEs of weight increase were reported.
Conclusion: Children and adolescents initiating DTG had a small overall increase in mean BAZ over 48 weeks in P1093 and IMPAACT 2019 and remained within mean BAZ >−1 to ≤1 at Week 48. Some participants with BAZ <−2 at baseline had a more marked increase in BAZ over 48 weeks of treatment, potentially suggesting a return to health.

Figure. BMI-for-age *Z*-scores for pediatric populations from P1093 and IMPAACT 2019.



987 Pharmaco-Virological Outcome and Resistance Profiles Among Togolese Adolescents Transitioning to DTG

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Background: Very few data are available regarding efficacy of the transition to tenofovir-lamivudine-dolutegravir (TLD) among adolescents living with HIV (ALHIV) in West Africa. Here, we assessed pharmaco-virological outcome and resistance profiles among ARV-treated Togolese ALHIV.
Methods: A cross-sectional study was conducted among 3 clinical centers in Lomé, capital of Togo, following ALHIV. Plasma HIV viral load (VL) was quantified and plasma ARV drugs concentrations were measured. NGS of protease, RT and integrase was performed using Oxford-Nanopore Technologies (threshold: 10%). Drug resistance mutations (DRM) were identified and interpreted using ANRS|MIE algorithm.
Results: 272 ALHIV were enrolled (median age: 16 years [IQR: 13-19], 47% men), 85% were receiving a DTG-based regimen and 10% a NNRTI-based regimen. Median duration since ARV initiation was 8 years (IQR: 5-12) and median duration of DTG-based regimen was 20 months (IQR: 13-25). Using a threshold of 50, 200 and 1000 c/mL; 60%, 75% and 82% of ALHIV achieved virological suppression, respectively. Regarding the 231 ALHIV receiving a DTG-based regimen, 80% had VL <200 c/mL, and DTG concentrations were adequate (i.e. >640 ng/mL), suboptimal and <LOQ in 74%, 7%, and 19% of cases, respectively. Overall, genotypic resistance tests were performed for the 68 samples with VL >200 c/mL. The most prevalent subtype was CRF02_AG (68%). Overall, at least one DRM was detected in 66% of the samples. 57%, 81%, and 1.6%, of ALHIV harbored viruses that were resistant to any NRTI, NNRTI, and PI. The most prevalent NRTI and NNRTI mutations were M184V (85%) and K103N (40%), respectively. A TDF DRM was detected in 5 RT sequences (8.8%). An INSTI major mutation was observed in 3 of the 32 (9.4%) available integrase sequences among ALHIV receiving a DTG-based regimen: R263K, E138A-G140A-Q148R, and N155H. Two of these latter patients were receiving TLD and the remaining one was receiving ABC-3TC-DTG; two had adequate DTG concentrations; and one had a virus also harboring M184V mutation.
Conclusion: In this large study of 272 ALHIV carried out in Togo, we showed a high level of virological response to TLD with high level of adherence, and a rate of DTG resistance mutations emergence of 9.4% in case of virological failure. These first findings on a large series of adolescents in LMIC advocate the need of VL monitoring and to survey HIV drug resistance to DTG in the context of transitioning to TLD with a limited access to VL monitoring.

988 Emerging Integrase Resistance in the Perinatal Virtual Clinic: The Need for Protease Inhibitors

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Background: The perinatal virtual clinic (PVC); a monthly multidisciplinary forum reviews complex management decisions for children and adolescents living with HIV (CALWHIV) referred from high (HIC) and low/middle income countries (L/MIC). We investigated the prevalence of emergent integrase drug resistance mutations (INSTI-DRMs) necessitating protease inhibitor (PI) based regimens.
Methods: Review of 5 years of PVC referrals; October 2018-September 2023. Demographic data included age, sex, country of residence. Clinical data included: comorbidities, antiretroviral therapy (ART) history, HIV viral load (VL) and CD4 count. Resistance mutations were interpreted using the Stanford HIV Drug Resistance database and CALWHIV with emergent INSTI-DRMs described.
Results: 341 CALWHIV were discussed; 51 (15%) from L/MIC, 106 (31%) with virological failure (VF) of which 96 (91%) had resistance sequences available. 17/96 (18%) had INSTI-DRMs, median (IQR) age 11 (6-14) years, weight 24 (17-49) kg, CD4 430 (77-805) cells/ul, and VL 35,000 (2380-132000) c/ml. Current region; Africa (7), Americas (2), Europe (5) and Western Pacific (2), with 11 (65%) from L/MIC. 12/17 (74%) were referred in 2022/23. Six had current AIDS diagnoses and 4 concomitant antimycobacterial therapy. 15/17 were on second/subsequent ART (median 2 [IQR 2-3] prior regimens) comprising nucleoside reverse transcriptase inhibitors (NRTI) with: dolutegravir (DTG) (7), raltegravir (4), DTG and darunavir/ritonavir (DRV/r) (4). One adolescent failed first line DTG/lamivudine (3TC)/abacavir (ABC) with E138K S147G Q148R N155H M184V (high-level DTG resistance (R)) after 5 years. A second suppressed on nevirapine/3TC/ABC for 11 years simplified to DTG/3TC/ABC but failed 4 years later with an R263RK (intermediate DTG-R). Cumulative resistance by number of ART classes was 1 (1), 2 (5), 3 (7), 4 (4) with DRMs described in Table 1. PVC recommendations were for tenofovir (TXF) with lamivudine or emtricitabine, using split adult tablets in 5, with DRV/r (17), twice daily (BD) in 6, with BD DTG (6), and novel agents sought for 2.
Conclusion: INSTI resistance is emerging in CALWHIV, most commonly in highly treatment experienced individuals from L/MIC. This highlights the global need for access to DRV/r, TXF and novel classes, including formulations for children <35kg.

Table 1 Cumulative DRMs by class, by number per patient, and by frequency.

DRM by class (n/17)	INSTI[1] (17)		NRTI (15)		NNRTI[2] (12)		PI (6)[3]	
DRMs per patient: 1/2/3/4+	10/3/1/3		4/0/3/8		3/1/5/3		0/1/3/2	
Frequency of common major DRMs (n/17)	E138K	5	M184VI	15	K103N	5	M46I	5
	G140SA	5	M184VI only	4	V106MI	4	**I47V**	1
	Y143CR	5	M184VI + TAMs	9	E138KQ	2	**I50VL**	2
	Q148HR	5	M184VI + other	2	Y181C	3	**I54LMV**	3
	N155H	6			G190A	4	**L76V**	1
	R263K	4			M230L	2	**I84V**	1

[1] Interpretation: high-level DTG-R (5), intermediate (5), low/other INSTI-DRM (7). [2]non-nucleoside reverse transcriptase inhibitor; NNRTI. [3]DRV-associated DRMs in bold, all 6 having ≥ 1 major DRV-DRM.

989 Pediatric HIV Hotspots: Machine Learning and Geostatistical Analysis for Enhanced Case Finding

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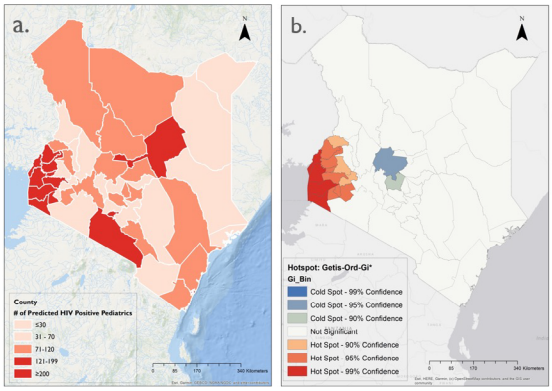
Background: Global data indicates a significant disparity in HIV case finding and treatment coverage between pediatrics and adults. To enhance HIV case finding and treatment for pediatrics within the HIV care continuum, targeting significant hotspot areas may be essential. This study investigates spatial patterns of the disease in Kenya, identifying hotspots to prioritize program resources for epidemic control efforts among pediatrics.
Methods: We utilized national HIV testing data for HIV-positive pediatrics under 15, combined with 2022 Kenya Demographic and Health Survey indicators, to train various supervised machine learning (ML) algorithms.

Prediction accuracy for the ML models was evaluated using root mean square error and mean absolute error. The most effective model, "tuned Lasso Regression", predicted the number of new HIV-positive pediatrics across 47 Kenyan counties based on national data between October 2022 and June 2023. These predictions were georeferenced at the county level for geostatistical analysis. Global spatial autocorrelation techniques based on Moran's I (MI) test revealed HIV infection distribution patterns, while hotspot analysis using Getis-Ord (Gi*) spatial statistics identified significant clusters of pediatric HIV cases among neighboring counties.

Results: By the end of June 2023, we predicted 3,160 pediatric HIV cases, a slight increase from the 3,092 cases reported by the national program between October 2022 and June 2023. A spatial autocorrelation analysis of pediatric HIV infections in Kenya revealed significant clustering for both reported (z-score=3.22, MI=0.21, p-value<0.001) and predicted cases (z-score=4.92, MI=0.36, p-value<0.001). The increased z-score in predicted cases suggests heightened clustering intensity, indicating that new pediatric HIV cases are predominantly localized. Hotspot analysis using the Getis-Ord Gi* statistic pinpointed these significant clusters to twelve counties in the Southwestern region of Kenya.

Conclusion: The spatial distribution of new pediatric HIV cases was non-homogeneous. This study pinpointed key geographical areas for prioritizing pediatric HIV infection control. This study will provide policymakers with essential insights to optimally allocate testing and treatment services to areas with the greatest needs.

Figure 1 (a.) Machine Learning-Predicted Distribution of Pediatric HIV Infections Across Kenyan County at end of June 2023. **(b.)** Hotspot Analysis of Predicted Pediatric HIV Positive Cases



990 Pediatric Emergency Department-Based Opt-Out HIV Screening Identifies Adolescents Living With HIV

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Background: The Centers for Disease Control and Prevention recommends universal HIV screening for all patients ≥13 years. Parts of Metro Atlanta have HIV+ rates at 8-times the national average. Adolescents are the least likely group to know their HIV status and have the lowest rate of linkage to care and viral suppression. Children's Healthcare of Atlanta (Children's) implemented an opt-out HIV testing program in its pediatric emergency departments (ED) for all patients ≥13 years undergoing venipuncture for any chief complaint in 1 of their 3 sites. The objective is to increase testing in adolescents in Atlanta leading to earlier HIV diagnosis and linkage to care.

Methods: Children's electronic medical record EPIC and its population discovery tool were used to compare HIV testing volumes of 13–24-year-old patients, 10 weeks pre- (April 26–July 5, 2023) and 10 weeks post (July 6–September 14, 2023) clinical implementation. Data for all 3 sites was reviewed but only 1 site received educational promotion for staff and poster placement in the ED. Results were cross-referenced to determine new diagnoses from known positive's; all newly identified adolescents living with HIV (ALHIV) were linked to care. The data was compared using descriptive statistics.

Results: A total of 309 patients were tested for HIV in the 10 weeks pre-implementation, 202(65%) girls and 107(35%) boys. Two new ALHIV were identified, 1 coinfected with syphilis, the median age was 17 and both were assigned male at birth. After 10 weeks of implementation, a total of 470 patients were tested: 322(69%) girls and 148(31%) boys. Four new ALHIV; the median age was 16 and their assignment at birth was (3) male, 2 coinfected with syphilis, and (1) female. This demonstrates an overall positivity rate of nearly 1%, and 1 in 49 boys tested positive. A 77% increase in testing was noted at the site receiving educational promotion vs 34% at the other 2 sites. Overall, the initiative showed a 50% increase in newly diagnosed cases; all were linked to care within 1-48 days.

Conclusion: Metro Atlanta remains a hotspot for new HIV cases. Four new cases in 10 weeks highlights the importance of universal HIV testing of adolescents and reflects a public health crisis. The new initiative significantly increased HIV screening among adolescents and will likely identify ALHIV at an earlier stage of infection, facilitating timely access to medical care. This can lead to improved clinical and immunological outcomes and a reduced risk of secondary transmission.

991 Evaluation of Electronic Peer Navigation to Prevent Engagement Failure for Youth in Kenya

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Background: Adolescents and Young Adults with HIV (AYAHIV) require innovative approaches to address lower rates of virologic suppression and HIV care engagement. While peer-based interventions have strong developmental justification, AYA have many competing demands including school, life transitions, and emerging social needs that may limit reach of in-person support services. The ubiquity of mobile phones and social media, however, offers an alternative route for peer engagement and support.

Methods: We randomized AYAHIV to trained virtual peer navigators who delivered structured peer support electronically (by phone) combined with biweekly automated text messages. We enrolled AYAHIV aged 14-24 years at three high volume public facilities in Kisumu County, Kenya between April 2021 and March 2022. Participants were block randomized to standard of care (SOC) or electronic navigations (eNAV) stratified by ages 14-19 and 20-24 years. Electronic navigators were trained youth with HIV. The primary outcome was AYAHIV engagement failure at one year defined as experiencing any of the following within the first year of follow-up: missed clinic visit (at least 14 days late for a scheduled visit) or viral failure (high viral load per national guidelines) or death. Targeted maximum likelihood estimation was used to estimate effect of virtual navigation versus SOC. We adjusted for baseline patient characteristics (e.g., sex, age, WHO stage, alcohol use, school attendance, etc.) to enhance precision.

Results: Of the 579 participants, 285 (49.2%) were randomized to eNAV and 294 (50.8%) to SOC. Among all patients, 403 (69.6%) were female and median age was 20 years (interquartile range 17-23). Treatment assignment was balanced by sex, age, WHO Stage, study site, or school attendance at study enrollment between arms (Table 1). Overall, 75 (26.3%) AYAHIV experienced and engagement failure in eNAV and 93 (31.6%) in SOC resulting in an estimated risk difference of -5.18% (95% confidence interval -12.54%, 2.19%, p=0.1684). The risk difference was also non-significant in unadjusted analysis.

Conclusion: Results from this trial comparing peer navigation and text messaging versus the standard of care demonstrate high levels of engagement failure in AYAHIV that are reduced, but not statistically significantly, through electronic navigation. Peer support to increase treatment success may require more intensive in-person interactions, despite the reach and flexibility provided by electronic approaches.

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992 Effectiveness of the mHealth Intervention, InTSHA, Among Adolescents With HIV in South Africa

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Background: Retention in care for adolescents with HIV during transition from pediatric to adult care is more challenging than for younger children or

older adults not transitioning. We describe the results of a pilot, type 3 hybrid, randomized clinical trial of a mobile phone-based intervention, InTSHA: Interactive Transition Support for Adolescents with HIV, compared to standard care.

Methods: InTSHA uses encrypted, closed group chats delivered via WhatsApp to provide peer support and improve communication between adolescents, their caregivers, and healthcare providers during transition from pediatric to adult care. We randomized 80 South African adolescents with perinatally-acquired HIV who were aware of their HIV status and aged between 15 to 19 years to receive either the InTSHA intervention or standard care. We measured acceptability (Acceptability Implementation Measure) and feasibility (Feasibility Implementation Measure) in those randomized to InTSHA as primary outcomes. We also measured retention in care (missed clinic visits and/or late pharmacy refills), viral suppression (viral load <200 copies/ml), depression (PHQ-9), transition readiness (HIV Adolescent Readiness for Transition), peer support (Adolescent Social Support Scale), and connection to clinical staff (Working Alliance Inventory) at baseline and 12 months after randomization. We examined the differences from baseline and 12 months in the InTSHA and standard care groups using independent sample t-tests and chi-square tests.

Results: Among adolescents randomized to the InTSHA intervention (n=40) versus standard of care (n=40), we found no difference in 12-month viral suppression rates n=32, 80% and n=34, 85%, respectively (OR 0.7, 95%CI 0.2 – 2.3; p=0.56). All participants were retained in care at one year. Among adolescents randomized to the InTSHA group, acceptability was 80% and feasibility was 78%. Non-significant improvement was seen in scores for depression 0.8 vs 1.47 (p = 0.68), peer support 2.1 vs -1.7 (p=0.19), transition readiness 0.4 vs 0.1 (p=0.35), and connection to clinic 1.3 vs 0.4 (p=0.55) comparing baseline to 12-month responses in InTSHA compared to standard care respectively.

Conclusion: InTSHA is an acceptable and feasible intervention for adolescents with HIV who are transitioning to adult care in South Africa. Although this pilot study did not improve viral suppression or retention in care, potential improvements were seen in depression, peer support, transition readiness, and connection to clinic.

993 Is HIV Outbreak Among Children in Larkana Over? Findings From a Large Test and Treat Initiative

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Background: An outbreak of HIV among children was reported in Ratodero (district Larkana, Sindh province, Pakistan) in April 2019. The main sources of transmission were nosocomial namely, unsafe injections and infusions in healthcare settings. In 2022, routine ART registration data suggested ongoing community transmission with more adults being diagnosed than children, but positivity rates were unclear given the lack of testing data. We present the results of a community-based educate, test and treat initiative in Ratodero to understand the status of outbreak nearly five years after it was first reported.

Methods: Door-to-door testing was done in partnership with CDC Sindh and local administration which focused on selected union councils (UCs) of Ratodero (370000 population), the epicentre of 2019 outbreak. Those aged 18 months to 60 years were eligible, while those who self-reported HIV test in the past 6 months or were already on ART were excluded. Thirty mobile teams of one trained male and female mobilizer each offered a single rapid HIV test (Abbott Early Detect) from house to house in pre-defined geographic areas. Those with a reactive result were referred to Ratodero ART centre for confirmation and ART initiation. Information, education and communication materials related to injection safety were displayed in health facilities and in the community.

Results: Between, September 6 and 21, 2023, 43877 HIV tests were performed (58% among females). Overall, 75 individuals (0.17%; male: 0.19%, female: 0.16%) had a reactive HIV result. The reactive rate varied by UC, ranging from 0% to 0.27%. Two-thirds (n=49) of all reactive results were among children (18 months-14 years). The reactive rate among children (0.24%) was higher than those 15 years and above (0.11%). Of those with reactive results, 55 (71%) were linked to ART centre as of January 9, 2024 (53 confirmed HIV-positive and initiated ART and two persons initiated TB treatment). The mode of transmission for 43 individuals (78%) was reported to be reuse of contaminated needles or syringes.

Conclusion: HIV positivity was comparable to national HIV prevalence (0.2%) suggesting low level community transmission. Children continue to be at a greater risk of acquiring HIV and reuse of contaminated needles and syringes continue to drive the transmission in this setting. Urgent action is needed to address unsafe injection practices to stop the transmission.

994 Data Informed Stepped Care (DiSC) to Improve HIV Care for Youth With HIV: A Cluster Randomized Trial

Pamela Kohler[1], Wenwen Jiang[1], Jacinta Badia[2], James Kibugi[2], Jessica Dyer[1], Julie Kadima[2], Dorothy Oketch[2], Kristin Beima-Sofie[1], Sarah Hicks[1], Barbra Richardson[1], Irene Inwani[3], Seema Shah[4], Grace John-Stewart[1], Kawango Agot[2]

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Background: Adolescents and young adults living with HIV (YLH) may benefit from differentiated care, however providers and policy makers are hesitant to assign YLH to differentiated care due to concerns over poor retention and viral suppression.

Methods: This cluster randomized trial tested effectiveness of a multi-component data-informed stepped care intervention that assigned YLH to different intensities of care according to need. YLH at 12 intervention facilities underwent risk assessment and step assignment at each visit; those at lowest risk were eligible for differentiated services including multi-month refill and pharmacy fast-track. At enrollment YLH received a standardized questionnaire to assess baseline characteristics and were followed for 12 months. Electronic medical record data were abstracted for clinic visit and viral load data. The primary trial outcome was proportion of missed visits during 12-month follow-up. Secondary outcomes included loss to follow-up, viral suppression, and differentiated care assignment. Mixed effects regression was conducted, clustered by individual and facility and adjusted for baseline retention and viral suppression during the pre-enrollment period and for any variable that differed by arm at baseline.

Results: Between April to July 2022, 1911 YLH ages 10-24 were enrolled (1016 at control and 895 at intervention facilities). Median age was 17, 1102 (57.9%) were female, and 1512 (79.5%) were in school, and were balanced between trial arms. More YLH attended clinic alone at baseline in the intervention arm. Among YLH in intervention arm, 574 (64.6%) were assigned to differentiated care services, 122 (13.7%) to standard care, 100 (11.3%) to mental health and retention counseling, and 92 (10.4%) to intensive case management. YLH at control sites received standard care. Missed visits were not significantly different between intervention (8.5%) and control groups (8.3%) (aRR 1.04, 95%CI: 0.89-1.20). Assignment to fast-track pharmacy visits increased at intervention sites (aRR 1.21, 95%CI: 1.01-1.45). Viral suppression was similar between arms (aRR 0.78, 95%CI: 0.49-1.23).

Conclusion: The data-informed stepped care tool resulted in increased assignment of low risk YLH to fast-track visits without additional loss to follow-up or viral non-suppression. Differentiated services were readily implemented in YLH and may align well with school schedules, decrease health system burden, and enable tailored intensive care for YLH with additional needs.

995 Prescription Opioid Use and Disorder Among Older Adults With HIV in the US From 2008-2019

Stephanie Shiau[1], Fabrizio Drago[1], Kylie Getz[1], Greta Bushnell[1], Hillary Samples[1], Alexis Bender[2], Laura Bennett[1], Perry N. Halkitis[1], Tobias Gerhard[1], Jason A. Roy[1], Silvia S. Martins[3], Michael T. Yin[3], Stephen Crystal[1]

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Background: Despite growing concern that people living with HIV receive prescription opioids at elevated rates and experience a disproportionate burden of opioid use disorder (OUD) compared to their HIV- counterparts, few studies have described opioid prescription and OUD trends over time. Our objective was to evaluate these trends among older adults comparing those with HIV to their HIV- counterparts.

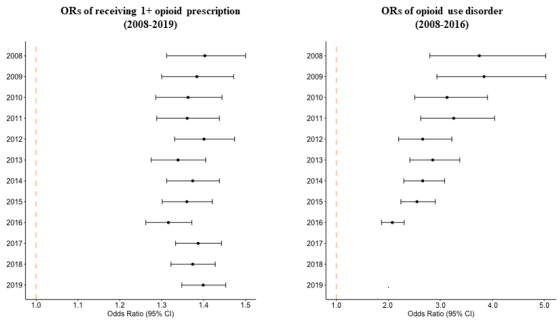
Methods: We constructed annual cross-sectional cohorts (2008-2019) using a nationally representative sample of fee-for-service Medicare beneficiaries 65+ years in the US with Part D coverage. Beneficiaries with HIV (n=124,488) were matched to HIV- beneficiaries (n=373,464) using propensity scores

based on age, sex, race/ethnicity, state, and dual eligibility status. Primary outcomes included receipt of 1+ opioid prescription and diagnosed OUD during that calendar year. Secondary outcomes included receipt of 'high-risk' opioid prescriptions [i.e., 2+ overlapping prescriptions >7 days, ≥90 mg total morphine milligram equivalent (MME) daily dose, and ≥90 consecutive days of coverage], use of medication for OUD, and opioid-related hospitalizations/emergency department (ED) visits. Logistic regression estimated the odds of each outcome comparing matched HIV and HIV- beneficiaries.

Results: The cohort was predominantly male (68.5-74.3%) and White (39.7-49.0%) or African American (34.7-41.4%). Among beneficiaries with HIV, the prevalence of receiving 1+ opioid prescription (31.7-43.0%) and an OUD diagnosis (2.1-4.7%) was higher than their matched HIV- counterparts (24.9-35.6 and 0.6-2.3%, respectively). Consistent across all years, beneficiaries with HIV had significantly increased odds of receiving 1+ opioid prescription (OR=1.32-1.40) and diagnosed OUD (OR=2.08-3.84) compared to their matched HIV- counterparts (Figure 1). Similar trends were observed for all secondary outcomes, including receipt of 2+ overlapping prescriptions >7 days (OR=1.41-1.70), ≥90 mg total MME daily dose (OR=1.41-2.17), ≥90 consecutive days of coverage (OR=1.50-1.72), use of medication for OUD (OR=2.73-7.51), and opioid-related hospitalizations/ED visits (OR=2.48-3.60).

Conclusion: Medicare beneficiaries with HIV have higher odds of receiving opioid prescriptions, diagnosed OUD, and receiving 'high risk' opioid prescriptions compared to matched HIV- beneficiaries. Trends are consistent across all years. Our findings may help guide opioid use management among this vulnerable population.

Figure 1: Logistic regression (odds ratio [OR] and 95% confidence interval [CI]) for odds of receiving 1+ opioid prescription or diagnosed opioid use disorder comparing Medicare beneficiaries with HIV vs. HIV- beneficiaries during each calendar year



996 The Impact of the COVID-19 Pandemic on Substance Use Disorder Risk Among People With HIV in the US

Jennifer P. Jain[1], Nadra E. Lisha[1], Carlos Moreira[1], David V. Glidden[1], Greer Burkholder[2], Heidi M. Crane[3], Jeffrey Jacobson[4], Edward Cachay[5], Kenneth H. Mayer[6], Sonia Napravnik[7], Richard D. Moore[8], Mallory Johnson[1], Katerina Christopoulos[1], Monica Gandhi[1], **Matthew A. Spinelli**[1]

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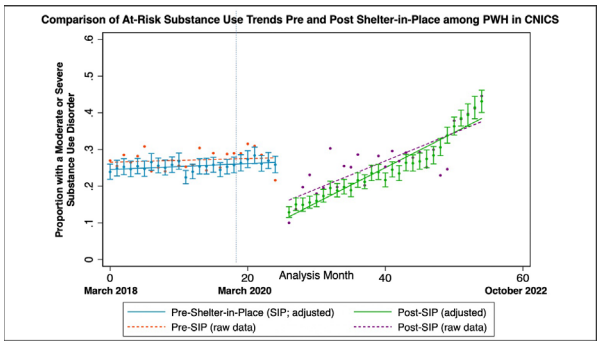
Background: The COVID-19 pandemic has disproportionately impacted vulnerable populations who experience syndemic conditions, including HIV and co-occurring substance use disorder (SUD). We examine here whether there was a significant change in moderate or severe SUD risk among people with HIV (PWH) enrolled in a large multisite clinic-based cohort in the US, before and after the COVID-19 shelter in place (SIP) mandate.

Methods: Data collected between March 2018 and October 2022, among PWH enrolled in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort across eight sites were used for this study. PWH were asked about their use of the following substances: cannabis, cocaine, amphetamines, inhalants, sedatives, hallucinogens, or opioids. Moderate or severe SUD risk was defined as having a score of 4 or greater on the validated ASSIST tool. Using interrupted time series (ITS) analyses, we evaluated whether there was a change in moderate or severe SUD risk over time, comparing trends before and after SIP within a mixed-effects logistic regression model. Analyses were adjusted for age, race/ethnicity, gender, study location, and current HIV viral load.

Results: Data from 7,126 participants, including 21,741 SUD assessments, were included. The median age was 51 (IQR 39-58); 47% of the sample identified as Black, 35% White, 13% Hispanic; and 17% were female. Overall, 43% had used marijuana in the last quarter, 34% cocaine, 15% methamphetamine, and 3% opioids. In the ITS analysis, the rate of moderate/severe SUD risk increased markedly during the pandemic with 43% (95% CI=40-46%) compared to 24% (95% CI=22-26%) having moderate/severe SUD risk post-SIP compared to pre-SIP (P<0.001; Figure).

Conclusion: We found a significant increase in moderate/severe SUD risk among PWH in a large multi-site network of HIV clinics throughout the US. This rising prevalence could be related to an increase in depression, anxiety, and social isolation among PWH during the COVID-19 pandemic. Substance use and misuse are often coping mechanisms for poor mental health conditions, and general life stress. Further, service disruptions due to the pandemic and a transition to telehealth may have caused substantial interruptions in substance use and mental health treatment services among PLWH. To address the combined epidemics of substance use and HIV following the COVID pandemic, a renewed investment in integrated substance use treatment and mental health services is vital.



997 The Opioid Use Disorder Care Cascade for PWH Experiencing Homelessness in Low-Barrier HIV Care

Ayesha Appa, Gabriela Steiner, Matt Hickey, Elizabeth Imbert, Caycee Cullen, John Friend, Rodrigo Avila, Joi Jackson, Pierre-Cedric Crouch, Jon Oskarsson, Francis Mayorga-Munoz, Janet Grochowski, Monica Gandhi

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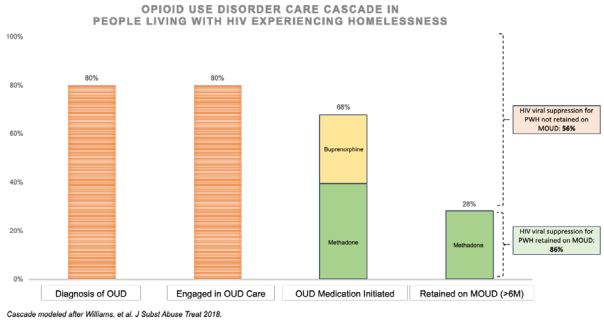
Background: Among people with HIV (PWH) with co-morbid opioid use disorder (OUD), initiation and retention in OUD treatment (e.g., buprenorphine, methadone) substantially reduces overdose deaths and improves HIV viral suppression. We sought to characterize the OUD care cascade for viremic PWH experiencing homelessness enrolled in a low-barrier HIV primary care model with embedded addiction support services.

Methods: The POP-UP clinic at Ward 86 provides comprehensive primary care for viremic PWH with housing instability using a drop-in model with interdisciplinary services including counseling, same-day buprenorphine initiation, methadone clinic in an adjacent building, and on-demand Addiction Medicine consultation. We conducted a retrospective chart review of enrolled patients from February 2019 to July 2023. We identified those with opioid use upon enrollment and tracked their progression through a previously published care cascade for OUD (Figure).

Results: Among 145 PWH experiencing homelessness enrolled in low-barrier primary care, 138 (94%) used substances (78% methamphetamine, 17% opioids, 10% cocaine). Of the 17% who used opioids (25/145), 84% identified as cisgender men, 58% identified as White, 20% Latine, and 16% Black. Almost all opioid use was fentanyl (24/25 fentanyl, 1/25 heroin). All 25 patients reported concomitant use of methamphetamine. Median follow up time was 28 months (interquartile range 12 - 39). Of n=25, 80% (20) were diagnosed with OUD and offered methadone or buprenorphine (i.e., engaged in OUD-specific care); 68% (17) initiated MOUD, but only 28% were retained on MOUD in the subsequent 6 months (Figure). Of n=5 not diagnosed with OUD, n=3 had remote history of OUD, n=2 reported unintentional exposure to fentanyl (with clinical opioid overdose). Of PWH retained on MOUD, 100% were on methadone. HIV viral suppression in PWH retained on MOUD was 86% (6/7) vs. 56% (10/18) HIV viral suppression in PWH with opioid use not initiated or retained on MOUD.

Conclusion: For PWH with a high degree of structural vulnerability, retention in MOUD was low (<30%) despite the availability of low-barrier addiction services in a program serving PWH with homelessness. As all patients retained on MOUD were on methadone, it is crucial to investigate barriers to buprenorphine retention and to enhance methadone clinic referrals from primary care. Finally, addressing the widespread stimulant use observed in this sample of PWH experiencing homelessness is a top priority.



Cascade modeled after Williams, et al. J Subst Abuse Treat 2018.

998 Validation of a Cumulative Substance Use Biomarker Improves Methamphetamine Use Detection in PWH

Ayesha Appa[1], Marjan Javanbakht[2], Rachel Bolanos[2], Hideaki Okochi[1], Karen Kuncze[1], Alexander Louie[1], Matthew A. Spinelli[1], Pamina Gorbach[1], Monica Gandhi[1]

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Background: Methamphetamine (MA) use is a predictor of poor HIV outcomes as well as forward transmission. Despite this, objective assessment of MA use is suboptimal; self-report can be skewed and short-term markers of MA use (e.g., urine tests) have limited sensitivity. We hypothesize that cumulative assessment of hair MA in people at risk of or living with HIV (PWH) who report at least weekly MA use but have negative urine MA tests will increase detection of MA use.

Methods: Leveraging the UCSF Hair Analytical Laboratory's expertise in the use of hair samples to monitor long-term antiretroviral adherence, we developed a hair analytical method to measure past-month MA use. We then examined stored samples from The mSTUDY, a well-established cohort of MSM that collected self-reported substance use data using validated tool (ASSIST), urine and hair specimens. We analyzed hair from participants who reported daily or weekly MA use but were MA urine test negative at the time of hair collection. Per Society of Hair Testing guidelines, hair was considered MA-positive if concentration was >200 picograms/mg. We defined sensitivity as proportion of positive hair samples from MSM who reported at least weekly use, despite negative urine tests. To determine specificity, we randomly selected n=22 hair samples from controls who reported no MA use and where urine testing was negative for substances, including MA.

Results: Demographics and HIV status of the 44 MSM included in the analysis are presented in the Table. Of the 22 MSM who reported daily or weekly MA use but had negative urine tests, 3 (14%) reported daily use and 19 (86%) reported weekly use. Hair analysis detected MA use above the established threshold in 17 additional individuals, yielding a sensitivity of 77% (95% CI 60-95%). Among the 22 control subjects with no reported MA use and negative urine tests for all substances, 3 were found to have MA-positive hair samples, with a specificity of 85% (95% CI 72-100%).

Conclusion: This novel hair-based biomarker identified twice as many individuals with past-month MA use than the urine MA test captured (20 additional individuals of 44 tested) in a cohort of MSM. The calculated sensitivity/specificity of hair tests are likely an underestimate, given inaccuracies in self-reported substance use. Our analysis underscores the potential advantage of hair-based assays in capturing cumulative MA exposure, offering a promising tool for objective assessment of MA use among people at risk for or living with HIV.

Table: Demographic Characteristics & HIV Status of mSTUDY Participants for Biomarker Validation of Methamphetamine Use in Hair

	Participants with self-reported daily or weekly methamphetamine use* N=22	Control participants without reported methamphetamine use** N=22
Age, mean (SD)	33 (6)	37 (7)
Race/ethnicity, n (%)		
Hispanic/Latinx	10 (45%)	12 (55%)
Black (non-Hispanic)	5 (23%)	4 (18%)
White (non-Hispanic)	5 (23%)	5 (23%)
Other	2 (9%)	1 (5%)
Living with HIV, n (%)	11 (50%)	22 (100%)
Proportion with HIV RNA <50 copies/mL	5/11 (45%)	18/22 (82%)

*Reported daily-weekly methamphetamine use but urine drug testing at time of hair sampling negative for methamphetamine.
**Reported never using methamphetamine and urine drug testing at time of hair sampling negative for methamphetamine.

999 Trends and Correlates of Methamphetamine Use Among Men Who Have Sex With Men in the US, 2014-2021

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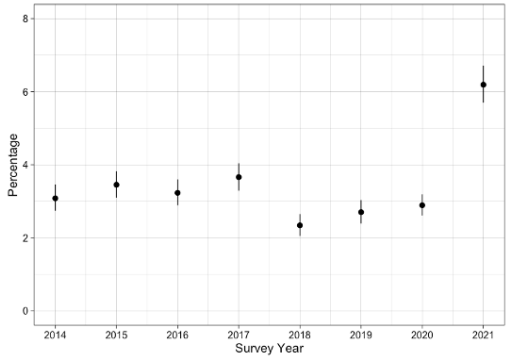
Background: Methamphetamine (MA) is a powerful, addictive stimulant drug disproportionately used among men who have sex with men (MSM) in the United States (US). MA facilitates HIV acquisition and undermines HIV care engagement, threatening the US's goal of Ending the HIV Epidemic. Using a large, national dataset, we examined trends and correlates of MA use among US MSM to identify which subpopulations of MSM in the US have the highest use burden.

Methods: We used data from the 2014-2021 American Men's Internet Survey, a serial, cross-sectional, web-based survey of cisgender MSM in the US conducted by PRISM Center at Emory University. Each year, approximately 10,000 MSM participate and provide behavioral and health data on the 12 months preceding the survey, including non-injection drug(s) used. We estimated the proportion of MSM who reported non-injection MA use in the past 12 months during each survey year. We used univariate log binomial regression to identify correlates associated with MA use and, with those variables, constructed a multivariate model. As a significantly higher proportion of MSM reported MA use in 2021 than in prior years, we repeated this analytic approach using data from only 2021.

Results: Between 2014 and 2017, the proportion of MSM who reported last-year MA use remained from 3.1%-3.7%. In 2018, that proportion dropped significantly to 2.3%, then increased to 2.9% in 2020 and more than doubled to 6.2% in 2021 (Figure 1). In the multivariate model including all survey years, last-year non-injection MA use had notable associations with: living with HIV and using antiretroviral therapy (ART, PR: 4.83 [4.43, 5.27]); living with HIV and not using ART (PR: 4.38 [3.65, 5.19]); being HIV-negative and using pre-exposure prophylaxis (PR: 1.54 [1.37, 1.72]); and Indigenous race (PR: 1.39 [1.18, 1.62]). Results were similar when limited to 2021 respondents.

Conclusion: From 2014-2020, non-injection MA use was largely stable, followed by a sharp increase in 2021. MSM living with HIV reported the highest use burden throughout the period. Those who did not use ART reported notably high rates of MA use, signaling potential for HIV transmission to their partners. Our finding that MA use increased after the first year of the COVID-19 pandemic suggests that there is an increased need for MA prevention efforts among MSM. Future work should explore the extent to which MA use has remained high post-pandemic.

Figure 1: Percentages of Men Who Have Sex with Men Reporting Non-injection Methamphetamine Use in the Last Year
American Men's Internet Survey, 2014-2021 (N=81,019)



1000 Association Between Substance Use Disorder and Sustained Viral Suppression Among People With HIV

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Background: Substance use disorder is an increasing problem among the population in many states of the US and is a potential risk factor for suboptimal viral suppression among people with HIV (PWH). This study aims to examine the association between substance use disorder and sustained viral suppression among PWH.
Methods: Electronic health record (EHR) data from the South Carolina Department of Health and Environmental Control (DHEC) was used to identify eligible adult (≥18 years old) PWH who were diagnosed with HIV between 01/01/2007 and 12/31/2019. Sustained viral suppression was defined as consecutive suppressed viral load tests (≤ 200 copies/mL) within one calendar year. Impact of substance use disorder on sustained viral suppression was evaluated by generalized linear mixed model. Potential confounders included age, sex, and chronic diseases history such as cancer, dementia, diabetes, etc.
Results: Among 9169 eligible participants, 6376 (69.54%) of them had reached sustained viral suppression status during their follow up periods. Substance use disorders, such as alcohol use (AOR=1.16, 95%CI: 1.03-1.29), illicit drug use (AOR=1.19, 95%CI: 1.07-1.33), and tobacco use (AOR=1.18, 95%CI: 1.11-1.26) were negatively associated with sustained viral suppression. Other significant covariates related to sustained viral suppression were also identified. Participants live without Dementia (AOR=2.65, 95%CI: 1.06-6.59) and Diabetes (AOR=1.21, 95%CI: 1.06-1.37) tend to have higher probability to maintain viral suppression.
Conclusion: Using a large cohort of PWH with a long follow up time, this study provided a comprehensive evaluation of the association between substance use disorder and sustained viral suppression. Our findings emphasize the negative impact of using alcohol, illicit drug, and tobacco on maintaining sustained viral suppression. Developing long-term problem substance reduction strategies could help HIV patients achieve long-term viral suppression.

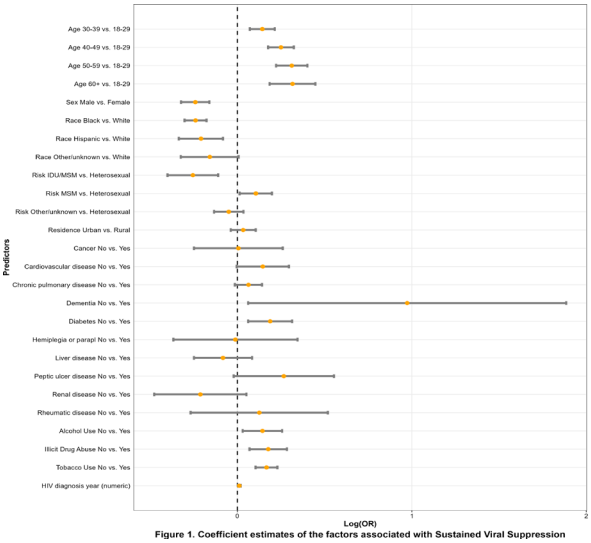

Figure 1. Coefficient estimates of the factors associated with Sustained Viral Suppression

1001 Hazardous Alcohol Use Predicts Detectable Viremia Among Ugandan Women: A Prospective Analysis

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Background: Hazardous alcohol use is associated with poor HIV care outcomes, including poor adherence to antiretroviral therapy (ART) and viral non-suppression. In Uganda, a setting with a generalized HIV epidemic, research has largely focused on understanding this relationship in men because they are more likely to engage in hazardous alcohol use. However, hazardous alcohol use is also prevalent among women. We explore prospective associations between hazardous alcohol use and detectable viremia among women recently diagnosed with HIV (WLWH) in Uganda.
Methods: We analyzed data from women in the standard-of-care control arm of The PATH (Providing Access To HIV Care)/Ekkubo Study, a cluster-randomized controlled trial of an enhanced linkage to HIV care intervention in rural Uganda. To analyze temporal associations between hazardous alcohol use (Alcohol Use Disorder Test- Concise, AUDIT-C, score ≥ 3) and subsequent detectable viral load (VL) (>20 copies per mL), we built prospective logistic regression models using 6- and 12-month follow-up data. Models were adjusted for age, baseline VL, wealth index and if participants were diagnosed pre/post universal test and treat (UTT). We also ran the model adjusting for self-reported adherence using a question form the Adult AIDS Clinical Trials Group (AACTG) adherence instrument.
Results: Our analytic sample included 128 women who were diagnosed with HIV at study enrollment and had VL data available at follow-up. Median age of participants was 25 years [IQR 21-32]; 31% were enrolled before UTT. Prevalence of hazardous alcohol use was 18% at 6-months follow up. The majority (85%) self-reported they were ART adherent at 12- months. In adjusted models, women who report hazardous alcohol use at 6-months had 2.84 greater odds of a detectable VL at 12-months (aOR 2.83, 95% CI 1.05, 7.62, p=0.039). When also controlling for self-reported adherence to ART at follow-up, the magnitude of this relationship is stronger, with women who reported hazardous alcohol use having four times greater odds of a detectable VL at 12-months (aOR 4.07, 95% CI 1.09, 13.8, p=0.025).
Conclusion: Our study provides insight regarding the relationship between hazardous alcohol use and detectable viremia among WLWH. While our adherence measure has limitations (e.g., short time frame), our findings suggest alcohol use may be impacting viremia, underscoring the need to screen for and intervene on hazardous alcohol use among WLWH.

1002 Biomarker Measure Strengthens Alcohol Use Association With HIV Viral Non-Suppression in PWH on ART

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Background: Alcohol use among persons with HIV (PWH) predicts poor antiretroviral (ART) adherence and other co-morbidities, but its association with HIV viral non-suppression is inconsistent. This may be due to the limitations of alcohol self-report. The biomarker phosphatidylethanol, PEth, is an objective blood-based alcohol measure correlated with past month alcohol use. We assessed the association between alcohol use (using a composite of PEth and self-report) and HIV viral non-suppression.
Methods: We pooled data from PWH on ART for ≥6 months from three RCTs and three observational studies conducted from 2012-2022 in the US, Russia, and Uganda, and measured alcohol use via PEth and the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) self-reported screener. We categorized PEth/AUDIT-C alcohol use as: (1) no/low risk (PEth<50 ng/mL and AUDIT-C 0-2/women or 0-3/men); (2) moderate risk (50≤PEth<200 ng/mL and AUDIT-C 3-5/women or 4-5/men); (3) high risk (PEth≥200 ng/mL and AUDIT-C≥6); if PEth and AUDIT-C were discordant, the higher-risk group was selected. We used mixed effects logistic regression to model the associations between alcohol use and HIV viral non-suppression (≥250 copies/mL) adjusting for sex, age, ART regimen, other substance use, study design and location. We accounted for within-individual and between-study clustering, examined associations using PEth and AUDIT-C alone, and explored interaction by the above variables.
Results: Among 2343 participants (4137 obs), 51% were male, 8% were HIV virally non-suppressed, median PEth was 53 ng/mL (IQR=<8-281), and median AUDIT-C was 4 (IQR=1-7). We found a significant association between PEth/AUDIT-C and HIV viral non-suppression (adjusted OR [95% CI]: high vs. no/low risk= 1.88 [1.07-3.31]). The associations were stronger for PEth/AUDIT-C and PEth alone versus AUDIT-C alone (see Table). We found significant interaction by sex (p<0.10) with a stronger association between high-risk alcohol

consumption and HIV viral non-suppression among men compared to the association in women, but no other interaction.

Conclusion: These findings suggest that alcohol use measured by a composite of biomarker/self-report is associated with HIV viral non-suppression, particularly among men with HIV on ART. Associations using both PEth/self-report and PEth alone were stronger than when using self-report alone. Objective measurement of alcohol use may lead to more accurate findings regarding the relationship between alcohol use and HIV outcomes.

Table 1. Associations between alcohol use and HIV viral non-suppression among PWH on ART using different alcohol measurement strategies

Level of alcohol use	Composite PEth/AUDIT-C		Peth		AUDIT-C	
	aOR for VNS (95% CI)	p*	aOR for VNS (95% CI)	p*	aOR for VNS (95% CI)	p*
All – Medium vs. No/Low	0.96 (0.51, 1.83)	0.02	0.74 (0.42, 1.32)	0.003	1.11 (0.65, 1.89)	0.28
All – High vs. No/Low	1.88* (1.07, 3.31)		2.00* (1.17, 3.42)		1.49 (0.90, 2.46)	
Women – Medium vs. No/Low	0.53 (0.22, 1.30)	0.25	0.64 (0.26, 1.55)	0.60	0.70 (0.31, 1.57)	0.64
Women – High vs. No/Low	1.05 (0.47, 2.37)		0.94 (0.39, 2.62)		1.01 (0.41, 2.51)	
Men – Medium vs. No/Low	3.36 (0.99, 11.41)	0.008	1.00 (0.43, 2.29)	0.001	1.77 (0.81, 3.84)	0.15
Men – High vs. No/Low	5.40* (1.82, 15.99)		3.91* (1.73, 8.80)		1.89 (0.97, 3.67)	

Abbreviations: aOR= adjusted odds ratio, ART= antiretroviral therapy, CI= confidence interval, p= p-value, PEth= phosphatidylethanol, PWH= persons with HIV, VNS=HIV viral non-suppression
*statistical significance (alpha=0.05)
*global p-values

1003 Associations of Alcohol Consumption With Long-Term Mortality of ART-Naive Persons Seeking HIV Care

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Background: HIV infection is associated with several chronic diseases. However, the impact of unhealthy alcohol use on clinical outcomes and survival is a matter of debate. We aimed to examine the role of excessive alcohol consumption on all-cause mortality among ART-naïve individuals admitted to HIV care.

Methods: Longitudinal study in the Spanish network on HIV/AIDS (CoRIS) among individuals enrolled between 2004 and 2021 in 47 HIV/AIDS units. We analyzed crude and adjusted mortality rates by alcohol consumption at first visit. Cox proportional hazard models were used to assess the association between excessive alcohol consumption (>40 gr/day) and mortality after controlling for confounders [i.e., age at first visit, sex, HCV infection (EIA+), CD4 cell count and HIV-RNA viral load and persons who inject drugs as mode of HIV acquisition (PWID)].

Results: 8,378 participants (15% women) were included; median age at first visit was 37 years (IQR: 29-44 years). Men who had sex with men (MSM) accounted for 61% of the participants, 28% were heterosexuals and 6.3% were PWID. Among drinkers (38% of the study population), mean alcohol consumption was 70 grams per week (± 23.6 gr). In addition, 4.3% of participants reported alcohol consumption >40 grams/day. The prevalence of alcohol consumption >40 grams/day was higher among PWID (26%) than among MSM (2.4%) or heterosexuals (5.3%) Prevalence of HCV infection was 8.8%, median log RNA-HIV load was 4.54 (IQR: 3.67-5.13) and median CD4 count was 398 cells/ mm³ (IQR: 219-596). After a median follow up of 5.6 years (IQR: 2.5-9.8 years) and a total follow-up of 52,799 person-years (p-y), 267 participants (3.1%) had died. Crude mortality rate of those who drank >40 grams/day was 2.09 x 100 p-y vs. 0.43 x 100 p-y among those who drank <40 grams/day [RR 4.85 (95% CI: 3.56-6.62), p <0.01]. In the unadjusted analysis, alcohol consumption >40 grams/day (HR 4.28; 95% CI: 3.13-5.83), age greater than the median (HR: 2.16; 95% CI: 1.62-2.89), HCV infection (HR: 5.05; 95% CI: 3.94-6.48), CD4 cell count below the median (HR: 2.58; 95% CI: 1.96-3.40) and PWID (HR: 4.72; 95% CI: 3.64-6.17) were associated with mortality. In the adjusted model, alcohol consumption >40 grams/day was associated with a higher risk of mortality [HR 2.39 (95% CI: 1.68-3.42), p <0.01)].

Conclusion: In this cohort of ART-naïve individuals entering HIV care, unhealthy alcohol use was associated with reduced survival.

1004 Pre-Pandemic Patterns of Cannabis Use Among Women With HIV in the United States

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Background: The regulatory environment for marijuana and other cannabis products is changing quickly across the United States, and use has increased over the past decade. The contemporary prevalence of use, frequency of use, and uptake of newer cannabis products, such as vape products, is unknown for women with HIV. Because cannabis products can pose health risks and have immunomodulatory effects mediated by cannabinoid receptors, it is important to understand patterns of cannabis use among women with HIV.

Methods: This analysis includes 1,246 women with HIV enrolled in the Women's Interagency HIV Study (WIHS) who attended three semi-annual study visits between April 2018 and September 2019. Data on cannabis use were collected at each visit. A Sankey diagram illustrates the flow of participants between different categories of use frequency over the follow-up period.

Results: The period prevalence of cannabis use was 27%. 26% reported smoking marijuana, 8% reported enteric consumption of cannabis products, and 5% reported vaping cannabis products. The prevalence of daily cannabis use was 15%. There was no significant difference in the prevalence of use between sites in states with laws permitting adult or medical use and in states without. Cannabis users were younger, less likely to be employed, and more likely to have used tobacco, alcohol, and other substances. The proportion of users who reported vaping cannabis products increased from 10% in 2018 to 14% in 2019. Compared to cannabis users who did not vape, cannabis users who vaped were more likely to be employed and have a college degree. They were less likely to have smoked cigarettes and more likely to have used e-cigarettes. They were more likely to attend a study site in a permissive jurisdiction. While half of all users reported the same frequency of cannabis use at all three visits, the remaining half of users reported different frequencies of use on at least two visits (Figure 1).

Conclusion: In a cohort of women who are representative of women with HIV in the United States, we found a high prevalence of cannabis use in the period immediately preceding the COVID pandemic. Our prevalence estimate is higher than in the general US population and higher than for women with HIV in the WIHS a decade prior, which was 14%. From 2018 to 2019, there was a small increase in the proportion of users who vaped cannabis products. It was not uncommon to report different frequencies of cannabis use at different study visits across 18 months of follow-up.

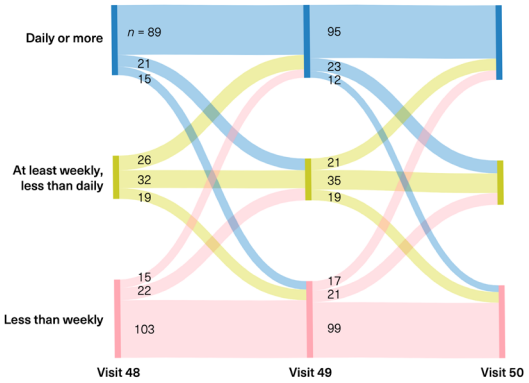

Figure 1. Participant flow between categories of cannabis use frequency among women with HIV who used cannabis in the Women's Interagency HIV Study, visits 48-50. 172 women reported the same cannabis use frequency across all visits, while 170 women reported different frequencies on at least two visits.

1005 Incarceration, Drug Use, and HIV: Optimizing Services for Women Who Use Drugs in Tanzania

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Background: Women who use drugs (WWUD) in sub-Saharan Africa (SSA) face elevated HIV risk, which is linked to structural vulnerability including high rates of incarceration and arrest. However, little is known about the experiences of formerly incarcerated WWUD in SSA or their drug use and HIV outcomes.
Methods: Using respondent-driven sampling (November 2018-February 2019), we recruited WWUD reporting past-month heroin use in Dar es Salaam, Tanzania and administered a structured survey (n=200). We described the prevalence of recent incarceration (being in jail or prison in the past six months) and characteristics of recently incarcerated WWUD. We used modified Poisson regression with robust variance estimation to calculate prevalence ratios (PRs) and 95% confidence intervals (CI) for the associations between recent incarceration and HIV and drug use outcomes, adjusting for age, education, and duration of heroin use in years.
Results: Over half of WWUD (n=119, 61%) reported incarceration in the past six months. The most common reasons for arrest were using drugs (47%) and selling sex (27%). In bivariate analyses, incarceration was associated with transactional sex, symptoms of depression and anxiety, physical violence victimization, and drug use stigma from family and healthcare providers (Table). In adjusted analyses, incarceration was associated with 46% higher prevalence of concurrent sexual partnerships (PR 1.46, 95% CI 1.17-1.82), five times the prevalence of concurrent stimulant use (PR 5.70, 95% CI 1.74-18.70), and 76% higher prevalence of lifetime non-fatal overdose (PR 1.76, 95% CI 1.08-2.85). Among WWUD living with HIV, incarceration was associated with missing HIV care appointments (p=0.02).
Conclusion: This study, one of the first to describe HIV-related outcomes among recently incarcerated WWUD in SSA, identified converging behavioral and structural risks related to incarceration, which may exacerbate HIV disparities among WWUD. Elevated stimulant use among recently incarcerated WWUD is of particular concern, given associations with adverse HIV outcomes. In the context of highly criminalized sex work and drug use, interventions that target policing practices such as drug diversion programs, may be effective at reducing incarceration-associated risks. For WWUD, including those living with or at risk for HIV, multilevel interventions may be needed to reduce service interruptions and ensure linkage to care during incarceration and reentry.
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1006 Differences in Healthcare Access Among Persons Who Inject Drugs by Medicaid Expansion Policy, 2022

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Background: Since 2014, 40 states expanded Medicaid, extending coverage to millions. Persons who inject drugs (PWID) are at increased risk for HIV, often have low income, and could benefit from Medicaid expansion. Yet, many PWID live in non-expansion states, mostly in the South. We compared healthcare access between PWID living in Medicaid expansion vs. non-expansion states. We conducted a subanalysis focused on PWID with HIV.
Methods: We analyzed 2022 data from CDC's National HIV Behavioral Surveillance in 19 US cities sampling PWID aged 18-64 years (n=6245). We used multilevel log-linked Poisson models to compare PWID's healthcare access by state-level Medicaid expansion policy (defined as expanding Medicaid by June 1, 2022), producing adjusted prevalence ratios (aPR) and 95% confidence intervals (CI). Significance was determined by CIs overlapping with the null.
Results: Most PWID lived in a Medicaid expansion state (85%). Most PWID in non-expansion states were Black (59%). Only 1 out of 10 PWID in expansion states were uninsured compared to 2 out of 3 PWID in non-expansion states (aPR=0.1, 95%CI=0.1-0.2). PWID in Medicaid expansion states were 5 times as likely to have Medicaid than PWID in non-expansion states (72% vs. 13%; aPR=5.3, 95%CI=5.3-5.3). PWID in Medicaid expansion states were more likely than those in non-expansion states to have visited a doctor in the past 12 months (76% vs. 66%; aPR=1.2, 95%CI=1.1-1.3) and have a usual source of healthcare (52% vs. 38%; aPR=1.4; 95%CI=1.1-1.9). PWID in expansion states were less likely than those in non-expansion states to have an unmet medical need due to cost (18% vs. 41%; aPR=0.4, 95%CI= 0.4-0.5). Only 4% of PWID with HIV in expansion states were uninsured compared to 54% of PWID with HIV in non-expansion states (aPR=0.1, 95%CI=0.0-0.1). PWID with HIV in expansion states were less likely to have an unmet medical need due to cost than those in non-expansion states (12% vs. 38%; aPR=0.3, 95%CI=0.2-0.5).
Conclusion: Medicaid expansion is associated with better access to healthcare and fewer unmet medical needs among PWID, a population that often has diverse medical needs and few resources. Non-expansion hinders efforts to end the HIV epidemic and disproportionately affects Black PWID, contributing to racial/ethnic inequities. Clinics in non-expansion states may link PWID patients to services and patient assistance programs to defray costs. States may consider expanding Medicaid.

1007 Unmet Need for Medication for Opioid Use Disorder Before and After the COVID-19 Pandemic

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Background: The COVID-19 pandemic substantially impacted harm reduction services for persons who inject drugs (PWID), including access to medications for opioid use disorder (MOUD) that reduce injection frequency, HIV and HCV transmission, and opioid-related overdose mortality. We sought to assess change in unmet need for MOUD among PWID from pre- to post-pandemic.
Methods: PWID were recruited using respondent-driven sampling to participate in CDC's National HIV Behavioral Surveillance in 19 U.S. cities in 2018 and 2022. This analysis included PWID who were ≥ 18 years and reported injecting drugs and opioid use in the past 12 months. We obtained prevalence ratios (PRs) and 95% confidence intervals (CIs) using log-linked Poisson models adjusted for city and participant network size and clustered on recruitment chain to assess differences in self-reported unmet need for MOUD between 2018 and 2022.
Results: The analysis included 9,282 PWID interviewed in 2018 and 5,882 PWID interviewed in 2022. Overall, fewer PWID reported unmet need for MOUD in 2022 than in 2018 (28% vs. 25%, PR 0.91; 95% CI: 0.85, 0.98). Additionally, unmet need for MOUD decreased from 2018 to 2022 among PWID who most commonly injected opioids (28% vs. 24%, PR 0.86; 95% CI: 0.77, 0.95), PWID who injected more than once a day (30% vs. 27%, PR 0.89; 95% CI: 0.82, 0.98), and PWID who received syringes from an SSP in the past 12 months (28% vs 25%, PR 0.87; 95% CI: 0.78, 0.97).
Conclusion: Decreases in unmet need for MOUD were observed among those at high need for MOUD, specifically those who injected most frequently and most commonly injected opioids. Unmet need for MOUD also decreased among those accessing SSPs, which are important service programs for PWID. Low-threshold, affordable access to MOUD is key to reducing injection-related risk for HIV and other infectious disease. Despite COVID-19 pandemic-related disruptions in services for PWID, policy changes to federal guidance for MOUD treatment providers or other innovations in service provision may have contributed to increases in access to MOUD. Additional research is needed to assess what factors or potential policies mitigated the effects of service disruptions due to the pandemic on unmet need for MOUD and the resulting impact on HIV and other infectious diseases.

1008 HIV Prevention Service Use Among PWID in Washington, DC, Pre- and Post-COVID Pandemic Eras

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Background: The COVID-19 pandemic disrupted access to critical healthcare and HIV prevention services for people who inject drugs (PWID). We explored the pandemic's potential impact on use of healthcare and HIV prevention services among PWID in the pre- and post-COVID pandemic eras.
Methods: We used data from the 2018 and 2022 National HIV Behavioral Surveillance system in Washington, DC. PWID were recruited via respondent-driven sampling (RDS) and were ≥18 years old, resided in the Washington metropolitan statistical area, and reported injecting non-prescribed drugs in the past 12 months. Self-reported healthcare and HIV prevention service utilization, drug-use behaviors, and drug treatment were assessed. RDS-weighted percentages were calculated; Rao-Scott chi-square tests identified significant differences in service utilization and drug use behaviors comparing 2018 and 2022.

Results: N=511 participants in 2018 and N=229 participants in 2022 were included in the analysis. More than 70% of both samples were male. Compared to 2018, a higher proportion of PWID were >65 years old and fewer identified as Non-Hispanic Black in 2022. In 2022, a higher proportion of PWID reported using ≥2 most frequently injected drugs (6.3% vs. 16.0%, p<0.0001). In 2022, more PWID owned naloxone (35.0% vs. 81.8%, p<0.0001) and sought out fentanyl (10.6% vs. 26.2%, p<0.001) in the past year. No differences were found in having a usual healthcare source, HIV testing, or PrEP awareness and uptake. However, a significantly lower proportion of 2022 participants reported sharing needles (40.5% vs. 21.6%%, p<0.01), cookers/cotton/water (53.4% vs. 35.8%, p=0.0058), or syringes (40.8% vs. 23.0%, p<0.01) than those in 2018. Fewer PWID obtained needles from syringe service programs (SSPs) over time (74.8% vs. 59.9%, p=0.03), but a larger proportion in 2022 obtained needles from places other than SSPs or HIV prevention programs (9.4% vs. 23.3%, p=0.01). In 2022, past year engagement in drug treatment programs also increased from 31.4% to 61.6% (p<0.0001).
Conclusion: Significant decreases in injection-related risk behaviors and increases in utilization of drug-related services were observed among PWID in Washington, DC. Changes in drug use behaviors over time and where PWID received services were also observed, suggesting the need to better understand how changes in service utilization and drug use patterns impact PWID health.

1009 Changes in HIV PrEP Awareness and Use Among PWID in 19 US Cities, 2018 and 2022

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Background: HIV pre-exposure prophylaxis (PrEP) awareness and use among persons who inject drugs (PWID) has been low since the introduction of PrEP in the U.S. in 2012. Limited data are available to monitor PrEP awareness and use specifically among PWID.
Methods: In 19 U.S. cities participating in 2018 and 2022 National HIV Behavioral Surveillance, PWID were recruited using respondent-driven sampling and offered a behavioral survey and HIV testing. We examined the prevalence of PrEP awareness and PrEP use in the past 12 months, overall and by key characteristics, among HIV-negative PWID in 2018 and 2022. We obtained adjusted prevalence ratios, 95% confidence intervals, and p-values using log-linked Poisson models accounting for clustering by recruitment chain and adjusting for city and participant network size to assess changes in PrEP outcomes over time.
Results: From 2018 to 2022, PrEP awareness among PWID increased from 25.6% to 35.3% (p<0.01), yet PrEP use in the past year remained stable at 1.2% (p=0.35). The approximate 10 percentage-point increase in PrEP awareness between 2018 and 2022 was consistent across demographic and behavioral subgroups. PrEP awareness increased significantly among PWID who had receptively shared syringes, shared injection equipment, had condomless vaginal or anal sex, and had a bacterial STI in the past year (all p-values <0.01). Minimal yet significant increases in PrEP use were observed for those who had receptively shared syringes, shared injection equipment, and received a recent HIV test (all p-values <0.05); nevertheless PrEP uptake in these groups did not surpass 2%. PrEP use was highest among those reporting past-year male-male sex and bacterial STI (both 4.8% in 2022); this was stable compared with 2018.
Conclusion: PrEP awareness significantly increased from 2018 to 2022 among PWID. Still, only about one-third were aware of PrEP in 2022. Increases in awareness were consistent across subgroups, suggesting that PrEP messaging is reaching groups with a greater risk of HIV acquisition, yet changes may be due to a generalized increase in awareness overall. PrEP use remained suboptimal. PWID at higher risk of injection-related HIV acquisition and those who obtained HIV-related services did experience significant increases in PrEP uptake unlike other subgroups; however, increases were small. Efforts to improve PrEP messaging, provider training, and access specifically for PWID may serve to further increases in PrEP awareness and use.
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1010 Changes in PrEP Awareness Among Men Who Have Sex With Men and PWID: 19 US Cities, 2018 and 2022

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Background: HIV preexposure prophylaxis (PrEP) is effective at preventing infection among persons at risk for acquiring HIV. PrEP campaigns have focused on sexual behaviors, particularly same-sex behaviors, and may not be reaching heterosexual-identifying men or people who inject drugs. This analysis aimed to explore changes in PrEP awareness and use among men who have sex with men and inject drugs (MSM-ID) in 2018 and 2022 by sexual orientation.
Methods: We analyzed data from 2018 and 2022 National HIV Behavioral Surveillance among people who inject drugs recruited via respondent-driven sampling in 19 US urban areas. The analytic sample was restricted to HIV-negative males who inject drugs and who had sex with another man in the past 12 months (MSM-ID). Using log-linked Poisson regression models, adjusted prevalence ratios (aPRs) and 95% confidence intervals (95% CIs) were calculated to estimate changes in PrEP awareness stratified by sexual orientation. Models were adjusted for age, race/ethnicity, city, and network size, and accounted for clustering by recruitment chain. Small sample size of PrEP users precluded statistical comparison on PrEP use.
Results: Of HIV-negative MSM-ID, 71.5% (331/463) in 2018 and 66.8% (197/295) in 2022 identified as gay/bisexual. Between 2018 and 2022, there was a significant increase in PrEP awareness among gay/bisexual MSM-ID (45.5% in 2018, 64.5% in 2022; aPR=1.51, 95% CI=1.32-1.72) but not for heterosexual MSM-ID (39.4% in 2018, 40.8% in 2022; aPR=0.98, 95% CI=0.73-1.31) (Figure). Among MSM-ID aware of PrEP, PrEP use was low in both years regardless of sexual orientation (gay/bisexual: 15.3% in 2018, 10.2% in 2022; heterosexual: 7.7% in 2018, 2.5% in 2022).
Conclusion: The increase in PrEP awareness was limited to gay/bisexual men, however, PrEP use was low overall among MSM-ID regardless of sexual orientation. Without adequate HIV prevention, MSM-ID may be at risk of acquiring or transmitting HIV through injecting drugs and sex. Provider training may be useful to encourage assessment of both injection- and sex-related indications for PrEP during provider visits. Educational campaigns tailored to MSM-ID are warranted, particularly around risk behavior and benefits of PrEP regardless of one's sexual orientation.

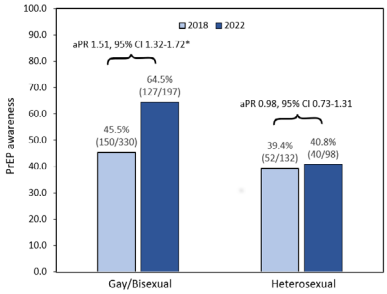

Figure: Changes in PrEP awareness among men who have sex with men and inject drugs by sexual orientation, NHBS-PWID, 19 US urban areas, 2018 and 2022
*significant at p-value<0.05; adjusted for age, race/ethnicity, city, and network size; accounted for clustering by RDS recruitment chain

1011 RDS Network Size Among People Who Inject Drugs in Kenya as a Predictor of HIV and HCV Positivity

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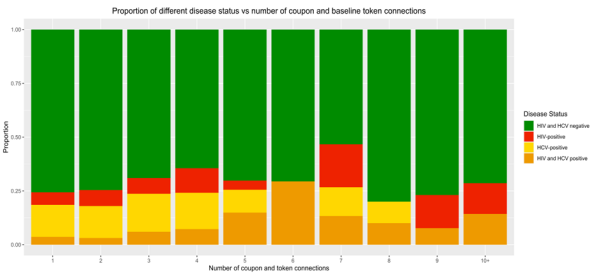
Background: People who inject drugs (PWID) are a key population for HIV and HCV transmission in sub-Saharan Africa. Understanding transmission networks is critical to reducing prevalence and incidence among PWID. Yet, network-related factors associated with seropositivity are poorly understood.
Methods: We are recruiting PWID using respondent driven sampling (RDS) from syringe services programs in Kenya. Upon enrollment, participants complete biobehavioral surveys, receive HIV, HCV, and HBV testing, and are provided with 3 coupons to recruit their peers who are not already in the study. Upon return of 3 coupons, 5 tokens are given to establish crossties among PWID

who are already enrolled in the study. We evaluated the relationship between RDS-network size and HIV and HCV infection using t-tests and permutation tests.

Results: Among 2135 PWID enrolled thus far from May 2022 to August 2023, participants are mainly male (89.8%) and 34.6 years old (SD=±8.7) on average. 236/2135 (11.1%) are HIV positive; with highest regional prevalence in the Coast (130/962, 13.5%), followed by Nairobi (83/770, 10.8%), and Western Region (21/393, 5.3%). HCV follows a similar gradation moving inland – 425/2135 (19.9%) overall; 248/962 (25.8%), 175/770 (22.7%) and 2/393 (0.5%), respectively. On average, participants report they know 11.1 (SD=14.9) PWID who also know them among whom they have seen 8.4 (SD=6.2) in the last 30 days and have injected with 5.4 (SD=5.4). The average network size as determined by coupon and token recruits was 2.2 with 7 (0.3%) having >10 connections. We observed a highly significant positive relationship between the number of RDS connections and likelihood of HIV/HCV co-infected vs uninfected ($p<0.001$), HIV-monoinfected vs uninfected ($p<0.001$), and HCV mono-infected vs. uninfected ($p<0.05$).

Conclusion: These data, while preliminary, may inform policy makers and programs on HIV and HCV treatment and prevention strategies among PWID. The robust link between network connectivity and elevated HIV and HCV risk highlights the importance of network dynamics in disease transmission. Further study is needed on the potential efficiency of network-based interventions compared with traditional testing and linkage to care to advance efforts toward ending the HIV epidemic and HCV elimination.



1012 HIV Incidence & Changes in Network Structure Among PWID in New Delhi Following the COVID-19 Pandemic

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Background: Identifying transmission predictors among people who inject drugs (PWID) is vital for curbing HIV spread. We previously described the role of a particular venue on transmission of HIV among PWID in New Delhi. COVID-19 lockdowns forced PWID at this venue to return home or relocate. The impact of such regulations on HIV transmission remains unknown.

Methods: From 2017-19 (Pre-COVID), 2,512 PWID were recruited into a dynamic cohort and followed semi-annually until March 2020. Over 1,000 participants were lost (migrated or deceased) when the site re-opened. An additional 987 PWID were recruited to replace lost participants using identical procedures between February 2022 and April 2023 (Post-COVID). In both samples, indexes initiated sampling; they recalled who they injected with in the past month and recruited them. Similarly, each recruit named and recruited their recent injection network. Biometric data was used to identify duplicates and establish cross-network links. Injection venues were captured via a survey. Individual and network factors were analyzed for associations with HIV seroconversion using Poisson regression.

Results: Since 2017, 3,499 PWID were recruited; 37.2% were living with HIV (37.0% and 37.6% in the pre- and post-COVID recruits, respectively). Among those without HIV, median age was 28 years; 98% were male, 69% reported daily injection and 48% reported needle sharing in the prior 6 months. 243 seroconversions were observed over 1912.5 person years (HIV incidence of 12.7 per 100 p-y); incidence in the pre- and post-COVID recruits was 13.8 and 7.3 per 100 p-y, respectively. In pre-COIVD recruits, individual and network factors, and one particular venue were predictors of seroconversion. In post-COVID recruits, depression, needle sharing, network distance to an HIV-positive person, and 19 venues were associated. Further, venues associated with seroconversion in the new recruits differed from those pre-COVID (Figure). The post-COVID network was sparser with greater diameter, path length, and fewer injection partners, featuring linear recruitment chains and fewer cross-network links.

Conclusion: Post-COVID, the network structure of PWID was altered. HIV seroconversion in the post-COVID recruits was more strongly driven by spatial ties rather than individual-level behavior, though behaviors were largely comparable to the original cohort. The diffusion of incidence across several newer venues could signal an impending outbreak of HIV at venues that were previously low risk.

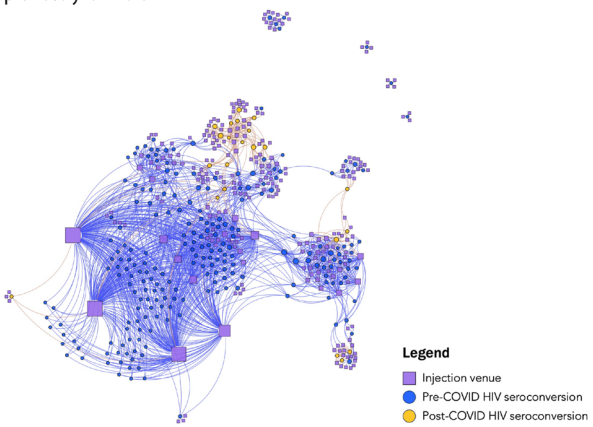

Figure. Spatial network of 243 people who inject drugs in New Delhi, India with observed HIV seroconversions 2017-23. Purple square nodes represent injection venues and are sized by degree. Circular nodes represent persons, are sized by degree, and colored to reflect whether they were recruited pre-COVID (2017-19) or post-COVID (2022-23). Edges represent a spatial tie (i.e., injecting at a particular venue). Social ties between participants are not depicted. Nodes are placed using a degree-dependent force-directed algorithm (ForceAtlas2).

1013 Spatial Clustering of HIV Viremia Among People Who Inject Drugs (PWID) in India

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Background: While India has made significant progress in engaging people on antiretroviral therapy (ART), people who inject drugs (PWID) living with HIV (PLWH) remain under-engaged in treatment with only ~26% on ART and 32% virally suppressed. Using geospatial data to identify geographical clusters of viremia could help find optimal locations to intervene.

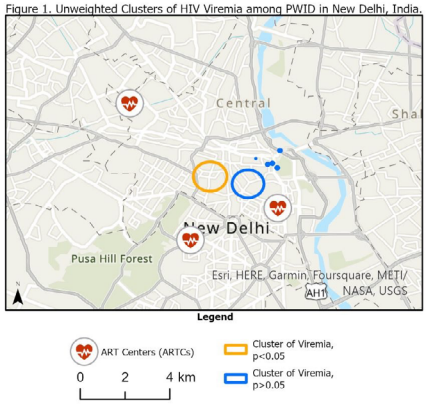
Methods: Respondent-driven sampling was used to enroll a sample of ~750 PWID in New Delhi from April-August 2023. Participants were ≥18 years and reported injection drug use in prior 2 years. Participants underwent HIV testing and provided up to 5 locations where they injected in the prior year. Viral load testing was conducted on all positive specimens. We mapped locations where PWID injected and used scan statistics to assess spatial clustering of HIV viremia (>1000 copies/mL). We explored distance from treatment centers (ARTCs) among PLWH and sociodemographic/risk behaviors associated with reporting injecting at a cluster location among PLWH with viremia using Fisher's exact test and logistic regression.

Results: Among the 752 enrolled PWID, median age was 27, 99% were male, 66% experienced recent homelessness, 74% inject daily, and 32% of PLWH were viremic. Participants injected in places a median distance of 2.4km (IQR, 2.3 – 2.6) from ARTCs. This did not vary by viremia status. Only 39% of PLWH were previously diagnosed. Seven clusters were identified, and one (C1) was statistically significant, located near 'Old Delhi' (Figure 1). A higher proportion of PWID with viremia injecting in C1 reported injecting daily (94% v. 72%), missing treatment due to drug use (75% v. 29%), and a larger network size (median 60 v 12 PWID) compared to those not in C1. PWID with viremia who injected in C1 also had higher proportions of moderate/severe depression (50% v 21%) and of injecting with multiple persons over half the time (72% v 37%).

Conclusion: In an urban setting with a growing HIV epidemic among PWID, there was a geospatial cluster of PWID with untreated HIV associated with higher levels of risk behaviors – potentially facilitating transmission. Most PWID injected daily and at least 2km from ARTCs. Finding additional areas of high

viremia using other point pattern and spatial autoregressive techniques can further assess spatial associations with ARTCs. Identifying distinct geographic areas characterized by high viremia can provide targets for field-based mobile strategies incorporating testing, prevention and treatment to interrupt transmission.

Figure 1. Unweighted Clusters of HIV Viremia among PWID in New Delhi, India.



1014 HIV-1 Transmission Dynamics Among People Who Inject Drugs on the US/Mexico Border Amid COVID-19

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Background: We assessed HIV prevalence, incidence, and patterns of phylogenetic clustering and cluster growth in networks among people who inject drugs (PWID) in the U.S./Mexico border region during the COVID-19 pandemic.
Methods: We conducted secondary analysis of a longitudinal study of PWID aged ≥18 years from 3 groups: PWID who live in San Diego county (SD) and engaged in cross-border drug use in Tijuana ≤24 months ago (SD CBDUs), and PWID who did not engage in cross-border drug use (NCBDUs), and who live in either SD or Tijuana (TJ). Between Oct/2020-Oct/2021, participants underwent semi-annual surveys and provided samples for HIV. We calculated HIV prevalence and bivariate incidence-density rates (IR) between baseline and 18-month follow-up visits. Bayesian phylogenetic analysis was used to identify local transmission clusters and estimate their age (as time to most recent common ancestor, TMRCA). We further applied a birth-death skyline model to estimate changes in the effective reproductive number of large local transmission clusters (Re).
Results: At baseline (n=612), HIV prevalence was 8% (4% SD CBDU, 4% SD NCBDU, 16% TJ NCBDU). Of HIV-seronegative PWID at 18 months follow-up, 9 HIV seroconversions occurred (IR: 1.357 per 100 person-years (95% CI: 0.470, 2.243) 7 of whom were TJ NCBDU and 2 were SD CBDU. We identified 16 phylogenetic clusters that included at least 1 sequence from the cohort (cluster size range 2-17), among which 9 (56%) had sequences from both the U.S. and Mexico. Three dyads had highest posterior density (HPD) intervals of TMRCA estimated to overlap with the COVID-related US-Mexico border closure in 2020 and all included participants from both sides of the border. One of the two identified large clusters (N=15) included TJ NCBDU and SD CBDU participants only, 47% of the cluster reported sex work, and continued to grow during the border closure (Re=4.8, 95% HPD 1.5 – 9.1].
Conclusions: During the COVID-19 pandemic, HIV phylogenetic clusters were detected with sequences from both sides of the border, one of which continued to grow despite the border closure. Despite relatively low HIV incidence overall, mobile harm reduction services providing syringes and HIV testing, and coordination with municipal HIV programs to initiate ART and PrEP are needed to reduce transmission, particularly in Tijuana.

1015 HIV-1 Outbreak Among PWID in Thessaloniki: Recent Expansion in the Midst of COVID-19 Pandemic

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Background: During the implementation of "ALEXANDROS", a community-based programme, an HIV-1 outbreak was identified among people who inject drugs (PWID) in Thessaloniki, the second largest city in Greece, between 2019 and 2021. Preliminary phylogenetic analysis suggested that 25 sequences from PWID sampled in Thessaloniki during 2019-2021, belonged to 3 phylogenetic clusters of subsubtype A6 and 1 cluster of subsubtype A1. We aimed to investigate the characteristics of this new outbreak by means of molecular epidemiology.
Methods: Phylodynamic analysis was performed for subsubtype A6 including 3 phylogenetic clusters consisting of 3 (2 PWID and 1 non-PWID sequences), 12 (10 PWID and 2 non-PWID sequences), and 19 (11 PWID and 8 non-PWID sequences) sequences from Thessaloniki. Additionally, we included in our analysis 5 PWID sequences obtained between 2010 and 2015 as well as several non-PWID sequences since these 3 phylogenetic clusters were part of a larger monophyletic cluster from Thessaloniki. Phylodynamic analysis was performed by using the Bayesian approach and birth-death skyline serial model in BEAST v2.7.4 program.
Results: Molecular clock analysis showed that the most recent common ancestor (tMRCA) of the largest (N=11) and the second largest (N=10) cluster from PWID, was estimated in the middle of October 2018 and in May 2014, respectively. For the third PWID cluster (N=2), the tMRCA was estimated in July 2017. Phylodynamic analysis showed that the effective reproductive number (Re) started to increase at the beginning of 2019 and remained high (Re > 1) until the end of the study period in the end of 2021. Moreover, the spatial origin of all the clusters was from Thessaloniki.
Conclusion: Our study provides a detailed figure about an HIV-1 outbreak in Thessaloniki. Phylodynamic analysis showed that the time of epidemic growth coincided with the time of the initial identification in 2019. Our findings showed that HIV-1 transmission continues at high rates (Re > 1) among PWID until the end of 2021. Notably, the covid-19 pandemic did not avert HIV-1 transmission among this group. The early origin of the three clusters suggests that HIV-1 virus spreading among this group was previously circulated in the same area. The continuous spread of HIV-1 among this highly vulnerable group is alarming and requires implementation of public health measures.

1016 Disparities in HIV Care Among Hispanic/Latino Persons by Birthplace and SVI: United States, 2021

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Background: Hispanic/Latino persons (Latino hereafter) comprise 19% of the U.S. population but accounted for 29% of new HIV infections in 2021. Latino persons have historically been treated as a homogenous group in public health research despite their social and cultural diversity. This study aimed to assess birthplace and Social Vulnerability Index (SVI) differences among Latino persons not linked to HIV care and without viral suppression in the U.S.
Methods: Data from CDC's National HIV Surveillance System were used for Latino persons aged ≥18 years with HIV diagnosed during 2021. Data were limited to 48 U.S. jurisdictions with complete reporting of laboratory results to CDC. Cases were linked via census tracts to CDC/ATSDR's SVI. Non-linkage to care was defined as no documentation of ≥1 CD4 or VL tests within 1 month of HIV diagnosis. Non-viral suppression was defined as no VL test result of <200 copies/mL within 6 months of HIV diagnosis. Adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) were estimated using Poisson regression model.
Results: Among 5,056 Latino persons with HIV diagnosed in 2021, approximately half (51.5%) were born in the U.S., 17.3% in Mexico, 9.2% in Central America, 11.1% in South America, and the remaining 10.9% in the Caribbean (including Puerto Rico and Cuba). Compared with persons born in the U.S. (U.S. states and DC), persons born in Mexico (non-linkage aPR 0.72, 95% CI 0.58–0.90) and South America (aPR 0.78, 95% CI 0.61–1.00) had a

decreased prevalence of non-linkage to care. Persons born in Mexico (non-viral suppression aPR 0.75, 9% CI 0.64–0.87), South America (aPR 0.69, 95% CI 0.57–0.84), and other Caribbean areas (excluding Puerto Rico and Cuba; aPR 0.48, 95% CI 0.30–0.77) had a decreased prevalence of non-viral suppression, compared with those born in the U.S. No significant differences were seen among SVI quartiles, compared to the lowest SVI (lowest vulnerability) quartile, for either care outcome.

Conclusion: Disparities in HIV care outcomes exist within the Latino population by birthplace, with those born in certain non-U.S. areas more likely to be linked to care and have viral suppression soon after diagnosis. Effective interventions that increase care and prevention access must be tailored and expanded for this diverse group.

1017 Prevalence of HIV Testing and HIV Positivity in the Hispanic Community Health Study/Study of Latinos

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Background: Although HIV disproportionately affects U.S. Hispanics/Latinos, over 50% of this population has never been tested for HIV. While factors such as healthcare access, English proficiency, acculturation, and nativity likely impact HIV testing among Hispanics/Latinos, few population-based studies have examined these associations. We aimed to describe patterns of HIV testing and test positivity among participants in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a population-based longitudinal cohort study of U.S. Hispanics/Latinos which recruited participants between 2008-2011 aged 18-74 years.

Methods: We analyzed data from HCHS/SOL participants who attended study visit 3 (between 2021 and 2023) at field centers in Bronx, NY; Chicago; Miami; and San Diego. Outcomes were lifetime HIV testing, past year testing, and test positivity, by self-report. We estimated prevalence of outcomes by assigned female at birth (AFAB) vs. assigned male at birth (AMAB), sexual orientation, nativity, preferred language, and level of acculturation (measured using the Short Acculturation Scale for Hispanics [SASH] social scale), and calculated 95% confidence intervals.

Results: Among 7074 participants, mean age was 60 years (SD 12.1), 63% were AFAB, 73% spoke Spanish as their primary language, 75% were born outside of the U.S. and had been living in the U.S. for an average of 30 years (SD 11.9), and most reported sexual orientation as straight/heterosexual (91%). In total, 3317 (47%) had ever tested for HIV, 205 (3%) tested within the past year, and 69 (1%) reported testing positive. Ever HIV testing was higher among AFAB vs AMAB (49% vs 43%; p<.0001), persons identifying as not heterosexual vs. heterosexual (84% vs 46%; p<.0001), U.S./U.S. territories-born vs non-U.S. born (56% vs. 44%; p<.0001), primary English vs Spanish speakers (61% vs 44%; p<.0001), and highest vs lowest tertiles of social acculturation score (52% vs 42%, p<.0001). Similar patterns were observed with respect to past year HIV testing and test positivity (Table).

Conclusion: In a large, representative study of Hispanic/Latinos at 4 U.S. sites, we observed large disparities in HIV testing and test positivity by nativity, language preference, and level of acculturation. Achieving CDC recommendations for universal lifetime HIV testing among Hispanic/Latinos will require targeted interventions to increase uptake among individuals who are less acculturated.

Table: HIV testing and positivity by nativity, preferred language, and acculturation level in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

Factor (n, %)[1]		Ever Tested for HIV		Tested for HIV in the past year		Ever tested positive for HIV	
		n	%, 95% CI	n	%, 95% CI	n	%, 95% CI
Nativity	- U.S./U.S. territories born (1741, 24.6%)	974	55.9 (53.6-58.3)	93	5.3 (4.3-6.4)	43	2.5 (1.7-3.2)
	- Non-US born (5333, 75.4%)	2343	43.9 (42.6-45.3)	112	2.1 (1.7-2.5)	23	0.4 (0.2-0.6)
Preferred Language	- Spanish (5435, 76.8%)	2376	43.7 (42.4-45.0)	110	2.0 (1.7-2.4)	31	0.6 (0.4-0.8)
	- English (1157, 16.4%)	701	60.6 (57.8-63.4)	80	6.9 (5.5-8.4)	24	2.1 (1.3-2.9)
SASH[2] Social Score Tertiles	- Tertile 1 (range 1.0-1.8, least acculturated)	942	42.2 (40.1-44.2)	50	3.5 (2.5-4.4)	13	1.4 (0.6-2.1)
	- Tertile 2 (range 2.0-2.3)	1034	47.5 (45.4-49.6)	54	4.1 (3.1-5.2)	17	1.7 (0.9-2.4)
	- Tertile 3 (range 2.5-5.0, most acculturated)	1405	51.7 (49.8-53.6)	105	6.6 (5.4-7.9)	38	2.7 (1.9-3.6)

[1]Row percentages
[2]Short Acculturation Scale for Hispanics (SASH) social score

1018 Association Between Social Vulnerability, HIV Testing, and Positivity: United States, 2020-2022

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Background: The estimated number of new HIV infections in the United States dropped 12% in 2021 compared to 2017, but the racial and ethnic disparities in HIV infection persist. Community-level factors contributing to social vulnerabilities (e.g., poverty, lack of access to health care and services) may affect HIV outcomes. This analysis assessed the association between county-level social vulnerability and CDC-funded HIV testing and HIV positivity rates, and whether the association varies by demographic characteristics, testing site type, and Phase I Ending the HIV Epidemic (EHE) jurisdiction status in 2020-2022.

Methods: We used testing data submitted to CDC by 60 state and local health departments (HDs) and 117 community-based organizations (CBOs). We combined HIV testing data with the latest county-level composite measure of economic, medical, and social vulnerability captured by the Minority Health Social Vulnerability Index (MHSVI). HIV testing and HIV positivity rates were analyzed by age, gender, race/ethnicity, testing site type, and Phase I EHE jurisdiction status and stratified by low, moderate, and high MHSVI scores. We calculated prevalence ratio (PR) with a 95% confidence interval (CI) to measure relative disparity by comparing county tracts with high vs. low MHSVI scores.

Results: In 2020-2022, CDC-funded HDs and CBOs conducted 4,906,507 HIV tests: 113,721 (2.3%) in low, 583,307 (11.9%) in moderate, and 4,209,479 (85.8%) in high social vulnerability counties. Overall HIV positivity rate was 1.03%, including 0.52% in low, 0.63% in moderate, and 1.09% in high social vulnerability counties. HIV positivity rate was higher in high than in low social vulnerability counties (PR=2.12; 95% CI=1.95-2.30). In addition, the relative disparity in HIV testing and positivity rates was consistently higher in high MHSVI counties than in low MHSVI counties regardless of age groups, gender, race/ethnicity, testing site type, and the Phase I EHE jurisdiction status.

Conclusion: HIV testing supported by CDC funding, and HIV positivity rates are higher in communities characterized by high levels of social vulnerability. These findings suggest that CDC's HIV testing efforts are directed to the most vulnerable communities and are identifying persons with HIV infection. Continued monitoring of the association between county-level social vulnerability and HIV positivity rates would be informative in guiding HIV testing efforts and resource allocation for achieving EHE goals.

1019 Using the ICE Method to Examine Income/Racial Segregation and HIV Outcomes: US, 2021

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Background: Assessing the role of segregation on poor health outcomes among Black persons in the United States (U.S.) can inform interventions aimed at increasing health equity. We examined associations between HIV outcomes (diagnoses, linkage to HIV medical care, and viral suppression) and Index of Concentration at the Extremes (ICE) measures for economic and racial segregation in the U.S. in 2021.

Methods: Census tract-level data on diagnoses, linkage to HIV medical care, and viral suppression from the CDC's National HIV Surveillance System were used. Three ICE measures of spatial polarization were obtained from the U.S. Census Bureau's American Community Survey: ICEincome (income segregation), ICErace (Black-White racial segregation), and ICEincome+race (Black-White racialized economic segregation). Rate ratios (RRs) for diagnoses, and prevalence ratios (PRs) for linkage to care within 1 month of diagnosis and viral suppression within 6 months of diagnosis were estimated with 95% confidence intervals (CIs). Differences across ICE quintiles were examined using the most privileged communities (Quintile 5, Q5) as the reference group.

Results: Across all outcomes and ICE measures, a general pattern of increasingly worse outcomes from most to least privileged quintile was observed. Among all 3 ICE measures, a higher likelihood of HIV diagnosis in Q1 compared with Q5 was observed for ICErace (RR =10.13; CI=9.58–10.70). For HIV diagnosis rates, RRs were consistently greatest for ICErace across quintiles. Among all 3 ICE measures for linkage to care and viral suppression, a lower likelihood in Q1 compared with Q5 were observed for ICEincome (linkage, PR=0.94; CI=0.92–0.95; viral suppression, PR=0.89; CI=0.87–0.91), followed

by ICEincome+race (linkage, PR=0.94; CI=0.92–0.96; viral suppression, PR=0.90; CI=0.87–0.92). For linkage to care and viral suppression, PRs were consistently lower for ICEincome+race.
Conclusion: We found that poor HIV outcomes and disparities were associated with income, racial, and racialized economic segregation as measured by ICE. Persons living in highly segregated and deprived communities experience a lack of access to quality, affordable health care. Expanded efforts are needed to address the social/economic barriers that impede access to HIV care among Black persons. Increased partnerships between government agencies and the private sector are needed to change policies that contribute to and sustain racial and income segregation.

1020 The TIME Study: Trans People Living With HIV Throughout Europe: Clinical Outcomes and Stigma

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Background: Transgender and gender-diverse (TGD) people are at up to 49x higher risk of acquiring HIV than general populations. We present findings from the TIME study (Transgender people living with HIV throughout Europe), assessing viral response to antiretroviral therapy (ART) in TGD people living with HIV (PLWH) in Europe; exploring demographics, risk behaviours, community needs, barriers and facilitators to ART adherence.
Methods: 6 HIV centres in London, Manchester, Brighton, Barcelona, Turin, Padua targeted recruitment of all patients >18 diagnosed with HIV, having ever been prescribed ART, and identifying as TGD. Clinics submitted observational data from medical records on gender identity, HIV viral loads (VL), CD4 counts, ART prescription adherence and comorbidities at enrolment and 6-monthly for 18 months. Participants completed questionnaires on their lifestyles, transitions, self and societal perceptions of gender, HIV, ART, stigma and discrimination.
Results: 100 participants were recruited to date, 88% were trans women, of mean age 41 (22-65). 66% had completed medical transition. 60% had one or more physical/mental comorbidities at recruitment; at 18 months 36% did. 25% experienced physical violence in the preceding year. Mean baseline CD4 counts were 685 (100-1846) and 696 (384-1229) at 18 months. 18% of patients had known detectable VLs (>50 copies/ml) at baseline, falling to 11% at 18 months. 5% had clinician-documented ART adherence issues during the study. 30% agreed or strongly agreed that having to take ART worried them. 57% were worried or very worried about long-term effects of ART. 22% found ART disruptive to their lives, and 22% experienced unpleasant ART side effects. 31% felt shame and 27% guilt relating to HIV. 10% described not always having sex as safe as they want, and 27% reported concern about rejection by a partner. 12% had recently received care for suicidal ideation, dropping to 7% at 18 months. 48% described their sex life as better since transition, and 61% the same or better since HIV diagnosis.
Conclusion: Although immune status was fair, adherence issues and participant concerns about ART adverse effects were high; VL detectability rates were over 8x higher than in UK PLWH generally. However, a significant proportion of TGD PLWH reported sexual satisfaction since their gender transition and/or HIV diagnosis, indicating that supportive gender and HIV care can promote better quality of life, thus the need for intersectional stigma-aware health service design.

1021 Hazardous Impact of Social Determinants of Health on HIV Incidence in Brazilian Transgender Women

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Background: Transgender women (TGW) are disproportionally affected by HIV in Brazil. Although HIV pre-exposure prophylaxis (PrEP) is available to vulnerable populations through the Public Health System, its uptake and persistence among TGW are low. We aimed to estimate HIV incidence and its risk factors among Brazilian TGW.
Methods: Transcendendo is an open, clinic-based cohort of TGW living with HIV or at HIV risk established in 2015 in Rio de Janeiro, Brazil. HIV testing for HIV-negative participants is performed on an annual basis, with HIV viral load determined for those reporting unprotected anal sex within 30 days of the appointment to assess acute HIV infection. HIV incidence rates were estimated using Poisson model overall and stratified by age and ever PrEP use (time-updated). Risk factors associated with HIV seroconversion were evaluated using Cox proportional-hazards models.
Results: Between August 2015 and December 2022, 255 HIV-negative TGW were enrolled with at least one follow-up visit, contributing to 355.37 person-years. The median age was 29 years (interquartile range: 24-38). Overall, 25 TGW seroconverted for HIV during follow-up (HIV incidence: 3.50%, 95% confidence interval[CI]: 2.30-5.06]). The HIV incidence was higher among younger TGW (18-24 years: 7.87[95%CI:1.17-3.67] vs. >24 years: 2.19[95%CI:1.17-3.67]) and those who have never used PrEP (10.68% [95%CI:6.74-15.92] vs. 0.77[95%CI:0.24-1.80] among those who ever used it). On multivariate Cox models, ever using PrEP was associated with a lower risk of HIV seroconversion, while younger age (18-24 years), earning less than one minimal wage/month, and four years or less of schooling were associated with increased risk of HIV seroconversion.
Conclusion: Despite the availability of prevention strategies provided by the Brazilian public health system targeting key populations, HIV incidence remains high among TGW in Brazil, especially among the younger, less educated, and disenfranchised. As the HIV response continues to fail the most vulnerable individuals, an urgent call to effectively reach this population at risk and address inequalities becomes an imperative need.

Table 1. Risk factors to IIIV seroconversion among TGW enrolled on the *Transcendendo* cohort, Rio de Janeiro, Brazil, 2016-2023.

Variables	RR	95%CI	p-value
Ever PrEP use **[Yes]**	0.01	0.00 – 0.08	**<0.001**
Age 18-24 years **[Yes]**	5.70	2.05 – 15.84	**0.001**
Income of <1 minimal wage/month **[No]**	4.78	1.35 – 16.92	**0.015**
Schooling equal to 4 years or less **[No]**	10.34	2.63 – 40.62	**0.001**

CI: confidence interval, RR: relative risk, TGW: transgender women

1022 HIV Situation in Areas Surrounding Larkana: Findings From Community Test and Treat Implementation

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Background: An outbreak of HIV among children was reported in Ratodero (district Larkana, Sindh province, Pakistan) in April 2019, with unsafe injections and infusions in healthcare settings as the primary mode of transmission. Anecdotal evidence suggests high HIV burden in surrounding districts of Larkana. To date, no data are available on HIV positivity or burden in these areas. We report the results of a first community-based educate, test and treat implementation to understand the HIV situation in surrounding areas of Larkana.
Methods: Community-based door-to-door testing was performed in partnership with CDC Sindh and local administration. Testing focused on two tehsils neighboring Larkana, one in district Jacobabad (159019 population) and one in district Shikarpur (316513), for which routine data and expert opinion suggested high burden of undiagnosed HIV. Those aged 18 months to 60 years were eligible, while those who self-reported HIV test in the past 6 months or were already on ART were excluded. Thirty mobile teams including one trained male and female mobilizer each offered a single rapid HIV test (Abbott Early Detect) moving from house-to-house. Those with a reactive result were referred to the nearest ART centre for confirmation and ART initiation. Information, education and communication materials related to injection safety were displayed in health facilities and in the community.
Results: Between, November 28 and December 12, 2023, 24536 HIV tests were conducted (57% among females). Overall, 160 individuals (0.65%; male: 0.67%, female: 0.64%) had a reactive HIV result. The reactive rate was 0.56% in one district and 0.78% in the other. Nearly one-third (n=58) of all reactive results were among children (18 months-14 years). The positivity was higher among

those 15 years and above (0.82%) compared to children (0.48%). Of those with reactive results, 69 (43%) were confirmed HIV-positive and initiated ART as of January 9, 2024. The mode of transmission for 36 individuals (52%) was reported as reuse of contaminated needles and transfusion of blood/blood products for 13 (19%) individuals.

Conclusion: HIV positivity in surrounding areas of Larkana is higher than national HIV prevalence (0.2%) suggesting ongoing community transmission. Both adults and children appear to be at risk of acquiring HIV from reuse of contaminated needles/syringes and unsafe blood. Actions need to be prioritized for identifying undiagnosed HIV and address unsafe injection and blood transfusion practices.

1023 Narrowing Disparities in HIV Incidence Between Males and Females in Rural KwaZulu-Natal South Africa

Elphas Okango[1], Paul Mee[2], Khai Hoan Tram[3], Hae-Young Kim[4], Alex Edwards[5], Dickman Gareta[1], Maxime Inghels[2], Kobus Herbst[1], Henry Mwambi[6], Adrian Dobra[3], Frank Tanser[7]

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Background: The disproportionate HIV burden among women in Sub-Saharan Africa has been a concerning and complex public health issue. Several factors have contributed to this including biological vulnerability, gender inequality, transactional sex, and economic dependence. The past few years have seen concerted efforts to address this public health challenge including geared up universal testing and treatment.

Methods: This study utilizes data from one of the world's largest HIV cohorts (Africa Health Research Institute (AHRI) population cohort) from rural South Africa that prospectively followed participants between 2005 and 2021. Poisson regression models were used to estimate the HIV incidence, incidence rates and confidence intervals. The outcome variable was seroconversion representing whether an individual tested positive or not over the observation period.

Results: A total of 152,663 person-years with 3565 seroconversions were observed between 2005 and 2021. Our most recent data indicates a narrowing disparity in HIV incidence rates between males and females. The relative decrease in HIV incidence rates from 2014 to 2017 was 30.02% (from 3.92 to 2.74 per 100 person-years) among females and 38.91% (from 1.53 to 0.93 per 100 person-years) among males. In contrast, during the period from 2018 to 2021, there was a substantial decline of 43.08% (from 2.30 to 1.31 per 100 person-years) among females and 24.92% (from 0.78 to 0.58 per 100 person-years) among males. In 2014, the female/male incidence ratio was 2.57 and this declined to 2.23 in 2021. HIV incidence for females increased with age from age 15 before reaching its peak at age 30 while in males it peaked at age 27. HIV incidence in females was higher across all ages (15-54) fig 1.

Conclusion: Although massive strides have been made in lowering HIV incidence among both men and women, it is crucial to examine the plateauing reduction in HIV incidence among men to safeguard against any erosion of the advancements made thus far. The pace of HIV incidence reduction among women on the other hand underscores the effectiveness of intervention strategies and HIV programs. It is imperative to expand these strategies to further decrease HIV incidence among women.

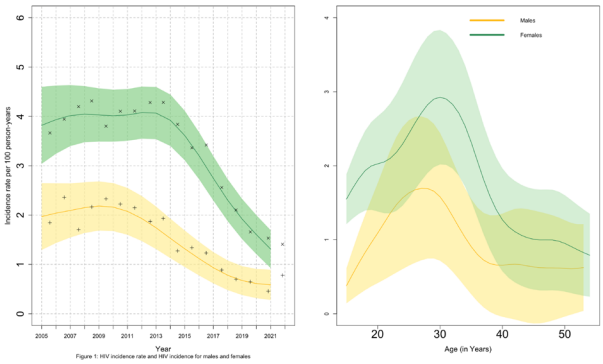

Figure 1: HIV incidence rate and HIV incidence for males and females

1024 Rapidly Changing Socio-Economic Patterns of HIV Incidence in Rural KwaZulu-Natal, South Africa

Paul Mee[1], Elphas Okango[2], Hae-Young Kim[3], Adrian Dobra[4], **Khai Hoan Tram**[4], Dickman Gareta[2], Kobus Herbst[2], Frank Tanser[5]

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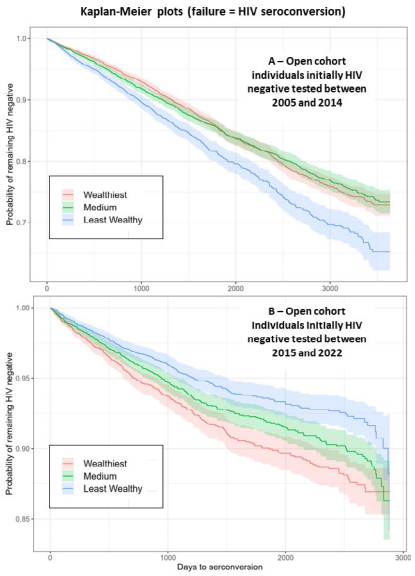
Background: Despite a decline in HIV incidence in South Africa associated with the increased provision of HIV prevention services, there remains a lack of evidence on whether this progress has been experienced equitably by those most economically disadvantaged. We assessed whether the risk of acquiring HIV has changed over time for those in different socio-economic strata.

Methods: The study used data from a population-based HIV testing platform run by the Africa Health Research Institute (AHRI) in KwaZulu-Natal, South Africa. Socio-economic status was derived using a Principal Components Analysis, with input variables representing asset ownership and services used. The households were stratified into three equal wealth quantiles in each year. Time to seroconversion was defined as the time between the first observation and the seroconversion date, randomly imputed between the dates of the last negative and positive HIV tests. Kaplan-Meier curves stratified by socio-economic strata were constructed using two open cohorts. For period 1 (2005 to 2014) the criteria for ART initiation was CD4 count <= 350 cells/ml. For period 2 (2015 to 2022) the criteria was CD4 count <= 500 cells/ml until 2016 and then ART initiation at any CD4 count starting in 2017. The p-value of a Mantel-Haenszel (MH) test was used to assess whether the trajectories of the curves differed significantly. A Cox PH model was developed to test statistical significance controlling for other covariates.

Results: During the 2005 to 2014 period (N=18,236) there were 2521 seroconversion events over 75086 person-years (PY) of observation (Fig A). Those in the least wealthy socio-economic strata had a higher rate of seroconversion (MH p-value <= 0.001) and a higher incidence than those in the wealthiest strata (4.19/100 PY vs 3.13/100 PY). During the 2015 to 2022 period (N= 14594), there were 901 seroconversions recorded over 51485 PY (Fig B). The wealth trend had reversed with the least wealthy having a lower rate of seroconversion (MH p-value <= 0.001) and a lower incidence than those in the medium and wealthiest strata (1.37/100 PY vs 1.76/100 PY and 2.12/100 PY respectively). A Cox PH multivariate analysis controlling for age and sex confirmed these findings.

Conclusion: This study provides clear evidence that dramatic changes have occurred over time in the association between wealth status and the risk of acquiring HIV, with those in the lowest wealth strata having the lowest seroconversion rate since the move towards universal ART.



1025 Ultra-High Resolution GPS to Measure Human Mobility in High HIV Prevalence Areas in Rural S. Africa

Khai Hoan Tram[1], Elphas Okango[2], Thulile Mathenjwa[2], Paul Mee[3], Hae-Young Kim[4], Till Bärnighausen[5], Adrian Dobra[1], Frank Tanser[6]

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Background: Mobility, including both short-term travel and migration, has been linked to increased risk of HIV infection. Ultra-high resolution GPS data collected from study participants who carry smartphones during their daily activities offers new insights into the mobility patterns of a representative sample of young adults in an HIV hyper-endemic setting in rural KwaZulu-Natal, South Africa.

Methods: This study involved a random sample of adults aged 20-30 years who were consented and tested for HIV in the 2019 Africa Health Research Institute survey. Between 6/2021 – 3/2023, participants either received a smartphone with a customized Ethica mobile app or installed the app on their own devices. Positional data were recorded at a frequency of up to ~1 second (depending on internet connectivity and movement) over a six-month period. Data was analyzed to explore space-time dimensions of mobility and to quantify time spent in known high HIV prevalence areas. In this analysis, the cluster where each individual recorded the most time spent was considered to be their residential cluster.

Results: In total, 27,151,329 time-stamped location records were collected for 202 individuals (median 74,864.5 data points), spatially distributed across 45 clusters within the study area and 57 municipalities across South Africa. Participants recorded a median of 129.7 days (IQR 71.8-161.8) inside the study area versus a median of 17.2 days (IQR 3.0-48.1) outside the study area. Nearly all (97.0%) made at least one trip outside the study area during this time. Similar proportions spent greater than 50% of their recorded time outside their own residential cluster: either in other clusters within the study area [internal mobility: 13.4%] or outside the study area entirely [external mobility: 14.4%]. Over half (88/157, 56.1%) of those participants who did not reside in a geographical HIV cluster spent time in those areas. Median percent of recorded time by non-residents in the HIV clusters was 0.6% (IQR 0.04-5.8).

Conclusion: Young adults in rural KwaZulu-Natal display highly dynamic patterns of mobility both locally and farther afield. Over forty percent of this population moved through clusters in the study area with known high HIV prevalence but did not reside in those places. Determining typologies of movement in this age group and quantifying movements in and out of known HIV hotspots can facilitate designing location-intelligent, real-time precision interventions for those at high risk of HIV acquisition.

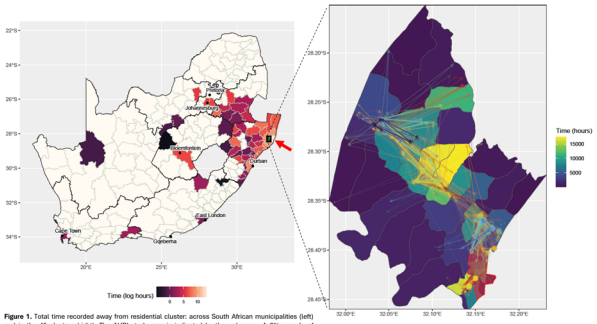

Figure 1. Total time recorded away from residential cluster: across South African municipalities (left) and in the 45 clusters (right). The AHRI study area is indicated by the red arrow. A 3% sample of trajectories (with spatial jittering) illustrates the range of micro-mobility. High prevalence HIV clusters are shaded in red.

1026 HIV Seroprevalence, Incidence, and Viral Suppression Among Ugandan Female Barworkers

Xinyi Feng[1], Slisha Shrestha[2], Fred Nalugoda[3], Godfrey Kigozi[3], Robert Ssekubugu[3], Larry W. Chang[1], Andrea Wirtz[2], Caitlin E. Kennedy[2], Arthur G. Fitzmaurice[4], Gertrude Nakigozi[3], Aaron A. R. Tobian[1], Steven J. Reynolds[5], Joseph Kagaayi[3], Mary Kate Grabowski[1]

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Background: Female bar workers (FBW) in eastern Africa often engage in sex work. However, population-level data on HIV seroprevalence, incidence, and viral suppression among FBW are rare.

Methods: FBW were identified through longitudinal population-based HIV surveillance in southern Uganda via the Rakai Community Cohort Study between 2012 and 2019. Surveillance was conducted across five surveys in four high HIV prevalence (>35%) Lake Victoria fishing communities and 36 moderate HIV prevalence (~12%) inland agrarian and trading communities. Participants were classified as FBW if they reported bar work as a primary or secondary occupation. Sociodemographics and sexual behaviors of FBW were compared with participants never classified as FBW (non-FBW). Primary outcomes included laboratory-confirmed HIV seropositivity, seroincident HIV infection measured via paired serologic testing, and HIV viral load suppression (<200 copies/ml). Prevalence and incidence rate ratios (PR, IRR) were estimated using age-adjusted Poisson regression models with 95% confidence intervals (95%CI).

Results: A total of 23,556 female participants contributed 52,708 person-visits. Overall, 1,205 (5.1%) women self-identified as FBW at one or more study visits. FBW were significantly older, more likely to report recent migration, and had substantially higher levels of HIV-associated risk behaviors, including higher numbers of lifetime and prior-year sexual partners and alcohol use before sex, compared to non-FBW. FBW also had significantly higher HIV seroprevalence irrespective of age or community (Figure). Among 364 FBW participating in at least four surveys, only 50 (13.7%) self-reported being a bar worker at all surveys, while 128 (35.2%) reported bar work at only a single survey. Overall, 377 HIV incident events occurred over 41,030 years of participant follow-up. Incidence among FBW was 1.76/100 person-years versus 0.90/100 person-years among non-FBW (adjIRR:2.24; 95%CI: 1.27-3.63). However, FBW living with HIV irrespective of antiretroviral use tended to have higher levels of population HIV viral load suppression compared to non-FBW (62.9% vs 54.9%; adjPR=1.08, 95%CI: 1.01-1.17).

Conclusion: Enhanced prevention services for female barworkers in Uganda are needed and may reduce HIV incidence in this population. However, high mobility and frequent fluctuation in and out of bar work may complicate delivery of interventions, such as long-acting injectable pre-exposure prophylaxis.

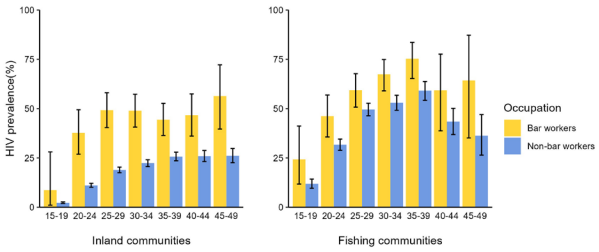

Figure: Age-specific HIV seroprevalence among female participants by self-reported history of bar work as a primary or secondary occupation in the Rakai Community Cohort Study, Uganda, 2012-2019.

1027 Large Decline in HIV Prevalence Among Female Sex Workers in Zimbabwe, 2011-2023

James Hargreaves[1], **Sungai Chabata**[2], Sanni Ali[1], Tsitsi Hove[3], Harriet Jones[1], Loveleen Bansi-Matharu[4], Owen Mugurungi[5], Raymond Yekeye[6], Sithembile Musumburi[2], Jeffrey Dirawo[2], Primrose Matambanadzo[3], Fortunate Machingura[3], Andrew Phillips[4], Frances M. Cowan[7]

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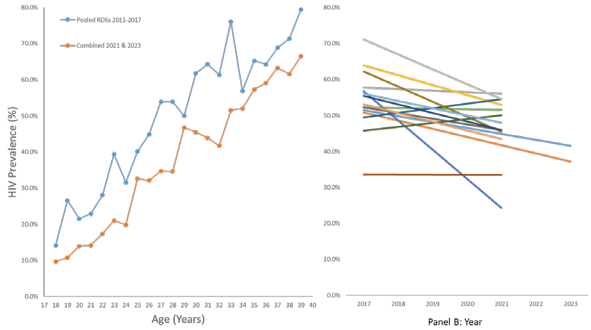
Background: Little is known about HIV trends among female sex workers (FSW) in Africa. We analysed data from a national-scale collaboration to explore trends in HIV prevalence and HIV incidence among FSW in Zimbabwe between 2011 and 2023, complemented by mathematical modelling.

Methods: Between 2011-2023 we collected data on HIV infection from 13,918 women aged 18-39 in multiple respondent driven sampling surveys (RDS) in Zimbabwe, including 13 towns where surveys were repeated in 2017 and 2021, and 2 cities where surveys were repeated in 2017 and, the most recently available data, from 2023. In 2021, we analysed 306 dried blood spot samples with a recent infection algorithm (LAg avidity+Viral load). Using RDS-II

weighting we explored HIV prevalence trends. We estimated HIV incidence pooled for 2011-2017 (since patterns were similar across years), and for 2021-2023, based on HIV prevalence rises with age ("prevalence to incidence method"). In 2021, we also estimated HIV incidence using recent infections ("RITA method", MDRI 130 days, false recency 0.2%). In addition, the HIV synthesis model was calibrated to data from Zimbabwe.
Results: HIV prevalence in 2021-23 was 16.9% lower than in previous surveys pooled (2011-2017, 4314/7964, RDS-II prevalence 54.2%; 2021-23, 2220/5954, 37.3%, Figure Panel A). HIV prevalence fell in 11/13 towns and in both cities with repeated surveys, between 2017 and 2021/2023, by an average of 8.5% (Figure Panel B). HIV incidence ("prevalence to incidence method") was similar in both 2011-2017 and 2021-23, estimated at 4.4/100pyar. HIV incidence in 2021 ("RITA method") was estimated at 1.9/100pyar (17 recent infections, 1396 long term positive, 2107 HIV negative samples). Modelled HIV incidence was higher than the empirical estimates, but fell from 12.1/100pyar (2015) to 4.5/10 pyar (2021).
Conclusion: Using population-based sampling we show a large reduction in HIV prevalence over time among FSW in Zimbabwe. Trends in incidence are harder to estimate, but incidence may be declining, partly driven by improved treatment coverage among men. PHIA data suggest that the proportion of males aged 15-49 living with HIV who had suppressed viral load increased from 48.9% (2015/16) to 68.1% (2020). HIV incidence remains unacceptably high among FSW. Persistence and innovation in HIV prevention for FSW are needed.



PANEL A: HIV prevalence by age for pooled respondent driven sampling surveys in 2011-17 and 2021-23
PANEL B: HIV prevalence by year in 13 towns and 2 cities with repeated respondent driven sampling surveys

1028 HIV Incidence by Self-Reported Frequency of Condom Use: A Population-Based Cohort Study in Uganda

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Background: Self-report of no or inconsistent condom use with non-marital partners is often used as an eligibility criterion for pre-exposure prophylaxis (PrEP), but recent data on HIV incidence by self-reported condom use frequency is limited. Here, we aimed to assess the relationship between HIV incidence and self-reported frequency of condom use among people reporting non-marital sexual partners in Uganda.
Methods: We used longitudinal population-based surveillance data from the Rakai Community Cohort Study collected between 2011 and 2018 to evaluate HIV incidence among persons reporting non-marital sexual partners in 40 communities, including four hyperendemic (~40% HIV seroprevalence) Lake Victoria fishing communities. Participants were included irrespective of their marital status. We characterized demographics, risk behaviors, and partnership characteristics by self-reported condom use frequency with non-marital partners. Our primary outcome was incident HIV infection, defined as the first HIV seropositive test result among persons seronegative at their prior visit. HIV incidence rates [IR] per 100 person years (pys) among participants reporting no condom use (never-users), inconsistent condom use (inconsistent-users), and consistent condom use (always-users) were estimated using Poisson regression.
Results: Overall, 19,384 participants, including 11,742 men (60.6%), reported 26,621 past-year non-marital partners. Approximately one-third of women (n=2,706; 35%) and half of men (n=6,216; 52.9%) reported consistent condom use with these partners. Both male and female self-reported never-users were more likely to be older and in non-marital monogamous relationships of significantly longer duration. HIV incidence rates were similar among men who reported never using condoms (0.9/100 pys; 95%CI 0.39-1.93), always using condoms (0.9/100 pys, 95%CI: 0.64-1.16), and men reporting inconsistent use (1.2/100 pys, 95%CI: 0.88-1.60). Among women, incidence was lowest among those reporting never using condoms (1.4/100 pys; 95%CI: 0.78-2.56) followed by always-users (2.0/100 pys: 95%CI: 1.40-2.91), and highest among inconsistent users (2.8/100 pys, 95%CI: 2.17-3.65).
Conclusion: In this study, self-reported never-users had lower or similar incidence compared to self-reported always-users, suggesting self-reported condom use is not a robust indicator of HIV risk. Reviewing self-reported condom use as a PrEP eligibility criterion might improve PrEP accessibility for those with increased HIV risk.

1029 An HIV-1 Risk Assessment Tool for Women in 15 African Countries: A Machine Learning Approach

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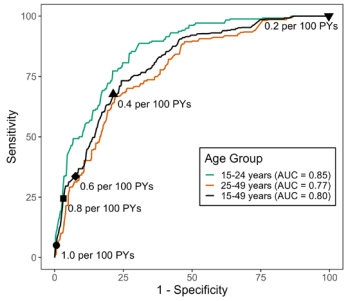
[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]University of Zimbabwe, Harare, Zimbabwe, [3]Albert Einstein College of Medicine, Bronx, NY, USA, [4]University of Minnesota, Minneapolis, MN, USA, [5]Partners in Hope, Lilongwe, Malawi, [6]University of Cape Town, Cape Town, South Africa, [7]Human Sciences Research Council, Pretoria, South Africa, [8]University of Maryland, Baltimore, MD, USA, [9]Columbia University, New York, NY, USA

Background: Women in Africa disproportionately acquire HIV-1. Understanding which women are most likely to acquire HIV-1 can guide focused prevention, including promotion of pre-exposure prophylaxis (PrEP). We used machine learning to develop a risk assessment tool to identify women most likely to acquire HIV-1 across African countries and to estimate HIV-1 infections averted with focused PrEP.
Methods: Nationally representative data were collected from 2015-2019 from 15 population-based household surveys. This analysis included women aged 15-49 years who tested HIV-1 sero-negative or had recent HIV-1, characterized by HIV limiting antigen avidity enzyme immunoassay, HIV-1 viral load, and detection of antiretroviral drugs in their survey blood samples. Least absolute shrinkage and selection operator regression models were fit with 28 variables to predict recent HIV-1. Models were trained on the full population and internally validated using five-fold cross validation. Performance was evaluated using area under the receiver-operating-characteristic curve (AUC). Sensitivity, specificity, and potential cases averted were estimated, assuming perfect PrEP adherence among all women at key HIV-incidence thresholds.
Results: Among 209,012 participants 248 had recent HIV-1 infection, representing 118 million women and 402,000 (95% CI: 309,000-495,000) new annual infections. Only two variables were retained: living in a subnational area with high HIV-1 viremia prevalence and having a sexual partner living outside the home. Overall AUC was 0·80 (95% CI: 0·76-0·84); cross-validated AUC was 0·79 (95% CI: 0·74-0·84). At one key HIV-1 incidence threshold (0.4 per 100 person-years), sensitivity was 67.7% and specificity was 78%. If the 26.1 million women at highest risk for HIV-1 perfectly adhered to PrEP, up to 264,000 cases could be averted.
Conclusion: HIV-1 acquisition is not evenly distributed, with two thirds of infections occurring among a small fraction of women. This predictive, generalizable, and parsimonious tool has the potential to guide high-impact PrEP delivery.



1030 Recent HIV Infections and HIV Incidence in PrEP Among Adolescents From Key Populations in Brazil

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Background: Over the last decade, HIV infection has increased among young men in Brazil, and PrEP is an effective prevention method that can help to reduce HIV incidence in this population. Recent HIV-1 infection (RHI) testing algorithms (RITAs) are used to estimate HIV incidence from cross-sectional data. We aimed to assess RHI among adolescents from key populations at enrollment and HIV incidence among adolescent men who have sex with men (aMSM) and transgender women (aTGW) who started using daily oral PrEP.

Methods: PrEP1519 study is a PrEP demonstration cohort in three Brazilian capital cities among sexually active aMSM/aTGW aged 15-19. 1) We conducted a cross-sectional analysis with baseline data from 2020 including participants who were screened with a fourth-generation HIV rapid test. The RITA tested blood specimens using Sedia LAg assay that detects antigen-driven antibody response (Sedia BioSciences, Portland, OR), an HIV-1 RNA test, viral load and a CD4 count prior to ART use. Among these participants, RITA-based HIV incidence was calculated using a mean duration of recency infection of 167 days and a false-recent rate of 0.02. 2). Data from adolescents that had a HIV negative test and initiated PrEP in 2020 were used to calculate HIV incidence on PrEP. Incidence was calculated considering the time from first PrEP prescription until the last HIV test, PrEP prescription, or visit in 2020. Tenofovir-diphosphate (TDF-DP) concentrations in dried blood spots were estimated for those who tested positive for HIV.

Results: Out of the 494 participants screened, 21 tested positive. Among those, 6 were classified as recent infections and 15 as long term infection. At baseline, the HIV prevalence was 4.3%, and the estimated RHI was 2.6 (95% CI 0.5-4.8) per 100 person-years. The HIV incidence over 418 adolescents who started PrEP was 2.5 (95% CI 0.7 – 6.4) per 100 person-years. All the adolescents who seroconverted had levels of TDF-DP below limits of quantification.

Conclusion: The estimated RHI rate highlights the need for targeted HIV prevention interventions for sexual minorities adolescents. Integrating RHI testing into routine can aid in monitoring the effectiveness of prevention efforts and improve early entry to HIV care. Low adherence and PrEP discontinuation are challenges that need to be addressed among adolescents to enhance PrEP effectiveness. One strategy to tackle these issues involves offering adolescents a range of choices, including long-acting PrEP.

1031 HIV Incidence and Factors Associated With Never Testing for HIV Among Young MSM: Conectad@s Study

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Background: New HIV cases are increasing among young men who have sex with men (YMSM) in Brazil. Research is needed to monitor new infections and examine HIV prevention engagement, including HIV testing. For this study, we estimated HIV incidence and explored HIV testing and factors associated with never testing for HIV in a large study of YMSM in Brazil.

Methods: Data are from the Conectad@s study of YMSM aged 18-24 years in Rio de Janeiro, Brazil. Participants were recruited between Nov/2021-Oct/2022 using respondent driven sampling. Participants were offered HIV testing and were surveyed on demographics, behavior, sexually transmitted infection (STI) and HIV knowledge (validated 12-items measure with scores ranging from 0 to 12; higher scores mean higher knowledge). Recent HIV infection was determined using the Maxim HIV-1 LAg-Avidity EIA assay as part of recent infection testing algorithm (RITA). Annualized HIV incidence and 95% confidence intervals (95%CI) were calculated using the UNAIDS/WHO incidence estimator tool, excluding participants with known HIV diagnosis and those currently on PrEP. We used logistic regression models to assess factors associated with never testing for HIV.

Results: We enrolled 400 cisgender YMSM; median age was 21 years (IQR: 20-23), 166 (41.6%) self-identified as Black, 241 (60.2%) completed secondary school, and 3 (0.8%) were currently using PrEP. Forty participants tested positive for HIV (HIV prevalence: 10%), 5.0% (N=20/400) newly tested positive for HIV, and of those, 5 (25.0%) had a recent HIV infection. The annualized HIV incidence rate was 2.81% (95%CI: 0.32-5.30). Overall, 108 (27.0%) never tested for HIV. Lower HIV knowledge was associated with never testing for HIV. Never testing was associated with being aged 18-19 years, reporting no STI in the last 12 months, fewer sexual partners and no chemsex (Table).

Conclusion: HIV prevalence and incidence among YMSM in our sample was high. Almost a third of YMSM in our study had never been tested for HIV, although all participants accepted testing when offered. These results point to an urgent need for focused policies and interventions to reach and improve HIV prevention engagement among younger MSM in Brazil. Strategies to raise knowledge and awareness of the impact of HIV among parents, in schools and among youth may be needed to create demand for HIV prevention methods such as testing and PrEP that are readily available in Brazil.

Table. Factors associated with never testing for HIV among young men who have sex with men (YMSM) in Rio de Janeiro, Brazil, 2021-2022.

	Never Tested for HIV		Bivariate Analysis		Multivariable Analysis	
	Yes (%) N=108 (27.0)	No (%) N=292 (73.0)	OR (95% Confidence Interval)	p-value	aOR (95% Confidence Interval)	p-value
HIV Knowledge scale (score; interquartile range)[1]	10 (8-11)	11 (10-12)	0.66 (0.57-0.76)	<.0001	0.62 (0.53-0.73)	<.0001
Age: 18-19 years (ref. 20-24 years)	41 (38.0)	38 (13.0)	4.09 (2.44-6.89)	<.0001	3.91 (2.15-7.20)	<.0001
Sexually transmitted infections (prior 12 months): no (ref. yes)	92 (85.2)	181 (62.0)	3.53 (2.02-6.50)	<.0001	4.22 (2.20-8.61)	<.0001
Number of partners (prior 12 months): < 5 (ref. ≥ 5)	64 (59.3)	103 (35.3)	2.67 (1.70-4.22)	<.0001	2.36 (1.40-4.02)	0.0014
Chemsex (prior 6 months):[2] no (ref. yes)	87 (80.6)	165 (56.5)	3.19 (1.91-5.53)	<.0001	2.99 (1.66-5.60)	0.00037

OR: odds ratio, aOR: adjusted OR, [1]12-items; scores range: 0-12; higher scores mean higher knowledge; [2]defined as any illicit substance use before or during sex.

1032 Declines in HIV Incidence Among Gay, Bisexual and Other MSM in Vancouver, Canada, 2012-19 to 2017-23

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Background: British Columbia (BC), Canada, has provided dedicated funding to support expanded access to HIV testing and engagement/retention in HIV care since 2010 and publicly funded PrEP since 2018. We compared HIV incidence for gay, bisexual and other men who have sex with men (GBM) in metropolitan Vancouver over an 11-year period.

Methods: Participants were sexually active GBM aged ≥16 years and were recruited through respondent driven sampling into two cohort studies: Momentum I (M1; 2012-2019) and Momentum II (M2; 2017- 2023). Participants completed a self-administered computer-based survey and tests for HIV and other sexually transmitted infections every 6 months. For participants HIV negative at enrollment, we measured HIV incidence over four years of follow-up through data linkages with the BC HIV Drug Treatment Program. We excluded participants from the M2 analysis who also participated in M1. We calculated HIV incidence rates and rate ratios across time periods and used Poisson regression to identify risk factors for HIV infection, stratified by time period.

Results: We recruited 774 participants in M1 and 753 in M2. Of these, 551 in M1 and 533 in M2 were HIV-negative at enrolment and included in the analysis. HIV PrEP use was reported by a maximum of 6.3% of participants at any visit in M1 and increased from 16.4% from 2017 to 59.6% in 2023 for M2 participants. We identified 16 new HIV infections in 2166.51 person-years (PYRs) of follow-up for an incidence rate [IR] of 0.74 per 100 PYRs in M1; and 6 new infections in 2124.22 PYRs for an IR of 0.28 per 100 PYRs in M2 (IRR= 0.38; 95% CI 0.15 – 0.97). In M1, HIV incidence was associated with age <30 years (IRR 2.74;p=0.056), having condomless anal sex (CAS) with an HIV-positive or unknown serostatus partner (IRR=4.88;p=0.002); sex work in the past six months (P6M) (IRR=4.27;p=0.02); number of male sex partners in P6M (IRR=1.01; p<0.001) and crystal meth use in P6M (IRR=4.08;p=0.007). HIV incidence in M2 was associated with CAS with an HIV-positive or unknown serostatus partner (IRR=8.50;p=0.035), P6M sex work (IRR=5.53;p=0.048) and crystal meth use in P6M (IRR=6.79;p=0.025), but not age, or number of male sex partners in P6M.

Conclusion: HIV incidence declined by 62% for GBM in Metro Vancouver over the study period, likely reflecting the combined effectiveness of Treatment as Prevention and publicly funded PrEP.

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1033 62% of New HIV Infections and 63% of Deaths Now Reported in Countries Outside Southern/East Africa

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Background: UNAIDS targets aim to reduce new HIV infections below 370,000 by 2025. However, there were 1.3 million new HIV infections worldwide in 2022. Most international funding for treatment and prevention is allocated to countries in Southern/East Africa, with the highest prevalence of HIV. However, countries in West Africa, South America and Asia have significant HIV epidemics despite lower overall HIV prevalence. As shown in clinical trials and incidence surveys, PrEP with TDF/FTC needs to be given to at least 60 people at high risk of HIV transmission to prevent 1 new infection.

Methods: Epidemiological data were collected from the UNAIDS AIDSinfo 2022 database, which analyses country-level HIV data using the Spectrum model. Key variables were epidemic size, annual HIV infections, HIV-related deaths, ART coverage, PrEP coverage and MTCT. Results were supplemented by PUBMED/EMBASE searches and national reports. We separated countries with epidemics of >40,000 cases into higher-prevalence (≥3.5%) countries (HPCs) and lower-prevalence (<3.5%) countries (LPCs).

Results: Overall, there were 19.5 million HIV infections in 14 HPCs in Southern/East Africa (53% of epidemic), versus 17.5 million in 54 LPCs (47%). In 2022, despite a smaller total epidemic size, there were more new HIV infections (770,000 vs 468,000), more HIV-related deaths (383,000 vs 225,000), higher rates of MTCT (16% vs 9%), lower ART coverage (67% vs 83%) in LPCs vs HPCs. The rate of HIV epidemic growth (new infections/epidemic size) was 4.4% in LPCs vs 2.6% in HPCs. PrEP was used by 1.3 million in HPCs vs 1.2 million in LPCs. Total use of PrEP is far below the 74 million people required to optimise preventative efficacy.

Conclusion: Worldwide, 62% of new HIV infections and 63% of HIV-related deaths are now reported in LPCs outside Southern/East Africa. Many of these countries in South America, Asia and West Africa are not as intensively targeted by access programmes, such as PEPFAR and GFATM. To bring global new infections below the UNAIDS target of 370,000 per year by 2025, ART coverage needs to be optimized worldwide, and PrEP coverage expanded to 74 million people, versus 2.5 million currently treated.

	Higher prevalence >3.5% (n=14)	Lower prevalence <3.5% (n=54)	Ratio higher:lower
Epidemic size (n)	19,462,000	17,459,263	
ART coverage	81.6%	67.4%	1.21
Mortality	225,100	383,190	0.59
New infections	468,400	770,703	0.61
Annual epidemic growth	2.41%	4.41%	0.55
PrEP initiations	1,323,493 (n=12)	1,174,539 (n=42)	1.13
MTCT	9%	16% (n=43)	0.56

1034 Factors Associated With Low-Level Viremia in People Living With HIV: 9-Year Retrospective Study

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Background: The goal of antiretroviral therapy (ART) is to sustain the suppression of human immunodeficiency virus (HIV) viral load. The prognostic value and clinical outcomes of low-level viremia (LLV) remain unclear. The goal of this study was to investigate the risk factors for LLV and their association with virologic rebound in Korea.

Methods: We retrospectively reviewed the records of all patients registered with HIV infection at Seoul Medical Center, South Korea from January 2014 to December 2022. Patients starting ART and achieving viral suppression were included in the study. LLV was defined as at least 2 consecutive viral loads between 40 and 199 copies/ml with >4 weeks interval. LLV patients were compared with patients who remained in viral suppression (viral loads < 40 copies/mL). We analyzed the association between the clinical factors and LLV using multivariable logistic regression.

Results: During the study period, 382 patients were enrolled and 13 (3.4%) patients experienced LLV. Compared to controls, LLV patients have higher incidence of diabetes mellitus than control patients (p = 0.04). Age, sex, Charlson comorbidity index, ART regimen, initial acquired immune deficiency syndrome (AIDS) defining conditions, and resistance-associated mutation did not differ between the two groups. During the study period, there was no virologic rebound, new onset AIDS-defining illness, or death in LLV patients. We analyzed a multivariate logistic regression model that incorporated age, diabetes mellitus, and resistance-associated mutation. Age was an independent risk factor for LLV (aOR, 1.07; 95% CI,1.01–1.12).

Conclusion: In this cohort, LLV was not associated with AIDS, virologic rebound, and death. The age at which patients achieve viral load suppression may be a risk factor for LLV. Further research with larger cohorts is warranted to evaluate the risk factors and outcomes of LLV.

Table 1. Demographic, clinical characteristics, and outcomes of study patients

Characteristics of patients	LLV† (n = 13) No. (%)	No LLV (n = 369) No. (%)	*P* value
Age (year), median (IQR)	39 (31.5-56.5)	37 (29-48)	0.40
Charlson comorbidity index, median (IQR)	0 (0-2)	0 (0-1)	0.18
Diabetes mellitus	3 (23.1)	20 (5.4)	0.04
NNRTI-based regimen	0	10 (2.7)	>0.99
PI-based regimen	2 (15.4)	59 (16.0)	>0.99
INSTI-based regimen	11 (84.6)	300 (81.3)	>0.99
Resistance-associated mutation	5/8 (62.5)	57/123 (46.3)	0.48
Virologic rebound‡	0	14 (3.8)	>0.99

LLV, low-level viremia; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor.
† At least 2 consecutive viral load measurements of 40-199 copies/mL with >4 weeks interval
‡After virologic suppression, confirmed HIV RNA level≥200 copies/mL

1035 Incidence of Viral Rebound and Associated Risk Factors Among Adults Living With HIV in Tanzania

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Background: Viral rebound (≥50 copies/ml) after a period of undetectable levels, increases the likelihood of HIV morbidity, mortality, and onward transmission, which slows progress to reaching 95-95-95 UNAIDS targets by 2025. We estimated the incidence and risk factors associated with viral rebound among adults living with HIV in Kagera, Geita, Tabora, and Dar es Salaam regions, Tanzania.

Methods: This was a retrospective cohort study, and we extracted 100,052 records of new PLHIV from the national care and treatment (CTC) database on ART in 2019 and reviewed client-level data for 3.6 years. A standard Cox model was used to determine hazard ratios (HR) for viral rebound across different demographic and clinical characteristics. An adjusted model was developed on variables that were significant in univariate analysis. The results of the regression analysis present HR and their corresponding 95% confidence intervals. All analyses were conducted using STATA Version 18.

Results: The overall viral rebound rate was 152.0 (95% CI:144.7-157.7) per 1,000 person-years. The rates were higher in Dar es Salaam (178.0; 95% CI:165.0-192.1) and Tabora (177.9;95% CI:163.2-194.2) followed by Kagera (137.1; 95% CI:125.5-149.8) and Geita (116.4; 95% CI:107.2-126.2) per 1000 person-years. Among patients with poor adherence to antiretroviral therapy (ART), viral rebound was 209.43; (95%CI:167.3-263.9), and with good adherence, viral rebound was 151.25; 95% CI;144.0-158.9). In the adjusted analysis, the following factors were found to be associated with viral rebound: WHO classification Stage IV at diagnosis (adjusted hazard ratio (aHR) 1.07, 95% CI 0.94-1.22); Not changing ART regimen (aHR 2.10, 95% CI 1.95-2.25); Poor ART adherence (aHR 1.49, 95% CI 1.22 -1.82); Female sex (aHR 1.49, 95% CI 1.22 -1.82);) (aHR0.89 95% CI 0.76-0.96) and viral load of 20-49 copies/mL (1.44, 95% CI 1.36-1.53).

Conclusion: These findings suggest that enhanced and targeted efforts to support adherence to ART and monitoring of viral load in adults living with HIV, especially for those with advanced HIV disease, females, and those who have not changed ART regimen for a long duration of time, and a viral load of 20-49 copies/ml to reduce their risk of viral rebound and improve long-term health outcomes.

1036 Detectable Viral Load Predicts Virological Failure at Follow-Up

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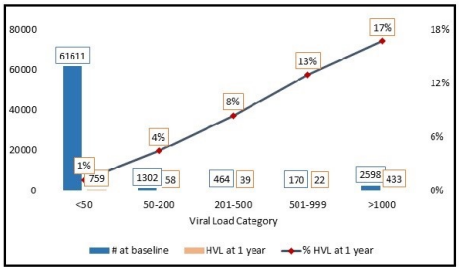
Background: Eswatini has adopted the WHO guideline-recommended cut-off of HIV RNA above 1000c/ml as a criterion for virologic treatment failure. Consequently, we describe the association between different detectable viral load (VL) levels and subsequent virological failure in a cohort of ART clients in Eswatini.

Methods: We conducted a cross-sectional secondary analysis of HIV care data from the Lubombo and Manzini regions. We used data from adult ART clients with a baseline and one-year VL result from October 2021 to September 2022 from the client management information system (CMIS). Data included clients' sociodemographic and clinical information. Clients with VL <1000 were suppressed, and VL ≥50 were suppressed but detectable. Viral load was categorized into <50, 50-200, 201-500, 501-999 and ≥1000. We analyzed the data using descriptive, comparative, and multivariate logistic regression analysis reporting adjusted odds ratios (AOR).
Results: Of 66,145 PLHIV in the database, 63,547 (96%) had a suppressed viral load. Most clients (N=43,394; 65.6%) were from the Manzini region, and 57,547 (87%) were on a Dolutegravir-based ART regimen. Median age was 39 (IQR: 32, 48); 43,879 (66.3%) were females, and the median duration on ART was six years (IQR: 4, 10). Of 2598 with a high viral load (HVL) (VL≥1000) at baseline, 1,550 (59.8%) had follow-up VL data; 1,117 (72%) were suppressed, and 433 (28%) remained unsuppressed. Amongst clients with suppressed baseline VL (n=63,547), 34,757 (54.7%) had follow-up VL data; 33,879 (97.5%) remained suppressed and 878 (2.5%) had HVL. Comparison of clients with HVL at follow-up with baseline categories of VL indicates a linear increase in the proportion of clients with HVL (Figure 1). Baseline predictors of HVL at follow-up were age <15 (AOR 2.0; 95%CI: 1.46,2.74; p<0.001), 15-24 (AOR 2.72; 95%CI:2.17,3.40; P<0.001), 25-34 (AOR 1.62;95% CI: 1.33, 1.99;p<0.001) compared to ≥45 years; males (AOR 1.15; 95%CI:1.01,1.31; p=0.029) compared to females; baseline viral load 50-200 (AOR 3.52; 95%CI:2.65,4.67; p<0.001), VL=201-500 (AOR 7.22; 95%CI: 5.1, 10.3; p<0.001), VL=501-999 (AOR 11.4; 95%CI: 6.9, 18.8; p<0.001), ≥1000 (AOR 13.1; 95%CI: 11.4, 15.1; p=0.001) compared to baseline VL<50.
Conclusion: Any detectable VL is a risk for virological failure.This requires strategies that support and strengthen stepped-up adherence counselling for all clients with a detectable VL to limit progression to virological failure and for contextualized care for males and PLHIV aged <35 years.



1037 HIV Data Informed Care: Using Routine Data to Identify Persons At Risk of Developing Viremia

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Background: Identifying persons with HIV (PWH) at increased risk of developing unsuppressed viral load or falling out of care could lead to improved resource allocation and improve the focus of public health data-to-care activities. We sought to evaluate factors associated with developing unsuppressed viral load in San Diego County, California using routinely reported HIV data.
Methods: Data were obtained from the Enhanced HIV/AIDS Reporting System (eHARS) for PWH who were diagnosed or resided in San Diego County. The analysis was limited to individuals whose diagnosis date was known and occurred after May 2017 (based on eHARS data availability) and had attained viral suppression (VL200 copies/ml after attaining viral suppression. Survival curves for each group were estimated separately using the Kaplan-Meier estimator and compared using log-rank tests. To compare viral load testing patterns between the rebound and no rebound group, we used Wilcoxon rank sum tests.
Results: Between June 2017 and December 2021, 1840 persons were diagnosed with HIV and achieved viral suppression. From these participants there was a total of 12,222 viral load measurements included in the analysis. Among these individuals, 244 (13.3%) subsequently developed an unsuppressed viral load (>200 copies/ml). Factors associated with an increased rate of unsuppressed viremia included younger age at diagnosis (p=0.013), Black race or Hispanic ethnicity (p=0.04), female birth sex (p=0.04), persons with any history of injection drug use (IDU, p=0.003), men who have sex with men (MSM) who also report IDU, and a later HIV stage at diagnosis (p=<0.001). Viral load testing pattern analysis indicated that among persons with at least 1 year of follow-up, less frequent testing (p=<0.001) and lower variance in testing interval (p=0.002) were associated with developing unsuppressed viral load.
Conclusion: Multiple demographic, HIV associated factors, and viral load testing patterns were associated with an increased risk of developing unsuppressed HIV viral load. These variables may be considered as part of a risk score to identify individuals before they develop unsuppressed viremia. Prospective evaluation is needed to determine if such a score could lead to greater clinical and social support services to prevent viral load rebound.
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1038 Longitudinal Viral Load Clustering for People With HIV Using Functional Principal Component Analysis

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Background: While multiple indicators like viral suppression (VS) and viral rebound (VR) exist for monitoring HIV viral load (VL), research on continuous VL clustering is limited. By characterizing people with HIV (PWH) into distinct groups, stratified long-term risks of virological failure can be assessed. Therefore, this study aims to use functional data clustering to identify continuous VL patterns and characterize each cluster by demographics, comorbidities, social behaviors, CD4 count, and antiretroviral therapy (ART) history.
Methods: We analyzed adult PWH diagnosed from 2005 to 2020 in South Carolina with a 5-year minimum follow-up from the first VS to the last VL test. Functional principal component analysis (FPCA) was used to categorize PWH to clusters based on sparse VL test. ANOVA were used to test the difference in VL characteristics, demographics, comorbidities, social behaviors, and longitudinal CD4 count during the follow-up period of each cluster. Subgroup analyses were conducted among PWH with ART, examining the ART patterns within each cluster, including initial, most recent, most frequently used ART, and any regimen switches.
Results: A total of 5,916 PWH were grouped into four clusters: long-term VS group (Cluster 1, 17.3%), short-term VS group (Cluster 2, 29.8%), suboptimal VS group (Cluster 3, 28.3%), and viral failure group (Cluster 4, 24.9%). In Cluster 1 with an average of 11-year follow-up, PWH displayed sustained VS (95.3%), lower mean CD4 count (28.1%), most NRTI+NNRTI in first and last 3 months (72.8% and 64.0%), and less regimen switches (32.0%). Results for Cluster 2 were similar except for shorter follow-up (6 years), more comorbidities (31.4%), and higher max CD4 count (48.4%). In Cluster 3, PWH were mostly under 30 years old (44.8%) and Black (77.2%), with relatively lower mean VL (92.9%), lower number of VR (18.4%), higher maximum CD4 count (47.6%), and were mostly prescribed with NRTI+NNRTI in first 3 months (50.9%). In Cluster 4, demographics were similar to Cluster 3, while PWH had higher mean VL (40.6%), lower mean CD4 count (31.4%), received most PI+NRTI (32.4%) in the first 3 months, and switched the regimen more frequently (55.2%).
Conclusion: The findings highlight the value of continuous clustering in understanding the distinct viral profiles of PWH. By identifying distinct clusters varied in VL patterns, demographics, substance use, comorbidities, CD4 count, and ART, we emphasize the importance of tailored treatment and insights for targeted interventions.

Summary Table for Selected Characteristics, including Viral Load, Demographics, Comorbidity, CD4 and ART Regimen (N=5,916)

Characteristics[1]	Long-term VS Group (Cluster 1) n = 1,008 ($^2n_{sub}$=250)	Short-term VS Group (Cluster 2) n = 1,763 ($^2n_{sub}$=299)	Suboptimal VS Group (Cluster 3) n = 1,673 ($^2n_{sub}$=326)	Viral Failure Group (Cluster 4) n = 1,472 ($^2n_{sub}$=386)
Mean VL				
≤ 10,000 copies/mL	1,008 (100%)	1,672 (99.9%)	1,154 (92.9%)	597 (40.6%)
Number of VR				
≥1	2 (0.2%)	0 (0.0%)	305 (18.4%)	756 (51.3%)
Race				
Black	647 (64.2%)	1,173 (66.5%)	1,292 (77.2%)	1,157 (78.6%)
Number of Comorbidity				
≥1	247 (24.5%)	554 (31.4%)	415 (24.8%)	397 (26.9%)
Mean CD4 Count				
<200 cells/mm³	282 (28.1%)	362 (20.8%)	390 (23.6%)	455 (31.4%)
ART Regimen in First 3 Months[2]				
NRTI+NNRTI	182 (72.8%)	148 (49.5%)	166 (50.9%)	152 (39.4%)
ART Regimen Switch Ever[3]				
No	80 (32.0%)	74 (24.7%)	131 (40.2%)	213 (55.2%)

[1]Selected categories for each characteristic. [2]n_{sub}: The number of PWH in subgroup with ART information. [3]Selected characteristics in subgroup with ART information.

1039 Progress Toward 95-95-95 and Viral Suppression Among FSW/CSEG in Unguja, Zanzibar, 2023

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Background: An integrated biobehavioral survey (IBBS) in Unguja Island, Zanzibar, in 2019 showed female sex workers and commercially and sexually exploited girls (girls <18 years given money/goods for sex) (FSW/CSEG) have a higher HIV prevalence (12.1%) than the general population (0.4%). HIV diagnosis, linkage to antiretroviral treatment (ART), retention, and viral suppression (VS) among FSW/CSEG are critical to epidemic control in Zanzibar. In a follow-up IBBS completed in August 2023, we measured progress towards UNAIDS 95-95-95 goals and VS among FSW/CSEG who completed ≥6 months of ART, in Unguja.

Methods: We recruited women aged ≥15 years who reported living in Unguja for ≥3 months and exchanging sexual intercourse for money in the prior month using respondent-driven sampling. We assessed HIV testing and treatment history through an interviewer-administered questionnaire and offered point-of-care HIV testing in accordance with national guidelines. For those testing HIV-positive, we quantified HIV viral load (VL). We defined VS as <1,000 HIV RNA copies/mL, which comprises low level viremia (LLV) (50–999 copies/mL) and undetectable VL (<50 copies/mL). Women who disclosed a positive HIV status or were virally suppressed were categorized as knowing their status. Women who self-reported ART use or were virally suppressed were classified as on ART. We produced weighted point estimates and standard errors, reported as percentages with 95% confidence intervals (CI).

Results: We enrolled 598 FSW/CSEG; median age was 31 years (range: 15–55 years). HIV weighted prevalence was 21% (95%CI: 17–25%) and was highest among women aged ≥45 years (47%; 95%CI: 31–62%). Among 138 FSW/CSEG who tested HIV-positive, 92% (95%CI: 85–100%) knew their status, 98% (95%CI: 78–100%) of those who knew their status were on ART, and 88% (95%CI: 79–98%) of those on ART were virally suppressed. Among 84 FSW/CSEG who reported being on ART for ≥6 months, 71% (95%CI: 60–82%) had an undetectable VL, 17% (95%CI: 8–25%) had LLV, and 13% (95%CI: 5–21%) were unsuppressed.

Conclusion: HIV prevalence among FSW/CSEG in Unguja remains high. While the UNAIDS target for ART coverage has been met among FSW/CSEG living with HIV, there are still gaps in HIV diagnosis and viral suppression. Finding a detectable VL among FSW/CSEG on ART for ≥6 months is alarming. Prioritizing interventions that address the 1st and 3rd 95 such as expanded HIV testing, including self-testing, and removing barriers to retention in ART will help to address these gaps.

1040 Individual- and Community-Level Predictors of HIV Care Continuum Progression: Clark County, Nevada

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Background: The HIV care continuum provides a comprehensive framework to assess the progress of people with HIV (PWH) from diagnosis to sustained viral suppression.

Methods: We investigated associations between HIV care progression (being diagnosed, being in care, and being virally suppressed) and individual- and community- level characteristics in Clark County, Nevada. Individual-level characteristics included: age at diagnosis, current age, being MSM or IDU, race, sex, education, income, and being HIV genetically clustered (distance threshold <1.5%). Community-level characteristics included aggregated metrics for education, employment, race, and poverty. We used LASSO (Least Absolute Shrinkage and Selection Operator) regression with a zip code-level random effect to simultaneously conduct model selection and multivariate analyses; model tuning parameter was estimated using cross-validation.

Results: We identified 5,122 diagnosed PWH in Clark County from 2011 to 2022. Of these individuals, 29% were Black, 36% Hispanic, 86% male, 69% men who have sex with men (MSM), and 56% with a high school education or less. More recent diagnosis year (estimate -0.14; SE 0.01; p-value: <0.001) and being MSM (est. -0.42, SE: 0.11, p-value: <0.001) were inversely associated with late-stage diagnosis, while older diagnosis age was associated with higher probability (est. 0.04, SE: 0.003, p-value: <0.001); no community-level predictors were associated with late-stage diagnosis. Individual-level predictors associated with being in-care include: MSM (est. 0.31, SE: 0.14, p-value: 0.03), being HIV genetically clustered with an another PWH (est. 0.63, SE: 0.20, p-value: 0.001), more recent diagnosis year (est. 0.15, SE: 0.01, p-value: <0.001), and older age at diagnosis (est. 0.03, SE: 0.004, p-value: <0.001). In addition, residing in areas with higher percentages of poverty (est. -2.67, SE: 1.32, p-value: 0.04) and Hispanics (est. -1.27, SE: 0.65, p-value: 0.050) were significantly associated with being out of care. Similar associations with an individual being in-care were identified for an individual being virally suppressed--though some predictors differed; see Table 1 for details.

Conclusion: Further studies are needed to identify the factors associated with poverty (e.g., access to HIV services) that may contribute to being out of care and virally unsuppressed. This analysis can serve as a basis for proactively identifying and supporting patients at risk of disengaging from HIV care through personalized care plans.

Table 1: LASSO Regression results for associations between HIV care progression (late-stage diagnosis, being in care, and being virally suppressed) and individual- and community- level characteristics in Clark County, Nevada. Only characteristics that were significant for at least one outcome are shown. Cells in red indicate significance.

Level	Characteristics	Late-stage diagnosis Estimate (SE)	Being in-care Estimate (SE)	Being virally suppressed Estimate (SE)
Individual	Year of diagnosis	-0.14 (0.01) p-value: < .001***	0.15 (0.01) p-value: < .001***	0.07 (0.01) p-value: < .001***
	Age at diagnosis	0.04 (0.00) p-value: < .001***	0.03 (0.00) p-value: < .001***	0.02 (0) p-value: < .001***
	Hispanic	-----	0.19 (0.1) p-value: 0.051	0.22 (0.08) p-value: 0.007**
	Men who have sex with men	-0.42 (0.11); p-value: < .001***	0.31 (0.14) p-value: 0.029*	0.26 (0.09) p-value: 0.003**
	HIV genetic cluster	0.0 (0.15) p-value: 0.993	0.63 (0.2) p-value: 0.001**	0.19 (0.14) p-value: 0.158
Community	Proportion under poverty line	-0.89 (1.16) p-value: 0.44	-2.67 (1.32) p-value: 0.042*	-3.65 (1.15) p-value: 0.002**
	Proportion Hispanic	-0.58 (0.54) p-value: 0.285	-1.27 (0.65) p-value: 0.050*	-0.42 (0.55) p-value: 0.441

1041 Multiple Care Disengagements and CD4 Restoration: A Comparative Analysis in People With HIV

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Background: While CD4 count trends following ART initiation are well-documented, limited attention has been given to CD4 count evolution after reengagement in care following disengagement from care, especially in cases of multiple disengagements. We aimed to characterize patients prone to disengage from care and compare CD4 trajectories among individuals who never disengaged and those who disengaged once or multiple times.

Methods: Data were obtained from the Athens Multicenter AIDS Cohort Study (AMACS). We included people with HIV (PWH) who initiated ART and were diagnosed after the age of 15. Disengagement was defined as an absence of clinic visits for at least 1.5 years. Multinomial logistic regression was employed to compare the profiles of individuals who have disengaged from care (once or multiple times) with those who have never disengaged. Linear mixed models (LMMs) with subject-specific knots at disengagement and reengagement were used to model CD4 trends on the square-root scale separately for those who disengaged once and twice. Another LMM including individuals who had never disengaged was also fitted for comparison. CD4 evolution conditional on baseline CD4 categories (ART initiation, first and second reengagement) was calculated using properties of the bivariate normal distribution.

Results: 6722 PWH were included, 86% male; 58% MSM and 12% IVDUs. The median age at ART initiation was 36 years. 27% of PWH disengaged from care once and 10% at least twice, with the median time from ART initiation to first and second disengagement being 3.5 and 7 years, respectively. Young IVDUs (≤40 years at diagnosis) and particularly those of non-Greek origin were most likely to disengage at least once, with female IVDUs being the most vulnerable. The average gradient of CD4 restoration after ART initiation was the highest among those who never disengaged from care, followed by those who

experienced one and 2 gaps in care, whereas the lowest was observed among those who drooped-out of care (Figure, A); CD4 restoration after reengagement in care, especially after the second time, was notably worse compared to the corresponding CD4 increase after ART initiation before disengagement, regardless of the baseline CD4 levels (Figure B).
Conclusion: While CD4 counts tend to increase after reengagement in care, it is evident that multiple disengagements cumulatively impact negatively CD4 evolution; young IVDUs and those of non-Greek origin are the most vulnerable for disengagement from care.

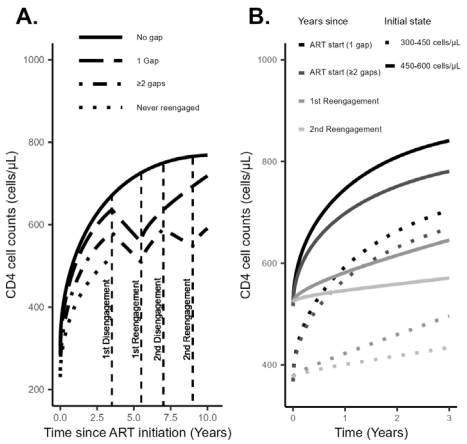

Figure. Estimated CD4 evolution by patterns of disengagement.

1042 A Multistate Analysis of Longitudinal Care Outcomes Among People Newly-Linked to Care in Missouri

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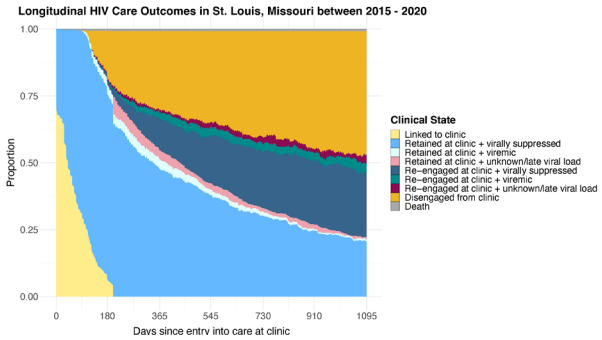
Background: Traditional metrics of retention in HIV care fall short of quantifying the dynamic process of engagement and disengagement from care over time. Novel longitudinal analytic approaches reveal more nuanced care trajectories for people living with HIV (PLWH), thus providing stronger evidence to improve service delivery. We conducted a multistate analysis to describe transitions in and out of care and comprehensively represent longitudinal outcomes in Missouri, an Ending the HIV Epidemic priority state.
Methods: We analyzed electronic health record data collected from PLWH ≥ 18 years who were newly or presumed newly linked to care at a large Ryan White-funded HIV primary care clinic in St. Louis, Missouri between January 1, 2015 and March 15, 2020. We estimated the prevalence of 9 mutually exclusive and exhaustive care states over the 3 years following linkage to clinic based on 1) retention status (retained, disengaged, re-engaged) and 2) viral load (VL) status (virally suppressed (VS), viremic, unknown/late VL). Disengaged was defined as > 90 days late for a scheduled appointment. VS was defined as a VL < 200 copies/mL ≤ 200 days; viremic as VL > 200 copies/mL ≤ 200 days; and unknown/late VL as a gap in VL measurement > 200 days.
Results: 1,110 patients were newly linked to the clinic during the observation period, contributing 2255.4 person-years of follow-up. Median age was 34 years (IQR 25-47), 865 (77.9%) were male, 745 (67.1%) identified as non-Hispanic Black, and 229 (20.6%) were 18-24 years at entry. Three years following linkage to clinic, 53.1% (95% CI: 50.0, 56.2) were in care (22.3% continuously retained, 30.8% re-engaged, Figure). Regarding VS, 92.7% of those continuously retained were VS compared to 78.7% who had re-engaged in care. Although 69.4% were retained with VS at 6 months, 29.2% and 46.2% disengaged at 1- and 3 years, respectively. Among those who disengaged, 61.2% (95% CI: 57.4, 65.0) re-engaged and 40.2% (95% CI: 36.4, 44.0) were VS after one year.
Conclusion: Disengagement, re-engagement, and viremia over time are far more common than previously reported in Missouri. While engagement is initially strong, subsequent disengagement and re-engagement are high in the first year following linkage to care, with uncertain outcomes among those who do not re-engage. Multistate analyses can strengthen our understanding of such tenuous timepoints in the care continuum, highlighting important targets for optimizing lost-to-care and re-engagement services to end the epidemic.



1043 Rethinking the Definition of Late HIV Diagnosis Using Florida Surveillance Data, 2015-2021

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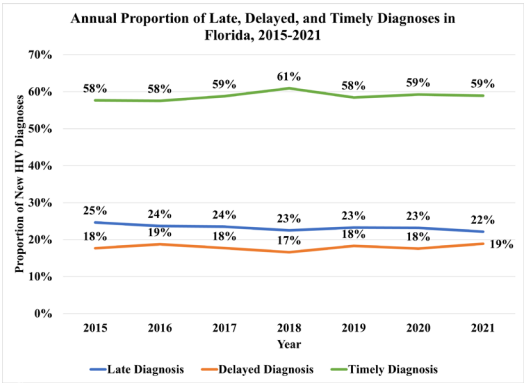
Background: Late HIV diagnosis is a barrier to ending the epidemic as it may be associated with prolonged transmission risk and worse HIV-related outcomes. The CDC defines late HIV diagnosis as a CD4+ T-cell count<200 cells/mm^3 at diagnosis. It is unclear if an expanded clinically relevant definition of CD4<350 would better represent those in need of resources to prevent poor outcomes. We aimed to examine trends in the annual proportion of different definitions (late/delayed) of late HIV diagnosis between 2015-2021 in Florida, characteristics associated with late/delayed diagnosis, and the association between diagnosis status and mortality.
Methods: Data included laboratory results for HIV care recipients, diagnosed 2015-2021, in the Enhanced HIV/AIDS Reporting System. Diagnosis status was categorized as late (CD4<200), delayed (200≤CD4<350), and timely (CD4≥350). Characteristics of interest were age, gender, race/ethnicity, birth region, and diagnosis facility. Multivariable multinomial logistic regression models examined characteristics by diagnosis status. Logistic regression, adjusting for characteristics, estimated risk of death during the study period.
Results: Of 27,460 individuals (21% female, 39% non-Hispanic [NH] Black, 35% Hispanic, 2% NH Other, mean age 38.3 years [SD 12.9]), 23% had a late and 18% had a delayed diagnosis overall, and this proportion was consistent annually. Older adults (ref=18-24; 25-34 [OR 1.6, 95% CI 1.4-1.8], 35-49 [2.4, 2.1-2.7], 50+ [2.7, 2.3-3.0]) and those of Caribbean birth region (ref=North America; 1.1, 1.0-1.3) were more likely to have a late diagnosis. Late and delayed diagnosis were similarly associated with female (ref=male; delayed: 0.9, 0.8-0.96, late: 0.8, 0.7-0.9), NH Black (ref=NH White; delayed: 1.6, 1.4-1.7, late: 1.5, 1.4-1.6) Hispanic (delayed: 1.4, 1.2-1.5, late: 1.1, 1.0-1.2), and inpatient diagnosis (ref=outpatient; delayed: 1.6, 1.4-1.7, late: 5.4, 5.0-5.9) characteristics. There were 1,176 deaths and delayed (1.3, 1.04-1.5) and late (1.9, 1.6-2.2) diagnosis were associated with death.
Conclusion: Expanding the late diagnosis definition captured an additional 18% of HIV diagnoses that may be at greater risk of poor outcomes such as death. Characteristics associated with late/delayed diagnoses were consistent and both were associated with greater mortality risk. Those with late/delayed diagnosis would benefit from enhanced intervention. Future research can target other late/delayed diagnosis factors to address missed HIV testing opportunities.



1044 Temporal Trends in CD4 Cell Count Soon After Seroconversion and HIV-RNA Viral Set-Point

Nikos Pantazis[1], Dominique Costagliola[2], Ard van Sighem[3], Inma Jarrin[4], Laurence Meyer[5], Caroline Sabin[6], Christina Carlander[7], John Gill[8], Shema Tariq[6], Bruno Spire[9], Fiona Burns[6], Elisa Ruiz-Burga[6], Kholoud Porter[6], Giota Touloumi[1], for the CASCADE Collaboration

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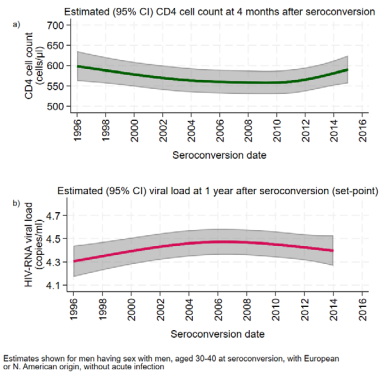
Background: We have previously reported on a temporal decrease in CD4 cell count at seroconversion (SC) and an increase in HIV-RNA viral load (VL) levels at 1 year (which we refer to as set-point) over the period 1980-2008. These markers of virulence reached a plateau in the mid 2000's. Here we update these analyses, focusing on changes since the introduction of combination ART in 1996.

Methods: Data were derived from the CASCADE Collaboration. Included individuals seroconverted ≥1996, were ≥16 years, had an HIV- to HIV+ test interval ≤1 year or other laboratory evidence of SC, and CD4/VL measurements while ART naïve and AIDS-free. Exploratory analysis revealed gradient changes at ~4 months and ~1 year after SC for CD4 and VL, respectively. Analyses were based on piecewise linear mixed models. Calendar time effects were introduced through natural cubic splines. For CD4 at 4 months after SC and viral set-point analyses, those seroconverting after 1/1/2015 and 1/1/2014, respectively, were excluded, as they tended to initiate ART very soon after SC and reliable estimation of these quantities was not feasible. Models were adjusted for age, sex, transmission mode, region of origin, acute infection (< or ≥30 day HIV test interval) and type of viral assay.

Results: Of 28556 individuals in CASCADE, 15059 (52.7%) fulfilled the inclusion criteria. The majority (70.5%) acquired HIV through sex between men and 10.3% men and 14.3% women through heterosexual contact. Median (IQR) age at SC was 33 (27, 41) years. Of 2701 with known subtype 2275 (84.2%) had a B subtype. Estimated (95% CI) CD4 cell count levels at 4 months after SC declined from 598 (562-635) for those seroconverting in 1996, to a plateau of ~559 (530-588) cells/μl for those seroconverting between 2006 and 2010 and slowly increased in more recent years (Figure, a). Viral set-point showed a similar but reversed trend with an increase from 4.31 (4.17-4.44) in 1996 to ~ 4.47 (4.36-4.58) log c/mL in 2006-2010 and a slow declining trend thereafter (Figure, b). Individuals with CRF02_AG subtype had approximately 62 cells/μl lower CD4 cell count at 4 months after SC (p=0.023) and all non-B subtypes were associated with non-significantly lower viral set-point compared to those with B subtype.

Conclusion: Our results showed minimal changes in levels of both CD4 soon after SC and viral set-point after 2004 suggesting that these markers of HIV virulence may have plateaued.



1045 Advanced HIV Disease and the Care Cascade: Trends From 2015-2021

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Background: The burden of advanced HIV disease (AHD) remains high in much of Africa despite expanded access to ART. Designing interventions to effectively prevent and manage AHD require an understanding of where the care cascade is failing. We analysed data from a series of studies in southern and east Africa, describing characteristics of individuals presenting with AHD between 2015 and 2021.

Methods: We compared demographics and ART status in i) a cryptococcal antigen screening program in Botswana with CD4 counts<100 cells/μL in 2015/16; (ii) a similar cohort recruited in 2018/19 after universal ART introduction; and (iii) the multi-country AMBITION trial of cryptococcal meningitis conducted 2018/2021.

Results: 1645 individuals were included in the 2015/16 cohort, 743 in the 2018/19 cohort, and 810 in the AMBITON trial. Median age, sex and CD4 counts were similar (37, 39, and 37 years; 50%, 55%, and 61% male; 54 cells/μL, 59 cells/μL, and 27 cells/μL). In the 2015/16 cohort 55% (911/1645) of individuals presenting with AHD were ART naïve; 40% (654/1645) had been newly diagnosed with HIV and 16% (257/1645) knew their HIV status but had not initiated treatment; 45% (734/1645) were ART experienced (either taking or previously taken ART). By 2018/19 and 2018/2021 individuals presenting with AHD were significantly more likely to be ART experienced (67% (499/743) and 64% (521/810), p<0.001). In the most recent AMBITION trial, of the 521 ART experienced patients, 14% (72/521) had initiated ART within the last 2 weeks, 23% (119/521) between 2 weeks and 6 months, 40% (207/521) had been on ART for over 6 months, and 24% (123/521) had started ART but discontinued after a median of 61 months (IQR 36-112); of those on ART for over 6 months, 31% (64/207) reported poor adherence and 88% (161/184) of those with viral load results available had a non-suppressed viral load.

Conclusion: The proportion of AHD due to late HIV diagnosis and ART initiation has declined since the introduction of universal treatment in 2016, with most people with AHD now presenting having previously initiated ART. In addition to ongoing AHD presentations due to delayed HIV testing and ART initiation or default from care, a substantial proportion of AHD is occurring in individuals in care, who have either recently initiated or re-initiated ART with low CD4 counts, or who are experiencing treatment failure due to adherence or resistance issues, reflecting the cyclical nature of the care cascade.

1046 Global Trends in CD4 Count Measurement and Prevalence of CD4 <200 cells/μL at ART Initiation

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Background: Since the 'Treat-All' era, people with HIV (PWH) start antiretroviral therapy (ART) regardless of CD4 count; consequently, CD4 measurement at ART initiation is declining in many countries. However, CD4 counts are still necessary to identify people with advanced HIV disease, to monitor and evaluate ART programs, and to inform epidemiological models. We described CD4 availability and prevalence of CD4 <200 cells/μL at ART initiation using observational data from a global HIV cohort collaboration, the International epidemiology Databases to Evaluate AIDS (IeDEA).

Methods: We included PWH who initiated ART at age 15–80 years during 2005–2019. We excluded those with HIV viral load <1000 copies/mL at ART start (assumed treatment-experienced). We described proportions of PWH with available CD4 (measured within 6 months before to 2 weeks after ART start); and among those with a CD4, those with CD4 <200 cells/μL; by year of ART start, region, age, and birth sex.

Results: We included 1, 355, 104 PWH from 8 regions (Asia-Pacific: 24, 446, Latin America: 33, 243, North America: 51, 469, East Africa: 236, 981, West Africa: 37, 956, Central Africa: 51, 667, Southern Africa excluding South Africa: 602, 948, South Africa: 316, 394); 63% were female. Median (interquartile range, IQR) age at ART start was 37 (31–44) in men and 32 (26–39) in women. Across regions, CD4 availability was 58–86% in 2005, and 48–87% in 2015. By 2019, it remained between 61–86% in North America, Latin America, Asia-Pacific, and South Africa; but declined to 13–53% in other participating sub-Saharan

African (SSA) countries. Prevalence of CD4 <200 was 54–90% in 2005, 29–45% in 2015, and 30–45% in 2019. Median (IQR) CD4 was 309 (156–497) in 2019. CD4 availability was similar between age and sex groups. Among those with a CD4 in 2015–2019, prevalence of CD4 <200 was higher in males than females in SSA, including South Africa (43% versus 28%), but not in the other regions (35% in males versus 38% in females); and higher in older ages in all regions (40% in ages ≥45 versus 19% in ages 15–24).
Conclusion: Our findings add to the evidence that CD4 measurement has declined in recent years to very low levels, especially in SSA, with the exception of South Africa. PWH with a CD4 might not reflect those without a CD4; however, among those with a CD4, the prevalence of CD4 <200 at ART initiation remains concerningly high. CD4 measurement around the time of ART initiation should be more widely adopted and adequately funded.
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1047 Difficult-to-Treat HIV in Sweden: Describing the Current Landscape

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Background: Our aim was to examine the prevalence and characteristics of difficult-to-treat HIV in the current Swedish HIV cohort and to compare treatment outcomes between people with difficult and non-difficult-to-treat HIV.
Methods: In this cross-sectional analysis of the Swedish HIV cohort, we identified all people with HIV currently in active care in 2023 from the national register InfCareHIV. We defined five categories of difficult-to-treat HIV: 1) advanced resistance, 2) four-drug regimen, 3) salvage therapy (ibalizumab, fostemsavir, enfuvirtide, maraviroc, etravirine, BID dolutegravir, BID darunavir), 4) virologic failure within the past 12 months, and 5) ≥ 2 regimen switches following virologic failure since 2008. People classified as having difficult-to-treat HIV were compared with non-difficult for background characteristics as well as treatment outcomes (viral suppression [< 50 copies/mL] and self-reported physical and psychological health [based on a validated health questionnaire]) using Pearson's $\chi 2$ test as well as logistic regression adjusted for sex, age, and risk group.
Results: Nine percent of the Swedish HIV cohort in 2023 met at least one criterion for difficult-to-treat HIV. The most frequent category was "≥ 2 switches following failure" (6%), followed by "advanced resistance" (2%) and "salvage therapy" (2%). Compared with non-difficult, people with difficult-to-treat HIV were older, had an earlier first year of positive HIV test and lower CD4+ T-cell counts. Women were overrepresented among people classified as having difficult-to-treat HIV, especially in the categories "recent virologic failure" and "≥2 switches following failure". The viral suppression rate among people with difficult-to-treat HIV was 84% compared with 95% for non-difficult ($p < 0.001$). This difference was similar both among men and women, and it remained statistically significant after multivariable adjustment (aOR, 0.28; 95% CI, 0.22–0.35). People with difficult-to-treat HIV reported worse physical (but not psychological) health, and this also remained statistically significant in multivariable analysis (aOR, 0.74; 95% CI, 0.60–0.92).
Conclusion: Although 9% of the HIV cohort in Sweden in 2023 were classified as having difficult-to-treat HIV, a large proportion of these were virally suppressed. Challenges such as advanced resistance and need for salvage therapy are rare in the current Swedish cohort.

1048 Life-Years Lost Associated With Mental Illness in People With HIV in South Africa and North America

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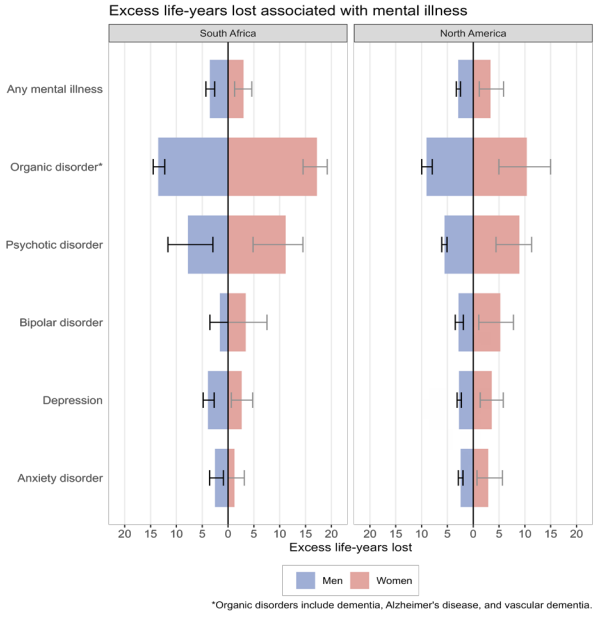
Background: Mental illness is known to reduce life expectancy in people with HIV (PWH). We estimated excess life-years lost (LYL) associated with mental illness among PWH in South Africa and North America, compared with PWH without a mental illness.
Methods: We conducted a cohort study using data from the Aid for AIDS (AfA) private sector disease management program in South Africa and from the NA-ACCORD collaboration of HIV cohorts in the United States and Canada. We included PWH aged 18-84 years with follow-up in AfA (2011-2020) or NA-ACCORD (2000-2020). We computed excess LYL associated with an ICD-9/10 diagnosis for any mental illness, organic disorder, psychotic disorder, bipolar disorder, depressive disorder, and anxiety disorder, by gender and region. Excess LYL measures the average difference in remaining life expectancy in PWH diagnosed with a mental illness compared with PWH of the same age without a mental illness. We disaggregated LYL into natural, unnatural (due to injuries or violence), and unknown causes of death.
Results: We included 126,058 PWH from South Africa (58% women, 4.6 median years of follow-up) and 85,296 from North America (9% women, 5.8 median years of follow-up). In South Africa, 45% of men and 50% of women were diagnosed with a mental illness. In North America, 63% of men and 65% of women were diagnosed with a mental illness. In both regions, depressive and anxiety disorders were the most common. In South Africa, mental illness was associated with 3.5 LYL (95% CI 2.6-4.3) in men and 3.0 LYL (95% CI 1.3-4.6) in women (Figure). In North America, mental illness was associated with 2.9 LYL (95% CI 2.5-3.3) in men and 3.4 LYL (95% CI 1.2-5.9) in women. In men, 68% of the LYL associated with mental illness in North America were attributable to natural causes of death, compared with 79% in South Africa. For women, in both regions the entire excess mortality burden was due to natural causes. The excess LYL ranged from 1.3 (95% CI -0.7-3.2) in South African women with anxiety to 17.2 (95% CI 14.5-19.2) in South African women with an organic disorder.
Conclusion: ICD diagnoses for mental illness were associated with excess mortality in South African and North American PWH. Death from natural causes was the main contributor to their excess mortality. These findings support the implementation of strategies for the prevention, early detection, and treatment of mental illnesses in PWH, and for the screening and treatment of physical comorbidities in PWH who have a mental illness.



1049 Modeled Estimates of Disease Burden Att ributable to Interactions Between HIV and Depression in Kenya

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Background: In sub-Saharan Africa, AIDS is the leading cause of mortality, while depression is the leading causes of morbidity. Depression is known to increase HIV acquisition and impede effective treatment, while people living with HIV have elevated risk of depression, but these interactions have not previously been modeled in the context of overlapping HIV and mental health crises. We used a simulation model to estimate how the HIV pandemic has

impacted depression and how the depression epidemic has impacted the HIV pandemic in Nyanza, Kenya, a geography where both conditions are prevalent.
Methods: We adapted a previously validated agent-based network transmission model calibrated to age- and sex-specific prevalence of HIV and coverage of treatment and prevention services. We augmented this model to include major depressive disorder. The model was calibrated to the age- and sex-specific incidence, recovery, and relapse rates of major depressive disorder in Kenya. Calibration was applied to a primary scenario, in which we included the following interactions between HIV and depression based on rapid review of literature: HIV increases incidence of depression (2x); depression increases HIV acquisition rate (1.6x); depression interferes with the HIV care continuum (2x delays to testing, 1.2x reduction in adherence to treatment, and 2x higher rates of treatment discontinuation). In a counterfactual scenario, we removed all interactions between HIV and depression. We estimated the number of episodes of depression, new HIV cases, and HIV-related deaths over 1985–2025.
Results: In the primary scenario, we estimated 1.24 million new HIV infections, 0.66 million HIV deaths, and 17.7 million episodes of depression in western Kenya over 1985–2025. We found a 9.96% (95% CI: 9.84%–10.1%) increase in episodes of depression attributable to HIV; a 9.18% (95% CI: 8.93%–9.44%) increase in new HIV cases attributable to depression; and a 10.5% (95% CI: 10.1%–10.8%) increase in HIV-related deaths attributable to depression. Sensitivity analysis is ongoing to identify interactions most strongly responsible for these effects and that contribute the greatest uncertainties.
Conclusion: Our findings suggest interactions between depression and HIV have substantially exacerbated both epidemics. Research is needed to more precisely quantify strengths of the interactions and how they differ across populations and settings.

1050 Prevalence of Diagnosed and Undiagnosed Depression Among US Adults With HIV

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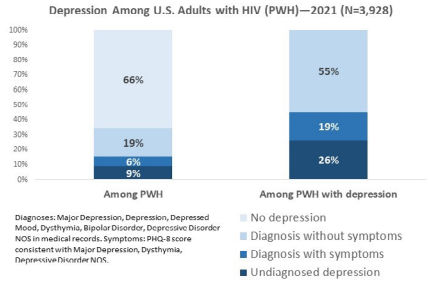
Background: People with HIV are disproportionately affected by depression. Effectively diagnosing and treating depression could improve quality of life (QoL) and HIV outcomes. We used data from CDC's Medical Monitoring Project (MMP) to report nationally representative estimates of diagnosed and undiagnosed depression among U.S. adults with HIV (PWH).
Methods: During 6/2021–5/2022, MMP collected interview data on depression symptoms consistent with a diagnosis using the Patient Health Questionnaire (PHQ-8) and depression diagnoses from medical records of PWH (Figure). We report weighted percentages and prevalence ratios (PRs) with predicted marginal means and 95% confidence intervals (CIs) to quantify differences between groups on key social and health factors.
Results: Overall, 34% of PWH experienced any depression (either by diagnosis or PHQ-8); of these, 26% had symptoms but no diagnosis (undiagnosed depression), 19% had both diagnosis and symptoms, and 55% had a diagnosis without symptoms (Figure). Among those with depression, cisgender men (PR: 1.34, CI:1.04-1.72) and transgender persons (PR: 1.77, CI:1.07-2.90) were more likely than cisgender women to have undiagnosed depression, as were those with a disability (PR: 1.52, CI:1.19-1.94) and food insecurity (PR: 1.67, CI:1.37-2.03) than those without. Unemployed persons (PR: 1.62, CI:1.11-2.38) were more likely than employed persons to have diagnosed depression with symptoms, as were those with a disability (PR:2.78, CI:2.13-3.64), who experienced housing instability/homelessness (PR: 1.37, CI:1.06-1.77), food insecurity (PR:1.46, CI:1.12-1.90), or discrimination in HIV care (PR: 1.71, CI:1.30-2.23) than those without. HIV stigma was higher with nonoverlapping CIs among the undiagnosed (median score, range 0-100: 40.4, CI:34.6-46.2) and diagnosed with symptoms (43.1, CI:36.2-50.0) than those diagnosed without symptoms (28.0, CI:26.1-30.0). Those with symptoms (undiagnosed or diagnosed) were less likely than those diagnosed without symptoms to be dose adherent (PR: 0.88, CI:0.78-0.98; PR: 0.73, CI:0.60-0.89) or have sustained viral suppression (PR: 0.62, CI:0.54-0.72; PR: 0.91, CI:0.82-1.00) and were more likely to have unmet needs for mental health services (PR: 2.38, CI:1.62-3.51, PR: 2.03, CI:1.45-2.83).
Conclusion: One-third of PWH experienced depression; nearly half of them were undiagnosed or still experiencing considerable symptoms. Expanding universal screening and high-quality treatment for depression could improve QoL and HIV outcomes.



1051 Trends in Suicide-Related Emergency Department Visits Among People With and Without HIV in Bronx, NY

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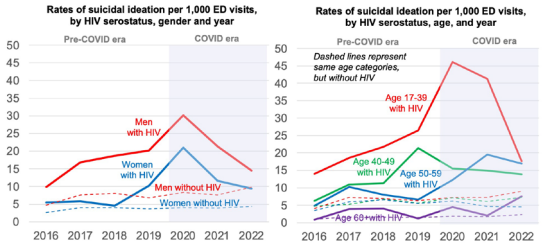
Background: People living with HIV (PWH) are at elevated risk for suicidality (i.e., suicidal ideation, plans, attempts), though little is known about population-specific factors driving potential disparities in Emergency Department (ED) visits in the context of suicide. Using longitudinal data from a large Bronx, NY health system, we measured trends and disparities in suicide-related ED visits between PWH (N=7,903) and people without HIV (N=560,977).
Methods: Using the Einstein-Rockefeller-CUNY CFAR's Clinical Cohort Database, we identified all ED visits among patients age 17+ years at 4 EDs in the Montefiore Health System between 2016 and 2022, and determined suicide-related visits using ICD-10-CM diagnosis codes for suicidal ideation/behavior. We measured rates of suicide-related visits by HIV status. Rates were annualized per 1,000 ED visits, age-standardized to the 2000 US Standard Population and stratified by gender, age, race/ethnicity and HIV transmission factor.
Results: Among 1,760,143 unique ED visits (40,475 among PWH) between 2016-2022, 8,994 (506 among PWH) were suicide-related. The overall rate of suicidal ideation/behavior among PWH was 14.9/1,000 ED visits (95% CI 13.3-16.4), compared with 5.2/1,000 (95% CI 5.1-5.3) among those without HIV. Rates were consistently higher among PWH versus those without HIV across gender and age categories (Figure). Among PWH, the highest rates were observed among those age 17-39 years (25.6/1,000, 95% CI 22.4-28.9), cisgender men (18.5/1,000, 95% CI 16.4-20.7, vs cisgender women, 6.6/1,000, 95% CI 5.0-8.3), and non-cisgender individuals (30.0/1,000, 95% CI 16.8-45.0). Before the COVID-19 pandemic, both the annual number and rate of suicide-related ED visits had increased steadily over time among PWH, from N=39 (7.8/1,000) in 2016 to N=74 (16.7/1,000) in 2019. Trends showed a further increase as COVID-19 became established, to N=86 (27.4/1,000) in 2020, particularly among PWH age 17-39, before decreasing in 2021 and 2022. Temporal increases in suicidal ideation/behavior were less pronounced among people without HIV.
Conclusion: Suicide-related visits were nearly 3-fold higher among PWH compared with those without HIV in this large, urban ED setting, and increased differentially over time, even after accounting for temporal changes associated with the COVID-19 pandemic. Younger PWH and transgender individuals may be at particular risk for suicidality; more research into associated factors is needed to help info.



1052 Progress Toward Achieving National Goals for Improved Quality-of-Life Among Black Women With HIV

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Background: U.S. Black/African American women have disproportionately high rates of HIV and face challenges to optimal health due to disproportionate burden of poor social and structural determinants of health. In 2022, 5 Quality of Life (QOL) indicators were added to the Medical Monitoring Project (MMP) and included in the National HIV/AIDS Strategy (NHAS) goals to achieve by 2025. We evaluated whether existing trends in these indicators are sufficient to meet NHAS goals for cis-gender Black women with HIV (CgBWH), an NHAS priority population.
Methods: We used data from the 2017–2021 cycles of the MMP, an annual probability sample of U.S. adults with diagnosed HIV. We calculated weighted percentages and confidence intervals (CIs) for QOL indicators from baseline (2017 or 2018) to 2021. For each indicator we calculated 1) the estimated annual percent change (EAPC) and associated test for significance ($p<0.05$) from baseline to 2021; 2) projected annual estimates for 2022 to 2024 to meet NHAS 2025 goals, assuming linear relationships between baseline and NHAS goals; and 3) the EAPC needed from 2021 to 2025 to meet NHAS 2025 goals, based on projected estimates. For each indicator, we compared the EAPCs from baseline to 2021 with EAPCs for 2021 to 2025 to determine whether existing rates of change are sufficient to meet goals.
Results: Unemployment, hunger/food insecurity, and unstable housing/homelessness significantly decreased from baseline to 2021 (Table). Conversely, progress in self-rated health regressed from baseline to 2021. An EAPC of 12% is needed to reach the NHAS goal for self-rated health, compared with an existing EAPC of -3.2%, and an EAPC of at least 18.5% is needed to reach the NHAS goal for unmet need for mental health services, compared with the existing EAPC of -0.2%.
Conclusion: If current trends continue, the U.S. will likely meet the NHAS goal for decreasing hunger/food insecurity among CgBWH. However, the magnitude of change needed to reach goals for self-rated good or better health and unmet needs for mental health services is substantial and will require enhanced and coordinated efforts to achieve. A national call-to-action is needed to improve health and QOL among CgBWH to equitably achieve NHAS goals.

Table supplemental text word limit 50/50

National HIV/AIDS Strategy (NHAS) quality of life indicators among cisgender Black women with HIV—United States, 2017-2021 (N=2,917)

NHAS Indicators	Baseline (2017[1]/2018[2]) Prevalence	2021 Prevalence	EAPC from Baseline to 2021		2025 NHAS Goal	EAPC needed 2021 to 2025 to Achieve NHAS Goal
	Wgt. % (95% CI)	Wgt. % (95% CI)	%	*P*	%	*n*
Self-reported Good or Better Health, current	68.3 (62.9-73.7)[2]	59.4 (53.4-65.4)	-3.2%	< .001	95.0	12.5%
Unmet need for Mental Health Services Among Those with a Need for Services	25.2 (18.3-32.1)[1]	28.6 (17.0-40.3)	-0.2%	0.45	12.6	-18.5%
Unemployment, current	15.7 (12.4-19.0)[1]	13.5 (9.9-17.0)	-3.0%	< .001	7.9	-12.7%
Hunger/Food Insecurity	22.3 (19.0-25.5)[1]	14.4 (11.0-17.8)	-13.4%	< .001	11.2	-6.2%
Unstable Housing or Homelessness	21.0 (17.8-24.3)[2]	18.7 (14.7-22.7)	-6.8%	< .001	10.5	-13.4%

[1]2017; [2]2018; Note: EAPC, estimated annual percent change; wgt, weighted; CI, confidence interval; all indicators self-reported and based on the past 12 months except where otherwise indicated; definitions available at https://files.hiv.gov/s3fs-public/2022-09/NHAS_Federal_Implementation_Plan.pdf.

1053 Mind the Gap: Life Expectancy and Mortality in Males & Females With HIV in British Columbia, Canada

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Background: Life expectancy (LE) of people with HIV (PWH) has risen considerably in the last decades, but LE gains among females with HIV have fallen behind.
Methods: We examined trends and sex differences in LE and mortality among all PWH in British Columbia (BC), using data from the Comparative Outcomes And Service Utilization Trends study. LE at ages 20, 40, and 55 was calculated using life tables stratified by sex and period (1996-2002, 2002-12, 2012-20). Using multivariable Cox regression, we modelled the association between female sex and all-cause mortality, adjusted for age and baseline confounders: history of injection drug use, residence in Vancouver's Downtown Eastside area, residence in a rural area, area-level income. Secondly, models were adjusted for CD4 count at antiretroviral therapy (ART) initiation. Models were repeated for each period and for mortality from communicable disease, non-communicable disease, and injuries/external causes (defined using ICD codes).
Results: A total of 11,739 males (82%) and 2,534 females (18%) with HIV were included; 92% and 88%, respectively, were ever on ART. LE for males aged 20 increased from 24.5 (95% CI 22.3–26.6) in 1996-2002 to 37.1 (35.4–38.8) in 2002-12, and to 48.0 (45.7–50.3) in 2012-20. LE for females aged 20 increased, but remained lower, from 22.1 (19.9–24.4), to 32.8 (30.6–34.9), and to 40.9 (37.7–44.2). Patterns were similar at age 40 and 55. The sex gap in LE increased over time, both at age 20 and 40 (from 3.2 in 1996-2002 to 5.3 years in 2012-20), but was not as discernible at age 55. In adjusted models, female sex was significantly associated with all-cause mortality, overall and in 2002-12 and 2012-20 (Table). Similarly, in adjusted models, female sex was associated with mortality from non-communicable disease, but not from injuries/external causes and communicable disease. Further adjustment for CD4 count at ART initiation did not affect the associations significantly.
Conclusion: In a setting with universal health care and free ART, the sex gap in LE among PWH continues to increase with time. Clinical and socio-economic factors do not explain that this gap in LE and HRs are increasing over time, but they do largely explain differences in mortality from communicable disease and injuries/external causes. If PWH followed the pattern observed among people without HIV in BC, we would expect the gap in LE to favor females. Our work suggests that addressing socio-structural factors may potentially reduce but not reverse the gap.

Table: Associations between sex, all-cause, and cause-specific mortality.

		Female sex, adjusted for baseline age HR (95% CI)	Female sex, adjusted for age and confounders HR (95% CI)	Female sex, adjusted for age, confounders, and CD4 at ART initiation HR (95% CI)
All-cause mortality	Overall	1.37 (1.27 – 1.48)	1.14 (1.06 – 1.24)[a]	1.11 (1.03 – 1.20)[a]
	1996-2002	1.24 (1.05 – 1.46)	1.04 (0.88 – 1.23)[a]	0.99 (0.84 – 1.17)[a]
	2002-2012	1.44 (1.28 – 1.62)	1.18 (1.05 – 1.33)[b]	1.15 (1.02 – 1.30)[b]
	2012-2020	1.52 (1.33 – 1.75)	1.24 (1.08 – 1.42)[ac]	1.24 (1.08 – 1.42)[acd]
Communicable disease mortality*		1.16 (1.03 – 1.30)	0.99 (0.88 – 1.11)	0.96 (0.85 – 1.08)
Non-communicable disease mortality*		1.60 (1.39 – 1.86)	1.35 (1.16 – 1.56)[a]	1.33 (1.15 – 1.54)[ac]
Mortality from injuries/external causes*		1.53 (1.28 – 1.82)	1.15 (0.96 – 1.37)[a]	1.10 (0.92 – 1.31)[a]

*Communicable disease: defined by ICD-9 (001-139.9) and ICD-10 (A,B,J00-22,U04) codes; non-communicable disease: ICD-9 (140-799.9) and ICD-10 (C-R); injuries/external causes: (ICD-9 (800-999.9) and ICD-10 (S-Y). Variables dropped during confounder selection (female sex coefficient change <5%): [a]rurality; [b]Downtown Eastside; [c]area-level income, [d]CD4.

1054 Leading Causes of Death Among People With HIV in the US, 2001-2019

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Background: People with HIV (PWH) face elevated risk of death due to AIDS, other comorbidities, and external causes. Yet, no published study has used population-based data to examine cause-specific mortality among PWH in the US. We report the frequency of major causes of death among PWH and compare overall and cause-specific mortality among PWH to the US general population.
Methods: Data on the underlying causes of death among PWH aged 20 or older who died during 2001–2019 were obtained from the HIV/AIDS Cancer Match (HACM) Study. HIV registries in the HACM Study capture vital registry data, including cause of death information, from 12 states, DC, and Puerto Rico. We report the number of deaths and proportions overall and for the leading causes of death. To compare the mortality rates of PWH to the general US population, we calculated standardized mortality ratios (SMRs), adjusting for sex, age-group, race/ethnicity, and calendar year. An SMR was not calculated for HIV as it is only a cause of death among PWH.
Results: During 2001–2019, there were 176,051 deaths among PWH over 7.3 million person-years of follow-up. Among decedents, 71.6% were male, 61.6% were aged 40–59 years, and 49.0% were non-Hispanic Black. The leading cause of death was HIV, accounting for 37.1% of deaths, followed by cancer (7.5% of deaths) and heart disease (6.1% of deaths) (see table). PWH had a 4 times higher risk of death (SMR: 4.15) compared to the general US population. Relative to the general population, mortality rates among PWH were elevated more among females (SMR: 6.18) than males (3.67), individuals aged 20–39 (8.86) vs. those aged 60 and older (2.15), and for Hispanic individuals (5.47) vs. Non-Hispanic Black and White people (3.78 each). SMRs steadily decreased with more recent calendar periods (8.56 during 2001–2004 vs. 2.34 during 2015–2019). SMRs were elevated for all leading causes, and highest for other infections, followed by accidents and adverse events. PWH were at 29% higher risk of death from cancer and 12% higher risk of death from heart disease.
Conclusion: Despite improvements over time, death rates among PWH remained more than twice as high as the general population during 2015-2019.

Death rates were elevated among PWH for several leading causes of death, including cancer, heart disease, and infections.

Overall and leading six causes of non-HIV death among PWH in the US, 2001–2019

Cause of death	No. of deaths	% of all deaths†	SMR (95% CI)
Overall	176 051	100.0	4.15 (4.13–4.16)
Cancer	13 248	7.5	1.29 (1.27–1.32)
Heart disease	10 790	6.1	1.12 (1.10–1.14)
Accidents and adverse events	5733	3.3	1.55 (1.51–1.59)
Other infections*	3376	1.9	2.75 (2.66–2.84)
COPD and allied conditions	1842	1.0	1.53 (1.46–1.60)
Chronic liver disease and cirrhosis	1769	1.0	1.38 (1.32–1.45)

COPD chronic obstructive pulmonary disease
* Includes all infections, except HIV and influenza/pneumonia.
† Additionally, influenza/pneumonia (1.0% of deaths), diabetes and cerebrovascular diseases (0.9% each), suicide (0.8%), and other/unknown causes (39.4%).

1055 Age-Adjusted Mortality Rates Among Persons With HIV, by Race and Ethnicity and Cause of Death

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Background: During 2010–2018, the age-adjusted mortality rate (AAMR) among persons with HIV (PWH) in the United States declined by 37%, primarily from a 48% reduction in HIV-associated deaths. We used public health surveillance data to determine how the COVID-19 pandemic affected mortality by race and ethnicity and cause of death (CoD) among PWH in California.
Methods: We analyzed death certificate data for PWH from California Vital Records during 2018–2021. We categorized immediate CoD using International Classification of Diseases, Tenth Revision codes and excluded records missing CoD. AAMRs/100,000 persons were calculated by race and ethnicity and by CoD. We calculated percentage changes in AAMRs from 2018–2019 (before COVID-19 pandemic) to 2020–2021 (during COVID-19 pandemic) by race and ethnicity and CoD.
Results: AAMR among PWH in California increased 14.6% from 2018–2019 (4.1 deaths/100,000 persons) to 2020–2021 (4.7 deaths/100,000 persons), with larger increases among multiracial (31.2%), Latinx (29.1%), Asian (16.3%), and Black (15.3%) PWH, compared with White (5.2%) PWH (Figure 1). Leading CoD among PWH during both 2018–2019 (29.5% of deaths) and 2020–2021 (25.4% of deaths) periods was HIV. AAMR because of HIV decreased 2.4% from 2018–2019 to 2020–2021. HIV-associated AAMR decreased among White (-7.9%) and Latinx (-0.2%) PWH, but increased among multiracial (13.9%), Asian (9.0%), or Black (4.8%) PWH. Overdose rose from the third-leading CoD (6.3% during 2018–2019) to second-leading CoD (8.8% during 2020–2021), with overdose AAMR increasing by 63.7%. Black (84.1.%), multiracial (83.1%), and Latinx (77.4%) PWH had higher overdose AAMR increases, compared with White (41.7%) PWH. COVID-19 was the fourth-leading CoD (5.9%) among PWH during 2020–2021. COVID-19 AAMRs were higher among Black (0.7/100,000 persons), multiracial (0.7/100,000 persons), and Latinx (0.5/100,000 persons) PWH, compared with White PWH (0.1 deaths/100,000 persons).
Conclusion: Mortality increased among PWH in California, particularly among non-White populations. Overall, HIV mortality declined, but increased among certain races and ethnicities. Although COVID-19 contributed to the pandemic mortality increase, overdose death rates increased substantially across all races and ethnicities, compared with prepandemic years. Interventions directed at overdose-associated deaths and disparities in HIV mortality, primarily for Black and multiracial PWH, might help reverse these pandemic-era mortality trends in California.

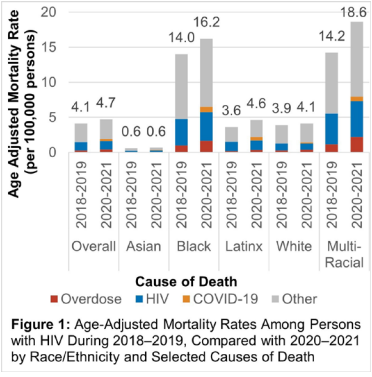

Figure 1: Age-Adjusted Mortality Rates Among Persons with HIV During 2018–2019, Compared with 2020–2021 by Race/Ethnicity and Selected Causes of Death

1056 Mortality Among People Living With HIV in India: Emergence of Noncommunicable Diseases

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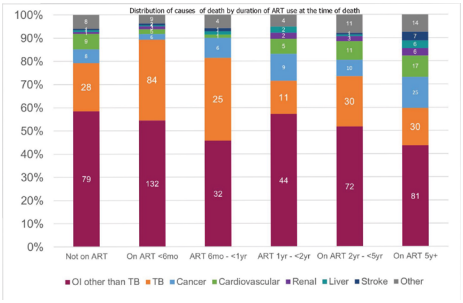
Background: Expanded access to antiretroviral therapy (ART) has significantly reduced HIV-related mortality in adults and children worldwide including a 77% decline in India between 2010 to 2021. Even with this reduction, from January 2019 to March 2020, 79,755 deaths among PLHIV were reported across all government ART centers in the country. While mortality patterns among PLHIV show a shift toward noncommunicable diseases (NCDs) in high income settings, mortality data among PLHIV in low-and-middle-income countries (LMICs) is limited.
Methods: Between January 2019 and March 2020, we collaborated with India's National AIDS Control Program to perform verbal autopsy assessments, a method to determine the most probable cause of death by interviewing caregivers of deceased PLHIV when official medical certification is not available. We conducted the exercise in 28 selected ART centers across 18 Indian states. Interviewers employed the WHO-VA-2016 tool, and two independent physicians utilized ICD classifications to determine the cause of death.
Results: Among the 1,001 deaths investigated, the median age was 42 years (IQR: 35-50), 68% were men and most deaths occurred in Northern India (32%). The primary cause of death was HIV-related opportunistic infections (76%) with tuberculosis counting for 31% of these, followed by cancer (7%), heart disease (6%), renal disease (2%), and liver disease (1%). However, for those who on ART for longer durations, the relative contribution of NCDs was higher – NCDs accounted for only 8% of mortality among those on ART for <1 year compared to 33% among those on ART for more than 5 years ($p<0.001$). People who died of NCDs were significantly older compared to those who died from OIs ($p<0.05$). The most common form of malignancy in men was head and neck cancer (24%), while cervical cancer (27%) was the most common in women.
Conclusion: Mortality attributable to AIDS-related OIs, particularly TB, remains high in this setting, particularly among individuals who are newly initiating ART. This reflects a continued need to detect and engage PLHIV early after infection and support high levels of adherence. As people living with HIV age, it is likely that the relative contribution of NCDs, including cancer, continues to increase highlighting the importance of screening and managing these conditions within ART programs in LMICs.



1057 Registered Causes of Death Remain Largely Unknown Among People With HIV in Latin America

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Background: Describing cause-specific mortality helps define public health prevention priorities. However, vital status records may omit causes of death among people with HIV (PWH), even HIV itself or associated conditions,

particularly in resource-limited settings. We therefore described mortality among PWH in the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) and identified characteristics associated with unknown causes of death.

Methods: Mortality and cause-of-death data from adult PWH in care in CCASAnet from 2003-2022 were extracted from local vital status registries and electronic health records (by ICD-10 code). Causes of death, whether primary, secondary, underlying, or contributing, were categorized as: 1. missing/unknown, 2. HIV or AIDS-defining events (ADEs; if ≥1 cause was: pneumonia, TB, other opportunistic infection, ADE malignancy, unspecified HIV/AIDS), or 3. non-ADEs (NADEs; all other causes, including: renal, liver, cardiovascular, NADE malignancy, trauma, etc.) We described overall mortality and compared characteristics by cause-of-death groups using χ2 and Kruskal-Wallis tests.

Results: Among 56,620 PWH, there were 6,507 (11%) deaths: 3,283 (50%) unknown (including 39% entirely missing), 2405 (37%) ADE, and 819 (12%) NADE causes. ADE causes included: 1403 (58%) unspecified HIV/AIDS, 477 (20%) unspecified pneumonia, 276 (11%) TB, 212 (9%) other opportunistic infections, and 125 (5%) ADE malignancies. Common NADE causes were: 284 (35%) NADE infectious diseases, 123 (15%) NADE malignancies, and 111 (13%) traumas. In the unknown-cause group, 45% were women vs. 29% in ADE and 26% in NADE groups. Median age at death was 42 [IQR:33-52] years in unknown-cause vs. 41 [IQR:33-50] in ADE and 47 [IQR:38-56] in NADE groups; median CD4 count at death was 84 [IQR:25-236] cells/μL in unknown-cause vs. 64 [IQR:18-185] in ADE and 211 [IQR:65-421] in NADE groups. Percentage on ART at death was highest in the unknown-cause group (91% vs. 72% for ADE and 83% for NADE groups). P-values were <0.01 for all comparisons.

Conclusion: Of the 11% of the cohort that died over two decades, more than half were recorded as from unknown causes, including a third completely missing, and 58% of ADE causes had an unspecified HIV/AIDS code. Unknown causes occurred mostly in women, younger PWH, and those with lower CD4 counts, similar to those dying from an ADE. More complete cause-of-death data is needed to better identify factors associated with, and prevent deaths due to, ADEs.

1058 Predicting Cause-Specific Mortality With the VACS Index 2.0 Among Persons With HIV

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Background: Predicting cause-specific mortality among persons with HIV (PWH) could facilitate targeted care to improve survival. We assessed discrimination of the Veterans Aging Cohort Study (VACS) Index 2.0 in predicting cause-specific mortality among PWH on antiretroviral therapy (ART) in Europe and North America.

Methods: The VACS Index 2.0 consists of thirteen variables: age, sex at birth, body mass index (BMI), CD4 count, creatinine, HIV-1 RNA viral load, haemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, white blood cell count, albumin, and hepatitis C infection. Using data from 12 cohorts contributing to the Antiretroviral Therapy Cohort Collaboration, VACS 2.0 was calculated for PWH who initiated ART between 2000 and 2018, around a randomly selected visit date within the period 1 year after ART initiation to last visit. Missingness in VACS 2.0 variables was addressed through multiple imputation. We estimated associations between VACS 2.0 and specific causes of death using Cox models, with discrimination evaluated using Harrell's C-statistic. Absolute mortality risks were modelled with flexible parametric survival models.

Results: Among 59,741 PWH, 80% were men and at follow-up start mean age was 43 and mean VACS 2.0 score was 41.0. VACS 2.0 values were measured a median of 3.2 years after ART initiation and ranged from 0 to 129: higher values indicate worse prognosis. There were 3,117 deaths during 217,257 person-years (median follow-up was 2.6 years). Non-AIDS-defining cancers were the most common cause of death (n=569), followed by AIDS (n=527). Discrimination for five-year all-cause mortality was C=0.83). Discrimination for specific causes of death was highest for deaths due to AIDS (0.91), liver-related causes (0.90) and respiratory causes (0.88). Discrimination was lowest for suicides/accidental deaths (0.65), unclassifiable causes (0.76), cardiovascular deaths (0.77) and "other" causes (0.78). Predicted probabilities of 5-year mortality were low for except for PWH with very high (>90) VACS 2.0 values e.g. the 5-year probability of AIDS death for those with VACS 2.0 score 40 was 0.1%, increasing to 7.6% for scores of 90.

Conclusion: To improve discrimination for causes for which discrimination is lower, future VACS Index analyses could incorporate additional measures, such as psychopathological risk factors, extra biomarkers (for example, lipid profiles and inflammatory markers), or conditions included in the Charlson Comorbidity Index.

Table: VACS Index 2.0 at follow-up start and association with causes of death

Cause of death (number of deaths)	Mean VACS Index 2.0 (95% CI)	Hazard ratio (95% CI)	C-statistic	Cause of death (number of deaths)	Mean VACS Index 2.0 (95% CI)	Hazard ratio (95% CI)	C-statistic
All-cause (3117)	66 (65-66)	1.84 (1.81-1.87)	0.83				
AIDS (527)	75 (73-77)	2.08 (2.00-2.16)	0.91	Non-AIDS-defining cancers (569)	65 (63-67)	1.77 (1.70-1.84)	0.83
Liver (including HCC) (197)	74 (71-77)	2.07 (1.94-2.20)	0.90	Other (457)	64 (62-66)	1.71 (1.63-1.78)	0.78
Cardiovascular (284)	59 (56-61)	1.58 (1.49-1.67)	0.77	Substance abuse (119)	60 (57-64)	1.65 (1.52-1.79)	0.81
Respiratory (125)	68 (65-72)	1.91 (1.76-2.06)	0.88	Suicide/accident (164)	50 (47-54)	1.32 (1.22-1.44)	0.65
Non-AIDS infection (195)	69 (66-72)	1.91 (1.80-2.03)	0.85	Unclassifiable (480)	62 (60-64)	1.65 (1.58-1.73)	0.76

HCC-hepatocellular carcinoma

1059 Care Interruptions and Mortality Among Adults on Antiretroviral Therapy in Europe and North America

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Background: Interruptions to the care of people with HIV (PWH) on antiretroviral therapy (ART) are associated with adverse outcomes. Studies to date mostly relied on composite outcomes, such as AIDS and death, due to insufficient number of indi-vidual outcome events. We investigated whether mortality rates following a care interruption differed from mortality rates after first starting ART.

Methods: Data from 2004-2020 were combined from 18 European and North American HIV cohort studies of adult PWH starting ART between 2004-19. We defined in-terruptions in HIV specialized health care as breaks of ≥365 days duration (no lab, CD4, RNA, ART, or visit records), with a subsequent return to care without a suppressed viral load; distinct from loss-to-follow-up. In sensitivity analyses, we used breaks of ≥180, ≥270, and ≥535 days. Follow-up time for each PWH was allocated across three groups: "no previous interruption", and "early" or "late in-terruption" (reinitiating after a gap starting <6 or ≥6 months of first ART initia-tion). Each PWH contributed follow-up to the pre/no interruption group. We used Cox regression to compare mortality rates across the three groups, adjusting for sex, HIV acquisition mode, year of ART initiation/re-initiation, and time-updated age and CD4 count on initiation or re-initiation of ART.

Results: Among 89,197 included PWH, median age at ART start was 39 years (IQR 31-48) and 83% were male. 7796 (9%) of PWH had at least one care interruption. There were 1300 "early interruption" group episodes (1300 PWH), and 9773 "late inter-ruption" group episodes (7832 PWH). Median CD4 count at ART start was 280 (IQR: 143-417), while after early and late interruptions (where available) it was 235 (IQR 95-456) and 352 (IQR 150-600) cells/μl, respectively. There were 6098 deaths in 536,870 person-years (rate 11.4 (95% CI 11.1-11.7) per 1000 person-years). Adjusted hazard ratios for the early and late interruption groups were 1.69 (95%CI: 1.39-2.06) and 1.80 (95%CI: 1.63-1.98), respectively, compared with the no/pre-interruption group. Results were robust in sensitivity analyses assuming ≥180-, ≥270- and ≥535-day gaps.

Conclusion: Mortality was higher among PWH reinitiating ART following an interruption with unsuppressed viral loads, compared with when PWH initially start ART, indicat-ing the importance of full adherence to ART. The mechanism for this higher mor-tality requires further investigation as care interruptions may be associated with other factors linked to higher mortality.

1060 Impact of Accessing Care at an Advanced Stage on Mortality in PWH in France, 2002-2016

Valérie Potard[1], Malamine Gassama[1], Emilie Lanoy[1], Sylvie Abel[2], Firouze Bani Sadr[3], Sylvie Bregigeon[4], Fabienne Caby[5], Blandine Denis[6], Pierre de Truchis[7], Guillaume Martin-Blondel[8], Lionel Piroth[9], Axel Ursenbach[10], Dominique Costagliola[1], Sophie Grabar[1], for the ANRS CO4 FHDH Late Presentation Study Group

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Background: Previous studies have shown the deleterious impact of access to care with an advanced HIV-disease (CD4 ≤200/ or AIDS, no primary infection) on the mortality risk in people living with HIV (PWH). Here, we explored the respective impact of access to care with AIDS or with CD4 ≤50/mm³ without AIDS or with CD4 50-200/mm³ without AIDS on the mortality risk up to 5 years after the first access to care, and whether availability of new antiretroviral regimen led to a smaller impact.

Methods: Adult participants newly included in the ANRS-CO4-FHDH cohort between 2002-2016, with HIV-1 infection were selected. Besides the 3 categories of advanced HIV-disease at access to care, 2 others were defined as follows: intermediate HIV-disease as CD4 between 200-350/mm³ without AIDS and early HIV-disease as either CD4>350/mm³ without AIDS, or primary infection. The impact of the stage at first access to care on the mortality risk was analyzed by using Fine & Gray competing risk models considering lost to follow-up ≥18 months as a competing event. Follow-up after access to care was categorized into 0 – 6, 6 – 12, 12 – 24, 24 – 48, 48 – 60 months. Models were adjusted for age, sex, acquisition mode, region of origin, delay between diagnosis and access to care and period of access to care (2002-2013 vs 2014-2016).

Results: Among the 64400 PWH included, 18305 (28.4%) presented with an advanced HIV-disease and 13042 (20.3%) with an intermediate HIV-disease. At 60 months, the cumulative incidence of death was estimated as 1.8% (95%CI: 1.7–1.9) overall, from 6.0% (95%CI: 5.4–6.7) among those with AIDS to 0.9% (95%CI: 0.8–1.0) among those with early HIV-disease (Table). Compared to people with an early HIV-disease, those with AIDS had a very high risk of death, with a sub-distribution hazard ratio (SdHR) of 18.4 (95%CI: 12.0-28.4) in the first 6 months of follow-up, which remained significant 48-60 months after inclusion 2.1 (95%CI: 1.3-3.3) (Table). In the other categories of advanced HIV-disease, the risk of death was also significantly higher while to a smaller extent. There was no statistical difference between calendar periods.

Conclusion: A delayed access to care remains associated with an increased risk of death even after 48 months of follow-up. There was no significant improvement in the risk of death after introduction of integrase inhibitors for combined antiretroviral initiation in 2014.

Table Risk of death according to stage at access to care and to calendar period: Cumulative incidence at 5 years and adjusted subdistribution hazard ratio (SdHR) with 95%CI estimated from Fine and Grey competing risk models (N=64 400)

Stage at access to care	Cumulative incidence of death at 5 years [95%CI]	SdHR [95% CI) 0-6 months	SdHR [95% CI) 6-12 months	SdHR [95% CI) 12-24 months	SdHR [95% CI) 24-48 months	SdHR [95% CI) 48-60 months
Advanced with an AIDS-defining event (n=5720)	6.0% (5.4-6.7)	18.4 (12.0-28.4)	11.0 (6.7-18.0)	3.8 (2.6-5.4)	2.7 (2.0-3.7)	2.1 (1.3-3.3)
Advanced with CD4≤50/mm³ no AIDS (n=3254)	4.2% (3.4-4.9)	10.0 (6.0-16.7)	6.9 (3.8-12.5)	3.5 (2.3-5.5)	2.6 (1.8-3.8)	1.5 (0.8-2.8)
Advanced with CD4 [50-200/mm³] no AIDS (n=9315)	2.5% (2.1-2.8)	6.8 (4.3-10.8)	3.4 (1.9-5.9)	1.9 (1.3-2.8)	1.7 (1.2-2.3)	1.4 (1.0-1.9)
Intermediate with CD4 [200-350/mm³] no AIDS (n=13042)	1.2% (1.1-1.5)	1.8 (1.0-3.2)	2.0 (1.1-3.6)	1.1 (0.7-1.8)	1.6 (1.1-2.3)	1.2 (0.8-1.8)
Early HIV disease with CD4>350/mm³ no AIDS or primary infection (n=20053)	0.9% (0.8-1.0)	1	1	1	1	1
Calendar periods						
2002-2013 (n=52234)	1.8% (1.7-1.9)	1	1	1	1	1
2014-2016 (n=11405)	1.9% (1.7-2.2)	1.1 (0.8-1.5)	1.2 (0.8-1.8)	1.1 (0.8-1.6)	1.3 (1.0-1.7)	1.2 (0.8-1.8)

1061 Trends in Hospital Readmission Among People With and Without HIV in the US, 2010-2020

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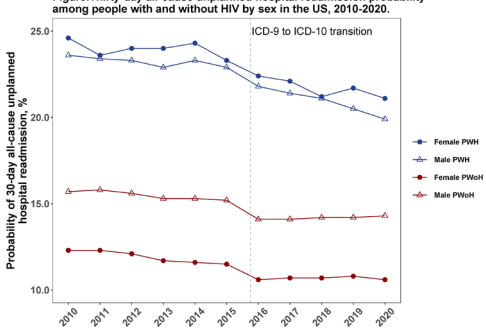
Background: Thirty-day readmission is a prominent US hospital quality metric. However, there are limited data to compare readmission trends among people with HIV (PWH) to people without HIV (PWoH) in the era of universal antiretroviral therapy in the US.

Methods: We used data from the 2010 to 2020 Nationwide Readmission Database (NRD), the largest readmission database in the US that includes ~18 million unweighted hospitalizations each year and represents ~60% of all US hospitalizations. Following Centers for Medicare & Medicaid Services methodology, we excluded those age<18 years; discharged dead, against medical advice or without 30-day post-discharge follow up window, and admissions for primary psychiatric diagnoses, rehabilitation, cancer treatment or COVID-19. The outcome was the probability of 30-day all-cause unplanned readmission since discharge from a prior (index) admission. A readmission could also be an index admission. ICD-9/ICD-10 codes were used to identify PWH. Crude readmission probability was estimated for PWH and PWoH each year. Subgroup analyses were stratified by age, sex, and median ZIP code household income. Survey weights were applied to all analyses to generate nationally representative estimates.

Results: The study population included 25,205,538 (weighted) index admissions in 2010, 24,338,782 in 2019, and 21,258,399 in 2020. In 2010 and 2020, PWH contributed 140,014 (0.56%) and 126,029 (0.59%) index admissions, respectively. Overall, PWH had higher readmission risk than PWoH. The readmission probability for PWH decreased gradually from 23.9% in 2010 to 20.3% in 2020. For PWoH, the readmission probability was stable except during 2015, the year of transition from ICD-9 to ICD-10. Stratified by sex, female PWH had slightly higher readmission probability than male PWH and the difference fluctuated over time. However, female PWoH continued to have similar lower readmission probability than male PWoH (Figure). Older PWoH consistently had higher readmission probability than younger PWoH. In contrast, different age groups of PWH had similar readmission risk over time. PWH residing in areas with the lowest median household incomes had the highest readmission risk for all the years.

Conclusion: The quality of hospital care for adult PWH in the US has improved in the past decade, but there is still a significant gap in readmission risk between PWH and PWoH, especially among women.

Figure.Thirty-day all-cause unplanned hospital readmission probability among people with and without HIV by sex in the US, 2010-2020.



1062 Wastewater Monitoring of HIV-1: Feasibility and Comparison to Surveillance Data

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Background: Wastewater-based epidemiology (WBE) is being used to identify and quantify infectious agents circulating in communities without the need to test individuals. HIV has previously been detected in wastewater and HIV RNA and DNA have both been amplified from urine and feces of people living with HIV (PLWH). Thus, measuring HIV in wastewater appears feasible, but has not been used for the purpose of monitoring HIV in communities.

Methods: We applied a previously developed hydrolysis-probe based PCR assay targeting the LTR region of HIV-1 to quantify nucleic acids (NA) in wastewater settled solids using droplet digital (RT-)PCR. We performed retrospective monitoring of HIV-1 concentration in longitudinal wastewater samples from two publicly owned wastewater treatment plants, one in San Francisco (OSP) and the other in San Jose (SJ) between February 2021 and April 2023. Samples were collected two times per week. To assess concordance between wastewater data and local surveillance data from public health departments, we compared trends in wastewater HIV-1 concentrations to HIV prevalence estimates per county.

Results: Highly abundant HIV-1 NA were detected in 94% (215/230) and 23% (53/229) of samples in OSP and SJ sewersheds, respectively. Samples from the OSP sewershed consistently yielded higher concentrations of HIV NA than samples from SJ (OSP median $7.3*10^3$ cp/g [range non-detect to $3.9*10^5$ cp/g], SJ median non-detect [range non-detect to $1.1*10^5$ cp/g], figure 1) mirroring

surveillance estimates of higher community prevalence of HIV in San Francisco County than in Santa Clara County in 2021 (1334.1 and 190.6 PLWH per 100,000 population, respectively). We observed similar concentrations of HIV-1 NA in analyses with and without a reverse transcription step during PCR suggesting that most, if not all, of measured NA in wastewater is HIV-1 DNA rather than RNA.

Conclusion: Our findings demonstrate the feasibility of monitoring HIV concentrations in communal wastewater and show good concordance with local surveillance data on HIV prevalence. Results from wastewater can be used to obtain information on HIV at a localized, community level and could serve as a complementary approach to existing HIV surveillance frameworks helping identify priority areas for intervention. Further work by our group will investigate dynamics of viral shedding in PLWH, develop assays for measuring antiretroviral drug-resistance in wastewater, and identify the optimal uses of wastewater surveillance of HIV-1.

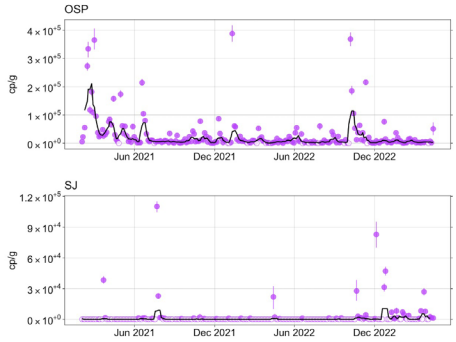

Figure 1. Concentrations of HIV-1 nucleic acids in wastewater from February 2021-April 2023. Solid points show concentration with standard deviations in copies of the target per grams dry weight solids in wastewater. Open circles show where HIV was not detected. The black line represents the 5-sample smoothed and trimmed average.

1063 Statewide Real-Time Integration of Molecular and Contact Tracing Data to Disrupt HIV Transmission

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Background: Tools beyond contact tracing are still needed to disrupt HIV transmission. Molecular cluster analysis helps stop outbreaks, but its precise benefit to routine public health actions is an existing knowledge gap. We hypothesized that integration of statewide molecular data with contact tracing by routinely re-interviewing new diagnoses who cluster molecularly will increase motivation and enhance contact tracing.

Methods: To address the hypothesis we (1) built an academic-governmental partnership in Rhode Island (RI); (2) maximized statewide representation of HIV-1 pol sequences; (3) developed an automated bioinformatics pipeline to aggregate de-identified data across systems; and (4) used phylogenetic tools to infer clusters in near-real-time, identify all new diagnoses who cluster, routinely attempt to re-interview and inform them of clustering, and assess this intervention's impact (1st interviews of all RI new diagnoses occur before sequence availability).

Results: In a 2-year (Jan '21-Dec '22) study, of 100 new RI diagnoses, 52 were in molecular clusters. Re-interviews were feasible for only 22/52 (42%), revealing an important gap. Of the 22, only one provided new data, rejecting our hypothesis. Persons were less engaged in re- vs. 1st interviews showing confusion, apprehensiveness and annoyance, raising concerns for damaged rapport with public health. For 15/52 (29%) 1st interviews were not feasible and they had a 'combined' interview and were therefore not eligible. The remaining 15/52 (29%) were unavailable for re-interview (unlocatable, refused, or out-of-state). Substantially higher clustering (52 vs. 22) was seen with phylogenetic vs. distance-only methods, highlighting importance of statewide comprehensive analyses. Of 3,720 RI persons with HIV in 2004-2022, 688 (18%) had no sequence availability, more in earlier year diagnoses. Sequencing 118 of those missing resulted in 11 new clusters, 14/118 joined known clusters, 9/118 formed new clusters and 8 previously-unclustered persons joined clusters.

Conclusion: Molecular epidemiology triggered re-interviewing of all new RI HIV diagnoses who cluster had no effect on HIV transmission disruption, informing future research and alternative approaches to define the added value of routine, near-real-time use of cluster analyses to benefit public health and disrupt HIV transmission. A strong academic-public health partnership, statewide epidemic representation, and comprehensive cluster inference tools are instrumental to achieve that goal.

1064 Incident HIV Infection Drives Community HIV Cluster Growth

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Background: Molecular HIV surveillance (MHS) is routinely used by U.S. public health departments to monitor HIV transmission dynamics within populations and regions. We analyzed MHS data to identify potential drivers of transmission by investigating genetically related infections (transmission clusters).

Methods: De-identified data were obtained from the epidemiology unit of the Health and Human Services Agency (HHSA) of San Diego County. A baseline HIV genetic network was inferred based on genetic distance of 0.5% (proxy for recent linkage) for all HIV diagnoses from 2006-2016, and links from newly diagnosed people with HIV (PWH) were added to the network from 2017-2023. The presence of a negative HIV test within 6 months of a new HIV diagnosis was used to indicate incident HIV infection. Cox proportional hazards models were used to identify factors associated with the rate of transmission cluster growth. These results were used to predict the possible impact of hypothetical interventions focused on attributes of clustering PWH.

Results: Among 3,676 individuals with diagnosed HIV, 1,938 PWH had at least one HIV sequence, collected a mean of 109 days following the date of HIV diagnosis (IQR 36). Overall, 16% of sequences were linked in 115 clusters (median cluster size 2; range 2-9). Cluster growth was strongly associated with larger size of the cluster (HR 2.5; 95% CI: 2.1, 2.8), proportion of PWH in the cluster with incident infection (HR 3.0; 95% CI: 1.6, 5.4), and proportion with a bacterial sexually transmitted infection (STI, including gonorrhea and syphilis) within 1 year of HIV diagnosis (HR 1.7; 95% CI: 1.1, 2.6) in univariate analysis. Only larger cluster size (HR 2.3; 95% CI: 2.0, 2.7) and incident infections (HR 2.4; 95% CI: 1.4, 4.4) were still associated with cluster growth in multivariable analysis (Table). Proportion of PWH with unsuppressed viremia (VL>200 copies/ml) in a cluster was not associated with growth of that cluster. None of the hypothetical interventions evaluated were shown to significantly reduce the predicted rate of cluster growth over the subsequent three years.

Conclusion: This is the first use of public health data demonstrating that incident infection is a driver of community HIV cluster growth. No special testing for incident infection was required, only the reliance on previous negative HIV test results. In contrast to published reports, these data suggest that incident infection may drive ongoing community HIV transmissions.

Predictor	beta	Standard error	Lower ci beta	Upper ci beta	HR	Lower ci HR	Upper ci HR
Proportion acute & early	0.89	0.3	0.3	1.48	**2.44**	1.35	4.4
Proportion unsuppressed	0.22	0.25	-0.28	0.71	1.24	0.75	2.04
Number in cluster	0.85	0.07	0.7	0.99	**2.34**	2.02	2.7
Proportion Hispanic	-0.12	0.25	-0.6	0.36	0.89	0.55	1.43
Proportion MSM	0.1	0.3	-0.49	0.69	1.11	0.61	1.99
STI	0.18	0.27	-0.35	0.71	1.19	0.7	2.03
Median age	-0.02	0.01	-0.05	0.01	0.98	0.96	1.01

1065 Contribution of HIV Transmission Bursts to Future HIV Infections, United States

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Background: HIV clusters show heightened transmission rates and may contribute disproportionally to new infections. However, the influence of these periods of rapid transmission on future HIV infections and the populations that they affect are incompletely characterized.

Methods: Using subtype B HIV pol sequences from the U.S. National HIV Surveillance System reported through 2022 for people with HIV (PWH) diagnosed during 2014–2019, we inferred separate, time-scaled phylogenetic trees with ETE3, FastTree2, and TreeTime for six geographic regions composed of 14 jurisdictions with >50% sequence completeness. We detected transmission bursts, defined as ≥3 connected internal nodes (or transmission events) in a

2-year detection period [Figure]. We first calculated the relative contribution of transmission bursts in a fixed detection period to future transmission in a follow-up period by dividing the number of internal nodes during 2017-2019 descended from bursts by the number of lineages associated with bursts during 2015-2016, compared to non-burst-descended internal nodes divided by non-burst-associated lineages. To characterize PWH diagnosed in the follow-up period who were ever members or descendants of a transmission burst, we then detected bursts within any sliding 2-year period during 2014–2019 and identified populations overrepresented among PWH associated with transmission bursts.

Results: The 2,795/86,006 (3.2%) lineages (or persons) associated with a transmission burst during 2015–2016 contributed to 493/3,926 (12.6%) transmissions during 2017–2019 across all jurisdictions. Lineages associated with transmission bursts were 4.3 times as likely as lineages not associated with bursts to contribute to future transmissions. Among PWH diagnosed during 2017–2019, 5,603/43,721 (12.8%) were ever members or descendants of transmission bursts during 2014–2019. Groups overrepresented among members or descendants of transmission bursts (i.e., >12.8%) included PWH aged 13–19 (24.5%) or 20–29 years (16.6%) at HIV diagnosis, diagnosed during acute or early HIV infection (17.9%), who reported male-to-male sexual contact (15.5%), or who were transgender, non-binary, or another gender (15.3%).

Conclusion: Lineages associated with transmission bursts contribute disproportionately to future transmission, underscoring the value of detecting and responding to clusters to prevent transmissions. Bursts of rapid HIV transmission likely contribute to disparities in overall HIV incidence for some key populations.

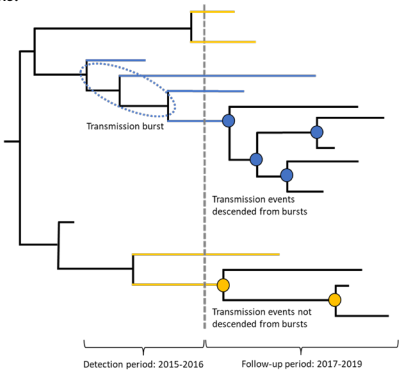

Figure. Mock phylogeny illustrating a transmission burst (blue oval) during the burst detection period (2015–2016) and transmission events in a follow-up period (2017–2019). Blue internal nodes represent inferred transmission events descended from blue burst-associated lineages and yellow internal nodes represent inferred transmission events descended from yellow non-burst-associated lineages.

1066 HIV Cases Averted in Phylogenetic Clusters via Preexposure Prophylaxis in British Columbia, Canada

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Background:Pre-exposure prophylaxis (PrEP) to prevent HIV acquisition is a key pillar in strategies for ending the HIV epidemic. However, PrEP access and adherence have been incomplete across key populations and population-level impacts of PrEP on HIV transmission are not fully understood. We hypothesized that widespread PrEP availability in British Columbia (BC), Canada since 2018 has averted hundreds of new HIV cases heterogeneously distributed across phylogenetic clusters.

Methods: Using data from the BC Drug Treatment Program, we aligned 42043 HIV partial pol sequences from 10740 individuals to the HXB2 reference and removed surveillance drug resistance mutations. Phylogenetic trees were inferred to identify clusters with 5 or more members with pairwise tree distance less than 0.02 substitutions/site. New diagnoses within clusters over time were used to estimate cluster-specific reproduction numbers (Re) over time. We tested whether PrEP availability significantly affected Re after 2018 in generalized estimating equations, adjusted for cluster size, median age, risk group composition, COVID-19, and treatment guidelines. We summarized characteristics of clusters without reduced growth following PrEP as missed opportunities. For clusters with significantly reduced Re, we fit counterfactual models to data preceding PrEP to predict growth in the absence of PrEP, with consideration for COVID-19. Predicted cases without PrEP were compared to observed cases to quantify cases averted via PrEP.

Results: BC HIV phylogenetic clusters exhibited differential growth and Re since widespread PrEP availability in 2018. Re of most clusters comprised predominantly of men who have sex with men (MSM) have declined since 2018. However, we identified missed opportunities for PrEP among a large cluster of young MSM with Re above 1 between 2018 and 2020, and in a cluster comprised primarily of people who use drugs (PWUD) with elevated Re from 2020-2022. Preliminary models of cluster growth in the absence of PrEP suggest averted HIV cases were heterogeneously distributed across phylogenetic clusters.

Conclusion: These results highlight the success of the PrEP program in averting new HIV cases, while emphasizing clusters and sociodemographic groups that could benefit from prioritized access and assistance with adherence to PrEP.

1067 Geospatial and Phylogenetic Clustering of Acute HIV Infections in Lilongwe, Malawi

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Background: HIV transmissibility spikes during the first months of infection, especially during acute (pre-seroconversion) HIV infection (AHI). Rapid propagation of HIV during early infection hinders universal test and treat interventions, which typically identify infections after the period of elevated transmission risk. To guide prospective interventions against transmission during this period, we evaluated the geospatial and phylogenetic clustering of acute and early infection in Lilongwe, Malawi.

Methods: We identified 144 persons with AHI, 30 people who recently acquired HIV (determined with the Sedia LAg-Avidity EIA), and 652 people with chronic HIV who came to a Lilongwe STI clinic between 2015 and 2019. We mapped the point locations of households with an AHI case and 721 sex-exchange venues identified with the PLACE method. To evaluate the spatial clustering of AHI, we used Tango and Takahashi's flexible scan statistic (α=0.2). Consensus HIV sequences were obtained from blood samples with the veSEQ-HIV protocol and shiver and aligned with MAFFT. Maximum-likelihood trees were built with IQ-TREE. Monophyletic sequences with genetic distances <5.3% were considered phylogenetic clusters.

Results: We identified 6 spatial areas (0.2-1.7 km^2) in Lilongwe where household locations of people with AHI were overrepresented, comprising 38% of AHI cases in 1% of the populated land area. These spatial areas contained 57 reported sex-exchange venues and were highly connected: the contiguous M1 and S124 roads run directly through 4 spatial clusters. Although viral sequencing failed for 39% of people with AHI and 60% with recent or chronic infections, we still identified 13 nonoverlapping two-person clusters in our phylogenetic analysis. Four pairs (3 acute-acute, 1 acute-recent) attended the clinic 0-95 days apart, suggesting transmission during acute and early infection. A fifth recent-recent pair (270 days apart) also suggested early transmission. Acute-acute pairs lived 0.2-4.5 km apart, but not in the same spatial clusters.

Conclusion: Spatial clustering of AHI exists in highly connected areas with sex-exchange venues in Lilongwe, suggesting that spatially focused interventions could be key in pursuit of HIV elimination. Evidence of extensive AHI transmission chains was limited: no phylogenetic cluster had >2 members. Mirroring earlier modeling estimates of the role of AHI in Lilongwe, 5 of 13 (38%) phylogenetically linked pairs suggested transmission during acute and early HIV infection.

1068 Increasing Intra- and Inter-Subtype HIV Diversity Despite Rapidly Declining HIV Incidence in Uganda

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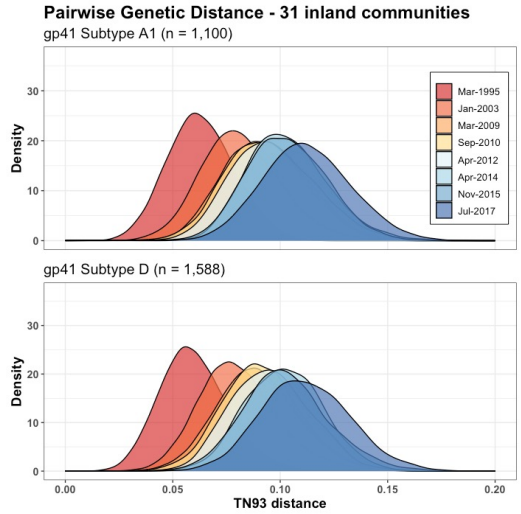
Background: HIV incidence has been declining in sub-Saharan Africa with scale-up of HIV interventions. However, there is limited data on HIV evolutionary trends in African populations with declining epidemics. Here, we evaluated changes in HIV diversity over a twenty-five-year period spanning the introduction and scale-up of HIV prevention and treatment programs in Uganda.
Methods: We used HIV sequence and survey data from the Rakai Community Cohort Study, a longitudinal population HIV surveillance cohort in southern Uganda. p24 and gp41 consensus sequence data were generated from blood samples of persons living with HIV (PLHIV) in 31 inland semi-urban trading and agrarian communities (1994 to 2018) and four hyperendemic Lake Victoria fishing communities (2011 to 2018) under continuous surveillance. HIV subtype was assigned using the Recombination Identification Program with phylogenetic confirmation. Inter-subtype diversity was estimated using the Shannon diversity index and intra-subtype diversity with the nucleotide diversity and pairwise TN93 genetic distances. Evolutionary dynamics were assessed among demographic and behavioral sub-groups and by migration status.
Results: HIV genomic data were available from 4,999 PLHIV, including 3,060 and 1,939 persons residing in inland and fishing communities, respectively, and from 1,484 HIV seroincident cases. In inland communities, subtype A1 viruses proportionately increased in p24 from 17% in 1995 to 32% in 2018 ($p<0.001$) and in gp41 from 21% in 1995 to 48% in 2018 ($p<0.001$), while those of subtype D declined in p24 from 80% in 1995 to 45% in 2018 ($p<0.001$) and in gp41 from 76% in 1995 to 38% in 2018 ($p<0.001$). In both genes, an increasing proportion of viruses were classified as recombinants (e.g., in p24 from 2.7% in 1994 to 21.4% in 2018 in inland communities). While p24 intra-subtype genetic diversity leveled off after 2014, diversity of gp41 increased through 2018. Inter- and intra-subtype viral diversity generally increased across all population sub-groups, including among individuals with no recent migration history or extra-community sexual partners.
Conclusion: Although HIV incidence has declined in Uganda, intra and inter-subtype HIV diversity has increased. Continued molecular surveillance may provide a better understanding of the dynamics driving population HIV evolution and yield important insights for epidemic control.



1069 HIV-1 A6 Variant Transmissions Poland Are Fuelled by War Refugees From Ukraine & Local MSM Clusters

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Background: Since February 2022, Poland has become a shelter for over 1.6 million Ukrainian refugees, a number comparable to the total migrant flow of the past decade. The HIV-1 A6 lineage, dominant in Eastern Europe, has become the most common variant in Poland in the recent years, previously dominated by subtype B infections. Phylogenetic analysis yields insights into transmission clusters and linkages, offering a deeper understanding of ongoing virus spread. In this study we explore the changing epidemic profile of the A6 lineage in Poland in the context of migration and refuge but also local transmissions.
Methods: We analyzed 1941 Polish HIV partial pol sequences, including 719 from Ukrainian-born individuals, supplemented with 11,807 location-annotated A6 sequences, collected up until November 2023. Phylogenetic inference and genetic distance-based clustering were employed to identify clusters and genetically linked individuals. Clusters were classified into singletons and dyads (≤2 sequences), networks (3–13 sequences), or large clusters (≥14 sequences). Further, in the Polish cohort, we delineated sequences from individuals born in Poland or Ukraine and analysed transmission routes within clusters.
Results: We identified six large clusters (n=855 sequences), 74 networks (n=353), and 590 singletons or dyads (n=733). In large clusters dominated internal Polish transmissions among men who have sex with men (MSM) accounting for the total of 41.9% of infections with known transmission route. There was also a marked rise in new, late diagnosed (lymphocyte count at baseline < 350 cells/μl) cases was observed among Ukrainian male (13.6%) and female (13.3%) migrants since the beginning of 2022, representing new introductions of the A6 lineage into Poland, primarily as singletons and dyads but without further spread into larger clusters. The most common international linkages were observed from Ukrainian migrants diagnosed before 2022 to individuals born in Poland (35.0% of the normalized links).
Conclusion: The influx of war-displaced people from Ukraine notably fuels sub-subtype A6 infections in Poland but majority of introductions resulted in dead-end transmissions. On the other hand, large clusters define independently growing national epidemic with this variant in MSM. Presented data imply urgent need for targeted HIV testing and intervention programs among key populations.
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1070 HIV Spread in Miami-Dade County

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Background: The Miami-Dade HIV epidemic is one of the largest and most active regional epidemics in the US. While predominantly an epidemic among men who have sex with men (MSM), there is significant diversity across ethnicity, race, risk group and geography. We characterized the dynamics of HIV transmission between neighborhoods and risk groups in the Miami-Dade region to inform the development of focused interventions.
Methods: A comprehensive public health dataset of 7274 HIV-1 subtype B partial pol sequences sampled from unique persons with HIV (PWH) between 2015-2020 was combined with a closely related background dataset of 4,250 publicly available sequences. A multistep phylogenetic approach was applied: (1) maximum likelihood phylogenetic inference to identify well-supported monophyletic clades of size ≥5 including ≥2 distinct Miami-Dade neighborhood groups (NBHD), as defined by Florida Department of Health; (2) local clades were used to perform a discrete phylogeographic inference to evaluate transmission dynamics between NBHD (but not within a NBHD) after 2010. Additional metadata including stage of infection was also incorporated into the analysis to estimate migration between NBHDs to evaluate migration between risk groups.
Results: We identified 3,737 HIV sequences forming 315 transmission clusters of ≥5 sequences (range 5–130) that included PWH from at least two NBHDs. PWH belonging to these clades were predominantly male (76%), Hispanic

(53%), and MSM (55%). Discrete phylogeographic analysis of identified clades suggested that the NBHD of Downtown/East Little Havana/Liberty City/ Overtown (21% of all dispersal events, after 2010), Brownsville/Coral Gables/ Coconut Grove (22%), and Aventura/Miami Beach (19%), were the major sources of viral flow to other NBHD in the Miami-Dade region (Fig. 1AB). Overall, heterosexuals and MSM accounted for 49.9% and 46.8%, respectively of putative sources of transmission linking different risk groups.

Conclusion: Phylodynamic analyses revealed complex HIV dispersal across NBHD in the Miami-Dade region with some key areas predominating as sources of viral dispersal in recent years. HIV transmissions between risk groups were nearly equally likely to arise from MSM and heterosexuals. These results highlight the role of the central east region in the geographic spread of HIV within Miami-Dade County. These analyses suggest earlier diagnosis and treatment of individuals in these neighborhoods may have outsized impacts across the region.

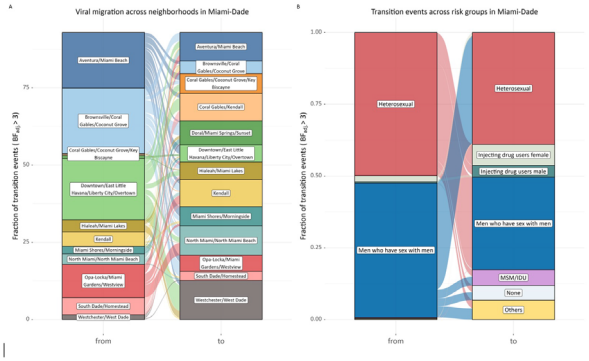


Figure. Relative contribution of NBHD and transmission risk groups to spread of HIV in Miami-Dade County. Inferred migration links included if adjusted Bayes Factor (BFafj) ≥3. **A.** Sankey plot representing the proportion of transition events "from" each source "to" recipient NBHD after 2010. **B.** Sankey plot representing proportion of transition events between risk groups.

1071 Genetic Diversity From Proviral DNA as a Proxy for Time Since HIV-1 Infection

Marius Zeeb[1], Paul Frischknecht[1], Karin Metzner[1], Michael Huber[2], Christine Leeman[1], Julia Notter[3], Andri Rauch[4], Marcel Stöckle[5], Alexandra Calmy[6], Matthias Cavassini[7], Enos Bernasconi[8], Dominique Braun[1], Huldrych F. Günthard[1], Roger Kouyos[1], for the Swiss HIV Cohort Study

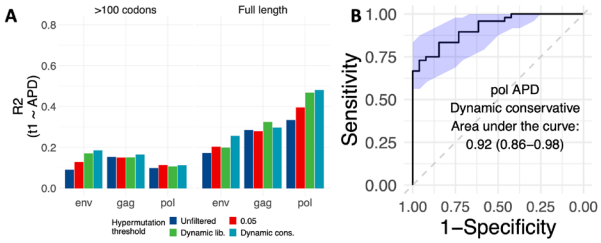
[1]University Hospital Zurich, Zurich, Switzerland, [2]University of Zurich, Zurich, Switzerland, [3]St Gallen Cantonal Hospital, St Gallen, Switzerland, [4]University Hospital of Bern, Bern, Switzerland, [5]University Hospital Basel, Basel, Switzerland, [6]University Hospitals of Geneva, Geneva, Switzerland, [7]Lausanne University Hospital, Lausanne, Switzerland, [8]Ospedale Regionale di Lugano, Lugano, Switzerland

Background: Knowing the time since infection in people with HIV (PWH) is relevant for transmission epidemiology, HIV pathogenesis and for many research questions in general. As viral genetic diversity accumulates over time in the absence of ART, diversity-based scores measured from ART-naive viral RNA sequences have been shown to be predictive of the time since infection. However, the validity of this approach is unclear for proviral NGS sequences sampled on ART. A particular challenge is noise from APOBEC3G/F induced hypermutations.

Methods: We assessed the association between time since infection (date of infection until ART initiation) and viral genetic diversity calculated as the average pairwise diversity score from proviral pol-, gag-, and env NGS sequences. Samples were taken after ART initiation from PWH with exact infection dates known via a comprehensive assessment of the medical history. All samples were from PWH enrolled in the Swiss HIV Cohort Study or Zurich Primary HIV Infection Cohort study. We used linear regression to determine the R2 and mean absolute error (MAE) of genetic diversity as a proxy for time since infection. We used AUC-ROC to quantify infection recency prediction. Over all analyses we applied different hypermutation filtering thresholds on NGS read level to account for APOBEC3G/F induced G-to-A mutations.

Results: We identified 261 PWH with accurate HIV infection dates and available NGS sequences for at least one gene (with >100 codon coverage) across all hypermutation thresholds (n= 233 gag, 233 pol, 208 env). Among those, 146 PWH had full codon coverage (n= 91 gag, 74 pol, 67 env). We found that proviral genetic diversity was predictive for the time since infection: average pairwise diversity scores calculated both with and without hypermutation filters were significantly associated with time since infection (p<5*10-10). The R2 ranged from 6% for env without hypermutation filtering to 48% for pol with the strictest filter (FigureA). The MAE ranged from +/-1.01 to +/-1.77 years. Recent infection prediction showed an AUC of 0.92 (95% CI 0.86, 0.98) for pol with the strictest filter (FigureB).

Conclusion: This work shows the utility of genetic diversity measured from proviral sequences as a proxy for the time between ART initiation and infection. While genetic diversity measured in ART-naive viral RNA is more accurate, a good performance can be achieved with hypermutation filtering and hence allows to determine infection recency in PWH without a baseline RNA sequence.



Abbreviations: APD (Average Pairwise Diversity score), Unfiltered (No hypermutation filtering), 0.05 (constant hypermutation filter), Dynamic lib./cons. (Genome position depended liberal/conservative hypermutation filtering)

1072 The Impact of COVID-19 on HIV Mortality Trends in United States Black, White, and Hispanic Adults

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Background: U.S. racial and ethnic minorities disproportionately impacted by HIV have also been severely impacted by COVID-19. This study investigates whether COVID-19 led to excess HIV mortality, using rigorous methods which account for age, gender, and race/ethnicity disparities in pre-pandemic HIV mortality trends.

Methods: Death data from CDC WONDER were analyzed for all decedents with HIV listed as either underlying or contributing cause of death. Pre-pandemic trends in HIV mortality were quantified by fitting log-linear models to HIV death rates for the period 2010-2019. Separate models were fit for groups defined by age (25-44, 45-54, 55-64, 65-74, 75+), reported gender (male, female), and race/ethnicity (Black, Hispanic, white). Regression coefficients were used to derive the average annual percent change in HIV mortality from 2010-2019, and to calculate expected death counts and rates for 2020-2022. Regression-estimated expected death rates were then compared with observed rates, and the number of excess deaths calculated. Finally, the number of excess HIV deaths for 2020-2022 was compared to the number of HIV deaths for which COVID-19 was listed as a contributing or underlying cause of death.

Results: Across all age groups, Black men suffered the highest rates of HIV mortality (see Figure). Across all gender-race/ethnicity groups, HIV mortality declined significantly among young adults (25-44 and 45-54 years). However, there were no declines in HIV mortality for those aged >55 years (Whites and Hispanic women) or >65 years (Blacks and Hispanic men). Moreover, statistically significant increases in HIV mortality were observed for white men >55 years, and for White women and Black women 65-74 years. During 2020-2022, there were 3,263 excess HIV deaths among all groups, and COVID-19 was mentioned on 73.2% of those death certificates. The percent of excess HIV deaths which listed COVID-19 as a contributing cause varied significantly by race/ethnicity, gender, and age.

Conclusion: Black and Hispanic adults have continued to experience disproportionately high HIV mortality during the COVID-19 pandemic. HIV mortality trends varied widely by age, with declines in young adults but no declines or increases in older adults. COVID-19 diagnosis may not have been listed for some excess HIV deaths, particularly among 25-44 year olds, Blacks, and Hispanics. Further investigation of direct SARS-CoV-2 infection effects vs. indirect pandemic effects in explaining observed excess HIV mortality is needed.

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1073 COVID-19-Related Shutdowns and Viral Suppression in the US and Canada

Keri N. Althoff[1], Brenna Hogan[1], Milton L. Wainberg[2], Kelly A. Gebo[3], Michael A. Horberg[4], John Gill[5], Peter F. Rebeiro[6], Mari Kitahata[7], Kathleen A. McGinnis[8], Jennifer Lee[1], Vincent Marconi[9], Michael J. Silverberg[10], Richard D. Moore[3], Angela Parcesepe[11], for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

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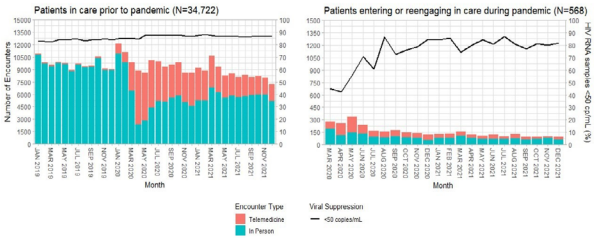
Background: COVID-19 disrupted in-person HIV care across North America. We compared frequency and type of HIV care encounters and viral suppression among people with HIV (PWH) prior to, during, and after COVID-19 shutdowns in the largest cohort collaboration of PWH linked to care in the US and Canada.

Methods: Adult (≥18yo) PWH in 13 NA-ACCORD clinical cohorts newly engaged or re-engaged (if absent since 1 Sept 2018) in HIV care (≥1 in-clinic or telemedicine [phone/video] visit, CD4 measure, or HIV RNA measure) during shutdowns (1 Mar 2020–31 May 2020) were compared with those in HIV care prior to the pandemic (1 Sept 2018–29 Feb 2020). Within each group, we described numbers of telemedicine visits and proportions of suppressed HIV RNA measures (<50 copies/mL) each month from Jan 2019-Dec 2021.

Results: There were 34,722 PWH in HIV care prior to the pandemic, of whom 51% received care during shutdowns, and 11% did not return to care as of 31 Dec 2021. There were 568 newly engaged (n=323, 57%) or re-engaged (n=245, 43%) PWH during shutdowns. Compared with those in prior care, those who newly engaged or re-engaged in care during shutdowns were younger (median=40.7 [30.9-51.8] vs. 49.7 [38.5-57.6] years), more likely to be Black (41% vs 38%), and a greater proportion had not initiated ART (20% vs. 2%, all p-values <0.01). Among PWH in care prior to the pandemic, telemedicine visits increased, and viral suppression was >80% during (n=9,159 viral load measures [VLs]) and after (n=81,994 VLs) shutdowns (Figure). Among those engaging or re-engaging in care during shutdowns, in-person visits were more common than telemedicine; viral suppression was 42% in April (n=131 VLs) and >85% in August 2020 (n=80 VLs). Among those in prior care, viral suppression remained stable, median time between care encounters were similar before and after (1 Jun 2020–31 Dec 2021) shutdowns (116 [40-182] vs. 109 [41-182] days, p<0.05), as was time between HIV RNA measures (182 [122-223] vs. 163 [105-203] days, p<0.05).

Conclusion: Among PWH newly engaged or re-engaging in care during the pandemic in the NA-ACCORD, >85% of HIV RNA measurements were suppressed 3 months after shutdowns ended. With the rapid scale-up of telemedicine, half of adults in HIV care prior to the pandemic connected to HIV care in March–May 2020, maintained a high proportion of viral suppression, and had similar frequency of HIV care encounters and viral load measures before and after shutdowns.



1074 Impact of COVID-19 Pandemic on HIV Ambulatory Services and Viremia in a US HIV Cohort, 2019-2022

Ellen M. Tedaldi[1], Qingjiang Hou[2], Carl Armon[2], Jonathan Mahnken[2], Frank Palella[3], Gina Simoncini[4], Jack Fuhrer[5], Cynthia Mayer[6], Alexander C. Ewing[7], Kalliope Chagaris[2], Kimberly Carlson[2], Jun Li[7], Kate Buchacz[7]

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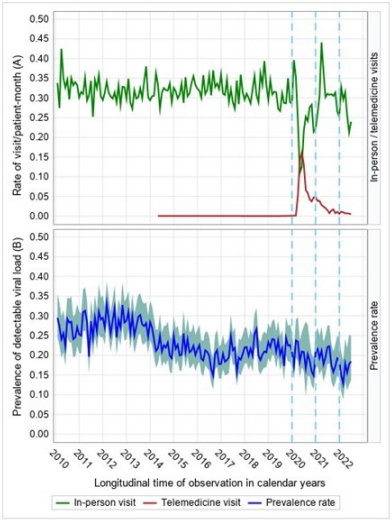
Background: In 2020, the SARS COV-2 pandemic caused an unprecedented strain on the spectrum of services for persons living with HIV, including in-person services at outpatient medical facilities. The extent of recovery for services has not been widely described.

Methods: We analyzed longitudinal cohort data from participants seen during 2019-2022 at eight HIV Outpatient Study (HOPS) sites. Generalized linear mixed models (GLMM) estimated all encounter, office, telemedicine visits, and HIV viral load (VL) monthly test rates, using 2010-2022 data. We examined demographic correlates of having detectable viral load before and during the pandemic using GLMM for logistic regression with 2017-2022 data.

Results: Of 2351 active HOPS participants, 76.0% were male, 57.6% aged ≥ 50 years, 40.7% non-Hispanic White, 38.2% non-Hispanic Black, 17.3% Hispanic/Latino, and 51.0% publicly insured. As of December 31, 2019, 71.2% had a CD4 cell count ≥500 cells/mm^3, and 92.6% had a VL <200 copies/mL. There was a sharp decline of in-person visits per person-month from 0.40 in January 2020 to 0.11 in April 2020, followed by a rebound to pre-pandemic levels in 2021, before a drop again to below 0.25 per person-month in May 2022. Correspondingly, there was an increase in telemedicine visits per person-month from 0.001 in January 2020 to 0.16 in May 2020, before declining to near pre-pandemic levels in 2022 (Figure 1A). The average rate of in-person visits per person-month decreased from 0.32±0.03 (mean±std) during 2010-2019 to 0.24±0.08 in 2020. The average rate of telemedicine visits per person-month was near zero during 2010-2019 and increased to 0.07±0.05 during 2020. In multivariable logistic regression models, persons with missing encounters were more likely to be male or have VL ≥200 copies/mL. For participants with ≥1 viral load test, the prevalence rate of detectable HIV viral load during 2020-2022 was close to the rate from 2014-2019 (Figure 1B). The change in probability of viral suppression was not associated with participant's age, sex, race/ethnicity, or insu**$$$**

Conclusion: In the HOPS, there were immediate changes in visit type in response to the early COVID-19 pandemic followed by a return to previous patterns over the subsequent 2 years albeit with overall declines for in-person visits. There was a relative maintenance of viral suppression. Ongoing recovery from the impact of COVID-19 pandemic on ambulatory care will require continued efforts to improve access to medical services and care retention.

Figure 1. Monthly rate of office and telemedicine visits (panel A) and prevalence rate of detectable viral load (panel B), January 2010 to June 2022



Note: prevalence rate of detectable HIV viral load (VL) refers to participants with at least one detectable VL test over total number of active participants during 2019 with at least one VL test during the study period (N=2,351), and is estimated by longitudinal generalized linear mixed models with logit link, January 2010 to June 2022.

1075 Variation in Viral Load Testing and Outcomes in Telehealth HIV Care During COVID-19

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Background: To maintain HIV care continuity during the COVID-19 pandemic, most HIV care facilities across the United States adopted telehealth. However, research on the impact of telehealth use on HIV care outcomes is conflicting. This study assessed variation in viral load (VL) testing and outcomes related to

visit type patterns among people living with HIV (PWH) receiving care from a large university-based clinic in North Carolina (NC) during the first year of the COVID-19 pandemic.

Methods: Aggregated electronic health record (EHR) data from the Duke University Infectious Disease clinic in NC were extracted using Epic's SlicerDicer tool to assess bivariate differences between visit type patterns and VL testing history and outcomes. Visit type patterns were categorized as PWH who have used only in-person, a combination of in-person and telehealth, or only telehealth HIV care between March 16, 2020 and March 15, 2021. Nonparametric Pearson's chi-square ($\chi 2$) tests were used to assess variation in VL testing history and outcomes in 2022 (i.e., not having any VL test recorded in 2022, VL was suppressed at all tests in 2022 [<200 copies per ml blood], or at least one VL test was unsuppressed in 2022 [≥200 copies]) by visit type pattern.

Results: EHR data from 1,835 PWH were included. Telehealth use steeply increased in the first months of the pandemic, surpassing in-person visits, and decreased thereafter, stabilizing approximately one year after the beginning of the pandemic with <3% of PWH receiving telehealth per month. Between March 16, 2020 and March 15, 2021, 970 PWH used in-person HIV care only, 583 used telehealth and in-person HIV care, 282 used telehealth only. $\chi 2$ tests indicated that telehealth only users were more likely to not have any VL test recorded in 2022 as compared to PWH using in-person only or a combination of in-person and telehealth HIV care ($p<0.001$; Table 1). The proportion of PWH having at least one VL test ≥200 was similar regardless of visit type use.

Conclusion: This study's results indicate that VL outcomes among telehealth users who have VL testing results documented in EHR one year later may not be inferior as compared to exclusive in-person HIV care users. However, VL testing uptake is lower among telehealth only users. As VL testing is crucial to monitor treatment success, strategies such as remote VL testing at home or a local lab are needed to ensure regular VL testing among PWH who use telehealth HIV care.

Table 1. Viral load testing and outcomes by HIV care visit type patterns

	Duke Infectious Disease clinic, North Carolina Time period: March 16, 2020 - March 15, 2021 N=1,835 patients			
	In-person only (N=970)	Telehealth and in-person (N=583)	Telehealth only (N=282)	p-value*
Viral load (VL) history in 2022				**<0.001**
<200 at all VL tests in 2022	717 (73.92%)	429 (73.58%)	171 (60.64%)	
At least one ≥200 in 2022	71 (7.32%)	49 (8.40%)	24 (8.51%)	
No VL test recorded in 2022	182 (18.76%)	105 (18.02%)	87 (30.85%)	

Notes: * Non-parametric p-values are calculated by Pearson's chi-square test; VL viral load

1076 Differences in Country-Level COVID-19 Mortality Across the Western Hemisphere

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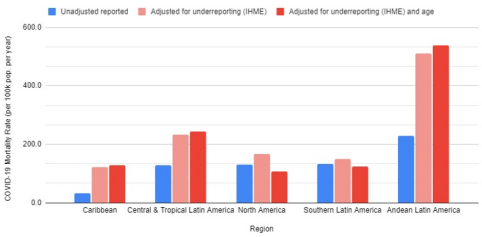
Background: Country-level differences in reported COVID mortality rates and their risk factors have been studied in some regions, however, country and region-level variations in COVID-19 mortality rates within the Western Hemisphere are not well understood.

Methods: Using data reported from each country's health ministry, we examined COVID-19 mortality rates across countries and regions in the Western Hemisphere starting from the first reported death to 12/31/2021. We adjusted for underreporting using three models developed by the Institute for Health Metrics and Evaluation (IHME), the World Health Organization (WHO), and the Economist. Age-adjusted analysis was performed to control for the association between COVID-19 mortality and older age. To account for additional country-level variations in mortality rates, we collected publicly available data on underlying medical conditions associated with higher risk for severe COVID-19 (identified by the Centers for Disease Control), as well as demographic and socioeconomic factors. Univariate and multivariate analyses were conducted to evaluate associations between each risk factor and adjusted COVID-19 mortality.

Results: The annualized reported COVID-19 mortality rate was 131.3/100,000 people in the Western Hemisphere, ranging from 31.4/100,000 in the Caribbean to 227.7/100,000 in Andean Latin America. Country-level mortality rates ranged from 1.8/100,000 (Nicaragua), 3.8/100,000 (Haiti), and 10.2 (Venezuela); to 142.4 (Argentina), 160.1 (Brazil), and 340.2 (Peru). After adjusting for underreporting, mortality rates increased between 20% and 64% depending on the model used, with the Caribbean having the lowest rates and Andean Latin America the highest. With adjustment for underreporting and age, Andean Latin America had the highest mortality rate and the Central and Tropical Latin American region had the second-highest mortality rate in all three models (Figure). After adjusting for underreporting and age, the countries with the highest mortality rates were Bolivia, Peru, Ecuador, and Mexico. In multivariate regression analyses, GDP emerged as the only significant predictor of COVID-19 mortality.

Conclusion: Countries in Andean Latin America consistently had the highest COVID-19 mortality rates, even after accounting for underreporting and age difference. Country-level differences were largely attributed to socioeconomic status, with lower- and middle-income countries having the highest rates of COVID-19 mortality in the Western Hemisphere.

Figure 1. COVID-19 mortality rates adjusted for underreporting and age by regions in the Western Hemisphere



1077 What's in a Wave: Using COVID-19 Data to Explore the Definition of Epidemic Waves

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Brown University, Providence, RI, USA

Background: Objectively defining and classifying epidemic or pandemic waves is critical in providing opportunities for timely resource allocation. However, there is no consensus about what composes a pandemic wave despite proposed definitions in the literature. This analysis aimed to identify, apply and characterize wave definition approaches using COVID-19 case data to build towards standardized definitions for improving pandemic preparedness and response.

Methods: We obtained daily United States (US) case data from February 2020 to March 2022 from the Johns Hopkins COVID-19 data repository. We identified three major definitions of epidemic waves by scoping review. The "eR approach" defined waves as periods where the effective reproduction number (eR) was greater than 1 for at least 14 days. The "fold approach" defined waves as periods where the weekly case rate increased by at least one-fold followed by a decrease by at least one-fold. The "threshold approach" defined waves as periods where the weekly case rate per 100,000 population surpassed 49.99, the US CDC threshold for moderate community transmission. We then compared wave characteristics across definitions.

Results: The eR approach generated 5 waves with an average length of time between waves of 79 (IQR 47–90) days and average wave duration of 65 (56–73) days. The fold approach generated 10 waves with 25 (7–44) days between waves and average wave duration of 47 (29–54) days. The threshold method produced 2 waves with 62 days between the two waves and average wave duration of 276 (251–301) days. The in-wave average daily case rates per 100,000 population were 24.2 (95% CI 20.9–28.1), 19.7 (17.2–22.5), and 30.4 (28.6–32.3) for the eR approach, fold approach, and threshold approach, respectively.

Conclusion: This analysis provides novel characterization of various approaches to epidemic wave definition. The fold approach produced the greatest number of waves, likely due to its sensitivity to weekly changes in case rates. The threshold approach produced the highest in-wave average case rate and lowest between-wave average case rate, indicating it may not adequately capture periods of inflection. These findings have public health implications, as overestimating waves may trigger preemptive allocation of limited health resources, and underestimating may result in a reactionary response with poor targeting of treatment and prevention. Further application of the definitions across countries and diseases are needed to build towards consensus.

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1078 National HIV Testing Trends and Sociodemographic Correlates in Black Cisgender or Transgender Women

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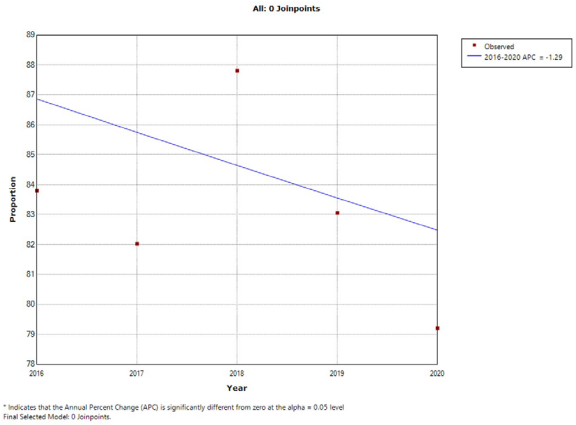
Background: Black cisgender and transgender women are disproportionally impacted by HIV in the United States. Having high-risk behaviors related to HIV but not receiving HIV testing could lead to delayed diagnosis and treatment in this population. We investigated the trend of HIV testing and associated sociodemographic characteristics among Black cisgender and transgender women at risk for HIV.
Methods: We analyzed data from the 2016-2020 Behavioral Risk Factor Surveillance System. Respondents who self-identified as Black, cisgender or transgender women, and reported high-risk behaviors were included. Variables examined in the analysis included ever been tested for HIV, age, education level, income, healthcare coverage, and geographic region. Unweighted counts and weighted percentages were used to describe study population's characteristics. Annual percent change (APC) and p-value were calculated to examine the trend of ever having been tested for HIV over 5 years, using the Joinpoint trend analysis software. The associations between sociodemographic characteristics and ever having HIV testing were assessed using multivariable logistic regression, controlling for explanatory variables with a $p<0.05$. Adjusted odds ratio (aOR) and 95% confidence intervals (95% CI) were reported.
Results: Among 3,509 (weighted n= 4,129,231) Black cisgender and transgender women (35 were excluded due to missing HIV testing status), 2,837 (83.1%) had ever been tested for HIV, and 647 (16.9%) had not. We observed a slight decrease in the percentages of HIV testing over 5 years, from 83.8% in 2016 to 79.2% in 2020 (APC = -1.29, p=0.5420). Black cisgender and transgender women aged 18-34 years (aOR: 0.47, 95% CI: 0.33-0.65) or ≥55 years (aOR: 0.18, 95% CI: 0.11-0.31) were less likely than women aged 35-54 years to get tested for HIV. Additionally, Black cisgender and transgender women with less than high school (aOR: 0.61, 95% CI: 0.38-0.99) or some post-high school (aOR: 0.63, 95% CI: 0.46-0.86) education were less likely to get tested for HIV compared to those with at least a college degree.
Conclusion: In this nationally representative sample of Black cisgender and transgender women, more than one in 6 with high-risk behaviors had not been tested for HIV, and this trend remained stable over the 5-year period. To address the missed opportunities in HIV testing, HIV prevention programs might consider targeting 18-34 years old and ≥55 years Black women and those with a lower level of education.

Figure 1. HIV testing trend among Black cisgender and transgender women who reported high risk behaviors, 2016-2020 Behavioral Risk Factor Surveillance System data



1079 Seroprevalence of Mpox IgG Antibodies in a Cohort of PLWH in Rome During the 2022 Outbreak

Pierluigi Francesco Salvo[1], Rebecca Jo Steiner[1], Damiano Farinacci[2], Valentina Iannone[1], Francesco Lamanna[1], Rosa Anna Passerotto[1], Alberto Borghetti[2], Simona Di Giambenedetto[1], Francesca Lombardi[2]
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Background: The 2022 outbreak of MPOX has unveiled atypical epidemiological and clinical features, setting it apart from previous outbreaks. On May 10th 2023 the WHO declared that MPOX is no longer a public health emergency of international concern. It was also emphasized that all countries worldwide should integrate MPOX prevention and care into national health programs to avoid future spreads. The clinical presentation of MPOX can range from mild to severe and mortality rates can vary. The high incidence rate further suggests that individuals who are infected but clinically asymptomatic may play an important role in the transmission of the virus. More research is needed to ascertain whether HIV can directly influence the clinical presentation in individuals affected by MPOX, focusing on the possibility of an asymptomatic course in this group of individuals. We undertook this study to assess the seroprevalence of IgG anti-MPV in a cohort of PLWH with no reported symptoms consistent with a diagnosis of MPOX, to try to analyze the actual size of the phenomenon of asymptomatic infections in clinical practice.
Methods: From October 2022 to February 2023, we serially collected serum samples from PLWH attending our outpatient clinic for their routine analysis. IgG against MPV have been assessed on stored cryopreserved serum samples with an ELISA. No significant cross-reactivity or interference between anti-MPV IgG and analogues was reported. For the purpose of this study, only people with no previous reported vaccine against smallpox or MPOX nor previous clinical manifestations consistent with an MPX diagnosis were included.
Results: A total of 104 PLWH were tested. 19 participants reported a previous vaccination against smallpox, 1 participant reported a previously confirmed diagnosis of MPOX. All the other 84 participants denied previous vaccination, infection or clinical manifestations consistent with MPX infection. Our analysis revealed 6 patients who tested IgG positive for MPX. Seroprevalence was equal to 7.1%. Demographical and viro-immunological characteristics of the entire population and PLWH who tested IgG positive are shown in Table 1.
Conclusion: Our findings from this setting showed a mildly high IgG MPX prevalence among PLWH with no previous clinical manifestations, suggesting the possibility of an asymptomatic course of the MPX infection. Early detection and appropriate management of MPOX infected people are of utmost importance for global public health and appropriate clinical management.

	N tot = 84 (100.0%)	PLWH with positive anti MPV IgG = 6
Male	68 (81.0)	6 (100.0)
Age, years (Median, IQR)	43 (38 – 46)	44 (37.5 – 48.3)
Caucasian ethnicity (n, %)	72 (85.7)	6 (100.0)
MSM (n, %)	56 (66.7)	4 (66.7)
Heterosexuals (n, %)	27 (32.1)	1 (16.7)
PWID (n,%)	1 (1.2)	1 (16.7)
Time since HIV diagnosis, years (Median, IQR)	10 (6 – 14)	12 (8 – 19)

Table 1: Demographical and viroimmunological of the study population.

1080 Impact of COVID-19 Pandemic on HIV Testing Among MSM: An Interrupted Time Series Analysis

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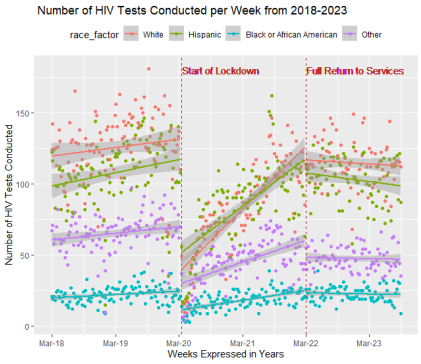
Background: No studies have examined the effects of the COVID-19 pandemic on HIV testing across substantial observation time among a large sample of gay, bisexual and other men who have sex with men (GBMSM), a priority population disproportionately impacted by HIV. We describe the extent to which COVID-19 pandemic-related disruptions to health clinic services impacted the level of HIV testing among sexual minority men in Los Angeles.
Methods: Data comes from the Los Angeles LGBT Center's health services program, one of the nation's largest Federally Qualified Health Centers providing health services to LGBTQ+ individuals. We include GBMSM who are 15 years or older. The primary outcome measure is the average number of HIV tests per week. Interrupted time series analyses were used to model and test changes in HIV testing across three phases of the pandemic: a pre-pandemic phase from March 1, 2018 to March 15, 2020, a pandemic phase from March 16, 2020 to February 28, 2022, and an endemic phase, from March 1, 2022 to August 31, 2023, which signifies the full return of Center services. Weekly HIV testing is estimated overall and by race/ethnicity.
Results: The sample included 25,844 unique participants (n=95,328 visits); 8% were Black/African American, 34% Hispanic/Latinx, 39% white, 8% Asian/Pacific Islander, and 11% some other race/ethnicity. Most participants were between 25-39 years old (48%). The average number of tests conducted weekly across the pre-pandemic, pandemic, and endemic phases are 321, 231, and 288, respectively. There was nearly a 50% reduction in the level of HIV testing conducted weekly after the transition from the pre-pandemic to pandemic phase (Incident Rate Ratio (IRR): 0.53, 95%CI: 0.47, 0.60). The number of HIV

tests decreased slightly going from the pandemic to endemic phase (IRR = 0.80, 95%CI: 0.7, 0.92) and HIV testing did not return to pre-pandemic levels (IRR = 0.77, 95%CI: 0.64, 0.93). Similar trends were observed when stratified by race/ethnicity, however greater decreases in number of tests during the pandemic phase were greater for White and Hispanic/Latinx participants compared to Black/African American and Asian/Pacific Islander participants (Figure).

Conclusion: The overall reduction of HIV testing levels compared to pre-pandemic suggests a new strategy needs to be developed to understand which participants are not returning for testing and why as well as what additional efforts are needed to increase the reach of these necessary preventive services.



1081 Late HIV Diagnosis in CoRIS, 2012-2022, and Impact of a Formative Session in 20 Primary Care Centers

Alejandro G. García-Ruiz De Morales[1], Javier Martínez-Sanz[1], Maria Jesus Vivancos[1], Santos Del Campo Terrón[1], Beatriz Romero Hernández[1], Marta Montero Alonso[2], María Remedios Alemán Valls[3], Enrique Bernal[4], Félix Gutiérrez[5], Antonio Rivero Román[6], Miguel Cervero Jiménez[7], Gemma Navarro[8], David Dalmau Juanola[9], María Jesús Pérez Elías[1], for CoRIS

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Background: Late HIV diagnosis is one of the main drivers of ongoing HIV transmission. We aimed to evaluate the evolution of late HIV diagnosis in CoRIS, a Spanish multicenter prospective HIV cohort, between 2012 and 2022, and assess the impact of a wide formative intervention at primary care centers assigned to Ramón y Cajal Hospital (RyC) in Madrid, Spain.

Methods: In 2017, we conducted two training sessions to encourage HIV screening among primary care providers in 20 primary care centers assigned to RyC. 454 out of a total of 630 (72%) primary care providers attended the sessions. We compared the rates of late HIV diagnosis (CD4 <350 cells/µL and/or AIDS-defining illness, excluding documented recent infection) and advanced HIV disease (CD4<200/µL or AIDS-defining illness) between the centers with intervention (intervention group) and the remaining centers included in CoRIS (control group) before (2012-2017) and after (2017-2022) the intervention. Association measures (adjusted odds ratio [AOR]) were obtained using a logistic regression. Covariates included age, sex, geographical origin, mode of transmission, and educational level.

Results: A total of 10,184 patients newly diagnosed with HIV were included, 341 of whom belonged to centers with intervention. 88.4% were male, the mean age at diagnosis was 36.45 years, 70.4% were men who had sex with men (MSM) and 51.8% were Spanish (Table 1). In the control group, late diagnosis significantly increased between both periods (39.0% before, 45.4% after; AOR 1.22 [95%CI 1.13–1.33], p<0.001). In contrast, the intervention group showed a non-significant decrease in late HIV diagnosis rates between both periods (58.9% before, 48.7% after; AOR 0.70 [95%CI 0.45–1.09], p=0.121). Notably, the intervention had a significant effect on reducing late diagnoses when comparing both groups (p = 0.017). When examining the proportion of advanced HIV disease, we noted an increase in the control group from 20.8% before the intervention to 22.7% after (AOR 1.10, [95%CI 1.00-1.22], p=0.061), compared to a non-significant reduction in the intervention group (35.6% vs. 24.1%; AOR 0.66 [95%CI 0.40-1.08], p=0.095). Importantly, the intervention had a significant effect on reducing advanced HIV disease when comparing both groups (p=0.044).

Conclusion: A training intervention regarding HIV screening delivered to a majority of primary care providers in a health area significantly reduced the proportion of late and advanced HIV diagnoses compared to a nationwide control group.

	Intervention		Control	
	2012-2017	2017-2022	2012-2017	2017-2022
HIV diagnoses, n	146	195	4838	5005
Gender male, n (%)	125 (85.6)	175 (89.8)	4270 (88.3)	4431 (88.5)
Mode of transmission MSM, n (%)	96 (65.8)	160 (82.1)	3383 (69.9)	3527 (70.5)
Origin Spain, n (%)	96 (65.8)	94 (48.2)	2702 (55.9)	2383 (47.6)
Late Diagnosis, n (%)	86 (58.9)	95 (48.7)	1930 (39.0)	2274 (45.4)
AHD, n (%)	52 (35.6)	47 (24.1)	1004 (20.8)	1138 (22.7)

1082 WITHDRAWN

1083 Test-All Model for SARS-CoV-2 Testing Is More Cost-Effective Than Screen & Test in Kenya & Cameroon

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Background: Cameroon and Kenya currently use a SARS-CoV-2 "screen and test" (ST) model, offering testing if clients have COVID-19-like symptoms or

were exposed. In a randomized control trial comparing two testing models, the test-all (TA) model (testing offered regardless of screening outcome) identified more SARS-CoV-2 positive cases than the ST model. It is important to determine costs and cost-effectiveness associated with implementation of the TA model compared to the ST model prior to expansion.
Methods: The total costs of implementing TA and ST in Cameroon and Kenya were estimated from a health systems perspective using a micro-costing method. The cost per client tested (PCT) and tested positive (PCTP) were estimated by dividing the total cost of each model by the number of clients tested and tested positive, respectively. A decision tree designed in TreeAge and cost-effectiveness acceptability curve were used to compare the cost-effectiveness of the two models. One-way sensitivity and probabilistic sensitivity analyses were used to assess the effect of uncertainties in key parameters on costs per client and cost-effectiveness, respectively.
Results: In Cameroon, the total cost of TA was $141,942 and ST was $48,020. In TA model, the cost PCT was US$8 and the PCTP for SARS-CoV-2 was $509, whereas in the ST model the cost PCT was $25 and the cost PCTP was $728. The biggest expenditure in the TA model was SARS-CoV-2 antigen rapid diagnostic tests (Ag-RDT), 61% ($86,853), and for ST was personnel, 39% ($18,592). In Kenya, the total cost of TA was $39,264 and for ST was $27,500. In the TA model the cost PCT for SARS-CoV-2 was $13 and PCTP was $1,190, whereas in the ST model the cost PCT for SARS-CoV-2 was $125 and PCTP was $1,250. In both models in Kenya, the biggest expenditure was personnel, which corresponded to 45% ($17,696) in TA and 56% ($15,267) in the ST model. In both countries, TA model was more cost-effective.
Conclusion: With the current global efforts to lower the price of SARS-CoV-2 Ag-RDT, TA model is likely to be more cost-effective. The widespread implementation of TA model, as done in this project, would help identify priority areas for vaccination and individuals with SARS-CoV-2 infection early for treatment/quarantine. When budgeting for expansion of TA model, the estimated population size, costs of SARS-CoV-2 Ag-RDT, and personnel must be accurate, since they were shown in the sensitivity analysis to have the biggest impact on costs per client and cost-effectiveness.

1084 Validation and Acceptability of SARS-CoV-2 Loop-Mediated Isothermal Amplification Test in Malawi

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Background: Real-time-reverse-transcription-Polymerase-Chain-Reaction (RT-PCR) is the gold-standard diagnostic test to confirm SARS-CoV-2 infection however RT-PCR is expensive requiring specialist laboratories. Alternatively, optimised nucleic-acid-tests such as SARS-CoV-2-reverse-transcriptase-Loop-mediated-isothermal-AMPlification (SARS-LAMP) could minimise costs and enable testing in settings without specialist laboratories. We evaluated the diagnostic test accuracy (DTA)-(sensitivity detecting cycle-threshold (CT) values <30; specificity >95%), acceptability and user-friendliness of SARS-LAMP test.
Methods: Following optimisation of SARS-LAMP, a DTA study was conducted at Queen-Elizabeth-Central-Hospital (QECH) COVID-19 testing centre in Southern Malawi between September 2021-January 2022. Nasopharyngeal swabs were collected and tested for SARS-COV-2 by laboratory technicians using SARS-LAMP at Kamuzu-University-of-Health-Sciences (KUHes) laboratory. The reference standard test was defined as RT-PCR or rapid-antigen-testing (RAT) for SARS-CoV2 performed using any commercial platform at QECH. We calculated sensitivity and specificity of SARS-LAMP compared to existing commercial tests. SARS-LAMP's user-friendliness by laboratory technicians (n=4) and acceptability by suspected cases of COVID-19 and contacts (n=68) were assessed using semi-structured interviews. Likert scales were analysed using summation analysis. Major themes and subthemes were identified.
Results: 105 retrospective nasopharyngeal swabs samples were analysed during optimisation and SARS-LAMP had sensitivity-73.7%(95% CI:65.3%-89.2%); specificity-100%(95% CI:100.0%-100.0%). The prospective DTA study recruited 450 participants using convenience sampling. Median age-37 years (IQR:28-57 years); 248/450(55%)-male, 61/450(13.6%)-contacts, 259/450(58%)-vaccinated. 233/450 (52%) had comorbidities, 192/450 (43%) were SARS-COV-2 positive, 5/192(3%) were admitted to ICU, 2 deaths occurred. 87/192(45.3%) had RT-PCR (CT<30); SARS-LAMP detected 64/87(73.6%):sensitivity-73.6%(95% CI:63.0.%-82.4%); specificity-100% 95% CI:98.6%-100.0%). 67/192(34.9%) were RAT positive; SARS-LAMP detected 37/67(55.2%) :sensitivity-55.2% (95% CI:42.6%-67.4%); specificity-100% (95% CI:98.6%-100.0%). SARS-LAMP was 67/68(98%) acceptable to cases and contacts of COVID-19; 4/4(100%) user-friendly to laboratory technicians.
Conclusion: SARS-LAMP's sensitivity was comparable to previous studies. It was acceptable patients and user-friendly to laboratory technicians.

1085 Estimation of Recent HIV Infections in Japan Using a Novel Testing Algorithm With Chronological Tree

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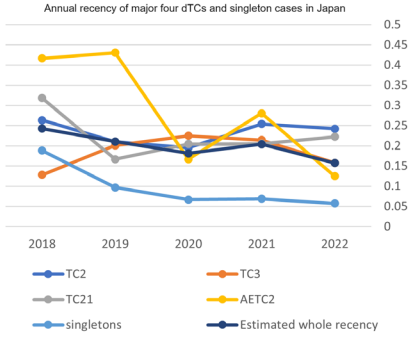
Background: In Japan, approximately 30% of newly diagnosed individuals with HIV are identified after the onset of AIDS symptoms, suggesting that the diagnosis of people living with HIV is delayed. The lack of a serological avidity assay in Japan's surveillance system makes it difficult to accurately estimate HIV incidence. Therefore, we developed a recent infection testing algorithm (RITA) using the viral sequence-based time of the most recent common ancestor (tMRCA), based on information from our drug resistance surveillance instead of the avidity assay, and investigated the recency of some major domestic transmission clusters (dTCs) in Japan.
Methods: The Japanese HIV Drug Resistance Surveillance Network has monitored the dTC dynamics of newly diagnosed HIV-1 cases in Japan using our search program for HIV nationwide clusters by sequence (SPHNCS), which stored 10,445 newly diagnosed cases between 2003 and 2022. We extracted the viral sequences and clinical information of three subtype B and one CRF01_AE dTCs prevalent during 2018–2022 and singleton cases from SPHNCS and inferred their chronological phylogeny using BEAST1. Based on the tMRCAs between neighboring cases in the phylogeny, CD4+ T-cell count, viral copy number, and possibility of an acute infection, we constructed a RITA estimating the probability of recent or late diagnosis of each case.
Results: The cases available for our RITA was 529 in 2018, which decreased to 441 in 2020 and halved to 332 in 2022. All four targeted dTCs had men who have sex with men as a major risk factor. The recency of major dTCs in 2018–2022 ranged from 23.4 to 28.9%, and the recency of singleton cases was 10.0%. The overall estimated recency was 20.3%, assuming that other dTC affiliation cases are similar to major dTCs. The annual recency for each dTC was mostly less than 25%; however, it was >30% in 2018 for B-TC21 and in 2018–2019 for AE-TC2, when outbreaks were observed in a region. The annual recency estimates for the total population consistently decreased, from 24.3% in 2018 to 15.7% in 2022.
Conclusion: Our results showed that before 2019, HIV testing in Japan rapidly diagnosed ongoing HIV transmission in some local risk populations, but this was not the case after 2020. As the number of positive cases decreased, HIV testing opportunities also decreased during the COVID-19 pandemic, which may have been a barrier to early detection. The decline in diagnoses of recent infections suggests a problem with the testing system in Japan.



The estimated frequencies of individuals diagnosed as HIV positive within one year were shown in the line plots by years. TC2, TC3 and TC21 are the three largest transmission clusters for subtype B, and AETC2 is the largest one for CRF01_AE.

1086 HIV Testing Pre- and Post-COVID-19 Pandemic Among Persons Who Inject Drugs: 19 Cities, 2018-2022

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Background: HIV testing decreased since the onset of the COVID-19 pandemic among persons who inject drugs (PWID). There is limited understanding of how changes in HIV testing pre- and post-pandemic affected different sub-groups of PWID. Using data from CDC's National HIV Behavioral Surveillance (NHBS) from 2018 and 2022, we assessed changes in past-year HIV testing among PWID by sociodemographic and health care characteristics. Results from this analysis will help inform efforts to improve HIV testing uptake among PWID in response to service gaps identified during the COVID-19 pandemic.
Methods: In 2018 and 2022, NHBS conducted biobehavioral surveys among PWID using respondent-driven sampling (RDS). Using log-linked Poisson regression models clustered on recruitment chain and adjusted for city and network size to account for RDS, we estimated the change in prevalence of past-year HIV testing between 2018 and 2022 overall and by sociodemographic and health care characteristics. Analyses were conducted among participants who did not self-report HIV-positive.
Results: Of participants (n=9,211 in 2018; n=6,162 in 2022), past-year HIV testing decreased from 55.1% in 2018 to 45.3% in 2022 (adjusted prevalence ratio: 0.84; 95% confidence interval: 0.80, 0.89). HIV testing prevalence significantly decreased over time across nearly all sub-groups of PWID, with large decreases among participants aged 18-29 years, participants living in the Midwest and West, and those who experienced homelessness, were incarcerated, or did not visit a health care provider in the past year (Table). There were also significant declines among participants accessing health care and prevention services, including those who visited a health care provider, used a syringe services program, and participated in drug treatment in the past year.
Conclusion: Decreases in HIV testing during the COVID-19 pandemic were observed for most sub-groups of PWID, although there were regional variations. There were decreases in HIV testing among PWID accessing and not accessing medical and harm reduction services, suggesting efforts are needed to better engage PWID, especially young PWID and PWID experiencing homelessness, in services and ensure those services are resourced to offer routine HIV testing. Integrating HIV testing across medical and harm reduction services accessed by PWID and expanding community-based HIV prevention efforts might improve HIV testing uptake among PWID.
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1087 Rapid Diagnosis of HIV Infection and Initiation of Antiretroviral Treatment

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Background: In Colombia, 39% of HIV infections are identified at stage 3, and the mean delay for starting antiretroviral treatment (ART) is 35 days after confirmed diagnosis. It is well known that once a diagnosis is established, the sooner ART is initiated, the highest the benefits in terms of therapeutic goals and reduction of transmission. There are several barriers to getting tested in real life: Medical prescription, informed consent might be requested, and administrative burden, among others. A potential solution could be a point of care test (POCT), which has been only implemented for pregnant women and in some community centers.
Methods: An open-label randomized clinical trial was initiated comparing a group who received POCT vs. standard diagnostic protocol in a Medellin (CO) clinic. Patients with an HIV test order were randomized via telephone to receive POTC or standard diagnostic protocol. POCT included HIV screening and other tests (Syphilis, Hepatitis B, Hepatitis C, CD4 count and HIV viral load). Recruitment stopped when 50 diagnoses of HIV have been done in the POCT arm.
Results: From Jan 31, 2022, and Jan 31 2023, from a universe of 17.859 HIV tests, 327 new infections were detected. Fifty patients were identified via POCT (per protocol) and 277 with the standard diagnostic approach. The time from test order to sampling was <48h in 95% of POCT vs. 15% in standard protocol ($p<0.05$). 100% of patients with POCT got a viral load measured in <8 days after the first positive test vs. 0% in the standard protocol. The mean time to initiation of ART after the first diagnostic test was 20 days in POCT vs. 52 days in standard protocol ($p<0.05$).
Conclusion: this study demonstrates the benefits of POCT vs. standard protocol, reducing by more than 60% the time between confirmed diagnosis and initiation of ART. There are still opportunities for improvement because an immediate start of ART for patients from the POCT could have happened if there were no additional administrative hurdles, such as a low opportunity for a timely doctor's appointment

1088 Targeted Outreach to Increase Linkage to Preventative Services for Patients Tested for Mpox

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Background: Early in the Mpox outbreak, patients presenting for Mpox testing often did not receive comprehensive sexually transmitted infection (STI) screening upon presentation. Increased coordination of care for linkage to comprehensive preventive services such as HIV pre-exposure prophylaxis (PrEP) and other STI screening is critical to improving both individual and public health outcomes. We hypothesized that targeted outreach to those tested for Mpox would increase rates of PrEP counselling and follow-up STI screening.
Methods: A retrospective chart review was conducted of individuals tested for Mpox between June 2022 and March 2023 at a large county health system in Dallas, Texas. This study assessed the impact of targeted outreach to Mpox-tested persons to promote comprehensive HIV and STI testing and linkage to preventive care services like PrEP. Chi-square (χ^2) test was used for categorical variable analysis.
Results: A total of 414 individuals were tested for Mpox with 203 PCR-confirmed cases. At the time of Mpox testing, 238/414 (57.6%) individuals were previously diagnosed with HIV. An additional 76/176 (43.2%) were screened for HIV, and six new cases of HIV were identified at the time of Mpox testing. Thirty-three percent (136/414) of patients were tested for other STIs (chlamydia, gonorrhea, or syphilis) at the same time as Mpox testing with 45 new cases of STIs identified. As part of targeted outreach following the initial presentation for Mpox testing, 94/414 (23%) individuals were contacted. Patients who were eligible for HIV screening that received targeted outreach were more likely to be tested for HIV (10/26 [38.4%]) compared with those who did not receive additional outreach (19/144 [13.3%]) ($p<0.001$). More individuals eligible for PrEP in the outreach group were counselled on starting PrEP than in the non-outreach group, (14/26 [53.8%] vs 8/144 [5.6%]) ($p=0.0016$). Similarly, more individuals that received outreach underwent additional STI testing compared to those without outreach (58/94 [62%] vs. 109/320 [34%]) ($p<0.001$).
Conclusion: Targeted outreach increased screening for HIV and other STIs and counselling for PrEP among patients presenting for Mpox testing. Strategies to increase and standardize linkage to comprehensive preventive services are needed to reduce co-infections of Mpox, HIV and other STIs, and promote public health.

1089 Detection of Diverse HIV Strains by the m-PIMA™ HIV-1/2 Detect Point-of-Care Assay

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Background: HIV displays exceptionally high virus diversity that can impact detection by diagnostic assays which fundamentally rely on sequence conservation. Therefore, it is important to confirm their performance on the breadth of known HIV strains. We tested the m-PIMA™ HIV-1/2 Detect point-of-care (POC) assay against a diverse HIV panel consisting of group M and N, group O, Circulating Recombinant Forms (CRF), Unique Recombinant Forms (URF), and HIV-2. *In silico* inclusivity analysis of HIV-1 and HIV-2 sequences from NCBI was performed to predict m-PIMA detection to an even broader range of circulating strains.
Methods: m-PIMA™ HIV-1/2 Detect (Abbott Rapid Diagnostics Jena GmbH, Germany) was performed according to the manufacturer instructions. Serum from HIV patients or virus cultures with known viral load (VL) and classified sequences were tested. The panel (n=274) consisted of HIV-1 subtypes A (n=11), B (n=19), C (n=25), D (n=13), F (n=9), F1 (n=2), G (n=5), H (n=5), J (n=3), K Basal (n=2), L (n=1), group N (n=2), group O (n=16), CRF01 (n=6), CRF02 (n=13), CRF06 (n=7), CRF09 (n=4), CRF11 (n=8), CRF13 (n=4), CRF14 (n=1), CRF22 (n=1), CRF36 (n=2), CRF37 (n=2), CRF43 (n=2), HIV-1 URFs (n=106), and HIV-2 (n=5). For in silico inclusivity, 1,107,963 HIV-1 and 7,289 HIV-2 NCBI

sequences were used. After removing low quality sequences or those lacking assay target regions, 53,503 HIV-1 and 68 HIV-2 sequences remained to assess assay target region percent identity.
Results: Across the cohort m-PIMA™ HIV-1/2 Detect test detected 264/274 (96.4%) samples. Mean (min-max) VL of the panel was 3.93 (2.18-6.14) log copies/mL. Among samples with HIV VL >1000 copies/mL (VL > limit of detection of the m-PIMA™ HIV-1/2 Detect) 219/222 (98.6%) were detected. At least one panel member from each subtype/CRF and all URFs were detected. *In silico* analysis found only 2/53,503 (0.0037%) HIV-1 (both group O) and 1/68 (1.47%) HIV-2 (subtype F) accessions with mutations in target regions which would reduce % identity below 90%, considered the threshold to ensure detection.
Conclusion: POC testing is a critical tool to identify HIV infections around the world. Here, we demonstrate that the m-PIMA™ HIV-1/2 Detect POC assay detects each of the major circulating HIV strains as well as rare divergent strains. *In silico* analysis predicted that m-PIMA™ HIV-1/2 Detect would detect the majority of HIV-1 and HIV-2 strains. These data indicate that this assay can detect the full range of HIV viral diversity.

1090 HIV & HCV Screen Rates for Hospitalized PWUD Are Heterogeneous & Suboptimal Across 11 US Hospitals

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Background: To end the HIV and HCV epidemics, people who use drugs (PWUD) need more robust opportunities for HIV and hepatitis C virus (HCV) testing, confirmation of infection and linkage to care. While inpatient hospitalizations are an essential opportunity to test PWUD for HIV and HCV there is limited research on rates of inpatient testing for HIV and HCV among PWUD and no data comparing testing rates between hospitals or parts of the country. This primary aim of this study is to quantify aggregate testing rates across a cohort of U.S. hospitals and hospital systems. Secondarily, we aim to explore how HIV consent requirements impact testing rates.
Methods: Eleven hospital sites were included in the study. Nine established a cohort of inpatient encounters from 1/1/2020 to 4/1/2022 tied to the presence of ICD-10 drug use diagnosis codes (Table 1). Two sites (CT and TX) identified inpatient cohorts from the same study period using Addiction Medicine consults. The unit of analysis was hospitalization. Data collected included: the number of hospitalizations, HIV antigen/antibody tests, HCV antibody tests, and HCV viral loads. HIV and HCV testing rates and positivity were derived as a percentage of total PWUD hospitalizations. All sites detailed their HIV screening and consent policies, where consent requires either written or oral patient approval. The impact of state consent requirements on screening was analyzed using a Student's t-test comparing hospitals with and without these mandates.
Results: We included 65,276 hospitalizations of PWUD at across 11 hospitals. Sites had an average HIV screening rate of 40.08% (SD = 23.29%) and an average HCV Ab screening rate of 31.58% (SD = 15.14%), with widespread heterogeneity in screening rates across facilities. HIV screening rates did not significantly differ between states that require consent and those that did not (p-value = 0.389). Average test positivity across hospitals was 4.5% for HIV tests and 41.4% for HCV tests.
Conclusion: In a study of 11 hospitals and hospital systems across the U.S., we found suboptimal HIV and HCV testing rates during inpatient encounters for PWUD. Testing rates for HCV were lower than those for HIV, with widespread heterogeneity across hospitals, regardless of consent requirements. Hospitalizations are a missed opportunity to offer HIV and HCV testing. As treatment (HIV) and cure (HCV) are necessary to end these epidemics, understanding and overcoming barriers to HIV and HCV testing need to be prioritized.
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1091 Development and Evaluation of Tasso-M50 Method for Dried Blood Viral Load Detection

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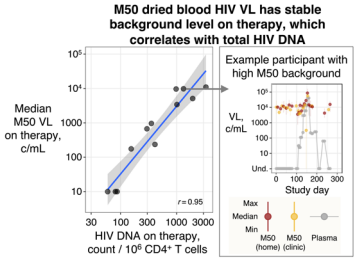
Background: At-home blood collection would enable HIV VL assessment for intensive monitoring without frequent access to a clinic – such as for PrEP programs, perinatal or breastfeeding pediatric monitoring, discordant couples, or participation in ART interruption studies. We present the development and qualification of a scalable, high-throughput PCR method using dried blood collected in Tasso-M50 cartridges.
Methods: We developed a dried blood assay ("M50 assay") with samples from 21 people with HIV (5% female, 67% African American, mean age 51 years, NCT03588715). At clinic visits (mean 20.5), we collected a) capillary blood in two 4-well Tasso-M50 devices and b) matched plasma samples (pVL). Between visits, participants self-collected in two devices that were mailed back. Automated RNA extraction and duplicate RT-qPCR reads with dual LTR/GAG FAM-labeled primers were performed (up to 16 M50 PCR reads per timepoint, sourced from 400 uL blood collection). DNase treatment was used in a subset of samples collected during suppressive ART. Assay performance was tested on separate M50 samples prepared from RNA diluted into whole blood.
Results: M50 assay PCR reagents/instruments were qualified on plasma samples (94% concordance to reference lab), and M50 VL was comparable between home- and clinic-collected samples. In the separate performance test, the M50 assay had 99.5% specificity and an estimated 95% limit of detection of 150 c/mL if all 16 reads from 2 devices are used. However, 64% of clinic visits with undetected pVL had median M50 read ≥ 200 c/mL, due to cell-associated HIV: M50 VL of these discordant samples correlated with total cellular HIV DNA (r = 0.95) and was stable on suppressive therapy (mean slope –3.1% per week [95% CI –8.4 to +2.3%]). DNase reduced M50 VL while preserving detectability of RNA standards, suggesting that ~28% of the stable M50 background is contributed by DNA and the remainder by RNA.
Conclusion: We introduce and qualify a new assay for total HIV burden in dried whole blood with an at-home sampling device. Discordant samples with high M50 VL and negative pVL are stable over time and reflect contributions from intracellular viral DNA and RNA. Home sampling of total HIV burden may be able to monitor new infections in prophylaxis-directed studies, assess changes in residual cell-associated virus in cure-directed studies, or detect viral rebound after correcting for the stable on-therapy signal.



1092 Declines in HIV Testing and Diagnoses: Unanticipated Consequences of Trump Adm 2019 Title X Policy

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Background: In 2019 the Trump administration instituted a regulation (hereinafter the Policy) which required that all Title X funded family planning clinics have financial and physical separation of abortion services from other health services and disallowed providers from referring clients for abortion. In response, 32% (1,280) of all Title X funded sites left the program. This exodus led to declines in Title X client numbers and contraception provision, however the Policy's impact on HIV testing and diagnoses has yet to be examined.
Methods: This secondary analysis uses public data from Title X Family Planning Annual Reports (2016-2021) and CDC HIV surveillance reports (2016-2021) to examine the Policy's impact on: 1) HIV testing at Title X clinics by region, and 2)

the proportion of a region's total HIV cases detected at Title X clinics. Regions were classified as high and low exposure to the Policy based on net loss of Title X clinics in 2019 (over 25% vs. under 25% of clinics). Multilevel linear regression modeling was used to examine interactions between Policy exposure and pre- and post-Policy implementation for HIV outcomes. Adjustment variables included demographic data on Title X clients and state-level metrics from 2018.
Results: Title X clinics provided an annual average of 913,903 HIV tests and diagnosed 7.1% of the country's HIV cases (regional range 3.1% - 12.5%) from 2016-2021. High exposed regions provided 611,276 more HIV tests and diagnosed 1.3% more HIV cases than low exposed regions pre-Policy and provided 433,115 fewer HIV tests and diagnosed 2.3% fewer HIV cases than low exposed regions post-Policy. Interaction models showed HIV testing in high exposure regions declined significantly compared to low exposure regions from pre- to post- Policy (β -69,626 95% CI [-108,893, -30,359], p<.01) and Title X clinics in high exposure regions identified a significantly smaller proportion of the region's total HIV cases compared to low exposure regions from pre- to post-Policy (β -0.04, 95% CI [-0.07, 0.00], p=.05).
Conclusion: The 2019 Policy had a notable negative effect on HIV testing and diagnoses in the Title X program. These results extend the known negative health consequences of the Policy to include HIV-related outcomes. Established sexual and reproductive health providers in the Title X program are a key provider of HIV services; anti-abortion policies that endanger the Title X network also threaten to weaken the U.S. HIV response.

1093 HIV Outcomes Among Partners Reached by Phone vs In-Person for Assisted Partner Services in Kenya

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Background: Assisted partner services (APS) are an effective strategy for identifying and testing people with undiagnosed HIV and traditionally conducted primarily by phone with in-person contact for those unreachable by phone. However, less is known about the characteristics or HIV outcomes of those reached by different methods of contact.
Methods: We analyzed data from 31 facilities in Kenya providing APS to female index clients newly diagnosed with HIV, their male partners, and female partners of those men testing newly HIV-positive. APS providers attempted to contact partners using phone first if a number was available and, if unsuccessful after three phone calls, traced partners in-person in the community. Using log-linear mixed models, we estimated relative risks (RR) between phone being the final (successful) contact method for notification and demographic characteristics (age, sex, income, education, key population membership, and clinic urbanicity) and HIV outcomes (testing, first-time testing, new diagnosis, and linkage to care, adjusting for age and sex).
Results: From May 2018-March 2020, 2534 female index clients named 7614 male partners, of whom 772 (10.1%) tested positive and named an additional 4956 non-index female partners. Overall, we reached 11,912 (94.7%) partners, 5179 (43.5%) via phone and 6733 (56.5%) in-person. Among reached partners, being male (RR:1.25, 95% Confidence Interval [CI]:1.17-1.35) and completing secondary education or higher (RR:1.22, 95%CI:1.09-1.36) was associated with successful contact by phone. Of the 11,912 partners eligible for testing (reached by APS and no prior HIV diagnosis), 99.7% tested and 11.2% first-time tested. Of those tested, 13.1% received a new diagnosis, of whom 87.0% linked to care. Partners who received a new diagnosis were less likely to have been reached by phone vs. in-person (9.8% vs. 15.9%; adjusted RR:0.61, 95%CI:0.53-0.70). Being reached by phone was not significantly associated with testing, first-time testing, or linkage to care.
Conclusion: In an APS program that reached 94% of elicited partners, fewer than half were successfully contacted by phone only. Men and those with higher education were more likely to be reached by phone, and partners receiving a new HIV diagnosis were more likely to be contacted in-person. Although phone-based tracing may reduce resources required for APS, a combined phone and in-person approach is likely essential to maintain a successful and equitable program.

1094 WITHDRAWN

1095 Community Network Driven COVID-19 Testing of Vulnerable Populations in the Central US: A RADx-UP RCT

En-Ling Wu[1], Xiaoquan Zhao[2], Makenna Meyer[1], Ellen Almirol[1], Gjvar Payne[3], Kavita Bhavan[4], Nickolas Zaller[5], Jerome Montgomery[6], Anna Hotton[1], Russell Brewer[1], Michelle Johns[7], Matthew Aalsma[8], Amelia Knopf[8], Faye Taxman[2], John Schneider[1], for the C3 Investigators
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Background: Community Network Driven COVID-19 Testing of Vulnerable Populations in the Central US (C3) is a multi-site Rapid Acceleration of Diagnostics Underserved Populations (RADx-UP) study designed to evaluate an intervention combining Social Network Strategy (SNS) with COVID-19 prevention education messages to improve COVID-19 testing and vaccination among criminal legal involved and/or low-income Hispanic community members most impacted by COVID-19.
Methods: C3 enrolled participants through peer referral across 8 study sites in the central United States – Texas, Louisiana, Arkansas, Indiana and Illinois – from April 2021 to December 2022. Participants were randomized 1:1 to the SNS arm, or to the SNS+messaging arm which included a staff-led activity to affirm participants' values and beliefs plus an educational video aiming to correct misinformation about testing and vaccination. Follow-up assessment for COVID-19 testing (primary outcome) and/or vaccination (secondary outcome among unvaccinated participants) was completed 3 weeks after baseline. Bivariate analyses were used to compare participant characteristics across

intervention arms. Logistic regression was used to compare primary and secondary outcomes, controlling for site differences.
Results: A total of 1328 participants enrolled, with 661 in the SNS arm and 667 in the SNS+messaging arm. Overall, participants identified as 39.8% Black (n=529), 32.4% Hispanic (n=430), and 51.3% (n=681) assigned female at birth. 41.6% (n=553) of participants reported criminal legal involvement prior to enrollment, with no differences between arms by sociodemographics. High numbers of participants were tested (66.3%) and unvaccinated participants vaccinated (11.9%) at three-week follow-up across both arms. Compared to the SNS arm, there were no differences between testing (OR 1.07, 95% CI 0.85, 1.34, p=0.20) or vaccination rates (OR 1.49, 95% CI 0.79, 2.81, p=0.48) among participants in the SNS+messaging arm.
Conclusion: Adding educational material including testimonial videos and misinformation correction to the Social Network Strategy (SNS) did not increase testing or vaccination compared to the SNS alone. COVID-19 testing and vaccination rates at follow-up were high among community members in both arms of the SNS intervention. Additional work is needed to address COVID-19 misinformation and implement SNS to increase testing and vaccination rates among communities most impacted by COVID-19 in the United States.
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1096 Targeting Key Populations With HIV Testing Services in Emergency Care in Nairobi, Kenya

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Background: Persons seeking emergency injury care have high-risk profiles for HIV. While facility-based HIV Testing Services (HTS) in Kenya are effective, emergency department (ED) delivery is limited, despite the potential of this venue to reach key populations (KPs) and vulnerable populations (VPs). This study assessed impacts of the HIV Enhanced Access Testing in the Emergency Department (HEATED) program in enhancing HTS delivery for high-risk ED patients.
Methods: The HEATED program employed evidence-based behavior-change interventions to promote ED-HTS utilizing resource reorganization and sensitization on HIV care for KPs/VPs. KPs included commercial sex workers, gay men, men who have sex with men, transgender persons, and persons who inject drugs. VPs included persons 18-24 years , interpersonal violence victims, persons with hazardous alcohol use (HAU). Data were collected in pre-implementation (6 March-16 April 2023), post-implementation (1 May-26 June 2023), with a two-week implementation period. Data were obtained from a sample of enrolled patient participants with injuries and via standard HTS records. Chi-squared tests and risk ratios were computed with Wald confidence intervals.
Results: Among 2,578 injury care encounters, 2,303 (89.3%) patients were screened, 605 (26.3%) met inclusion and were enrolled. Overall, 442 (73.1%) participants identified as a KP (7.7%) or VP (89.4%). Commercial sex workers accounted for 68.4% of KPs, and interpersonal violence victims 23.7% of VPs. HTS delivery per 100 patient encounters increased significantly among KP/VP from pre- to post-implementation (RR=12.2; 95% CI: 7.50-19.68). Post-implementation, HTS delivery was significantly greater among participants identifying as a KP/VP than other enrolled participants (p=0.03). Identification of persons living with HIV (PLHIV) increased non-significantly from pre-implementation (n=26) to post-implementation (n=53) (RR=1.15; 0.73-1.87). 73% of these PLHIV were newly diagnosed, and new diagnoses increased non-significantly across phases (RR=1.26; 0.72-2.12), in addition to linkage of new diagnoses to care (RR=1.10; 0.54-2.25).
Conclusion: The HEATED program increased HTS delivery targeting KP/VP and enhanced identification and linkage of new HIV diagnoses, suggesting that broader implementation in Kenya ED settings could support service improvement for high-risk persons already in contact with health systems, who are integral to achieving HIV control targets.

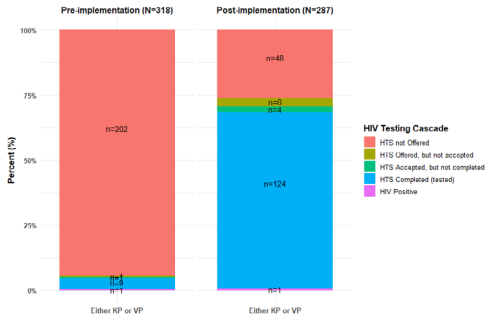

Figure. HIV testing cascade outcomes across implementation phases among enrolled KPs/VPs in the HEATED Program

1097 Method for Analyzing Cabotegravir and Rilpivirine in Hair May Help Identify Risk Factors for Failure

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Background: Long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV) is a promising approach to improve virologic suppression, including among those with adherence challenges. However, resistance can occur among virologic failures. Risk factors for virologic failure defined in the clinical trials include high body mass index (BMI) which can decrease CAB levels, low RPV troughs, HIV subtypes A1/A6 and RPV resistance mutations. Population pharmacokinetic (PK) models of CAB and RPV are sparse given limited real-world roll-out but may help define risk factors for low levels and failure. LA therapies may need long-term metrics to define exposure as exemplified by hair levels. The UCSF Hair Analytical Laboratory (HAL) has experience in validating methods to analyze antiretrovirals in hair.
Methods: For CAB and RPV, the two drugs were extracted from hair from a patient on LA CAB/RPV (approximately 2 mg) into a mixture of methanol and trifluoroacetic acid, which included stable isotopic internal standards. This extraction was carried out through overnight incubation at 37˚C. The sample was then evaporated to dryness and reconstituted for analysis via liquid chromatography/mass spectrometry (LC-MS/MS) using an Agilent Infinity II 1290 system coupled with a triple quadrupole mass spectrometer. To separate CAB and RPV, a gradient analysis was performed using a mobile phase composed of methanol, water, formic acid, and acetic acid over 100% methanol. A reverse phase column was used for the separation of CAB and RPV.
Results: Detection of CAB, [13C, 2H2, 15N]-CAB, RPV, and RPV-d6 was achieved using multiple reaction monitoring. Intra-day precision ranged from 1.98% to 4.88% for CAB and 1.31% to 4.09% for RPV, and intra-day accuracy ranged from −9.44% to +10.8% for CAB and −15.0% to +6.92% for RPV. The quantitative linear dynamic standard curve range for CAB was determined to be 0.00625 to 3.20 nanograms (ng)/milligrams (mg) hair, while for RPV, the range was 0.0625 to 32.0 ng/mg hair.
Conclusion: The UCSF HAL has developed and validated a method to analyze CAB and RPV in hair samples. The UCSF HIV Clinic (Ward 86) has ~250 patients on long-acting CAB/RPV with demographics typically assessed in population PK models (age, sex, BMI, etc.) available in the medical record. A research study to analyze CAB and RPV levels in hair and plasma, construct population PK models, and define risk factors for low LA CAB/RPV exposure, portending virologic failure, will be launched at Ward 86 using the hair method described here.
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1098 Toward Near-Patient HIV Drug Level Feedback: Implementing an Enzymatic Assay on a Portable Reader

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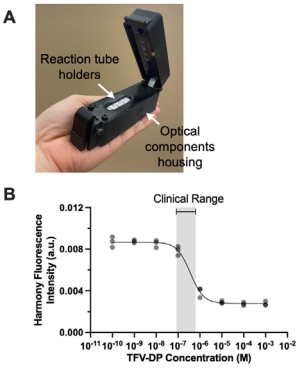
Background: Tenofovir diphosphate (TFV-DP) is used in most HIV prevention and treatment regimens. TFV-DP levels in whole blood correlate with efficacy, and providing regular drug level feedback (DLF) leads to higher medication adherence and improves clinical care. However, the gold-standard for DLF, liquid chromatography tandem mass spectrometry (LC-MS/MS), is centralized to a few highly equipped laboratories, leading to long delays, high costs, and limited

utility in routine care. We previously developed the REverSe TRanscriptase Chain Termination (RESTRICT) assay to rapidly determine TFV-DP levels based on the drug's inhibition of DNA synthesis by HIV reverse transcriptase (RT). Here, we demonstrate the potential of a low-cost (<$300 USD) portable fluorometer, the Harmony reader, to provide semi-quantitative RESTRICT readout in near-patient settings.

Methods: We validated semi-quantitative fluorescence measurements on the Harmony reader with RESTRICT assays containing DNA template, primers, nucleotides, recombinant HIV RT and TFV-DP. Reactions were incubated for 30 minutes at 37 °C, and PicoGreen intercalating dye was added to quench reactions and provide fluorescence readout. Harmony fluorescence measurements were compared to those obtained on a traditional benchtop plate reader (~$30,000 USD).

Results: The Harmony reader (Fig 1A) integrates low-cost LEDs and sensors into a 3D-printed housing, is lightweight and portable, and can be USB-powered. Harmony was able to detect TFV-DP in buffer at clinically relevant concentrations (Fig 1B). The resultant enzyme inhibition curve has a 50% inhibition concentration (IC_{50}) of 367 nM (95% confidence interval: 317-427 nM) corresponding to 750-1000 fmol/punch, demonstrating that the RESTRICT+Harmony platform can identify patients with TFV-DP concentrations that indicate moderate adherence (4 doses/week) . Harmony measurements were highly correlated with plate reader measurements ($R^2 = 0.96$, $p<0.0001$, N=120).

Conclusion: Translation of RESTRICT fluorescent measurements to a portable reader eliminates reliance on expensive laboratory equipment and could enable deployment in near-patient settings (i.e. PrEP delivery settings, pharmacies, and clinics). Overall, RESTRICT+Harmony is rapid (<30 mins) and low-cost, and with the integration of sample preparation and a larger clinical validation, could accelerate global HIV prevention and treatment efforts by providing real-time DLF to support medication monitoring and adherence.



1099 Full Pol-Gene PCR and Rapid ONT Library Preparation for Accurate Drug Resistance Sequencing

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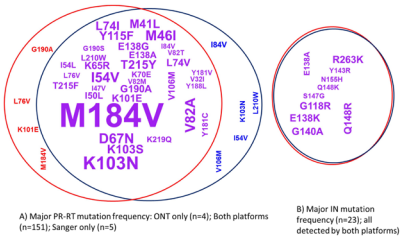
Background: Oxford Nanopore Technologies (ONT) third generation sequencing has the benefit of long read-length that allows the efficient and rapid sequencing of long DNA fragments. With the global rollout of integrase strand transfer inhibitors for treatment naïve and treatment experienced patients, drug resistance sequencing increasingly requires the sequencing of the protease (PR), reverse transcriptase (RT) and integrase (IN). We have therefore developed a rapid assay workflow that involves PCR amplification of a ~3 kb target, including all drug resistance mutations in pol, with rapid ONT barcode ligation followed by ONT real-time sequencing.

Methods: HIV RNA was extracted with the NucliSens EasyMag (bioMeriuex) and amplified with a one-step reverse transcriptase PCR and nested PCR amplifying the ~3 kb PR-RT-IN target. Library preparation was with a fast ONT barcoding kit. We used residual HIV viral load samples (HIVVL) (n=71) to assess amplification success at various viral load strata. Residual samples from patients that had undergone Sanger Sequencing for protease and reverse transcriptase (n=35) with Applied Biosystems™ HIV-1 Genotyping Kit (ThermoFisher Scientific) and a published homebrew assay for integrase (Van Laethem 2008) (n=19) to assess assay accuracy. ONT sequence processing and drug resistance interpretation was with NanoRecall and the Stanford HIVdb 9.5.0.

Results: PCR amplification success rates at viral load strata 200-1 000, 1 000-10 000 and >10 000 copies/mL were:15/28 (53.6%),15/20(75.0%) and 22/23(95.7%) respectively. Pairwise % identity between ONT and Sanger nucleotide sequences was 99.3% (98.3-100.0) for PR-RT and 99.4%(97.7-99.8) for IN; with a good agreement in major drug resistance mutations detected by both platforms (Figure).

Conclusion: The novel fast ONT-based full pol-gene provides an alternative to Sanger Sequencing, especially in patients with higher viral loads. Discordant cases with Sanger Sequencing are likely a combination of PCR resampling error and small differences in the sequencing platforms. Our assay combined with NanoRecall interpretation provides an assay suitable for the use cases of drug resistance surveillance and individual patient management in resource limited settings.



1100 A Rapid Emtricitabine Urine Lateral Flow Assay for Monitoring Daily Adherence to ART and PrEP

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Background: Adherence monitoring at point-of-care is challenging in the absence of rapid and accurate measures of antiretroviral drug levels. Emtricitabine (FTC) is a fixed dose component of most antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) regimens that is rapidly excreted in urine at high concentrations making it a suitable candidate for adherence measurement. We developed a test for daily adherence to FTC with a low-cost, rapid lateral flow assay (LFA) that detects FTC in urine. Here, we evaluate the performance of this LFA to discriminate daily adherence in people with HIV (PWH) on ART and individuals on daily PrEP.

Methods: FTC-specific LFAs were designed and optimized in collaboration with a commercial manufacturer using a monoclonal antibody developed by our group. FTC LFA measurements were objectively read by a CubeReader (Chembio, Germany) with urine FTC concentrations >20 µg/mL indicating adherence to daily dosing. LFA performance (sensitivity and specificity) was evaluated on 273 urine samples which included (a) drug naïve, uninfected individuals (n = 62), (b) PWH prescribed ART (n = 67), and (c) people on PrEP (n = 144). FTC concentrations in urine and in plasma were measured by liquid chromatography tandem mass spectrometry for comparison with LFA results and to confirm adherence, respectively.

Results: The FTC LFA provides results within 20 minutes. We evaluated the LFA for its ability to discriminate adherent from non-adherent individuals. FTC levels in plasma were used to stratify individuals for adherence based on a cutoff for daily adherence (>= 49 ng/mL plasma FTC concentration) optimized for greater than 90% sensitivity and specificity (Hendrix et al, 2016). The sensitivity of the LFA was 87.3% and its specificity was 93.5%. Thus, the FTC LFA performed well as a tool to determine daily adherence. Interestingly, median FTC levels in both plasma and urine were slightly higher (1.5-fold and 1.4-fold, respectively) in PWH on ART than in individuals on PrEP.

Conclusion: We describe a lateral flow assay specific for FTC that is designed to detect whether a dose was taken within the past day. This daily adherence urine test has high sensitivity and specificity and can enhance point-of-care adherence monitoring for both ART and PrEP.

1101 User-Friendly and Efficient Multiplex HIV, Syphilis, and Hepatitis B & C Self-Screening in Thailand

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Background: Affordable and reliable rapid test kits pave the way for widespread screening. However, it is crucial that the process be user-friendly, quick, confidential, cost-effective and include medical support when needed. It should also save healthcare workers (HCW) time. The Napneung project is working towards efficient HIV screening methods.

Methods: The Napneung project offers free and anonymous self-screening for HIV, syphilis and hepatitis B and C at five locations in northern Thailand to anyone aged ≥15 years. The medical team in collaboration with IT specialists developed an advanced web app, available in several languages, to automate most processes: online appointments to avoid queues and waiting times, instructions for user-guided self-screening, and standardized information provided on sexually transmitted infections while awaiting results. The app allows a HCW to assist multiple users at once. Only two drops of blood from a finger prick are needed to screen for the four infections. If a test is positive, confirmatory tests are performed, then post-test counseling and personalized referral for evaluation and treatment are provided. High-risk HIV-negative users are encouraged to start PrEP and re-test regularly. For demand creation, the service is promoted online through social media and search engines, and offline through posters and vouchers. No incentives are offered.

Results: 16,753 screening sessions were provided to 12,175 users between Oct 19, 2015 and Jun 7, 2023. 49% of users were male at birth, 45% were aged 15-24 years, 17% reported being MSM or transgender women, and 63% had never tested for HIV. Median (interquartile) time from arrival to reading of test results was 36 (30-44) minutes. >99% reported being satisfied with the self-screening process. 222 (1.7%, excluding those already aware) were newly diagnosed with HIV (50% had never tested for HIV, and 62% were MSM or transgender women), 230 (1.9%) with syphilis, 193 (1.6%) with hepatitis B and 67 (0.5%) with hepatitis C. The relatively high median CD4 count at diagnosis (370 cells/mm^3, versus 200 nationwide) and recency assay testing showed that the service is used shortly after HIV acquisition. 95% of users newly diagnosed with HIV subsequently confirmed that they initiated treatment.

Conclusion: This effective, well-received and affordable system saves time for HCW and users. Associating multiplex tests with IT resources enables the integration of efforts to fight these four chronic infections without additional burden.

1102 Effectiveness of Using HIV Self-Tests as an Incentive for Testing Within Assisted Partner Services

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Background: There is a need for interventions to increase the success of offering HIV self-testing (HIVST) within assisted partner services (APS) in low resource settings. Financial incentives have shown success in increasing HIV testing rates but results on non-monetary incentives remain mixed. We investigated the effectiveness of offering an additional HIV self-test as an incentive to increase HIV testing among partners receiving APS in Kenya.

Methods: We conducted a single crossover study nested within a cluster-randomized controlled trial at 24 facilities in western Kenya. 12 control sites offered only provider-delivered testing to partners of index clients with HIV for one year. 12 intervention sites, in addition to provider delivered testing, offered partners the opportunity to pick up a HIVST at a local pharmacy during the first six months (pre-implementation), then during the next six months (post-implementation) the sites switched to offering two HIVSTs. A difference-in-differences approach using generalized linear mixed models, accounting for clustering by facility and adjusting for age, sex, and income, was used to estimate the effect of the incentive of two HIVSTs on overall and first-time testing among APS partners who reported no prior HIV diagnosis.

Results: From March 2021-June 2022, 1127 index clients received APS and named 8155 partners, of whom 2333 reported a prior HIV diagnosis and were excluded from analyses, resulting in 5822 remaining partners: pre-implementation, 1489 (40.8%) and 2157 (59.2%) partners were in the control and intervention arms, and post-implementation, 815 (37.5%) and 1361 (62.5%) partners were in the control and intervention arms. Pre-implementation, 1422/1489 (95.5%) in the control arm tested for HIV versus 2111/2157 (97.9%) in the intervention arm; post-implementation the numbers were 699/815 (85.8%) and 1204/1361 (88.5%) in the control and intervention arms. Comparing partners offered one vs. two HIVSTs showed no difference in HIV testing (DID relative risk [RR]:1.01, 95%Confidence Interval [CI]:0.951-1.07) or first-time testing (DID RR:1.23, 95%CI:0.671-2.24). Of partners offered a second HIVST, 940/1204 (78.1%) opted for HIVST, 322/940 (34.3%) picked up two kits, and 231/322 (71.7%) reported that the second kit encouraged HIV testing.

Conclusion: Offering a second HIVST to partners of index clients as an incentive within APS did not significantly impact HIV testing or first-time testing, likely since HIV testing rates were already high at baseline.

1103 Increased HIV RNA Testing of PrEP Users Following 2021 CDC Guidance: United States, 2019-2023

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Background: Persons using PrEP can have ambiguous HIV test results for viral inhibition during use that might delay the diagnosis of HIV infection. In December 2021, CDC recommended HIV RNA nucleic acid testing (NAT) in addition to HIV antigen/antibody (Ag/Ab) testing at initiation of long-acting cabotegravir injections (CAB-LA), and for follow-up testing of users of all PrEP regimens. We estimated the impact of CDC guidance on combined HIV RNA-Ag/Ab testing associated with PrEP use in the U.S.

Methods: We analyzed data in the HealthVerity database of longitudinally linked prescriptions and HIV testing laboratory data from 2019 through June 2023. We identified persons prescribed oral or injectable PrEP and extracted their HIV testing records. A combined test is defined as Ag/Ab and RNA tests ordered within an interval of less than 7 days. We defined testing at PrEP initiation if it occurred ±7 days from the first prescription, and testing for follow-up if it occurred from 30 days after the first prescription to 14 days after the end of the last prescription. For oral PrEP users, we estimated the rate of combined testing among patients' follow-up testing pre- and post-2021 CDC guidelines. For CAB-LA users, we estimated the rate at PrEP initiation or follow-up in the post-2021 guideline period.

Results: We identified 10,856 oral PrEP users with follow-up testing during the pre-2021 guideline period; 552 (5%) received combined testing, 613 (6%) had NAT only, and 9,592 (88%) had Ag/Ab testing only. During the post- updated guideline period, among 10,972 oral PrEP users with follow-up tests, 3,109 (28%) received combined testing, 1,068 (10%) had NAT only, and 6,691 (61%) had Ag/Ab only. We found 691 CAB-LA users; only 130 (19%) received combined testing at PrEP initiation. Among 540 CAB-LA users with follow-up tests, 333 (62%) received combined testing, 118 (22%) had NAT only, and 78 (14%) had Ag/Ab testing only.

Conclusion: The rate of combined HIV RNA-Ag/Ab testing among oral PrEP users increased substantially after CDC published updated guidance in 2021 but the rates are sub-optimal, as is the rate of combined testing at CAB-LA initiation. However, the rate of combined testing during CAB-LA follow-up is higher. Further research is required to investigate the extent of long-acting early viral inhibition syndrome in individuals using PrEP, as well as to assess the cost-effectiveness of HIV RNA testing for PrEP users of different regimens.

Table. CDC-recommended antigen/antibody testing (Ag/Ab) plus HIV RNA nucleic acid amplification testing (NAT) of persons prescribed oral PrEP at follow-up and persons prescribed long-acting injectable cabotegravir (CAB-LA) at initiation and follow-up, United States, January 2019 – June 2023

	Pre-guidance (January 2019 – December 2021)			Post-guidance (January 2022 – June 2023)		
Type of PrEP	Overall (N)	With Follow-up Test (N)	With Combined Test N (%)*	Overall (N)	With Follow-up Test (N)	With Combined Test N (%)*
Oral PrEP						
Follow-up	17,223	10,856	552 (5.1)	16,295	10,972	3,109 (28.3)
CAB-LA						
Initiation				691		130 (18.8)**
Follow-up				691	540	333 (61.7)

CAB-LA was approved by the FDA in December 2021. Initiation: ±7 days of the first CAB-LA prescription date; Follow-up: first PrEP prescription date + 30 days to prescription end + 14 days.
* Denominator is patients with follow-up testing; ** Denominator is all CAB-LA users

1104 Evidence of HIV Infection Prior to Rapid Antibody Test Positivity in PrEP Breakthrough Infections

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Background: Exposure to antiretrovirals in PrEP users with breakthrough infection can suppress viral replication early after HIV acquisition, leading to delayed or inconsistent seroconversion. Limitations in HIV diagnostic accuracy in this context are higher for assays with lower sensitivity, such as point-of-care rapid antibody tests (RT).
Methods: We obtained plasma samples from visits prior to the first positive RT from 251 participants with incident HIV during randomized PrEP trials (iPrEx and Partners PrEP), which used 3rd generation RT (state-of-the-art for HIV diagnosis at the time). Samples were categorized into time intervals and analyzed using higher performance tests (Abbott Alinity s HIV Ag/Ab Combo, Roche Elecsys HIV Duo, and Ortho VITROS HIV Combo for antigen/antibodies detection; Roche cobas MPX for RNA detection) to address positivity comparing participants assigned to active PrEP (N=101) to those assigned to placebo (N=150).
Results: A large percentage of samples had positive results in higher performance tests before infection detection by RT. Rates were consistently higher for participants assigned to active PrEP compared to placebo, with statistical significance for the <8 weeks timepoint in 2 of 4 assays. The combination of RNA and antigen/antibody tests further increased overall positivity, although not reaching statistical significance when compared to antigen/antibodies tests alone. We also analyzed signal-to-cutoff/cutoff index results in antigen/antibodies tests over time prior to the first positive RT, by treatment assignment; levels were somewhat higher, and positivity was identified earlier in participants assigned to active PrEP, suggesting longer duration of infection prior to the first positive RT.
Conclusion: Compared to point-of-care RT, higher sensitivity lab-based serologic and nucleic acid detection assays can enhance the identification of breakthrough HIV infections in PrEP users. Our findings suggest consideration of adopting higher sensitivity tests in PrEP programs that rely exclusively on point-of-care 3rd generation RT for follow-up. For blood banks, our results reinforce that screening with parallel lab-based serologic and RNA tests should be ensured. Study limitations include sample storage beyond the manufacturers' labeled claims and possible laboratory errors.
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1105 Costs and Clinic Flow of Point-of-Care Urine Tenofovir and HIV Viral Load Testing in South Africa

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Background: Point-of-care (POC) urine tenofovir (TFV) tests can monitor real-time ART adherence in clinics and complement POC viral load (VL) tests for HIV treatment management. However, clinic flow and implementation cost of both tests is uncertain. We sought to estimate costs of integrated POC TFV and VL testing for persons initiating ART in South Africa to inform implementation of new diagnostic technologies for person-centered HIV care.
Methods: We conducted microcosting within STREAM HIV, a randomized implementation trial evaluating POC HIV TFV and VL testing in a government clinic in KwaZulu-Natal, South Africa. We collected time-and-motion data to assess staff and client time needed for POC TFV testing. We estimated financial and economic costs for capital, clinic consumables, and personnel using a provider perspective. We updated costs for POC VL testing from 2018 to 2022 USD using the gross domestic product price deflator and new prices for test cartridges. We estimated instrument costs assuming five-year lifespans with a 3% annual discount rate.
Results: The per-client test costs, including both financial and economic costs, of POC TFV and VL testing were USD $12 and $21, respectively, assuming a clinic volume of individuals 50 initiating ART clients per month. Key cost drivers for POC TFV and VL tests were the test strip and cartridge consumables, accounting for 52% and 70% of total test costs, respectively. The median time clients spent in the clinic for a visit with a POC TFV test was 49:31 (minutes: seconds). The POC TFV testing took a median time of 9:36 (19% of total clinic visit) including sample collection, sample loading, TFV test processing, and counselling provision based on test results. Overall, 29% of the clinic visit time included direct clinical care and assessment with a provider, with clients spending a median time of 14:15 getting vitals checked, adherence monitored via POC TFV testing, and collecting ART. Waiting in line for ART took most (48%) of the clinic visit time with a median wait time of 23:42.
Conclusion: POC TFV testing is low-cost, requires less than 10 minutes, and may be feasible to implement in South African clinics. Findings can inform the policy decisions and budgetary planning for ART monitoring, in South Africa and similar settings that are considering using POC TFV and VL testing to support adherence monitoring in lieu of lab-based VL testing.

1106 A Capillary Blood-Based Self-Collection Method for Monitoring HIV Viral Load During ART Interruption

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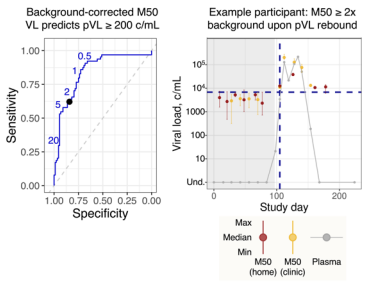
Background: Multiple barriers limit participation of people with HIV (PWH) in studies in which frequent viral load (VL) monitoring is required such as cure studies involving a treatment interruption (ATI). Convenient, home-based VL testing may increase equitable participation. Here we report a novel VL test based on capillary blood collection, comparing its specificity and sensitivity to conventional clinic-based plasma-based VL (pVL).
Methods: We enrolled 21 PWH (5% female, 67% African American, mean age of 51 years) undergoing planned ATIs as part of the BEAT-HIV trial (NCT03588715). At contiguous visits (mean 20.5), we collected A) capillary blood using two 4-well Tasso-M50 devices, and B) matched plasma samples. Between visits, participants self-collected capillary blood using two devices that were mailed back (home collection). We employed a robotic automation process for magnetic bead RNA extraction and RT-qPCR readout with dual LTR/GAG FAM-labeled primers that amplify on the same fluorescence channel. Samples and standards underwent qPCR in duplicate.
Results: The devices were well-accepted, with a collection failure rate <10%. We analyzed a total of 5392 M50 PCR reads (3058 clinic, 2334 home collection). Among the 14 participants where M50 background levels could be determined from ≥ 4 weeks of suppressive treatment, M50 VL 2x above median background was predictive of matched pVL ≥ 200 c/mL (Figure 1. Sensitivity 66%, specificity 81%, PPV 71%, NPV 76%, ROC curve AUC 85%). When M50 VL was < median background, pVL was reliably low (NPV 84% for pVL ≥ 200 c/mL, NPV 90% for pVL ≥ 1000 c/mL). 13 of 14 (93%) participants experienced an increase in M50 VL at the collection immediately following pVL rebound ≥ 200 c/mL (median increase 9-fold, range 1.8- to >1000-fold); the remaining participant experienced an increased M50 VL at the subsequent collection (to 1.6-fold above background). An M50 VL ≥ 2x background was always followed by pVL rebound ≥ 200 c/mL within 4 weeks.
Conclusion: Our new M50 assay showed good NPV for pVL > 200 c/ml in a cohort of PWH undergoing ATI. This suggests that, upon clinical validation, the assay could be used for home monitoring of VL during ATIs. This approach could enhance equitable participation in HIV research by minimizing participants' visit burden. Other potential applications, such as monitoring new infections in prophylaxis studies or assessing changes in residual cell-associated HIV in cure studies, are warranted.



Left: ROC for M50 prediction of rebound (thresholds next to curve). Right: Case where M50 ≥ 2x background (horizontal line) matches pVL rebound (vertical line). Shading: time when M50 background is established.

1107 First Case of HIV Seroconversion With Emergence of InSTI Resistance on CAB-LA PrEP in Routine Care

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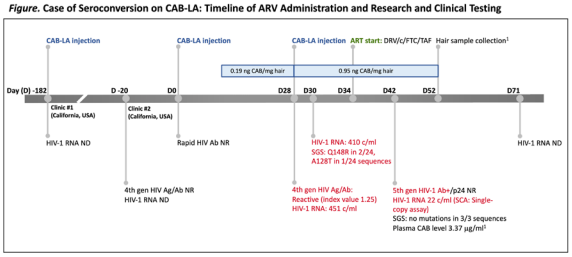
Background: Long-acting cabotegravir (CAB-LA) PrEP is highly effective but delayed diagnoses and INSTI resistance were observed with incident infections in registrational trials. As CAB is scaled up, continued vigilance is needed to assess HIV acquisition, pharmacokinetics (PK), resistance, and ART outcomes after infections. We report the first case outside of trials, to our knowledge, of HIV infection on CAB with emergence of INSTI resistance.

Methods: A 23-year old gender-nonbinary person, male at birth (on estradiol, spironolactone; BMI 19) with history of CAB PrEP use restarted CAB 6 months after discontinuation (Figure). On Day(D) 20 before CAB restart, HIV Ag/Ab was non-reactive (NR) and HIV RNA not detected (ND). Point-of-care HIV Ab was NR on the day of the 1st CAB injection (D0). On D28, when the 2nd CAB injection was given, the HIV Ag/Ab was reactive (index value 1.24), HIV RNA 451 c/mL. The patient enrolled in SeroPrEP, a study of breakthrough infections on PrEP across the U.S. Blood and hair samples were collected for sensitive diagnostic, PK and resistance assays. RNA below routine thresholds was quantified via single copy assay (SCA). INSTI mutations were identified by single genome sequencing (SGS) of full-length integrase, and compared to the partner's viral genotype (GenoSure PRime NGS). We measured CAB levels by LC-MS/MS in plasma and segmental hair analysis.

Results: SGS of plasma HIV-1 RNA identified INSTI mutations Q148R in 2/24 and A128T in 1/24 sequences 2 days after diagnosis and the 2nd CAB injection (D30), while the commercial genotype failed (HIV RNA 410 c/mL). The partner's plasma viral genotype had no INSTI mutations, indicating CAB resistant variants arose after HIV infection and were selected by CAB in this case. Plasma from D42 (14 days post-diagnosis/8 days post-ART start [DRV/c/F/TAF]) was HIV-1 Ab reactive/HIV-1 Ag NR (BioPlex 2200), HIV RNA 23 c/mL (SCA); CAB level 3.37 µg/mL. CAB levels in hair were 0.19 ng/mg 2 weeks pre-diagnosis and 0.95 ng/mg 3 weeks post-diagnosis and 2nd injection. HIV RNA was ND 1 month post-ART start.

Conclusion: In this first case in routine care of HIV infection on CAB with emergence of INSTI resistance, infection likely occurred around the time of CAB reinitiation. CAB resistance emerged rapidly and was only detected by a sensitive research assay. This case highlights the value of RNA testing as close as possible to CAB start and the need to assess resistance, PK, and treatment outcomes to inform clinical and public health strategies.

Figure. **Case of Seroconversion on CAB-LA: Timeline of ARV Administration and Research and Clinical Testing**



1.Cabotegravir levels in plasma and hair segments consistent with expected PK exposure after on-time injections.
CAB-LA: long-acting cabotegravir; ND: not detected; Ag/Ab: antigen/antibody; NR: non-reactive; SGS: single-genome sequencing; ART: antiretroviral therapy; DRV/c/FTC/TAF: Darunavir/cobicistat/emtricitabine/tenofovir alafenamide

1108 Implementing Long-Acting Cabotegravir for HIV Preexposure Prophylaxis in a Large Urban HIV Clinic

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Background: Long-acting cabotegravir (CAB-LA) offers a novel HIV PrEP option for individuals unable to effectively take or tolerate oral PrEP and may expand access to PrEP to populations that have been difficult to reach. We describe the development of a CAB-LA program in a large urban HIV clinic and characterize the program's first patient cohort.

Methods: The UC San Diego Owen Clinic is a Ryan White-funded HIV primary care clinic that also provides PrEP to over 400 patients. Starting in January 2021, individuals interested in initiating CAB-LA were referred to a PrEP pharmacist and a navigator for an insurance check and as-soon-as same-day initiation with on-site delivery of injection. Patients were included who initiated CAB-LA and had at least one follow-up injection. Demographic data were collected through EMR review, and reasons for discontinuation and missed doses were documented and continually reviewed. Logistic regression was performed to evaluate predictors of discontinuing CAB-LA.

Results: Between 1/2021 and 6/2023, providers referred 215 patients to the CAB-LA program, and 162 patients (75%) received at least one injection. Median age was 31.5 (IQR 27, 39) among 48% White, 3% Black and 30% other race individuals with 40% (n=65) reporting Hispanic ethnicity. Ninety-one percent (n=148) identified as cisgender male, and 78% (n=126) reported previous oral PrEP use. Twenty-six (16%) discontinued therapy, with n=11 citing injection site reactions or pain caused by injection. Other reasons for discontinuation included moving or transferring care (n=4), change in HIV risk (n=3), insurance change (n=3), lost-to-follow up (n=3), and other side effects (n=2). Ninety patients were covered through pharmacy benefits (42 with Medicaid, 48 with private insurance), 46 through medical benefits, and 28 by a patient assistance program (PAP). Younger age (OR 1.05, 95% CI 1.01-1.11, p=0.049), having non-PAP coverage (OR 12.5, 95% CI 1.4-111.11, p=0.013), and missing an injection (OR 7.68, 95% CI 1.53-38.65, p=0.023) were associated with discontinuation of CAB-LA.

Conclusion: We observed robust uptake of CAB-LA for HIV prevention among individuals with a clinical need or preference for non-oral PrEP. Most were prior oral PrEP users, highlighting the desire for choice among people who use PrEP for HIV prevention. Younger individuals, those without patient assistance program support and those who miss injection doses may need additional support to keep them engaged in CAB-LA.

1109 Preexposure Prophylaxis With Cabotegravir Long-Acting Injectable in the OPERA Cohort

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Background: Cabotegravir long-acting (CAB LA) was approved as pre-exposure prophylaxis (PrEP) for the prevention of HIV by the FDA on 20DEC2021. It is initiated with two 600mg injections given one month apart (initiation injections), followed by a 600mg injection every two months. We aimed to describe uptake of CAB LA for PrEP and injection patterns in routine clinical care in the US.

Methods: Individuals ≥12 years old who received ≥1 CAB LA injection between 21DEC2021 and 31MAR2023 in the OPERA cohort were followed through 30JUN2023. Incomplete initiation was defined as the receipt of the first injection, with no additional injection within 68 days of the first. Discontinuation and non-adherence were assessed among complete initiators. Discontinuation was defined as ≥128 days without a CAB LA injection. Non-adherence consisted of ≥1 delayed or missed injection (see Table for definitions). Baseline characteristics were compared between adherent and non-adherent individuals. Multivariable logistic regression was used to assess predictors of non-adherence.

Results: Of 560 CAB LA for PrEP users identified, 13% were women, 32% Black, 29% Hispanic, and 26% had a BMI ≥30; median age was 31 years (IQR 25-38). Within 12 months prior to CAB LA for PrEP initiation, 42% of individuals had an STI diagnosed and the median number of HIV tests was 3 (IQR: 2, 5). The initiation injections were completed by 498 individuals (89%) who had a median of 4 injections over a median 7 months of follow-up. Of the 498 with ≥2 injections, 7% discontinued CAB LA for PrEP (Table). Over two-thirds of CAB LA users received all injections on-time and 11% missed an injection (Table). Those with prior PrEP use were more likely to have delayed or missed injections (32%) than those without (21%), with a non-statistically significant odds ratio of 1.78 (95% CI: 0.91, 3.47). Oral bridging was not well documented in EHR; oral PrEP for oral bridging may be prescribed at the start of CAB LA injections but actual use is difficult to ascertain. There was 1 HIV seroconversion concurrent with third injection (all on time); HIV testing at oral PrEP start but not at CAB LA PrEP start.
Conclusion: Early adoption of CAB LA for PrEP was successful in OPERA, a US cohort of EHR from routine clinical care. A sizeable proportion of CAB LA PrEP initiators had diagnoses of STI and multiple HIV tests in the preceding 12 months. While 11% of individuals missed an injection, this may be an overestimate of true therapeutic gaps if oral bridging was used.

Table. Follow-up and injection patterns among individuals who completed initiation of CAB LA for PrEP[a]

	Completed Initiation N=498
Months of follow-up, median (IQR)	7.0 (4.7, 9.5)
Number of injections received, median (IQR)	4 (3, 5)
Discontinuation (≥128 days without injection), n (%)	34 (7)
Any delayed injection (2nd injection ≥38 to ≤52 days after the 1st; ≥3rd injection ≥68 to ≤112 days after the last), n (%)	107 (22)
Any missed injection (2nd injection ≥53 to ≤67 days after the 1st; ≥3rd injection ≥113 to ≤127 days after the last), n (%)	56 (11)
Any delayed and/or missed injection, n (%)	154 (31)

[a] Complete initiation: First 2 injections received <68 days apart

1110 Real-World Use of Cabotegravir Long-Acting for Preexposure Prophylaxis: Trio Health Cohort

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Background: Cabotegravir (CAB) long acting (LA) for pre-exposure prophylaxis (PrEP) was approved in the United States in December 2021 to reduce the risk of sexually acquired HIV-1 infection. The Centers for Disease Control and Prevention (CDC) guidelines state that both HIV antigen (Ag)/antibody (Ab) and HIV RNA testing should be conducted at every injection. Real-world testing, effectiveness, and adherence were assessed among individuals initiating CAB LA for PrEP in the US.
Methods: Individuals without HIV initiating CAB LA for PrEP were identified from electronic health record data in the Trio Health cohort between December 2021-May 2023. HIV testing and incidence were assessed among individuals with at least one injection of CAB LA. HIV testing was assessed at baseline within 90 days prior to the first injection and during follow-up within ±14 days of injection. Incident HIV was identified with either a positive HIV Ag/Ab lab result with confirmatory HIV RNA test or one detectable HIV RNA. Adherence was assessed among individuals with ≥2 injections of CAB LA. On-time injections were defined as occurring within ±7 days of target date and missed injections were defined as a missed injection cycle.
Results: Among the 85 individuals with at least one documented injection of CAB LA for PrEP, the majority were male (93%), White (60%), from the Southern region of US (82%), and the median age was 41 years. Prior to initiation, all individuals had at least one documented HIV Ag/Ab or HIV RNA, and 77% had both tests. During follow-up, 74% of individuals had either HIV Ag/Ab or HIV RNA results at all injections, while 44% had HIV Ag/Ab results, 40% had HIV RNA results, and 20% of individuals had both HIV RNA and HIV Ag/Ab results. No incident HIV diagnoses were identified. Of the 64 individuals with ≥2 injections of CAB LA, 48 (75%) had on-time 2nd injection (Table). Among 43 individuals with ≥3 injections, 27 (63%) had all injections after 2nd on-time. There were no missed injections. 94% continued on CAB LA for PrEP at analysis date.
Conclusion: Initial data from Trio cohort suggest CAB LA for PrEP is effective at preventing HIV acquisition. Injections were administered on-time among the majority of individuals. HIV testing practices in this real-world setting during the early days of CAB LA for PrEP did not align with the CDC testing guidelines among a significant proportion of users.

Table 1. Adherence to CAB LA for PrEP by Initiation and Continuation Injections

	Initiation Injections among Individuals with ≥2 Documented Injections N=64	Continuation Injections among Individuals with ≥3 Documented Injections N=43
Median days from prior injection* (IQR)	31 (29-37)	62 (59-63)
Individuals with all on-time injections, n (%)	48 (75%)	27 (63%)
Individuals with ≥1 delayed injection, n (%)	16 (25%)	16 (37%)
Individuals with ≥1 missed injection, n (%)	N/A**	0 (0%)

IQR – Interquartile Range
*Per label, second injections are administered one month after the first, and all subsequent injections are administered every two months.
**Individuals missing 2nd injection were considered as not initiated on CAB LA

1111 Drug Level Monitoring for PrEP Users: Feasible and Acceptable, but Is It Necessary?

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Background: Good adherence is vital for PrEP efficacy. Most adherence data come from clinical trials but real-world data for long-term PrEP use are lacking. Optimal support for PrEP adherence is not fully established and tenofovir (TFV) drug level monitoring (DLM) could identify those not taking PrEP. It is not known whether DLM would be acceptable to PrEP users or feasible within clinic. Aims: 1. Is PrEP DLM testing acceptable and feasible? 2. Describe adherence in those attending routine care. 3. Compare biochemically verified to reported adherence.
Methods: PrEP users aged >18 years attending a large London sexual health clinic were invited to complete a survey on PrEP use and offered a point of care urine test (UrSure®) for TFV. This detects TFV concentration >1000 ng/mL, consistent with PrEP use in the last 48 hours, validated for emtricitabine-tenofovir disoproxil fumarate (F/TDF) and emtricitabine-tenofovir alafenamide fumarate (F/TAF).
Results: We enrolled 213 people from September 2021-October 2022, 199 completed the survey and DLM test, 14 completed the survey alone. Characteristics of participants were; 94.8% cisgender male; 3.8% trans/nonbinary; 70.9% white; 94.8% gay/bisexual; median age 39 years (IQR 30-51). In the last 12 months 37.6% used any recreational drugs and 10.3% used crystal. PrEP use: 71.8% daily, 23.5% event based dosing (EBD); 88.3% F/TDF and 11.7% F/TAF. Median duration of PrEP use was 4 years, (IQR 2-5, range 1-10). Urine DLM was highly acceptable; 79.8% reported that they were quite/very likely to accept it; when offered, 94.3% completed a DLM test. DLM was feasible; median test completion time was 11.4 minutes (IQR 11.2 – 12.5), only 2 invalid results. Reported PrEP adherence matched DLM verified adherence in >95% of cases. Almost all participants had PrEP adherence consistent with efficacy; for 96.7% of daily users adherence was consistent with >4pills/week. For EBD, 73.1% reported >80% of recent condomless sex was covered by PrEP; EBD was often not used with primary partners or partners who are undetectable. Common reasons for missed PrEP were forgetting, running out, busy or not having sex.
Conclusion: Point of care PrEP urine DLM was highly acceptable and feasible but in this study did not add to self-reported adherence. PrEP adherence in this population attending for routine care was extremely high despite long-term PrEP use.

1112 A Point-of-Care Urine Test Improves Accuracy of Self-Reported PrEP Adherence Among Women in Uganda

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Background: Accurate self-reported behavior could facilitate open discussions between providers and PrEP users about HIV risk and effective use of prevention products. We evaluated a recently developed point-of-care urine tenofovir (POC TFV) test to determine whether its use improves the accuracy of self-reported PrEP adherence and influences reported sexual behavior by young African women.
Methods: We enrolled sexually active, HIV-negative women ages 16-25 years in Kampala, Uganda. Women were followed quarterly for 24 months with HIV

prevention counseling, PrEP dispensation, and adherence counseling. Midway through the study, the POC TFV test (Abbott Diagnostics®) was introduced as part of routine study procedures alongside self-reported data captured by interviewer-administered questionnaires and dried blood spots (DBS) for TFV-diphosphate (DP) quantification. We defined accurate self-reported PrEP use if participants reported high PrEP adherence and had detectable levels of TFV-DP in DBS. We examined changes in self-reported adherence, sexual behavior, and accuracy of self-reported PrEP adherence before and after the introduction of the POC TFV test using a generalized estimated equation logistic regression model with independence correlation structure.

Results: A total of 146 women receiving PrEP refills had ≥1 visit with a POC TFV test administered before study exit. The median age was 19 years (interquartile range [IQR]: 18-21) and the majority (76%) reported having condomless sex within the last three months at baseline. Comparing self-reported adherence before and after the introduction of the POC TFV test, participants more frequently reported low PrEP adherence (OR: 2.96, 95% confidence interval [CI]: 1.89-4.67, p=0.001) and condomless sex (OR: 1.47, 95% CI: 1.04-2.06, p=0.03) during the 146 visits with the test compared to the 146 visits without the test. Accuracy of self-reported PrEP adherence assessed by DBS TFV-DP levels was greater when the test was used (61% versus 24%, OR: 4.86, 95% CI: 2.85-8.30, p<0.001).

Conclusion: We saw greater report of condomless sex and low PrEP adherence, behaviors that are socially less desirable, when the POC TFV test was used indicating that the test could play a vital role facilitating honest conversations between clients and providers. The POC TFV test could be evaluated for real-time adherence monitoring in public sector PrEP programs.

1113 PrEP Counseling Based on a Tenofovir Urine Assay Decreases Overall Non-Adherence Among Kenyan Women

Monica Gandhi[1], David V. Glidden[1], Matthew A. Spinelli[1], Charlene Biwott[2], Gakuo Maina[2], Irene Njeru[3], Catherine Kiptinness[3], Phelix Okello[2], Purba Chatterjee[1], Guohong Wang[4], Vallery Ogello[2], Hideaki Okochi[1], Deepalika Chakravarty[1], Nelly R. Mugo[3], Kenneth Ngure[5]

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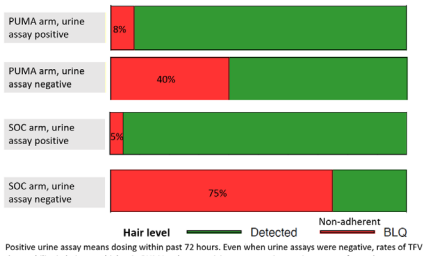
Background: Adherence to oral pre-exposure prophylaxis (PrEP) with tenofovir (TFV)-based PrEP among women in Africa in non-serodiscordant partnerships can be low based on clinical trial and real-world data. A point-of-care (POC) urine assay to objectively assess TFV in urine was recently developed by our group and POC urine monitoring of adherence-informed counseling (PUMA) increases virologic suppression rates among people with HIV on antiretroviral therapy. We performed a pilot trial examining the impact of PUMA on long-term PrEP adherence among HIV-negative women in Kenya.

Methods: A pilot study randomized 100 women in non-serodiscordant partnerships in Thika, Kenya to standard-of-care (SOC) adherence counseling every 3 months for 12 months versus PUMA with visualization of the POC test by providers and participants. Urine tests were collected for 12-month analysis in the SOC arm, without providing results to participants or staff. Hair samples were collected at month 12 to assess the primary outcome of TFV levels in hair as a long-term metric of adherence in both arms. TFV levels in hair were measured by the UCSF Hair Analytical Laboratory using validated methods; TFV levels below the limit of quantification (BLQ) in hair, specifically <0.002 nanograms/milligrams, defined long-term non-adherence.

Results: The trial enrolled 49 women in the PUMA arm and 51 women in the SOC arm with counseling performed every 3 months. Retention in the study was 86% in both arms. Hair was collected and tested from 42 participants in the PUMA arm at month 12; hair was collected from 43 participants and testing completed for 41 of those samples in the SOC arm. The percent of hair samples at 12 months with TFV levels BLQ in the SOC arm was 37% versus 21% in the PUMA arm. The relative odds of long-term non-adherence in the SOC arm compared to the PUMA arm was 3.53 (95% confidence interval 1.03, 12.03, p value 0.04). Knowledge that the urine assay was being performed in the PUMA arm seemed to decrease overall non-adherence as compared to the control arm, even when the urine assay showed no TFV (Figure). One seroconversion occurred over the 12-month study in the SOC arm.

Conclusion: Scalable low-cost adherence interventions to increase pill-taking with oral PrEP are needed. PrEP counseling informed by a POC urine TFV test among at-risk Kenyan women on PrEP decreased overall non-adherence to PrEP at 12 months as determined by hair levels. The real-time urine TFV assay may have a role in improving long-term PrEP adherence.

Figure: Percent with long-term nonadherence (hair levels) in the PUMA vs SOC arm, stratified by urine assay result



Positive urine assay means dosing within past 72 hours. Even when urine assays were negative, rates of TFV detectability in hair were higher in PUMA, where participants new urine testing was performed

1114 Point-of-Care Urine Tenofovir Test Predicts Future PrEP Discontinuation Among Young PrEP Users

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Background: Young men who have sex with men (MSM) and transgender women (TGW) have both disproportionately high HIV incidence and greater challenges with PrEP persistence. POC urine tenofovir (TFV) testing permits real-time objective monitoring for non-adherence within clinical settings at a low cost. We performed urine point-of-care (POC) testing among young PrEP users (age<30) at a high-volume PrEP clinic to examine: 1) the relationship between low PrEP adherence and future PrEP discontinuation, and (2) the accuracy of POC testing vs. liquid chromatography tandem mass spectrometry (LC-MS/MS).

Methods: Participants (age<30) were recruited at the time of a daily PrEP (F/TDF or F/TAF) visit and asked to provide a urine sample and complete a survey. Adjusted logistic regression models analyzed the relationship between the primary predictor of urine POC lateral flow assay results (cut-off of 1,500 ng/mL) and the primary outcome of PrEP discontinuation, defined as no PrEP follow-up within ≥120 days of observation, given that only 90-day prescriptions were provided.

Results: Overall, the participants (n=100) had a median age of 27 (IQR 21-29) years; 12% identified as gender queer, 2% as TGW; 23% Hispanic, 20% Asian, 10% Black, 2% Native American, 2% Pacific Islander; 33% used F/TAF; 95% had at least 2 partners of unknown status. At the index PrEP visit (6/2021-5/2023), 19% had low urine TFV, and 21% discontinued PrEP without follow-up within 120 days. A low urine TFV predicted future PrEP discontinuation (AOR 6.1; 95% CI: 1.4-11; p=0.005) and was 71% sensitive and 90% specific for future discontinuation. All participants with low TFV at the index visit reported condomless anal sex with ≥2 partners of unknown status. Self-reported low adherence (<4 pills weekly) was not associated with PrEP discontinuation (p=0.18); and was only 43% sensitive and 84% specific in predicting low TFV levels. When compared to LC-MS/MS testing, POC testing was 98% sensitive/100% specific. Most (98%) wanted to be able to use the urine test on their own, 94% if it could only be administered by a clinician.

Conclusion: In a diverse sample of young MSM and transgender women using oral F/TDF or F/TAF PrEP, POC urine TFV testing predicted future PrEP discontinuation more accurately than self-report and was highly accurate when compared to LC/MS-MS. Urine POC testing can be a powerful tool for targeting PrEP adherence interventions towards those most likely to discontinue PrEP in the future.

1115 Accuracy of PrEP Adherence Measures Among Transwomen and Young MSM in Latin America: ImPrEP Study

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Background: HIV incidence is high among young men who have sex with men (YMSM) and transgender women (TGW). PrEP is a key strategy to reduce new HIV infections, and monitoring PrEP adherence is essential to guide implementation programs. We aimed to assess the accuracy of indirect PrEP adherence measures with drug concentrations in dried blood spots (DBS) among YMSM and TGW enrolled in the ImPrEP study.
Methods: ImPrEP was an implementation project offering same-day oral PrEP for 9509 MSM/TGW in Brazil, Mexico, and Peru (Feb/2018-Jun/2021), with follow-up visits scheduled 4 weeks post-enrolment and quarterly thereafter, that included YMSM aged 18-24 years and TGW (all ages) who collected at least one DBS during follow-up. We compared two indirect adherence measures with DBS: medication possession ratio (MPR) (ratio between tablets dispensed in prior visit and days between the two visits) and self-reported information (single-question at each visit; 30-days recall). We used generalized estimating equations and area under the curve (AUC) to assess the accuracy of each indirect measure with protective drug DBS levels (TFV-DP ≥ 550 fmol/punch [week 4] and ≥ 800 fmol/punch [other weeks]), and the DeLong test to compare the curves. We calculated optimal cut-off points for discriminating protective drug levels based on Youden index and their respective sensitivity, specificity, negative (NPV) and positive (PPV) predictive values.
Results: We included 4274 DBS samples from 2096 participants (week 4: 1905[44.6%], week 28: 1170[27.4%], week 52: 745[17.4%], week 76: 254[5.9%], week 100: 135[3.1%], week 124: 65[1.5%]). Overall, 1692 (80.7%) participants were MSM and 404 (19.3%) TGW; most were aged 18-24 years (1802; 86.0%), non-white (1582; 75.5%), and had ≥12 years of education (1374; 65.5%). Of all DBS samples, 2871(67.2%) had protective drug levels. AUC was 0.75(95%CI:0.74-0.77) for MPR and 0.76(95%CI:0.74–0.78) for self-report adherence (Table), with no difference between adherence assessment methods' curves (p>0.38). Calculated cut-off points for MPR and self-reported adherence were 97.0% and 93.3%, respectively.
Conclusion: Self-reported adherence and MPR adequately discriminated protective levels of PrEP among key populations in Latin America at different time points during the study follow-up. These measures are low-cost, easy to implement, and allow for immediate action to support PrEP adherence at health service level and ultimately contribute to monitoring PrEP programs.

Table. Association between indirect PrEP adherence measures and protective drug levels (TFV-DP ≥ 550 fmol/punch [week 4] and ≥ 800 fmol/punch [other weeks]).

Population	Measure	AUC (95% CI)	Cut-off (%)	Sensibility (%)	Specificity (%)	PPV (%)	NPV (%)
All participants	MPR	0.75 (0.74-0.77)	97.0	76.8	63.0	80.4	57.9
	Self-report	0.76 (0.74-0.78)	93.3	83.3	62.7	81.6	65.6
TGW (all ages)	MPR	0.75 (0.72-0.78)	97.0	70.2	68.0	74.6	63.1
	Self-report	0.76 (0.72-0.79)	90.0	87.8	58.2	73.7	78.0
Young (18-24 years) MSM/TGW	MPR	0.75 (0.73-0.77)	89.0	88.2	52.2	80.2	66.7
	Self-report	0.76 (0.74-0.78)	93.3	83.8	62.3	83.0	63.6

MSM: men who have sex with men; TGW: transgender women; AUC: area under the curve; MPR: medication possession rate; PPV: positive predictive value; NPV: negative predictive value.

1116 Inequities in PrEP Annualized Pill-Day Coverage: United States, 2018-2022

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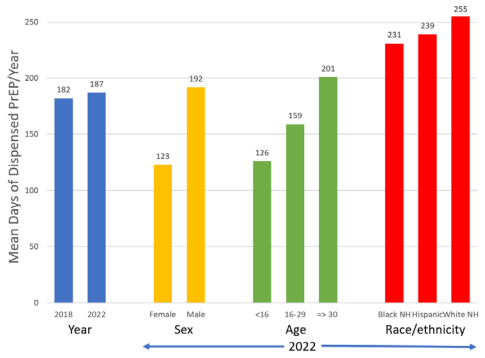
Background: Pre-exposure prophylaxis (PrEP) is highly effective to reduce risk of HIV infection, but the population-level impact of PrEP depends on the proportion of people with PrEP indications who use it and how long they stay on it (persistence).
Methods: We used previously reported methods and commercial pharmacy data to identify PrEP users and the duration of PrEP use calculating by dates of all prescriptions and number of pills dispensed in a year (pill-days per year). PrEP users include all patients who, at any point during the year, filled a prescription for Emtricitabine-Tenofovir Disoproxil Fumarate, Emtricitabine-Tenofovir Alafenamide Fumarate, and/or Cabotegravir, but were not on any other antiretroviral medications. We calculated mean length of PrEP use for the US in 2018 and 2022 overall, by gender, by race/ethnicity, and by age groups. Differences in median days on PrEP per year were assessed by gender, race/ethnicity, and age. To assess the potential impact of 2-1-1 PrEP dosing on median days of PrEP use, we compared data from 2018 (before CDC recommendation of 2-1-1 dosing) to data from 2022.
Results: We evaluated data from 225,180 PrEP users in 2018, and 459,984 PrEP users in 2022. In 2022, the mean number of days covered by dispensed PrEP prescriptions among PrEP users was 187 (SD: 129.8; Figure). Mean days was lower among female (median 123 days) than male (median 192 days) users (P<0.01). Among PrEP users with race/ethnicity data, mean days of use were higher for White non-Hispanic (NH) (255 days) than for Hispanic (239 days) or Black NH (231 days) users (p<0.01 for each comparison). Older users had more days covered by PrEP than younger users (<16 years: 126 days; 16-29 years: 159 days; >30 years: 201 days; p<0.01 for comparisons between <16 years and other groups). A comparison of overall data for 2018 (182 days) versus 2022 (187 days) did not suggest that the USPHS 2021 inclusion of 2-1-1 PrEP in PrEP guidelines was associated with fewer days of coverage.
Conclusion: PrEP programs are often evaluated by enumerating people who used PrEP at any time during a year; our data indicate that there are significant differences in PrEP coverage during a year's time, and that an annual use indicator might mask inequities in PrEP protection, with women, Black NH and Hispanic people, and younger people having fewer dispensed days of coverage. Assessments of days of PrEP coverage should be included in assessments potential impact of PrEP and to address and monitor PrEP equity.



1117 Out-of-Pocket Payments for PrEP Ancillary Services Among US Commercially-Insured Persons, 2017-2021

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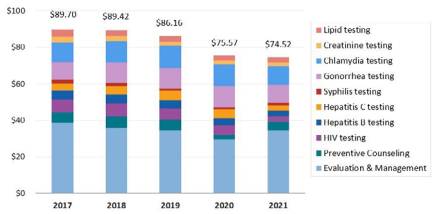
Background: In June 2019, HIV preexposure prophylaxis (PrEP) received a grade A recommendation from the U.S. Preventive Services Task Force (USPSTF). Under the Affordable Care Act, private health plans and Medicaid expansion programs must cover the costs of all PrEP services without any patient cost-sharing starting in January 2021, including PrEP medications and ancillary services such as clinical visits and laboratory testing. The objective of this study was to monitor trends in out-of-pocket (OOP) payments for PrEP ancillary services from 2017–2021 using a large commercial claims database.
Methods: We analyzed data from the Merative™ MarketScan® Commercial Database that contains adjudicated medical claims. Using a validated algorithm, we identified persons aged ≥18 years prescribed PrEP from 2017–2021 and restricted the sample to those continuously enrolled in their plans for at least 6 months. We extracted all medical claims submitted for PrEP services within 1 week before each PrEP prescription using Current Procedural Terminology codes. We analyzed only fee-for-service claims and computed mean annual total and OOP (sum of copayment, deductible, and other coinsurance amounts) payments for each service. We also summed each service's total and OOP payments for combined amounts. All payments were inflated to 2021 U.S. dollars using the medical Consumer Price Index.
Results: Between 2017–2021, we identified 127,055 adults prescribed PrEP. In 2021, PrEP users paid an average out-of-pocket cost of $34.60 for evaluation and management, $4.67 for preventive counseling, $3.08 for HIV testing, $2.98 for hepatitis B testing, $2.87 for hepatitis C testing, $1.30 for syphilis testing, $9.85 for gonorrhea testing, $10.42 for chlamydia testing, $1.91 for creatinine testing, and $2.84 for lipid testing. For most laboratory testing, the proportion of persons paying zero OOP payment increased over time, and more than 70% paid

zero OOP payment in 2021. The mean total payment of combined PrEP ancillary services decreased from $403.97 in 2017 to $268.11 in 2021, and the mean OOP payments decreased from $89.70 in 2017 to $74.52 in 2021 (Figure).
Conclusion: Despite a decreasing trend in total and OOP payments for PrEP ancillary services from 2017-2021, about 30% of commercially insured PrEP users paid OOP payments after the ACA provision of no cost sharing went into effect in 2021. Efforts are needed to ensure that patient OOP payments are not required by applicable third-party payers.

Figure. Mean annual patient out-of-pocket payments for PrEP ancillary services, 2017-2021 (2021 U.S. dollars)



1118 PrEP Indicators by Race/Ethnicity Among Heterosexual Women Receiving CDC-Funded HIV Testing Services

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Background: Pre-exposure prophylaxis (PrEP) is effective at reducing the risk of HIV acquisition. However, PrEP utilization among women remains low, especially among Black/African American (hereafter referred to as Black) and Hispanic/Latina women. We examined indicators for PrEP use and PrEP-related services by race/ethnicity among heterosexual women testing negative for HIV infection via CDC-funded HIV testing.
Methods: We used 2019-2021 HIV testing data submitted by CDC-funded state and local health departments (n=60) and community-based organizations (n=150) to the National HIV Prevention Program Monitoring & Evaluation system. We analyzed the following indicators for heterosexual women: current PrEP use, eligibility for PrEP referral among those testing negative and not currently using PrEP, referral to a PrEP provider among those eligible, and assistance with linkage to a PrEP provider among those who received a referral. To compare each indicator by race/ethnicity, we calculated adjusted prevalence ratios (aPRs) with 95% confidence intervals (CIs) and p-values—adjusting for age, U.S. Census region, and year—with White women as the referent group.
Results: The prevalence of current PrEP use ranged from 0.5% to 1.1%; in adjusted models, current use was higher for multiracial (1.1%; aPR: 1.73) and Black (0.9%; aPR: 1.30) women compared to White women (0.7%; all p<0.05). Eligibility was higher for multiracial (47.2%; aPR: 1.23), Black (44.0%; aPR: 1.22), and Asian (43.3%; aPR: 1.16) women, and lower for Hispanic/Latina (32.0%; aPR: 0.90) and Native Hawaiian/Pacific Islander (33.5%; aPR: 0.89) women, versus White women (38.1%; all p<0.05). Referral was higher for American Indian/Alaska Native (50.8%; aPR: 1.59) and Black (36.4%; aPR: 1.09) women, but lower for Asian women (25.4%; aPR: 0.85), versus White women (31.7%; all p<0.05). Assistance with linkage was higher for Black women (75.8%; aPR: 1.05), but lower for Hispanic/Latina (65.0%; aPR: 0.94), Asian (60.8%; aPR: 0.88), and multiracial (63.8%; aPR: 0.93) women, versus White women (69.5%; all p<0.05).
Conclusion: PrEP use was low among all heterosexual women testing negative for HIV infection. PrEP-related services reached a greater proportion of Black heterosexual women; however, PrEP-related services need to reach all racial/ethnic groups, especially Hispanic/Latina women, to increase PrEP use and reduce HIV acquisition for all heterosexual women at greater risk for HIV.

Current PrEP Use, Eligibility for PrEP Referral, Referral to PrEP Provider, and Assistance with Linkage to PrEP Provider by Race/Ethnicity among Heterosexual Women Receiving CDC-Funded HIV Testing Services

	Current PrEP Use		PrEP Eligibility		PrEP Referral		Linkage Assistance to a PrEP Provider	
Race/Ethnicity	%	aPR	%	aPR	%	aPR	%	aPR
White	0.7	Ref	38.1	Ref	31.7	Ref	69.5	Ref
Black/African American	0.9	1.30 (1.16 - 1.45)	44.0	1.22 (1.20 - 1.23)	36.4	1.09 (1.06 - 1.12)	75.8	1.05 (1.03 - 1.07)
Hispanic/Latino	0.7	1.05 (0.91 - 1.21)	32.0	0.90 (0.88 - 0.91)	29.4	0.97 (0.94 - 1.00)	65.0	0.94 (0.91 - 0.96)
Asian	0.6	1.02 (0.69 - 1.50)	43.3	1.16 (1.12 - 1.20)	25.4	0.85 (0.79 - 0.92)	60.8	0.88 (0.82 - 0.95)
American Indian/Alaska Native	0.5	0.62 (0.36 - 1.08)	38.1	1.00 (0.95 - 1.06)	50.8	1.59 (1.48 - 1.71)	68.5	1.02 (0.96 - 1.08)
Native Hawaiian/Other Pacific Islander	1.1	1.63 (0.78 - 3.43)	33.5	0.89 (0.80 -0.999)	33.0	1.06 (0.86 - 1.29)	68.3	0.98 (0.83 - 1.16)
Multiracial	1.1	1.73 (1.26 - 2.37)	47.2	1.23 (1.19 - 1.27)	31.3	1.01 (0.94 - 1.08)	63.8	0.93 (0.87 - 0.999)

1119 Optimizing PrEP Outcomes for MSM Who Sell Sex: The Role of Stigma, Violence, and Mental Health

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Background: Among gay men and other men who have sex with men (MSM) in the U.S., those who sell sex are disproportionately affected by HIV and report decreased uptake of pre-exposure prophylaxis (PrEP) and other HIV prevention methods. We sought to understand stigma experiences of MSM who sell sex and stigma's role as a potential barrier to PrEP in this population.
Methods: Data were from two rounds of repeat cross-sectional online surveys of U.S. MSM (n=12,601) conducted from September 2021 through June 2023. We described stigma, violence, mental health, and PrEP experiences using chi-square tests to compare among MSM who sold sex for money, drugs, or something else in the last year to other MSM. Among MSM who sold sex who were PrEP eligible and not living with HIV, we used modified Poisson regression with robust variance to calculate prevalence ratios (PR) and 95% confidence intervals (CI) for the association between stigma and (1) maximum oral PrEP adherence (reporting 30 of 30 doses in the last month) and (2) willingness to use injectable PrEP if available. Analyses adjusted for age, race, education, and survey year.
Results: Compared to other MSM, those who sell sex reported higher levels of stigma from family and friends, general social stigma, physical violence, symptoms of post-traumatic stress disorder, and depressive symptoms (Table). Maximum daily oral PrEP adherence were lower among MSM who sell sex than other MSM (54% v 75%, p<0.001). In adjusted analyses with PrEP-eligible MSM who sell sex, decreased PrEP adherence was associated with lifetime exposure to violence (PR 0.68, 95% CI 0.47-0.99) and social stigma (PR 0.57, 95% CI 0.33-0.96. MSM who sell sex were more willing to use injectable PrEP (57% vs 43%, p=0.001) and on-demand PrEP (75.2% vs 63.6%, p=0.004). Those willing to try injectable PrEP most preferred delivery at home (39%) or in STI clinics (20%). Increased willingness to use injectable PrEP was associated with anticipated healthcare provider stigma (PR 1.38, 95% CI 1.01-1.90).
Conclusion: Using data from over 12,000 MSM, we saw increased stigma, violence, and mental health concerns among MSM who sell sex. These issues should be concurrently addressed to optimize HIV prevention in this marginalized population. Addressing stigma and violence toward MSM who sell sex may improve adherence for those who intend to use daily. On-demand or injectable PrEP may more effectively reach MSM who sell sex if concerns about healthcare stigma are adequately addressed.
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1120 Behavioral and Structural Interventions for PrEP Adherence Among Young Female Sex Workers in Kenya

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Background: In Kenya, estimated HIV incidence is substantially higher among young female sex workers (YFSW) compared to similar-age women not engaged in sex work (2.2% vs. 0.15%). Pre-exposure prophylaxis (PrEP) for HIV prevention is recommended for at-risk populations, but its effectiveness requires consistent access and adherence. We assessed the effectiveness of two behavioral and structural interventions on PrEP adherence among YFSW in Kisumu, Kenya. Study follow-up (F/U) coincided with national restrictions on travel and gatherings due to the COVID-19 pandemic.
Methods: We conducted an unblinded, randomized-controlled trial enrolling 18-24 year-old HIV-negative YFSW with no current or recent PrEP use. Participants were provided oral PrEP and randomized to either weekly adherence support from a trained peer supporter (PS), or SMS reminders and resource transfer (RRT) for 12 months, and received PrEP with no adherence support interventions for another 12 months to assess durability of our interventions. Primary outcomes compared adherence in study arms via detectable metabolites in whole blood samples and self-report at 12, 18, and 24 months of F/U. We conducted an intention-to-treat analysis of differences in intervention effectiveness at months 12, 18 and 24. Sensitivity analyses used

inverse probability weighting with stabilized weights to correct for selection bias due to lost to F/U.

Results: We screened 289 YFSW and enrolled 200 (100 per arm). Socio-demographic and sexual behavior characteristics are presented in Table 1. At 12-month F/U (n=179), 86% in PS and 93% in RRT arms reported decreases in number of weekly clients. At 12, 18, and 24 months, detectable levels of PrEP were 3%, 1%, and 0% in the PS arm compared to 9%, 9%, and 1% in the RRT (p-value = 0.4). Our sensitivity analysis found similar results. In contrast, 85%, 81% and 83% in the PS arm, and 86%, 87% and 76% in the RRT arm self-reported perfect 7-day adherence at months 12, 18 and 24, respectively. Two seroconversions were identified; one at 12- and one at 18-months F/U.

Conclusion: In this population of YFSW, no difference in adherence by drug levels or self-report was noted across study arms. The very low levels of drug metabolites in contrast to high self-reported adherence may be due to perceived lower HIV risk resulting from decreased sex work during COVID-19 and to socially desirable responses. Findings highlight the urgent need for long-acting PrEP for this population.

Table 1: Socio-demographic and sexual behavior characteristics of study participants at baseline, by study arm

Characteristic	Total N=200	Study Arm PS (n=100)	Study Arm RRT (n=100)
Age, Median (IQR)	22 (20-23)	21 (20-23)	22 (20-23)
Secondary education or more	157 (79%)	85 (85%)	72 (72%)
Condom use (male and female)	92 (46%)	49 (49%)	43 (43%)
Currently using contraception	159 (79%)	81 (81%)	78 (78%)
Number of clients in past month, Mean (SD)	26 (32)	23 (31)	28 (35)
Frequency of alcohol use 4+ times a week	29 (15%)	10 (10%)	19 (19%)
Non-prescribed drug use, past year	20 (10%)	8 (8%)	12 (12%)
Depressive disorder (4+ symptoms)	22 (11%)	14 (14%)	8 (8%)

1121 Factors Associated With Inadequate PrEP Adherence Among TGW and Young MSM: ImPrEP Study

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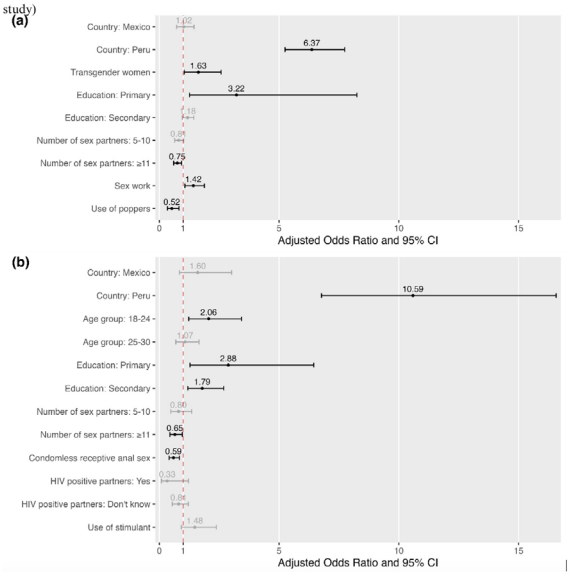
Background: The HIV epidemic disproportionally affects transgender women (TGW) and young men who have sex with men (YMSM) in Latin America. Monitoring adherence is key to designing tailored strategies to improve PrEP persistence, targeting these vulnerable populations. We aimed to identify factors associated with non-protective TDF-FTC levels in dried blood spots (DBS) in TGW and YMSM using PrEP.

Methods: ImPrEP was an implementation study offering same-day oral PrEP (TDF/FTC) for 9509 MSM/TGW in Brazil, Mexico, and Peru (2018-2021). Follow-up visits were scheduled 4 weeks post-enrolment and then quarterly. In this analysis, YMSM (18-24 years) and TGW (all ages) who had at least one DBS obtained during study follow-up were included. We used generalized estimating equations to identify factors associated with inadequate PrEP adherence (tenofovir diphosphate [TFV-DP]<550 fmol/punch [week 4] or 800 fmol/punch [weeks 28-124] in DBS) among MSM/TGW (18-24 years) and TGW (all ages), separately.

Results: We analyzed 3573 DBS samples of 1,802 young participants [week 4: 1645 (46%); weeks 28-124: 1928 (54%)], and 928 DBS samples of 404 TGW [week 4: 358 (39%); weeks 28-124: 570 (61%)]. Of young participants, 94% were MSM, 14% aged 18-19 years, 75% non-white and 70% had post-secondary education. Among TGW, 27% were 18-24 years, 77% non-white and 57% had secondary education. For both populations, being from Peru and low educational level (primary or secondary education) increased the odds of inadequate PrEP adherence, while having more than 10 partners decreased the odds of inadequate adherence. Sex work and being TGW were associated with inadequate adherence among young participants, while for TGW, being 18-24 years showed the same association. Use of poppers (for young participants) and reporting condomless anal sex (for TGW) decreased the odds of inadequate adherence (Figure).

Conclusion: Sexual behavior might have influenced HIV risk perception, leading to higher PrEP adherence. Social determinants of health such as education played a major role in PrEP adherence among TGW and young MSM/TGW in Latin America. In Latin America, PrEP programs for young MSM/TGW must implement tailored interventions to tackle stigma within health services and optimize adherence among the most vulnerable, such as those with lower education and sex workers. Long-acting PrEP can be strategical to improve PrEP adherence in these populations.

Figure. Factors associated with inadequate PrEP adherence, TFV-DP levels in DBS suggestive of <4 doses of TDF/FTC per week, according to characteristics of **young (a)** and **TGW (b)** participants (ImPrEP study)



1122 Alcohol Use and the Preexposure Prophylaxis Continuum of Care Among Men in Rural South Africa

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Background: Despite freely available pre-exposure prophylaxis (PrEP), HIV incidence among young men in South Africa is high. There is conflicting evidence around the association between alcohol use behaviors and PrEP utilization. We explore the impact of hazardous alcohol use on PrEP initiation and retention among South African men.

Methods: We performed a secondary analysis of data from a trial that included men aged 16-29 randomly selected from a demographic surveillance site in KwaZulu-Natal. All participants were referred to HIV and sexual reproductive health services, where those at risk for HIV were offered oral PrEP. Alcohol consumption was assessed at monthly visits and categorized as: non-drinking (0), low/moderate risk drinking (1-5), and high/very high-risk drinking (6-12) based on AUDIT-C criteria. Primary outcomes were PrEP initiation and retention in PrEP services for >3 months. We fitted logistic regression models, adjusted for potential clinical and demographic confounders, to estimate relationships between PrEP initiation/retention and hazardous alcohol consumption.

Results: Of the 847 men referred to study clinics, 528 (62%) attended at least once. 156 were excluded due to missing data (n=107), positive HIV testing (n=20) or declined HIV testing (n=29), leaving 372 men in the analytic cohort. Average age was 22.5 years (SD 3.6) and 131 (35%) had high/very-high alcohol consumption (AUDIT-C score ≥6). Men with the highest risk alcohol use also reported frequent condomless sex (89%, vs 56% in no alcohol group). We found the greatest uptake of PrEP among the high/very high-risk group (46/131, 35%), followed by the low/moderate risk group (17/63, 27%) and the no alcohol group (25/172, 17%). The high-risk group remained significantly more likely to initiate PrEP compared to the non-drinking group in multivariable models adjusted for confounders (aOR 2.02 95%CI 1.07-4.02; p-value 0.045). 30% (26/88) of men remained on PrEP at 3 months. Men with high/very high-risk drinking had similar PrEP retention at 3 months compared to men who identified as non-drinkers (aOR 1.43 95% CI 0.33-6.12; p-value 0.63).

Conclusion: High-risk alcohol use is common among men in rural South Africa and associated with increased PrEP initiation. PrEP retention was low overall,

but similar across all levels of alcohol use. Hazardous alcohol use should not discourage PrEP implementation efforts to engage and retain young men.

1123 Characterizing HIV Preexposure Prophylaxis (PrEP) Discontinuation Among Men Who Have Sex With Men

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Background: For PrEP to have optimal impact, persons indicated for PrEP must not only initiate it but also be retained in care. However, few studies have assessed characteristics associated with PrEP discontinuation among men who have sex with men (MSM).

Methods: We conducted a descriptive analysis using data from the 2022 American Men's Internet Survey, a web-based behavioral survey of U.S. MSM. Eligible participants for this analysis were cisgender males aged≥15 years, resided in the U.S., HIV negative, and were gay, bisexual, or had a history of sex with other men. To explore the characteristics of MSM who have discontinued PrEP, we categorized participants into three groups: persons who never used PrEP, are currently using PrEP, or have discontinued PrEP (used in the past but not currently using). We performed multivariate logistic regression, adjusting for all covariates presented.

Results: Over half (54%, 2033/3785) of MSM had never used PrEP, over one-third (36%, 1365/3785) were using PrEP, and 10% (387/3785) had discontinued PrEP. Half of these (190/387) had discontinued PrEP within the past 12 months. MSM who discontinued PrEP were younger (mean=41) than those never using (mean=45) or currently using PrEP (mean=45). MSM discontinuing PrEP were less likely to have private health insurance (63%) than PrEP users (79%) and had similar insurance levels compared to MSM who never used PrEP (67%). There were no differences in PrEP discontinuation by race and ethnicity. MSM discontinuing PrEP had elevated sexual risk relative to those who never used PrEP: condomless anal sex with HIV-discordant partners was higher (33% vs 20%, aOR=1.83, 95%CI=1.43-2.34) and sexually transmitted diseases (STDs) were more frequent (14% vs 5%, aOR=2.69, 95%CI=1.86-3.90). These relationships were similar for MSM who had discontinued PrEP over a year ago and for those who discontinued PrEP within last year.

Conclusion: One in ten MSM participants in this national survey had discontinued PrEP. Risk for this group, in terms of condomless sex and STDs, was elevated relative to MSM who never initiated PrEP. Structural barriers, such as health insurance and lower educational attainment, were associated with PrEP discontinuation indicating that discontinuation may not solely be due to decreased risk. Tailored intervention is needed to support persons who have discontinued PrEP, such as health messaging, clinical discussions, and ensuring few barriers to care, to optimally address the sexual health needs of this group.

Table 1. Sociodemographic and Behavioral Characteristics Among MSM with Different PrEP Use Status, 2022 (*n*=3785)

	Overall (n=3785, %)	Non-user (n=2033, %)	Currently user (n=1365, %)	Discontinuer [1] (n=387, %)	Discontinuer vs. Non-user aOR (95%CI) [2]	Discontinuer vs. User aOR (95%CI) [2]
Age in years (mean, SD)	45.2, 14.9	44.7, 16.2	44.7, 13.4	40.9, 13.7	0.98 (0.98, 0.99)**	0.98 (0.97, 0.99)**
College education and above (missing=4)	2504 (66.2)	1210 (59.6)	1037 (76.0)	257 (66.4)	1.71 (1.33, 2.19)**	0.76 (0.58, 0.98)*
Private health insurance	2692 (71.1)	1370 (67.4)	1077 (78.9)	245 (63.3)	0.74 (0.58, 0.95)*	0.46 (0.35, 0.59)**
Condomless anal sex with HIV-discordant partners within last year	1192 (31.5)	407 (20.0)	657 (48.1)	128 (33.1)	1.83 (1.43, 2.34)**	0.58 (0.45, 0.74)**
STD diagnosis within last year	515 (13.6)	95 (4.7)	367 (26.9)	53 (13.7)	2.69 (1.86, 3.90)**	0.43 (0.31, 0.59)**

[1] Prior PrEP use, but not currently using PrEP.
[2] Race/ethnicity data included in multivariate models, are not presented due to space limitations.
* p<0.05, **p<0.01

1124 PrEP Non-Persistence and New HIV Diagnoses: A Real-World Analysis of >120,000 People Prescribed PrEP

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Background:HIV pre-exposure prophylaxis (PrEP) uptake has increased, but discontinuation and inconsistent use (referred to here as non-persistence) remain common. The impact of PrEP non-persistence on new HIV infections at the population level is not well characterized. In this study, we leveraged a large real-world dataset in the United States to evaluate the impact of non-persistence on HIV diagnosis rates.

Methods: PrEP-naïve adults with at least one oral F/TDF or F/TAF for PrEP prescription dispensed between April 2021 and March 2022 were identified from the IQVIA Real-World Longitudinal Prescriptions and Diagnosis Database, a retail pharmacy claims dataset, and were followed for up to 12 months from first prescription claim submitted. Periods of PrEP non-persistence were defined as gaps in prescription claims of >30 days following the end of the calculated PrEP supply. This approach allowed for the determination of HIV diagnosis rates during periods when individuals had PrEP on-hand (on-PrEP) versus periods of PrEP non-persistence (off-PrEP). HIV diagnosis rates were calculated by dividing the number of new HIV infections by the observed person-years (PY) for each period using Poisson regression.

Results: Among 123,901 PrEP-naïve adults (median age, 31 years; IQR, 25–40), 1,343 were diagnosed with HIV while on-PrEP (rate: 2.15 per 100 PY [95% CI: 2.04–2.27]) and 2,488 were diagnosed while off-PrEP (4.22 per 100 PY [95% CI: 4.06–4.39]). Overall, off-PrEP periods were associated with a 2-fold higher risk in the relative HIV infection rate compared to on-PrEP periods (rate ratio [RR]: 1.96 [95% CI: 1.84–2.10]). Higher rates of new HIV diagnosis during off-PrEP periods were observed across various subgroups, including cisgender men (RR: 2.26 [95% CI: 2.10–2.44]) and transgender women (RR: 3.64 [95% CI: 1.59–8.31]), as well as all age groups and geographic regions.

Conclusion: In this real-world study involving >120,000 persons prescribed PrEP, off-PrEP periods were associated with an overall two-fold higher rate of new HIV diagnoses. These findings demonstrate how PrEP discontinuations and inconsistent use hamper the maximum public health impact of PrEP, underscoring the urgent need for strategies that can enhance persistence, including broader availability of long-acting PrEP options.
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1125 Outcomes of a Community-Clinic Hybrid PrEP Trial in China During COVID Lockdowns, 2021-2023

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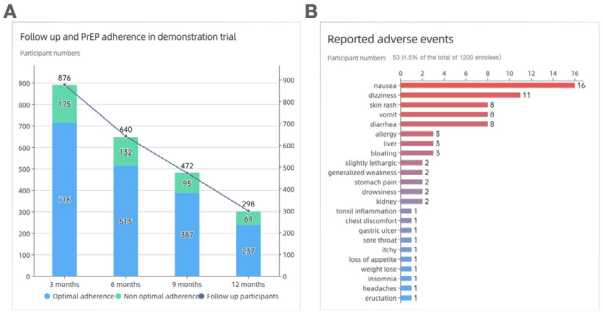
Background: Data on PrEP uptake, persistence, discontinuation, adverse events, and HIV incidence among Chinese at-risk PrEP users is limited.

Methods: We conducted a 12 month PrEP demonstration project in Wuhan and Guangzhou, China, using a community and clinic hybrid delivery model for recruitment, participant engagement, and PrEP delivery. Healthcare providers implemented prescribing, medical consultation, and PrEP dispensing through clinic visits or courier delivery (Through community-based organizations). PrEP refill was monthly for the first quarter and trimonthly thereafter. PrEP continuation and adherence information (defined as self-reported taking more than 4 pills in 7 days for daily and over 75% strict adherence to 2+1+1 for events-driven) was surveyed quarterly. Enrollment, PrEP persistence, adherence, discontinuation, and adverse events were descriptively summarized. Lockdowns occurred during 2021-2022 due to covid restrictions.

Results: From September 2021 to July 2023, a total of 3649 GBMSM were screened, and 1200 were enrolled. Of those, 1138 participants started oral PrEP, with a median age of 29.1(SD=5.9). Most participants identified as gay or bisexual(93.7%, 1066/1138), and 99.6% were cis-gender men(1134/1138). After initiation, PrEP persistence rates at 3, 6, 9, and 12 months were 84.2%(876/1059), 75.8%(640/845), 67.1%(472/703), and 55.5%(298/537) respectively(ongoing). 45.2%(396/876) and 54.8%(480/876) choosed the daily and on-demand regimen initially. At the end, 37.2% of participants reported regimen transition(111/298) in a inceasing trend (32, 41, 61, and 67 at 3, 6, 9, and 12 months). 62.7%(126/201) participants transferred from daily to on-demand regimen. The self-reported adherence rate was 75.4%(716/950), 67.1%(515/768), 58.6% (387/660), and 47.1%(237/503) at months 3, 6, 9 and 12. 239 participants (21.0%, 239/1138) discontinued PrEP use during study. 52.8% and 46% of subjects reported alcohol use and nitrates at baseline and 12 month.Overall STIs incidence within study period is 4.9%-8%. Six participants seroconverted, resulting in an HIV incidence rate of 0.73 per 100 person-years.

Conclusion: The hybrid CBO and clinic-based model proved feasible for reaching and dispensing PrEP among Chinese at-risk populations. On-demand use and mail order drugs were popular alternatives, and one half of participants engaged in sex using alcohol and nitrates. Long-term PrEP persistence and optimal adherence continuously decreased among Chinese users during the 12-month period.



1126 Homelessness, HIV Vulnerability, and PrEP Willingness Among Young Transgender Women in Lima, Peru

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Background: Globally, transgender women continue to face a high burden of HIV. In Peru, there has been no decrease in the incidence of HIV among transgender women over the last 15 years. Better understanding homelessness among young transgender women is critical to inform HIV prevention and treatment strategies and to ending the HIV epidemic. We sought to estimate the proportion of young transgender women experiencing homelessness and the associations between homelessness, HIV-related vulnerability, and PrEP willingness.

Methods: We recruited young transgender women aged 16-24 through peer workers to participate in a biobehavioural survey and testing for HIV and other STIs (chlamydia, syphilis, gonorrhea, hepatitis B). Poisson regression with robust standard errors was used to estimate the association between past experiences of homelessness and HIV-related outcomes, adjusted for potential confounding by age and education.

Results: A total of 211 young transgender women participated in the study, of whom 156 completed HIV and STI testing. The median age of participants was 23 years, 72.7% had completed secondary school, and the overall prevalence of HIV was 41.5%. A total of 64 participants (30.6%) had been homeless at least once in their life and 4.8% has been homeless in the past 30 days. Currently 35.9% lived in their own apartment or room, 27.7% stayed in a relative's home, and 34.0% stayed with a friend or sexual/romantic partner. Among participants who tested positive for HIV, 35.8% reported past homelessness compared to 31.6% of those testing negative for HIV (p = 0.69). After adjusting for age and education, past homelessness was not associated with testing positive for HIV or other STIs but did increase risk of recent (past 30 days) sex work (aPR = 1.48, 95% CI: 1.15 – 1.90), condomless anal sex in the past 6 months (aPR = 1.90, 95% CI: 1.50-2.41), and ever attempting suicide (aPR = 1.82, 95% CI: 1.14-2.90). Among HIV-negative participants, homelessness was associated with having heard of PrEP (aPR=1.94, 95% CI: 1.26-2.98) and willingness to try oral PrEP (aPR=1.63, 95% CI: 1.20-2.21).

Conclusion: The prevalence of past homelessness is high among sampled transgender women aged 16 to 24 and past experiences of homelessness can elevate HIV vulnerability. HIV prevention and treatment programs for transgender women, particularly youth, must consider past and on-going experiences of homelessness to reduce barriers to program access that persist despite interest and willingness to engage.

Table: Association between past homelessness and HIV-related vulnerability

	HIV	STI	Recent sex work	Recent condomless anal sex	Ever attempted suicide	Ever heard of PrEP[1]	Willing to try PrEP[1]
	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)
Past homelessness	1.13 (0.78-1.64)	0.98 (0.77-1.24)	**1.48 (1.15-1.90)**	**1.90 (1.50-2.41)**	**1.82 (1.14-2.90)**	**1.94 (1.26-2.98)**	**1.63 (1.20-2.21)**
Age (per 1 year)	1.08 (0.98-1.18)	1.06 (0.99-1.12)	1.03 (0.97-1.10)	1.01 (0.95-1.08)	.85 (0.78-0.94)	1.00 (0.91-1.10)	0.94 (0.88-1.00)
Education							
< Secondary school	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
≥ Secondary school	0.86 (0.59-1.27)	0.72 (0.59-0.89)	0.69 (0.53-0.89)	1.01 (0.76-1.34)	1.05 (0.61-1.80)	1.61 (0.85-3.02)	0.85 (0.61-1.19)

[1]Among 140 participants testing negative for HIV or self-reporting a negative HIV status (among those who did not participate in HIV testing)

1127 PrEP Uptake and Persistence Among Incarcerated People in Zambia: Early Results From a Cohort Study

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Background: The time during and immediately after incarceration can be high-risk periods for HIV acquisition, particularly in sub-Saharan Africa (SSA). Incarcerated people often have very limited access to effective HIV prevention measures. In 2019, Zambia began offering HIV pre-exposure prophylaxis (PrEP) in correctional facilities. We report early results from one of the first longitudinal studies of PrEP uptake and persistence in a correctional setting in SSA.

Methods: In August 2023, we launched a cohort study of PrEP users and non-users in three correctional facilities in Lusaka, Zambia. Following HIV testing, HIV-negative incarcerated persons were offered PrEP by the corrections health system, and then were approached by study staff for participation. Consenting participants were followed from incarceration through release into the community for PrEP outcomes, including uptake, persistence, and adherence. A subset of participants on PrEP underwent urine tenofovir (TFV) screening for adherence, and another subset of both PrEP users and non-users will be consented to participate in qualitative interviews in October 2023.

Results: From 8 August to 21 September 2023, we screened 124 incarcerated persons; 120 (97%) were eligible and consented. Participants were 18-52 years old, majority (84%) male, less than half (36%) completed secondary education, and three (3%) indicated previous incarceration. Of the 120 enrolled, 93 (78%) initiated PrEP while 27 (22%) declined. As of 21 September, 39 were eligible for one-month study follow-up and 74% (29/39) had completed a visit, all in a correctional facility. Of these, 22/29 (76%) had initiated PrEP at enrollment and all were HIV-negative at follow-up. Two (9%) who had initiated PrEP at enrollment chose to discontinue PrEP at follow-up. Two of 7 (29%) who had not initiated PrEP at enrollment chose to initiate at follow-up. Of the 22 who initiated PrEP at enrollment and had ≥1 follow-up visit recorded, 13 (59%) were randomized to the TFV screening sub-cohort and tested. Of these, 62% (8/13) demonstrated TFV metabolites consistent with adherence.

Conclusion: Early results suggest high demand for PrEP among incarcerated persons in Zambia. This is one of the first observational studies of PrEP uptake, persistence, and adherence among incarcerated persons, and may have future implications for HIV prevention efforts in this population.

1128 Social Determinants of Health and PrEP Uptake in the US: Repeated Measures Correlational Study

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Background: Pre-exposure prophylaxis (PrEP) is a cornerstone of the United States (US) Ending the HIV Epidemic plan. PrEP use was evaluated in jurisdictions with highest HIV diagnosis rates to address disparities at state and county levels on national scale.

Methods: PrEP data from 2012-2019 was analyzed using linear mixed methods modeling. Within the model, dependent variables were county and state PrEP rates. Fixed effects were year, new HIV diagnoses rates, mean income, population insurance coverage, proportion of democratic presidential candidate votes in 2020 and race, while random effects were states and counties. Public health data was from AIDSVu; demographic data from US Census Bureau ACS; 2020 presidential election results from MIT.

Results: County Level: Beginning in 2012, each sequential year was associated with increased PrEP use by 7.22/100,000, 95%CI [2.87, 11.8]. For each $10,000 increase in mean income, there was increase in PrEP use by 65.7/100,000 persons, 95%CI [47.7,83.3]. Increased presidential election votes for the democratic candidate were associated with increased PrEP by 633/100,000 for each percentile point increase in proportion of votes, 95%CI [314, 999]. Higher HIV diagnosis rates were associated with decreased PrEP use by -1.9/100,000 for each new diagnosis per 100,000 in the population, 95%CI [-2.8,-0.9]. Jurisdictions with higher proportion of Asians were associated with decrease in PrEP by -1991/100,000 for each percentile point increase in population proportion, 95%CI [-3357, -632]. State Level: For each $10,000

increase in income, there was increased PrEP use by 45.9/100,000 persons, 95%CI [24.1,67.6]. Increased proportion of presidential election votes for the democratic candidate were associated with decrease in PrEP by -126/100,000 for each percentile point increase in proportion of votes, 95%CI [-218,-34]. Higher insurance coverage was associated with decreased PrEP by -0.54/100,000 for each new insured person per 100,000, 95%CI [-1.0,-0.08]. States with higher proportion of Asian persons had decreased PrEP use -3078/100,000 for each percentile point increase in the population, 95%CI [-4520,-1637]. States in the Midwest were had higher PrEP uptake by 18.4/100,000 95%CI [8.63-28.3] when compared to the South as reference.

Conclusion: Region and demographic data display associations of regional characteristics with inequitable PrEP rates. Displayed variances between state and county levels may be accounted for by differences in HIV preventative medicine policy.

1129 Association of US Medicaid Expansion and Number of Persons Prescribed PrEP, 2017-2021

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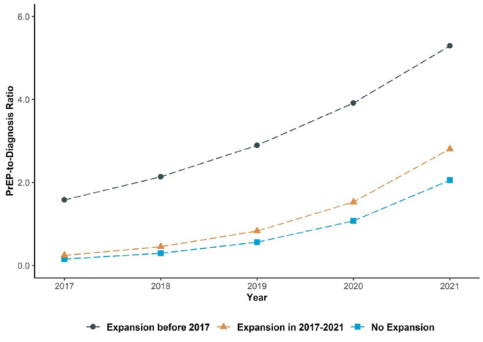
Background: To accomplish goals of the Ending the HIV Epidemic in the U.S. initiative, increased PrEP uptake is needed especially in jurisdictions with higher HIV incidence. Expanded Medicaid eligibility and enrollment can provide PrEP financial access for persons who otherwise might not be able to afford its cost. The Affordable Care Act of 2010 included a provision for states to expand Medicaid coverage starting in 2014. Since then, 41 states and the District of Columbia have expanded Medicaid access. Our objective was to estimate the association between state Medicaid expansion and the use of PrEP.

Methods: We analyzed national Medicaid data from the Centers for Medicare and Medicaid Services to estimate the PrEP-to-Diagnosis Ratio (PDR) among persons aged 16 years and older from 2017–2022. The PDR is a measure of PrEP coverage that estimates the need for increased PrEP implementation. It was calculated as the annual number of persons prescribed PrEP divided by the annual number of new HIV diagnoses. We identified persons prescribed PrEP using a validated algorithm with diagnostic and drug codes. We identified persons with newly diagnosed HIV using ICD diagnosis codes for HIV. We categorized states and the District of Columbia in three cohort groups based on the year they expanded Medicaid: before 2017, 2017–2021, and never. We calculated the estimated annual percentage change (EAPC) and 95% confidence intervals (CIs) for PDR trends by state Medicaid expansion cohort.

Results: Among persons with Medicaid, the overall number of persons prescribed PrEP increased from 24,279 in 2017 to 53,434 in 2021. Among 32 states that expanded Medicaid before 2017, the PDR was 1.6 in 2017 and increased to 5.3 by 2021 with an EAPC of 35.3 (95% CI 35.3, 35.3) (Figure). Among 7 states that expanded Medicaid in 2017 through 2021, the PDR was 0.2 in 2017 and 2.8 by 2021 with an EAPC of 83.8 (83.3, 84.2). Among 12 states that did not Medicaid before 2022, the PDR was 0.2 in 2017 and 2.1 by 2021 with an EAPC of 91.0 (90.9, 91.1).

Conclusion: Our study found that expansion of Medicaid was associated with increased PrEP coverage among persons with Medicaid insurance, suggesting that Medicaid expansion is an effective policy to increase access to HIV prevention services. Medicaid expansion can provide access to many services, including PrEP, that protect the health and wellbeing of the U.S. population.

Figure. PrEP-to-Diagnosis Ratios among persons with Medicaid by state Medicaid expansion cohort, United States, 2017–2021



1130 A Matter of Time: Factors Associated With Delayed nPEP Initiation

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Background: Nonprofessional Post-Exposure Prophylaxis (nPEP) protects against HIV infection after risk exposure, but a prompt start is essential. According to the Italian guidelines, nPEP should be started within 24 hours after the exposure (preferably in the first 4 hours), but can be prescribed up to 72 hours. Aim of this study is to describe factors associated to users' presentation time to our Emergency Department (ED) asking for nPEP.

Methods: Retrospective Monocentric Observational study including all individuals who consecutively accessed our ED asking for nPEP between January 2011 and July 2023. We collected demographic data, information about type of exposure, sexual orientation and additional risky behaviours, eventual previous nPEP courses or HIV testing, and presentation time to ED. Descriptive statistics and nonparametric tests were used to describe study population. Unadjusted and adjusted binary regression analyses were performed to test factors associated to an early (within 24 hours) presentation.

Results: The analysis included 522 persons who accessed ED asking for nPEP: 486 (93.1%) were males, 354 (67.8%) MSM, 97.2% of them declared sexual intercourse as risk exposure. Median presentation time overall between biological exposure and ED presentation was 14.7 hours: 519 (99.4%) individuals accessed to our ED within 72 hours, 391 (74.9%) in the first 24 hours but only 111 (21.3%) within 4 hours (Figure 1). Median waiting time in ED before nPEP start was 1.4 hours. Multivariate binary regression analysis found that Italian nationality (OR 2.04, 95% CI 1.06-3.91, p=0.032), semen/ano-genital direct contact (OR 2.09, 95% CI 1.21-3.59, p=0.008) and previous HIV testing (OR 3.00, 95% CI 1.48-6.07, p=0.002) were significantly associated with presentation within 24 hours after exposure, while sexual intercourse under the effect of alcohol or recreational drugs was associated with late presentation after 24 hours (OR 0.33, 95% CI 0.15-0.73, p=0.006). No significant effect was detected for type of sexual intercourse, sexual orientation, HIV status of source individual, and previous nPEP courses.

Conclusion: The majority of nPEP users accessed the ED within 24 hours after at risk contact, even if they had to wait often more than 1 hour for nPEP prescription. Use of alcohol and recreational drugs (including Chemsex practices) during sexual intercourses represents an important risk factor for HIV acquistion not only in terms of dangerous exposure, but also for delayed nPEP start.

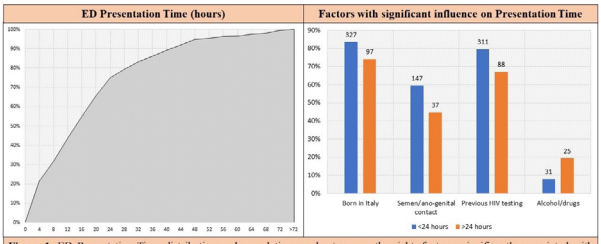

Figure 1. ED Presentation Time distribution and cumulative perchentage; on the right, features significantly associated with Presentation within (N = 391) and after (N =131) 24 hours since risk exposure.

1131 HIV Post-Exposure Prophylaxis Prescription Trends: United States, 2013-2022

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Background: HIV post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) are effective HIV prevention interventions. PEP is the only intervention that can reduce the likelihood of HIV acquisition after exposure, yet U.S. population-level estimates of PEP are lacking. Our objective was to estimate trends in the number of persons prescribed PEP and compare with PrEP trends.

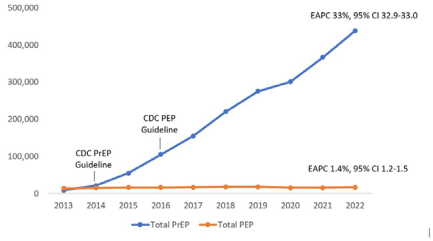
Methods: We analyzed data from IQVIA Real World Data-Longitudinal Prescriptions database, representing 94% of all prescriptions from retail pharmacies in the U.S. We developed an algorithm to identify persons aged ≥16 years prescribed PEP between 2013–2022. We estimated the number of PEP users each year, stratified by sex, age, payer type, region, and prescriber type and specialty. We assessed trends by calculating the estimated annual

percentage change (EAPC) with 95% confidence intervals (CI) and compared with trends in persons prescribed PrEP.

Results: During 2013—2022, the annual number of PEP prescriptions ranged from 13,999—17,996. Among 16,826 PEP users in 2022, 51.2% were women, 60.1% were aged 25-44 years, 35.6% resided in the South, 37.5% had public insurance paying for their PEP, and 43.1% had private insurance. Among 12,042 PEP prescribers in 2022, 60.4% were physicians, and 38.3% were nurse practitioners or physician assistants. Among physicians, 47.2% were primary care doctors, followed by emergency care doctors (31.0%) and infectious diseases doctors (12.0%). Comparing with trends in number of persons prescribed PrEP (EAPC=33.0%, 95% CI 32.9-33.0), we observed modest increases in number of persons prescribed PEP during 2013-2022 (EAPC=1.4%, 95% CI 1.2-1.5, Figure). PEP increases were uneven between age groups. For persons aged 16-24 years, PEP prescriptions increased from 199 in 2013 to 1,373 in 2022 (EAPC=22.1%; 95% CI: 21.0-23.2); for persons aged 25-34 years, it increased from 1,864 in 2013 to 6,205 in 2022 (EAPC=11.8%; 95% CI: 11.4-12.2).

Conclusion: We did not observe a consistent trend in PEP prescriptions, unlike the markedly increasing trend in PrEP over the last decade. PEP may be an underutilized tool for HIV prevention, particularly among the groups mostly experiencing new HIV infections. Interventions such as clinical decision support in electronic health systems, provider and population education, and structural interventions are needed to increase PEP use. Interventions to support PEP prescribing are particularly important in the primary care and emergency department clinical settings.

Figure. HIV PEP and PrEP Prescription Trends in the United States, 2013-2022



1132 Efficacy of Long-Acting Cabotegravir and Rilpivirine for PEP in a Macaque Model of RT SHIV Infection

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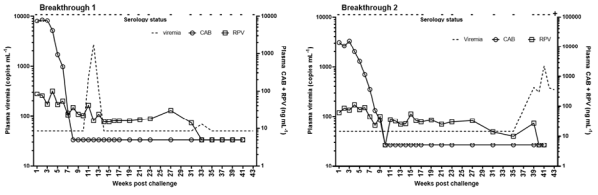
Background: Current recommendations for post-exposure prophylaxis (PEP) for non-occupational HIV exposures include 28 days of daily oral antiretroviral drugs. However, low adherence, and inadequate regimen completion represents an important challenge. We examined whether a single injection of the combination of long-acting cabotegravir and rilpivirine (CAB LA and RPV LA) could be an effective PEP regimen in macaques.

Methods: Human equivalent doses of CAB LA (50 mg/Kg) and RPV-LA (100 mg/Kg) were administered intramuscularly to 6 rhesus macaques 24 hours post rectal exposure to a single high dose of RT SHIV ($10^{3.3}$ $TCID_{50}$). Infection outcome was compared to 7 untreated controls (3 real-time, 4 historical). Blood was collected through 43 weeks post challenge to monitor for plasma CAB and RPV levels and SHIV infection. Plasma CAB and RPV levels were monitored by LC-MS/MS. Poisson regression with robust error variance was applied to estimate PEP efficacy and confidence intervals.

Results: Median concentrations of CAB and RPV in plasma during the first 28 days after injection were within clinically relevant levels (5,860, range= 2,130-15,650 and 64.5, range= 20-127 ng/mL), respectively. All controls became viremic 7 days post challenge with a median plasma viral peak of 5.13 x 10^6 copies/mL. Four of the six treated macaques remained aviremic and seronegative through week 43 post challenge. The remaining 2 animals had detectable SHIV RNA at week 11 (breakthrough 1) and 39 (breakthrough 2) post-exposure. The calculated efficacy of CAB LA/RPV LA was 0.667 (95% CI= -0.0335, 0.893) (p=0.0571). Breakthrough 1 was characterized by transient low-level viremia between weeks 11 to 13 (range 327-2736 SHIV RNA copies/mL), a virus blip at week 33 (68 copies/mL), and absence of seroconversion. Breakthrough 2 had detectable viremia between weeks 39 and 43 (range 309-1033 SHIV RNA copies/mL) when CAB and RPV were low or undetectable in plasma and seroconverted at week 43 (Figure 1).

Conclusion: We observed in our high dose rectal SHIV challenge model that a single dose of CAB LA and RPV LA given 24 hours after virus exposure provided clinical drug exposures for 4 weeks but was partially effective. Late and transient detection of SHIV RNA in breakthrough infections with or without seroconversion is similar to findings in persons failing prophylaxis with CAB LA and highlights diagnostic challenges of this PEP modality. Our results underscore the limitations of single-dose CAB LA and RPV LA use for PEP in humans.



1133 PrEP Following PEP: An Effective HIV Risk-Reduction Strategy

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Background: From January 2021, individuals attending a sexual health service in London, UK who receive HIV post-exposure prophylaxis following sexual exposure (PEPSE) are offered quick-start opt-out PrEP with a 1-month supply to take immediately following completion of PEP, PEP2PrEP, a risk reduction strategy for individuals with ongoing risk of HIV acquisition. We present the uptake of PrEP in GBMSM and transwomen attending our service for PEP and their subsequent PrEP follow-up.

Methods: We performed a case note review of PEPSE recipients at our service from 1st March to 30th April 2022, collecting demographics, characteristics of the PEPSE risk, previous PrEP use and follow-up consultations up to 31st August 2023. Statistical analysis was done using chi-square and Mann-Whitney U tests.

Results: 282 GBMSM and 6 transwomen received PEPSE during March- April 2022. Median age was 29 y (IQR: 25-37 y). Primary PEPSE indication was condomless anal intercourse: receptive (244, 84.7%) and insertive (43; 14.9%) and receptive vaginal intercourse (1; 0.3%). During the encounter, 31 (10.8%) used chems, 63 (21.9%) had sex with more than one individual. 126 (43.8%) PEPSE recipients stated previous PrEP use. Common reasons for not using PrEP were: having no supply (38, 30.2%), on break (30, 23.8%), spontaneous sex (19, 15.1%), incorrect PrEP dosing requiring PEPSE (16, 12.7%), reason not given (23, 18.3%). 212 (73.6%) subsequently started PrEP. Of these, 114 (54.2%) reattended for a subsequent PrEP consultation in the follow-up period. PEPSE users who subsequently started PrEP compared with those who did not were more likely to have used PrEP previously (50.0% vs. 26.3%, p=0.00036) and to have had sex with multiple individuals during their PEPSE exposure (25.0% vs. 13.2%; p=0.036).

Conclusion: Almost half of PEPSE recipients have previously used PrEP. The most common reason for not using PrEP was having no supply. In PEPSE recipients, the subsequent uptake of PrEP is high with a majority reattending for PrEP in the subsequent year. Efforts to increase retention in PrEP care are required for those with ongoing risk of HIV acquisition.

1134 BIC/FTC/TAF as HIV PEP Was Well-Tolerated With High Adherence and No Seroconversions

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Background: Integrase inhibitor-based regimens are the standard of care for HIV post-exposure prophylaxis (PEP), but no such single tablet regimens are recommended in current guidelines. We analyzed tolerability, adherence and HIV seroconversions with bictegravir, emtricitabine and tenofovir alafenamide (B/F/TAF) as HIV PEP in an ongoing clinical trial of text-messaging support versus standard of care for PEP users.

Methods: Adults initiating a standard PEP regimen within the preceding five days for a confirmed or potential sexual exposure to HIV were randomized to either receive short message service (SMS) check-ins using the WelTel platform,

or standard care. All participants underwent baseline HIV testing and were switched from their original PEP regimen (if applicable) to B/F/TAF to complete 28 days. CBC, ALT and creatinine were assessed at week 2; medication adherence at week 4; HIV serology at weeks 6 and 12; and adverse events at all visits.
Results: Of 120 individuals screened for participation in the trial, 119 participants were enrolled and are included in this analysis; all were HIV-negative at baseline. Median (interquartile range) age was 29 (25, 34) years and 22% had previously used PEP. Most (86%) were men who have sex with men. Medication adherence was high; among 101 participants with available data, all took all 28 days of PEP except for two who stopped prematurely after 7 and 8 days respectively. B/F/TAF was well-tolerated, with only 11% experiencing adverse events of grade ≥2 severity; 38% experiencing AEs at least possibly related to study drug (Table), most often gastrointestinal. No HIV seroconversions were observed.
Conclusion: B/F/TAF PEP was associated with high tolerability, high adherence and no HIV seroconversion in this cohort. These data support the use of this single tablet regimen as HIV PEP after sexual exposures.

Table: Adverse events occurring in >3% of participants receiving B/F/TAF PEP

Adverse event	Overall N (% of participants)	Severity grade ≥2 N (% of participants)	Any grade, at least possibly related to study drug N (% of participants)
Diarrhea	11(8%)	4 (3%)	10 (8%)
Dizziness	5 (4%)	0 (0%)	5 (4%)
Fatigue	21(18%)	2 (2%)	21 (18%)
Headache	9 (8%)	0 (0%)	9 (8%)
Insomnia	4 (3%)	0 (0%)	4 (3%)
Lethargy	3 (3%)	0 (0%)	3 (3%)
Nausea	13 (11%)	0 (0%)	13 (11%)

1135 Uptake and Predictors of PEP Uptake in the SEARCH Dynamic Choice HIV Prevention Trials

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Background: Post-exposure prophylaxis (PEP) remains underutilized in sub-Saharan Africa. PEP could respond to user preferences for on-demand biomedical prevention, including for vaginal exposures, and could serve as a gateway to PrEP; data are limited on this strategy.
Methods: We assessed PEP uptake in 3 randomized trials of Dynamic Choice HIV Prevention (DCP) among persons >15 years with current or anticipated HIV risk recruited from Outpatient Departments (OPD), Antenatal Clinics (ANC), and community settings in rural western Kenya and Uganda (SEARCH; NCT04810650). The DCP intervention included structured participant choice of: 1) PrEP or PEP, with option to change over time; 2) service location; 3) HIV self-testing (HIVST) option, together with 24/7 phone access to clinician. Providers were trained on client-centered care, emphasizing support for flexible product choice (PrEP or PEP). In the DCP arm, PEP pill-in-pocket was offered (5 pills with HIVST) for rapid PEP start; participants notified the provider for HIV testing and refill of the remaining PEP supply. In this pre-specified secondary analysis, we conducted a by-arm comparison of self-reported PEP use and describe use patterns across these settings.
Results: From April-July 2021, 1,233 participants (612 DCP; 621 standard of care [SoC]) enrolled (ANC 400, OPD 403, Community 430): 72% were women, 41% aged 15-24 years. Over 18 months of follow-up, 129 courses of PEP were dispensed. In DCP arm: 101 PEP courses among 50 participants; 28 participants used multiple PEP courses; 10 transitioned to PrEP the month after PEP start. In SoC: 28 PEP courses among 20 participants; 8 participants used multiple PEP courses; 2 participants transitioned to PrEP the month after PEP start. Biomedical covered time (% of follow-up using PrEP or PEP) was 51% (4422/8712) in DCP vs. 16% (1424/8994) in SoC; PEP accounted for ~2% of covered time in both arms (101/4422 vs. 28/1424). Overall, DCP significantly increased PEP covered time (% of follow-up time when using PEP): 1.1%(DCP) vs. 0.3%(SoC); difference of 0.8% (95%CI: 0.1-1.15%) p=0.03. Among DCP participants, PEP covered time was highest in the community (2.2%), men (1.8%) and youth (1.1%). There were no discontinuations for drug toxicity or seroconversions among those who used PEP.
Conclusion: Across 3 settings in rural Africa, PEP was feasible to deliver, a desired choice for some individuals, and a gateway to PrEP. Event-driven interventions such as PEP should be included in prevention choice approaches.

1136 CAPRISA 018 Trial: Acceptability of Tenofovir Alafenamide Implants for HIV PrEP in African Women

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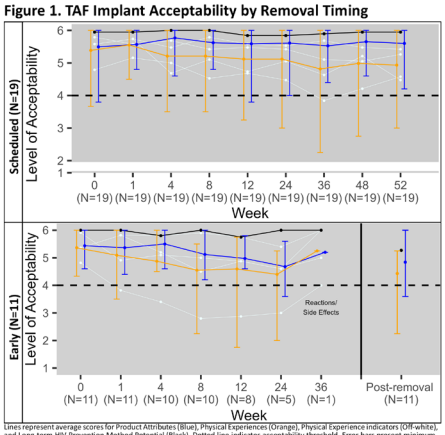
Background: In South Africa, young women carry a disproportionately higher HIV risk. Long-acting HIV pre-exposure prophylaxis (PrEP) methods may better align with women's preferences, behaviors, and lifestyles-potentially improving PrEP uptake, adherence, and persistence. We studied the acceptance of implants for PrEP in women participating in a tenofovir alafenamide (TAF) implant trial.
Methods: CAPRISA 018, a Phase I trial, assessed the safety and efficacy of sub-dermal TAF implants for PrEP. After receiving 1 or 2 TAF (110 mg) or placebo implants (4:1 randomization), participants (N=30) completed longitudinal (0-52 weeks) acceptability assessments on product attributes (implant size, quantity, insertion site, palpability, visibility), physical experiences (insertion procedures, pain, reactions/side effects, scarring), removal procedures, and method likes and dislikes. We averaged scores (range: 1-6, increasing with acceptability), reported minimum temporal means [min-max values] to assess acceptability (scores >4), and performed sub-group analyses by removal timing (scheduled [Week 48] vs. early). For early removals, acceptability was assessed 4 weeks post removal.
Results: Participants were young (median age: 26 years) Black African women. Overall pre-removal product attributes (5.4 [3.6-6.0]) and physical experiences (4.9 [1.7-6.0]) remained acceptable over time (Figure 1). On average, women with scheduled removals had high levels of acceptability for product attributes and physical experiences during the study and 4 weeks after implant removal. Early removals occurred on average 4 months (0-8 months) after implant insertion among 11 (37%) of women. Women with early removals, on average, reported acceptable pre-removal and post-removal product attributes and physical experiences; however, all reported unacceptable levels of side effects at least once during the study (100% in early removals versus 47% in scheduled removals, p=0.004). Both groups reported that implants were acceptable as a potential long-term PrEP method (5.3 [3.0-6.0]), and the most-cited reason for liking the implants was possibility of long-term HIV protection.
Conclusion: Although women in the trial reported high levels of acceptability for implant attributes, physical experiences, and insertion and removal procedures overall, higher than expected early discontinuation rates due to side effects were observed. The implants potential for long-term HIV protection was its most favored attribute for acceptability.

Figure 1. TAF Implant Acceptability by Removal Timing



Lines represent average scores for Product Attributes (Blue), Physical Experiences (Orange), Physical Experience indicators (Off-white), and Long-term HIV Prevention Method Potential (Black). Dotted line indicates acceptability threshold. Error bars present minimum-maximum values. Scheduled removals occurred on Week 48.

1137 Safety and Pharmacokinetics of Ultra-Long-Acting Dolutegravir In-Situ Forming Implant

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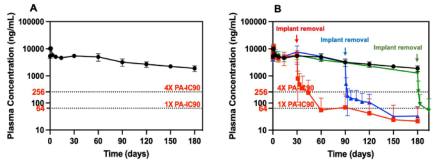
Background: Long-acting injectables (LAIs) for HIV PrEP can increase user acceptability, adherence, and reduce stigma. Current LAIs are not removable

and elicit a long pharmacokinetic (PK) tail. In previous studies, investigational LAI Dolutegravir (DTG) formulations failed to sustain plasma DTG concentrations above the 4× PA-IC_{90} beyond two months. To overcome these limitations, we propose to develop an ultra-long-acting (ULA) biodegradable and removable in-situ forming implant (ISFI) with DTG. Here, we performed long-term safety and PK studies evaluating time-to-completion (ongoing), depot removal at various intervals, PK tail, and drug biodistribution in plasma, tissues, and organs post implant removal.

Methods: ISFIs were comprised of high concentration DTG (350 mg/mL) in a stable suspension. Female BALB/c mice (n=6) were injected subcutaneously (SC) with 50 µL of DTG ISFI formulation. Plasma samples were collected longitudinally to quantify drug concentration and TNF-α and IL-6 levels over ≥180 days. At day 30, 90, and 180 post administration, implants were removed via a small skin incision to quantify residual DTG and determine implant degradation over time. Plasma samples were collected longitudinally post-implant removal to assess the PK tail. Biodistribution of DTG in plasma, organs, and SC tissue was assessed post implant removal.

Results: ULA DTG ISFIs sustained plasma DTG concentrations well above the 4× PA-IC_{90} for ≥180 days (Fig A) and with low plasma TNF-α and IL-6 concentrations. Significant decrease in plasma DTG was achieved within 1 week post implant removal with 17-, 22-, and 24-fold decrease for implants removed at 30, 90, and 180 days respectively; however, complete elimination of DTG was not yet achieved post depot removal (Fig B). Tissue DTG concentrations revealed high DTG accumulation in the proximal SC tissue as a likely explanation of the long PK tail. ISFIs were easily retrievable at 30, 90, and 180 days post-injection with ~69%, ~45%, and ~41% DTG remaining and ~13%, 49%, and 58% decrease in implant mass at 30, 90, and 180 removal respectively.

Conclusion: Here we report a biodegradable, removable, and ULA DTG ISFI and demonstrated safety and plasma PK for ≥180 days and assessed the PK tail. We demonstrated the first ULA injectable of DTG for HIV PrEP that can be removed if needed. This comprehensive study further characterized the PK tail via a full biodistribution, and future directions include safety, PK and efficacy studies in non-human primates.



(A) Plasma concentration of DTG ISFIs over 180 days (last timepoint analyzed; ongoing time-to-completion study). (B) DTG concentration in plasma post implant removal at 30, 90, and 180 days respectively and compared to no implant removal (black line; ongoing time-to-completion study).

1138 RCT of *Lactobacillus crispatus* CTV-05 to Lower HIV Risk in Young South African Women

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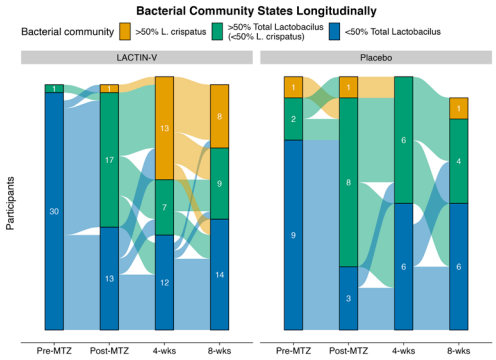
Background: Absence of vaginal lactobacilli and corresponding genital inflammation is associated with adverse reproductive health outcomes, including female HIV acquisition. In women in sub-Saharan Africa, a high prevalence of vaginal dysbiosis may offer an opportunity to develop *Lactobacillus crispatus* biotherapeutics for HIV prevention.

Methods: We conducted a randomized, placebo-controlled, trial of cis-women age 18-23 with Nugent score 4-10 on vaginal Gram stain who completed a course of oral metronidazole (MTZ). Women were randomized (2:1) to use vaginal applicators containing $2X10^9$ CFU of *L. crispatus* CTV-05 (LACTIN-V) or placebo for 4 weeks. Vaginal samples were collected prior to MTZ, at enrollment (0-wks), immediately after study product (4-wks), and 4 weeks later (8-wks). The vaginal microbiota was assessed by 16S rRNA gene sequencing, endocervical immune cells by flow cytometry and vaginal fluid inflammatory markers by Luminex.

Results: 45 black South African women were randomized to LACTIN-V (N=32) and placebo (N=13). At enrollment, immediately after MTZ, 54.8% (LACTIN-V) vs. 66.7% (placebo) presented with *Lactobacillus*-dominant microbiota other than *L. crispatus*, most often *L. iners* (Figure). A *L. crispatus*-dominant microbiome was identified in 40.6% (4-wks) and 25.8% (8-wks) of participants in the LACTIN-V arm compared to 0% and 9%, respectively in the placebo arm (4-wks: p= 0.047; 8-wks: p= 0.096). The proportion of activated HIV target cells (CD3+/CD4+/CD38+/HLA-DR+/CCR5+ T cells) within the total T cell population (CD3+) increased from post-MTZ (0-wks) to 4-wks in the placebo arm (0.38 log_{10} fold change) which was not observed in the LACTIN-V arm (0.03 median log_{10} fold change; p = 0.009). The change in 13 cyto/chemokines between pre-MTZ and 4-wks was not statistically different by arm. Three quarters of participants in both arms "strongly agreed" or "agreed" they would use the product again. Adverse events (AEs) occurred in 77.8% of all participants. All local solicited AEs, most commonly vaginal discharge, were grade 1 with no significant difference by arm.

Conclusion: LACTIN-V after MTZ increased L. crispatus colonization. Women treated with LACTIN-V had fewer activated cervical CD4+ HIV target cells than those in the placebo arm. We did not observe statistically significant differences in vaginal cytokines between arms. The product was safe and highly acceptable (clinicaltrials.gov:NCT0502221).



1139 A Dual Prevention Pill for HIV and Pregnancy Prevention: A Pilot Study Among Young Women in Zimbabwe

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Background: Effective use of oral pre-exposure prophylaxis (PrEP) has been sub-optimal among young women in sub-Saharan Africa at greatest risk of HIV. We hypothesized that a single dual prevention pill (DPP) combining PrEP and an oral contraceptive (OC) would be preferred, acceptable and increase PrEP adherence compared to PrEP alone.

Methods: We enrolled 30 HIV-uninfected, non-pregnant, 16-24-year-old cisgender females currently using OCs in a crossover study in Harare, Zimbabwe, who were randomized (1:1) to the order of using an over-encapsulated DPP and 2 separate pills (PrEP, OC) for 3 28-day cycles each. We assessed if the proportion preferring the DPP vs 2 separate pills was >0.5 (exact binomial test) and the effect of regimen on 4 acceptability domains: use attributes, product attributes, side-effects, impact on sex (Wilcoxon signed-rank tests). We compared adherence by regimen and sequence (generalized estimating equations) via self-report and via tenofovir diphosphate (TFV-DP) levels in dried blood spots indicative of ≥4 doses per week (≥500 fmol/punch at Month 1, 700 fmol/punch at Months 2-6). Population Council Institutional Review Board and 6 ethics committees/regulatory bodies in Zimbabwe approved the protocol.

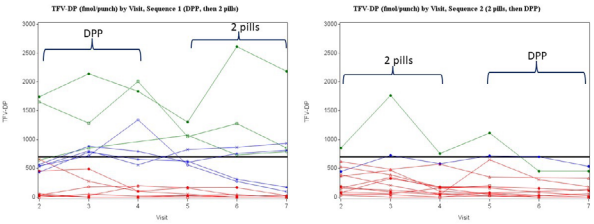
Results: 26/30 women (mean age, 19.4 years) completed the study (Nov 2022-Sep 2023); 4 terminated early. Most were married (47%)/divorced (27%), 97% had completed secondary school, 93% had ≥ 1 child, 84% were somewhat/very worried about getting HIV in the next 3 months, and 93% thought it was somewhat/very important to avoid pregnancy. At study exit, preference for the DPP was 64% vs 36% for 2 separate pills (p=0.16). Most rated both regimens as acceptable, with no differences between regimens in any domain (all p>0.05). Self-reported adherence was high (>96%), yet 17-18% were adherent to the 2 pills and DPP, respectively, based on TFV-DP levels, with mean TFV-DP levels only 384 fmol/punch (2 pills) and 392 fmol/punch (DPP). There was no difference in adherence by regimen or treatment period (all p>0.05). Adherence

was higher overall among participants starting with DPP vs those starting with 2 pills (not significant, Fig 1).

Conclusion: While we did not find differences between the DPP and 2 separate pills for any outcome, this small study used an over-encapsulated pill as a proxy for the co-formulated DPP. A larger study with the actual DPP – a smaller pill – will be a better indicator of the potential impact of the DPP on HIV and pregnancy prevention in this population.

Figure 1: Individual Participant Levels of TFV-DP by Visit, by Randomization Sequence

Green=Always adherent, Blue=Sometimes adherent, Red=Never adherent



1140 Enabling Mobility of Health Workers With Motorcycles to Improve PrEP Uptake Among Key Populations

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Background: In Tanzania HIV prevalence among key populations (KP) including female sex workers (FSW), men who have sex with men (MSM) and people who inject drugs (PWID) is estimated to range from 25% to 36% compared to the 4.7% in the general population. Reaching and engaging KP in HIV prevention and treatment services is challenging in Tanzania due to several challenges such as geographical locations, and limited access to transport. Previously, community-based health workers used public transport or hired vehicles to reach out to KP in remote areas, which hindered the effective provision of HIV prevention and treatment services. Recognizing this challenge Tanzania Health Promotion Support (THPS) collaborated with Pwani Regional and Council Health Management teams (R/CHMT) to enable mobility of community-based health workers with motorcycles to improve Pre-exposure prophylaxis (PrEP) uptake to KP

Methods: In October 2022, THPS procured and allocated 40 motorcycles and drivers to various health facilities (HF) identified to enable mobility of health workers in provision of PrEP services in Pwani region Tanzania. The objective is to bolster the efforts of community-based health workers in accessing KP and offering PrEP services regardless of their location. Targeted areas included mapped community hotspots such as local bars, brothels, truck parking areas and fishing and constructions sites. The initiative ensured that KP could easily access PrEP services where they lived, worked, or socialized

Results: Clients newly initiated on PrEP increased by 100% (1212 to 2428) and clients returning for PrEP refills increased by 154% (674 to 1714) between pre- (January-September 2022) and post- (October 2022-June 2023) implementation periods. Ninety percent of new clients (2185/2428) enrolled through mapped community hotspots, while 10% (243) enrolled in facilities. FSW comprised 97% (2354), PWID 2% (56) and MSM 1% (18) of total new clients. From October 2022 to June 2023, 88% (1510/1714) of PrEP clients refilled through community hotspots, and 12% (204/1714) through health facilities.

Conclusion: Enabling mobility of community-based health workers with motorcycles improved PrEP uptake among KVP particularly those from hard-to-reach areas. Community-based health workers enabled with motorcycles brings PrEP services closer to KP, therefore addressing the gaps on accessibility of PrEP services. THPS will continue to work with R/CHMT to strengthen and expand implementation of motorcycle enabled health workers

1141 Enhancing HIV PrEP Coverage Through Primary Care Initiation: A French Nationwide Study

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Background: In France, until mid-2021, as HIV pre-exposure prophylaxis (PrEP) initiation (PrEPi) was limited to hospitals and sexual health centers, access to PrEP remained mainly limited to socio-economically advantaged MSM living in large urban areas. To improve access to PrEP, PrEPi has then been extended to any practitioner, including primary care (PrC) practitioners. The aim of this study was to describe the deployment and characteristics of the PrC PrEPi in the French health system.

Methods: Using the National Health Data System (SNDS) covering healthcare reimbursements of 99% of French residents, we included all people ≥15 years-old, receiving a PrEPi in a PrC setting from 06/01/21 to 12/31/22. Monthly numbers of PrEPi over the period, characteristics of PrEP initiators and PrEPi modalities (including prescribers profile and assessment of biological tests) and renewals were reported.

Results: Overall 13,500 PrEPi were done in PrC during the study period. The mean number of PrEPi increased from 654/month (2nd semester of 2021) to 783/month (2nd semester of 2022). PrEP initiators were predominantly men (96.3%), mean age 36 years, mostly living in large urban areas (72.0%). A minority (7.5%) were socio-economically disadvantaged. Among PrEPi prescribers, 88.0% were general practitioners, 77.0% had a fully private practice and 44.6% were the patient's family practitioner. Reimbursements for HIV, renal and liver function tests, 60 days before to 30 days after the first PrEP dispensation, were available for 72.5%, 66.8% and 54.7% of PrEPi, respectively. Syphilis, chlamydia or gonorrhea screenings were reimbursed for 64.7% and 59.7% of PrEPi, respectively. In the six months post PrEPi, 70.8% of PrEP initiators had at least one renewal (2.3 renewals on average). Most of them (80.0%) had the PrEP renewal by the PrEPi prescriber, especially when the PrEPi prescriber was the family practitioner (92.5%).

Conclusion: While the number of PrEP initiations in primary care steadily increased over time, the profile of users remains similar to that observed before PrC initiation. The high rate of PrEPi not done by the patient's family practitioner highlights potential barriers of sharing sexual health concerns with his own family practitioner. Tracking of biological tests required at PrEPi could be improved to confirm compliance with national guidelines. Extending PrEP to women and socio-economically disadvantaged people still requires raising awareness among target audiences and practitioners.

1142 Uptake of HIV prevention by Notified Seronegative Partners in HIV-Discordant Couples in Uganda

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Background: Assisted Partner Notification (APN) is an effective HIV epidemic control strategy and is part of the interventions to increase case identification and reduce HIV transmission in Uganda. The focus for APN is un diagnosed contacts of index clients living with HIV. APN facilitates in linkage of sexual partners to HIV prevention (negative contacts in HIV status-discordant relationships) or treatment. However, failure of notified contacts to disclose their negative results to positive partners might expose them to ongoing HIV risk. Our objectives were to assess uptake and factors associated with HIV prevention among notified HIV-negative partners.

Methods: We analyzed cross-sectional data from partners of index clients tested January 2019–December 2022 at Mengo Hospital, Kampala, Uganda. After APN and testing seronegative at the hospital, we determined uptake of HIV retesting; disclosure of seronegative status to current sexual partner; reporting of abstinence, being faithful, condom use, and/or pre-exposure prophylaxis (PrEP); and safe male circumcision (SMC). We used multiple logistic regression (R4.22) to generate adjusted odds ratios and 95% confidence intervals (CIs) of uptake of prevention methods.

Results: Among 3,068 elicited partners of 1,977 index clients, 89% (2,732) were notified; 61% (1,672/2,732) tested HIV-seronegative, 24% (657) positive,

12% (334) were in care, and 2.5% (69) declined testing. Of those testing negative, 93% (1,547) were reached for follow-up after 3-6 months; mean age was 32.1 years; 60% (929/1,547) were male. Only 44% (675) had retested. HIV status disclosure to seropositive partner was 24% (376); 86% (1,330) reported at least one prevention measure [SMC (35%), PrEP (5.8%), abstinence (17%), being faithful (33%), condoms (49%)]. Retesting was associated with age <20 (AOR=3.46; 95%CI 1.56-4.52), disclosure (AOR=8.83; 95%CI 6.54-11.9), and use of a prevention method (AOR=3.31; 95%CI 2.22-4.93). Partners reporting being faithful were 46% less likely to retest (AOR=0.54; 95%CI 0.41-0.70). Those using PrEP were three times more likely to disclose (AOR= 3.31; 95%CI 1.93-5.08). Ten (1.5%) partners seroconverted.

Conclusion: Low uptake of HIV prevention suggests ongoing HIV risk. Low retesting rates, such as among those who reported being faithful as a prevention method, suggest seronegative partners would not receive timely treatment. It is critical for HIV-seronegative partners to be actively followed up for disclosure, behavior change, and HIV prevention methods.

1143 NLPrEP Trial 24-Week Data: Nurse-Led PrEP Superior to Physician-Led PrEP Among Cis Women in Zambia

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Background: There is significant interest in HIV pre-exposure prophylaxis (PrEP) among women in sub-Saharan African countries like Zambia. Oral PrEP uptake with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) may be limited by access to physicians to prescribe PrEP, and concern for kidney and bone mineral density abnormalities. PrEP with tenofovir alafenamide (TAF) and FTC has fewer bone and kidney side effects and thus may require less physician oversight and laboratory monitoring. We designed a 48-week trial to assess outcomes of a nurse-led PrEP service delivery model using TAF/FTC compared to standard-of-care (SOC) physician-led PrEP using TDF/FTC.

Methods: Quasi-experimental (pre-post) design study comparing TDF/FTC to TAF/FTC for oral PrEP among cis-gender women in six Ministry of Health facilities in Lusaka, Zambia. Inclusion criteria included HIV-negative, assigned female at birth, ≥18 years of age, and eligible for PrEP per national guidelines. The control group was enrolled first and received SOC with physician-led oral TDF/FTC. The intervention group was enrolled thereafter and received nurse-led oral TAF/FTC. Study outcomes included uptake of PrEP, PrEP refill rates at 4 weeks, TFV metabolite concentrations at 24 and 48 weeks, PrEP persistence at 48 weeks, and HIV seroconversion.

Results: We screened 1,005 cis-gender women, of whom 900 (89.6%) were eligible for PrEP. 432 were enrolled in the SOC TDF/FTC group, and 450 were enrolled in the interventional TAF/FTC arm. PrEP refill rates at 1 month were 80% (347/432) in the TDF arm vs. 91.6% (412/450) in the TAF arm (p<0.001). Retention in PrEP services at 24 weeks were 35% (150/432) for the TDF arm vs. 77% (348/450) for the TAF arm (p<0.001). Participants in the intervention arm were 6 times more likely to continue PrEP at 24 weeks (odds ratio (OR)=6.36, p<0.001). At 24 weeks, TFV metabolite concentrations were ascertained in 106 (71%) of 150 individuals in the TDF arm compared to 280 (80.5%) of 348 in the TAF arm. HIV seroconversion rates at 24 weeks were identical in both study arms, with 1 (0.2%) of 432 participants in the SOC arm vs. 1 (0.2%) of 450 in the intervention arm.

Conclusion: In this non-randomized pre/post-trial, nurse-led PrEP with TAF/FTC showed significant advantages, including higher PrEP refill rates and improved PrEP persistence at 24 weeks compared to the physician-led SOC with TDF/FTC. HIV

1144 No Significant Interactions From Hormone Therapy on F/TAF-Based PrEP in Trans Women: iFACT3 Study

Akarin Hiransuthikul[1], **Narukjaporn Thammajaruk**[2], Stephen Kerr[1], Rena Janamnuaysook[2], Siriporn Nonenoy[2], Piranun Hongchookiat[2], Rapee Trichavaroj[2], Yardpiroon Tawon[3], Jakkrapatara Boonruang[2], Nipat Teeratakulpisarn[2], Tim R. Cressey[3], Peter L. Anderson[4], Nittaya Phanuphak[2], for the iFACT[3] Study Team

[1]Chulalongkorn University, Bangkok, Thailand, [2]Institute of HIV Research and Innovation (IHRI), Bangkok, Thailand, [3]Chiang Mai University, Chiang Mai, Thailand, [4]University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Background: We previously observed comparable plasma and urine levels of tenofovir (TFV) and emtricitabine (FTC), as well as intracellular tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) concentrations in peripheral blood mononuclear cells (PBMCs), when F/TAF-based oral daily PrEP was administered with and without feminizing hormone therapy (FHT) in trans women in Thailand. We assessed the potential impact of FHT on antiretroviral drug concentrations in the rectal compartment of trans women receiving oral daily F/TAF-based PrEP.

Methods: iFACT3 was a pharmacokinetic and safety study assessing the potential drug-drug interactions between FHT and oral daily F/TAF-based PrEP among trans women Thailand. Between January and February 2022, 20 trans women who had not undergone orchiectomy and had not received injectable FHT within the last 3 months were enrolled. Oral FHT (estradiol valerate 2 mg and cyproterone acetate 25 mg) was prescribed to participants at baseline until week 9, while oral daily PrEP (FTC 200 mg/TAF 25 mg) was initiated at week 3 until week 12. PK sampling was performed at week 3 (FHT without PrEP) and 9 (FHT with PrEP) for estradiol; and weeks 9 (PrEP with FHT) and 12 (PrEP without FHT) for PrEP drug parameters. Plasma, urine, and PBMCs samples were collected from all participants; and rectal tissue samples in subset.

Results: Ten participants who underwent rectal tissue sampling were included in this analysis. Median age and body mass index were 28.5 (IQR: 24-32) years and 21.2 (IQR: 19.9-21.9) kg/m², respectively. Median TFV-DP and FTC-TP concentrations in rectal tissue between weeks 9 and 12 were not statistically significant (TFV-DP, 37.6 [IQR: 21.4-45.8] vs 27.4 [IQR: 21.4-56.3] fmol/mg, p=0.72; and FTC-TP, 14.5 [12.4-17.0] vs 11.6 [8.0-14.5] fmol/mg, p=0.20). All participants had quantifiable TFV-DP and FTC-TP concentrations at both visits.

Conclusion: Intracellular TFV-DP and FTC-TP concentrations in rectal tissue were comparable when F/TAF-based PrEP was administered with and without FHT. These findings align with our previously data in the plasma, urine, and PBMCs compartments, indicating no clinically significant drug-drug interactions from FHT towards F/TAF-based oral daily PrEP are anticipated.

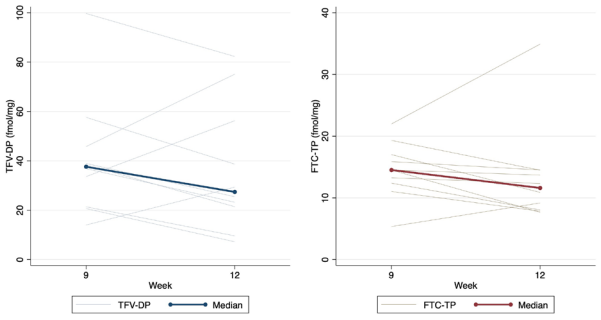

Figure. Median TFV-DP and FTC-TP concentrations at week 9 (with FHT) and week 12 (without FHT) in rectal tissue

1145 No Significant Interactions From Hormone Therapy Toward F/TDF-Based PrEP in Trans Men: iMACT Study

Akarin Hiransuthikul[1], Narukjaporn Thammajaruk[2], Stephen Kerr[1], Rena Janamnuaysook[2], Siriporn Nonenoy[2], Piranun Hongchookiat[2], Rapee Trichavaroj[2], Yardpiroon Tawon[3], Jakkrapatara Boonruang[2], Nipat Teeratakulpisarn[2], Tim R. Cressey[3], Peter L. Anderson[4], Nittaya Phanuphak[2], for the iMACT Study Team

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Background: Potential drug-drug interactions between masculinizing hormone (MHT) and oral PrEP in trans men is not well understood. We previously observed that plasma total testosterone concentrations were comparable when oral daily PrEP was administered with and without MHT.

Herein, we report the impact of MHT on the PK parameters of F/TDF in trans men using oral daily PrEP.
Methods: iMACT was a PK study evaluating the potential drug-drug interactions (DDI) between MHT and oral PrEP among trans men in Thailand. Trans men who had not undergone oophorectomy were enrolled between May and October 2022. MHT (testosterone enanthate 200 mg intramuscular) was administered at baseline and every 2 weeks until week 12, while oral daily F/TDF-based PrEP (200/300 mg) was initiated at week 6 and prescribed until the end of study at week 16. PK sampling was conducted at week 12 (PrEP with MHT) and 16 (PrEP without MHT). Plasma FTC and tenofovir (TFV); and intracellular TFV-diphosphate (TFV-DP) and FTC triphosphate (FTC-TP) concentrations in peripheral blood mononuclear cells (PBMCs), rectal, and cervical tissues were assessed.
Results: 19/20 participants completed the PK visits and were included in this analysis. Median (IQR) age and body mass index were 34 (28-39) years and 22.1 (21.3-24.7) kg/m^2, respectively. The geometric mean ratios (GMRs) (90%CI) of area under the concentration-time curve from 0 to 24 hours (AUC0-24) and maximum concentration (C_{max}) at week 12 and 16 (reference) were as follows: TFV, 1.03 (0.96-1.11, p=0.55) and 1.17 (1.03-1.32, p=0.08); and FTC, 1.05 (1.00-1.09, p=0.12) and 1.09 (1.00-1.18, p=0.17). Median pre-dose TFV-DP and FTC-TP concentrations were not significantly different between week 12 and 16 in PBMCs (C24 TFV-DP, 83.6 [72.0-102.3] vs 81.3 [36.1-100.8] fmol/10^6 cells, p=0.19; and C24 FTC-TP, 3433.5 [2692.9-4635.5] vs 4008.6 [2608.3-5025.2] fmol/10^6 cells, p=0.47), rectal tissue (TFV-DP, 211.7 [82.4-517.7] vs 61 [33.1-388.7] fmol/mg, p=0.65; and FTC-TP, 8.33 [4.9-11.9] vs 5.23 [4.4-7.2], fmol/mg, p=0.11), and cervical tissue (TDF-DP, 8.7 [4.0-12.4] vs 5.9 [2.8-9.1] fmol/mg, p=0.51; and FTC-TP, 30.3 [5.1-143.0] vs 34.0 [29.0-153.8] fmol/mg, p=0.28).
Conclusion: Plasma levels of TFV and FTC, and intracellular concentrations of TFV-DP and FTC-TP in PBMCs, rectal and cervical tissue, were comparable when F/TDF-based PrEP was administered with and without MHT, suggesting no clinically significant DDI from MHT towards F/TDF-based PrEP.
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1146 Potential Drug Interactions From Hormone Therapy Toward F/TAF-Based PrEP in Trans Men: iMACT Study

Akarin Hiransuthikul[1], Narukjaporn Thammajaruk[2], Stephen Kerr[1], Rena Janamnuaysook[2], Siriporn Nonenoy[2], Piranun Hongchookiat[2], Rapee Trichavaroj[2], Yardpiroon Tawon[3], Jakkrapatara Boonruang[2], Nipat Teeratakulpisarn[2], Tim R. Cressey[3], Peter L. Anderson[4], Nittaya Phanuphak[2], for the iMACT Study Team
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Background: We previously reported that plasma total testosterone concentrations were comparable in trans men receiving oral daily PrEP with masculinizing hormone therapy (MHT). Herein, we report the impact of MHT on the PK parameters of oral daily F/TAF-based PrEP.
Methods: iMACT was a PK study evaluating the potential drug-drug interactions between MHT and oral daily PrEP among trans men Thailand. Trans men who had not undergone oophorectomy were enrolled between May and October 2022. MHT, testosterone enanthate 200 mg intramuscular, was administered at baseline and every 2 weeks until week 12, while oral daily F/TAF-based PrEP (200/25 mg) was prescribed from week 6 until the end of study at week 16. PK sampling was performed at 12 (PrEP with MHT) and 16 (PrEP without MHT) to assess plasma FTC, TAF, and tenofovir (TFV); and intracellular TFV-diphosphate (TFV-DP) and FTC triphosphate (FTC-TP) concentrations in peripheral blood mononuclear cells (PBMCs), rectal, and cervical tissues.
Results: Among 20 participants, median (interquartile range [IQR]) age and body mass index were 27.5 (22.5-33) years and 23.8 (20.5-25.2) kg/m^2, respectively. The geometric mean ratios (GMRs) (90%CI) of area under the concentration-time curve from 0 to 24 hours (AUC_{0-24}) and maximum concentration (C_{max}) at week 12 and 16 (reference) were: TAF, 0.99 (0.80-1.21, p=0.93) and 1.00 (0.69-1.44, p=0.99); TFV, 1.03 (0.94-1.14, p=0.63) and 0.97 (0.84-1.43, p=0.64); and FTC, 1.02 (0.99-1.05, p=0.48) and 0.97 (0.85-1.12, p=0.80). There were no statistically significant differences in median TFV-DP and FTC-TP concentrations in PBMCs (C24 TFV-DP, 564.2 [IQR: 280.7-927.4] vs 631.9 [IQR: 347.1-727] fmol/10^6 cells, p=0.77; and C24 FTC-TP, 3341.2 [IQR: 2522.7-5352.9] vs 3888.3 [IQR: 2096.9-5592.5] fmol/10^6 cells, p=0.60) and rectal tissue (TFV-DP, 53.4 [30.3-185.4] vs 65.3 [32.8-92.3] fmol/mg, p=0.51; and FTC-TP, 7.6 [6.4-14.7] vs 7.7 [5.6-11.1] fmol/mg, p=0.51) between the two visits. However, both TFV-DP and FTC-TP concentrations in cervical tissue were significantly lower at week 12 than 16 (TFV-DP, 12.90 [6.8-14.6] vs 20.6 [7.5-53.4] fmol/mg, p=0.04; and FTC-TP, 67.1 [27.2-77.2] vs 120.4 [66.0-245.8] fmol/mg, p=0.02).
Conclusion: Plasma TAF, TFV, and FTC; and intracellular TFV-DP and FTC-TP levels in PBMCs and rectal tissue were comparable when F/TAF-based PrEP was co-administered with MHT. However, TFV-DP and FTC-TP concentrations trended significantly lower in cervical tissue.
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1147 One-Year Declines in Bone Mineral Density Among Young Women in Uganda Using TDF-Based PrEP and DMPA

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Background: Injectable depot medroxyprogesterone acetate (DMPA) is the most common contraceptive choice among young women in Uganda and nearby countries, where HIV burden is also high and HIV PrEP may be offered. DMPA and TDF-based PrEP have been associated with reductions in bone mineral density (BMD) when used consistently over multiple years. For young women who have not yet reached peak bone mass and choose to use DMPA, it is unknown whether concurrent PrEP use exacerbates declines in BMD.
Methods: We conducted a 2-year prospective observational study with women ages 16-25 years in Kampala, Uganda, who desired prevention for pregnancy and HIV. Women were provided either condoms or injectable DMPA for contraception and either condoms or FTC/TDF as oral PrEP for HIV prevention, according to their choices. Annual dual x-ray absorptiometry (DXA) scans were performed to measure BMD. We used tenofovir-diphosphate (TFV-DP) quantification in dried blood spots and delivery of DMPA injections to determine exposure to each agent. Linear regression models estimated the difference in % BMD change from baseline to month 12 for women using oral PrEP and DMPA versus women using either agent individually or neither agent.
Results: Of 499 enrolled women with median age 20 years (IQR 18-21) and normal baseline distribution of BMD z-scores, discontinuation and re-starting of contraceptive and PrEP use was common during follow-up. Women using neither agent (n=39) experienced BMD growth of 2.01% at lumbar spine, 1.22% at hip, 0.10% at femoral neck. Women with consistent use of both agents during 1 year (n=22) experienced an average BMD loss of 1.04% in the lumbar spine and hip and 1.77% in femoral neck. These losses were statistically different relative to women who used neither agent: difference in % BMD change of -3.05% at the lumbar spine (95% CI -4.77%, -1.33%, p=0.001), -2.26% in total hip (95% CI -3.38%, -0.69%, p=0.006), and approached significance at the femoral neck (-1.87%, -3.84%, 0.11%, p=0.067). When examining exposure to each agent independent of the other (Table), we observed some significant declines but in smaller magnitude.
Conclusion: Despite limited sample size, we observed a trend for women with concurrent DMPA and PrEP use to have 1-3% lower BMD than unexposed women after 12 months. Given participant ages and exposure time, this difference may be clinically significant and further work is need to quantify the impact of longer concurrent exposure to TDF-based PrEP and DMPA.

Table. Estimated difference in the percentage change in bone mineral density after 12 months of exposure to PrEP, DMPA, or both relative to exposure to neither product in young women in Uganda

	The estimated difference in % bone mineral density (BMD) change from baseline to 12 months (95% CI), p-value		
	Lumbar spine BMD	Total hip BMD	Neck of femur BMD
Any use of DMPA and PrEP (n=22) vs. neither (n=39)	-3.05% (-4.77%, -1.33%) p=0.001	-2.26% (-3.38%, -0.69%) p=0.006	-1.87% (-3.84%, 0.11%) p=0.067
Consistent DMPA (n=120) vs. no DMPA (n=166), irrespective of PrEP use	-1.55% (-2.40%, -0.69%) p<0.001	-0.64% (-1.51%, 0.23%) p=0.152	-0.33% (-1.38%, 0.72%) p=0.537
Consistent PrEP (n=16) vs. no PrEP (n=48), irrespective of DMPA use	-2.18% (-4.27%, -0.10%) p=0.041	-2.78% (-4.86%, -0.70%) p=0.009	-1.76% (-4.28%, 0.77%) p=0.174

1148 Objective Assessment of Doxycycline PEP Use Among Cisgender Women in Kenya

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Background: Doxycycline postexposure prophylaxis taken following a condomless sexual exposure reduces incident bacterial STIs among men who have sex with men but not among cisgender women in initial trials. Adherence is a key component of effective biomedical interventions, and some initial trials of HIV PrEP among cisgender women reported null results due to low adherence, especially among those under 24 years old, despite having increased risk of HIV acquisition. Lack of efficacy reported in the dPEP Kenya Study were likely due to low use of doxycycline; factors associated with use have not yet been reported.

Methods: We conducted an analysis of doxycycline use among all follow-up visits of a randomly selected subset (n=50; 200 person-visits) of participants assigned to doxycycline PEP (doxycycline hyclate 200mg taken within 72 hours of sex) within an open-label randomized trial among 449 women aged 18-30 years in Kisumu, Kenya. Participants returned quarterly over one year for STI testing and behavioral surveys; and provided hair samples for objective detection of doxycycline. The 1cm hair segment from the scalp, representing exposure over approximately the preceding month, was tested for doxycycline detectability (>0.020 ng/mg) using liquid chromatography-tandem mass spectrometry. Baseline and time-varying covariates potentially associated with doxycycline detection were assessed using modified Poisson regression with robust standard errors and generalized estimation equations.

Results: Doxycycline was detected in 29.0% (58/200) of hair samples, 32.6% (58/178) when censoring pregnancy time off doxycycline. Age of 24 years or older, an independent income source, more than one partner, and no primary sex partner were all associated with detection of doxycycline. After adjustment, older age and not having a primary partner both remain significantly associated with exposure. Common risk factors for STI exposure, e.g., higher frequency of sex, transactional sex, or prior STI, were not associated with detection of doxycycline. Participants reporting concern about getting an STI 34.4% (22/64) or concern that primary partner had other partners 29.1% (23/79) did not exhibit an increase in doxycycline detection.

Conclusion: Among young cisgender women taking HIV PrEP with a high prevalence and incidence of STIs, the use of doxycycline for STI prevention was overall low. Detection of doxycycline using objective measures was associated with older age and not having a primary sex partner.

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1149 Doxycycline Postexposure Prophylaxis to Prevent Trichomonas vaginalis Among Cisgender Women

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Background: Trichomonas vaginalis, the most prevalent curable sexually transmitted infection (STI), disproportionately affects cisgender women, leading to reproductive complications and increased HIV acquisition risk. In-vitro studies suggest doxycycline as a potential treatment; however, no study has explored the ability of doxycycline to prevent T. vaginalis infection.

Methods: We conducted an open-label randomized trial among 449 women (18-30 years) taking oral HIV preexposure prophylaxis (PrEP) in Kisumu, Kenya. Participants were randomized to doxycycline postexposure prophylaxis (dPEP), 200mg within 72 hours of condomless sex, or standard of care (SOC), quarterly STI screening and treatment. All participants were followed for 12 months with quarterly visits for STI testing, including T. vaginalis testing (Cepheid GeneXpert) and data collection on various health and behavioral parameters. The trial had over 90% power to detect a 50% reduction in incident T. vaginalis infections. An intention-to-treat analysis utilizing generalized estimating equations was performed.

Results: Baseline characteristics were similar in the dPEP (n=224) and SOC groups (n=225). Overall, participants had a median age of 24 years, reported a median of 2 sexual partners, and 36.7% engaged in transactional sex. Retention in our study was high at 97% of expected scheduled visits. There were 56 incident T. vaginalis infections: 27 in the dPEP group and 29 in the SOC group, contributed by 46 participants. There was no significant decrease in T. vaginalis incidence when comparing the dPEP group to the SOC group (RR: 0.96, 95% CI: 0.54-1.73, p=0.9). In an analysis censoring participants upon pregnancy (n=80), there was no notable decrease in incident T. vaginalis infection (RR: 1.07, 95% CI: 0.58-1.97). Subgroup analyses by age groups, hormonal contraceptive use, transactional sex, and STI detected at baseline revealed similar findings. In a subset of 50 participants assigned to dPEP, doxycycline was found in all quarterly hair samples for only 29% of participants.

Conclusion: Randomization to the doxycycline PEP group was not associated with a decreased incidence of T. vaginalis infections among cisgender women taking oral PrEP in Kenya. Low use of doxycycline may have contributed to this null result, highlighting the need to explore its role in preventing T. vaginalis in future research.

Table 1. Incident *T. vaginalis* by Study quarter

Characteristic	Standard of Care	Doxycycline PEP	TOTAL
Number of participants enrolled	225	224	449
Participants with incident *T. vaginalis* in 1st quarter	6/220(2.7%)	8/217(3.7%)	14/437(3.2%)
Participants with incident *T. vaginalis* in 2nd quarter	2/220(0.9%)	7/212(3.3)	9/432(2.1%)
Participants with incident *T. vaginalis* in 3rd quarter	13/221(5.9%)	6/208(2.9%)	19/429(4.4%)
Participants with incident *T. vaginalis* in 4th quarter	8/222(3.6%)	6/212(2.8%)	14/434(3.2%)
Number of unique participants ever experiencing an incident *T. vaginalis*	22	24	46
Total, all quarters	29/883(3.3%)	27/849(3.2%)	56/1732(3.2%)

1150 Bacterial STI Trends Associated With the October 2022 Doxy-Prophylaxis Recommendation, San Francisco

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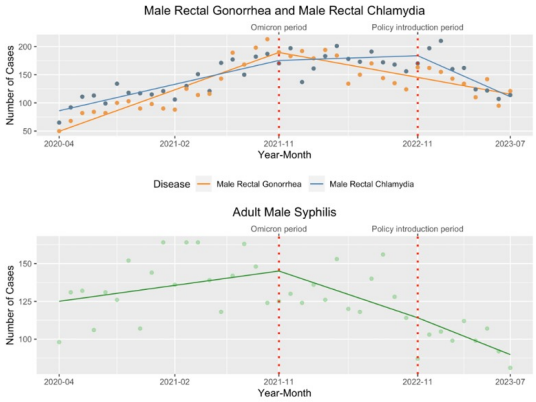
Background: Sexually transmitted infections (STIs) have been on the rise in the United States over the past decade and disproportionately impact men who have sex with men and transgender women. The San Francisco Department of Public Health (SFDPH) issued guidance in October 2022 recommending clinicians to prescribe doxy-prophylaxis as an STI prevention strategy to cis men and trans women who report condomless sex with a cis male or trans female partner and have had a bacterial STI in the past year. We assessed the trends of male rectal chlamydia, male rectal gonorrhea, and adult male syphilis cases to explore the association between the doxy-prophylaxis policy and bacterial STI rates among males in San Francisco.

Methods: We reviewed publicly available monthly STI reports on male rectal chlamydia, male rectal gonorrhea, and adult male syphilis between April 2020 and July 2023. The mean difference of the number of monthly STI cases from 12 months before vs. 8 months after the policy and 95% confidence intervals were calculated. We conducted a segmented linear regression analysis of the trends for each STI. To account for temporal trends related to COVID-19, we included two breakpoints, November 2021 (period of Omicron) and November 2022 (period of policy introduction). We compared the slopes of the fitted regression lines before and after. Two-sided P<0.05 was considered statistically significant. All statistics were performed in R version 4.3.1.

Results: The mean monthly difference before vs. after the doxy-prophylaxis policy for male rectal chlamydia cases was a decrease of 24 cases per month (95% CI: -2 to 51), the difference for male rectal gonorrhea was a decrease of 32 cases per month (95% CI: 9 to 55), and the difference for adult male syphilis was a decrease of 31 cases per month (95% CI: 20 to 42). Before the policy recommendation, male rectal chlamydia cases increased by 0.7 per month (95% CI: -1.2 to 2.6) and after decreased by 9.1 per month (95% CI: -13 to -5.3) (p<0.001). Male rectal gonorrhea cases decreased by 3.7 per month before the policy and decreased by 3.7 cases per month after (p=0.994). Adult male syphilis cases decreased by 2.6 cases per month before the policy and decreased by 3.0 per month after (p=0.843).

Conclusion: The SFDPH doxy-prophylaxis recommendation was associated with a significant decrease in male rectal chlamydia and continued decline in male rectal gonorrhea and syphilis. Given the ecologic nature of the study, further confirmation is needed.

Figure. The number of cases of male rectal gonorrhea, male rectal chlamydia, and adult male syphilis per month before and after the doxy-prophylaxis policy recommendation



1151 Doxy-PEP Effectiveness in Men Who Have Sex With Men (MSM) and Transgender Women (TGW) on HIV PrEP

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Background: Doxycycline post-exposure prophylaxis (doxy-PEP) reduced the risk of chlamydia (CT), gonorrhea (GC) and early syphilis (ES) in MSM and TGW in randomized trials. Little is known about doxy-PEP effectiveness on STI positivity outside of clinical trials.
Methods: Starting 11/3/22, doxy-PEP was offered to patients receiving PrEP at San Francisco City Clinic who were eligible according to citywide guidelines. We assessed visit-level STI positivity at all visits among MSM and TGW PrEP patients who had at least one clinic visit pre (11/3/21-11/2/22) and post (11/3/22-11/2/23) guideline release. STI positivity was defined for GC and CT as the proportion of visits with a GC or CT test with at least one positive result, and for ES as the proportion of visits with a syphilis test that identified a new ES case. For those who ever initiated (i.e., were prescribed or self-reported use of) doxy-PEP (users), we compared STI positivity at visits pre and post doxy-PEP initiation. For those who did not initiate doxy-PEP (non-users), we compared STI positivity at visits pre and post 11/3/22. We compared the reduction in positivity for users vs. non-users using a generalized estimating equation model with robust variance to account for repeated measures. All data were routinely collected during clinic visits.
Results: 506 patients had visits in both periods: 367 users and 139 non-users. Positivity decreased for CT (RR 0.10, 95% CI 0.05–0.21) significantly in users but not in non-users (RR 0.73, 95% CI 0.44–1.21) (Table); the decrease in positivity was significantly greater among users (p<.0001). ES positivity decreased significantly (RR 0.44, 95% CI 0.21–0.92) in users but not non-users (RR 0.68, 95% CI 0.20–2.30) (Table); these decreases were not significantly different (p=0.56). GC positivity decreased non-significantly for both groups (Table).
Conclusion: Doxy-PEP significantly reduced positivity for CT and early syphilis among MSM and TGW receiving PrEP at an STI clinic. The difference was significantly greater than the reduction in CT seen in doxy-PEP non-users. There was no significant reduction in GC in doxy-PEP users or non-users. The reasons for reduction in CT positivity and new early syphilis cases in non-users is unclear and warrants further investigation.

Table: Chlamydia, Gonorrhea, and Early Syphilis Case Positivity by Doxy-PEP Initiation and Pre (11/3/21-11/2/22) and Post (11/3/22-10/30/23) Time Period, San Francisco City Clinic

STI	Doxy-PEP Group and Exposure	# patients	Positivity: + tests/visits (%)	% decrease in positivity	Relative risk (95% CI)
Chlamydia	Ever doxy-PEP, pre-initiation	366	164/1520 (10.8)	90%	**0.10 (0.05–0.21)**
	Ever doxy-PEP, post-initiation	293	8/708 (1.1)		
Chlamydia	Never doxy-PEP, pre	135	26/320 (8.1)	27%	0.73 (0.44–1.21)
	Never doxy-PEP, post	133	16/271 (5.9)		
Gonorrhea	Ever doxy-PEP, pre-initiation	366	170/1518 (11.2)	23%	0.77 (0.58–1.02)
	Ever doxy-PEP, post-initiation	293	61/710 (8.6)		
Gonorrhea	Never doxy-PEP, pre	135	28/321 (8.7)	32%	0.68 (0.37–1.23)
	Never doxy-PEP, post	133	16/271 (5.9)		
Early Syphilis	Ever doxy-PEP, pre-initiation	366	40/1427 (2.8)	56%	**0.44 (0.21–0.92)**
	Ever doxy-PEP, post-initiation	289	8/648 (1.2)		
Early Syphilis	Never doxy-PEP, pre	135	7/298 (2.4)	32%	0.68 (0.20–2.30)
	Never doxy-PEP, post	134	4/252 (1.6)		

1152 Early Adopters: Implementation of Doxycycline Postexposure Prophylaxis in a Boston Health Center

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Background: The use of 200 mg of doxycycline within 72 hours after condomless sex ("doxyPEP") has been shown to decrease the incidence of bacterial sexually transmitted infections (bSTI) in 2 randomized trials that enrolled cisgender men who have sex with men (MSM) and transgender women. However, limited data are available to inform the implementation of this novel STI prevention intervention in primary care settings. This report describes the doxyPEP roll-out in a Boston health center that specializes in primary care for sexual and gender minorities.
Methods: Data from the clinic's electronic medical records were abstracted. Among all patients screened for a bSTI in 2023, bivariate logistic regression was used to compare characteristics of those receiving doxyPEP and those not receiving doxyPEP. DoxyPEP uptake (proportion receiving doxyPEP in 2023) among those with an active PrEP prescription in 2022-2023, PLHIV, and those tested for, and those diagnosed with, a bSTI in 2022 were also calculated.
Results: Between January 26 and September 6, 2023, 1120 patients received a doxyPEP prescription. By March, monthly doxyPEP starts exceeded 100, with >250 patients initiating doxyPEP in June, 2023. Most doxyPEP patients were White (73.3%), non-Latinx (81.7%), and cisgender MSM (92.2%), with a mean age of 39.1 years. Among all patients screened for a bSTI in 2023 (N=4976), those receiving doxyPEP were more likely to be PrEP users (73.8% vs. 39.9%, odds ratio [OR]=4.25, 95%CI=3.67-4.93), have private insurance (85.4% vs. 71.3%, OR=2.37 [1.96-2.81]), have been diagnosed with a bSTI in 2022 (31.3% vs. 15.0%, OR=1.67 [1.42-1.98]), and less likely to be people living with HIV (PLHIV; 8.6% vs. 18.1%, OR=0.42 [0.34-0.53]) than those who did not receive doxyPEP. DoxyPEP users did not differ from non-users by age, race or ethnicity. DoxyPEP uptake was 24.1% (827/3427) among patients with an active PrEP prescription, 4.8% (96/2012) among PLHIV, 13.7% (900/6568) among those screened for a bSTI in 2022 and 24.7% (350/1416) among those diagnosed with a bSTI in 2022.
Conclusion: Over 1,000 patients initiated doxyPEP in less than 6 months at a Boston health center. PrEP users were more likely to initiate doxyPEP than PLHIV, but most patients recently diagnosed with a bSTI had not received doxyPEP. The increased uptake among patients with private insurance compared to those with public insurance highlights the need for programs to facilitate doxyPEP access in an equitable manner.

1153 National Survey on the Use of Antibiotics as Sexually Transmitted Infection Prophylaxis in the US

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Background: Doxycycline postexposure prophylaxis (doxyPEP) is effective for preventing bacterial sexually transmitted infections (STIs) among people assigned male sex at birth. However, little is known about real-world use of antibiotics as STI prophylaxis, including prevalence and patterns of use, reasons for use, and potential user concerns.
Methods: We conducted a national online survey in September 2023, with participants recruited via sexual networking apps used mainly by gay and bisexual men (GBM). Survey domains included sociodemographics, use of antibiotics as STI prophylaxis (including but not limited to doxyPEP), HIV/STI

diagnosis history, HIV PrEP use, and sexual behavior. We used chi-square tests to compare characteristics of STI prophylaxis users and non-users.

Results: As of 27 September 2023, 649 respondents in 50 states, DC, and Puerto Rico had completed the survey. Most (89%) were GBM, and 42% were HIV PrEP users, 19% living with HIV, 59% White, 23% Black, and 13% Latinx. Overall, 95% were interested in using STI prophylaxis; 49% had previously heard of it, and 22% and 16% had used it ever or in the past 12m, respectively. Of the 143 respondents with any STI prophylaxis use, 45% had used it before sex and 72% after sex; of those who used it after sex, 45% had taken it within 24h. Those with STI prophylaxis use in the past 12m used it for some (47%), most (32%), or all (21%) sex acts with casual partners. Medications used as STI prophylaxis included doxycycline (78%), amoxicillin (19%), and azithromycin (16%), and medication sources included leftover from treatment of a past STI (11%) or other condition (20%) and bought online without a prescription (12%). Compared to non-users, STI prophylaxis users were younger (mean age 39 vs 43, P=0.007) and a higher proportion were HIV PrEP users (56% vs 38%, P<0.001), reported >10 partners (61% vs 31%, P<0.001) or group sex (74% vs 49%, P<0.001) in the past 12m, and ever had an STI (75% vs 47%, P<0.001). Reasons for interest/use and concerns about use varied (Figure). For doxyPEP specifically, 36% had heard of it and 13% had used it in the past 12m, of whom 24% had used a dosage other than the 200mg dose shown to be effective.

Conclusion: Interest in STI prophylaxis is nearly universal and use is already common among GBM engaged in online networks. Some are using medications and dosing that are untested as STI prophylaxis. Findings can inform doxyPEP implementation strategies, including education on effective dosing and monitoring of actual use.

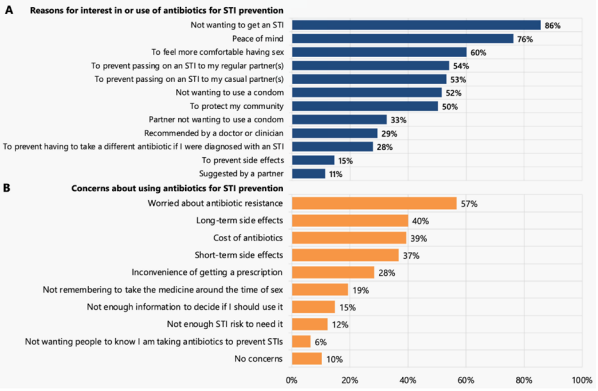

Figure: Proportion of survey respondents reporting specific reasons for interest in or use of antibiotics (panel A) and potential concerns about using antibiotics (panel B) for STI prevention.

1154 Impact of Doxycycline as STI PEP on the Gut Microbiome and Antimicrobial Resistance Gene Expression

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Background: Doxycycline post-exposure prophylaxis (doxy-PEP) reduces bacterial sexually transmitted infections in men who have sex with men (MSM) and transwomen (TW) living with HIV or on HIV pre-exposure prophylaxis (PrEP). The impact on the gut bacterial microbiome and its associated antimicrobial resistance genes (ARGs) is unknown.

Methods: The DoxyPEP trial compared doxy-PEP use (DP) to standard of care (SOC) for 501 MSM/TW living with HIV or on PrEP. Metagenomic sequencing of DNA and RNA (DNA-seq, RNA-seq) was performed on self-collected rectal swabs from enrollment (M0) and month 6 (M6) from 50 SOC and 100 DP participants matched by HIV infection status. We analyzed all samples passing minimum sequencing quality control standards. From DNA-seq data, we compared bacterial microbiome diversity and total bacterial abundance in 59 DP and 30 SOC participants, and assessed baseline tetracycline (TCN) ARG abundance at enrollment. We then compared changes in ARG expression at M0 and M6 using RNA-seq data of samples from 46 DP and 24 SOC participants. Bacterial abundance was normalized per million reads sequenced (reads per million, rpm); ARG abundance and expression were additionally normalized by gene length (depth per million, dpm). P-values were obtained by the Wilcoxon rank-sum test and adjusted for multiple comparisons. Linear regression tested the association between number of DP doses taken since enrollment to TCN ARG expression.

Results: Gut bacterial microbiome alpha diversity, beta diversity, and total bacterial abundance did not differ between SOC and DP arms at M0 or M6, or over time by arm. TCN ARGs were detected in all M0 DNA-seq samples, with 46% of all ARG abundance derived from TCN ARGs. Median TCN ARG expression increased 4.4-fold between M0 and M6 in the DP group (0.07 to 0.31 dpm; p<0.01) and was 5-fold higher at M6 in the DP versus SOC group (0.31 versus 0.06 dpm; p<0.01; Figure). There were no significant differences in ARG expression between M0 and M6 DP samples for non-TCN class ARGs. DP participants with M6 RNA-seq samples took a median of 42 DP doses between M0 and M6 (IQR: 29-65 doses), and we found that a higher number of DP doses was associated with greater TCN ARG expression (p<0.01).

Conclusion: Doxy-PEP did not significantly alter bacterial gut microbiome diversity or composition but was associated with an increase in TCN ARG expression, without affecting non-TCN ARG classes. The clinical impact of these findings remains undetermined and should be further studied.

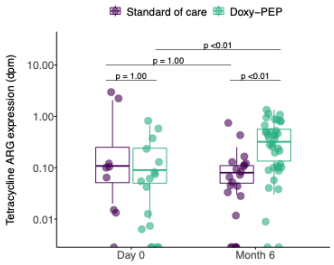

Figure. Tetracycline antimicrobial resistance gene (ARG) normalized expression, measured in average ARG sequencing depth per million reads sequenced (dpm), between the Month 0 and Month 6 samples in the doxy-PEP and SOC arms.

1155 WITHDRAWN

1156 Prevalence of Syphilis and HIV/Syphilis Coinfection in an Inner-City Emergency Department

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Background: Syphilis has had a resurgence in the United States. Untreated syphilis infections have detrimental health effects, and improved screening procedures are needed to control the epidemic. We performed a retrospective, deidentified cross-sectional analysis of individuals attending the Johns Hopkins Emergency Department (JHHED) to determine the prevalence of syphilis and HIV, as well as the socio-demographic characteristics associated with presumed active infection (PAI) of syphilis.
Methods: Remnant serum samples from 1951 unique patients attending the JHHED in Baltimore, between January and February 2022 were collected. Demographic variables were extracted from the electronic medical record, and personal identifiers were removed prior to sample testing. Testing was performed with the CAPTIA Syphilis T-Palladium, Sure-Vue RPR, and Serodia TP-PA treponemal and non-treponemal assays. PAI was classified by positive treponemal serology and a RPR non-treponemal titer ≥ 1:8. "Not Presumed Active Infection" (NPAI) was classified by positive treponemal serology, and no high RPR titer. "True Negative" patients had a nonreactive initial serology. Patient HIV status was determined with the BioRad HIV ½+O ELISA and the BioRad Geenius HIV ½ assays. Fisher's exact and Wilcoxon rank-sum tests were performed to determine the sociodemographic factors associated with PAI.
Results: Among 1951 samples tested, 1.2% (23/1951) had PAI, 4.1% (80/1951) had NPAI, and 4.5% (87/1951) were living with HIV. Of the 103 treponemal positive samples, 17.4% (18/103) were living with HIV. Prevalence of positive treponemal serology was higher in men (6.7%) than women (3.0%), and was differential by race (Hispanic 7.8%, non-Hispanic black 6.9%, non-Hispanic white 2.2%). Patients with PAI were significantly younger than those without (median: 35 [IQR: 29-48]; median: 47 [IQR: 32,62], p=0.019). Six of nine women with PAI were in childbearing age. Though PAI was higher among people living with HIV than those not (5.8% vs 1.0%, respectively, p=0.003), the majority of PAI 78.3% (18/23) were found in HIV-negative people. In comparison to those who reported having a primary care provider (PCP), patients who did not had 5.7-time higher odds of having PAI (OR, 5.7 [95% CI: 2.1-15.5]).
Conclusion: One in 20 ED patients had positive treponemal serology for syphilis and several were also living with HIV. Updated screening protocols to include populations most recently infected are imperative to mitigate the resurgence of syphilis nationally.

1157 Jarisch-Herxheimer Reaction in Patients With Syphilis With or Without Prior Antibiotic Prophylaxis

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Background: Jarisch-Herxheimer reaction (JHR) is a transient clinical phenomenon that may occur within 24 hours after penicillin treatment in individuals with syphilis infection. JHR incidence ranges from 9 to 31%, reaching 56% in early syphilis when proactively investigated. Aim of our study is to determine the incidence of proactively investigated JHR in individuals with or without prior antibiotic prophylaxis.
Methods: We enrolled consecutive patients diagnosed with syphilis from April to September 2023 undergoing penicillin treatment. Twenty-four hours after receiving the first penicillin dose, a phone call was made by a healthcare professional to assess symptoms referable to JHR and the exposure to antibiotics (active against Treponema pallidum) before penicillin administration. JHR was defined, after excluding other possible causes, by the presence of at least one of: fever, chills, new or worsening rash, headache and myalgias. Individuals were categorized as exposed or not to antibiotics before penicillin if they received at least a 48-hours course of antibiotics in the 7 days before the first penicillin dose.
Results: Ninety-five individuals were enrolled, with a median age of 41 years (IQR 33-50), including 93 (98%) males and 78 (82%) people living with HIV, of whom 61 (78%) with an HIV-RNA <50 cp/mL. Seventy patients (74%) were MSM, 14 (15%) transgender women and 11 (11%) heterosexuals. The distribution of syphilis stages was: 5% primary, 12% secondary, 41% early latent, 41% late latent and 1% neurosyphilis. Previous penicillin treatment was reported in 50 patients (53%). Median RPR titer at diagnosis was 1:8 (IQR 1:2-1:16). We identified 71 patients (75%) with a study-defined antibiotic exposure: 67 (94%) amoxicillin and 4 (6%) doxycycline. The median cumulative dose of amoxicillin was 9.5 g (IQR 6-12 g) and doxycycline 1200 mg (IQR 950-1400 mg). Six patients [incidence 6.3% (95% CI 2.3-13.7%)] developed JHR, with fever being the most common clinical manifestation (4 in the antibiotic exposed and 2 in the antibiotic unexposed group). Among the subset of 55 patients with early syphilis (58%), 4 [incidence 7.3% (95% CI 1.1-10.2%)] had JHR (2 in the antibiotic exposed and 2 in the antibiotic unexposed group).
Conclusion: The observed overall low incidence of JHR, even lower in the early syphilis group (which accounted for a higher proportion of cases when compared to previous studies), could be attributable to antibiotic prophylaxis, although a relatively low RPR titer might also play a role.

1158 Increasing Syphilis Prevalence Among MSM Across India Despite Improvements in the HIV Care Continuum

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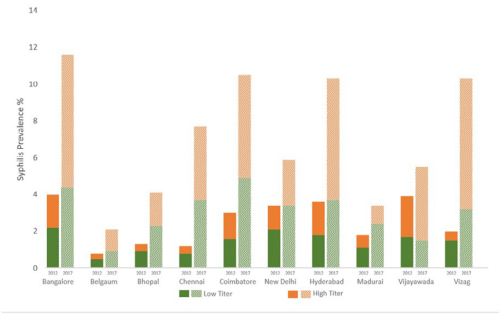
Background: Syphilis rates have increased in men who sex with men (MSM) in high income countries. Infectious syphilis is associated with HIV acquisition in MSM. Nationally representative syphilis prevalence data from MSM in low-and-middle income settings are lacking. We evaluated changes over 5 years in syphilis and high titer (HT) RPR prevalence across 10 Indian cities.
Methods: As part of a cluster-randomized trial to evaluate integrated HIV prevention, testing, and treatment services, respondent-driven sampling (RDS) accrued samples of MSM (n=1000/city) in 10 Indian cities between 2012-2013 and again in 2016-2017. Participants underwent serological testing for syphilis (RPR). Additional testing was performed on RPR-positive stored sera to determine titers (high ≥ 1:8, low <1:8). The integrated services intervention did not have a statistically significant effect on syphilis prevalence. We evaluated associations with HT prevalence from 2016-17 using RDS-weighted multivariable multilevel multinomial regression models stratified by HIV status.
Results: 9984 and 9991 MSM were sampled in 2012-2013 and 2016-2017, respectively. During this time, HIV prevalence increased from 7.4% to 15.3% with improvements across the HIV care continuum (33.4% vs 59.1% viral suppression). At the same time, syphilis prevalence increased in all cities; the median prevalence increase from 2013 to 2017 was 4.7% (range: 1.6 - 7.5%) with increase in HT (2.7% [1.2 - 4.8%]) accounting for more of the overall increase than low titer (1.6% [1.3 - 2.2%) (Fig 1). Of 9991 MSM with lab confirmed syphilis, only 3.2% reported a prior diagnosis. Among MSM living with HIV, significant correlates of HT (vs. negative) included being older, HIV viral load >1000 copies/ml, and reporting running out of money in the prior 12 months. Among MSM without HIV, correlates of HT included being older, having prior gonorrhea or chlamydia diagnoses and any STI symptom. Regardless of HIV status, kothi identity (prefer receptive anal sex) and recent condom use with male partners was associated with higher HT prevalence.
Conclusion: Syphilis prevalence increased within all 10 cities in 5-years. Associations with HT suggests targeted interventions like STI-PEP are needed. Of concern, HT was associated with viremia in men living with HIV suggesting a greater likelihood of HIV transmission to sex partners not on HIV PrEP. Augmented adherence support and early syphilis treatment is required.

Fig 1. Syphilis prevalence in Indian MSM by City and by high (≥1:8) and low (<1:8) RPR titer



1159 Gaps in the Prevention of Mother-to-Child Transmission of Syphilis in South Africa, 2020-2022

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Background: Congenital syphilis (CS)-vertical transmission of syphilis during pregnancy-can lead to adverse fetal outcomes including stillbirth and neonatal death. In South Africa (SA), CS is notifiable, however, notifications have been low leading to concerns of underreporting. In addition, infant data accompanying CS surveillance reports (CNFs) are minimal limiting evaluation of missed prevention opportunities. Since January 2022, CNFs were supplemented with CS-specific case investigation forms (CIFs) with additional maternal and infant clinical history. We reviewed CS CNFs and CIFs reported in SA from January 2020–June 2022 to identify gaps in the CS prevention cascade.
Methods: We reviewed CNFs prospectively collected during January 2020–June 2022 and matched them to submitted CIFs to review infant and maternal clinical history and determine the proportion of pregnant women (PW) (1) enrolled in antenatal care (ANC), (2) tested for syphilis during pregnancy, and (3) treated for syphilis, amongst those diagnosed, ≥28 days before delivery.
Results: During January 2020–June 2022 938 CNFs and 667 CIFs were submitted. Record linkage provided a final dataset of 343 matched CNF-CIF pairs, 37% (343/938) of total CNFs. Among 343 matched CNF-CIF pairs, 56% (n=195) of pregnant women (PW) had ≥1 ANC visit documented, 87% (n=298) were tested for syphilis and of these 88% (n=261) tested positive and 70% (n=210) were treated. Of those tested during pregnancy, 40% (n=120) were tested ≥28 days before delivery. Limiting to PW with ≥1 ANC visit documented (n=195), 98% (n=191) were tested, and of these 86% (n=164) tested positive and 78% (n=152) were treated. Overall, 28% of treated PW received the first dose ≥28 days before delivery, while 18% of PW treated <28 days before delivery tested positive for syphilis ≥28 days before delivery.
Conclusion: Total SA CS cases reported during January 2020-June 2022 translated to a crude CS rate (36 per 100,000 live births) half the CS rate estimated by the World Health Organization (86 per 100,00 live births) for SA in 2022. Evaluation of the CS prevention cascade relied on supplemental infant and maternal information and was limited to less than half of total cases reported. PW with early engagement in ANC had improved syphilis testing and treatment outcomes, but testing earlier in pregnancy did not always guarantee timely treatment highlighting need to identify barriers to timely treatment following a positive syphilis test during pregnancy.

1160 Routine Emergency Department Screening Increases Syphilis Diagnosis Among Pregnant Patients

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Background: Considering the recent surge in congenital syphilis, novel means of reaching vulnerable populations for testing and treatment are needed. The CDC recently suggested screening outside traditional prenatal care settings might be an effective strategy. As the primary source of healthcare for many communities with limited access to care, visits to the emergency department (ED) may represent a crucial opportunity for syphilis detection and congenital syphilis prevention.
Methods: A routine, opt-out, syphilis screening program for all ED patients under age 65 was implemented in the ED of a large, urban, tertiary care hospital in Chicago. Prior to that, testing occurred at clinician discretion following the standard of care. This study retrospectively reviewed all ED encounters among pregnant people for the two-year periods before and after implementation of the screening program. Syphilis cases were defined by a combination of positive serology, rapid plasma regain (RPR) titers, and clinical history derived from chart review. Descriptive statistics were used to evaluate changes in screening and diagnosis rates, as well as demographic and clinical trends.
Results: A total of 9,165 ED encounters involving pregnant patients were identified. In the two years before the intervention, 296 of 4,764 (6.2%) encounters included testing for syphilis, which increased almost eight-fold after the intervention, to 2,307 of 4,401 (52.4%) encounters. There were 3 (1.1% of screened population) syphilis cases identified before the intervention, which quintupled to 16 (0.7%) after the intervention. Screened patients were predominantly non-Hispanic Black (94.3% before, 92.1% after) and had public insurance (72.3% before, 72.5% after), reflecting local demographics. Notably, of all pregnant patients diagnosed with syphilis through the screening program, only 5 (31.2%) were tested for other sexually transmitted infections (STIs), 7 (43.8%) presented to the ED with abdominal or pelvic pain, and none presented with symptoms of an STI.
Conclusion: This study found that a non-targeted screening program dramatically increased syphilis screening and diagnosis rates among pregnant patients, the majority of whom did not present with concern for STI. Implementing routine ED syphilis screening in high prevalence communities will be key to addressing the syphilis epidemic, eradicating congenital syphilis, and addressing major health care disparities.

1161 Syphilis Screening and Incident Infection Rates in HIV Treatment and HIV PrEP Programs in BC, Canada

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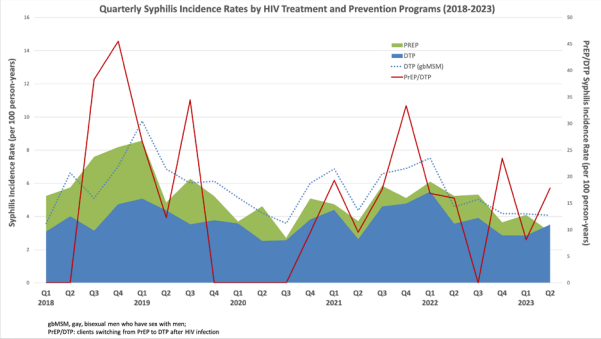
Background: In Canada, syphilis continues to affect gay, bisexual and other men who have sex with men (gbMSM), and increasingly heterosexual persons and youth. We characterize syphilis testing and incidence rates among British Columbia (BC) HIV PrEP and HIV Drug Treatment Program (DTP) clients.
Methods: Adults ≥18 years enrolled in BC PrEP and DTP with program contact (lab test, drug dispensed) between 1-Jan-2018 to 31-Dec-2022 were included (followed to 30-Jun-2023). Demographics, HIV risk group, syphilis testing rates (per person-year (PY)), using a reverse-sequence algorithm with treponemal EIA, and incidence rates (per 100PY) were estimated.
Results: Overall, 20,033 clients [median (Q1-Q3) age 44 (33-57) years; 90% cis-men, 9% cis-women, 1% trans-women, 0.3% trans-men, 0.3% other genders were included [PrEP (n=10,422), DTP (n=9557), and PrEP/DTP (n=54), the latter including clients switching from PrEP to DTP after HIV infection]. 95% of clients had ≥1 syphilis test [PrEP (n=10,240), DTP (n=8643) and PrEP/DTP (n=54)], for which the testing rates were 3.40, 2.75, and 3.13 per PY, and incidence rates were 5.03, 3.78, and 14.73 cases per 100PY, respectively. See Figure. Among PrEP clients, those reporting prior bacterial rectal STI or syphilis as their PrEP eligibility criteria, had the highest incident syphilis rate (10.84 per 100PY), followed by those with baseline HIRI-MSM score ≥10 plus ≥1 other HIV risk factor (8.44 per 100PY). High syphilis rate (8.19 per 100PY) among clients with baseline HIRI score ≥25 was observed. Youth (under 30), and those aged 30-39 had higher syphilis rates in DTP than in PrEP (8.45 and 7.09 per per 100PY, respectively) vs. (4.98 and 5.36 per 100PY, respectively). gbMSM in the DTP had similar syphilis rate to the PrEP program overall (5.68 vs. 5.03 per 100PY), as well as similar screening rates (3.15 vs 3.40 per PY). For heterosexual clients, and persons who have ever injected drugs in DTP, syphilis rates were 1.33 and 1.13 per 100PY, respectively. For cis-women with ≥1 syphilis test (n=1470/1748, 84%), testing rate was 1.97 per PY and incidence rate 0.96 per 100PY across programs.
Conclusion: High syphilis rates were observed in PrEP clients reporting baseline STI, multiple HIV risk factors, and HIRI-MSM score ≥25. This was similar for gbMSM and younger persons living with HIV. Notably, PrEP clients who subsequently acquired HIV had very high incident syphilis rates. These findings will help inform future public health interventions, such as doxyPEP



1162 Altered Cellular Immune Response in the Context of Syphilis and Acute HIV Coinfection

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Background: The co-infection of syphilis and acute HIV infection is gaining clinical significance due to rising co-infection rates and the unique interaction between these two sexually transmitted infections. Syphilis enhances HIV transmission and acquisition, while HIV accelerates the progression of syphilis. This study aimed to investigate the cellular immune responses in the context of acute HIV/syphilis co-infection.

Methods: A cross-sectional analysis was conducted, comparing four cohorts of 15 patients each (total N=60): acute HIV infection with syphilis (aHIV/S), acute HIV infection without syphilis (aHIV), chronically coinfected syphilis/HIV+ patients on antiretroviral treatment (cHIV/S), and healthy controls (CTRL). Flow cytometry assessed PD-1, HLA-DR, and CD38 expression on various T-cell subsets (CD3+CD4+ (TCD4), CD3+CD8+ T cells (TCD8)), memory T cells (CD4+CD45RO+ memory T-cells (TM), CCR7±CD27± memory subsets (TCM: T central memory, TEM: T effector memory, TTM: T transitional memory), antigen-naive cells (CD4+CD45RO- TN)), regulatory T-cells (CD49b+LAG-3+(TR1)), and plasmacytoid dendritic cells (BDCA2+CD123+ (pDC)). IFN gamma (IFNγ) levels were measured in plasma using Simoa technology (Quanterix).

Results: In patients with acute HIV/syphilis co-infection, the frequency of TCD4 ($p<0.0001$) and TCD8 ($p<0.0001$) cells was significantly lower compared to other groups, while CD38 expression was highest ($p<0.0001$). The frequency of pDC ($p<0.0001$) and TR1 ($p=0.0365$) decreased significantly in aHIV/S, aHIV, and cHIV/S groups compared to CTRL. Interestingly, T central memory cells were significantly increased in aHIV/S ($p=0.0005$). Notably, the highest PD-1 expression on type 1 regulatory T cells was observed in acutely HIV-coinfected patients ($p=0.0003$), and it correlated positively with viral plasma load ($r=0.6$ $p=0.0314$). Furthermore, the highest levels of IFNγ were found in acutely HIV-coinfected patients.

Conclusion: The impaired T-cell function, activation, and exhaustion observed in acute HIV/syphilis coinfection result in reduced control of HIV replication. Longitudinal studies of patients coinfected with HIV and syphilis, especially after initiating antiretroviral treatment, are warranted to investigate their effects on the HIV reservoir.

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1163 Gaps in Sexual and Reproductive Health Care Among Cisgender Women With Diagnosed HIV

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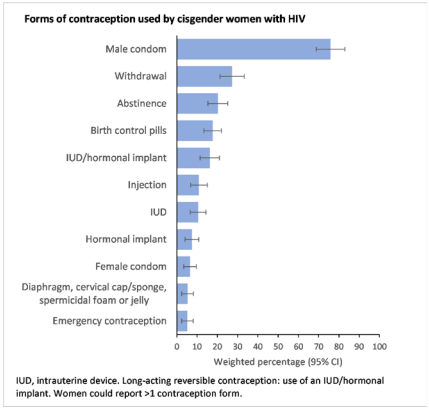
Background: Cisgender women with HIV (WWH) are defined by more than their HIV viral loads. Comprehensive women's health, including sexual and reproductive health (SRH), is an important component of overall health and well-being. We used data from the CDC's Medical Monitoring Project (MMP) to describe nationally representative estimates of SRH outcomes among WWH of reproductive age.

Methods: During 6/2018–5/2021, MMP interviews were conducted and medical records were abstracted to ascertain data on SRH among WWH. Among WWH aged 18–44 years (N=855), we report weighted percentages and calculated prevalence differences (PDs) with predicted marginal means and accompanying 95% confidence intervals (CIs) to quantify differences between groups.

Results: Overall, 86.4% of WWH reported receiving a cervical Pap smear in the past 3 years. Of sexually active WWH, 38.5% had documented sexually transmitted infection (STI) testing for syphilis, gonorrhea, and chlamydia in the past 12 months, per CDC guidelines. Of WWH who engaged in vaginal sex, 88.9% used ≥1 form of contraception in the past 12 months, including 16.3% who used long-acting reversible contraceptive methods (Figure). Over half (53.4%) had ≥1 pregnancy since their HIV diagnosis, of whom 81.5% had ≥1 unplanned pregnancy, 24.6% had ≥1 miscarriage or stillbirth, and 9.8% had ≥1 abortion. WWH living in households <100% of the federal poverty level (FPL) were less likely to receive Pap smears (PD: -9.13; 95% CI: -14.77– -3.50) and more likely to have unplanned pregnancies (PD: 16.57; 95% CI: 2.63–30.50) than those living in households ≥139% of the FPL. However, WWH attending Ryan White HIV/AIDS Program (RWHAP)-funded clinics were more likely to receive STI testing at their HIV care facility than those who did not attend RWHAP-funded facilities (PD: 20.08; 95% CI: 10.55–29.61). In MMP states that did not expand Medicaid, WWH with Medicaid coverage were less likely to have Pap smears (PD: -12.39; 95% CI: -20.49– -4.29) and more likely to have unplanned pregnancies (PD: 27.17; 95% CI: 11.15–43.19)* than those with private coverage. *Should be interpreted with caution due to small sample sizes.

Conclusion: Many WWH have suboptimal SRH screening and pregnancy outcomes, particularly those living in poverty. Expansion of safety net programs that provide substantial coverage of SRH services, including Medicaid, RWHAP, and Title X, could help improve care access and outcomes among WWH.



1164 Genital and Extragenital Sexually Transmitted Infections Among Reproductive Age Women in Southern US

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Background: Sexually transmitted infections (STI) are highly prevalent among women of reproductive age (WRA) and increase the risk of HIV acquisition and transmission. However, the burden of genital and extragenital STIs is understudied among WRA in the U.S. Estimates of disease are urgently needed, including among women with and without HIV, to inform sex-specific screening guidelines.

Methods: Cross-sectional data from 519 cisgender women, 18-45 years-old enrolled in the STAR cohort from March 2021 to January 2023 at 6 Southern US sites were analyzed. Women with and without HIV (at least one HIV risk behavior in the previous 5 years). Socio-demographic and behavioral assessments were performed using structured interviewer-administered questionnaires. Nucleic-Acid Amplification Test (NAAT) was performed regardless of symptoms on self-collected urine, rectal, and pharyngeal swabs to detect chlamydia, gonorrhea, and trichomoniasis. Sociodemographic characteristics, risk factors, and rates of STIs were tabulated and group comparisons by HIV status were examined.

Results: Mean age was 34.6 ± 6.95 years; 79.6% were Black, 15.5% White, and 11.4% Hispanic. Overall, 52.8% had never married, 45.7 % had a monthly income

of $1500 or less, and 36.0% completed high school. Women had a median of 1 (IQR 1-2) male sexual partners in past year, 44.1% reported condomless vaginal sex in the past year, and 49% reported a prior STI: 35.2% reported a lifetime history of chlamydia, 26.0% gonorrhea, and 30.6% trichomoniasis. Current STI detected by NAAT did not differ by HIV status (22.0% HIV+ vs. 20.5% HIV-; p=0.946): vaginal chlamydia (2.1% HIV+ vs. 1.5% HIV-; p=0.915), rectal chlamydia (2.7% HIV+ vs. 3.1% HIV-; p=0.968), pharyngeal chlamydia (1.3% HIV+ vs. 0.0% HIV-; p=0.42), vaginal gonorrhea (3.8% HIV+ vs. 2.3% HIV-; p=0.727), rectal gonorrhea (0.9% HIV+ vs. 1.6% HIV-; p=0.843), pharyngeal gonorrhea (1.3% HIV+ vs. 0.8% HIV-; p=0.892), and trichomoniasis (14.3% HIV+ vs. 13.0% HIV-; p=0.937).

Conclusion: Prevalence of genital and extragenital chlamydia and gonorrhea, and genital trichomoniasis are high among WRA with and without HIV infection. The implications for women's reproductive health and HIV transmission highlight the importance of extragenital STI testing for women with HIV or vulnerable to HIV infection.

1165 Prevalence and Risk Factors Associated With HPV Infections Among Women with HIV Women in Meru, Kenya

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Background:Cervical cancer, caused by, Human Papilloma Virus (HPV) is the leading cause of preventable deaths among women. High incidence and high mortality for cervical cancer are reported in low- and middle-income countries where immunocompromised HIV-infected women exhibit an increased risk. We determined circulating high-risk HPV genotypes in HIV-infected women in Meru, Kenya and identified risk factors associated with HPV infections in a cross-sectional study of 273 women aged 25 to 64 years.

Methods: Sociodemographic and clinical details were collected using a questionnaire. Cervical specimens were obtained using a self-sampling technique, followed by HPV DNA extraction and real time PCR targeting 24 high-risk genotypes with differentiation of HPV 16, 18, and 45. Descriptive statistics were used to summarize baseline characteristics, while logistic regression analysis was utilized to determine the risk factors associated with HPV infection.

Results: Out of the 273 tested samples, 60.81% (N=166) tested positive for high risk HPV broken down as HPV 18 (37.73 %), HPV 45 (32.23 %), other high-risk HPV types (14.29 %), and HPV 16 (12.45 %) .The prevalence of multiple infections with HPV 16 and 18 was 8.42% (N=23). We further found 54.82% (N= 90) had undergone Pap smear and 45.18% (n=75) had undergone VIA/VILI within the last six months with 4 individuals reporting abnormal results. Notably, among the 161 participants who reported normal results in their Pap smear/VIA tests, HPV positivity was detected. In our tentative analysis we used logistic regression to show the risk factors for high risk HPV were age of 35 to 44 years (OR: 0.45, 95% CI [0.206-0.981], P=0.045), and contraceptive use (OR: 0.496, 95% CI [0.247-0.996], p=0.047).

Conclusion: Our study reveals a concerning high prevalence of high-risk HPV in Kenya and identifies two significant risk factors among HIV-infected women in Meru. Women aged 35-44 years exhibit an increased risk for HPV, while contraceptive use is another risk factor. This underscores the urgent need for tailored interventions and enhanced screening strategies among HIV-infected women in Meru, Kenya. The identified risk factors highlight areas where proactive measures can make a significant impact on reducing cervical cancer risk. Our findings contribute to the growing evidence on HPV burden in Kenya, reinforcing the call for effective public health measures to prevent cervical cancer.

1166 One-Dose HPV Vaccine Durability in a Moderate HIV Prevalence Setting: Mathematical Modeling Analyses

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Background: The World Health Organization recommends a 1-dose human papillomavirus (HPV) vaccination strategy to increase coverage and accelerate cervical cancer elimination. However, the duration of efficacy of 1-dose is uncertain among women living with HIV (WLHIV); immune dysregulation may limit vaccine durability. We modelled the potential impact of a 1-dose HPV vaccination strategy on cervical cancer outcomes for WLHIV in Kenya.

Methods: Using a validated dynamic compartment transmission model for Kenya simulating bidirectional interactions between HIV and HPV, we modelled the impact of a) expanded HIV interventions on cervical cancer outcomes, b) going from a multi-dose to 1-dose HPV vaccine strategy assuming 90% coverage of 9-year-old girls and lifelong efficacy, c) reduced durability scenarios with an efficacy period (EP) of 15-30 years and waning period (WP) of 10-20 years, and d) leveraging 5-year cost savings from a potential switch to a 1-dose strategy on a catch-up vaccination program. Multi-dose vaccine efficacy was assumed to be 100%, and 1-dose efficacy for WLHIV assumed to be aligned with women without HIV at 97.5% (95% CI, 90.0-99.4%). We evaluated the percent reduction in cervical cancer incidence and mortality.

Results: If Kenya achieves UNAIDS targets by 2030 without additional HPV vaccination, we expect a 1.7% cervical cancer incidence reduction amongst WLHIV compared to a baseline of no vaccination and current ART coverage. Achieving UNAIDS targets as well as 90% coverage of a 3-dose HPV vaccine for WLHIV would further reduce incidence to 85.1%. A 1-dose scenario with lifelong efficacy would have similar reductions in incidence and mortality. The worst-case waning scenario of 15-year EP/10-year WP would weaken the incidence reduction by a difference of 17% compared to the 1-dose lifelong efficacy scenario, while the best-case waning scenario of 30-year EP/20-year WP would limit the reduction by 0.1%. Catch-up vaccination has the potential to avert some of the impact of HPV vaccine waning.

Conclusion: Assuming 1-dose efficacy results are consistent for women living with and without HIV, durability differences between dosing strategies will not significantly impact cervical cancer outcomes for WLHIV. While waning vaccine efficacy for 1-dose could increase cervical cancer cases compared to multi-dose strategies, general population vaccination could mitigate some of this change. Empiric data on single-dose HPV vaccine efficacy and duration for women living with HIV are needed.

Cervical Cancer Outcomes for Women Living with HIV in Kenya Under Different HPV Vaccination and ART Coverage Scenarios over a 100-Year Time Horizon

	Single age vaccination, 9-year-old females			Catch-up vaccination of 10 to 24-year-old females, 31% coverage	
Scenario	**Percent reduction in age-adjusted cervical cancer incidence, WLHIV (IQR)**	**Percent reduction in cervical cancer mortality, WLHIV (IQR)**	**Number of HPV vaccines, population, millions (IQR)**	**Percent reduction in age-adjusted cervical cancer incidence, WLHIV (IQR)**	**Number of HPV vaccines, population, millions (IQR)**
No additional HPV vaccination, ART coverage remains at current levels	Reference	Reference	0 (0 0)	-	-
No additional HPV vaccination, ART coverage scaleup to 95-95-95 targets	1.67% (1.18, 2.04)	-14.49%* (-16.14%, -12.98%)	0 (0-0)	-	-
3-dose, 90% coverage	85.06% (84.67, 85.78)	75.99% (74.73, 76.62)	227.5 (222.5, 229.6)	-	-
1-dose, 90% coverage, lifelong efficacy	84.47% (83.73, 85.10)	75.12% (73.93, 75.82)	113.8 (111.2, 114.8)	84.92% (84.32, 85.45)	116.4 (113.8, 117.5)
1-dose, 90% coverage, 30-year EP, 20-year WP	84.37% (83.60, 84.91)	74.8% (73.35, 75.45)	113.8 (111.2, 114.8)	84.88% (84.17, 85.42)	116.4 (113.8, 117.5)
1-dose, 90% coverage, 15-year EP, 10-year WP	67.14% (62.24, 71.63)	54.3% (49.35, 59.08)	113.8 (111.2, 114.8)	67.79% (62.81, 72.38)	116.4 (113.8, 117.5)

* Note that ART coverage scaleup without HPV vaccination is expected to increase cervical cancer mortality due to decreasing HIV mortality.

1167 Integrated Antenatal HIV, Hepatitis B, & Curable STI Testing: A Pragmatic Study in Harare, Zimbabwe

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Background: Many STIs are known to cause neonatal death and other adverse outcomes among pregnant women, but most antenatal clinics in the Global South do not routinely screen for STIs outside of HIV and syphilis. Building on existing HIV and syphilis testing in antenatal care (ANC) may provide a platform for integrating testing for other STIs. We aimed to evaluate the feasibility of integrated ANC STI testing and determine the prevalence of chlamydia (CT), gonorrhoea (NG), trichomoniasis (TV), hepatitis B (HBV), HIV and syphilis in ANC in Zimbabwe.

Methods: A prospective pragmatic study was conducted in two ANC clinics in Harare, Zimbabwe, over a nine month period in 2023. Clients were screened for CT, NG, TV, HBV, HIV, and syphilis, using point-of-care tests. Treatment, partner notification, and onward referral were provided as per national guidelines. The primary outcome was composite prevalence of CT, NG, TV, syphilis and HBV. Using a MRC complex evaluation framework, we assessed the number of people who received same-day results, treatment, and referrals.

Results: Of 11921 clients attending ANC, 953 (8.0%) were approached for participation, and 881 (92.4%) were enrolled (figure 1). Prevalence of HIV was

10.2% (90/881), with 19 (21.1%) new diagnoses. Prevalence of STIs was: CT 18.3% (161/881); NG 4.2% (37/881); TV 12.5% (110/881); syphilis 3.9% (34/881); and HBV 1.5% (13/881). 31.7% (279/881) had at least one non-HIV STI (CT, NG, TV, syphilis, or HBV). 879/881 (99.8%) of participants collected their results, with 98.9% (871/881) receiving same-day results. Of 272 (30.9%) participants with a curable STI (CT, NG, TV, or syphilis), 270 (99.3%) received same day treatment. Partner notification slips were provided to 260 participants with a curable STI, with 81 (31.2%) partners attending for treatment. 84.6% (11/13) of individuals diagnosed with hepatitis B were linked to secondary care.
Conclusion: There is limited testing for CT, NG, TV, or HBV available across public sector health services, including ANC, in Southern Africa. There is urgent need to implement strategies for prevention, detection, and treatment for these highly prevalent STIs. The high uptake and provision of same-day results and treatment in this study demonstrate acceptability and feasibility. However, less than 10% of pregnant clients were approached, owing to limited testing capacity. Further implementation research is urgently needed to address scalability, in order to expand integrated STI testing at ANC clinics.

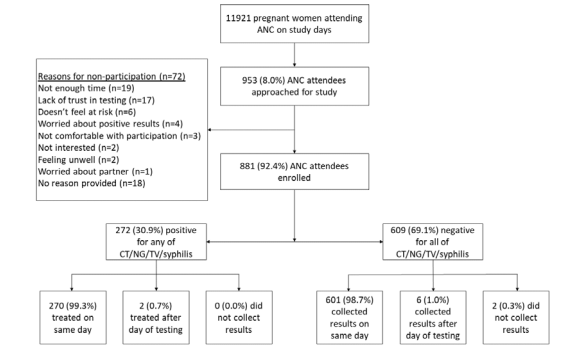

Figure 1: Uptake of testing, prevalence, and treatment of curable STIs (CT/NG/TV/syphilis) in pregnant women attending antenatal care in Zimbabwe

1168 Genital Immune Correlates of Prevalent and Incident Herpes Simplex Virus 2 (HSV-2) Infection

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Background: Most herpes simplex virus type 2 (HSV-2) infections are asymptomatic, but infection increases genital CD4+ T cell activation and risk of HIV acquisition. We examine associations of seroprevalent and seroincident HSV-2 infection with genital immune parameters, including soluble E-cadherin (sE-cad), a biomarker of epithelial barrier disruption.
Methods: This longitudinal study was nested within the Maisha Fiti cohort of 1003 females who sell sex in Nairobi, Kenya. Among 731 HIV-negative participants, HSV-2 serostatus was assessed by Kalon HSV-2 IgG assay at baseline and follow up. Soluble genital immune factors were assayed in cervicovaginal secretions using a multiplex electro-chemiluminescent immunoassay (MSD), and socio-behavioural characteristics assessed by questionnaire. Socio-behavioural characteristics and immune parameters were compared between HSV-2 seropositive and seronegative participants using chi-square and Mann-Whitney U tests and examined using linear regression models controlling for potential confounders. Socio-behavioural characteristics and immune parameters reported to be predictive of HSV-2 acquisition were also similarly compared between participants with incident infection and those who were seronegative throughout the study period.
Results: 414 (57%) participants were HSV-2 seropositive at baseline. Compared with women who were HSV-2 seronegative, women who were HSV-2 seropositive were older ($p<0.01$) and more likely to report intravaginal washing ($p=0.02$). Cervicovaginal sE-cad levels did not vary based on HSV-2 serostatus (median = 73590 vs 69934 pg/mL, $p=0.21$), and IL-6 levels were lower in seropositive participants ($p<0.01$). HSV-2 seroincidence was 10.7 per 100 person years among the 317 initially seronegative participants; incident infection was associated with increased age ($p<0.01$), a higher number of clients ($p<0.01$), and bacterial vaginosis (BV; present in 32% vs 15% of seroconverters, $p<0.01$). Although women who acquired HSV-2 infection had higher baseline cervicovaginal sE-cad levels and lower cervicovaginal MIP-3α levels, there was no evidence of an association after controlling for BV Nugent score.
Conclusion: Subclinical epithelial barrier disruption is unlikely to be a major mechanism underpinning increased HIV acquisition among individuals with HSV-2 infection. No immune predictors of increased HSV-2 susceptibility were apparent, although the genital microbiome may play an important role.

1169 HIV and STIs in US Bisexual Men and Gay Men: Clinical Implications and Service Needs

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Background: Bisexual individuals comprise over half of LGBTQ+ persons in the United States (US), yet remain understudied in HIV and STI research. Goals to end the US HIV epidemic require reaching bisexual cisgender men who have sex with men (MSM) who may have different sexual health behaviors and prevention/care needs than gay-identified MSM.
Methods: We analyzed data from self-identified bisexual (n=778) and gay (n=3290) MSM who participated in the 2022-2023 American Men's Internet Survey (AMIS), a cross-sectional online study of MSM aged 15 and older in the US who have had same-sex anal sex within the past 12 months. We evaluated self-reported HIV and STI diagnosis (chlamydia, gonorrhea, syphilis, and mpox) within a past year, testing activities, sexual practices, PrEP use, experiences of outness, and healthcare-related stigma, and associations with sexual identity.
Results: Lifetime HIV testing was 9.1% less prevalent in bisexual men compared to gay men ($p=0.001$), and 58.7% (n=451) of bisexual men received an HIV test in the prior year (Table). Lifetime PrEP use was 18.6% lower in bisexual compared to gay men ($p=0.001$). Among MSM who had initiated PrEP, 73.1% of bisexual men (n=182) reported PrEP use in the past 12 months, compared to 78.0% (n=1235) of gay men. Bisexual men reported lower rates of past-year STI testing ($p=0.001$) and diagnosis (chlamydia, mpox: $p<0.01$; syphilis: $p=0.016$). Compared to gay men, bisexual men were 32.5% less likely to be out to providers ($p=0.001$) and 12.5% less likely to discuss sex with providers ($p=0.001$). Among bisexual men, outness to healthcare providers was not associated with anticipated healthcare stigma, but among gay men, outness was associated with lower anticipated healthcare stigma ($p=0.001$).
Conclusion: Despite lower HIV and STI prevalence among bisexual men in our study, we found disparities in uptake of PrEP, suggesting a need for research into barriers to PrEP and/or tailored messaging for this group. Greater anticipated healthcare stigma, lower outness, and less frequent conversations about sexual practices among bisexual men highlight a need to ensure healthcare providers adequately address the HIV and sexual health needs of this population. These findings provide a more comprehensive understanding of considerations to inform testing, prevention, and reducing anticipated healthcare stigma among bisexual men.
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1170 Relevance of Asymptomatic STIs in a High-Risk Population of MSM Undergoing Periodic Screening

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Background: One of the limitations in the control of STIs is that many of them are asymptomatic, making diagnosis, treatment, and contact tracing challenging. The objective of this study is to analyze the significance of asymptomatic STIs in a high-risk population (MSM) that undergoes regular screening for these infections
Methods: This was a single-center study involving two populations: our cohort of MSM on PrEP (Pre-Exposure Prophylaxis) and People Living with HIV (PLHIV) followed up at our clinic, both at risk of STIs, who undergo STI screening every 3-6 months (including serological tests, cultures, and nucleic acid amplification tests in pharyngeal, rectal, and urethral/urine samples). The following STIs were analyzed: Neisseria gonorrhoeae (NG), Chlamydia trachomatis (CT), Lymphogranuloma venereum (LGV), and syphilis. Study period: November 1, 2022, to June 30, 2023. Proportions were compared using the chi-squared test or Fisher's exact test. Statistical analysis was performed using SPSS 24.0 software.
Results: During this period, STI screening was conducted on 788 individuals on PrEP and 456 PLHIV, all MSM. A total of 560 STIs were diagnosed (359 in

individuals on PrEP and 201 in PLHIV; p=0.755): NG 194 (34.6%), syphilis 130 (23.2%), CT 121 (21.6%), and LGV 79 (14.1%) and 36 (6,4%) were other STIs; 416 (74.2%) were asymptomatic. Table 1 provides details of symptomatic and asymptomatic STIs in both groups. Some subjects had NG and/or CT in multiple sites. Coincident STIs were detected in 20.3% of the cases. There were no seroconversions among individuals on PrEP.

Conclusion: Asymptomatic STIs are strikingly prevalent in this high-risk MSM population. No differences in clinical presentation were observed between individuals on PrEP and PLHIV for any of the studied STIs. There is an urgent need to implement new prevention strategies to control STIs in these high-risk populations.

		PrEP (N = 788)		PLHIV (N = 456)		p
	N	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	
Pharyngeal NG	89	0	64/64 (100)	0 (0)	25/25 (100)	-
No-pharyngeal NG	131	20/101 (19,8)	81/101 (80,1%)	8/30 (26,6)	22/30 (73,3)	0.625
Pharyngeal CT	19	2/15 (13,3)	13/15 (86,6)	0/4 (0,0)	4/4 (100)	0,520
No-pharyngeal CT	104	13/84 (15.4)	71/84 (84.5)	5/20 (25)	15/20 (75)	0.526
LGV	79	16/37 (43.2)	21/37 (56.7)	17/42 (40.4)	25/42 (59.5)	0.873
syphilis	130	17/56 (30,3)	39/56 (69,6)	19/74 (25,6)	55/74 (74.3)	0.657

Table 1: STI in individual on PrEP and PVHIV: n (%)
Some subjects had NG and/or CT in multiple sites.

1171 Lymphogranuloma Venereum Among Men Who Have Sex With Men: 7 Versus 21 Days Doxycycline Effectiveness

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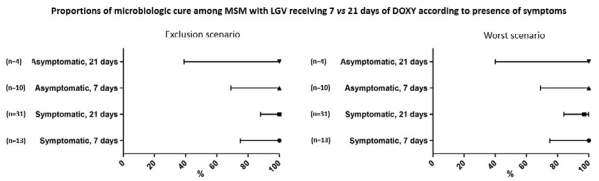
Background: Current guidelines on treatment of symptomatic Lymphogranuloma venereum (LGV) caused by Chlamydia trachomatis (Ct) serovars L1-3 recommend 21 days of doxycycline (DOXY).

Methods: Retrospective study on men who have sex with men (MSM) diagnosed with rectal or urethral Ct, treated with 7 or 21 days of DOXY between 2015-2022 at San Raffaele Scientific Institute, Milan, Italy. Nucleic acid amplification test with sequencing serovar determination was used; only people with available test of cure (TOC) were included. Microbiologic cure (MC) was defined as negative TOC or positive TOC with different genotype (re-infection). Proportions of MC according to presence of symptoms and treatment durations were compared using exact binomial test; these comparisons were performed either including (counted as failure of cure; worst scenario) or excluding (exclusion scenario) samples with non-amplifiable positive TOC.

Results: Overall, 158 MSM included: 59 (37%) had LGV, 72 (46%) non-LGV and 27 (17%) non-amplifiable. LGV serovars were L1 5%, L2 39%, L2b 19%, L2c 37%; rectal LGV was detected in 95%, urethral 2%, both 3%. Symptomatic LGV cases were 45 (76%); 23 (40%) received 7 days of DOXY and 36 (60%) 21 days according to physician preference. Median age was 40 (IQR=34-48) years; 95% Caucasian, 3% Hispanic, 2% Caribbean; 53 (90%) PLWH, with a median CD4+ 759 (622-930) cells/µL at LGV. Median time to TOC was 0.66 (0.3-1.4) years since LGV diagnosis. MC occurred in 58 people (98%; 90% negative and 8% Ct infection, non-LGV); all symptomatic MSM were clinically cured after treatment. Proportions of MC among MSM with LGV receiving 7 vs 21 days of DOXY according to presence of symptoms shown in Figure; 100%MC was found either among MSM with LGV symptomatic or asymptomatic treated with 7 and 21 days of DOXY (exclusion scenario). In the worst scenario, no significant effect of treatment duration on %MC in symptomatic MSM with LGV (100% vs 97%, p=0.99); 100%MC were also observed in MSM asymptomatic in both treatment groups. No significant differences of %MC between LGV and non-LGV either symptomatic (worst 100% vs 88%, p=0.62; exclusion 100% vs 100%) or asymptomatic (worst 100% vs 81%, p=0.32; exclusion 100% vs 94%, p=0.99) treated with 7 days of DOXY in both scenarios.

Conclusion: Among MSM with LGV or non-LGV serovars, comparable clinical and virologic cure proportions were found after 7 or 21 days of DOXY, regardless of presence of symptoms. These data support the use of DOXY short course for Ct treatment.



1172 Low Prevalence of Sexually Transmitted Infections Among Adolescents and Young Adults Living With HIV

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Background: Approximately 50% of sexually transmitted infections (STIs) are concentrated in people within the age range of 15 to 24 years. This coincides with age estimates at sexual debut. This cohort is of particular public health concern due to the potential consequences of STI transmission to new sexual partners. In a longitudinal cohort study of young females and males living with HIV, we assessed the prevalence of Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) infections.

Methods: We enrolled 158 participants who had previously received the quadrivalent HPV vaccine and collected genital samples for CT and NG infections at enrolment and again at month 12. Nucleic acid amplification testing (NAAT) was performed on genital swabs to detect NG and CT, using the Gen-Probe APTIMA test. Cross-sectional data on demographic, medical and sexual history were gathered at enrolment. Descriptive statistics were employed to establish the baseline demographic characteristics. STI diagnoses were correlated with the age at sexual debut, gender, partner's age at first sexual activity, education level, financial dependency and viral load.

Results: At enrolment 158 participants provided samples and 155 at month 12 visit. At enrolment 9/158 (5.7%) were diagnosed with CT or NG and at month 12, 16/155 (10.3%). Two participants had a positive result at both time points. Among those diagnosed with STIs at 12-month visit, 12/16 (75.0%) were females, 13/16 (81.3%) had never married and 9/16 (56.3%) were financially dependent. HIV RNA viral load (VL) ≥ 1000 was noted among 3/16 (26.6%) of those diagnosed with an STI, while more than 50% of participants with VL≤ 1000 had STIs, 12/16(75%). In a multivariable logistic model, STI and older age reduced odds by 0.56 times per year (aOR 0.56, 95% CI 0.34-0.85). Tertiary education lowered odds by 0.03 times versus primary education (aOR 0.03, 95% CI 0.04-3.30). Substance use in the past six months increased the odds by 6.75 times (aOR 6.75, 95% CI 1.29-46.84). Having an older first sexual partner increased odds by 1.25 times (aOR 1.25 (1.06-1.50), while abstaining at younger age reduced odds by 0.65 times (aOR 0.65, 0.46-0.90).

Conclusion: Young men and women living with HIV had lower STI prevalence than other comparable population level age cohorts. Higher education and delayed sexual debut were protective while older sexual partner, female gender and financial dependency had increased risk, emphasizing the need for structural social protection interventions.

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1173 Reaching ECP Users With HIV and PEP Services in Kenyan Pharmacies

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Background: Adolescent girls and young women (AGYW) seeking emergency contraceptive pills (ECP) to prevent conception also face increased risk of HIV acquisition due to implied unprotected sex. AGYW who are eligible for ECP are therefore likely to also be eligible for post-exposure prophylaxis (PEP) to reduce their risk of HIV acquisition. Pharmacies, where most AGYW purchase ECP, can serve as convenient outreach points for HIV prevention services including PEP. We assessed the willingness of AGYW seeking ECP to test for HIV and initiate PEP

Methods: We assessed willingness to test for HIV and initiate PEP as the main outcomes in a study among AGYW aged 15-24 seeking ECP in 5 pharmacies in Kisumu and Nairobi, Kenya, between May and August 2023. We trained pharmacy providers on research ethics, documentation, screening and

consenting. They collected data via REDCap at baseline, with follow-up conducted within 10 days post enrollment. Baseline data captured socio-demographics, use of ECP, HIV risk perception, HIV testing history, willingness to test for HIV and willingness to initiate PEP. Post survey data captured their experience in seeking HIV testing and PEP. Participants were issued an information sheet on HIV testing and PEP and those interested referred to nearby health facilities for services. Data were summarized using descriptive statistics.

Results: We screened 297 AGYW and enrolled 200; mean age was 22 years; 90.0% were single; 10.0%, 41.7% and 48.2% had primary, secondary, and post-secondary education, respectively. 41.5% perceived themselves to be at high HIV risk and 28.5% at medium risk; 28.5% felt at low-no risk despite seeking ECP. Table 1 shows those willing to test for HIV and to initiate PEP compared to those who actually went for testing after being educated on why they would be eligible. Overall, 50.7% AGWY took up testing compared to 95.5% who were willing. The most preferred testing modality was self-testing but since this was unavailable, most tested at the pharmacy; 25% tested at government facilities. Of those who tested, 80.2% tested within 3 days of enrolment. The 49.3% who did not test/take PEP cited low perceived risk (20.3%), fear of knowing HIV status (10.8%), awareness of partner's status (9.5%), distance (6.8%), and procrastination (20.3%) as barriers.

Conclusion: The findings underscore the potential of pharmacies to enhance access to HIV testing and PEP initiation among at-risk AGYW by providing convenient outreach points

Table 1. Willingness to test and initiate PEP vs. actual testing

Willingness to test & initiate PEP	Willing n (%)	Tested n (%)
Yes	191(95.5)	76 (50.7)
No	2 (1.0)	74 (49.3)
Unsure	7 (3.5)	0 (0.0)
Preferred vs actual testing modality		
Pharmacy staff	/0 (37.0)	52 (68.4)
Self-test	117 (61.9)	N/A
Unsure	2 (1.1)	0 (0.0)
Public facility	N/O	19 (25.0)
Private facility	N/O	5 (6.6)

N/A - HIV self-testing was not available
N/O - Option not provided

1174 Stability of Penile Bacteria Associated With HIV Seroconversion, Inflammation, and Cells (BASICs)

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Background: Studies have defined specific penile anaerobic bacteria associated with HIV Seroconversion, Inflammation and Cells (BASICs) in uncircumcised men. However, little is known regarding the colonization dynamics of BASICs in the coronal sulcus, or if they colonize other male genital tract sites outside of the coronal sulcus.

Methods: Swabs from 97 uncircumcised men were collected at the coronal sulcus, outer foreskin, penis shaft, and distal urethra in a cross-sectional study in Rakai, Uganda; 47 participants were then sampled longitudinally over 8 weeks. We characterized the penile microbiome and determined three key BASICs (*Prevotella bivia*, *Peptostreptococcus anaerobius*, and *Dialister micraerophilus*) prevalence, proportional and absolute abundance by 16S rRNA qPCR and V3V4 amplicon sequencing. We compared overall microbiome composition by PerMANOVA and BASIC abundances between sites by pair-wise Mann-Whitney Test. We also compared stability of BASICs in the coronal sulcus to other penile commensal bacteria using residence and return times, which measure the time between disappearance and subsequent re-emergence of a taxon, respectively. We imputed abundance thresholds associated with increased HIV seroconversion risk for *P. bivia*, *P. anaerobius*, and *D. micraerophilus* using published data (Prodger et al., 2021) to characterize dynamics of BASICs abundance over the 8-week study.

Results: Overall microbiome composition differed significantly across penile sites, with BASICs most prevalent and abundant in the coronal sulcus as compared to other sites. In most study participants, P. bivia, P. anaerobius, and D. micraerophilus were detected at least once over the 8-week study period (62%, 70%, 64%, respectively), but fewer participants were colonized at all visits (17%, 17%, and 9% respectively) (Fig. 1A). All BASICs had shorter residence times in the coronal sulcus than Corynebacterium, a ubiquitous skin-associated bacterium, and 43% of participants had at least one visit with a BASIC above the high-risk abundance threshold (Fig. 1B).

Conclusion: BASICs were detectable in the coronal sulcus of nearly two-thirds of uncircumcised participants over an 8-week study period, although only 9-17% of individuals were persistently colonized by a single BASIC species. High abundance colonization by BASICs is transient and uncommon. Targeted interventions to reduce BASIC abundance in the coronal sulcus may be an effective approach to decrease HIV risk.

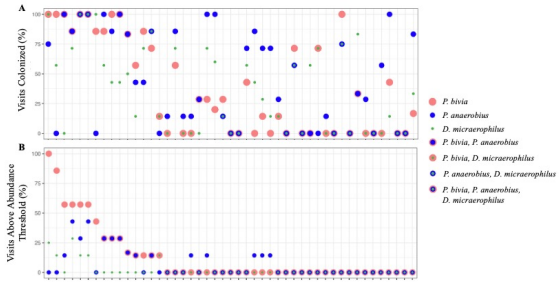

Figure 1: Proportion of visits each participant is colonized with BASICs (A) and proportion of visits BASIC abundance was above the risk threshold (B).

1175 Vaginal Immune Dysregulation in Transgender/Non-Binary Individuals on Masculinizing Hormone Therapy

Matilde P. Jacobson[1], Janja Kovacic[1], Eleanor Capozzi[1], Megan Gooding[1], Huberth Garcia[1], Fernando Cabezas Mejia[1], Janelle Schrag[2], Lynsay MacLaren[2], Christopher Cannon[2], Mimi Ghosh[1]

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Background: Many transgender men and non-binary (TMNB) people receiving gender-affirming care take synthetic testosterone as part of their masculinizing hormone therapy (MHT) regimen. This population is disproportionately affected by HIV and other sexually transmitted infections (STIs). Testosterone is known to have immunosuppressive activity and may modulate HIV/STI susceptibility. Yet little is known about the immunological characteristics of the vaginal mucosa in people assigned female at birth (AFAB) on MHT. Our objective in this study was to characterize the vaginal immune microenvironment of AFAB TMNB individuals on MHT to provide baseline immunological knowledge and guide future research.

Methods: We recruited 72 AFAB participants from the Washington, DC metro area (aged 18-44, sexually active, HIV-negative) and conducted a cross-sectional study comparing 36 TMNB participants who had been on MHT for at least six months with a control group of 36 cisgender/non-binary participants not on MHT. Participants provided clinical and demographic data and self-collected vaginal swabs. The concentrations of a panel of inflammatory and antimicrobial immune biomarkers in samples were assessed by ELISA. Statistical analyses were performed using Mann-Whitney U tests to compare biomarker values between the MHT and non-MHT groups (GraphPad Prism 10.0.2).

Results: Compared to non-MHT controls, the MHT group had significantly elevated levels of inflammatory biomarkers Myeloperoxidase ($p=0.0101$), TNFα ($p=0.0053$), and MIP1α ($p<0.0001$). The MHT group also had significantly lower levels of antimicrobial biomarkers Elafin ($p<0.001$), SLPI ($p=0.0085$), and Human Beta-Defenisn-2 ($p=0.0033$) compared to the control group. Age, race, income, hormonal contraceptive use, and sexual behavior were similar between the groups.

Conclusion: We found evidence of vaginal immune dysregulation in TMNB individuals receiving MHT. Dysregulation of inflammatory and antimicrobial biomarkers is a potential underlying mechanism that can affect HIV/STI susceptibility. Our findings add to the scant body of knowledge available on the immunomodulatory effects of synthetic testosterone in the vagina and may inform future studies on sexual health in TMNB. Our findings do not negate MHT as a clinically safe standard of care in TMNB, but point to an indication for integrating HIV/STI prevention services into gender-affirming care programs for individuals on MHT.

1176 Forced Vaginal Sex Is Associated With Genital Immune Changes That May Increase HIV Susceptibility

James Pollock[1], Mary Kung'u[2], Sanja Huibner[1], Rhoda Kabuti[2], Hellen Babu[2], Erastus Irungu[2], Pauline Ngurukiri[2], Helen Weiss[3], Janet Seeley[3], Tanya Abramsky[3], Joshua Kimani[2], Tara Beattie[3], Rupert Kaul[1], for the Maisha Fiti Study Champions

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Background: HIV risk is increased among women exposed to forced vaginal sex, both in the short- and long-term. While the epidemiological pathways between forced sex and HIV infection have been previously explored, genital inflammation is a key biological determinant of HIV susceptibility that has not been well-investigated in the context of forced sex. Here we define the impact of recent forced vaginal sex on cervicovaginal inflammation and epithelial barrier disruption as potential biological mediators of HIV risk.

Methods: This study was nested within the longitudinal Maisha Fiti cohort study, which investigates violence and HIV susceptibility among female sex workers (FSWs) in Nairobi, Kenya. Levels of proinflammatory cytokines and soluble E-cadherin (sE-cad), a novel biomarker of epithelial barrier disruption, were measured in self-collected cervicovaginal secretion samples from 746 HIV-uninfected Maisha Fiti participants using a multiplex electrochemiluminescent immunoassay (Meso Scale Discovery, MSD). Sociodemographic factors were compared between participants who were physically forced to have sex in the 7 days preceding the study visit and those not recently exposed to forced sex using chi-square tests and Welch's t-tests. Genital inflammation was defined using a composite score of inflammatory cytokines (IL-1α, IL-1ß, IL-6, IL-8, IP-10, MCP-1, MIP-1α, MIP-1ß, TNFα) that has been previously associated with HIV acquisition. The presence of inflammation was compared between groups using mixed-effects logistic regression models to control for potential confounders.

Results: 44 (6%) of 746 participants reported recent forced sex exposure at the baseline visit, and 42 of these 44 women continued to have sex with other clients during this time (median = 4). Poverty ($p = 0.02$), adverse childhood experiences ($p < 0.001$), and mental health issues (depression, anxiety, or PTSD; $p < 0.001$) were strongly associated with recent forced sex exposure. Recent forced sex was associated with increased genital inflammation (aOR = 2.74; 95% CI: 1.33 – 5.68; $p < 0.01$) independent of previously-defined biological confounders. There was no evidence that sE-cad concentrations differed by recent forced sex exposure ($p = 0.56$).

Conclusion: Cervicovaginal inflammation is increased for at least a week in FSWs exposed to recent forced vaginal sex. This has important implications for HIV prevention programs that provide care to women who are experiencing gender-based violence and survival sex.

1177 Charting Achievable Milestones for HIV Care Enhancement and Prevention in the US Through 2035

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Background: Despite recent progress in reducing HIV infections, many cities in the US are not on track to reach the ambitious targets set by the Ending the HIV Epidemic initiative. We sought to identify attainable ten-year goals for the US HIV epidemic through improved pre-exposure prophylaxis (PrEP) programming and efforts to strengthen the HIV cascade of care.

Methods: We adapted the Johns Hopkins Epidemiological and Economic Model, a dynamic model of HIV epidemics in US cities, to quantify the impact of improved PrEP coverage, linkage to HIV care, retention, and viral suppression among key risk groups across 18 metropolitan statistical areas (MSAs) in the US. Interventions were scaled up from 2025-2035 in three groups: young (age <35) Black and Hispanic men who have sex with men (MSM); all MSM and persons who inject drugs (PWID); and the full city population. Our primary outcome was the average projected reduction in HIV incidence across modeled MSAs from 2025 to 2035.

Results: Assuming continuation of current trends in HIV transmission and care, HIV incidence was projected by fall by 20% on average across all MSAs (ranging from 14% in Dallas and Los Angeles to 46% in Detroit). Combined improvements to PrEP coverage, linkage, retention, and viral suppression provided an additional 47% reduction, resulting in an average total incidence reduction of 67% (ranging from 60% in Miami to 78% in Detroit). Among interventions considered, expansion of PrEP coverage and increasing retention in care had the greatest individual impact: averaged across all MSAs, HIV incidence was projected to fall by 49% if PrEP were scaled up to 25% of the eligible city population, and by 39% if retention in HIV care were increased to 95%. Some cites (such as Los Angeles) benefited more from improvements in PrEP coverage, while others (such as Baltimore) benefited more from increased retention. The impact of expanding interventions to different populations also varied. In Atlanta, 51% of the maximum added benefit of the combined intervention came from targeting only young Black and Hispanic MSM. By contrast, in San Francisco, 64% of the maximum added benefit resulted from expansion from this group to include all MSM and all PWID.

Conclusion: This analysis provides information to local decision-makers as they seek to identify the combinations of interventions and risk groups that will maximize impact with limited resources in their cities, ultimately helping chart a strategic roadmap to the US HIV policy through 2035.

Figure: Reduction in HIV Incidence from 2025 to 2035 for Intervention Scenarios Targeted to Three Risk Groups, Across Two Example Metropolitan Statistical Areas. Values represent the mean percent reduction in incidence (and 95% credible interval) across 100 independent model simulations. Combined intervention includes all individual interventions.

Targeted Subgroups	No intervention	25% PrEP	95% Linkage	95% Retention	95% Gain of suppression	All Interventions Combined
Baltimore-Columbia-Towson, MD						
Black/Hispanic MSM, age <35	34% [25-44]	40% [32-50]	34% [25-44]	40% [34-49]	35% [26-45]	47% [40-54]
All MSM & PWID		47% [37-56]	34% [25-44]	58% [52-63]	39% [30-48]	68% [63-73]
Full city population		52% [44-61]	34% [25-44]	60% [54-65]	40% [31-49]	75% [72-78]
Los Angeles-Long Beach-Anaheim, CA						
Black/Hispanic MSM, age <35	14% [5-26]	31% [25-39]	14% [5-26]	22% [14-32]	16% [8-27]	38% [33-45]
All MSM & PWID		44% [39-51]	15% [6-26]	38% [30-45]	23% [15-34]	66% [62-69]
Full city population		45% [40-52]	15% [6-26]	38% [31-45]	24% [15-34]	67% [63-70]
Total (across all 18 metropolitan statistical areas)						
Full city population	20% [13-27]	49% [45-53]	21% [14-28]	39% [35-42]	28% [21-34]	67% [64-68]

1178 Evolving Trends in Early ART Initiation in South Africa: An Analysis of Integrated HIV Program Data

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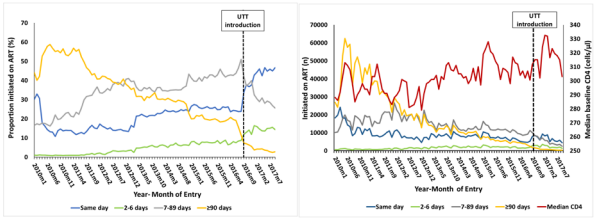
Background:South Africa (SA) has progressively improved HIV treatment guidelines to ensure rapid and sustained viral suppression. We describe the trends of the time between HIV diagnosis and the initiation of antiretroviral therapy (ART) for patients entering HIV care between 2010 and 2017.

Methods: We conducted a prospective cohort study, utilizing integrated data from the clinic-based Three Integrated Electronic Registers (TIER.net) and the National Health Laboratory Service (NHLS) databases across four SA provinces (KwaZulu Natal, Mpumalanga, Limpopo and North West). The study population consisted of individuals diagnosed with HIV, entering in care between January 2010 and September 2017. Entry into care date was defined as either the first CD4 date from the NHLS data or the HIV diagnosis date from the TIER data. The time from entry to ART initiation (date of ART start noted in TIER data) was classified as same-day (HIV diagnosis date), 2-6 days, 7-89 days, and ≥90 days after entry into care. A trend analysis of the number of patients and proportions initiated by these subgroups was compared over time.

Results: Among the 1,319,239 individuals with linked NHLS and TIER data, entering care within the study period, 1,316,410 had started ART. Most were female (69.5%), with a median age of 31 years (Interquartile Range(IQR): 24-39). The number of patients starting ART decreased over time but the median CD4 at entry increased from 298 cells/µl (IQR: 171-463) in 2010 to 321 cells/µl (IQR: 173-500) in 2017. In the early stages of the epidemic, the majority of HIV patients initiated >90 days after entering HIV care, but by the end of the study period this was less than 10.0%. The percentage of patients starting ART ≥90 days after diagnosis decreased from 57.3% for 2010-2011 to 11.4% in 2016-2017. Conversely, same- day ART increased from 17.4% (2010-2011) to 36.0% (2016-2017). The percentage of patients initiated between 2-6 days post-diagnosis showed an upward trend, from 1.2% in 2010-2011 to 12.0% in 2016-2017. Additionally, the percentage of patients initiated within 7 to 89 days varied, starting at 24.1% in 2010-2011, increasing to 42.6% in 2012-2013 but then decreased to 12.0% in 2016-2017. Consistent trends were observed across provinces.

Conclusion: Our results reveal evolving trends in rapid ART initiation in South Africa, underscoring the importance of ongoing efforts to ensure timely ART initiation for all individuals living with HIV.



(A) (B)

Figure 1. Proportion (A) and number (B) of patients initiated, Days to ART start by year/month of entry into care.

1179 Routine Collection of Patient-Reported Outcomes in HIV Clinics: Findings After >100,000 Assessments

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Background: Patient-reported measures and outcomes (PROs) provide important information to improve clinical care and facilitate clinical research. Technological advances have decreased PRO collection barriers. We integrated routine PRO collection into a network of busy, multi-provider, outpatient HIV clinics. Here we describe notable findings among people with HIV (PWH) in care across the US.

Methods: PWH presenting for HIV care at 8 geographically diverse sites in the CFAR Network of Integrated Clinical Systems (CNICS) were asked to complete a touch-screen-based assessment at routine clinic visits every 3-6 months using a web-based application. Assessments are available in English, Spanish, Amharic, Haitian Creole, and Brazilian Portuguese. The length and number of instruments are optimized based on prior responses, skip patterns, time since last PRO, and other factors. The assessment includes instruments validated in PWH measuring antiretroviral medication adherence, depression, anxiety, drug/alcohol use, quality of life, symptom burden, HIV stigma, social support, sexual risk behavior, intimate partner violence (IPV), and other clinically relevant domains.

Results: 20,600 PWH have completed 116,895 unique PRO assessments. Mean age of PWH at first assessment was 44 (range 18-93), 17% were female, and over half (57%) were non-White. 41% of PWH endorsed moderate-severe depression symptoms at least once, and 22% endorsed moderate-severe depression symptoms on their most recent PRO. Over 1/3 of PWH reported currently smoking and ~1/3 reported binge alcohol use within the prior year. Additionally, 71% of PWH endorsed ever using illicit drugs, while 18% reported past 3-month use of cocaine/crack, methamphetamines, and/or illicit opioids. 18% reported concern about a sexually transmitted infection, and 11% reported experiencing past year IPV. In addition to facilitating clinical care, the PRO data have also been used in >80 research papers to date to improve care beyond CNICS sites.

Conclusion: We identified a high prevalence of depression, anxiety, substance use, and IPV – all important domains to facilitate ending the HIV epidemic and improve clinical outcomes. Many of these behavioral health challenges are not measurable by physical exam or laboratory testing and may not be elicited by providers during routine visits without PROs. Collection of PROs is feasible and generates important information to enhance clinical care as well as data to address research questions on clinically important topics.

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1180 Ending the HIV Epidemic in Atlanta: A Mixed-Methods Study to Support the Local HIV/AIDS Response

Micah Piske[1], Bohdan Nosyk[2], Justin C. Smith[3], Bianca Yeung[1], Benjamin Enns[1], Xiao Zang[4], Patrick S. Sullivan[5], Wendy S. Armstrong[5], Melanie Thompson[6], Gaea Daniel[5], Carlos del Rio[5]

[1]University of British Columbia, Vancouver, Canada, [2]Simon Fraser University, Burnaby, Canada, [3]Positive Impact Health Centers, Atlanta, GA, USA, [4]University of Minnesota, Minneapolis, MN, USA, [5]Emory University, Atlanta, GA, USA, [6]Thacker, Thompson and Bernard, MD, Atlanta, GA, USA

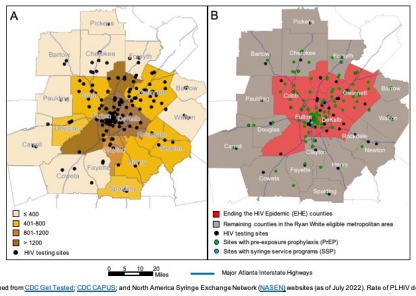
Background: Four counties within the Atlanta, Georgia 20-county eligible metropolitan area (EMA) are currently prioritized by the US 'Ending the HIV Epidemic' (EHE) initiative which aims for 90% reduction in HIV incidence by 2030. Disparities driving Atlanta's HIV epidemic warrant an examination of local epidemiology, service availability, and organizational capacity to reach EHE targets. We conducted a mixed-methods evaluation of the Atlanta EMA to assess geographic HIV epidemiology and distribution of services, service needs, and organization infrastructure to implement or expand services for each pillar of the EHE initiative.

Methods: We collected 2021 county-level data from multiple sources including: AIDSVu (HIV prevalence and new diagnoses), the Centers for Disease Control and Prevention web-based tools (HIV testing and pre-exposure (PrEP) locations), and the Georgia Department of Public Health (HIV testing, PrEP screenings, viral suppression, and partner service interviews). We additionally distributed an online survey to key local stakeholders working at major HIV care agencies across the EMA to assess availability of services, unmet needs, and organization infrastructure during June to December 2022. The Organizational Readiness for Implementing Change (ORIC) questionnaire assessed organization climate for services in need of scale-up or implementation.

Results: We found racial/ethnic and geographic disparities in HIV disease burden and service availability across the EMA - particularly for HIV testing and PrEP in the EMA's southern counties. Five counties not currently prioritized by EHE (Clayton, Douglas, Henry, Newton, and Rockdale) accounted for 16% of the EMA's new diagnoses, but <9% of its 177 testing sites and <7% of its 130 PrEP sites. Survey respondents (N=48; 52% care providers, 42% other health agency staff, 10% people living with HIV) reported high unmet need for HIV self-testing kits, mobile clinic testing, HIV case management, peer outreach and navigation, integrated care, housing support, and transportation services. Respondents highlighted insufficient existing staffing and infrastructure to facilitate the necessary expansion of services, and the need to reduce inequities and address intersectional stigma.

Conclusion: Service delivery across all EHE pillars must substantially expand to reach national goals for metro Atlanta. High-resolution geographic data on HIV epidemiology and service delivery with community input can inform equitable strategies for local EHE efforts.

Figure. Atlanta Eligible Metropolitan Area (**A**) Rate of people living with HIV per 100,000 county population in 2021 and facilities with HIV testing (N=177); (**B**) Ending the HIV Epidemic jurisdictions and sites with HIV testing, pre-exposure prophylaxis (N=130) and syringe service programs (N=2).



HIV service locations obtained from CDC Get Tested; CDC CAPUS; and North America Syringe Exchange Network (NASEN) websites (as of July 2022). Rate of PLHIV derived from AIDSVu 2021 data.

1181 Barriers of Early Enrollment and Rapid ART Initiation Among US HIV Care Facilities

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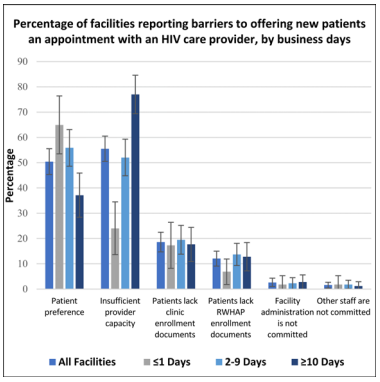
Background: Rapid linkage to HIV care and antiretroviral therapy (ART) initiation is now the standard of care for treating people with HIV (PWH). Understanding and intervening on barriers to rapid enrollment and ART initiation are needed to meet the goals of the Ending the HIV Epidemic in the U.S. initiative.

Methods: We analyzed 2021 data from the Medical Monitoring Project on characteristics of 514 facilities providing care to a national probability sample

of U.S. PWH. Facility data on number of business days to offer new patients an appointment, availability of, and barriers to, rapid intake and ART initiation and Ryan White HIV/AIDS Program (RWHAP) funding were collected. Weighted percentages with 95% confidence intervals of characteristics were reported by barriers, days to appointments, and by RWHAP funding. We assessed significant ($p<0.05$) differences among facilities using Rao-Scott chi-squared tests.

Results: Overall, 20%, 48%, and 32% of HIV facilities could routinely offer a first appointment in <1, 2-9, and ≥10 business days, respectively (median 5 business days). Insufficient provider capacity (56%), patient preference (50%), and patient lacking required documents (19%) were the most reported barriers to offering new patient appointments (Figure). The prevalence of insufficient provider capacity as a barrier to offering an appointment within <1 day was significantly higher for non-RWHAP-funded facilities than funded facilities (62% vs. 48%, p=0.0048). The most reported documents required for scheduling the first appointment were positive HIV antibody or detectable viral load (52%), government-issued identification (36%), proof of residence (24%), proof of income (22%); percentages increased as days to offer an appointment increased and were significantly higher in RWHAP-funded than non-funded facilities (all p-values < 0.05). Most facilities (73%) were routinely able to obtain a 30-day supply of ART during the first HIV care provider visit. The most reported barriers to obtaining a 30-day supply of ART at the first HIV care provider visit included unavailable test results (56%), delays in getting medication paid for (49%), unavailable starter packs (36%), cannot afford copayment (31%), and patient preference (29%).

Conclusion: Structural, personal, or provider-related barriers may delay rapid clinic enrollment or ART initiation. HIV care programs can benefit from removing barriers to care, easing requirements for clinical enrollment and ART prescriptions, and improving patient readiness.



1182 Strategic Advice and Expert Procurement Accelerates the Optimization to DTG in the Americas

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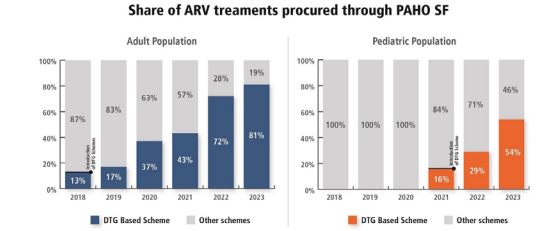
Background: The WHO guidelines recommend dolutegravir (DTG) as the preferred anchor drug for first-line ART, as for second-line ART after a NNRTI failure. DTG has a higher resistance barrier and efficacy, fewer side effects, and a safer profile than other options. The transition to DTG increases viral suppression and ART durability. The Strategic Fund (SF) of the Pan American Health Organization (PAHO) is a technical cooperation mechanism for pooled procurement of essential medicines and health supplies that meet international standards. PAHO provides technical assistance to countries on rational selection and use of medicines and health technologies, demand planning, and strengthening of supply management systems. Here we describe our experience supporting countries to access DTG for adults and children

Methods: Quantitative, descriptive analysis of purchase orders from Latin American and Caribbean countries between January 2018 to September 2023. All products containing DTG were included in the analysis. For comparison, we included all NNRTIs, PIs, and other integrase inhibitors, but excluded NRTI drugs to avoid duplication. We calculated the average annual cost of treatment per unit procured, weighted by the number of units procured. Correlations were calculated using the Pearson coefficient (r).

Results: Adult DTG-based treatments procurement increased from 13% in 2018 (58,135 annual treatments) to 81% in 2023 (240,282 annual treatments procured up to September). Non-DTG treatments decreased from over 390,000 treatments in 2018 to 97,000 in 2022 and 57,880 by September 2023. In addition, the annual unit prices of DTG-based treatments decreased by 40% since 2018 (from 69 USD to 37.45 USD a year), while non-DTG regimens increased by 15% in the same period (from 75.72 USD to 86.76 USD a year). The acquisition of treatment was inversely associated with the cost (r 0.925). For pediatrics, dispersable pDTG 10mg was introduced in 2021 and continued to increase from 16% to 54% by September 2023. The use of pDTG represented a 90% price reduction compared to other regimens (53 USD a year compared to 549 USD a year).

Conclusion: SF and PAHO technical cooperation increased the access to generic DTG-based ART for adults and children in Latin America and the Caribbean. The transition to DTG represented significant savings due to the lower price of DTG compared to non-DTG regimens, in particular for children, which was a strong incentive for transitioning to more effective and safer treatments in the Region.



1183 Evaluating Barriers to Care Among Adults With HIV Who Are Virally-Unsuppressed in Philadelphia

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Background: Barriers to HIV care lead to decreased access to and engagement in care resulting in lower rates of viral suppression, and in turn delays in progress towards Ending the HIV Epidemic (EHE). We sought to assess the proportion of virally unsuppressed individuals whose detectable viral load can be attributed to identified barriers of HIV care.

Methods: We used weighted data from the 2015-2021 cycles of the Medical Monitoring Project (MMP) among residents of Philadelphia, Pennsylvania. Weighted frequencies for barriers to care were calculated overall and by viral suppression status. We used generalized linear regression models to calculate the prevalence ratios for each barrier, adjusted for age and gender. We calculated the population attributable fraction (PAF) for the proportion of virally detectable PWH who could have become virally suppressed had they not experienced that specific barrier to HIV care. All relative risks and PAFs were stratified by race/ethnicity.

Results: There were an estimated 7,541 individuals with a detectable viral load (>200 copies/ml) in Philadelphia included in analyses. Being busy with personal things, like family or work and difficulty getting to care, was the most commonly reported barrier to HIV care among individuals with a detectable viral load (30.1%), followed by mental health (21.7.5%), feeling well (17.2%), and problems with money or health insurance (11.8%) .The PAF of financial barriers on detectable viral load was highest among non-Hispanic Whites (8.3%), with non-Hispanic Black and Latine having similar PAFs. The PAF of mental health on detectable viral load was highest among non-Hispanic Blacks (5.8%), with non-Hispanic White and Latine having similar PAFs. Non-Hispanic Black and Latine had similar PAFs of personal reasons on detectable viral load, but there was an inverse association between the barrier of personal reasons and detectable viral load among non-Hispanic Whites.

Conclusion: No single barrier to HIV care accounts for the plurality of individuals with a detectable viral load. System-level implementation strategies for increasing viral suppression will need to be tailored to specific populations with a health equity lens. Better access to mental health services and supportive services for retention in care may be the best strategies for increasing viral suppression among racial/ethnic minorities. Future research should assess the PAF of barriers in combination to optimize service delivery.

Table 1: Population attributable fractions for each barrier to HIV care by Race/ Ethnicity

	Financial PAF (95% CI)	Mental Health PAF (95% CI)	Feeling Well PAF (95% CI)	Personal Reasons PAF (95% CI)
Non-Hispanic White	8.3% (6.6, 9.7)	3.5% (0.2, 6.0)	3.5% (0.8, 5.7)	-8.3% (-15.0, -3.0)
Non-Hispanic Black	0.8% (0.2, 1.5)	5.8% (4.8, 6.5)	3.7% (2.8, 4.4)	6.3% (5.1, 7.3)
Hispanic/Latine	1.5% (-0.7, 3.3)	3.5% (1.3, 5.2)	0.6% (-2.0, 2.7)	5.9% (1.9, 9.6)

1184 Novel Post-Hospitalization Care Model Decreases Mortality in People With HIV in Zambia: Pilot Study

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Background: Despite progress in HIV epidemic control in Zambia, HIV-related mortality remains high. Deaths are often preceded by hospitalization, and post-discharge mortality among people with HIV (PLWH) reaches 20-40% within six months due to individual, psychosocial, and systemic factors. We conducted a feasibility study of a community health worker (CHW)-led model to improve patient health outcomes and reduce mortality post-discharge.
Methods: A quasi-experimental feasibility and acceptability study was conducted at two tertiary hospitals in Lusaka, Zambia, using the PRISM implementation science framework. Adults hospitalized with HIV in Lusaka and then discharged were enrolled and followed up for 6 months post-discharge. The control group received standard of care (SOC) with telephonic follow-up. The intervention group received a novel care package, based on formative qualitative work, consisting of a discharge summary card, CHW home visits within one week of discharge, and screening and referral for depression and alcohol abuse at 1-3 months post-discharge. A physician-clinical liaison officer team based at the discharging hospital oversaw the CHW home visits, which included psychosocial counseling, vital signs check, medication counseling, and outpatient follow-up. Home visit data were collected by CHWs using electronic devices.
Results: Among 124 patients (median age, 41 years; 57.8% women; median CD4, 299 cells/mm^3) in the SOC group, 23 (18.6%) died within 6 months of discharge. From 18 August to 20 September 2023, 21 patients enrolled in the pilot intervention group. To date, 13 (61.9%) received at least one home visit (7 of these were within 1 week of discharge) and 5 two visits, 15 (71.4%) received a discharge summary card, and 12 (57.1%) were screened for behavioral health problems. At one month, 12 were alive, 1 (7.7%) had died (from extrapulmonary tuberculosis), and 1 (7.7%) was readmitted based on the findings of the CHW at a home visit. Acceptability among participants and caregivers has been high.
Conclusion: A novel discharge model of care, involving enhanced discharge instructions, CHW home visits, and screening and referral for behavioral health problems, appeared to be feasible and acceptable in urban Zambia. Post-hospital CHW visits have potential to reduce post-discharge mortality among PLWH in countries with generalized HIV epidemics such as Zambia. Focusing on the peri-discharge period can strengthen health systems as countries move into HIV epidemic control.

1185 The HIV Care Cascade in Medicaid, 2001-2015

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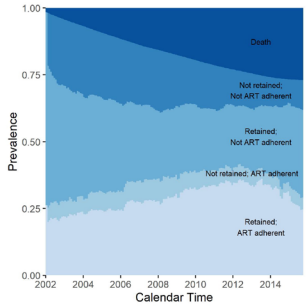
Background: Medicaid serves as the largest single source of insurance for people with HIV (PWH) in the US, with approximately 40% of PWH covered by Medicaid. Not only does Medicaid represent a large, diverse population of PWH in US, it also represents some of the most vulnerable PWH, since eligibility is based on low income or disability. While the HIV care cascade is well characterized among all PWH in the US and among those linked to HIV care clinics, less is known about the state of the care cascade among PWH on Medicaid or how the cascade has changed over time.
Methods: We analyzed data from 273,799 Medicaid beneficiaries with HIV, enrolled in 14 US states, 2001-2015. All beneficiaries identified as having HIV through claims records are aware of their diagnosis and linked to care; thus, we focused on the later steps of the care cascade. We estimated prevalence of 4 levels of the HIV care cascade: retained in care and adherent to ART; retained but not on ART; not retained but on ART; not retained and not on ART. Beneficiaries were considered retained in care if they had an office visit, viral load measurement, or CD4 cell count every 6 months. Adherence to ART in each month of follow-up was defined as having a medication possession ratio of at least 80%. Prevalence of each state in each month 2001-2015 was estimated using a non-parametric multi-state approach, accounting for death as a competing event and for loss of Medicaid coverage using inverse probability of censoring weights. Analyses were conducted overall and by US state.
Results: As shown in the Figure, 20% of beneficiaries with HIV were retained and ART adherent in 2001; this proportion reached a peak of 36% in 2013. The proportion not retained in care but ART adherent did not meaningfully change across follow-up (5-8%). In contrast, the proportion retained in care but not ART adherent decreased from 53% to 32%, and the proportion not retained in care and not ART adherent decreased from 20% to 13%. Death remained an important competing event in this era, with a cumulative incidence of 27% by 2015. Results differed by US state.
Conclusion: Despite being linked to care, less than half of beneficiaries with HIV were classified as ART adherent across all of follow-up, likely indicating that many Medicaid beneficiaries with HIV were not virally suppressed during this time period. These findings were seen even in the post-2012 "Treat All" era. Future work will explore whether HIV care engagement improved between 2015-2021.



1186 Prevalence and Predictors of Advanced Disease Among People Living With HIV in Masaka Region, Uganda

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Background: A large percentage (22%) of people living with HIV (PLHIV) present for care with advanced HIV disease (AHD), threatening the achievement of the 95-95-95 goals to end AIDS by 2030. For anyone over the age of five, AHD is defined as CD4 count <200 cells/mm^3 or with a current WHO stage 3 or 4 events. This study aimed to examine the prevalence and factors related to AHD among newly diagnosed PLHIV in Masaka Region, Uganda.
Methods: A cross-sectional study was conducted from October 2021 through September 2022 among newly diagnosed PLHIV enrolled in care from 12 districts in Masaka Region. Data from electronic medical records (EMR) at health facilities were extracted for analysis. Variables included sex, age, marital status, location of facilities, and points of entry into care. Using a bivariable analysis, we determined the prevalence of AHD. A multivariable modified Poisson regression analysis was used to determine predictors with 95% confidence intervals (CIs).
Results: Of 3,452 newly diagnosed PLHIV on ART included in this study, 2,254 (65.3%) were females. The prevalence of AHD was 15% (518). The results from multivariable modified Poisson regression revealed that participants aged 18-35 years had lower risk of AHD compared to those aged 5-17 years (aPR=0.45; 95% CI: 0.27, 0.78). Married individuals were at lower risk of AHD compared to unmarried participants (aPR=0.67; 95% CI: 0.57, 0.79). Male participants (269/1,198, 22.5%) had higher risk of AHD compared to females (249/2,254, 11.1%; aPR=1.85; 95% CI: 1.57, 2.19). Participants receiving ART services from urban facilities had higher risk of AHD compared to participants receiving ART from rural sites (aPR=1.61; 95% CI: 1.35, 1.93). Participants who were enrolled into care through HIV testing service outreaches (aPR=0.72; 95% CI: 0.58, 0.90) had lower risk of AHD while participants from other care points (aPR=1.28; 95% CI: 1.06, 1.53) had higher risk of AHD compared to the general outpatient point.
Conclusion: The proportion of AHD in this cohort (15%) was lower than the national proportion of 22%. However, this work can be used to design interventions to address higher AHD prevalence among males, in urban facilities, and at care points other than HIV testing outreach sites and the general outpatient point.
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1187 Met and Unmet Health and Welfare Services Needs Amongst People With HIV in the UK

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Background: Despite accessible and effective HIV treatment, the health and wellbeing of many people with HIV (PWH) is negatively impacted by social and economic disadvantage and unmet need for services. We assessed unmet health and welfare services needs in a large UK survey.
Methods: Positive Voices 2022 is the largest survey of PWH accessing care in the UK. Participants completed a questionnaire on demographics, socioeconomic status (money to meet basic needs), health and lifestyle factors, met and unmet needs, and sexual behaviour. We analysed factors associated with increased need for services, defined as follows: (i) Mental health/drug services: psychological/stress support, alcohol/drug counselling, chemsex/drug detox; (ii) Physical health: weight management, sex life support, smoking cessation, family planning, home services; (iii) Welfare: housing, meal services, employment/benefits/financial advice, legal/immigration support. We conducted multivariable logistic regressions to quantify odds of reporting any need, and the odds of any unmet need amongst those with need. Each model was adjusted for age, demographics, time since HIV diagnosis, and other covariates if significant in unadjusted analysis (Table 1).
Results: 4620 people participated; 2464 (53%) gay, bisexual and other men who have sex with men (GBMSM), 911 (20%) heterosexual women, 585 (13%) heterosexual men; 1117 (24%) were of Black ethnicity; median (IQR) age of 52 years (43-60). 1617 reported any mental health/drug service need, of whom 1066 (65.9%) had unmet need; 1879 any physical health need, of whom 1290 (68.7%) had unmet need; and 1454 any welfare need, of whom 1008 (69.3%) had unmet need. Table 1 shows all results. Need and unmet need were highest for younger people, except for unmet mental health need. Mental health need and unmet physical health need were higher for GBMSM, whilst physical health and welfare service needs were higher amongst Black African respondents. Lack of money to meet basic needs was associated with both mental and physical health needs, with mental health needs not met. Having depressive symptoms was associated with both physical health and welfare needs.
Conclusion: There is a significant burden of unmet health and welfare service need amongst PWH in the UK, despite universal healthcare access. HIV services should assess unmet need and identify routes to accessing available support, especially for younger people, those from minority groups, and those facing poverty or mental health challenges.

Table: Odds of service need or unmet need

Full multivariable logistic regressions, adjusted OR (95% confidence interval)	Population (n=4620)	Any mental health need (n=3844)[1,2]	Unmet mental health need, given any need (n=1444)	Any physical health need (n=3652)[1,2]	Unmet physical health need, given any need (n=1566)[1,3]	Any welfare need (n=3640)[2,3]	Unmet welfare need, given any need (n=1296)[2]
Age (per 10 years)		0.66 (0.61 - 0.71)	0.99 (0.89 - 1.11)	0.88 (0.82 - 0.95)	0.88 (0.78 - 0.99)	0.84 (0.78 - 0.90)	0.83 (0.74 - 0.94)
Demographics (ref – GBMSM, n=2464)	Black African heterosexual men (n=250)	0.49 (0.35 - 0.68)	1.33 (0.72 - 2.45)	1.47 (1.08 - 2.00)	0.32 (0.20 - 0.49)	3.57 (2.63 - 4.86)	2.78 (1.58 - 4.88)
'Undisclosed' category included but not shown (n=456)	Heterosexual men, all other ethnicities (n=335)	0.50 (0.37 - 0.66)	0.71 (0.43 - 1.17)	0.82 (0.63 - 1.08)	0.63 (0.41 - 0.99)	1.21 (0.91 - 1.62)	1.62 (0.97 - 2.71)
	Black African women (n=622)	0.53 (0.42 - 0.66)	0.51 (0.36 - 0.73)	1.72 (1.36 - 2.17)	0.33 (0.24 - 0.46)	3.60 (2.85 - 4.54)	1.55 (1.09 - 2.21)
	Women, all other ethnicities (n=493)	0.92 (0.73 - 1.16)	0.98 (0.69 - 1.40)	1.33 (1.06 - 1.68)	0.91 (0.62 - 1.31)	1.55 (1.22 - 1.98)	0.98 (0.68 - 1.41)
Able to meet basic needs (ref – yes, n=2255)	No, not always meeting basic needs (n=1918)	2.50 (2.15 - 2.91)	1.33 (1.05 - 1.68)	1.98 (1.70 - 2.30)	*	**	**
Depression symptoms (ref – no, n=2758)	Yes, PHQ9 ≥10 (n=1490)	**	**	1.79 (1.54 - 2.09)	1.30 (1.01 - 1.67)	3.18 (2.71 - 3.73)	1.13 (0.88 - 1.46)

Adjusted for years since HIV diagnosis, and covariables with unadjusted p≤0.1: [1]employment, [2]detectable viral load, [3]education (early high school, high school graduate, vocational, university). Participants excluded if missing any outcome or independent variable.
*Excluded: unadjusted p>0.1
**Excluded from model for specific outcome

1188 Real-World Utilization of HIV PrEP Medication in a Population-Level PrEP Program in BC, Canada

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Background: Publicly funded, centrally distributed HIV PrEP with emtricitabine-tenofovir has been available in British Columbia (BC) since January 2018. We evaluated PrEP persistence and estimated medication utilization using longitudinal prescription data from BC's PrEP program.
Methods: BC PrEP participants with ≥1 dispensed PrEP prescription (Rx) between 1-Jan-2018 to 30-Jun-2022 and ≥1 year follow-up opportunity were included. Demographics and PrEP Rx data were described, and PrEP persistence characterized by 1, 2 or ≥3 Rx. Multinomial logistic regression was used to obtain the univariate odds ratio (OR) to compare persistence in ≥3 vs. 1 Rx for variables of interest. For those with ≥3 Rx, PrEP utilization was estimated by calculating proportion of days covered (PDC), and stratified by prescribed daily vs. non-daily use.
Results: Overall, 9375 participants were included [median (Q1-Q3) age 32 (27-41) years; 96.9% cis-men, 1.3% trans-women, 0.9% cis-women, 0.5% trans-men; 54.3% reside in Vancouver]. 98.4%, 0.7%, and 0.2% qualified with men who have sex with men (MSM)-, heterosexual-, and injection drug use-based risk criteria, respectively. 80% (n=7520) of participants persisted with PrEP ≥3 Rx, while 9% and 11% received only 1 and 2 Rx's, respectively. A significant difference in the odds of PrEP persisting ≥3 vs. 1 Rx was observed in several subgroups: age category 18-28 years (Ref. >48 years) (OR 0.7 [95% CI, 0.5-0.8], p=0.0002); gender cis-women (Ref. cis-male) (OR 0.2 [0.1-0.3], p<0.0001); trans-women (OR 0.3 [0.2-0.4], p<0.0001); trans-men (OR 0.4 [0.2-0.8], p=0.0077); non-MSM HIV acquisition risk group (Ref. MSM) (OR 0.5 [0.3-0.9], p=0.0323); no prior PrEP use (Ref. prior use) (OR 0.6 [0.5-0.7], p<0.0001); residence outside Vancouver (Ref. Vancouver) (OR 0.6 [0.6-0.7], p<0.0001). Of 7520 participants with ≥3 Rx, 93% were prescribed daily PrEP, with median (Q1-Q3) PDC 0.83 (0.6-0.96), median PDC follow-up time of 30 (15-50) months and median Rx count of 8 (5-14). For non-daily PrEP (7%), median PDC was 0.49 (0.3-0.67), median PDC follow-up time was 42 (21-54) months, and median Rx count was 7 (5-11). 77% of daily users had median overall PDC >0.57 and 53.6% had PDC >0.8.
Conclusion: In a population-level program, 80% of participants demonstrated PrEP persistence ≥3 Rx. Persistence was decreased amongst younger, non-cis-men participants, and those residing outside the urban centre. Overall estimates of PrEP utilization suggest non-daily or interrupted use in many prescribed daily PrEP.

1189 Community and Facility-Based PrEP Uptake and Adherence Among People Who Use Drugs in Uganda

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Background: People who use drugs (PWUD) in Uganda experience a high HIV burden and limited access to HIV prevention services, which are often delivered in parallel to harm reduction programs and by different implementing organizations. Integrating HIV pre-exposure prophylaxis (PrEP) into harm reduction services could substantially enhance service uptake and reduce risk of HIV acquisition.
Methods: From January 2022-August 2023, we enrolled PWUD into TDF-based oral PrEP programs integrated into harm reduction services at a community-based needle and syringe program (NSP) and a facility-based medication-assisted treatment (MAT) program located in Kampala, Uganda (NCT05040308). The 6-month PrEP refill data were abstracted from medical records to estimate PrEP persistence. We enrolled a subset of participants into a research cohort to measure tenofovir concentration levels in plasma to estimate PrEP adherence. We compared the frequency of PrEP persistence and adherence across program type using log binomial regression models.
Results: Through August 2023, 100% of HIV-negative NSP clients (n=265) and 98.9% of MAT clients (n=91) with 6 months of follow up initiated PrEP. The median age was 31 (IQR 25-39), 90.7% were male, 63.7% reported using street opioids with injection and smoking being the most common route of use. Among 64% (n=227/355) of times when 1 bottle (30 pills) of PrEP was dispensed, a refill was sought within 30 days. When 60 pills were dispensed, 65% of participants returned within 60 days and when 90 pills were dispensed, 45% returned within 90 days. Six-month PrEP persistence in MAT and NSP was 12% and 62% (relative risk=0.16, 95% CI: 0.09-0.27, p<0.0001). In the subset using PrEP, 6-month plasma TFV levels were high (>31ng/ml) in 52% and moderate (0.1-31ng/ml) in 37% of NSP participants and high in 34% and moderate in 32% of MAT participants (global p-value p=0.07).
Conclusion: In integrated PrEP and harm reduction programs, PrEP uptake was very high. We observed greater PrEP persistence in the community-based NSP

program and moderate adherence overall. Since these programs serve people with different harm reduction preferences, further research is needed to explore how to effectively integrate PrEP into community- and facility-based programs.

1190 Modeling the Potential Impact of Scaling Up Event-Driven PrEP Among Gay, Bisexual, and Other MSM

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Background: Oral HIV preexposure prophylaxis (PrEP) is effective at preventing HIV acquisition among gay, bisexual, and other men who have sex with men (MSM). A small proportion of PrEP users in the United States practice event-driven PrEP (EDP), despite high interest in and willingness for the dosing regimen. EDP has also been found to be useful for daily PrEP users with low adherence. However, the population-level HIV impact of EDP given real-world empirical data on time-varying adherence is unknown.
Methods: We extended an existing network-based mathematical HIV transmission model for MSM to allow initiation of EDP with varying adherence across sex acts. EDP is implemented as the 2-1-1 dosing schedule: 2 pills on the day of sex, 1 pill a day after, and 1 pill 2 days after. Daily and EDP users may switch regimens. Adherence and efficacy of EDP were parameterized using data from IPERGAY, HPTN 067/ADAPT, and AMPrEP. We simulated counterfactual scenarios over 10 years, including incremental increases in EDP initiation rates among MSM with daily PrEP indications who do not start daily PrEP, expanding EDP eligibility to any MSM sexually active in the last 6 months, and targeting EDP eligibility to daily PrEP discontinuers with low adherence. These scenarios were compared to a reference scenario with only daily PrEP. Models were calibrated to HIV prevalence and PrEP coverage levels among MSM in Atlanta, Georgia.
Results: In the reference scenario, HIV incidence was 0.38 per 100 person-years. The percent of infections averted (PIA) was 1.0% when MSM were equally likely to start EDP as daily PrEP with the same indications and 2.2% when MSM were 1.5 times as likely to start EDP. Expanding eligibility for EDP to any sexually active MSM yielded a PIA of 7.5%, while tailoring eligibility to daily PrEP discontinuers with low adherence led to 1.4% more infections. 373,726 pills were needed to prevent an HIV infection when EDP indications were the same as daily PrEP, compared to 193,567 pills with expanded EDP eligibility.
Conclusion: EDP yielded modest population-level reductions in HIV incidence and infections averted over 10 years given the non-inferiority of EDP to daily PrEP. Providing EDP with a low indication threshold (any sexually active MSM) provided greater benefits than targeted provision of EDP to MSM with daily PrEP adherence challenges. In terms of medication efficiency, expanding EDP among MSM with recent sex reduced overall pill burden in the population while maintaining PrEP effectiveness.

1191 PrEP Persistence and Ongoing HIV Risk Among Patients Initiating PrEP at an Urban Malawi STI Clinic

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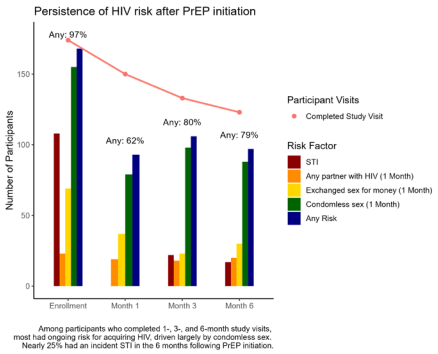
Background: Persons presenting with sexually transmitted infections (STI) are a priority group for HIV prevention, including biomedical pre-exposure prophylaxis (PrEP). Longitudinal risk and persistent use of oral PrEP among STI patients in sub-Saharan Africa (SSA) has not been well characterized.
Methods: We enrolled men and women ≥15 years presenting to an urban STI clinic who were eligible for and initiated on PrEP according to Malawi PrEP guidelines. All PrEP care was provided by Ministry of Health staff. Participants were tested for Chlamydia trachomatis (Ct), and Neisseria gonorrhoeae (Ng) at enrollment, month 3, and month 6, and completed behavioral surveys. PrEP persistence was derived from PrEP record review, defined as no >7 days without pills based on visit date, pills distributed, and self-reported missed pills.
Results: We enrolled 174 participants initiating PrEP between March-December 2022. Nearly two-thirds were male (109/174; 63%), and 70/174 (40%) were <25 years. In the month preceding PrEP initiation, 23/174 (13%) reported having a partner living with HIV and 69/174 (40%) had exchanged sex for goods, money, or favors. Four (4%) men endorsed ever having anal sex. Of 173 with linked PrEP records, 66 (38%) were persistent on PrEP at 6-months, 58 (34%) were not persistent but retained in the study, and 49 (28%) were not persistent and lost to follow-up. Approximately half (94/173; 54%) were persistent at 3 months. 6-month persistence was higher for women (29/65; 45%) vs men (37/108; 34%) and for those aged ≥25 (43/103; 42%) vs <25 (23/70; 33%). Persistent HIV risk was common among those retained in the study, regardless of PrEP persistence. Among those with at ≥1 follow-up study visit (153/174; 88%), 25 (16%) reported having a partner living with HIV, and 58 (38%) reported exchanging sex for goods, money or favors in the preceding month. Among the 136/174 (78%) with ≥1 follow-up Ct/Ng test, 32 (24%) had ≥1 incident STI (Ct: 15; Ng: 7, Ct and Ng: 10).
Conclusion: Despite ongoing HIV risk, including frequent incident STIs in a short follow-up period, PrEP persistence among a cohort of persons initiating PrEP from an STI clinic in Malawi was poor. Persistence was particularly low among men, who accounted for nearly two-thirds of the study population. Strategies to address barriers to persistent PrEP use, especially for the relatively understudied population of heterosexual men in SSA, are urgently needed.



1192 PrEP Knowledge and Use: Results From the Zambia Population-Based HIV Impact Assessment 2021

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Background: Pre-exposure prophylaxis (PrEP) taken daily has been shown to be effective prevention against HIV acquisition and has been recommended by WHO for people at substantial risk for HIV since 2015. Zambia has been implementing the PrEP program since 2017 and rolled it out nationwide in 2018.
Methods: We analyzed data from the 2021 Zambia Population Based HIV Impact Assessment (ZAMPHIA). We used descriptive analysis (with chi-square test) to analyze demographic and behavioral characteristics of PrEP knowledge and PrEP use, and a weighted multivariable logistic regression model to identify key predictors of PrEP use among all participants. All results were weighted to account for complex survey design.
Results: Among 22,183 participants aged 15+ year who answered the PrEP questions, 21.2% (95% CI: 20.3- 22.2) reported ever having heard of PrEP: 18.9% (95% CI: 17.6-20.2) among men and 23.5% (95% CI: 22.3-24.8) among women. Within age groups 17.5% (95% CI 16.1-18.9) of young adults aged 15 to 24 years and 17.2% (95% CI: 15.8-18.7) of those aged 45+ years had ever heard of PrEP. Other characteristics associated with having ever heard of PrEP were being married (22.1% [95% CI: 20.9- 23.3]), living in urban areas (30.3% [95% CI:28.5-32.1]) and having more than a secondary education (56.7% [95% CI:52.8-60.4]). Of those who have ever heard of PrEP, 3.9% (95% CI: 3.2- 4.8) reported ever using PrEP. PrEP use was highest among those who reported having a sexual partner who is HIV positive 16.5% [95% CI: 12.3- 21.7]). Those who reported a HIV positive sexual partner were more likely to report ever having used PrEP compared to those who did not know the HIV status of their partner (aOR 5.84 [95% CI: 3.27-10.41]; P<0.001).
Conclusion: Although PrEP has been available country wide since 2018, just over one-fifth of adults age 15+ years were aware of PrEP. This is of concern particularly among young adults aged 15-24 who have the highest incidence of HIV as seen in ZAMPHIA. These results can guide the Ministry of Health to target the dissemination of PrEP information to populations with low knowledge of PrEP, including men, those aged 45+ years, living rural areas, and with lower

education levels. These results demonstrate that having a sexual partner who is HIV positive is a strong predictor for ever having used PrEP. More efforts, however, are needed to increase uptake in other populations that are at substantial risk for HIV infection, such as persons with multiple sexual partners and low condom use.

Table 1: Demographic and Behavioral Characteristics Associated with PrEP use and knowledge among Participants in ZAMPHIA 2021 (Weighted)

Characteristic		Ever Heard of PrEP, % [95% CI] (n = 4,530)	Number	P-Value	Ever Used PrEP, % [95% CI] (n = 171)	Number	P-Value
	Total	21.2 [20.3- 22.2]	22,183		3.9 [3.2- 4.8]	4,530	
Age Group (in years)	15-24	17.5 [16.1-18.9]	7,323	0.395	3.4 [1.9- 5.9]	1,241	<0.001
	25-34	27.5 [25.8- 29.3]	5,451		3.9 [3.0- 5.2]	1,474	
	35-44	24.7 [22.2- 27.3]	3,988		5.0 [3.5- 7.1]	963	
	45+	17.2 [15.8- 18.7]	5,421		3.2 [2.0- 4.9]	852	
Gender	Men	23.5 [22.3- 24.8]	12,536	0.589	4.0 [3.2- 5.1]	2,748	<0.001
	Women	20.4 [20.3- 22.2]	22,183		3.8 [3.2- 4.8]	4,530	

1193 Sexual Health Outcomes Among Daily and On-Demand Oral PrEP Users in China

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Background: Longitudinal data on sex behaviors and STIs among Chinese PrEP users is limited. Here we reported self-reported newly diagnosed STIs and sex behaviors among MSM who are on daily and on-demand PrEP regimens in China.

Methods: MSM in Wuhan and Guangzhou were recruited by online ads, clinic flyers, and community referrals to a PrEP demonstration trial. Behavioral survey data were collected at baseline and quarterly follow-ups over 12 months (M3, M6, M9, M12). MSM were prescribed TDF/TFC as oral PrEP and could opt for daily or on-demand regimens. Descriptive analysis and multivariable logistic regressions were conducted in Stata 15.0.

Results: From September 2021 to September 2023, 1,209 MSM were enrolled and initiated PrEP (mean age=28.0, IQR 24.0-31.4), with 164 (16.0%) dropping out before the trial ended. About half of the participants opted for daily PrEP, while the rest chose on-demand (2+1+1). MSM reporting not having penetrative sex during the three months increased from 3.9% at baseline to 11.1% at M12 (p<0.001). Regarding condom use behaviors, we observed a notable increase of MSM reporting "never to seldom using condoms in sex" at M9 & M12 (17.3%, 18.6%) compared to baseline (10.1%) (p<0.001). The proportion of people having sex under the influence of substance use (predominantly alcohol & nitrate inhalants) remained persistently high (52.8% at baseline vs. 46.0% at M12). The proportion of people who self-reported any STI diagnosed in the past 3 months remained 4.9 to 8.0% during the study period, with the syphilis prevalence stabling from 3.6-5.0%. Multivariate analyses indicated that PrEP dosing strategies were not associated with newly diagnosed STIs, condom use habits change, or sex under the influence of substances over time. However, MSM of higher income levels (OR=3.9, 95% CI: 1.7-9.1) and those who seldom to not use condoms (OR=3.4, 95% CI: 1.8-6.7) were more likely to report having sex while using substances.

Conclusion: Our study results showed comparable impact on risks of STIs or sex behavior changes between once-daily and on-demand oral PrEP dosing strategies. Nonetheless, the observed increased number of MSM not having sex, less condom use habits, and persistent prevalence of engaging in sex activities under the influence of substance use underscore the evolving sexual behavior patterns within Chinese MSM PrEP users. Engaging PrEP users in routine testing and safe sex counseling is critical to the holistic health promotion of MSM communities.

Table 1. Sexual health outcomes among once-daily and on-demand PrEP users in China

In the past 3 months	Baseline (n=1,209)	Month 3 (n=1,035)	Month 6 (n=678)	Month 9 (n=503)	Month 12 (n=307)
Condom use					
Always to often times	90.5%	85.5%	82.5%	80.9%	79.1%
Seldom to never	9.5%	14.5%	17.5%	19.1%	20.9%
Substance use (e.g., nitrates inhalants, marijuana, cocaine, amphetamine, etc.)					
Yes	35.2%	N/A	26.5%	N/A	25.7%
No	64.8%	N/A	73.5%	N/A	74.3%
Sex under influence of substance use (e.g., alcohol, nitrates inhalants, etc.)					
Yes	52.8%	N/A	46.8%	N/A	45.9%
No	47.2%	N/A	53.2%	N/A	54.1%
Newly diagnosed STIs by doctors					
Yes	8.2%	8.6%	7.2%	7.5%	4.9%
No	91.8%	91.4%	92.8%	92.5%	95.1%

1194 HIV Recency Surveillance Improves PrEP Uptake: Evaluation With Synthetic Controls

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Background: Eswatini's HIV-1 Recent Infection Surveillance (EHRIS) program, implemented since 2019, identifies trends in recent and long-term HIV infections. EHRIS flags hotspots (HIV testing centers with ≥4 monthly recent infections) for public health responses focused on fidelity to index testing, partner notification, and linkage to PrEP for contacts testing negative. We used synthetic control methods (SCM) to evaluate the impact of this public health response on PrEP enrollment.

Methods: We used October 2019-December 2022 data to conduct a difference-in-difference analysis with SCM to compare trends in PrEP enrollment between intervention (n=9) and non-intervention facilities (n=93) pre- and post-intervention. SCM is a data-driven technique that manufactures a weighted synthetic control (SC) from a pool of possible controls to best approximate pre-treatment trends observed in the intervention unit(s). The intervention point was August 1, 2020. Pre-intervention trends were estimated using facility-level characteristics associated with historic PrEP enrollment trends. To ensure the SC did not create differences unrelated to the intervention, we completed an "in-time" placebo test, using March 1, 2021 as our fake intervention time.

Results: Similar pre-intervention trends were observed in the intervention clinics and the SC (Figure 1a). The average treatment effect for the post-intervention period was 10.2 additional PrEP enrollees a month, from an average of 6.7 in the SC to 16.9 in the intervention (p=0.004). Six months post intervention, PrEP enrollment increased in both groups but increased more in intervention facilities; this was sustained during the rest of the study period. Between April-December 2022, intervention clinics averaged roughly twice the monthly PrEP enrollment of the SC. Decreases in June 2021 in both arms occurred during a period of political unrest. The mean squared prediction error for the model was 3.41, demonstrating adequate predictive accuracy of the model for program data. The placebo test (Figure 1b) showed no difference in outcome trends unrelated to the intervention.

Conclusion: EHRIS-informed interventions resulted in increased and sustained PrEP enrollment in intervention facilities in Eswatini compared to the SC. Recency data strengthened linkages to PrEP services among HIV negative contacts and increased PrEP uptake.

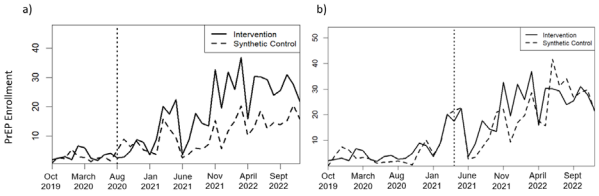

Figure 1. a) Trends in PrEP Enrollment Between Intervention and Synthetic Control; b) Placebo Test: Trends in PrEP Enrollment with a Placebo Fake Time Point

1195 Expanding Event-Driven PrEP to People Assigned Male at Birth Across 3 African Countries

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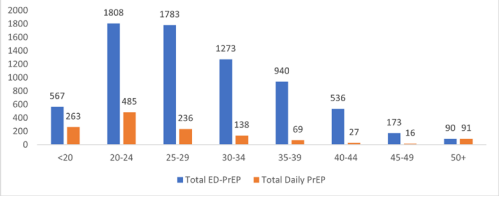
Background: In 2022, World Health Organization recommended the expansion of event-driven pre-exposure prophylaxis (ED-PrEP) to prevent HIV not only among men who have sex with men (MSM) but also all people assigned male at birth (AMAB) who are not using estradiol-based exogenous hormones. The USAID- and PEPFAR-funded Meeting Targets and Maintaining Epidemic Control (EpiC) project offered ED-PrEP as another option to oral daily PrEP to people AMAB not using estradiol-based exogenous hormones across three sub-Saharan African countries.

Methods: Using various differentiated service delivery (DSD) models, EpiC offered HIV-negative people AMAB who are MSM, who purchase sex, who are transgender, and other people AMAB options for daily PrEP and ED-PrEP in Ghana, Liberia, and Eswatini. ED-PrEP was recommended for people who had infrequent and predictable sexual encounters or anyone who wanted to enroll. Routinely collected programmatic data was analyzed to understand preference and uptake by population and age groups across the three countries.
Results: Between October 2021 and May 2023, EpiC newly initiated 8,495 individuals AMAB on oral PrEP in the three countries, among whom 7,101 (84.40%) initiated on ED-PrEP. A larger proportion of people AMAB who were not MSM chose ED-PrEP over traditional daily PrEP (95.36%) compared to MSM (76.85% chose ED-PrEP). The proportion of those who initiated ED-PrEP over daily PrEP was highest among individuals 40–44 years of age (95.20%; 536/569) and lowest among those 50 and over (49.72%; 90/195) (Figure 1) Oral PrEP uptake among people AMAB who were not MSM (84.58%) was higher than among MSM (75.92%). PrEP uptake among those to whom it was offered increased from 39.99% (October 2020–September 2021) to 72.57% (October 2021–May 2023) after ED-PrEP was offered in Ghana and Eswatini. The increase was most pronounced among those aged 50 year and older, from 18.95% to 75.58%.
Conclusion: The results demonstrate the feasibility of offering ED-PrEP to all people AMAB and the preference of some of these individuals for ED-PrEP compared to daily oral PrEP. Scale-up of ED-PrEP may improve oral PrEP uptake among all people AMAB warranting ED-PrEP expansion efforts beyond MSM. More efforts are needed to improve access to ED-PrEP through various DSD models as we scale oral PrEP provision. More research is needed to understand preferences for all individuals AMAB-not just MSM-and to improve uptake strategies.

Figure 1. Number of oral PrEP initiations among all people AMAB across three countries by ED-PrEP vs. daily PrEP (October 2021 - May 2023)



1196 HIV Risk Factors and PrEP and Contraceptive Use Among Women Seeking Postabortal Care in Kenya

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Background: Adolescent girls and young women (AGYW) in Kenya are a priority population for HIV prevention and face high rates of HIV incidence, recurrent unintended pregnancies, and sexually transmitted infections.
Methods: Between March 2021 and March 2023, we implemented a project on HIV PrEP delivery among AGYW seeking postabortal care (PAC) in 15 public and private health facilities in Kenya. Eligible AGYW aged 15-30 years were offered PrEP. In women initiating PrEP and enrolling for research procedures, study questionnaires (at enrollment and month 1) and tenofovir point of care urine tests (at month 1) were administered. We assessed the association between sexual behavior, HIV risk perception, and PrEP readiness on 1) 1-month PrEP continuation, 2) 1-month PrEP adherence, and 3) contraceptive uptake at enrollment. Multivariable modified Poisson regression analyses were performed to estimate relative risks (RRs) for these associations, adjusting for key confounders.
Results: Among 401 AGYW participants, the median age was 22 years (IQR 20-25), three quarters received financial support from their sexual partners, and 18% had a new sex partner within the last 3 months. Among the 96 participants who returned at month 1, 72% self-reported good adherence and 66% had tenofovir detected in urine. In the full cohort (imputing missing data as not detected), there was a trend for people with higher risk perception scores to have TFV detected in urine (aRR: 1.48, 95% CI: 0.99-2.22). In addition, participants reporting no sex partners in the last 3 months were twice as likely to self-report good adherence (35% of the time) than participants reporting 1 sex partner (16% of the time) (aRR 2.0; 95% CI 1.1-3.7). Any condom use in the past 3 months was positively associated with initiating contraception (aRR: 0.85; 95% CI: 0.70-1.0).
Conclusion: While we observed low PrEP continuation overall, women with greater awareness of their HIV risk were more likely to be adherent to PrEP. Strategies focusing on AGYW understanding of their risk level and tailored messaging for PrEP and contraception may improve PrEP use in this population.

1197 High Individual- and Community-Level Variability in Male Circumcision Coverage in Rakia, Uganda

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Background: Voluntary medical male circumcision (VMMC) is a proven intervention for reducing HIV incidence in men. Identifying specific populations and geographic areas with low VMMC coverage for targeted service outreach may help prioritize limited resources and achieve HIV epidemic control.
Methods: We used data from the Rakai Community Cohort Study, a population-based HIV surveillance cohort in Uganda, collected June 2018-November 2020, to assess individual and community-level factors associated with MC coverage among non-Muslim HIV-negative men across 39 communities. Muslims participants were excluded because circumcision is routine religious practice. Individual factors assessed included age, marital status, religion, education level, and past year number of sexual partners. Community-level factors included community type (agrarian, trading, and Lake Victoria fishing), percentage of population <30 years, percentage with primary education or less, percentage Muslim, average distance of households to the nearest health facility (level III/IV), average distance of households to a main road, and HIV seroprevalence. Hierarchical multivariable Poisson regression with community random effects was used to estimate individual- and community-level associations with MC coverage.
Results: Of the 8,757 men in the cohort, 86.4% (7,570) identified as non-Muslim, and 85.2% of these (n=6,448) were HIV-seronegative and enrolled in the study; Muslims were excluded from this analysis due to the expected full MC coverage as a religious practice. Of those enrolled, 61.7% were circumcised. Being circumcised was strongly associated with age, with 77% of boys and young men 15-24 years circumcised, compared to 51% of men 40-49 years old (prevalence ratio (PR)=0.64, 95% CI: 0.59-0.70). Median community coverage of MC was 66% ranging from 32% to 88% across communities. MC coverage was lower in communities with a greater percentage of people living with HIV (adj. PR=0.87,95% CI: 0.77,0.97). MC coverage decreased with greater distances to the main road (adj. PR=0.81, 95% CI: 0.69,0.95) and non-significantly with health facilities. Communities with larger Muslim populations had significantly higher MC coverage among non-Muslim HIV-negative men (adj. PR=1.13, 95% CI: 1.04,1.23).
Conclusion: We observed individual and community-level variation in VMMC coverage among HIV-negative non-Muslim men. Prioritizing VMMC services in communities with higher HIV burden and limited health facility access may improve VMMC coverage .
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1198 Increased Viral Suppression With Adherence Counseling Incorporating a Point-of-Care Urine TFV Test

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Background: Innovative approaches are needed to achieve the third UNAIDS 95-95-95 target, to increase and sustain virologic suppression (VS) in patients on ART, specifically co-formulated tenofovir (TFV)-lamivudine-dolutegravir (DTG) or TLD. Virologic failure in patients on TLD is likely due to non-adherence because of DTG's high resistance barrier. Identifying non-adherence to TLD

with a point-of-care (POC) metric and tailored counseling on the test may help patients achieve viral suppression (VS). We integrated a low-cost, POC urine test to detect TFV into standard WHO-recommended enhanced adherence counseling (EAC) to improve VS in adults with non-VS on TLD in Namibia.
Methods: Patients on TLD with viral load (VL) >1000 copies/mL after completing ≥1 round of EAC were enrolled from 42 clinics across Namibia. At each monthly ART pick-up, participants completed the POC urine test and received EAC informed by test results. After 3 months (round 1), participants received a viral load (VL) test. If VS was not achieved, up to 3 additional rounds of POC urine testing with EAC was provided, with an HIV drug resistance test sent at month(M) 9. Acceptability of the urine assay was assessed via surveys administered to participants and providers.
Results: Of 211 participants enrolled (median age 33 years, interquartile range 22-46, 61% female), 195 reached M3 and received a follow-up VL, with 169 (87%) achieving VS within M3 and 182 (93%) by M9. Moreover, in those who achieved VS, positive TFV in urine increased from 81% at baseline to 96% at M9 compared to a change from 31% to 41% among unsuppressed individuals. Drug resistance testing was performed in 5 remaining participants with high VL at M9. All 5 had variable urine TFV results over visits and one had DTG resistance (N155H and R263K mutations). Overall, 84% of participants and 89% of interviewed providers agreed/strongly agreed that the urine test improved EAC.
Conclusion: Nearly 90% of patients on TLD with VL >1000 copies/mL achieved VS within 3 months (93% at M9) following EAC that incorporated a urine-based POC TFV test, compared to 33% of individuals receiving 1-3 rounds of standard WHO-recommended EAC. Encouraging results of this pre-post intervention support rigorous testing in a future randomized clinical trial. Given the cost of VL and resistance testing in lower-and middle-income countries, this POC urine test has great potential to help achieve the third 95-95-95 target in a low-cost, scalable manner.

1199 Persistent Challenges With Viral Suppression a Year After Return to Care: Evidence From South Africa

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Background: Even though 94% of people living with HIV in South Africa knew their status in 2021, only 74% were actually on antiretroviral therapy (ART) and 67% were virologically suppressed: undermining the potential of ART programmes to improve individual and public health outcomes. Understanding which populations drive this poor treatment success could focus efforts to improve outcomes.
Methods: This retrospective study describes the incidence and impact of ART treatment interruptions using routine health data from the Provincial Health Data Centre, South Africa. The cohort includes individuals ≥15 years old who initiated ART under universal test-and-treat (≥01-Sep-2016), sought care in Khayelitsha or Gugulethu (low-resource, high HIV burden settings) and had ≥1 year follow-up. Treatment interruptions were defined as >90 days late for an expected visit (based on duration of treatment dispensed) or being lost to follow-up (no visit within 180 days of database closure on 30-Sep-2022). One-year retention was defined as a visit 9-15 months after ART initiation or restart, and suppression as a viral load (VL) ≤50 copies/mL.
Results: The cohort included 68888 individuals, with 69% (47631/68888) female, 25% (17078/68888) under 25 years and a median follow-up time of 4 years (Interquartile Range [IQR] 3-5). The cumulative incidence of interruptions was 71% (95% Confidence Interval [CI] 71-72) by 5 years after initiation, with a median of one interruption (IQR 1-2) and a median of 4 months (IQR 1-9) to interruption after initiation or restart (Figure 1). Most returned to care (cumulative incidence of return: 73% [95% CI 72-73] by 5 years), after a median of 7 months (IQR 4-15). Of the 40384 individual interruptions, there was sufficient follow-up time to evaluate outcomes a year after re-engagement for 29967 (74%): 67% (20030/29967) were retained and 29% (8578/29967) had a VL that was suppressed year after return. In the 34% (23578/68888) who never had a treatment interruption, 73% (17201/23578) had a suppressed VL a year after ART initiation.
Conclusion: Treatment interruptions are common. Even after reengagement, those with interruptions have poor treatment outcomes. Health services need to improve care after return to better support retention and adherence, particularly in the first six months after ART restart. People returning to care should be a priority population for the development of differentiated service options, if we are to improve retention and VL suppression for the whole population on ART.

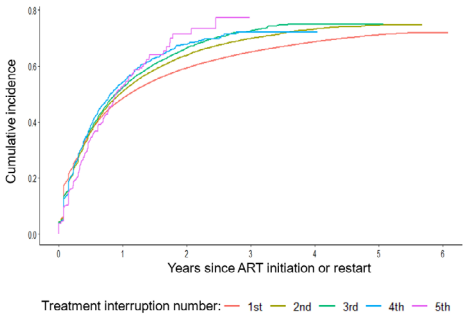

Figure 1. Cumulative incidence of time to treatment interruption from ART initiation or restart, stratified by the sequential treatment interruption number

1200 Durability of Viral Suppression Among People on HIV Treatment in S Africa: A National Cohort Study

Jacob Bor[1], Evelyn Lauren[2], Dickman Gareta[1], Khumbo Shumba[2], Mazvita Muchengeti[3], Wendy Stevens[3], Dorina Onoya[2], Koleka Mlisana[3]
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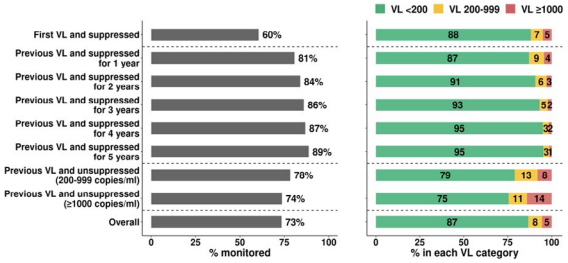
Background: People on HIV treatment with a viral load (VL) < 200 copies/ml cannot transmit HIV sexually: "Undetectable = Untransmittible" (U=U). However, the utility of U=U as a prevention strategy has been questioned due to concerns about viral blips and viral rebound. We assessed durability of viral suppression in a national longitudinal cohort in South Africa.
Methods: Data were obtained from the National Health Laboratory Service (NHLS) National HIV Cohort. The NHLS Cohort, created through deduplication of South Africa's national laboratory database, includes all viral loads in the public sector HIV program. People living with HIV (PLHIV) aged 15-59 years were included in the analysis if they had at least one VL <200 copies/ml between March 2015 – September 2016. PLHIV entered the study on the date of their first VL<200 and were followed for 18 months. PLHIV were defined as "monitored at 12 months" if they had any VL test 6-18 months after baseline. Durability of viral suppression was defined based on the value of the 12-month VL, reported in three categories: <200 copies/ml (zero transmission risk), 200-999 copies/ml (minimal transmission risk), and ≥1000 copies/ml (elevated transmission risk). Analyses were stratified by age, gender, province, and viral load history reflecting prior experience in HIV care.
Results: Of 2,383,871 PLHIV with VL<200 copies/ml at baseline, 73% were virally monitored at 12 months. Of those, 87% had a 12-month VL <200 copies/ml and 95% had a 12-month VL <1000 copies/ml. PLHIV whose VL at entry was their first ever VL had the lowest probability of being monitored at 12 months, at 60% (Fig 1). Those with a history (>2 years) of viral suppression had the highest rates of 12-month viral monitoring (>84%) and suppression (>97%) (Fig 1). Individuals with previous VLs between 200-999 or >1000 copies/ml faced the greatest challenges remaining suppressed (Fig 1). VL monitoring rates were lowest among PLHIV under 35 years, but among those monitored, durability of viral suppression was relatively consistent across age and gender. Monitoring rates were similar across provinces, with higher variability in durability of viral suppression.
Conclusion: 95% of PLHIV with VL<200 who returned for their 12-month VL had zero risk or minimal risk of transmission one year later. Our results highlight the importance of regular monitoring and the durability of viral suppression for PLHIV who remain in clinical care.



1201 Motivational Interviewing Training Effect on HIV Viral Suppression: A Cluster Randomised Pilot Trial

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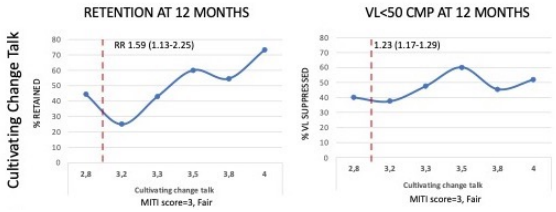
Background: We developed a Motivational Interviewing (MI) skills training program for lay counsellors (The Thusa Thuso program) to improve the quality of patient-centred HIV retention counselling in South Africa (SA). We report the effect of the Thusa Thuso intervention on HIV patient outcomes at 12 months after HIV diagnosis.
Methods: We randomized eight primary healthcare clinics (PHC) in Johannesburg (SA) to either the intervention condition (n= 4 clinics) where all lay counsellors were supported for 12 months before the patient enrolment or the standard of care support (n=4 clinics). Recorded Motivational Interviewing Treatment Tntegrity (MITI) coding of training was used to determine counsellor MI technical skills level (Cultivating Change Talk (CCT), Softening Sustain Talk (SST), Empathy and Partnership towards clients. A total of 554 adult (≥ 18 years) patients were recruited immediately after HIV diagnosis from March 2020 to August 2021 (n=293 intervention, n=261 control). We conducted cluster-adjusted Poisson regression to assess the intervention effect on retention in care (being within 90 days after a scheduled appointment) and viral suppression (<50 copies/ml) at 12 months after HIV diagnosis, reporting risk ratios (RR) with 95% confidence intervals (CIs).
Results: We observed modest retention rate improvement in patients supported by intervention clinic counsellors compared to control patients (RR 1.3, 95% CI: 0.9-2.0) and a marked increase in retention rates proportional to increasing MI skill levels (Fig 1.) (CCT, RR 1.6, 95%CI: 1.1-2.5; SST, RR 1.5, 95%CI: 0.8-2.9; Empathy, RR 1.4, 95%CI: 1.0-1.8); Partnership RR 1.5, 95%CI: 1.2-1.9). Viral suppression at 12 months also increased in the intervention group (RR 1.4, 95%CI: 1.1-1.8. Similarly, to the retention outcome, increasing counsellor MI skills resulted in higher patient VL suppression at 12 months (CCT, RR 1.2, 95%CI: 1.2-1.3; SST, RR 1.3, 95%CI: 0.8-2.2; Empathy, RR 1.1, 95%CI: 0.9-1.4; Partnership, RR 1.2, 95%CI: 1.1-1.3).
Conclusion: Appropriately tailored MI training for lay counsellors, resulting in documented improvement in counsellor skills, can improve retention and VL suppression outcomes. While these preliminary data indicate potentially significant effects, statistical significance is limited by the pilot's small cluster sample size and statistical power.



1202 Undisclosed ART Use Found by Urine LFA Is Common in South Africa, Not Associated With Lower TB Risk

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Background: People with HIV (PWH) not on ART are at high risk for TB and low CD4 counts. TB screening and CD4 count measurement are recommended at ART initiation or re-initiation. In South Africa, estimated undiagnosed TB prevalence is 5-10% in PWH not on ART. An interim analysis of an ongoing cohort study of intensive TB screening in ART initiators found <1% TB prevalence. We used a urine tenofovir (TFV) assay to objectively assess the prevalence of undisclosed ART use as a potential explanation of the low TB prevalence in the cohort.
Methods: Adults with confirmed HIV reporting no ART use within 90 days had CD4 count testing and were systematically tested for TB at the time of ART initiation at 2 public clinics in KwaZulu-Natal, South Africa using sputum TB culture, sputum Xpert Ultra and urine TB-LAM testing. Remaining urine was frozen and stored. Participants were followed for >6 months to identify incident TB. We tested thawed urine samples for TFV, indicating undisclosed ART use, using a novel lateral-flow urine assay (96% sensitive, 100% specific vs. LC-MS/MS). TB was defined as a positive Xpert Ultra or culture, or initiation of TB treatment within 3 months. We assessed predictors of ART nondisclosure and the relationship between ART nondisclosure and TB.
Results: Between 12/2021-8/2023, 315 PWH (126, 40% male) reporting no ART use presented for ART initiation and provided urine; of these 63 (20%) had detectable TFV indicating undisclosed ART use. Median CD4 count among persons with vs. without undisclosed ART was 503 cells/mm³ (IQR 280-637) vs. 336 (IQR 178-510, p=0.001). Undisclosed ART was more common in PWH attending a remote rural vs. a peri-urban clinic (35% vs 12.5%, p<0.001). In a multivariable model, undisclosed ART was associated with older age, rural clinic site, and increasing CD4 count, but not with gender, education, or employment. TB screening identified 15 (5%) PWH with undiagnosed TB (11/15 male, 15/15 reporting TB symptoms, 8.7% prevalence in men). There was weak evidence for undisclosed ART being more common in persons with undiagnosed TB, after adjusting for gender (aOR 2.70, 95% CI 0.91-8.03).
Conclusion: In the mature South African ART program, undisclosed ART use is common at 20% but is not associated with a reduced risk of undiagnosed TB. Undisclosed ART use may result in inappropriate use of resources and baseline testing. Use of a point-of-care urine assay to assess TFV could triage costly CD4 testing, however TB testing among all ART initiators should continue.

Predictors of undisclosed ART use in a cohort of people with HIV reporting no ART use in South Africa

Characteristic of PWH	n/N (%)	Adjusted OR (95%CI) for Undisclosed ART	P value
Gender: Male (vs. Female)	126/315 (40)	0.74 (0.38-1.44)	0.38
Age: 30-49 (vs. 18-29 ref)	188/315 (60)	4.79 (2.02-11.36)	<0.001
>=50 (vs 18-29 ref)	19/315 (6)	8.95 (2.53-31.65)	0.001
CD4: 100-499 (vs. 0-99 ref)	179/315 (57)	0.59 (0.20-1.74)	0.35
500-999 (vs. 0-99 ref)	85/315 (27)	1.67 (0.56-5.01)	0.36
>=1000 (vs. 0-99 ref)	23/315 (7)	3.09 (0.78-12.27)	0.11
Clinic location: Peri-Urban (vs. Rural ref)	208/315 (66)	0.35 (0.19-0.66)	0.001

1203 Impact of Proactive Adherence Interventions on HIV RNA Using Prescription Claims

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Background: Adherence interventions are often implemented after virologic failure is identified. Antiretroviral therapy (ART) prescription claims data can guide adherence interventions for people with HIV (PWH) at risk of virologic failure. This study determined the effectiveness of using ART prescription claims to provide adherence interventions and achieve virologic suppression (VS).
Methods: Participants were deemed eligible if they: 1) received care at a collaborating clinic; 2) failed to pick up ART at least 30, 60, and 90 days from prior fill date; 3) eligible to receive an intervention between November 2020 and December 2021; and 4) had an HIV RNA 12 months prior to and following the index date (date of intervention). Interventions were categorized as "no" (no patient contact), "soft" (indirect patient contact: e.g., voicemail), or "full" (direct patient contact: e.g., in-person visit). Across intervention groups, mean difference in HIV RNA was calculated and proportion of patients with VS (HIV RNA <200 copies/mL) was reported. We compared the pre- and post-index VS proportions by intervention group and reported differences using the Chi-square test with an a priori significance level of 0.05.
Results: A total of 508 patients were eligible. The mean age was 50 years, 41% of the sample was female, and 79% of the sample was African American. Sixty-seven percent (n=343) received an intervention (full =241; soft =102). The change in HIV RNA from baseline across the full, soft, and no intervention groups was -3,394, -4,266, and 237 copies/mL, respectively. Of the 343 patients that received an intervention, 107 did not have VS at baseline; of which 50% (n=54/107) achieved VS at follow-up. The proportion of patients who were viremic (HIV RNA >200 copies/mL) decreased pre- to post-index in the full (30% to 27%) and soft (33% to 24%) intervention group while the proportion of viremic patients increased in the no intervention group (4% to 7%).
Conclusion: Individuals who received the adherence intervention achieved lower HIV RNA values on average compared to PWH who did not receive an

intervention. Proactive dissemination of fills information from pharmacy claims data to health care providers can guide targeted adherence interventions, potentially leading to VS.

1204 Antiretroviral Therapy Outcomes at 6 Months by HIV Recent Infection Classification, Rwanda 2021-2022

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Background: Globally, over 25 countries have implemented HIV-1 recent infection surveillance to help detect and monitor recent infections among those newly diagnosed. As countries approach epidemic control and focus on early detection and life-long effective antiretroviral therapy (ART), we expect that an increasing proportion of persons newly diagnosed with HIV may be recently infected. However, there is limited evidence on whether persons with recent infection are more or less likely to initiate and stay on effective ART compared to persons with long-term infection.

Methods: We analyzed longitudinal data on newly diagnosed adults (>15 years old) enrolled in a cohort study conducted across 60 facilities in Rwanda from August 2021 to October 2022. Per study procedures, all participants received both rapid testing for recent infection (RTRI) and viral load at baseline and were classified as recent (RTRI-recent and baseline viral load >1000 copies/mL) or long-term (RTRI-long-term and baseline viral load >1000); participants with baseline viral load <1000 were presumed previously diagnosed and on ART and excluded from analyses. Demographic and clinical HIV data were abstracted from Rwanda's case-based surveillance system at baseline, and monthly through 6 months follow-up. We compared 6-month ART retention and viral suppression outcomes by recency status using Fisher's exact and Wilcoxon rank tests.

Results: A total of 1,238 newly diagnosed persons were identified from the study. Overall, 99.4% (n=1,231) of clients initiated ART. Of these, 8.0% (n=98) were classified as recent. ART initiation was same-day on average (median=0 days [interquartile range: 0-1 days]), and did not differ by recency status (p=0.159). Among the 98.5% (n=1,219) of persons who initiated ART and had longitudinal data available, 78.2% (953) persons were retained on ART at 6 months, and retention did not differ by recency status (p=0.618). Among those retained on ART, 86.1% (n=821) were virally suppressed at 6 months (<1000 copies/mL), and viral suppression did not differ by recency status (p=0.766).

Conclusion: Our findings suggest that ART initiation and 6-month longitudinal outcomes do not differ between clients classified as recent or long-term. Regardless of population trends in recent infections among persons newly diagnosed over time, programmatic efforts to continue to ensure timely ART initiation and retention will be needed.

1205 Impact of Natural Disasters on HIV Risks and Viral Suppression in Ugandan Fishing Village

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Background: Understanding the impact of natural disasters on the HIV epidemic in populations with a high HIV burden is critical for effective control efforts. We assessed HIV outcomes in a high-HIV prevalence Lake Victoria fishing community before and after COVID-19 pandemic and a severe lake flooding event in 2020.

Methods: We used data from the largest Lake Victoria fishing community in the Rakai Community Cohort Study, a population-based HIV surveillance cohort in south-central Uganda, collected prior to (September- December 2018) and after (October-December 2021) COVID-19 pandemic and a severe flooding event, to evaluate the impact of natural disasters on population-level HIV outcomes including HIV risk behaviors, seroprevalence, and viral suppression among people living with HIV. Households impacted by flooding were identified using drone images and through consultation with community health workers. Differences in HIV- related outcomes before and after flooding/COVID-19, and between residents of flooded and non-flooded households were assessed using difference-in-difference statistical modeling.

Results: 1,226 people participated in the pre- and post-COVID surveys, of whom 506 (41%) were affected by flooding and 513 (41.8%) were female. HIV seroprevalence pre-COVID was 37% in both flooded and non- flooded households. Following onset of the COVID-19 pandemic, there was a decline in HIV risk behaviors. Transactional sex declined from 29.4% to 24.8% (p=0.011), inconsistent condom use with non-marital partners declined from 41.6% to 37% (p=0.021) in the pre-and post-COVID periods. ART coverage significantly increased from 91.6% to 97.2% (p<0.001). There was also a non-statistically significant increase in HIV viral load suppression in both flooded and in non-flooded households following COVID-19

Conclusion: Despite a high background HIV burden, the COVID-19 pandemic and serious flooding, had no adverse impact on key HIV risk and outcomes. This may be attributable to innovative programming and or population resilience. Understanding what HIV strategies helped maintain good public health outcomes despite extreme conditions may help improve HIV epidemic control during future natural disasters.

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1206 Prevalence of HIV and Viral Load Suppression Among Refugees in Uganda, October to December 2021

Samuel Biraro[1], Shannon M. Farley[2], Joshua Musinguzi[3], Wilford Kirungi[3], David Okimait[1], Veronicah Mugisha[2], Ronald Nyakoojo[4], Sam Sendagala[5], Herbert Kiyingi[5], Jennifer Nel[5], Lisa Nelson[6], Brittany Gianetti[6], Christine West[6], David Hoos[2], Wafaa El-Sadr[2]

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Background: Uganda hosts the largest number of refugees in Africa and provides HIV services to people living with HIV (PWH) in refugee settlements. However, limited HIV-related data exist for this population. A representative population-based HIV household survey was conducted in refugee settlements to estimate HIV prevalence, the prevalence of viral load suppression (VLS) (HIV RNA <1,000 copies/mL), and progress toward the UNAIDS 95 95 95 targets.

Methods: Using a multistage probability sampling design, 11 settlements, 40 enumeration areas and 1,296 households were selected. All adults (>15 years) in a selected household were eligible to complete the survey, and venous blood samples were tested for HIV, CD4+ cell count, viral load (VL) and presence of antiretrovirals (ARV). VLS estimation included all PWH, irrespective of their awareness of their HIV status. Weighted estimates for the UNAIDS targets were based on self-report of awareness of HIV status or of HIV treatment, combined with detectable ARVs in the blood to provide 95 95 95 estimates.

Results: Overall, 93.4% of 1,250 eligible households, and 84.2% of 2,999 eligible adults (87.3% women, 79.5% men) participated. Most participants (44.7%) were aged 15-24 years; 61.6% reported living in the settlements for 3 to 5 years at the time of the survey; and the most common countries of origin were South Sudan (61.4%) and the Democratic Republic of Congo (31.9%). The prevalence of HIV among adults aged >15 years was 1.5% (95% CI: 0.8-2.1): 1.8% (95% CI: 1.0-2.7) among women and 1.1% (95% CI: 0.3-1.8) among men. HIV prevalence was highest among women aged 45-49 years at 6.2% and men aged 50-54 years at 5.8%. The prevalence of VLS among all PWH, irrespective of awareness of HIV status, was 72.4% (95% CI: 59.8-85.1) among those aged ≥15 years. Among PLHIV ≥15 years, 81.8% were aware of their HIV status, 89.5% of those aware of their status were on antiretroviral treatment (ART), and among those on ART, 92.5% had VLS.

Conclusion: In this refugee population, overall HIV prevalence was at 1.5%; however, prevalence among older women and men was above 5%. Overall, one out of five PWH was not aware of their HIV status and overall VLS was low at 72.4% indicating that more than a quarter of PWH had unsuppressed VL. These findings suggest that a substantial number of PWH in this refugee population would benefit from expansion of tailored case-finding and treatment support efforts.

1207 COVID-19–Associated ART Disruptions and HIV Suppression: A Population-Based Study in Uganda

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Background: Following confirmation of SARS-CoV-2 in Uganda, a national lockdown was imposed. Subsequent movement restrictions limited access to HIV services, including antiretroviral therapy (ART). We assessed the population burden of COVID-19-associated ART disruptions and their impacts on viral load suppression (VLS) among people living with HIV in Uganda.

Methods: We used cross-sectional data collected between October 2020 and March 2023 from the Rakai Community Cohort Study (RCCS), a population-based HIV surveillance cohort in south-central Uganda, to assess occurrence of COVID-19-related ART disruptions and impact on VLS (<1,000 RNA copies/ml). Participants reported ART disruptions in the year preceding COVID-19 emergence (March 2019 to March 2020) and after its emergence (March 2020 to interview date). Disruptions included missed HIV care appointments, running out of ART before the next refill, and reducing ART use to conserve medication supply. Proportions of participants reporting ART disruptions before and after the lockdown were compared using chi-squared tests. We used modified Poisson regression models to estimate prevalence ratios for two outcomes: COVID-19-associated ART disruptions and VLS

Results: Overall, 2,634 of 2,786 (94.5%) people living with HIV self-reported being on ART, of whom 4.8% (n=126) and 13.5% (n=355) respectively reported ART treatment disruptions prior to COVID-19 emergence and 13.5% (n=355) following it. All ART disruption types increased significantly following COVID-19 emergence: missed HIV care appointments (3.3% to 9.8%, p<0.001), running out of ART medications before the next refill (2.3% to 5.4%, p<0.001), and reducing ART use to conserve medication supply (1.1% to 2.5%, p<0.001). Females (aPR=1.89 95%CI: 1.32-2.71), fishing community residents (aPR=1.97 95%CI: 1.42-2.71), and persons aged 25-34 years (aPR=1.85 95%CI: 1.31-2.59) exhibited significant increases in ART disruption. The overall VLS following COVID-19 emergence was 94.5%, differing significantly between people who did (91.0%) and did not (95.1%) report ART disruptions (aPR=0.96; 95%CI: 0.93-1.00).

Conclusion: ART disruptions, especially missed HIV care appointments, increased significantly following COVID-19 emergence in Uganda. VLS was significantly lower among individuals who experienced COVID-19- related ART disruptions. Developing interventions effective in maintaining HIV patients in care is crucial to mitigate treatment disruptions during future pandemics.

1208 WITHDRAWN

1209 Scaling Up COVID-19 Vaccine Uptake Among PLHIV: Insights & Lessons From Kigoma, Shinyanga, and Pwani

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Background: People with underlying and chronic medical conditions continue to be at greater risk of severe Coronavirus disease 2019 (COVID-19) and its sequelae. Specifically, people living with HIV (PLHIV) with severe COVID-19 have a greater risk of dying compared to those without HIV. Despite evidence of COVID-19 vaccination reducing serious illness and death, and the availability of free vaccines across the country since July 2021, uptake in Tanzania was initially low. Despite PLHIV being treated as a priority group, by end of October 2021, less than 1% of the eligible PLHIV in the Pwani, Shinyanga, and Kigoma regions of Tanzania were fully vaccinated. We described changes in COVID-19 vaccine uptake among PLHIV within the three regions, from 0.2% in October 2021 to 99.8% by September 2022.

Methods: A total of 110,733 PLHIV aged 20 years and older, from high-volume PEPFAR-supported health facilities were eligible for COVID-19 vaccination (Shinyanga 60,986; Pwani 36,033; and Kigoma 13,714). Planning meetings with the regional and district health management teams were held, aiming to vaccinate 90% of PLHIV by September 2022. Sensitization meetings with grassroots influential leaders were conducted using the available information, education, and communication materials (IEC) provided by the government of Tanzania. Vaccination points were added to outpatient departments, reproductive and child health clinics, and HIV care and treatment clinics. Community vaccination outreach services were conducted with the support of expert clients as peer educators and vaccine champions to reach PLHIV on 3 and 6 multi-month ART dispensing.

Results: By 31 December 2022, 110,544 (99.8%) age-eligible PLHIV enrolled in care and treatment were fully vaccinated against COVID-19 across the three regions: Pwani 35,848 (99.5%), Kigoma 13,710 (99.9%), and Shinyanga 60,986 (100.0%).

Conclusion: Data insights from the routine program monitoring indicate that nearly all age-eligible PLHIV have been fully vaccinated in these three regions. Collaboration with local health authorities, political leaders, and grassroots leaders coupled with the availability of vaccines and community outreach services enabled the scaling up of COVID-19 vaccination to PLHIV.

1210 COVID-19 Vaccine Effectiveness Against Different Variants Among a Population-Based HIV Cohort

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Background: COVID-19 vaccine effectiveness among people with HIV (PWH) was understudied as they were not representatively included in clinical trials. Using a test-negative design, we estimated vaccine effectiveness (VE) against the SARS-CoV-2 infection in different periods of circulating variants of concern (VOC) among a statewide cohort of PWH in South Carolina (SC), USA.

Methods: A population-based cohort was retrieved from the integrated statewide HIV electronic health record (EHR) data up to December 31, 2020 in SC. The adult PWH dataset was linked to COVID-19 vaccination dataset with

record from January 2, 2021 and June 14, 2022 to identify the vaccination status. Outcome was any SARS-CoV-2 infection. Then we compared the odds of vaccination between test-positive cases and test-negative controls using logistic regression models in different period of circulating VOC, adjusting for include age, sex, race/ethnicity, and number of comorbidities (Charlson Comorbidity Score [CCI]). VE was derived as (1-adjusted odds ratio)×100%.

Results: Among a total of 6,239 PWH, 2,180 were test-positive cases and 4,059 were test negative controls. Among them, 48.3% aged 50 years and above, 68.7% were male, 71.2% were black. The coverage rate of fully vaccination rate was similar between cases (33.0%) and controls (32.0%), while a higher coverage of booster dose (8.3%) was observed among cases than controls (7.0%). When stratified by different VOC, VE was 61.47% and 79.31% for partial and fully vaccination status in the Alpha dominant period. In the Delta dominant period, VE was 13.88%, 37.46%, and 69.17% for partial, fully, and booster vaccination status. In the Omicron dominant period, the VE was only 22.20% for individuals who received booster dose. When look at the VE in different vaccine brands, BNT162b2 indicated a higher VE during Alpha period, mRNA-1273 revealed a high VE (54.26%) during Delta period. In contrast, Ad26.COV2.S showed the higher VE during Omicron period.

Conclusion: The VE against SARS-CoV-2 infection among PWH substantially decreased during Omicron dominant period compared with the other periods. Fully vaccination, especially boosted vaccination, offered sustained protection prior to the emergency of the Omicron VOC. In terms of vaccine brands, our findings suggested that both BNT162b2 and Ad26.COV2.S had lasting protection effect prior to the Omicron period while the protection effect of mRNA-1273 gradually diminished along with periods.

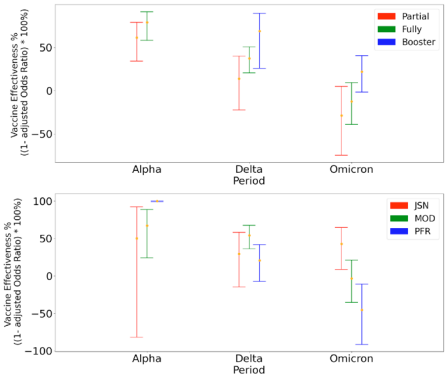

Figure 1. COVID-19 Vaccine Effectiveness by Vaccination Status and Vaccine Brands Among PWH
Note:"JSN" refers to Ad26.COV2.S, "MOD" refers to mRNA-1273, "PFR" refers to BNT162b2

1211 A Network-Based Modeling Analysis of Interventions for SARS-CoV-2 Prevention Among Jailed Adults

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Background: Managing COVID-19 in jails/prisons is challenging due to high density of contacts. The state of Georgia has limited COVID vaccine uptake plus high incarceration. Using a network-based SARS-CoV-2 transmission model parameterized with data from Atlanta GA's Fulton County Jail (FCJ, population 3000, rated capacity 2600), this study investigates the impact of three SARS-CoV-2 prevention strategies: vaccination, contact tracing and quarantining, and release of residents to decrease population to the jail's capacity.

Methods: Contact networks were simulated at 2 different overlapping network layers: cell and housing block. Cell-level contacts represented shared confined sleeping space, whereas block-level contacts represented shared common space. Contact tracing and quarantining were simulated at the cell-level, or both the cell- and block- levels. A reference scenario and 9 intervention scenarios using different combinations of the 3 prevention strategies – vaccination, contact tracing/quarantining, and resident release – were simulated to estimate median and interquartile range (IQR) of the outcome measures. Each scenario was simulated 300 times with each simulation measuring the prolonged effects of the interventions amid a potential COVID outbreak in the jail over a 185-day period. The cumulative incidence, number of infections averted (NIA), and percentage of infections averted (PIA) were calculated for all scenarios. For the 7 scenarios involving contact tracing and quarantining, total quarantines and the number of quarantines/day were calculated to determine the quarantine requirements. Also, a sensitivity analysis was conducted to compare the interaction between vaccination and contact tracing rates.

Results: Our model demonstrated cell-level contact tracing was relatively ineffective by itself (3.2% PIA), but its effectiveness increased when combined with other interventions (i.e., vaccination or jail release). Each of the other intervention strategies produced a PIA > 10% independently, with the 13% jail release scenario producing a PIA of nearly 20%. The all-level contact tracing only scenario was effective at both 50% and 100% of contacts traced, but feasibility is limited without a reduction in the jail population.

Conclusion: Implementing combined interventions could substantially reduce the morbidity and mortality from COVID-19 and future airborne pathogens in a jail setting while providing secondary protection to the community.

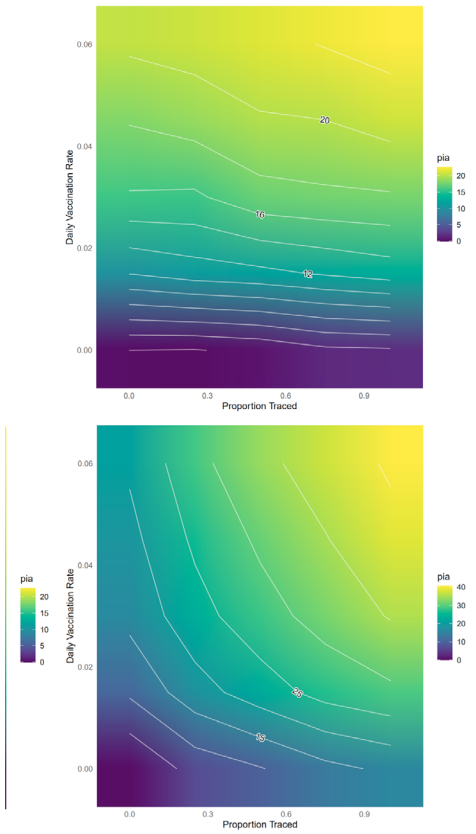

Figure. Sensitivity analysis with varying daily vaccination rates and contact tracing, FCJ. The percentage of infections averted (PIA) varies between blue (low) and yellow (high). Panel (A) cell-level contact tracing only or (B) all-level contact tracing. For the same proportion traced and vaccinated, PIA is higher in B.

1212 Safety Outcomes in Trial of COVID-19 mRNA Vaccine Among People With HIV in Sub- Saharan Africa

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Background: CoVPN 3008 (Ubuntu), the largest multicenter phase 3/4 trial of mRNA vaccines in sub-Saharan Africa (SSA), provided a unique opportunity to prospectively study safety outcomes among people with HIV (PWH).

Methods: The study enrolled adults age ≥18 years living with HIV or another comorbidity associated with severe Covid-19, who were not previously vaccinated. Participants were assigned vaccinations based on their baseline point-of-care SARS-CoV-2 serostatus: those with a positive result received one dose at baseline, those with a negative result received a dose at baseline and month 1. There were no exclusions for pregnancy, HIV viral load, CD4 count, or antiretroviral therapy (ART) use. Solicited local and systemic adverse events (AEs) (for 7 days after each injection) and unsolicited AEs (for 28 days after

injection) were collected in a safety subset (SS). Data on serious AEs (SAEs) were collected throughout the study for all participants. Pregnancy outcomes were captured even after participant exit. We report on the first 6 months of follow-up.

Results: 14,237 participants were enrolled December 2021 to September 2022, of whom 14,001 participants (median age 39 years, 72% female sex at birth) were included in the Full Analysis Subset (FAS). 83% (11,681) were PWH, with median CD4 count 635 cells/mm³ and 6.6% with <200 cells/mm^3. 18.5% had a detectable HIV viral load, and 14.5% were not on ART. The SS participants had similar baseline characteristics. The most common solicited AEs among 1,491 SS participants after month 0 and month 1 vaccinations were pain/tenderness at injection site (26.7%), headache (20.4%), and malaise (20.3%). Severe reactions were rare (0.9%); none were fatal/life-threatening. 120 (8%) in the SS experienced an unsolicited AE: 9 (0.6%) potentially vaccine-related, including one severe unsolicited AE. There was one related SAE (grade 3 angioedema). The most common causes of death were tuberculosis, carcinoma, and homicide. Among 236 pregnancy outcomes reported, there were 23 premature live births, 12 spontaneous abortions, 9 still births, and 4 congenital anomalies. There were no Covid-19 deaths or admissions to the intensive care unit.

Conclusion: Severe Covid-19 was rare in this large, diverse population of PWH during the Omicron wave. In SSA, the mRNA vaccine demonstrated an acceptable reactogenicity and safety profile, including in PWH, people with prior SARS-CoV-2 infection, and pregnant participants.

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1213 Data Science Linkage of Public Jail Registries and Surveillance Data for Public Health Action

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Background: Jail bookings represent an important opportunity for diagnosis and care linkage for people living with HIV (PLWH). However, jurisdictional data protections and decentralization of facilities can make connecting public health resources to correctional programs challenging. The purpose of this study was to evaluate the use of a novel approach using data scraping of publicly available jail inmate data to develop a real- time dataset of public jail rosters and to estimate the number of PLWH who have regular interactions with jails in Washington State (WA).

Methods: We developed scripts to collect public-facing online jail rosters from local and tribal facilities in WA using R software. Between 11/14/2022 and 8/13/2023, we ran these scripts daily and developed a longitudinal database of the incarcerated population. We used a deterministic matching algorithm to link this database to the state HIV registry (as of 7/1/2023) using name, date of birth, and county of residence. We described the population that was jailed by demographic characteristics and CDC-defined viral suppression status on 12/31/2022. We used a zero-truncated Poisson model to estimate the total population of PLWH who are jailed on a regular basis and the subset of this population who was not virally suppressed.

Results: We successfully captured data from 57 of the 59 jails identified by the authors in WA. The remaining two jails were small county facilities which were not in compliance with state reporting requirements. In the 9- month study period, we collected 2,270,716 person-days of incarceration data representing 79,088 individuals. We identified 411 PLWH in this population who were jailed 573 times. We estimate that this is a subset of a population of 827 PLWH (95% CI 741-913) who are regularly jailed, which represents 6% of the 14,872 PLWH living in WA (Table 1). Of the 411 identified PLWH, 135 were not virally suppressed (33%, estimated population size: 253, 95% CI 212-294).

Conclusion: Public facing jail registries can be used to describe the intersection of PLWH and the criminal legal system and to identify the location of PLWH who are not virally suppressed. Public health programs looking to increase their ability to reach justice-involved populations may consider whether public-facing jail rosters could be a useful data source.

Table 1. Factors associated with the intention to initiate PrEP among Peruvian MSM/TGW (adjusted PR and 95%CI**)

	MSM*	TGW*
Engaging in transactional sex	**1.37 (1.15-1.63)**	**1.26 (1.02-1.57)**
Prior PreP awareness	1.19 (0.97-1.45)	**1.23 (1.01-1.49)**
Any prior HIV testing	**1.21 (1.02-1.44)**	1.20 (0.94-1.53)
Post-secondary education	**1.20 (1.02-1.40)**	1.11 (0.90-1.36)
Age (years)	**0.99 (0.98-0.99)**	1.00 (0.99-1.01)

* Each model was additionally adjusted for: monthly income, ≥5 sex partners in past 6 months, and STI diagnosis in the past year; **bolded aPR: p-value<0.05

1214 Undetectable = Untransmissible: Key Populations With HIV Lag in Sustaining Undetectable Viral Load

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Background: Undetectable viral load (UVL) is the optimal suppression level in people with HIV (PWH) required to maintain health, prevent transmission, and assure safer sex with partners. In Nigeria, about 80% of PWH achieve UVL on treatment. However, this must be sustained over the course of life-long anti-retroviral treatment (ART) for continued benefits. We compared durable UVL levels among key population (KP) groups — female sex workers (FSW), men having sex with men (MSM), and people who inject drugs (PWID) — and the general population (GP).

Methods: A cross-sectional retrospective study of PWH diagnosed from 2020 to 2021 using data retrieved from electronic medical records in 57 health facilities across four states (Gombe, Kaduna, Kogi, and Lagos) in Nigeria. We defined durable UVL as viral load of <50 copies per ml from two tests conducted at least 6 months apart. We compared distributions between KP groups and GP using chi-squared tests. Multivariate logistic regression with robust variance estimation was used to obtain adjusted odds ratio (AOR) with 95% confidence interval for durable UVL and other variables in these categories.

Results: Within this period, 6,680 client records were reviewed and 5,286 (79%) had achieved UVL within 6 months of ART. This was significantly higher amongst KP (92% [329/358] than GP (78% [4,957/6322]), [$\chi2 = 38.9$, $p<0.001$]. Among those with UVL, the median age was 33 years (IQR 28 — 40), 65% were females, 59% attained at least secondary education, 77% were unemployed, 62% were married, and 87% received care in their state of residence. Four thousand, three hundred and forty-five clients (82%) had durable UVL, and this was higher among GP (84%) than amongst KP (FSW — 38%; MSM — 50%; and PWID — 61%.) [$\chi2 = 268.7$, $p<0.001$]. Multivariate analysis showed lower odds of durable UVL among KP groups compared to GP (FSW: AOR = 0.16 [0.12 — 0.20]; MSM: AOR = 0.25 [0.20 — 0.32]; PWID: AOR = 0.41 [0.31 — 0.53]). The odds of durable UVL were lower among the employed than unemployed (AOR = 0.63, [0.45 — 0.89]), and higher among clients aged 40 — 44 years than those 15 — 19 years old (AOR = 1.70 [1.03 — 2.80]).

Conclusion: These findings from these four states suggest that although KP groups appear to be more likely than GP to achieve early UVL, they are less likely to sustain it. Providing insights for these differences will help develop appropriate interventions to achieve and sustain viral suppression amongst clients with HIV on ART irrespective of subpopulation.

1215 PrEP Persistence Among Adolescents Men Who Have Sex With Men and Transgender Women in Brazil

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Background: Adolescent men who have sex with men (AMSM) and transgender women (ATGW) are at a heightened vulnerability for HIV in Brazil. Promoting the use and persistence of HIV prevention strategies, including Pre-Exposure Prophylaxis (PrEP), is a relevant challenge for controlling the epidemic in these populations. We aim to analyze the persistence of daily oral PrEP among AMSM and ATGW and their associated factors.

Methods: The PrEP1519 study is a daily oral PrEP demonstration cohort study with AMSM and ATGW aged 15 to 19 years, implemented in three large capital cities in Brazil: Salvador, Belo Horizonte and São Paulo. We included in this analysis participants who initiated PrEP between Feb 2019 and Feb 2021 and were followed up until Feb 2022. Study visits occurred at baseline, 30 days, 60 days and quarterly thereafter. PrEP persistence was defined as being in PrEP possession in Feb/2022 or having less than 90 days without PrEP possession. Logistic regressions were used to estimate the odds ratios (OR) of sociodemographic and behavioral factors with persistence in PrEP use.

Results: In the first two years of the cohort, 755 adolescents initiated daily oral PrEP. The majority of them was between 18 and 19 years old (79.5%), were MSM (91.1%), black and brown (70.1%), and had 12 years of schooling or more (50.8%). 330 (43.7%) adolescents persisted on PrEP, their mean followed time was 18.7 months (95% IC 17.9% – 19.4%). Adolescents who persisted on PrEP use had more chance to be black or mixed race (OR: 1.49; IC 1.08 – 2.06) and with moderate and high adherence according to self-report (OR 3.07: IC 1.99 – 4.77). No association was observed between PrEP persistence with sexual behavior and HIV risk perception.
Conclusion: The persistence of daily oral PrEP use was observed in approximately half of the adolescents, those who had higher PrEP adherence. Our results emphasize the need for strategies to support PrEP persistence in the clinics. Besides, other alternatives for prevention, such as PrEP on-demand and long-acting injectable, may be more attracted and fit better with adolescents, considering their experiences and preferences.

1216 NICE: A Structural Intervention to Increase Status Neutral Care Among Sexual and Gender Minorities

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Background: Black and Hispanic Sexual and Gender Minorities (SGM) are highly impacted by HIV. Significant structural determinants of health, such as access to care, are major drivers of status neutral care engagement, an ending the epidemic imperative. We designed an insurance navigation intervention – NICE (Navigating Insurance Coverage Expansion) - that tested the impact of navigation at the point of community HIV testing and evaluated the effects of the intervention on successful insurance enrollment and linkage to status neutral care among SGMs.
Methods: NICE aimed to test whether providing in-person assistance (enrolling, changing or learning how to use health insurance), at the HIV testing event would improve linkage rates for participants, particularly among persons living with HIV (PLWH). Black/Hispanic SGM aged 18 or older and living in Chicago were enrolled at community outreach testing events and randomized to NICE versus standard of care. Logistic regression was performed to see if there were differences in HIV linkage, PrEP linkage, and/or both (status neutral) by intervention assignment.
Results: A total of 630 participants were enrolled, with 281 in the health insurance enrollment assistance arm and 349 in the control, with a third of the sample living with HIV (29.2%), trans* representing 8.1%, and a sizeable proportion insured at baseline (68.4%). There were no differences in sociodemographic factors at baseline across study conditions. Overall, about 46.7% PLWH were linked to care (OR 1.37, 95% CI 0.74-2.48, p=0.32), while only 16.5% for those HIV negative who attended PrEP providing clinic within 90 days (OR 0.84, 95% CI 0.50-1.43, p=0.53), however, not significant by intervention condition. Overall, about a quarter of participants were considered linked (25.8%) and there were no differences in status neutral outcomes across conditions when analysis was limited to the uninsured.
Conclusion: Health insurance navigation, while likely an important component in accessing status neutral care, did not significantly impact linkage to care. Overall, linkage was low among SGM who had high rates of insurance at baseline. Future research should examine SGM understanding of their insurance and the ways in which it impacts their care decision making (e.g. obtaining prescribed medications, clinic choice) as well as how insurance navigation might impact care engagement in states newly adopting Medicaid or where insurance rates are low among minoritized SGM.

1217 DREAMS RE-AIM Assessment in Zambia Demonstrates High Uptake and Reach of AGYW With HIV Prevention

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Background: Adolescent girls and young women (AGYW) in sub-Saharan Africa countries like Zambia are at high risk of HIV acquisition. The Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe (DREAMS) initiative provides comprehensive interventions to prevent HIV among AGYW. We conducted a multi-year assessment of DREAMS program effectiveness in delivering HIV services to AGYW in Zambia.
Methods: Using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) implementation science framework, we assessed DREAMS implementation from 2016 to 2022 in 14 Zambian districts. We used a mixed-methods approach including aggregate and line-listed client-level data for quantitative analyses across programs, costing analyses, and a three-site qualitative case-study with 134 interviews and 6 focus group discussions with beneficiaries, implementers, and stakeholders. Data were analyzed using R-Studio and Atlas.ti.
Results: From October 2016 to September 2022, 1,091,641 AGYW were enrolled, with 976,689 accessing DREAMS services. Among enrolled AGYW, 350,127 (32.1%) were 10-14 years, 441,402 (40.2%) were 15-19 years, and 295,291 (27.1%) were 20-24 years. Engagement in the primary package of social asset building was high with 97.3% (922,947) of enrolled AGYW completing all 13 Stepping Stones sessions. Socioeconomic support services were the most commonly accessed DREAMS secondary service with 29.6% participation, while biomedical services, including condom distribution, family planning, and HIV testing, followed closely with 27.2%, 11.2%, and 9.6% participation, respectively. Overall, 2,328 (2.2%) of 104,859 AGYW tested positive for HIV. Qualitative data revealed high levels of satisfaction with the program, especially concerning the primary intervention package. Beneficiaries reported that the program enabled them to adopt condom use, increased their awareness of PrEP benefits, and enhanced their assertiveness and control over their sexual health and decision- making within intimate relationships. However, qualitative findings indicated need for further measures to improve the program's capacity to reach AGYW most at-risk of HIV acquisition.
Conclusion: DREAMS successfully reached large numbers of at-risk AGYW in Zambia with HIV services, demonstrating potential effectiveness, high adoption rates, and effective implementation. Maintenance efforts are ongoing and yet to be determined. Holistic prevention programs like DREAMS should be considered for further scale-up of HIV prevention.

1218 Intention to Initiate PrEP Among Men Who Have Sex With Men (MSM) and Transgender Women (TGW) in Peru

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Background: Recently, Peru incorporated PrEP into their combination HIV prevention strategy. However, data from the ImPrEP demonstration project shows that PrEP adherence and persistence are problematic among Peruvian MSM/TGW. As national scale-up of PrEP has begun, reasons behind poor progression along the PrEP cascade need to be fully understood. We aimed to explore factors associated with the intention to initiate PrEP among Peruvian MSM/TGW using national surveillance data
Methods: Between April and July 2019, the HIV/STI Sentinel Surveillance was conducted in 11 Peruvian cities, enrolling 1768 MSM and 1198 TGW aged 18+ who provided informed consent. The survey collected socio-demographics, sexual behavior, self-reported STI diagnosis and HIV testing history, PrEP awareness and intention to initiate PrEP, along with sample collection for HIV/STI testing. Respondents who self-reported as HIV negative and had not initiated PrEP were included in the analysis. We used Poisson regression to identify factors associated with the intention to initiate daily oral PrEP, using covariates selected a priori, and stratifying by population.
Results: The analysis included 1582 MSM and 904 TGW. Median age was 25 yo (interquartile range, [IQR] 21-32) among MSM and 28 (IQR 23-37) among TGW. Intention to initiate PrEP was 48.9% among MSM and 60.7% among TGW. Other covariates included in the analysis included monthly income (MSM: median US$243 [IQR 162-324]), TGW: median US$243 [IQR 135-324]), post-secondary education (MSM 36.5%, TGW 21.0%), prior PrEP awareness (MSM 16.1%, TGW 23.3%), having ≥5 sex partners in the past 6 months (MSM 30.9%, TGW 63.6%), engagement in transactional sex (MSM 24.6%, TGW 54.5%), prior HIV testing (MSM 66.4%, TGW 80.0%), and self-reported STI diagnosis (MSM 12.0%, TGW 23.4%). Age, post-secondary education, prior HIV testing remaining, and engagement in transactional sex, were significant covariates for intention

to initiate PrEP among MSM; while prior PrEP awareness and engagement in transactional sex were significant covariates for TGW (Table 1).

Conclusion: Factors significantly associated with intention to initiate PrEP varied by population, though engagement in transactional sex was associated with intention to initiate PrEP in both groups. In the context of national PrEP scale-up, these findings could inform differentiated interventions to improve PrEP uptake among MSM/TGW. Issues of PrEP awareness and steps along the PrEP cascade toward planning and uptake should be addressed.

Table 1. Factors associated with the intention to initiate PrEP among Peruvian MSM/TGW (adjusted PR and 95%CI**)

	MSM*	TGW*
Engaging in transactional sex	**1.37 (1.15-1.63)**	**1.26 (1.02-1.57)**
Prior PreP awareness	1.19 (0.97-1.45)	**1.23 (1.01-1.49)**
Any prior HIV testing	**1.21 (1.02-1.44)**	1.20 (0.94-1.53)
Post-secondary education	**1.20 (1.02-1.40)**	1.11 (0.90-1.36)
Age (years)	**0.99 (0.98-0.99)**	1.00 (0.99-1.01)

* Each model was additionally adjusted for: monthly income, ≥5 sex partners in past 6 months, and STI diagnosis in the past year; **bolded aPR: p-value<0.05

1219 WITHDRAWN

1220 The Motivational PrEP Cascade Among Peruvian Men Who Have Sex With Men (MSM)

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Background: In several recent studies, MSM HIV incidence was >5/100 person-years in Peru, where PrEP scale-up is urgently needed. The Motivational PrEP Cascade (MPC) explains dynamic movement on a PrEP continuum including planning, uptake, and persistence. We aimed to describe key MPC steps and interest in tailored mHealth interventions among Peruvian MSM, at the time the National PrEP Program (NPP) began in mid-2023.

Methods: We conducted an online survey from June to August 2023. MSM were recruited through social media ads. Following informed consent, respondents answered a survey on demographics, sexual behavior, key MPC steps, smartphone use, and mHealth intervention preferences. Only PrEP candidates based on NPP guidelines (HIV negative by self-report with condomless anal sex in past 6 months) were included in this analysis. We describe the distribution of MSM by MPC steps and identified associated factors using multivariate Poisson regression.

Results: Among the 464 included respondents, median age was 29yo (IQR: 25-35). Most respondents earned Conclusion: Peruvian MSM who completed a PrEP survey when the NPP began showed great interest in PrEP, self-identified as good PrEP candidates, and/or decided to start PrEP. However, most MSM struggled to progress to later MPC steps, highlighting access barriers outside of research studies. The MPC could help identify subgroups with unique informational and/or skill development needs, which can be used in the design of tailored mHealth interventions supporting the NPP implementation in Peru.

Table 1: Associations of selected covariates* with key MPC steps (adjusted prevalence ratio with 95%CI**)

PrEP candidates N = 464 (100%)	Interested in PrEP (88.8%)	Self-ID as good PrEP candidate (83.2%)	Decided to start PrEP (81.9%)	Identified a PrEP clinic (39.7%)	Discussed PrEP with physician (32.8%)	Initiated PrEP (8.6%)	Adherent to PrEP (8.0%)
Post-secondary education **(57.5%)**	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.1 (0.9-1.4)	1.0 (0.7-1.4)	1.4 (1.0-2.0)	1.5 (0.7-3.4)	1.8 (0.8-4.4)
Income ≥US$550 per month **(32.3%)**	1.0 (0.7-1.2)	0.9 (0.7-1.2)	0.9 (0.7-1.1)	1.4 (1.0-2.0)	1.0 (0.7-1.5)	**3.0 (1.4-6.4)**	**2.8 (1.3-6.2)**
≥5 anal partners **(37.5%)**	1.0 (0.8-1.3)	1.1 (0.9-1.3)	1.1 (0.9-1.3)	1.2 (0.9-1.7)	1.4 (1.0-1.9)	**2.3 (1.2-4.7)**	**2.6 (1.3-5.5)**
Former research participant **(25.2%)**	1.0 (0.8-1.3)	1.1 (0.8-1.4)	1.1 (0.8-1.3)	**1.4 (1.0-2.0)**	**2.3 (1.6-3.2)**	**5.8(2.9-12.3)**	**6.1(3.0-13.4)**
Unsure of HIV status **(11.2%)**	1.0 (0.7-1.3)	1.0 (0.7-1.4)	0.9 (0.6-1.2)	0.8 (0.5-1.4)	0.7 (0.4-1.2)	0.3 (0.0-1.3)	0.3 (0.0-1.5)
Self-perceived at HIV risk **(78.2%)**	1.2 (0.9-1.5)	1.2 (1.0-1.6)	1.3 (1.0-1.7)	0.9 (0.6-1.2)	1.1 (0.7-1.6)	1.1 (0.5-2.5)	1.2 (0.5-2.7)
Have costs concerns **(89.4%)**	1.2 (0.8-1.6)	1.1 (0.8-1.6)	1.1 (0.8-1.6)	0.9 (0.6-1.5)	0.8 (0.5-1.4)	1.1 (0.5-3.2)	1.0 (0.4-3.0)

*Each model additionally adjusted for age, city, STI diagnosis, transactional sex, condom use, and partner HIV status
**bolded: p-value<0.05

1221 The Need to Address Violence for PrEP Uptake Among Adolescent Girls and Young Women in South Africa

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Background: Adolescent girls and young women (AGYW) account for 25% of new HIV infections in South Africa. We have conducted several NIH-funded studies with AGYW to address HIV risk and prevention and gender-based violence, yet pre-exposure prophylaxis (PrEP) had not been approved. Working with the national government as PrEP was approved and rolled out in South Africa, we conducted an NICHD-funded cluster- randomized implementation trial to assess the effectiveness of a multilevel intervention to increase uptake of sexual and reproductive healthcare, including PrEP. This study focuses on understanding factors that may contribute to PrEP uptake among a large community-based sample of AGYW attending public healthcare clinics.

Methods: We examined multilevel factors associated with PrEP uptake among AGYW in 12 clinic catchment areas in Tshwane (Pretoria), South Africa from 2019-2022. After consent/assent, PrEP-eligible AGYW (n = 802) completed a questionnaire assessing factors at the individual, interpersonal, and community levels and those who were interested in initiating PrEP were referred to the study clinic.
Results: A multivariable model, adjusting for clustering, assessed factors associated with PrEP uptake over a 9- month period. Overall, 77% (n = 620) were prescribed PrEP. Of those who were prescribed PrEP, 76% (n = 471) were prescribed Truvada, 24% (n = 148) were prescribed Tenemine. At 9-month follow-up, 75% (n = 565) of AGYW reported that they started taking PrEP at some point during the study. At the individual level, age ($p < 0.05$) was inversely correlated with PrEP uptake. At the interpersonal level, physical and sexual gender-based violence were related to a lower odds of PrEP uptake (ps < 0.05).
Conclusion: These findings are highly relevant given the high rates of physical and sexual violence toward AGYW, especially since the COVID-19 pandemic. To support AGYW to initiate PrEP, clinicians, legislators, and key decision makers should address gender-based violence. While PrEP has the potential to substantially reduce HIV in South Africa, its impact may be tempered if we do not also address the context in which AGYW live.

1222 Stigma in Young Kenyan Women Offered PrEP in a Peer-Supported, Community-Based PrEP Delivery System

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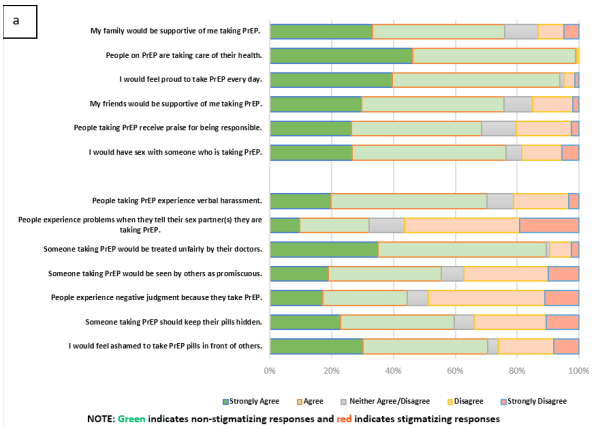
Background: PrEP and HIV stigma are common and potential barriers for PrEP use. We used multiple approaches to measure stigma among young women accessing PrEP in a trial of a novel, peer-supported, community-based delivery system.
Methods: In Kisumu, Kenya, 18-24-year-old women were recruited at PrEP initiation (July 2021-March 2022) and followed for 6 months. Participants received peer-supported, community-based delivery of PrEP and other sexual health services vs standard-of-care clinic-based services. We measured PrEP stigma at 0 and 6 months using a 13-item Likert response scale (range 1-5) and a 10-item semantic differential scale (the HIV PrEP Stigma Scale). We similarly measured HIV stigma with a 4-item modified Berger scale (range 1-4). Baseline socio- behavioral and demographic factors were assessed for association with each stigma type by multivariable linear regression analysis. PrEP use was determined at 6 months with dried blood spots.
Results: Of 150 women, 75 received the intervention and 75 received standard-of-care. Mean baseline HIV stigma was 2.8 (SD 0.6) and mean PrEP stigma was 3.5 (SD 0.5); neither differed by trial arms. Mean HIV stigma increased to 3.2 (SD 0.8) at Month 6 ($p<0.001$) and mean PrEP stigma increased from 3.5 (SD 0.5) to 3.8 (SD 0.6) ($p<0.001$). Using the Likert scale, most reported strongly agreeing/agreeing to positive feelings about PrEP use (taking care of their health, receiving support/praise, having sex with someone taking PrEP). To a lesser extent, most also strongly agreed/agreed with negative feelings (experiencing harassment, being treated unfairly/judged, feeling ashamed). On the semantic differential scale, almost all reported "People on PrEP are..." motivated, in control, supported, proud, safe, and responsible. Views on faithfulness, honesty/trust, attractiveness, and modesty/promiscuity varied. Education was associated with less HIV and PrEP stigma (-0.05 and -0.04 points/year, respectively; p=0.04). History of STI was associated with PrEP stigma (0.5, p=0.003). PrEP use at 6 months was modest (16/123, 13%) in women with ongoing HIV prevention needs and not associated with either stigma type.
Conclusion: PrEP and HIV stigma are moderately high among young women accessing PrEP in Kenya and multidimensional. Stigma was not improved by peer-supported, community-based PrEP delivery. As we work to scale up PrEP, more research is needed to understand and address stigma as a barrier to PrEP use.



1223 A Social Network-Based Intervention to Promote HIV Prevention and Treatment Among Fishermen in Kenya

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Background: Men in sub-Saharan Africa are less likely than women to know their HIV status and utilize HIV prevention and treatment services. We previously showed a social-network based intervention increased HIV testing uptake by 50% among men in Kenya. Here, we evaluate the impact of the intervention on HIV prevention and treatment outcomes using objective metrics.
Methods: Data are from the Owete study (NCT04772469), a RCT of an HIV status-neutral, social-network- based intervention to promote HIV self-testing and linkage to prevention and treatment among men in Lake Victoria fishing communities. After a census of fishermen, distinct social networks with a network-central "promoter" were mapped and randomized to study arms. Promoters were asked to (1) distribute self-tests to men in their network and encourage linkage and retention in prevention and care (intervention clusters) or (2) distribute vouchers for free self-tests redeemable at study-affiliated health facilities (control clusters). We evaluated PrEP adherence measured via urine assay for tenofovir among men initiating PrEP, and HIV RNA viral load assessed via the Xpert assay (40 copies/ml threshold) among people with HIV (PWH), at 3 months. We coded missing viral load as failure (detectable). We conducted logistic regression controlling for site (beach) and with a random intercept for cluster to evaluate the intervention's impact on PrEP adherence and viral suppression.
Results: Of 934 men in the intent-to-treat sample, 733 were interviewed at baseline (374 intervention) and 339 linked to study-affiliated clinics: 71 initiated PrEP, and 169 were PWH. Urine tenofovir was detected among 12 of 71 participants on PrEP (14% of control vs. 12% intervention), and 107 of 169 participants on ART had undetectable viral loads (58% of control vs. 69% intervention). We did not detect a statistically significant difference between study arms in PrEP adherence (odds ratio [OR]: 0.85; 95% CI: 0.17, 4.23, p= 0.84) or viral suppression (OR= 0.59; 95% CI: 0.29, 1.22; p=0.16).

Conclusion: A social network-based, status-neutral intervention in Kenya that successfully promoted testing among men did not impact PrEP adherence or viral suppression, although we demonstrate preliminary indications of intervention effect at a relaxed alpha of 0.2. Given the small number of men on PrEP and ART, an adequately powered study is required to evaluate whether social-network-based interventions can improve these outcomes among fishermen and other hard-to-reach populations.

1224 Hopefulness as a Predictor of Viral Suppression in Patients Newly Diagnosed With HIV

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Background: In the context of the COVID-19 pandemic, and the major political instability and gang violence in Haiti, it is optimal to minimize the number and duration of patient visits.
Methods: We conducted a pilot randomized trial of immediate fast-track vs. standard care among patients newly diagnosed with HIV in Port-au-Prince, Haiti. Patients were randomized in a 1:1 ratio to immediate fast- track care (expedited nurse-led visits with pre-packaged, point-of-care dispensing of ART) vs. standard care. The primary outcome was the proportion of patients with HIV-1 RNA <200 copies/mL at 48 weeks after enrollment. We also administered multiple questionnaires to assess predictors of viral suppression.
Results: From January 3, 2019 to April 15, 2020, 103 participants were enrolled in the trial (48 standard; 55 immediate fast-track). The median age was 38 years (IQR: 32, 47), 46.6% were female, and median CD4 count was 330 cells/mm^3 (IQR: 227, 520). In the standard group, 42 (87.5%) were retained, 2 (4.2%) died, and 4 (8.3%) were LTFU; 37/42 (88.1%) retained patients received 48-week viral load testing, and 32 had HIV-1 RNA <200 copies/mL (86.5% among those tested; 66.7% among those enrolled). In the immediate fast-track group, 52 (94.5%) were retained, 1 (1.8%) died, and 2 (3.6%) were LTFU; 44/52 (84.6%) retained patients received 48- week viral load testing, and 40 had HIV-1 RNA <200 copies/mL (90.9% among those tested; 72.7% among those enrolled). There was no difference in the primary outcome between the two groups (p=0.65). In multivariable analysis, the only predictor of virologic suppression was a higher score on the State Hope Scale, indicating a higher degree of hopefulness about the future.
Conclusion: Retention and viral suppression rates were high in both the immediate fast-track and standard groups. Hopefulness was the most important predictor of retention in care with viral suppression. Further study is necessary to determine if this finding is reproduced in other cohorts.
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1225 Homelessness and Antiretroviral Use Among MSM in the Context of Varying Levels of Federal Funding

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Background: Homelessness is associated with poor health outcomes among people living with HIV(PLHIV); gay men and other men who have sex with men (MSM) account for over 50% of PLHIV in the United States and over 70% of new diagnoses. The Housing Opportunities for Persons With AIDS (HOPWA) Program is operated by HUD to fund initiatives addressing the housing needs of PLHIV. There is limited research examining the relationship between homelessness and HIV-related outcomes in varying policy and funding contexts.
Methods: 3,636 cisgender MSM who participated from 2017-2021 in the American Men's Internet Survey (AMIS) and self-reported a prior HIV diagnosis were included in analyses. Homelessness in the survey was defined as living on the street, in a shelter, in a Single Room Occupancy hotel, or in a car in the past 12 months. We used a multilevel mixed-effects logistic regression model to assess the association between homelessness and current antiretroviral therapy (ART) use, adjusting for age, race, education, recruitment year, injection drug use, and state-level Ryan White Part B funding. Analyses were stratified by state-level HOPWA funding per person: state-level HOPWA funding was divided by the number of sheltered and unsheltered people experiencing homelessness (Point-in-Time Count) multiplied by the 2021 HIV prevalence for each state.
Results: Overall, experiencing homelessness was associated with decreased likelihood of current ART use (aOR: 0.53, 95%CI [0.32, 0.88]). Among states who received at or below the median level of HOPWA funding per person (~$300K), homelessness remained associated with ART use (aOR: 0.49, 95%CI [0.27, 0.89]), while there was no association among states who received above the median (aOR: 0.72, 95%CI [0.26, 2.00]), suggesting effect measure modification by funding level.
Conclusion: Homelessness impedes ART use among MSM living with HIV. In states that received a greater level of per-person funding, this relationship was attenuated, providing preliminary evidence that housing supports and interventions to address basic needs can have important impacts on community-level HIV service uptake and subsequent outcomes. Further research is needed to document the immediate and long-term impacts of this Program.
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1226 Violence and HIV Sexual Risk Behaviours Among Adolescent Girls and Young Women: Eswatini Experience

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Background: Experience of violence is reported as a precursor to multiple risk behaviors including HIV sexual risk behaviors (SRB). HIV SRB remains a public health concern as a possible cause of HIV, impacting progress towards achieving HIV epidemic control. However, there are limited contemporaneous national-level assessments of HIV prevalence, magnitude and impact of violence. We explored HIV SRB associated with history of violence among females ages 13-24 years in Eswatini
Methods: Data from the 2022 Eswatini Violence Against Children and Youth Survey (VACS) was analyzed. VACS is a nationally representative household survey using a multi-stage sampling approach for males and females ages 13-24 years. Participants completed a questionnaire on demographics, sexual behaviors and practices, HIV/AIDS services history, and experience of any violence (physical, emotional, and sexual), and conducted HIV testing. The current study was limited to only females (N=6,318), aged 13-24 years. Using stepwise logistic regression with forward selection approach, we assessed the association between experience of any violence and HIV SRB. We controlled for HIV SRB: multiple sexual partners (two or more sexual partners in the past 12 months); infrequent condom; transactional sex; HIV status; history of STIs and age.
Results: The prevalence of any violence (sexual, physical or emotional) was 25.5% (95% CI=23.3-27.7) from the 6,318 females interviewed. In the logistic regression all the following variables were significantly associated with experience of any violence; transactional sex (AOR 2.7, 95% CI 2.0 – 3.7) compared to none, STI history (AOR 2.1, 95% CI 1.5 – 3.2) compared to those with no history of STIs, multiple sexual partners (AOR 1.7, 95% CI 1.2 – 2.3) compared to having one partner or none; infrequent condom use (AOR 2.0, 95% CI 1.5 - 2.6) and never using a condom (AOR 1.4, 95% CI 1.2 – 1.7) compared to always using a condom; age group of 13- 17 years (AOR 1.5, 95% CI 1.1 – 1.9) compared to 18-24 years and HIV positive status (AOR 1.3, 95% CI 1.0 – 1.8).
Conclusion: Experience of any violence was associated with HIV SRBs among adolescent girls and young women. Targeted multi-pronged interventions including violence and HIV prevention, sexual reproductive health education services need to be intensified to address sexual risk behaviors among females in Eswatini.

1227 Older Adults Living With HIV Have Low Expectations Regarding Aging, Despite Improved Survival

Alice Zhabokritsky[1], Darrell H. Tan[2], Marianne Harris[3], Graham Smith[4], Julian Falutz[5], Nisha Andany[1], Silvia Guillemi[3], Gordon Arbess[1], Mona Loutfy[1], Ron Rosenes[6], **Sharon Walmsley**[1], for the CHANGE HIV Study Team
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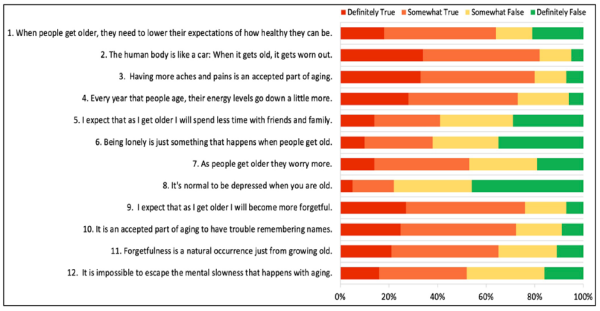
Background: The life expectancy among people living with HIV approaches that of the general population but little is known about the expectations people living with HIV have regarding aging. Studies suggest that an individual's perception of aging can have a significant impact on their personal health behaviors, healthcare utilization and quality of life. We set out to evaluate what expectations older adults living with HIV have regarding aging and whether expectations differ according to sociodemographic and clinical factors, hypothesizing that those living longer with HIV have lower expectations regarding aging.
Methods: We performed a cross-sectional analysis of the Correlates of Healthy Aging in Geriatric HIV (CHANGE HIV) study, a Canadian cohort of people living with HIV age 65 and older. Participants completed the Expectations Regarding Aging Survey (ERA-12) at cohort entry; subscale (physical health, mental health and cognitive function) and total scores were calculated on a scale of 0-100 with lower scores indicating lower expectations regarding aging. Multivariable linear regression was used to estimate the association between ERA- 12 score, duration of HIV infection, and sociodemographic and clinical factors selected a priori (age, gender, race, depression, social support).
Results: 320 participants were included in the analysis, of whom 91% identified as men and 78% as white, with a median (interquartile range [IQR]) age of 69 [67,73]. The median [IQR] ERA-12 score was 47 [33,58]. Expectations regarding mental health (median [IQR] score 58 [42, 83]) were higher than those for physical health (median [IQR] score 33 [17,50]) and cognitive function (median [IQR] score 42 [25,58]). In multivariable analysis, ERA-12 scores did not differ according to age, race, or duration of HIV infection. After accounting for other factors, women (β -9.87, 95% CI -18.39, -1.38, p 0.023), persons experiencing depression (β -15.96, 95% CI -22.34, -9.59, p <0.001) and those with greater degree of social isolation (β -0.05, 95% CI -0.22, -0.04, p 0.007) had lower expectations regarding aging.
Conclusion: Older adults living with HIV seem to have have low expectations regarding their physical health and cognitive function, regardless of how long they've been living with HIV. Gender-specific differences in expectations persist after taking into account demographic factors, depression and lack of social supports. This reinforces the need to address physical and cognitive health concerns among persons aging with HIV.

Figure 1. Expectations Regarding Aging Survey results among persons living with HIV age 65 and older.



Questions 1-4 correspond to physical health, 5-8 correspond to mental health and 9-12 correspond to cognitive function domain.

1228 Strategies for Eliminating Racial/Ethnic Disparities in HIV Incidence in the United States

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Background: Elimination of racial/ethnic (r/e) disparities is a goal of the Ending the HIV Epidemic in the U.S. (EHE) initiative. Despite progress in HIV prevention and treatment, large r/e disparities in HIV incidence remain. We used the HIV Optimization and Prevention Economics (HOPE) model to analyze which interventions provide the most effective path towards eliminating r/e disparities in HIV incidence.
Methods: We considered a baseline Scenario A, which assumed continuation of HIV continuum of care and prevention efforts (pre-exposure prophylaxis (PrEP) and syringe services programs (SSPs) at 2022 levels from 2023-2035. We considered three r/e groups: Black, Hispanic/Latino (H/L), and the remaining mostly White population grouped as Other. The primary outcome is the incidence-rate-ratio (IRR) compared to Other, with the goal of IRR≤1 for both Black and H/L by 2035. We considered four intervention scenarios, B through E, by adjusting input values from 2023-2027, then we observed outcomes from 2027-2035: •Scenario B: Continuum- only - HIV testing, linkage to care and viral suppression among Black and H/L brought to parity with Other by 2027 •Scenario C: Prevention-only – PrEP and SSP uptake among Black and H/L brought to parity with Other by 2027 •Scenario D: Continuum+Prevent- Combined B and C •Scenario E: Max reach- Black and H/L populations reach 98% awareness, linkage to care, and viral suppression coupled with increases in PrEP and SSP uptake by 2027
Results: Scenario B was more effective in reducing incidence in 2035 (9.1 new infections per 100,000) than Scenario C (12.1) compared with baseline Scenario A (13.3) (Table). The combined Scenario D resulted in only slight improvements (8.4 new infections per 100,000) compared to Scenario B. All scenarios reduced IRRs, but only Scenario E eliminated incidence disparities by 2035, with respective IRRs of 0.9 and 1.1 among the H/L and Black populations.
Conclusion: With no changes, disparities in IRR will persist through 2035. Eliminating r/e disparities in the continuum-of-care by 2027 can reduce, but not eliminate, incidence disparities by 2035. Prevention-based interventions are less effective than continuum-based interventions in reducing both overall incidence and r/e incidence disparities; and provide only small added benefit when supplementing continuum-of-care intervention parity. Elimination of r/e incidence disparities by 2035 is only possible if Black and H/L populations reach highest possible care and prevention levels by 2027.

Table: 2035 incidence per 100,000 persons and 2035 incidence rate ratio

	Racial/ethnic group	A: Baseline	B: CoC only	C: Prevent only	D: CoC + Prevent	E: Max reach
2035 incidence per 100,000	Overall	13.3	9.1	12.1	8.4	3.4
	Black	37.0	22.6	33.5	20.2	3.3
	Hispanic/Latino	23.4	14.9	20.4	13.0	3.7
	Other	5.7	4.8	5.5	4.7	3.4
2035 incidence rate ratio*	Black vs Other	6.5	4.7	6.1	4.3	0.9
	Hispanic/Latino vs Other	4.1	3.1	3.7	2.8	1.1

CoC=continuum-of-care

* Calculated by dividing the annual incidence per 100,000 for Black or Hispanic/Latino populations by the annual incidence per 100,000 for the Other population

1229 Cost-Effectiveness of Differentiated HIV Treatment Delivery in Sub-Saharan Africa: A Modeling Study

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Background: Differentiated service delivery (DSD) for HIV treatment is rapidly expanding in Sub-Saharan Africa (SSA). Current evidence suggests that DSD leads to enhanced patient retention but is associated with higher costs compared to the standard of care (SoC) of clinic-based HIV treatment. We conducted a cost- effectiveness (CE) analysis to assess the health and economic implications of DSD in SSA.
Methods: We adapted two pre-validated mathematical models (EMOD-HIV and Synthesis) to project health outcomes (disability-adjusted life years, DALYs) and costs (2021 USD) of DSD relative to SoC from 2022 to 2062, with a 3% discount rate. We covered four settings: South Africa/EMOD, Malawi/EMOD, Zambia/EMOD, and SSA low- and middle-income countries (LMICs)/Synthesis; and three DSD modalities for people with HIV aged 15+: community adherence groups (CAG), urban adherence groups (UAG), and home ART delivery (HomeART). Retention was defined as consistent engagement in care with no loss to follow-up (i.e., missing for > 28 days since last scheduled visit) or death. Model inputs were sourced from published literature. The effectiveness of DSD was modeled as percentage increases in annual retention rates, with values set at 25% for CAG, 38% for HomeART, and 50% for UAG for all settings. Country-specific costs included SoC and DSD visits, medications, and lab tests. We calculated incremental cost-effectiveness ratios (ICERs) of DSD versus SoC from the

healthcare perspective, as compared to CE thresholds ($590-$3525/DALY for South Africa and $500-$750 for other settings). One-way sensitivity analyses included CE threshold, DSD effectiveness, cost, and disability weight.

Results: CAG was cost-effective for all country/model settings under upper CE thresholds (ICERs: $295– $678/DALY). UAG yielded higher DALYs averted at higher costs than CAG (ICERs: $512–$773/DALY). In all settings, HomeART was dominated by UAG. All ICERs decreased with longer time horizons of analysis, making DSD cost-effective over 30 to 40 years, depending on the setting. CE of CAG remained robust in sensitivity analyses on DSD effectiveness, cost, and disability weight, except when effectiveness decreased from 25% to 10% in Malawi. However, CE of UAG and HomeART was sensitive to the aforementioned three factors.

Conclusion: CAG and UAG can provide cost-effective alternatives to the SoC clinical-based HIV treatment in SSA, depending on the setting and time horizon of interest. These findings support current efforts to scale DSD in SSA.

1230 Model Comparison of the Cost-Effectiveness of Long-Acting Cabotegravir for HIV PrEP in South Africa

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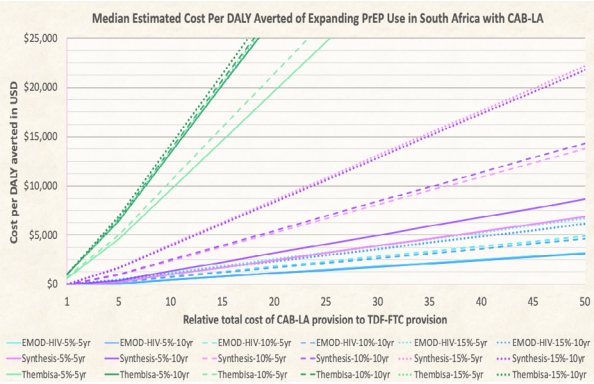
Background: Long-acting injectable cabotegravir (CAB-LA) is superior to oral emtricitabine / tenofovir disoproxil fumarate (TDF-FTC) for HIV pre-exposure prophylaxis (PrEP) and has the potential to expand PrEP usage. Evaluation of the cost-effectiveness (CE) in sub-Saharan Africa is needed to optimize health resource allocation.

Methods: Three independent age- and risk-stratified HIV transmission models (EMOD-HIV, Synthesis, and Thembisa) were calibrated to epidemiological data for South Africa. Expanding PrEP usage to 5, 10, or 15% of the sexually active population via leveraging CAB-LA to supplement and increasingly replace TDF-FTC within 5 or 10 years and sustaining initiations until 2042 was simulated and compared to status quo PrEP use. Use by risk exposure varied by model. Effects were assessed in disability-adjusted life years (DALYs) over 50 years. Costs incorporated PrEP provision, outpatient antiretroviral therapy provision, and HIV-related inpatient costs by CD4 count. The potential annual total delivery cost of CAB-LA was varied from 1 to 50 times that of TDF- FTC's (US$124). Costs and DALYs were discounted at 3%/year. An empirically estimated CE threshold of US$3,767/DALY was utilized.

Results: All models showed diminishing CE with higher PrEP usage, at least partly because higher usage reaches more people with lower risk. Expansions in 5 vs 10 years typically had similar CE, with Thembisa showing the largest differences in favor of 5 years. On average, 5% usage in 5 years had the best CE and 15% in 10 the worst. With Thembisa, the median CE for 5% in 5 years was $605/DALY if CAB-LA is delivered at cost parity with TDF-FTC, and $49,617/DALY at 50-fold costs, compared to $1,076 and $72,147, respectively, if 15% PrEP usage is reached within 10 years. Compared to Thembisa, the EMOD-HIV and Synthesis models assumed more risk-informed PrEP delivery, modeled lower HIV incidence declines without CAB-LA, and had higher continuing TDF-FTC provision. Both projected expanding PrEP use with CAB-LA to be cost-saving if delivered at cost parity with TDF-FTC under all scenarios. At 50-fold costs, median estimates were $3,206 and $6,845/DALY at 5% PrEP usage in 5 years and $6,135 and $21,782 at 15% usage in 10 years for EMOD-HIV and Synthesis, respectively.

Conclusion: Three independent models predict expanding PrEP coverage with CAB-LA would be cost- effective if delivered at a cost near that of TDF-FTC, and highlight the importance of reaching people with high risk for CE at higher prices.



1231 Cost-Effectiveness of a Urine Tenofovir Point-of-Care Assay for ART Adherence Feedback in Namibia

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Background: Virologic failure (VF) in patients on TLD often results from non-adherence given dolutegravir's high resistance barrier. Real-time adherence measurement could improve counseling, help patients achieve virological suppression (VS), reduce viral load (VL) tests, and promote cost-effective (CE) adherence interventions. In Namibia, we found that a new point-of-care (POC) urine-based tenofovir (TFV) assay-based intervention increased VS to 90% among those with VF on TLD after 3 months of WHO-recommended enhanced adherence counseling (EAC). These results contrast with an overall 71% VS rate worldwide for those on ART as estimated by the UNAIDS July 2023 report.

Methods: We modeled the health and cost impacts of two possible implementation scenarios with the urine assay over a year, comparing them to the standard of care (SoC) involving monthly EAC alone for VF, with VL tests every 3 months. Scenario 1 involved monthly TFV POC testing and EAC with a VL test after 3 consecutive positive POC tests; scenario 2 further restricted the use of VL testing to patients with no record of VS throughout the intervention period and an assumption that those who achieved VS remained adherent for a year. In 2020, the cost of VL and TFV POC testing was $63 and $1.33, respectively, for both SoC and the two scenarios. The cost of EAC ranged from $1.17 to $1.92 based on duration of session. Baseline ART adherence and VS data were obtained from the clinical study and UNAIDS. We assumed no patients would drop out of care.

Results: When following SoC guidelines, in a hypothetical cohort of 100 patients with VF on TLD, EAC alone increases VS to 71% at a total cost of $27,348. Scenario 1, in which POC tests were used to determine eligibility for VL tests, saved a total of 46 VL tests with a cost-savings of $2000, and resulted in 97% adherence and 90% VS. Scenario 2, where VL testing was not performed after VS was achieved, averted another 242 VL tests and an additional $15,190 (Table). It was assumed this large reduction in VL testing would not impact overall VS rates.

Conclusion: The study evaluates the cost and cost-effectiveness of incorporating a POC urine TFV test into counseling for ongoing viremia on TLD; the intervention was less expensive and improved health compared to SoC. An upcoming clinical trial will compare SoC EAC to urine assay counseling in a large sample with further CE analysis with hopes of eventual wide implementation of the urine assay worldwide to reduce VF, viral resistance, and transmission.

Table: Comparison between 100 patients with virologic failure on TLD receiving standard-of-care adherence counseling versus adherence counseling based on a point-of-care urine tenofovir assay

	Cost[1]	Cost-savings	Patients with viral suppression (VS)	Difference in patients with VS	Cost-effectiveness
Standard care	$27,348		71		
Intervention with VL re-testing after suppression	$25,221	$2,127	90	19	Dominant[2]
Intervention with no additional VL retesting after suppression	$10,031	$15,190	90	0	Dominant[2]

Assumed counseling cost $5.77/hour and those who achieve VS would remain adherent to ART.

[1] All costs in 2020 USD. [2]Less costly and improves health outcomes.

1232 Increased Medicare Spending Among Beneficiaries With HIV in the 12 Months Prior to Death

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Background: Medicare spending tends to be disproportionately higher among beneficiaries in their last year of life. We currently lack empirical data on how spending differs among Medicare beneficiaries with HIV in the last 12 months of life compared with Medicare beneficiaries with HIV who survive 12 months.
Methods: Using a 20% yearly sample of Medicare fee-for-service claims data (2016-2018), we identified beneficiaries with HIV aged 65 and older with Part D (prescription) coverage. We examined mean annual Medicare spending among beneficiaries with HIV who survive the calendar year compared with mean spending in the 12 months prior to death among beneficiaries with HIV who died, stratifying results by age group. After 1% winsorization, we calculated mean total spending, as well as mean spending across seven subcategories: direct medical treatment of HIV (excluding drugs); HIV-associated conditions and infections; mental health disorders; other medical spending; total drug spending; spending on antiretroviral therapy (ART); and spending on other drugs.
Results: The study sample included 5,601 beneficiaries with HIV who survived the study period, and 706 beneficiaries who died. Mean annual Medicare spending was substantially higher among decedents in the 12 months prior to death compared to people who survived, with the largest difference observed among beneficiaries aged 65-69 ($126,969 vs. $55,662). Mean annual spending was higher among decedents with HIV (compared with survivors) across most subcategories, except total drug spending. Beneficiaries of all age groups who died had lower spending on ART ($23,256-$16,532 vs. $30,650-24,159) with the greatest decrease among older beneficiaries.
Conclusion: In a national study of older Medicare beneficiaries with HIV and Part D, beneficiaries in their last year of life incurred substantially higher spending compared to survivors, particularly among younger beneficiaries. In contrast, ART spending declined markedly in the last year of life, especially among older beneficiaries, which suggests ART cessation at the end of life. These findings have important implications as the HIV population grows older, and a greater number of people with HIV receive healthcare coverage through the Medicare program at the end of life.

Mean Medicare spending over 12 months among Beneficiaries with HIV and Part D who died vs. Beneficiaries with HIV who survived, 2016-2018

Age Group	Age 65-69 years		Age 70-74 years		Age 75-79 years		Age 80+ years	
	Died (N=276)	Survived (N=6,151)	Died (N=205)	Survived (N=3,760)	Died (N=125)	Survived (N=1,461)	Died (N=100)	Survived (N=766)
Total Spending	$126,969	$55,662	$113,665	$54,348	$111,245	$54,345	$103,490	$50,034
Direct Medical Treatment of HIV (Excluding Drugs)	$11,163	$1,669	$8,478	$1,586	$6,505	$1,648	$6,635	$1,873
HIV-Associated Conditions and Infections[1]	$11,787	$896	$10,595	$820	$11,065	$973	$7,995	$1,111
Mental Health Disorders	$978	$334	$895	$274	$514	$223	$562	$176
Other Medical Spending	$67,380	$13,396	$62,283	$14,332	$62,106	$15,465	$62,460	$16,899
Total Drug Spending	$34,204	$37,952	$31,315	$36,189	$29,868	$34,883	$25,614	$28,622
Spending on ART	$23,256	$30,650	$21,430	$29,629	$22,234	$29,235	$16,532	$24,159
Spending on Other Drugs	$10,787	$7,205	$9,775	$6,470	$7,561	$5,518	$8,736	$4,457

[1] HIV-associated conditions and infections as defined in Figueroa et al *Health Affairs* 2022.

1233 Estimated Costs of Eliminating Medicaid Prior Authorizations for Antiretrovirals in Washington State

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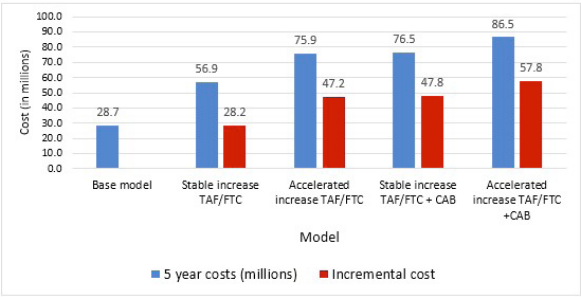
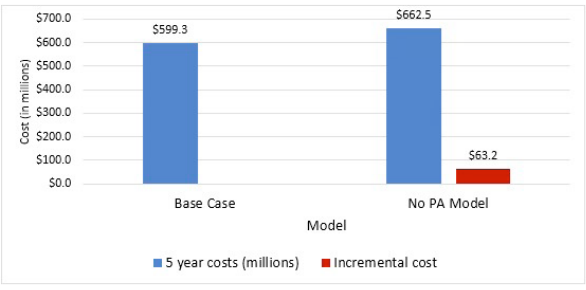
Background: Medicaid is the largest insurer of persons living with HIV (PLWH) in the U.S. Some Medicaid programs use prior authorizations (PAs) to limit drug expenditures. In 2023, WA State eliminated PAs for antiretrovirals (ARVs).
Methods: We modeled the impact of PA elimination on HIV treatment and pre-exposure prophylaxis (PrEP) costs, 2023-2027. All models used 2021 net drug costs reflecting costs minus rebates. PrEP models assumed a 10% annual increase in the number of PrEP users and evaluated the impact of annual declines in the relative percentage of PrEP users on TDF/FTC with compensatory increases in TAF/FTC use; some models assumed the percentage of PrEP users on cabotegravir (CAB) would increase 1% annually. We modeled 5 scenarios: 1) Base – no change in the percentages of PrEP users on TDF/FTC and TAF/FTC and no CAB; 2) Stable change – 3.5% decrease in TDF/FTC and no CAB; 3) Accelerated change – 7% decrease in TDF/FTC and no CAB; 4) Stable change + CAB – 3.5% decrease in TDF/FTC and 1% annual increase in CAB; 5) Accelerated change + CAB – 7% decrease in TDF/FTC and 1% annual increase in CAB. For HIV treatment, we assumed a 2% annual increase in the number of PLWH on ART. Our Base Model assumed no change in the percentage of PLWH on different drugs. Our No PA Model assumed: 1) 18% annual relative increase in the percentage of PLWH on bictegravir/TAF/FTC; 2) the percentage of people on tenofovir/FTC taking TAF/FTC (vs. TDF/FTC) increases 9% annually; 3) CAB/rilpivirine increases 1% annually; 4) no change in darunavir/cobisistat; and 5) use of other ART drugs decline in proportion to their 2022 use. To place costs in context, we estimated the number of PLWH who might be housed using money required to meet new ART costs; this estimate reflects local 2023 costs for emergency or temporary housing with 5% annual inflation.
Results: The 5-year cost of PrEP in our Base Model was $28.7 million. Elimination of PAs increases that cost by $28.2 to $57.8 million. The annual cost of PrEP in 2027 was $9.5 to $20.1 million more in no PA models than the base model. Changes in HIV treatment will result in $63 million in new costs over 5 years. In our most costly scenario, elimination of PAs will cost $121 million over 5 years. This cost would pay for 5 years of housing for 817 PLWH, which exceeds the total number of unhoused PLWH in King County, WA.
Conclusion: Elimination of Medicaid PAs will likely result in substantial new costs. Changes in drug formulary policy should consider opportunity costs.

Figure: Estimated cumulative and incremental cost associated with changes in PrEP (A) and HIV treatment (B) over 5 years.

A.



B.



CAB=Cabotegravir

1234 Cost-Effectiveness of Integrated Multi-Month Dispensing for HIV and Hypertension in South Africa

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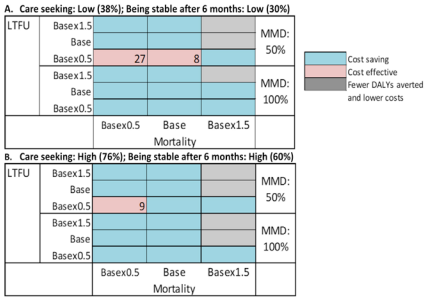
Background: In the current era of universal antiretroviral treatment (ART), health systems have the dual challenge of a growing number of people living with HIV and on ART who are also receiving chronic, life-long treatment for non-communicable diseases. Current evidence suggests that multi-month dispensing (MMD) for HIV can maintain at least equivalent clinical outcomes to conventional care and reduce costs, but little evidence exists when integrating MMD for multiple conditions. We examined the cost-effectiveness of integrated MMD for people living with HIV and hypertension.

Methods: Using an age and sex-specific hybrid decision tree and Markov state-transition model, we constructed a 100,000-person simulated population cohort who may develop HIV and hypertension and initiate treatment at clinics in South Africa over a 10-year time horizon. We assessed the incremental costs and effectiveness of MMD versus conventional care from a health system perspective under different conditions of care seeking, eligibility, and uptake of MMD for clinically stable patients. Model inputs were sourced from previously published literature. MMD was defined as reducing the frequency of clinic visits by increasing the number of medications dispensed to stable patients at each visit from 3 to 6 months. For the integrated MMD, we assumed that comorbid patients receive both HIV and hypertension drugs at the same facility on the same day.

Results: Our study demonstrates that integrated MMD for HIV and hypertension in South Africa can avert between 0.08 and 0.11 DALYs and save between $166 and $208 health systems costs per patient per year. Across all scenarios, HIV prevalence, care seeking level, mortality rate and LTFU rate were key drivers in DALYs averted; HIV prevalence, outpatient costs per visit and ART cost were key drivers in health systems cost. Overall, greater MMD integration, higher care seeking and a greater proportion of well-controlled patients in care led to greater cost savings or better (lower) ICER values.

Conclusion: Integrated MMD is likely cost-saving (or highly cost-effective at ≤$30 per DALY averted) in various care-seeking scenarios and proportions of patients in care. Scale-up of MMD strategies is most effective when multiple conditions are addressed simultaneously. The benefit of integrated MMD may be greater than what we have estimated here through the potential for greater care-seeking and disease control among patients already in care with less LTFU and fewer deaths through high-quality care.

Figure. ICERs (i.e., 2022 US dollars per DALY averted) for three-way sensitivity analyses of integrated multi-month dispensing (MMD) for people living with HIV only and people living with HIV and hypertension comorbidity in South Africa, compared with a baseline of no MMD.



1235 Implementing Long-Acting ART in a Community Health Center: Insights and Early Outcomes

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Whitman-Walker Health, Washington, DC, USA Presenting Author: Dr David Fessler

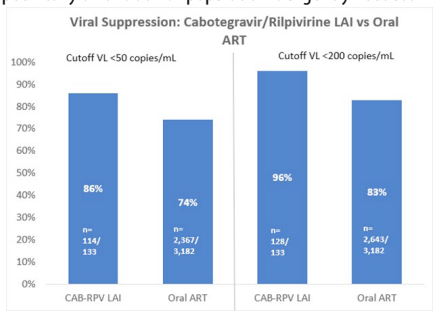
Background: Long-acting injectable Cabotegravir-Rilpivirine (CAB-RPV LAI) offers people living with HIV (PLWH) a safe and effective alternative to daily oral ART. In 2021, Whitman-Walker Health, a Federal Qualified Health Center (FQHC), began scaling up implementation of CAB-RPV LAI in appropriate patients.

Methods: A multidisciplinary working group developed a protocol for providers and a workflow to streamline processes involving insurance authorizations, coding/billing, and patient and medication tracking. Most patients were consistently virologically suppressed at baseline, consistent with FDA guidance and trial protocols. However, with early promising data in treating non-suppressed PLWH (Gandhi et al., CROI 2023), carefully selected viremic patients were also offered treatment, using a monthly dosing schedule. These were generally PLWH who were struggling with adherence but who maintained consistent care engagement, and who were verified to have no relevant resistance mutations. We conducted a cross-sectional analysis comparing virologic suppression in patients on CAB-RPV LAI with patients prescribed oral ART, recognizing the presence of selection bias. The two groups were similar across age, sex, gender identity, insurance status, and baseline CD4 count.

Results: To date, we have 133 PLWH receiving CAB-RPV LAI, who have received a total of 715 doses of which 96% have been given within the appropriate treatment window. Navigators track to ensure injection visits are scheduled at the correct time intervals and work with medical providers to reschedule quickly for missed appointments. Most CAB-RPV LAI patients (86%,114/133) had a VL <50 copies/mL on most recent assay,

compared to 74% (2367/3176) of PLWH receiving oral HIV medication, X2 (1, N=3309) = 8.7, p<.01. Twenty- one patients were started on CAB-RPV LAI with a VL ≥ 50 copies/mL who had a VL drawn at least one month after their initial dose. This group's median baseline VL was 100 copies/mL, and 76% (16/21) have subsequently achieved VL <50 copies/mL. Of the five patients who remain non-suppressed, median VL has dropped from 140 copies/mL to 60 copies/mL.

Conclusion: We successfully developed a robust cohort of PLWH on CAB-RPV LAI in an FQHC setting. These patients have maintained viral suppression at a high rate. We also provide further evidence suggesting efficacy of CAB-RPV LAI in non-suppressed PLWH who struggle with adherence to oral ART. Research focused specifically on this at-risk population is urgently needed.



1236 Injectable Cabotegravir/Rilpivirine Reach and Effectiveness in a South Side Chicago HIV Clinic

Geoffroy Liegeon[1], Chris Kaperak[1], Eleanor Friedman[1], Alicia Dawdani[1], Paul Djuricich[1], Kane Stafford[1], Jessica Schmitt[1], Aniruddha Hazra[1], Katerina Christopoulos[2], John Schneider[1], Moira McNulty[1]
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Background: Long-acting injectable (LAI) cabotegravir (CAB) and rilpivirine (RPV) represent a new treatment option for people with HIV (PWH). We sought to understand early reach and effectiveness outcomes in an academic Ryan White clinic serving a primarily Black/African American patient population.

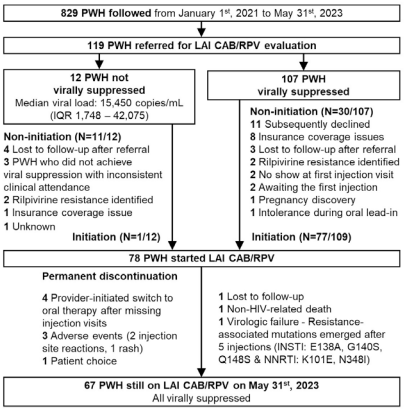
Methods: We conducted a retrospective cohort analysis of all PWH referred for LAI CAB/RPV at the University of Chicago HIV clinic from January 1, 2021 to May 31, 2023. We described the socio-demographic and clinical characteristics of the referred PWH. We compared the initiation rate categorized by viral suppression (VS), defined as a viral load <50 copies/mL, using a Fisher's exact test and described early clinical outcomes. Per guidelines, PWH without VS initiated LAI CAB/RPV after VS on oral antiretrovirals.

Results: Of the 829 PWH in the program, 119 (14%) were referred for LAI CAB/RPV with median age 34, 65% cisgender male, 30% cisgender female, 5% transgender or non-binary, 85% Black, 56% sexual minority men, 32% with psychiatric illness, 8% with substance use, and 61% Medicaid insured. Half of referred PWH had comorbidities, 69% took other pills daily, and 37% had a BMI >30kg/m². At referral, the median time living with HIV was 7 years, 78% received an integrase inhibitor (INSTI)-based regimen, and 12/119 (12%) did not have VS. After a median period of 1 month (IQR 0-3), 78 PWH (66%) started LAI CAB/RPV, of whom 57% had no prior HIV drug resistance test available, 24% received an oral lead-in, and 77% initiated with a bimonthly dosing schedule. The reasons for non-initiation are detailed in Figure 1. PWH without VS at referral were less likely to start treatment (P<0.001). After a median of 5 injections (IQR 3 to 7) and a median follow-up time of 8 months (IQR 5-12 months), all maintained VS except for one virologic failure, with 11/78 (14%)

discontinuing LAI CAB/RPV after a median time of 4 months (IQR 1-6 months). Missing visits and adverse events explained two- thirds of discontinuations (Figure 1).

Conclusion: We found significant referrals for and uptake of LAI CAB/RPV in a clinic serving primarily Black/African American PWH. However, challenges exist in starting PWH on LAI CAB/RPV, especially among those without VS. More work is needed to support providers, patients, and clinic systems to deliver LAI- CAB/RPV to this group.

Figure 1. Flowchart of PWH referred and initiating LAI CAB/RPV.



1237 Associations Between Interest in Oral vs Long-Acting Injectable ART Among US Women With HIV

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Background: Long-acting injectable (LAI) ART has the potential to improve suboptimal medication adherence and health outcomes for people with HIV, yet studies of patient interest and acceptance are mixed and may differ by sex. We surveyed U.S. women to examine factors associated with preferences for LAI vs oral ART.

Methods: From Sept. 2020- Nov. 2021, we administered a cross-sectional survey to 1,078 women with HIV across MACS/WIHS Combined Cohort Study sites in Atlanta, GA; Birmingham, AL/Jackson, MI; Bronx, NY; Brooklyn, NY; Chapel Hill, NC; Chicago, IL; Miami, FL; San Francisco, CA; and Washington, DC. The survey assessed demographic characteristics and ART modality preferences. Multinomial logistic regression assessed factors associated with preference for LAI vs oral ART vs undecided, controlling for age, education, race/ethnicity, income, adherence and site.

Results: Median age was 54, the majority of women were Black (72%) and Hispanic (13%), and most (58%) had an annual income of ≥$12K. Over one-third (37%) of women finished more than high school while 88% reported ≥95% oral ART adherence. In the sample, 43% preferred LAI ART, 36% oral ART, and 21% were undecided. In adjusted models, women who reported ≥95% oral ART adherence (relative risk (RR): 0.39; CI: 0.24-0.63) and older age (RR: 0.98 per year; CI: 0.97-1.00) were less likely to prefer LAI ART vs oral ART. Compared with women in Miami, those in other sites (RR: 2.12-3.05) preferred LAI to oral ART. Comparing women who preferred LAI ART vs being undecided, women with ≥95% oral ART adherence were less likely to prefer LAI ART (RR: 0.58; CI:0.33-0.99) whereas Hispanic women were more likely (RR: 2.30; CI:1.01-4.87). When comparing oral ART vs undecided, women whose racial category was 'other' were more likely to prefer oral ART (RR: 3.32; CI: 1.17-9.46) whereas women whose income was ≥$12K were less likely to prefer oral ART (RR: 0.58; CI: 0.39-0.86). Women in sites other than Miami (RR: 0.26-0.32) were less likely to prefer oral ART vs undecided.

Conclusion: In a geographically diverse cohort of US women, we found a preference for LAI vs oral ART, while about 20% remained undecided. Findings suggest potential differences in ART preference by adherence, age, site, income and race/ethnicity. To maximize the benefits of LAI ART and ensure equitable access to treatment for all women across the US and globally, it is critical to tailor education and support around LAI ART that is specific to each patient's unique needs and experiences.

Adjusted models of Women's Preferences for LAI ART vs oral ART vs undecided

Variable		LAI ART vs oral ART	Oral ART vs Undecided	Oral ART vs Undecided
Age	Age	**0.98 (0.97-1.00)**	0.98 (0.96-1.00)	1.00 (0.98-1.02)
Education	HS	1.18 (0.82-1.70)	0.80 (0.52-1.24)	0.68 (0.43-1.06)
	>HS	1.25 (0.86-1.80)	1.13 (0.72-1.77)	0.90 (0.57-1.44)
Race/Ethnicity	Hispanic	1.26 (0.66-2.40)	**2.30 (1.08-4.86)**	1.82 (0.86-3.89)
	African American	1.36 (0.80-2.31)	1.60 (0.89-2.88)	1.18 (0.66-2.10)
	Other	0.80 (0.36-1.77)	2.65 (0.91-7.74)	**3.32 (1.17-9.46)**
Income	≥ 12K/yr	1.27 (0.93-1.74)	0.74 (0.50-1.08)	**0.58 (0.39-0.86)**
Adherence	Taking ART ≥ 95% of time	**0.39 (0.24-0.63)**	**0.58 (0.33-1.00)**	1.48 (0.79-2.77)

1238 Uptake of Long-Acting Injectable Antiretroviral Therapy in Florida: An Assessment of EHR Data

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Background: In January 2021, the US Food and Drug Administration approved the first long-acting injectable antiretroviral therapy (LAI ART) regimen, cabotegravir/rilpivirine, providing an alternative to daily oral regimens. However, scarce literature exists on the uptake of LAI ART using real-world data. Leveraging electronic health records from a large clinical research network in the Southern US - OneFlorida+ linked with Medicaid (updated to 08/2022) - we identified a cohort of people with HIV (PWH) who received LAI ART and characterized their demographics, clinical characteristics, and HIV care outcomes.

Methods: LAI ART recipients were identified by screening both prescribing and dispensing records using a combination of medication name, RxNorm, and National Drug Code.

Results: A total of 234 LAI ART recipients were identified: 56.8% female, mean age 44.9, 51.3% non-Hispanic Black, 20.9% non-Hispanic White, 19.7% Hispanic, 78.2% on Medicaid and 4.7% on private insurance. About 20% of LAI ART users did not have two or more visits at least 90 days apart in the year before LAI ART initiation (i.e., were not engaged in care). Lifetime substance use disorder diagnoses included18.8% with cannabis use disorder, 13.7% with cocaine use disorder, and 8.5% with opioid use disorder. After the initiation of LAI ART, 53.8% exclusively used LAI ART, 15% concurrently used other oral ART, and 31.2% potentially switched back to oral ART (i.e., receiving oral ART after last record of LAI ART). Most people (68.4%) had 2+ records of LAI ART injections, among them the average time gap between injections is 50.6 days (SD 45.2) and more than half had at least one time gap greater than 65 days. Of the 54 people with HIV viral load test results after the initiation of LAI ART, only 1 record of virologic failure (viral load>200 copies/ml) was observed.

Conclusion: Our study demonstrates that people with suboptimal care engagement and substance use disorder were not excluded from the treatment with LAI ART. While LAI ART is considered a complete regimen for HIV, a small proportion of individuals concurrently received other oral ART, possibly due to personalized treatment plans or bridging treatment. Our study reveals a likely noteworthy discrepancy between the current guidelines, which suggest a two-month interval between LAI ART injections, and the observed common prolonged time gap between injections. Despite limited evidence for optimal LAI ART adherence, virologic failure remains rare among LAI ART users.

1239 Interest in Long-Acting Injectable PrEP Among Transgender Women in the United States

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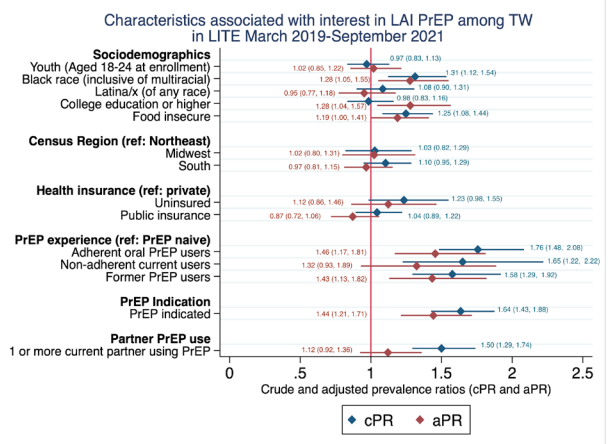
Background: Long-acting injectable (LAI) PrEP is a highly efficacious HIV prevention tool. Among communities with high HIV burden, such as transgender

women (TW) in the United States (US), uptake among those at risk of acquiring HIV could potentially reduce new infections and contribute to Ending the HIV Epidemic efforts. However, a lack of data on LAI PrEP interest among TW in the US has limited scientific understanding of the potential impact of LAI PrEP scale-up on new infections within TW communities. Thus, our objective was to identify correlates of interest in LAI PrEP among a large sample of TW.

Methods: Data were drawn from the LITE cohort, which followed TW with risk factors for HIV acquisition in the eastern and southern US. Participants who completed 12-month surveys between March 2019 and September 2021 (corresponding to the period between establishing LAI PrEP efficacy and prior to FDA approval) were asked about their interest in using LAI PrEP. We estimated crude and adjusted prevalence ratios for LAI PrEP interest with sociodemographic characteristics, healthcare access indicators, prior PrEP experience, and PrEP indication correlates using Poisson regression with robust variance.

Results: Among 867 TW, 23% reported they were very interested in LAI PrEP, 22% somewhat interested, 19% neutral, 7% somewhat uninterested, 12% very uninterested, and 16% unsure. In the adjusted model, interest in LAI PrEP (somewhat or very interested) was more common among TW who identified as Black, college- educated TW, and TW indicated for PrEP based on CDC guidelines (Figure). LAI PrEP interest was also more common among adherent users of oral PrEP and those who had discontinued oral PrEP, compared to PrEP-naïve participants. There were no statistically significant differences in LAI PrEP interest for young adults ages 18-24 years compared to those >=25 years, those who identified as Latina/x, and those who were publicly insured or uninsured compared to those privately insured.

Conclusion: Interest in LAI PrEP among TW in the eastern and southern US varied by several demographic and clinical characteristics. Increased interest in LAI PrEP among Black TW, those who were PrEP indicated, and those who had previously discontinued oral PrEP underscores the need to increase LAI PrEP access for TW who express interest. Efforts to increase awareness of and access to LAI PrEP among young TW and Latina/x TW are needed to ensure equitable scale-up among TW most impacted by HIV.



1240 Healthcare Staff Acceptability and Feasibility of Telehealth Delivery of Cabotegravir for PrEP

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Background: Telehealth can be leveraged to support PrEP delivery; however, limited evidence exists on how it is being used with injectable PrEP. We report interim findings from the PILLAR study, a Phase IV implementation science study, on healthcare staff acceptability and feasibility of long acting cabotegravir (CAB LA) for PrEP, use of telehealth, and utility of implementation supports for CAB LA delivery in the U.S.

Methods: 17 sites were randomized 2:1 to Dynamic (DI) or Routine (RI) implementation. RI received standard toolkits and DI received standard and enhanced toolkits and supports. Staff study participants (SSPs) completed the acceptability of intervention (AIM) and feasibility of intervention measures (FIM) for CAB LA delivery and for implementation support at Month 1 (M1; n=86) and Month 4 (M4; n=80). Change in mean FIM and AIM scores (scores averaged over four items measured as 1=completely disagree to 5=completely agree) was assessed. SSPs completed questions on the utility of implementation supports and telehealth delivery of CAB LA at M4.

Results: Of 86 SSPs at M1, 50% were cisgender female, 55% White, 15% Black, and 24% Hispanic, with mean age 41 (range: 23-72). SSPs reported high levels of acceptability and feasibility of CAB LA and implementation support at M1 (mean scale scores≥4.0) and M4 (mean scale scores≥3.9). Except for FIM for CAB LA in RI, mean scores decreased slightly over time for both arms (≤0.4). At M4, toolkits with the highest use (>40% SSPs) were found useful/very useful by over 58% of SSPs (Table). DI only toolkits and support with the highest use (>33% SSPs) were found useful by over 47% of SSPs (Table). 69% of DI SSPs found one-on- one and group facilitation support useful/very useful. Of 51 DI arm SSPs at M4, 57% reported using telehealth for CAB LA delivery. Of those using telehealth, the systems used included virtual visits (83%), online appointment scheduling (52%)/reminders (76%), and at home testing (38%)/injections (24%). DI SSPs found the systems very/somewhat easy to use (range: 71%-86%), very helpful/helpful (range: 71%-93%) and were very/somewhat satisfied (range: 80%-94.7%). DI SSPs reported high levels of acceptability and feasibility of telehealth delivery of CAB LA (mean scale scores≥4.1).

Conclusion: Findings suggest that CAB LA telehealth delivery is acceptable and feasible. Scaling telehealth and implementation resources may support efficient integration of CAB LA into care and user adherence and retention on CAB LA. The figure, table, or graphic for this abstract has been removed.

1241 Insurance Type Drives Cabotegravir Delays: Real-World Long-Acting PrEP Outcomes in the Midwest US

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Background: Long-acting cabotegravir (CAB-LA) is the first FDA-approved injectable agent for HIV PrEP. However, limited data exist on its use in a real-world setting. We describe clinical characteristics and outcomes of CAB-LA for PrEP at a federally qualified health center and the largest PrEP clinic in the Midwest US.

Methods: We conducted a single-center retrospective cohort study of all patients without HIV who received at least one dose of CAB-LA at Howard Brown Health between July 1, 2022 and December 31, 2023. Demographics and clinical characteristics were collected; associations between delays in initiation as well as therapy interruption and discontinuation were assessed by logistic regression.

Results: A total of 270 patients met the inclusion criteria with median age 33, 80.4% cisgender men, 54.1% White, 23.7% Hispanic, 60.4% with private insurance, and 29.6% residing in a high HIV vulnerability community area. The majority (90.4%) had been on oral PrEP in the past, 72.2% transitioned directly from oral PrEP, 2.2% had a CAB oral lead-in, and 31.1% had a BMI >30kg/m^2. Patients experienced a median delay of 24 days (IQR 11-51) between a provider initiating a CAB-LA prescription and their first injection, 41.9% of patients experienced delays >30 days. The median number of CAB-LA doses received was 4 (range, 1-12); 8.1% experienced at least one delayed or missed injection and 10% of patients discontinued CAB-LA of which 25.9% were placed on an oral PrEP regimen after discontinuation. While on CAB-LA, 67% had HIV screening by viral load assay at every injection visit; 49.6% had STI screening at the recommended 4-6 month intervals with 26.3% testing positive for an STI during the study period. Insurance status was the only variable associated with delays in initiation. Compared to patients with private insurance, those without insurance were significantly more likely to experience delays while those with public insurance were significantly less likely to experience delays >30 days in initiating CAB-LA (OR 1.97 vs 0.60, p=0.03).

Conclusion: CAB-LA for PrEP was successfully implemented at a large urban community health center. Most patients experienced delays in initiation which were associated with insurance type; interruptions and discontinuation of injections were less common without any significant associations. More work is needed to support patients and health systems with challenges specific to long-acting agents, particularly regarding insurers and payors.

1242 Rapid Long-Acting Injectable PrEP Implementation in a Vulnerable Urban Safety Net Clinic Population

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Background: Despite effective oral PrEP, barriers to uptake and adherence persist, including stigma, substance use (SU), housing/food insecurity, and mental health issues. Long-acting cabotegravir (CAB) PrEP is highly efficacious and may address barriers for patients with adherence challenges, but uptake has been low and real- world data is lacking.

Methods: We describe a CAB demonstration project at Ward 86, an urban safety-net clinic in San Francisco serving vulnerable patients with high rates of homelessness, mental illness, and SU living with or at risk for HIV. Patients were initiated on CAB via a structured process of provider referral and multidisciplinary review and monitored for on-time injections. Patients were offered low-barrier, multidisciplinary care with rapid PrEP initiation. We report CAB PrEP program evaluation data from chart extraction and PrEP tracking logs for patients initiated on CAB between 3/1/2022-6/1/2023 and followed through 9/1/2023. On-time injections were defined as given 28±7 days for initiation/re-initiation doses or 56±7 days for maintenance doses.

Results: We initiated 30 participants on CAB PrEP: 70% cisgender men, 13% cisgender women, 7% transgender women, 10% nonbinary people. Median age was 39 years (range 21-63); 10% of participants were Black, 30% Hispanic, 7% Asian/Pacific Islander, 3% multi-racial. Of the 30, 20% were homeless; 23% were unstably housed. All participants had public insurance (93%) or were uninsured (7%). Active SU disorder was documented in 67%; 53% had at least 1 serious mental illness. We administered 184 injections during the study period, with a median of 6 injections/person (range 1-10). Median time from CAB referral to first injection was 14 days (range 0-111). The median duration of follow-up was 271 days (IQR 87-469). All patients had direct-to- inject CAB; 50% were not on oral PrEP at CAB initiation. Of 157 scheduled follow-up injections, 86% were on time, 4% early, 8% late, and 2% missed/not done. Of late or missed/not done injections, 47% were ≥1 month late, of which 43% were covered by oral PrEP bridging. CAB was discontinued by 3 participants for risk change (1), loss-to-follow-up (1), and transfer of care (1). All remain HIV-negative.

Conclusion: This demonstration project shows that a rapid start CAB PrEP program serving patients with numerous psychosocial stressors is feasible and has high retention. Delivery of CAB via a low-barrier, comprehensive care model may expand uptake to high-risk, adherence-challenged populations.

1243 High Acceptability of Long-Acting Injectable PrEP and ART Among MSM and PWID in India

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Background: Long-acting injectable PrEP (LA-PrEP) and ART (LA-ART) hold significant potential to overcome challenges of daily adherence to oral modalities. Their population-level impact requires acceptability and uptake by populations with the most need, such as people who inject drugs (PWID) and men who have sex with men (MSM) in low/middle income settings.

Methods: We used respondent-driven sampling to accrue samples of PWID and MSM in India Nov 2022-Aug 2023 (3 PWID sites; 2 MSM sites; ~750/site). Participants were ≥18 years old and reported injection drug use in the prior 2 years (PWID) or sex with a man in the prior year (MSM). Participants completed a survey and blood draw. Those reporting a prior HIV diagnosis were asked questions about LA-ART and those without a prior diagnosis were asked about LA-PrEP. We present acceptability and correlates of LA-PrEP and LA-ART using multilevel logistic regression models by modality and population separately.

Results: 2250 PWID and 1502 MSM were enrolled. PWID HIV prevalence was 41%, of whom 45% were on ART and 34% suppressed (≤150 copies/mL). MSM HIV prevalence was 21%, of whom 65% were on ART and 75% suppressed. Of those not reporting a prior HIV diagnosis, 10/14% (PWID/MSM, respectively) reported no/very little chance they would be willing to get injections to prevent HIV and 65/78% a very good chance. Main reasons for LA-PrEP unwillingness among PWID were inconvenience of injections and low risk perception; among MSM, reasons were injection pain and cost. Among PWID, women and those homeless were less willing to take LA-PrEP and those with more sexual partners were more willing; injection behaviors were not associated (Table). Among MSM, those with more partners were less willing to take LA-PrEP; unprotected sex was not associated. Of those with a prior HIV diagnosis, 3/2% (PWID/MSM, respectively) reported no/very little chance they would willing to take LA-ART and 83/89% reported a very good chance. Among PWID, those injecting daily were more willing to take LA-ART but those viremic were less likely. Among MSM, those with more partners and viremic were more willing. ART use was not associated with LA-ART willingness for either population.

Conclusion: There was high interest in using LA-PrEP and LA-ART among populations that experience a disproportionate HIV burden and barriers to HIV treatment engagement. However, there remain vulnerable subgroups for which these may not be appropriate and other prevention and treatment approaches will be required.

Table Correlates of acceptability of LA-PrEP and LA-ART among of 2250 PWID and 1502 MSM in India

Correlate	LA-PrEP: PWID aOR (95% CI)	LA-PrEP: MSM aOR (95% CI)	LA-ART: PWID aOR (95% CI)	LA-ART: MSM aOR (95% CI)
Age 26 to 35 years (vs. 18 to 25 years)	0.81 (0.78 – 0.85)	0.84 (0.69 – 0.90)	0.68 (0.36 – 1.28)	2.49 (2.49 – 2.49)
Married	--	--	0.53 (0.43 – 0.66)	--
Female	0.24 (0.23 – 0.25)	--	--	--
Homeless	0.45 (0.29 – 0.71)	--	--	--
Daily drug injection in prior 6 months	--	--	2.08 (1.56 – 2.78)	--
Hazardous alcohol use	--	--	2.01 (1.03 – 3.93)	0.08 (0.04 – 1.17)
Number of sexual partners in prior 6 months	2.03 (1.22 – 3.36) [2+ vs. none]	0.99 (0.98 – 0.99) [6 to 15 vs. none]	0.13 (0.08 – 0.20) [2+ vs. none]	5.32 (4.71 – 6.02) [6 to 15 vs. none]
HIV viral load >150 copies/mL	--	--	0.71 (0.52 – 0.97)	3.14 (2.00 – 4.94)

LA-ART: long-acting injectable antiretroviral therapy; LA-PrEP: long-acting injectable pre-exposure prophylaxis
PWID: people who inject drugs; MSM: men who have sex with men
aOR: adjusted odds ratio; CI: confidence interval

1244 Gender Affirmation and Incentives for Long-Acting PrEP: Stated Preferences of Transgender Adults

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Background: Transgender and nonbinary (trans) people face a disproportionately high HIV risk, yet adherence to pre-exposure prophylaxis (PrEP) remains low. Conventional approaches to PrEP programming have not sufficiently engaged trans populations. Gender affirmation and conditional economic incentives could help improve the uptake of PrEP, but user-centered approaches are needed to inform the optimal design of trans- specific PrEP programming.

Methods: We conducted a discrete choice experiment among 385 trans adults in Seattle/King County, Washington State to inform the optimal design of a conditional economic incentive (CEI) program that would provide free long-acting injectable PrEP (LA-PrEP) and gender-affirming care. We used a best-best elicitation method where respondents were first asked to select their best option from three hypothetical choice profiles (Program A, Program B, or No Program), and to then select their second-best option from the remaining two profiles. We used a rank-ordered mixed logit model for main results, and estimated respondents' marginal willingness-to-accept each program attribute.

Results: We find the optimal program design would: (1) deliver incentives in cash, (2) confirm LA-PrEP adherence via blood testing, (3) provide counseling in-person, and (4) provide co-prescriptions for injectable gender-affirming hormones. From a maximum yearly incentive amount of $1,200, respondents were willing to forgo up to $795 to receive incentives in cash (instead of voucher) and up to $587 to receive injectable rather than oral hormones. As shown in the figure, the probability of choosing a hypothetical program over no program waned as adults aged (>40 years) and as annual income increased (>$75,000/year).

Conclusion: Conditional economic incentives may be effective for improving LA-PrEP adherence among trans adults who are younger and have fewer financial resources. A randomized trial is needed to confirm the validity of the DCE for predicting actual program uptake.

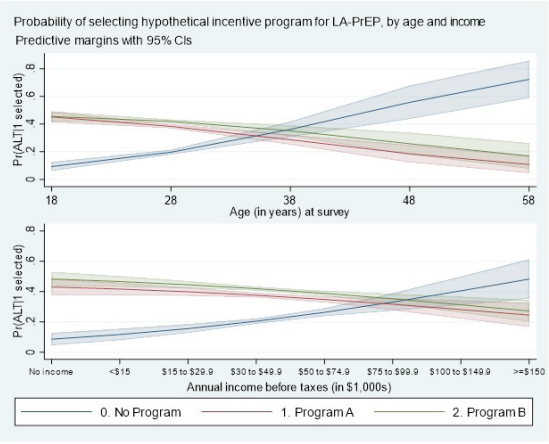

Figure presents choice probabilities over respondents' age and income. Solid lines show average linear prediction values of program selection and shaded areas show 95% CIs. To estimate probabilities, Stata's margins command was run after McFadden's choice model that included all alternative-specific variables selected through best-best elicitation. LA-PrEP: long-acting pre-exposure prophylaxis.

1245 Access to Long-Acting Injectable ART Through State AIDS Drug Assistance Programs

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Background: Long-acting injectable (LAI) antiretroviral therapy (ART) may help address barriers to treatment adherence among people with HIV. Due to cost and operational issues, low-income individuals, including clients of the federal Ryan White HIV/AIDS Program (RWHAP), may face greater challenges in accessing LAI ART. Of 1.09 million people with diagnosed HIV in the US, 301K (28%) access treatment through state AIDS Drug Assistance Programs (ADAPs) funded by the RWHAP. State ADAPs are required to cover at least one drug from each therapeutic class of HIV antiretrovirals (ARVs). They are not required to cover long-acting formulations of drugs from existing therapeutic classes, such long-acting cabotegravir/rilpivirine (Cabenuva). We sought to determine the extent of access to Cabenuva through state ADAPs, and to describe the population of ADAP clients without access to Cabenuva.
Methods: Data on state ADAP medication formularies were collected by the National Association of State and Territorial AIDS Directors (NASTAD) in January 2023. Data on the characteristics of ADAP clients were obtained from the 2020 RWHAP ADAP Annual Client-Level Report. Data on the characteristics of all people with diagnosed HIV were obtained from the US Center for Disease Control and Prevention's AtlasPlus Tool. We compared the characteristics of ADAP clients in states with and without ADAP coverage of Cabenuva, and of ADAP clients vs. non-clients in states without ADAP coverage of Cabenuva.
Results: In contrast to the 2 oral ARVs most recently approved by the US Food and Drug Administration, which were listed on 92-98% of state ADAP medication formularies in January 2023, Cabenuva (approved in January 2021) was covered by 78% of state ADAPs. Nearly two thirds (64%) of the 56,020 ADAP clients in states without ADAP coverage of Cabenuva were living at or below the federal poverty level, compared to 43% of the 221,539 ADAP clients in states that did cover Cabenuva. In states that did not cover Cabenuva, ADAP clients were more likely than non-clients to be Black (36% vs. 34%) or Hispanic (30% vs. 26%).
Conclusion: Gaps in coverage of Cabenuva affect large numbers of people who access ART through state ADAPs, and disproportionately affect low-income and racially minoritized people with HIV. States should consider expanding access to Cabenuva, including working to reduce supply and payment chain barriers, to promote equitable access to LAI ART. Future work should examine access to Cabenuva using patient-level data.

1246 Effect of Changes in Script Renewal Period on HIV Viral Non-Suppression Among Insured South Africans

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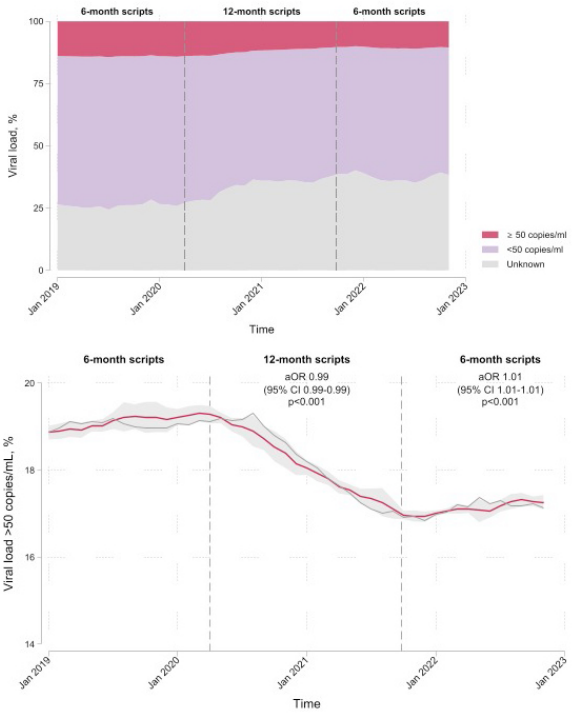
Background: Evidence is needed to inform antiretroviral therapy (ART) delivery models which allow people with HIV to attend health facilities less frequently. While COVID-19 lockdown measures were in place, South Africa temporarily changed the validity of "repeat" prescriptions for ART from 6 to 12 months. We evaluated the effect of these changes on HIV viral non-suppression in the private health sector in South Africa.
Methods: We analysed routine laboratory and pharmacy claim data between November 1, 2019, and November 30, 2022 from Aid for AIDS (AfA), a large South African medical insurance scheme. Adults living with HIV over the age of 15 years who had received ART for ≥3 months were included. We conducted an interrupted time- series analysis comparing rates of viral non-suppression (viral load (VL) ≥50 copies/mL) during the following periods: November 1, 2019 to April 23, 2020 when conventional 6-monthly script renewal was in place; April 24, 2020 to September 25, 2021 when the 12-monthly script renewal period was implemented; and September 26, 2021 to November 30, 2022, when 6-monthly script renewal was re-instated. Monthly suppression rates were modelled using binomial generalized linear regression models. We measured the slope change in suppression rates between adjacent time periods by including an interaction term between time and a binary indicator for the 12-monthly script renewal period in the model. Inverse probability weighting was used to account for changes in viral load testing during the period.
Results: The study population included 73884 in January 2019, increasing to 76321 in May 2020 and 72026 in November 2022. The proportion with unknown VL increased during the study. (Figure A) Compared to the period prior to lockdown, the odds of viral non-suppression was lower among patients when 12-monthly script renewal was in place [adjusted odds ratio (aRR) 0.99, 95% confidence interval (CI) 0.99-0.99, p<0.001]. When 6-monthly script renewal was re-introduced the odds of viral non-suppression increased [aOR 1.02 (95%CI 1.02- 1.02, p<0.001). (Figure B)
Conclusion: Our results show longer script renewal period was associated with slight improvements in viral suppression. Measures implemented during COVID-19 to ensure continued access to chronic medication in South Africa provided a unique opportunity for evidence to guide efficient ART delivery models involving less frequent visits to healthcare providers without negatively affecting treatment outcomes.

Recorded viral load (panel A) and observed and predicted proportions with viral non-suppression (panel B) before, during and after 12-monthly script renewal was implemented



1247 High Viral Load Suppression Rates Among People Living With HIV Receiving Multi- Month Dispensing

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Background: The World Health Organization (WHO) recommended differentiated service delivery (DSD) with multi-month dispensing (MMD) as a way of improving care for people living with HIV (PLHIV). Uganda adopted MMD in the 2020 consolidated guidelines for the prevention and treatment of HIV and AIDS in Uganda. We sought to determine the likelihood of viral load (VL) non suppression among PLHIV on MMD in Mubende region, central Uganda.
Methods: A cross sectional review of Uganda Electronic Medical Records (Uganda EMR) System program data was conducted at 10 purposively selected high volume facilities in eight districts of central Uganda. We included PLHIV who had one recent documented VL result from January 2022 to February 2023 at last visit. Data on history of advanced HIV disease status and frequency of MMD were retrieved from information over the 13 months of patient care. Logistic regression models were used to assess the effect of MMD on VL suppression among PLHIV. Analysis included PLHIV switched to MMD after being determined stable i.e., on ART for more than 6 months, with a suppressed VL, absence of Advanced HIV Disease (AHD) and not pregnant or not lactating for less than 6 months. PLHIV who didn't fall in these criteria were considered as non-MMD.
Results: We reviewed records for 19,455 PLHIV for whom 67% were women. Median age of the participants was 37 years (Interquartile range- (IQR): 29-47) with 10% of the participants being <20 years. 97% (18,960/19,455) of the participants had a suppressed VL of less than 1,000 copies/mL Median duration on ART for clients initially not on MMD but switched to MMD was 74 months (IQR: 45-105) and 52 months ((IQR): 21.5-89.5) for non MMD. Participants on MMD had significantly lower odds of VL non suppression compared to those on non-MMD (Adjusted Odds Ratio (aOR) of 0.09 (95% CI: 0.07-0.12). However, participants on MMD but with a history of AHD and those on MMD on 2nd line ARV regimen had increased odds of attaining VL non suppression, aOR of 4.71 (95% CI: 2.82-7.86) and 2.31 (95% CI: 1.69-3.16) respectively compared to those with no history of AHD and those on 1st line ARV regimen.
Conclusion: PLHIV on MMD with history of AHD and PLHIV on MMD on second line ARVs have increased likelihood of VL non suppression and therefore need to be monitored closely monitored. An in-depth qualitative study may be helpful to understand other factors that contribute to increased odds of suppression among clients on MMD.

1248 HIV Care Retention in 3 Multi-Month ART Dispensing: A Retrospective Cohort Study in Mozambique

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Background: In Mozambique, enrolment of people living with HIV (PLHIV) into three multi-month dispensing (3MMD) of antiretroviral therapy (ART) has been contingent on clinical stability and ≥6 months on ART. As a COVID-19 control measure, the required time on ART was shortened to ≥3 months. We assessed the effect of 3MMD on the retention in care of PLHIV considering their time on ART prior to enrolment.
Methods: A retrospective cohort study of routine patient data was conducted including PLHIV ≥10 years who started ART between January 2018 and March 2021 in Manhiça District. PLHIV were followed until December 2021. Attrition included lost to follow-up, death and transfer out. Kaplan-Meier estimates were used to calculate cumulative retention in care probabilities after ART initiation. Cox proportional-hazards models, with inverse probability weights of 3MMD enrolment, were used to compare attrition between 3MMD and monthly ART dispensing, stratifying by "established enrollers" (≥6 months on ART) and "early enrollers" (<6 months on ART). Analyses were stratified by adolescents and youth (AYLHIV) (10-24 years) and adults (≥25 years).
Results: A total of 7,378 PLHIV were included, 25% AYLHIV (86% female and median age of 21) and 75% adults (57% female and median age of 35), of whom 59% and 62% were enrolled in 3MMD. Over 90% of early enrolments occurred after COVID-19 measures. Median follow-up time was 11.3 (IQR: 5.7-21.6) and 10.2 (IQR: 4.8-20.9) months in AYLHIV and adults, respectively. Both established and early 3MMD enrollers showed higher retention rates compared to individuals on monthly dispensing (p-value <0.001, Figure). Likewise, the attrition risk was lower for both established (aHR AYLHIV=0.65; 95%CI: 0.54-0.78 and aHR adults=0.50; 95%CI: 0.44-0.56) and early enrollers (aHR AYLHIV=0.70; 95%CI: 0.58-0.85 and aHR adults=0.63; 95%CI: 0.57-0.70). Lastly, among individuals in 3MMD, male gender (aHR=1.30; 95%CI: 1.18-1.44) and receiving care in a medium/low-volume healthcare facility (aHR=1.18; 95%CI: 1.03-1.34) increased attrition risk. Conversely, longer ART time before 3MMD enrolment (aHR=0.93; 95% CI: 0.92-0.94 per one-month increase) and age ≥45 years (aHR= 0.77, 95%CI: 0.67-0.89) reduced risk.
Conclusion: 3MMD improves retention in care compared to monthly dispensing among established and early enrollers, although to a lesser extent among the latter. To reap maximum benefits, shortening the required time on ART prior to 3MMD enrolment should be accompanied by additional support services.
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1249 Using Best-Worst Scaling Experiments to Identify Profiles of Client & Provider Preferences in Zambia

Njekwa Mukamba[1], Musunge Mulabe[1], Marksman Foloko[1], Noelle Le Tourneau[2], Kombatende Sikombe[1], Sandra Simbeza[1], Anjali Sharma[1], Laura K. Beres[3], Jake M. Pry[1], Carolyn Bolton[1], Elvin H. Geng[2], Izukanji Sikazwe[1], **Aaloke Mody**[2]
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Background: People living with HIV (PLWH) who reengage after falling out of care remain high risk for repeat disengagement, but few tailored reengagement strategies exist to support sustained engagement in this diverse. We used best-worst scaling (BWS) experiments to understand client and health care worker (HCW) preferences for features of reengagement strategies.
Methods: We conducted BWS surveys among clients returning to care after being >30 days late to an appointment without ART as well as HCWs at 4 public HIV clinics in Lusaka, Zambia. Participants identified the statements about varied reengagement care features and services that they most and least preferred across multiple choice sets. For both groups, we used multinomial-logit models to quantify relative preference scores, scaled from 0-100, and latent class analysis to identify unique preference profiles for strategies.
Results: We administered BWS surveys among 144 PLWH returning to care (55% female, median age 38 [IQR 19-81]) and 171 HCWs (8% clinical officers,16% nurses, 46% lay HCWs, 30% other). Overall, clients preferred rapid ART reinitiation (normalized score 14.9), longer ART refills (12.0), kind reception at return (11.1),empathy for care challenges (10.9),timely viral load (VL) monitoring (10.2) and coordinating drug pick-ups at other clinics when travelling (9.8).HCWs prioritized timely VL monitoring (11.2), longer drug refills (8.8), flexible ART access after unexpected life events (ULEs) (8.8), kind receptions (8.6), and rapid ART restart (8.3).We identified 3 unique preference profiles for each group.46% of clients preferred improved reengagement experiences (e.g.,rapid ART restart, kind receptions),27% desired easier ART access for travel/ULEs (e.g.,longer refills, travel drug pick-ups, flexible ART access), and 27% sought more convenient clinic experiences (e.g.,longer refills, rapid ART restart, flexible ART access). Amongst HCWs, 41% prioritized improving client experience (e.g.,flexible appointments, kind receptions), 30% focused on ART access and client outreach (e.g., longer refills, community ART delivery), and 29% prioritized clinical needs (e.g.,rapid ART restart,VL monitoring) (Figure).
Conclusion: Although clients and HCWs had similar overall preferences, there are unique preferences profiles that differentially prioritize improvements to client experience, access to medications, or addressing clinical needs. Multipronged, tailored reengagement strategies are needed to address the needs for all returning PLWH

Appendix 1:

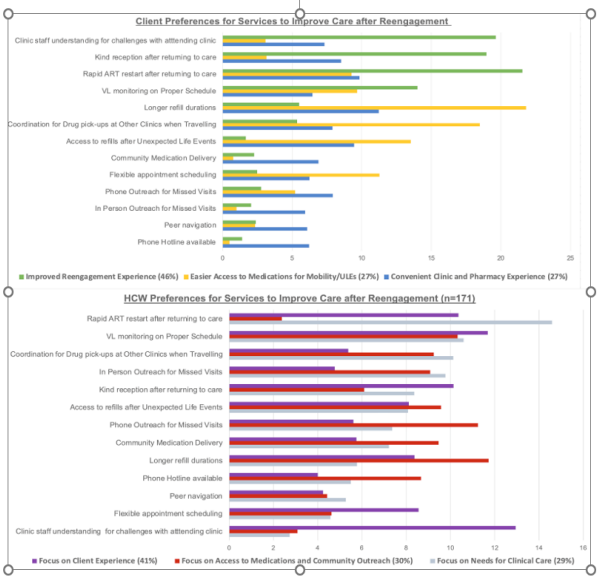

Figure 1: Preferences for Services to Improve Care after Reengagement by Cadre (Client=144, HCWs=171)

1250 Automated Condom Distribution for HIV Prevention: Mwanza, Tanzania, 2021-2023

Aafke Kinemo[1], **Julie Franks**[2], Emmanuel Mihayo[3], Macdonald Mahiti[1], Joyce Thomas[1], Oresto Munishi[1], Omari Msumi[1], John Kahemele[1], Kokuhumbya Kazaura[4], Nyagonde Nyagonde[5], Mbaraka Amuri[5], Haruka Maruyama[1]
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Background: In Tanzania, factors such as fear of stigma associated with getting condoms, concerns about cost, stock outs, and limited outlets beyond the health facility make it hard for people to access condoms. Barriers to access limit condom use among key and vulnerable populations (KVPs) highly impacted by HIV, including adolescent girls and young women (AGYW), female sex workers (FSW), men who have sex with men (MSM), and people who inject drugs (PWID). Automated dispensing technology is a standalone unit consisting of simple electro-mechanical systems to automate the entire distribution process. The unit's interactive digital display, aesthetically pleasing and ergonomically designed, improves the user experience, and increases access to condoms. We describe the use of automated digital dispensing machines in community settings to increase access to condoms.
Methods: We installed six machines at hotspots in Mwanza City frequented by KVPs. Peer outreach workers from the KVP communities were trained on use of the machines and sensitized peers in surrounding communities. Machines dispensed free condoms to people with access codes. Peers distributed unique personal identification numbers to KVP for up to 15 free condoms per day. Non-KVP clients received single-use access for up to three condoms per day. Machines captured user demographics and number of condoms dispensed through a self-guided questionnaire using the machine's touch screen. All data was stored in a secured server to ensure information security and confidentiality.
Results: Between October 2021 and June 2023, a total of 545,581 condoms were distributed to 6,572 KVP; users had a mean age of 29 (range: 25-29) years. Among users, 68% were female, and 77% (n=418,512) of condoms were collected by females. In addition, 57% of condoms were retrieved by FSWs; 15% by AGYW; 14% by MSM; and 14% by PWID. A mean of 93 (range: 62–210) condoms were accessed per female user compared to 61 condoms (range: 4–112) per male user. Machines were accessible 24 hours, 7 days a week. Machine peak access days were over weekends with peak access times between 4 p.m. to 8 p.m.
Conclusion: The proportion of female clients that accessed condoms is generally high. Machines installed in key locations and incorporated with community-based, peer-led approaches can expand condom access beyond health facilities and to times when most health facilities were closed. Technology-based condom distribution solutions are crucial in addressing barriers to condom access in KVPs.

1251 Cost-Effectiveness of an Agricultural Intervention Among Adults With HIV and Their Children in Kenya

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Background: Agricultural interventions to address food insecurity have been shown to improve HIV health outcomes through nutritional, mental health, and health behavior pathways, but little is known about their costs and cost-effectiveness
Methods: We estimated costs and incremental cost-effectiveness of implementing a multisectoral agricultural intervention (Shamba Maisha) compared to control within a cluster-randomized trial in 8 matched health facilities during 2016-2019. Shamba Maisha included loans to purchase a human-powered irrigation pump, fertilizer, seeds and pesticides, and provision of training in sustainable agriculture and financial literacy. Participants were adults in HIV care at participating clinics who were followed for 24 months. We estimated cost per person using site visits, conversations with study coordinators, micro-costing techniques, a time-and-motion personnel study, and administrative record review. Costs were categorized into capital goods, personnel costs, and recurrent goods and services. We observed effects of the intervention on food insecurity, depression, and social support among participants and length/height for age among their young children (aged 6-23.9 months). Results from the study were translated into disability-adjusted life years (DALYs) averted. We estimated the incremental cost per DALY averted among participants and their young children in the intervention compared to those in the control arm.
Results: Participants included 720 adults with HIV (366 intervention, 354 control). Results were also assessed among 207 young children (95 intervention, 112 control). Overall, the incremental cost of implementation of Shamba Maisha compared to control was $642 per person ($841 intervention, $199 control). This included an added cost per person of $209 for capital goods, $387 for personnel salaries and benefits, $22 for recurring goods, and $24 for recurring services. The intervention averted an estimated 0.158 DALYs per person, including 0.027 DALYs for decreased food insecurity, 0.053 for decreased depression, 0.044 for increased social support, and 0.034 for greater length/height for age among young children. The overall incremental cost-effectiveness ratio was $4027 per DALY averted
Conclusion: The Shamba Maisha multisectoral agricultural intervention was cost-effective based on the WHO threshold of three times the annual GDP per capita ($6020 USD in 2021). Future analyses will account for reduced health care costs associated with improved health outcomes.

1252 Integrated HIV+NCD Care in Community Microfinance Groups: Harambee Cluster Randomized Trial Results

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Background: In Sub-Saharan Africa, distance to health facilities, vertical care delivery, increased burden of non-communicable diseases (NCDs), and limited socioeconomic resources are barriers to patients maintaining HIV viral suppression. The Harambee cluster randomized trial tested a differentiated care model delivering HIV+NCD care within microfinance (MF) groups of people living with HIV in western Kenya.
Methods: Fifty-seven MF groups (n=855 participants) were randomized in a 1:1 ratio to receive integrated community-based (ICB) care or standard facility-based care (SOC). The ICB intervention included: (1) clinical care visits during MF group meetings inclusive of clinical consultations, NCD management, distribution of antiretroviral therapy (ART) and NCD medications; (2) support for ART adherence; and (3) facility referrals as needed. Primary outcome was viral

suppression (<400 HIV-RNA/mL before January 1, 2023; <200 HIV- RNA/mL on or after January 1, 2023) at 18 months. Effectiveness was estimated as the difference in viral suppression at 18-months comparing the two trial arms using a doubly robust generalized estimating equation accounting for dropout and adjusting for baseline viral load. The primary outcome from both trial arms were also compared to an additional n=300 propensity-matched controls receiving usual care (UC) alone.

Results: The sample was 52 years of age, 75% female and viral suppression at baseline was 94%. There was no intervention effect on viral suppression at 18-months when comparing MF+ICB to MF+SOC (odds ratio, OR: 1.20, 95% Confidence Interval CI: [0.90, 1.60], p-value =0.23). There was an increase in viral suppression in the MF+ICB (OR: 2.16, 95% CI [1.48, 3.19], p-value <0.001) and MF+SOC (OR: 1.42, 95% CI [1.05, 1.92], p- value = 0.023), compared to the matched UC group.

Conclusion: Among MF groups, those who received integrated HIV+NCD care did not have statistically higher viral suppression compared to SOC. This may be due to high viral suppression at baseline in both arms. However, improvements in viral suppression among MF group participants compared to matched usual care patients suggests that microfinance improves HIV treatment outcomes among patients in rural Kenya, yet additional research is necessary to understand the mechanisms for how MF improves viral suppression. Differentiated care models for addressing multilevel barriers to the maintenance of HIV viral suppression may be more effective if socioeconomic barriers are mitigated.

1253 Persistence on Contraception and PrEP in Hair Salons in South Africa

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Background: Young women have high HIV incidence and risk for unintended births in sub-Saharan Africa. Women congregate regularly in hair salons; these may be useful community settings for providing HIV prevention and family planning. Our objective was to assess PrEP and contraceptive persistence following dispensing in hair salons in South Africa.

Methods: We conducted a pilot randomized trial to evaluate uptake and persistence of a nurse-supported intervention offering PrEP (TDF-FTC) and contraception (oral/injectable) in 5 salons in urban KwaZulu-Natal. Women could start PrEP and/or contraception at the initial visit or opt in at a later visit. We defined persistence as one additional visit within 6 months with continued treatment (PrEP, contraception, or both). We assessed the association of PrEP persistence among intervention participants using contingency tables. Factors assessed included age, self-perceived risk of HIV, partner ≥5y older, primary sex partner having other partners, intimate partner violence, curable STI at enrollment, and persistence on contraception.

Results: Among 125 participants in the intervention salons, median age was 26y (IQR 22-29). 93 (75%) reported visiting the salon at least every 2 months; 34 (27%) were taking hormonal contraception at enrollment. 25 (28%) described themselves as having moderate or greater chance of getting HIV in the next year and 35 (32%) think their primary sex partner has other partners. 46 (37%) initiated PrEP during the study; among the 40 returning for at least 6 months of follow-up, 17 (43%) persisted. 39 (31%) opted for oral contraception and 77 (62%) for injectable contraception; among the 94 with at least 6 months follow-up, 66 (70%) persisted on contraception. Persistence on salon-based PrEP was associated with age ≥25y (RR: 3.45 [95% CI: 1.16,24.5]) and intimate partner violence (2.57 [1.24,4.91]). PrEP persistence was also related to no/low perceived risk of HIV and contraceptive persistence (RR undefined).

Conclusion: Young women in South Africa found receipt of HIV prevention services and family planning in a hair salon acceptable over time, with persistence for contraception (70%) greater than for PrEP (43%). Factors related to PrEP persistence include age ≥ 25y, intimate partner violence, a low or no perceived risk of HIV, and persistence on contraceptives. Hair salons are a novel venue for delivering long-term sexual reproductive health services, however, a menu of PrEP delivery methods may be required to support persistence.

Table 1. Association of Potential Predictors with PrEP Persistence

	Level	Persistence*	Level	Persistence*	Relative Risk (95% CI)	P-value[x]
Age group	25 or older	61% (14/23)	Under 25	18% (3/17)	3.45 (1.16, 24.45)	0.0097
Self-perceived risk of HIV	None or low	57% (16/28)	Moderate or high	0% (0/6)	Undefined	0.0198
Partner ≥ 5y older	No	48% (11/23)	Yes	40% (6/15)	1.20 (0.56, 3.10)	0.7442
Partner has other partners	No/Don't know/Maybe	54% (13/24)	Yes	29% (4/14)	1.90 (0.83, 8.55)	0.1812
Intimate partner violence	Yes	86% (6/7)	No	33% (11/33)	2.57 (1.24, 4.91)	0.0295
Curable STI at enrollment	No	58% (14/24)	Yes	27% (3/11)	2.14 (0.87, 15.17)	0.1464
Persistence on contraceptives	Yes	67% (14/21)	No	0% (0/12)	Undefined	0.0002

* Entries are % (Number persisting/N in category)
[x] Fisher's Exact test

1254 Persistence in Care After PrEP Initiation Through a Community-Based Mobile Clinic

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[1]University of Miami, Miami, FL, USA Presenting Author: Dr Susanne Doblecki-Lewis University of Miami - University of Miami (Miami, FL, USA)

Background: PrEP can reduce HIV infections substantially when implemented effectively. Miami, the area of the United States (US) with the highest rate of new HIV infections, has significant structural, social, and logistic barriers to PrEP care. Alternative care models, such as mobile clinics, can increase access to PrEP. There are no available data on persistence in PrEP care through a community-based mobile clinic.

Methods: Clients sought PrEP services through one of 5 mobile sites or at the fixed site from August 2018- March 2023 excluding March-September 2020 due to the COVID-19 pandemic. 24-week persistence was defined as at least 1 follow-up appointment within 24 weeks of initiation, and 48-week persistence as having at least 1 additional follow-up appointment between 24 and 48 weeks. Cox proportional hazards models were used to estimate adjusted Hazard Ratio (aHR) of risk factors for discontinuation of care by 48 weeks by gender, race, ethnicity, insurance status, and visit site.

Results: 919 clients initiated PrEP before March 2022. Clients were primarily self-reported male (86.8%), white (69.7%), Hispanic (74.6%), insured (50.6%), and initiated services at the mobile clinic (52.2%). Overall persistence on PrEP was 56.7% at 24 weeks and 41.5% at 48 weeks. Individuals who were uninsured, identified as male, and initiated services in the mobile clinic were more likely to continue PrEP (HR:1.20, p=0.01; HR:2.02, p<0.01; HR:1.68, p<0.01, respectively). Overall persistence in care (including visits for other sexual health services) was 76.2% to 24 weeks and 55.7% at 48 weeks. Individuals who identified as male, and those who initiated services at the mobile clinic had increased continuation (HR:1.51, p=0.02; HR:2.21, p<0.01, respectively).

Conclusion: Persistence in PrEP and sexual health care is improved for those initiating services in a community-based mobile clinic compared with a fixed clinic with otherwise identical services, staff, and barrier- lowering strategies. In our analysis, uninsured clients had improved persistence on PrEP compared with those who were insured, suggesting that our no-cost service model with aggressive navigation to available assistance programs can successfully overcome barriers due to insurance coverage. Race and ethnicity were not associated with persistence in our analysis. Persistence among women initiating PrEP in both the mobile and fixed clinics was decreased. Future research to assess the potential role of mobile clinics in PrEP delivery are warranted.

1255 Availability of Onsite Substance Use Disorder Services in HIV Facilities by Urbanicity in the US

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Centers for Disease Control and Prevention, Atlanta, GA, USA

Background: HIV outbreaks related to injection drug use continue to be reported in the U.S., including in rural communities, where accessing HIV care services and substance use disorder (SUD) services may be challenging. We describe availability of onsite SUD services at HIV care facilities attended by a representative sample of people with HIV (PWH) in the U.S. and the percentage of persons receiving these services by urbanicity.

Methods: We analyzed 2021 survey data from 514 HIV care facilities representing all facilities providing care to a national probability sample of

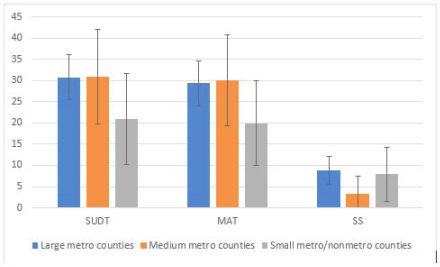
U.S. adults with HIV. Facility data on availability of SUD services, including SUD treatment (SUDT), medication-assisted treatment (MAT), and syringe services (SS), were collected. Data were linked to Medical Monitoring Project (MMP) participant data from 2019. Weighted percentages of characteristics at the facility and patient-level were reported by urbanicity, as defined by the Rural-Urban Continuum Code codes. Urbanicity was categorized as follows: counties in metropolitan areas of ≥1,000,000 people (large metro); counties in metropolitan areas of 250,000–1,000,000 people (medium metro); and counties in metropolitan areas of <250,000 people (small metro/nonmetro).

Results: Of facilities attended by MMP participants, 72% were in large metro counties, 15% were in medium metro counties, and 13% were in small metro/nonmetro counties. The percentage of PWH receiving HIV care was highest in large metro counties (73%), followed by medium (18%) and small/nonmetro counites (9%). The availability of onsite SUD services at HIV facilities varied by urbanicity (large metro, medium metro, and small/nonmetro), with SUDT at 31%, 31%, and 21%; MAT at 29%, 30%, and 20%; and SS at 9%, 3%, and 8% of facilities, respectively. (Figure 1A). Corresponding percentages of persons attending facilities with onsite SUD services varied by urbanicity (large metro, medium metro, and small/nonmetro), with SUDT at 35%, 42%, 23%, MAT at 36%, 22%, and 17%; and SS at 7%, 5%, and 7%, respectively (Figure 1B).

Conclusion: Onsite SUD service availability is limited at HIV care facilities and may vary by urbanicity, with potentially lower access in less urban counties. Ensuring access to SUD services could help limit risk of HIV outbreaks related to injection drug use, a national priority for achieving goals for the Ending the HIV Epidemic initiative.

Figure. Proportion of facilities (Panel A) and proportion of persons receiving HIV (Panel B) with onsite SUD treatment (SUDT), Medication-assisted treatment (MA Services (SS) by urbanicity.

A



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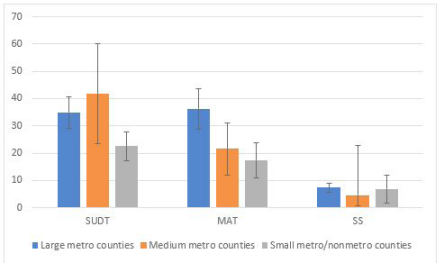

Footnote: weighted percentages with 95% CIs are included

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